To Catherine, Jean-Jacques and Jean
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<td>Benzyl.</td>
</tr>
<tr>
<td>Bpin</td>
<td>Boron pinacolate.</td>
</tr>
<tr>
<td>B_{2}pin_{2}</td>
<td>Bispinacolate diboron.</td>
</tr>
<tr>
<td>CALB</td>
<td>Candida Antarctica lipase B.</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane.</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory.</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate.</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine.</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane.</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide.</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide.</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio.</td>
</tr>
<tr>
<td>EDCI/EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess.</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography.</td>
</tr>
<tr>
<td>HOBt</td>
<td>Hydroxybenzotriazole.</td>
</tr>
<tr>
<td>Hoveyda-Grubbs 2^{nd} generation</td>
<td>(1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene) ruthenium.</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography.</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium aluminium hydride.</td>
</tr>
</tbody>
</table>
LDA  Lithium diisopropylamide.
LiHMDS  Lithium hexamethyldisilazide.
MIQ  Monoisoquinoline based carbene ligand.
MsCl  Mesylate chloride.
MTBE  Methyl tert-butyl ether.
NCS  N-chlorosuccinimide.
NHC  N-heterocyclic carbene.
NMR  Nuclear magnetic resonance.
Piv  Pivalate.
PMB  para-methoxybenzyl.
PMHS  Polymethylhydrosiloxane.
PMP  para methoxyphenyl.
Rac  Racemic.
SM  Starting material.
SMB  Simulating moving bed.
(R)-(S)-Taniaphos  (R<sub>p</sub>)-1-[(S)-α-(Dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrrocene.
TBDPS  tert-Butyl diphenylsilyl.
TC  Thiophencarboxylate.
TFA  Trifluoroacetic acid.
Ti<sub>2</sub>O  Triflate anhydride.
THF  Tetrahydrofuran.
TMS  Trimethylsilyl.
TsCl  Tosylate chloride.
V<sub>Bur</sub>  % buried volume.
Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

DEVELOPMENT OF NEW CHIRAL DIAMINOCARBENE LIGANDS AND THEIR APPLICATIONS IN COPPER-CATALYZED REACTIONS

By

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August 2010

Chair: Sukwon Hong
Major: Chemistry

N-Heterocyclic carbene (NHC) ligands are considered strong σ-donors and can be used in various catalytic reactions. Asymmetric catalysis using NHCs has been widely spread over the past 10 years. Comparing to chiral phosphine ligands, the choice of chiral NHCs still remains limited. Several designs have been developed such as attaching chiral alkyl groups directly to the nitrogen atoms, installing a chiral backbone on the NHC ring and using a chiral tethered group for second point metal binding. In this work, new designs were explored to further diversify the choice in chiral NHCs.

C$_2$-symmetric biisoquinoline-based diaminocarbene ligands were designed to create a chiral environment extended toward the metal center, which was confirmed by an X-ray structure. The concise ligand synthesis is highlighted by a modified Bischler-Napieralski cyclization of bisamides prepared from readily available chiral phenethylamines, and allows easy variation of the stereodifferentiating groups. The cyclohexyl-biisoquinoline based carbene-copper complex is an efficient catalyst for enantioselective S$_N$2' allylic alkylation with Grignard reagents showing S$_N$2' regioselectivity higher than 5:1 and enantioselectivity in the range of 68-77% ee.
A novel acyclic diaminocarbene-copper complex has been prepared for the first time, conveniently from a chloroamidinium salt and Cu(I)-thiophenecarboxylate. The in situ generated acyclic diaminocarbene-Cu complex was characterized by $^{13}$C-NMR experiments using a $^{13}$C-labeled carbene precursor. The acyclic diaminocarbene-Cu complex is a highly efficient catalyst for S$_{N}2′$-allylic alkylation with alkyl Grignard reagents, showing high S$_{N}2′$ selectivity.

$C_1$-symmetric monoisoquinoline based chiral diaminocarbene ligands were envisioned to expand the chiral pool of NHC structures and further optimize previously reported $C_2$-symmetric biisoquinoline carbene ligands. This new ligand was synthesized from readily available chiral phenethylamine. The synthetic scheme allowed easy variation of the ligand structure within the final steps. Both $C_2$ and $C_1$-symmetric carbene ligands could be compared by their respective X-ray structures of Au(I) complexes. Monoisoquinoline based carbene ligand was tested in the copper-catalyzed borylation of $\alpha,\beta$-unsaturated amides giving good yields (80-99%) and enantioselectivities (85%) for various substrates.
CHAPTER 1
INTRODUCTION

1.1 N-Heterocyclic Carbene Background

N-heterocyclic carbenes (NHC) have been isolated for the first time by Arduengo et al. in 1991.\(^1\) NHCs are stabilized by the vicinal nitrogen atoms and exhibit singlet state configuration. The two nitrogen lone pairs increase the energy of the empty \(p_\pi\) orbital by mesomeric effects and the carbene lone pair \(p_\sigma\) is stabilized by inductive effects of electronegative nitrogen atoms (Figure 1-1). Those two effects increase the \(\sigma-p_\pi\) gap and favor the singlet state.\(^2\) NHCs are strong \(\sigma\)-donors and their metal complexes show better air and thermal stability than the analogous phosphine complexes.\(^3\) As a result of these superior properties, carbene ligands are replacing bulky electron-donating phosphine ligands in various catalytic reactions\(^4\) such as cross coupling reactions,\(^5\) and olefin metathesis.\(^6\)

![Figure 1-1. Electronic effects of the substituents for diaminocarbenes](image)

Recently, the discovery and isolation of several types of stable carbenes\(^7\) has been reported (Figure 1-2). From four-, to seven-membered N-heterocyclic rings have been reported. Most of the stable aminocarbenes reported are five-membered rings (1-2 to 1-8). This might be due to an increase of stability compared to other ring sizes. In the carbene infancy, Arduengo et al. reported an easy and practical synthesis of typical five-membered N-heterocyclic ring (Scheme 1-1).\(^8\)
Figure 1-2. Stable diaminocarbenes

Bisimines 1-13 were obtained by condensation of glyoxal and respective amines. Then, either it was reduced to the corresponding diammonium salt 1-14 by NaBH₄ or it was cyclized to the imidazolium salt 1-15 using chloromethyl ethyl ether. The diammonium 1-14 was converted to the imidazolinium 1-16 with triethyl orthoformate. This synthesis allows for a wide variation of the starting amines.

Scheme 1-1. Synthesis of imidazolium and imidazolinium salts
1.2 Chiral NHC

Asymmetric catalysis using chiral carbene ligands has exploded in the last 10 years. There are two ways of introducing chirality into the carbene ligand framework (Figure 1-3).

![Figure 1-3. Basic chiral carbene ligand framework](image)

The first method, reported by Herrmann et al., involves attaching chiral substituents on the nitrogen atoms. The second method, first developed by Grubbs et al., uses a chiral backbone which tethers two nitrogen atoms in saturated carbenes to relay chiral information to the metal. Monodentate, bidentate or multidentate chiral amino carbene ligands have been developed. An overview of monodentate aminocarbene ligands as well as their synthesis will be discussed.

1.2.1 Chiral Substituents at The Nitrogen Atoms

This strategy is based on the introduction of N-substituents containing a chiral center on the carbon attached to the nitrogen atom. In the first report by Herrmann, the chiral unit was incorporated as a commercially available chiral amine 18. The imidazolium 19 was synthesized in a one pot synthesis based on modified Arduengo’s procedure (Scheme 1-2). This synthesis can be used with various chiral amines to generate an array of chiral imidazoliums. Those NHC ligands were tested in the hydrosilylation of acetophenone using rhodium complexes but only poor enantioselectivity was observed with 19 (Ar = α-napht, 90% yield, 32% ee). The chiral induction of these ligands remained low which is probably due to the rapid internal rotation of the chiral substituents around the C–N axis. This leaves the active chiral space at the metal center relatively ill-defined.
Scheme 1-2. One pot synthesis of chiral imidazoliums

In other reactions, this rotation was beneficial and gave up to 62% ee in the addition of zinc reagent to cyclohexenone 1-20 (Scheme 1-3).\textsuperscript{15} This reaction employed a silver-NHC complex 1-21 as a transmetallating agent.

Scheme 1-3. Enantioselective copper-catalyzed 1,4-addition of zinc reagent using 1-21

In 2003, Andrus et al. reported the use of chiral planar [2,2]paracyclophane amines 1-25 and 1-26, obtained by chiral resolution,\textsuperscript{16} as precursor in the imidazolinium synthesis (Scheme 1-4).\textsuperscript{17} The amine 1-23 can be functionalized by Suzuki coupling using NHC 1-24 as ligand then it was converted to the imidazolinium using Arduengo’s conditions.\textsuperscript{8}

1-28 exhibited the best results in the ruthenium catalyzed ketone reduction (Scheme 1-5).\textsuperscript{18} The enantioselectivity stayed high for most aromatic substrates but it dropped to 58% ee for some aliphatic substrates.
Scheme 1-4. Synthesis of chiral [2.2]paracyclophane imidazoliums

Scheme 1-5. Ruthenium catalyzed asymmetric ketone hydrosilylation

In 2001, Hartwig and co-workers reported the first enantioselective intramolecular α-arylation with chiral carbene ligands. The best chiral NHC 1-33 was derived from (-)-isopinocampheyl amine and produced all carbon quaternary centers in 76% ee (Scheme 1-6). In this paper, carbene ligands gave better results than various chiral phosphines.¹⁹

Scheme 1-6. Enantioselective α-arylation of oxindole with 1-33
Following this report, Kundig et al. explored new bulky benzylamines derived NHCs 1-34 which showed increased enantioselectivity for the substrate 1-31 (Scheme 1-7). In a following report, the reaction was extended to the formation of tertiary alkoxides as well as trisubstituted tertiary amines by replacing the methyl group with protected heteroatoms.\textsuperscript{20}

![Scheme 1-7. Enantioselective α-arylation of oxindole with 1-34](image)

Glorius et al. developed a new series of ligand based on the bisoxazoline framework 1-4.\textsuperscript{21} Those ligands were applied in the Suzuki-Miyaura coupling and tetra-ortho-substituted biaryls were synthesized for the first time from nonactivated aryl chlorides.\textsuperscript{22} The first ligand generation 1-35 was derived from natural amino acids and showed only 43\% ee in the α-arylation of oxindole. The second generation 1-36 consisted of a spiro cyclohexyl substitutent which was representative of a flexible steric bulk (chair conformation).\textsuperscript{23} In the third generation 1-37, this spiro compound was made chiral (Figure 1-4).\textsuperscript{24}

![Figure 1-4. Bisoxazoline derived NHC evolution](image)

Starting with a Bucherer-Bergs reaction,\textsuperscript{25} (-)-menthone 1-38 was converted to the corresponding hydantoin 1-39 using potassium cyanide and ammonium carbonate. The urea
hydrolysis was realized under vigorous conditions using aqueous sulfuric acid at 150 °C, and this was followed by reduction to the quaternary center amino alcohol 1-40 using sodium borohydride combined with iodine. The bisamide 1-41 synthesis was achieved by coupling with diethyloxalate. Then the alcohol moiety in 1-41 was substituted by chloride using thionyl chloride. The bisoxazoline moiety 1-43 was produced under basic conditions at reflux in excellent yields. Silver triflate in combination with chloromethyl pivalate, instead of the typical chloromethyl ethyl ether developed by Arduengo, gave the imidazolium 1-37 in good yields (Scheme 1-8). This alternative method was necessary to prevent ring opening of the oxazoline ring by chloride counterion (Scheme 2-3).

Scheme 1-8. Synthesis of the (-)-menthone-derived IBiox salt

This third generation imidazolium 1-37 was applied in the same α-arylation of oxindole described previously (Scheme 1-9). Excellent ee and expansion to unactivated chloride substrate 1-44 was achieved.
Scheme 1-9. Enantioselective α-arylation of oxindole with 1-37

Herrmann and coworkers also developed a rigid chiral carbene structure based on the isoquinoline framework (Scheme 1-10). Benzonitrile 1-45 was converted to the phenylethyl amine 1-46 by addition of benzyl Grignard reagent followed by LAH reduction of the imine formed in situ. The racemic amine rac-1-46 was resolved by recrystallization of ammonium salts using tartaric acid as a chiral counterion. Then the amine 1-46 was transformed into a formamide and subjected to a modified Bischler-Napieralski cyclization to yield the corresponding monoimine 1-47. Then it was dimerized using Zinc and TMSCl as coupling agent. The resulting diamine 1-48 was obtained as a single diastereomer. Typical cyclization conditions using triethyl orthoformate generated the desired imidazolium 1-49.

Scheme 1-10. Synthesis of imidazolinium salts with restricted flexibility
The ligand **1-49** was tested in the iridium catalyzed hydrogenation of amidoacrylate **1-50** (Scheme 1-11). Excellent conversion was observed as well as modest enantioselectivity (60% ee).

![Reaction Scheme](attachment:image.png)

Scheme 1-11. Asymmetric hydrogenation of methyl 2-acetamidoacrylate with **1-52**

### 1.2.2 Backbone Chirality

In order to transfer the chirality from the backbone to the front, the substituents off the nitrogen atoms need to be rather bulky or restricted in movement for an effective interaction with the chiral substituents at the back. C₂-symmetric chiral vicinal diamines²⁹ offer a good starting point for the generation of those ligands. Phenyl or cyclohexyl substituted diamines are commercially available but still relatively expensive (around $80 for 1g). Other substitution such as tert-butyl required a three step synthesis using a chiral auxiliary (Scheme 1-12).³⁰ The chiral bisimine **1-54** was first synthesized by condensation of chiral amine **1-53** with glyoxal. Then diastereoselective addition of Grignard reagent followed by removal of the auxiliary group furnished the desired chiral diamine **1-56**.

![Diamine Synthesis Scheme](attachment:image.png)

Scheme 1-12. Tert-butyl substituted vicinal diamine synthesis
Using palladium catalyzed Buchwald-Hartwig coupling, various aryl groups could be added on the nitrogen atoms of 1-57. Triethyl orthoformate furnished the desired imidazolinium 1-59 (Scheme 1-13).

\[
\begin{array}{c}
\text{R} \quad \text{NH} \quad \text{NH}_2 \\
\text{H}_2\text{N} \quad \text{H}_2\text{N} \\
\text{ArBr} \quad \text{Pd(OAc)}_2 \\
\text{BINAP} \quad \text{NaOtfBu} \\
\end{array}
\xrightarrow{\text{ArNH}}
\begin{array}{c}
\text{R} \quad \text{Ar} \quad \text{NH} \quad \text{HN} \quad \text{Ar} \\
1-58 \\
\end{array}
\xrightarrow{\text{HC(OEt)}_3} \\
\begin{array}{c}
\text{R} \quad \text{N} \quad \text{N} \quad \text{Ar} \\
\text{NHBF}_4 \\
1-59 \quad \text{BF}_4^- \\
\end{array}
\]

Scheme 1-13. Synthesis of N-aryl substituted chiral imidazoliniums

N-alkyl substituted imidazolinium salts were synthesized by another pathway because primary amines would lead to dialkylated products (Scheme 1-14). Instead, secondary amine 1-55 was converted to the aminal 1-60 followed by deprotection of the chiral groups which yield the imidazole 1-61. Substitution using primary alkyl halides gave imidazoliniums 1-62.\(^{15}\)

\[
\begin{array}{c}
\text{Ph} \quad \text{NH} \quad \text{HN} \quad \text{HN} \quad \text{Ph} \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{H}_2\text{C}=\text{O} \quad \text{Et}_2\text{O} \quad \text{rt} \quad \text{77}% \\
\end{array}
\xrightarrow{\text{HCO}_2\text{NH}_4} \\
\begin{array}{c}
\text{Ph} \quad \text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Me} \\
\text{HCO}_2\text{NH}_4 \quad \text{Pd(OH)}_2 \\
\text{EtOH} \quad 60 \text{ } \circ \text{C} \quad 6 \text{ h} \quad \text{95}% \\
\end{array}
\xrightarrow{\text{RX}} \\
\begin{array}{c}
\text{R} \quad \text{N} \quad \text{N} \quad \text{Ar} \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{K}_2\text{CO}_3 \quad \text{DCM} \quad \text{rt} \quad \text{60-90}% \\
\end{array}
\]

Scheme 1-14. Synthesis of N-alkyl substituted chiral imidazoliniums

In 2001, Grubbs and co-workers reported the first enantioselective ruthenium olefin methatisation bearing NHC ligands.\(^{32}\) The reaction consisted on a desymmetrization of achiral trienes 1-63 by asymmetric ring closing metathesis (Table 1-1). In this first report, it was observed that 1-66 prepared from (1R,2R)-diphenylethylenediamine showed higher enantioselectivities than 1-68 prepared from (1R,2R)-1,2-diaminocyclohexane (entries 2 and 6).

Moreover, mono arylsubstituted 1-66 exhibited higher reactivity than symmetrically substituted 1-65 (entry 1 and 2). Also if chloride ligands are exchanged in situ with iodides, the enantioselectivity increased drastically (entries 2 and 3). The iodide ligand might have an
On the other hand, when a $C_1$-symmetric NHC ligand 1-67 was used, higher enantioselectivity was observed compared to $C_2$-symmetric versions with chloride ligand (entries 2 and 4).

Table 1-1. Asymmetric ring closing metathesis with various chiral NHC ruthenium complexes

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>additive</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1-65" alt="Image" /></td>
<td>No</td>
<td>DCM</td>
<td>67</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td><img src="1-66" alt="Image" /></td>
<td>No</td>
<td>DCM</td>
<td>98</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td><img src="1-66" alt="Image" /></td>
<td>Nal</td>
<td>THF</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td><img src="1-67" alt="Image" /></td>
<td>No</td>
<td>DCM</td>
<td>98</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td><img src="1-68" alt="Image" /></td>
<td>Nal</td>
<td>THF</td>
<td>98</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td><img src="1-68" alt="Image" /></td>
<td>No</td>
<td>DCM</td>
<td>95</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td><img src="1-68" alt="Image" /></td>
<td>Nal</td>
<td>THF</td>
<td>95</td>
<td>3</td>
</tr>
</tbody>
</table>
Additionally, when iodide was added with 1-67, the inverse effect was observed, the enantioselectivity decreased by 50% (entries 4 and 5). 1-67 could be synthesized by combining the two methodologies developed previously (Schemes 3 and 4).

Other structures with backbone chirality were developed to further expand the field of chiral NHC ligands. Tricyclic carbene structures were first developed by Herrmann and co-workers.\textsuperscript{35} Chiral imidazolinium ligands 1-84 and 1-83, derived from 2,2'-bipiperidine 1-73 and partially reduced biisoquinoline 1-81, were prepared from achiral heterocyclic compounds. Bipyridine 1-69 was first over reduced, using Ni/Al alloy,\textsuperscript{36} to give a mixture of meso and \textit{dl} 2,2'-bipiperidine 1-70 in 83\% yield (Scheme 1-15). The meso compound 1-71 was more soluble in ethanol which allowed the isolation of the racemic bipiperidine hydrobromide salt 1-72 in 45\% yield.

In order to resolve \textit{rac}-1-73, menthol based phosphine complexes were synthesized and the two diastereomers 1-74 and 1-75 were separated by recrystallization (Scheme 1-16).\textsuperscript{35}

Phenethylamine 1-76 was first converted to isoquinoline 1-77 using the Bischler-Napieralski cyclization.\textsuperscript{37} Then reductive coupling of imines with the couple Zn/Me\textsubscript{3}SiCl afforded the vicinal diamine 1-78.\textsuperscript{28} The \textit{dl}-bishydroisoquinoline 1-80 was isolated from an aqueous solution of hydrobromic acid in 44\% yield (Scheme 1-17).
Scheme 1.6. Synthesis and chiral resolution of bipiperidine

Scheme 1.7. Synthesis and separation of meso and dl forms of biisoquinoline

The resolution was achieved in high yield by using D-(+)-α-bromocamphor-π-sulfonic acid as a chiral counterion (Scheme 1.8). Both vicinal diamines 1-81 and 1-73 could be cyclized into imidazolinium using triethyl orthoformate.

Scheme 1.8. Synthesis and chiral resolution of biisoquinoline
Rhodium \textbf{1-83} and iridium \textbf{1-84} complexes were synthesized by transmetallation from silver-NHC complexes. They were both tested in the asymmetric hydrosilylation of acetophenone \textbf{1-29}. Both showed good activity at low catalyst loadings. Low enantioselectivity was observed which was probably due to the absence of transferrable groups from the ligand backbone chirality (Scheme 1-19).\textsuperscript{35}

![Scheme 1-19. Asymmetric hydrosilylation using Rh and Ir complexes with NHC ligands based on reduced biisoquinoline and bipiperidine framework](image)

Stahl and co-workers were the first to report a seven member ring NHC.\textsuperscript{38} This ligand was based on a torsional twist of the phenyl rings to relieve ring strains and induced a $C_2$-symmetric structure. This scaffold required chiral resolution at the amidinium stage which could be troublesome. To overcome this difficulty, the chirality of the biphenyl diamine \textbf{1-85} was set by adding two methyl substituents at the 6 and 6’ positions (Scheme 1-20). This chiral amine was resolved by simulated moving bed (SMB) chromatography which involves a series of preparative column in series in order to separate close binary systems.\textsuperscript{39} As it was observed in the previous example (Scheme 1-19), the backbone chirality was not sufficient to induce high enantioselectivity. Grubbs and co-workers showed better results (Table 1-1) when the chiral backbone was used as a relay for the substituents close to the metal sphere. Following this strategy, phenyl groups were installed \textit{ortho} to the nitrogen substituents by a Daugulis-Zaitsev\textsuperscript{40}
coupling reaction developed recently by Stahl and co-workers.\textsuperscript{41} Then the acetyl directing group was removed by strong basic conditions. Sequential addition of cyclohexyl aldehyde and LAH gave the secondary amine 1-88 in 94% yield. Cyclization of this bisamine afforded the chiral amidinium 1-89 (Scheme 1-20).

Scheme 1-20. Synthesis of chiral resolved seven-membered ring amidinium salts

The racemic version of this ligand was used in the aerobic intramolecular oxidative amination of alkenes catalyzed by palladium complexes.\textsuperscript{42} Following this work, the chiral amidinium 1-89 was tested in the asymmetric oxidative amination; this is the first report of the use of NHC in this reaction (Table 1-2).\textsuperscript{43} In the best case, the product was obtained in 63% ee but only 35% yield (entry 1). With Kundig’s complex 1-93, only racemic product was obtained using similar conditions (entry 2); but varying the base, which is known to facilitate substrate oxidation by Pd(II), increased only the yield (entry 3).
Table 1-2. Aerobic oxidative cyclization catalyzed by Stahl’s and Kundig’s ligands

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>additives</th>
<th>yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Catalyst" /></td>
<td>AgTFA/iPr₂NEt, 3Å MS</td>
<td>35%</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Catalyst" /></td>
<td>iPr₂NEt, 3Å MS</td>
<td>34%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Catalyst" /></td>
<td>Na₂CO₃</td>
<td>66%</td>
<td>7%</td>
</tr>
</tbody>
</table>

1.3 Acyclic Carbene and Methods of Preparation

Acyclic diaminocarbenes (ADC) are called acyclic because the nitrogen atoms surrounding the carbene are not included within the same ring (Figure 1-5).

![Figure 1-5](image)

Figure 1-5. Major structure difference between NHC and ADC

In 1996, Alder et al. reported the first ADC (Bis(diisopropylamino)carbene) 1-96 as a crystalline solid stable both in the solid and solution state. ADCs have been shown to be more electron donating than NHCs, and more sterically demanding resulting from a greater N-C-N...
bond angle (121.0° vs 104.7°). The lack of reports concerning ADC might be attributed to the difficult preparation of acyclic carbenes and ADC-metal complexes.

In the first reports by Alder and co-workers,\textsuperscript{45} the amidinium 1-95 was synthesized through intermolecular Vilsmeier-Haack chemistry (Scheme 1-21). This route often gives low yield along with byproduct resulting from mixture of counterion from the formamidinium precursor. Alder and co-workers found a recrystallization route by exchanging with hexafluorophosphate salts which increased the yield and purity of the product formed. The amidinium 1-95 has a higher pkA than imidazolinium 1-2 (27.9 vs 22.3 in DMSO)\textsuperscript{47} so stronger bases are needed to deprotonate those species such as LDA, LiHMDS and NaH in NH\textsubscript{3} to give ADC complexes with a variety of metals.\textsuperscript{46} At first glance, free carbene seem to be generated but the base counterion actually plays a role in stabilizing the carbene from dimerization. All attempts to remove the metal ion from ADC have been unsuccessful such as using crown ether to trap Li or K cations.

\begin{center}
\begin{tikzpicture}
  \node [above] at (0,0) {1-94};
  \node [above] at (1,0) {1-95};
  \node [above] at (2,0) {1-96};
  \draw [->] (0,0) -- (1,0) node [midway, left] {1) POCl\textsubscript{3} \ Et\textsubscript{2}O
2) i-Pr\textsubscript{2}NH
25\%};
  \draw [->] (1,0) -- (2,0) node [midway, right] {LDA, THF
rt, 30 min
55\%};
\end{tikzpicture}
\end{center}

Scheme 1-21. Formamidinium formation and deprotonation

Bielawski et al. reported the first N-aryl acyclic diaminocarbene synthesis (Scheme 1-22).\textsuperscript{48} The formamidinium 1-98 was formed by mild basic dialkylation of the corresponding formamidine 1-97 and the carbene 1-99 was obtained by deprotonation with sodium hydride. Further metal complexation was possible with rhodium or ruthenium (olefin metathesis catalyst).\textsuperscript{49}
Scheme 1-22. N-aryl acyclic carbene synthesis

Bertrand and co-workers described a methodology using Hg(SiMe₃)₂ as a silylating agent to form free acyclic diaminocarbenes 1-12 from chloroamidinium precursors 1-100 (Scheme 1-23). The proposed mechanism involves first a σ-bond metathesis with generation of a mercury derivative 1-101 and liberation of TMSCl. The chloride ion can then induce a fast elimination of a second equivalent of TMSCl followed by decomplexation of the metal to give free carbene 1-12.

Scheme 1-23. Synthesis of metal free ADC and proposed mechanism

Alternative routes were developed to improve the free carbene synthesis as well as the complex formation. Slaughter reported bidentate Chugaev-type ADC-metal complexes which
were synthesized by nucleophilic addition of either hydrazines **1-103** (a) or amine **1-107** (b) to metal-bound isocyanide **1-106** (Scheme 1-24).

![Scheme 1-24. Synthesis of Chugaev-type ADC-Pd complexes with hydrazine or amine](image)

Fürstner et al. reported the synthesis of monodentate ADC Pd complex **1-111** through oxidative addition of chloroamidinium precursor **1-110** which was easily synthesized from urea **1-109** (Scheme 1-25). Five and six member rings as well as dimethyl substituted ADCs were synthesized through this route. Nickel complexes could also insert into the C-Cl bond. The main drawback of this method is the incorporation of phosphine ligand into the ADC metal complex limiting its applicability.

![Scheme 1-25. Pd complex formation from oxidative addition of chloroamidinium precursor](image)
Recently Hong et al. reported a general methodology of chloroamidinium activation by lithium-halogen exchange (Scheme 1-26). Using this new methodology, a Pd complex without phosphine ligand **1-116** was synthesized as well as Rh and Ir complexes **1-114** and **1-115**.

![Scheme 1-26. Metal complex formation through lithium-halogen exchange from chloroamidinium precursors](image)

### 1.4 Copper-Catalyzed Applications

#### 1.4.1 Copper-Catalyzed Allylic Alkylation

Typical palladium catalyzed allylic alkylation\(^5^4\) goes through a metal-allyl intermediate which is usually attacked at the least hindered position. Generally soft nucleophiles are used such as malonate, amine, alcohol and thiol. On the other hand, copper-catalyzed allylic alkylation\(^5^5\) proceed with high S\(_{N2'}\)-selectivity and allow the use of hard nucleophiles such as Grignard reagents,\(^5^6,5^7\) dialkyl zinc\(^5^8\) or aluminum reagent creating new tertiary or quaternary all carbon stereogenic centers from simple linear allylic substrates (Scheme 1-27). The allylic alkylation can lead to two types of product: the chiral \(\gamma\) product **1-118** (branched compound) and/or the achiral \(\alpha\) product **1-119** (linear compound). Due to extensive research in this area, only Grignard reagent as nucleophiles will be covered.
Scheme 1-27. General picture of the copper-catalyzed allylic alkylation

In 1995, Bäckvall reported the first enantioselective copper-catalyzed allylic alkylation.59 A thiolate ligand 1-122 with pendant amino group was used (Scheme 1-28). Excellent regioselectivity and low ee were observed with ester leaving group in 1-120. In the transition state proposed by the author, the second coordination site of the ligand binds to the leaving group through magnesium ion.

Scheme 1-28. First example of enantioselective copper-catalyzed allylic alkylation by Grignard reagents

After an extensive screening of phosphorus ligand, Alexakis et al. obtained good enantioselectivity using a TADDOL phosphoramidite ligand 1-125 (Scheme 1-29).60 A chloride leaving group in 1-123 was key to the success of this reaction, in the case of an acetate leaving group such as 1-120 only racemic compound was produced. Moreover slow addition of the Grignard reagent was crucial for the chirality.
Scheme 1-29. First generation of phosphoramidite ligand applied in the allylic alkylation

In a second generation system, CuCN was exchanged with CuTC which increased the ee by 10% (Scheme 1-30, a). The reaction was expanded to aliphatic substrates with the help of a second generation phosphoramidite ligand 1-128 which possessed a chiral binaphthol unit (Scheme 1-30, b).\(^{56g}\)

Scheme 1-30. New condition with CuTC and second generation of phosphoramidite ligand applied for the allylic alkylation

For the third generation of phosphoramidite ligand 1-132, the binaphthol unit chirality and the ortho OMe were found to increase drastically the ligand activity and selectivity (Scheme
If the OMe substituents were not present the enantioselectivity dropped to 55% ee with a ratio of 79:21 between branched and linear products. On the other hand, if the atropoisomerism is switched to (S), only 46% ee was obtained with a regioselectivity of 73:27. It was believed that the OMe substituents act as pendant groups which would make this ligand bidentate. As an application of the use of OMe substituents, 1-129 was converted to chiral cyclopentene 1-131 by ring closing metathesis in a one pot process.

Scheme 1-31. Third generation of phosphoramidite ligand applied in the allylic alkylation

Feringa and coworkers studied also the allylic alkylation and described the use of commercially available Taniaphos ligand 1-134 in this reaction. Interestingly, a chloride leaving group gave only linear product but aliphatic substrates with a bromide leaving group gave 92-94% ee of S_N2' products. In order to synthesize 1,2-dialkyl motifs, the author developed a one pot process combining allylic alkylation and cross metathesis with methyl acrylate. The subsequent product 1-135 can be subjected to copper-catalyzed enantioselective 1,4 addition of Grignard reagents described in a previous report. Using the two enantiomers of this phosphine ligand, syn and anti products could be obtained in excellent dr (Scheme 1-32).

Following this report, Feringa et al. extended the scope of this reaction to chiral allylic esters 1-139. The temperature of the reaction was found to be a key element. If the reaction was run at -85 °C, the major product was linear. Careful temperature optimization gave only the
branched product \textbf{1-140} (Scheme 1-33). This product gave chiral furanone \textbf{1-141} by ring closing metathesis.

Scheme 1-32. Synthesis of \textit{syn} and \textit{anti} 1,2-dialkyl motifs

Scheme 1-33. Synthesis of chiral furanone.

Toward the goal of making chiral building blocks, Feringa and coworkers expanded this reaction to nitrogen substituted substrates with Boc and tosylate as protecting groups.\textsuperscript{62} Using typical condition, the chiral protected amine \textbf{1-143} was obtained in 96\% yield and 95\% ee (Scheme 1-34). Slow addition of the substrate (2.5 mL/60 min, 3M) was crucial to obtain high ee.
Scheme 1-34. Allylic alkylation with allylic bromide containing nitrogen functional group

This chiral protected amine was converted to several building blocks to show the applicability of this reaction (Scheme 1-35).

Scheme 1-35. Synthesis of bifunctional chiral building blocks from chiral protected β-amine

β-Amino acid 1-146 was obtained in one step through Ru-catalyzed oxidation of the terminal olefin 1-143 with NaIO₄. The tosylate protecting group could be selectively removed to give 1-145 by treatment with magnesium under sonication. Catalytic Wacker oxidation afforded the β-amino ketone 1-144 in 82% yield. A combined ozonolysis/reduction protocol
transformed the olefin moiety into either 1,3-aminoalcohol 1-148 with both protecting groups on the nitrogen atom or a tosylated amine 1-149 with Boc protected alcohol, depending on the workup procedure. Direct quenching of the reaction mixture with 1 M aqueous HCl gave exclusively compound 1-148. In contrast, prior concentration of the reaction mixture at 60 °C (e.g., by removal of solvent in vacuo) led to a 1,5-migration of the Boc-group to the newly formed alcohol, thus yielding compound 1-149.

Hall and co-workers reported boron substituted substrates 1-150 which could be subjected to the allylic alkylation. Using phosphoramidite ligand 1-153, chiral allylic boronate esters 1-151 could be readily converted to functionalized homoallylic alcohols 1-152 (Scheme 1-36).

Scheme 1-36. Enantioselective preparation of α-substituted allylboronates

Okamoto et al. first reported the use of monodentate chiral NHC ligands in this reaction (Scheme 1-37). Acetate and 2-pyridyl ether 1-154 were found to give better results as leaving groups than chloride leaving group in 1-123 (different observation with phosphoramidite ligands). Using the bisoxazoline based carbene ligand developed by Glorius, copper complex 1-156 was synthesized and tested in this reaction but only moderate ee was obtained (50%).
157 gave better results (70%). A proposed transition state shows magnesium halide as counterion of the cuprate intermediate binding to the leaving group. Then the cuprate is brought close to the double bond by some ionic interaction (Scheme 1-37).

Scheme 1-37. Cu-catalyzed allylic alkylation using monodentate NHC ligands and proposed transition state

In another report, Hoveyda and co-workers reported a copper free enantioselective allylic alkylation57b where carbene ligand was proposed to act as a Lewis base to activate Grignard reagent (Scheme 1-38). By varying the NHC structure, 1-160 was found to be the most efficient reagent in this reaction giving excellent enantioselectivities for various secondary alkyl Grignard reagents. All carbon quaternary centers could be obtained using this metal free reaction condition. The bidentate ligand design was found to be crucial for good regioselectivity in the allylic alkylation. If the hydroxyl group of the ligand 1-160 was replaced by a proton or protected with a methyl, only 2% of product formation was observed.
Scheme 1-38. Cu-free enantioselective allylic alkylation on γ-chloro-α,β-unsaturated esters

One of the last challenges remaining was the use of aryl Grignard reagent as nucleophile. When using this reagent, linear product was usually obtained as the only product. The first example was reported by Alexakis et al. in 2001.\textsuperscript{52} When CuCN and TADDOL derived ligands were used, 2-MeOC₆H₄MgBr was successfully added in good regioselectivity and modest 21\% ee. Kobayashi reported the use of a picolinoxy leaving group \textbf{1-161} to obtain high regioselectivity in allylic alkylation with aryl Grignard reagents (Scheme 1-39).\textsuperscript{67} Even though the reaction was stoichiometric in copper, excellent transfer of chirality was observed with a chiral leaving group. Both Grignard reagent and copper source needed to match halide source to generate \textit{in situ} MgBr₂. This Lewis acid could then activate the leaving group to facilitate its displacement by the phenyl cuprate.

Scheme 1-39. Anti selectivity with Grignard reagent

A catalytic version of this reaction was reported by Tomioka et al. using an amidophosphane ligand \textbf{1-165} (Scheme 1-40).\textsuperscript{68a} For symmetrical substrate \textbf{1-163}, only S\textsubscript{N}2'
products were obtained whereas other unsymmetrical substrates ranged from 4:1 to 3:1 mixtures of branched to linear products.

Scheme 1-40. Allylic alkylation with phenyl Grignard reagent using phosphine ligand

Tomioka and co-workers explored more ligand structures to generalize this reaction (Scheme 1-41). Using chiral NHC 1-181 developed by Grubbs, they replaced the phenyl substituents at the front by bulkier and more extended diarylmethyl.\(^{68b}\)

Scheme 1-41. Allylic alkylation with phenyl Grignard reagent using monodentate NHC ligand
This new monodentate NHC ligand 1-168 was found to be very successful in the aryl Grignard addition to allylic substrates. High regioselectivity and enantioselectivity were produced for various substrates.

### 1.4.2 Copper-Catalyzed β-Borylation of α,β-Unsaturated Carbonyl Compounds

Cu-catalyzed borylation incorporates a boron-ester in the β position of unsaturated carbonyls\(^{69}\) which can be subsequently converted into useful functional groups.\(^{70}\) Hosomi (a) and Miyaura (b) first reported independently this transformation (Scheme 1-42). Hosomi and co-workers found catalytic conditions and showed that both phosphine ligand and DMF were needed to achieve high yields.\(^{69q}\) The reaction conditions were also successful on cyclic ketones. Miyaura et al. reported reactions with a wider range of 1-171 from ketones, esters to nitriles.\(^{69o,p}\) Miyaura introduced the base potassium acetate to activate the copper catalyst.

\[
\begin{align*}
\text{(a)} & \quad \text{1-169} + \begin{array}{c}
\begin{array}{c}
\text{B-B}
\end{array}
\end{array} \\
& \quad \xrightarrow{\text{CuOTf (10 mol%), Bu$_3$P (11 mol%)}} \text{DMF, rt, 10 h} \quad 96\% \text{ yield} \\
& \quad \xrightarrow{} \begin{array}{c}
\text{1-170}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{(b)} & \quad \text{R-EWG} + \begin{array}{c}
\text{B-B}
\end{array} \\
& \quad \xrightarrow{\text{CuCl, AcOK}} \text{DMF, rt, 16 h} \quad 90\% \text{ yield} \\
& \quad \xrightarrow{} \begin{array}{c}
\text{rac-1-172}
\end{array}
\end{align*}
\]

EWG: ketones, esters and nitriles
R: CH$_3$, H
yield: 50-90% yield

Scheme 1-42. First reported examples for β-borylation of unsaturated ketones

Yun and co-workers disclosed a general methodology using chiral (R)-(S)-josiphos ligand for the first asymmetric version of this reaction (Scheme 1-43).\(^{69b-g}\) A protic reagent such as
methanol was discovered as a key component for increased yields. The reaction gave good yields and ee from a wide range of acyclic and cyclic substrates.

Scheme 1-43. First asymmetric version using chiral josiphos phosphine ligand

Recently, Shibasaki et al. reported the generation of tertiary organoboronic esters 1-175 in cyclic ketones (Scheme 1-44). The use of MeOH with DMF (dimethylformamide) or DMSO (dimethylsulfoxide) solvent drastically decreased the yields to 10%. Here the conditions are more closely based on Miyaura’s (Scheme 1-42(b)). The generation in situ of LiPF₆ seems to be crucial for rate acceleration as well as increased enantioselectivity.

Scheme 1-44. Generation of quaternary centers using chiral phosphine ligands

Using chiral carbene ligands, Fernández and co-workers disclosed the synthesis of chiral β alcohol in 73% ee after oxidation of boron reagent using acyclic α,β-unsaturated esters as
substrates (Scheme 1-45).\textsuperscript{69i-1} The reaction conditions were the same as reported by Yun.\textsuperscript{69c} Chiral NHC 1-180 gave poor enantioselectivity while 1-181 (developed by Grubbs) increased ee by two fold and C\textsubscript{1}-symmetric NHC ligand 1-182 gave better results than its C\textsubscript{2}-symmetric variant 1-181. By varying the ester group 1-183, enantioselectivity could be increased up to 73%.

Scheme 1-45. First asymmetric version using chiral NHC ligands

Hoveyda and co-workers reported a copper free reaction using NHC 1-186 as a Lewis base (Scheme 1-46).\textsuperscript{71} The carbene ligand served as an activator for the diboron reagent. Good yields were obtained for various cyclic and acyclic ketones. MeOH was discovered to be unnecessary for this reaction when using NHC ligand.

Scheme 1-46. Copper and MeOH free β-borylation of unsaturated ketones

Several mechanistic studies\textsuperscript{72} were realized and after compilation of most of them, here is a proposed mechanism of this transformation (Figure 1-6). In a first stage, ligand, base and copper
are premixed to yield ligated copper alkoxide 1-187 which undergoes σ-bond metathesis with pinacolate diboron reagent. The newly formed borylated copper complex 1-188 inserts into the α,β unsaturated alkene to give a 3,4 addition product 1-189. Then the C-copper bound species 1-189 isomerizes to the O-copper bound enolate 1-190 which is more likely to undergo the next σ-bond metathesis due to the oxygen lone pairs. From this species, σ-bond metathesis occurs either with methanol or diboron reagent when present. In the first case, copper alkoxide 1-187 is regenerated and a borylated product 1-172 is freed. On the other hand, borylated copper complex 1-188 is formed and a borylated boron enolate product 1-191 is synthesized which can be further derivatized if needed.

Figure 1-6. Proposed mechanism for β-borylation of unsaturated ketones
CHAPTER 2
C₂-SYMMETRIC BIISOQUINOLINE N-HETEROCYCLIC CARBENE LIGAND

2.1 Introduction: Ligand Design for C₂-Symmetric Ligands

Structural diversity is far from being fully explored or available with N-heterocyclic carbene ligands. Key topological features of NHC ligands that are desirable for asymmetric catalysis still need to be identified. Thus, exploring new types of chiral carbene ligands, especially focusing on creating an effective chiral space around the metal center, would be of great use.

Limited successes so far with the current chiral carbene ligands might imply that the chiral environment created by chiral directing groups either on the nitrogens or the backbone is too far from the metal center to discriminate effectively between the two enantiotopic faces. To induce more selectivity, chosen chiral carbene ligands have been optimized to furnish new ligands (Figure 2-2). The chiral design developed by Grubbs accounts for over 90% ee in asymmetric ring closing metathesis reactions (Figure 2-1). However a substrate dependence on enantioselectivity in these reactions might suggest that the chiral space created by the ligand is remote from the metal center and therefore less discriminating for less sterically demanding substrates. In addition, the X-ray crystal structure shows that the aryl groups on the nitrogen atoms are pointing orthogonal to the plane of NHC-Ru. Therefore, it would be interesting to extend and reposition the stereodifferentiating groups more toward the metal center. We envisioned that this possibility could be explored through optimized structure (Figure 2-1) where the chiral groups are installed within a ring structure which directs the components in a defined position. From this design, we are hoping for an increase in selectivity.
Figure 2-1. C₂-symmetric ligand design

Additionally, the X atom in the ligand structure 2-2 could be varied and different properties could be obtained. In a first part, where X = O, we decided to optimize Glorius’ ligand²³ by changing the chiral groups (Figure 2-2) to amino indanol 2-6 which would give more bulk. Later, we wanted to add R groups on the phenyl ring to extend further the chiral pocket toward the metal. The ligand 2-6 will be called the bisoxazoline derived NHC ligand. The ligand 2-3, which was first developed by Glorius, gave excellent results in the Suzuki reaction between aryl chlorides and substituted boronic acids.²² In a second part, where X = N, the known bisimidazoline ligand⁷³ (Figure 2-2) could be converted by cyclization into a carbene ligand 2-7. The latter would induce more donating character within the carbene structure thanks to the donating effects from the nitrogen atoms. The known bisimine ligand 2-4 has been used for allylic alkylation and showed modest activity.⁷³ In a third part, where X = C, we decided to use the frame of the biisoquinoline carbene ligand⁷⁴ (Figure 2-2) and incorporate stereogenic centers α to the nitrogen atoms and make an unsaturated carbene ligand 2-8.
Figure 2-2. Tricyclic ligand design with variation of X

### 2.2 Bisoxazoline Derived NHC Ligand

Starting from *trans*-aminoindanol 2-12, the bisamide 2-11 was made followed by a cyclization leading to the bisoxazoline 2-10. The imidazolium formation was carried out using known procedures (Scheme 2-1). Two different ways were found to make the bisoxazoline compound (Scheme 2-2). The *trans*-aminoindanol 2-12 was refluxed in toluene with diethyl oxalate for 12 hours to lead to the bisamide 2-11 in 95% yield. Then it was reacted with mesylate chloride in THF to give the O-mesylated product 2-13 in 90% yield. Biscyclization in an excess of KOH in reflux methanol for 1 hour led to the bisoxazoline 2-10 in quantitative yield. Moreover, another shorter path was discovered using Burgess reagent,\(^{75}\) but the overall yield was diminished.
Scheme 2. Synthesis from *trans*-aminoindanol

Then the focus was on the last step which is the imidazolium formation. Usually, the common reagent is chloromethyl ethyl ether, but in this particular substrate, the chloride anion liberated in the course of the reaction can attack the oxazoline ring 2-15 and regenerate an amide 2-17 (Scheme 2-3).
Scheme 2-3. Decomposition pathway using chloromethyl ethyl ether

For this reason, AgOTf was used to trap the chloride anion as an AgCl salt. As a trial, the known bisoxazoline 2-14 was reacted with chloromethyl pivalate and AgOTf to yield the desired imidazolium product 2-18 in 60% yield (Scheme 2-4).

Scheme 2-4. Bisoxazoline-imidazolium synthesis

Unfortunately, it could not be reproduced for 2-10. The AgOTf salt seemed to be a very sensitive reagent so a fresh bottle was used and stored in the glove box. This time the reaction proceeded in 35% yield. After this success, reaction of the Pd-NHC metal complex with imidazolium 2-19 was attempted. Known conditions reported by Glorius21,22 using KOtBu followed by addition of Pd(II) was attempted but only starting materials were isolated. A transmetallation route was also attempted using Ag₂O but it also failed. Later it was found out that the imidazolium 2-19 seemed to decompose over time and its synthesis was not reliable.
With all those issues, this project was stopped. We then decided to synthesize the bisimidazoline derived NHC ligand variation 2-20. This ligand has nitrogen atoms instead of oxygen atoms which should influence the electronic properties.

### 2.3 Bisimidazoline Derived NHC Ligand

Starting from commercially available amino acids 2-22 (Scheme 2-5), the corresponding amino alcohol was obtained by reduction and converted to the bisamide 2-21. Then it was cyclized in two consecutive steps to make the imidazoline moiety 2-4 which gave the corresponding imidazolium by typical ring closing conditions.

Scheme 2-5. Bisimidazolone retrosynthesis

Valine 2-23 was reduced with LAH to valinol 2-24 in a modest yield, and the amine 2-24 was coupled with diethyl oxalate to form the bisamide 2-25. Thionyl chloride was used to convert the alcohols to chlorides. Using PCl₅, the amide 2-26 was converted to the imidoyl chloride 2-27. The toluene was evaporated under vacuum followed by the addition of benzyl amine in acetonitrile to give 2-28 or aniline to give 2-29 (Scheme 2-6). The yields were low but the mechanism involved four nucleophilic substitutions and provided two new rings. So a 40% yield represented actually a 65% yield for each ring formation.
Unfortunately, the final step (Scheme 2-7) was not promising; both known conditions gave a mixture of products. Moreover, the crude NMR did not show the characteristic imidazolium peak between 8 and 10 ppm. **2-28** was the first bisimine synthesized and we supposed that the lone pairs of the nitrogen atoms might be in conflict with the imidazolium synthesis. To solve this issue, **2-29** was synthesized hoping that the phenyl substituents would delocalize these lone pairs away from the imine moiety.

So far, electronegative atoms seemed to perturb either the imidazolium synthesis or the complex formation. This led us to think the donating effect coming from the lone pairs of the oxygen or nitrogen atoms is probably weaker than their electronegativity effect. So the third part involving **X = Csp^2** (Figure 2-2) atoms instead of **X = O** or **X = N** atoms should inhibit electronic effects and be closer in reactivity to a typical NHC.
While our group was working on the BIQ (biisoquinoline) ligand 2-8, Herrmann and coworkers reported the synthesis of the saturated version, 2-32, of our target structure. From the saturated BIQ imidazolium, the unsaturated NHC-metal complexes were unexpectedly formed in moderate yields. This oxidation happened during the preparation of NHC-Rh or Ir complexes 2-34 and 2-35 via transmetallation with Ag₂O, when bromide was the counterion for the saturated imidazolium salt 1-49 (Scheme 2-8). Their synthesis was based on the homocoupling of the isoquinoline moiety (Scheme 1-10). Only phenyl substituted BIQ imidazolium was reported, probably the diastereoselectivity ratio of this coupling reaction might decrease for other chiral substituents. In contrast, our retrosynthesis scheme would allow a wide variety of chiral substituents (Scheme 2-9).

A chiral amine 2-39 was synthesized from commercially available amino acids 2-22 followed by typical bisamide synthesis (Scheme 2-9). It was cyclized using Bischler-Napieralski cyclization. Several R groups were tried such as isopropyl, isobutyl, tert-butyl, cyclohexyl, methyl cyclohexyl, fused cyclohexyl and phenyl.
Scheme 2.8. Bisdihydroisoquinoline-based carbene ligands

Scheme 2.9. Biisoquinoline retrosynthesis

2.4.1 Synthesis of Isopropyl, Isobutyl, Tert-Butyl and Cyclohexyl Alanine Substituted Amines

The commercially available amino acid 2-23 was reduced by LAH to give the corresponding amino alcohol 2-24 (Scheme 2-10). Then in a one pot process, the alcohol was removed. First the amine 2-24 was protected with a tosylate group then the alcohol was converted into a leaving group with mesylate chloride followed by the substitution of the alcohol by the amine to form the aziridine 2-46. Addition of a phenyl cuprate, made in situ, onto the
aziridine moiety led mainly to the compound **2-50**. Deprotection of the tosylated amine gave the desired chiral amine **2-54**. All these reactions could be run on a 10g-scale with no significant drop in yield for various amino acids. Other conditions were tried for the deprotection of the tosylate group such as Mg (sonication) in MeOH and Na with naphthalene. The Mg conditions worked well only in a small scale and the Na conditions were very sensitive to air and moisture. The reported procedure using Li (14 equiv.) and a catalytic amount of naphthalene was robust and did not need extra precaution.

![Scheme 2-10. Chiral amine synthesis from amino acids](image)

### 2.4.2 Cyclohexyl Substituted Amine Synthesis

The cyclohexyl substituted amino acid being more expensive, the amine **2-62** was synthesized by another route. (S)-Phenylglycine **2-58** was reduced to the corresponding alcohol **2-59**. A 60:40 mixture of oxazolidines **2-60** were then formed by the addition of cyclohexyl aldehyde (Scheme 2-11). Then addition of benzyl magnesium chloride gave only the diastereomer **2-61**. Mild hydrogenation was not strong enough to cleave the phenethyl alcohol **2-61**; therefore an autoclave was used to increase the hydrogen pressure up to 800 psi (54 atm) and

<table>
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<th>Compound</th>
<th>Yield</th>
<th>Conditions</th>
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<tr>
<td>i-Pr</td>
<td><strong>2-23</strong></td>
<td>60%</td>
<td>LAH, THF, reflux, 12 h</td>
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<tr>
<td>i-Bu</td>
<td><strong>2-40</strong></td>
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<td>i-Pr</td>
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<td>i-Pr</td>
<td><strong>2-50</strong></td>
<td>95%</td>
<td>Li, Naphthalene, THF, -78 °C to rt, 12 h</td>
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<td>CH₂Cy</td>
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the temperature to 75 °C to give the pure chiral amine 2-62. Here, it is interesting to note that the chirality in the compound 2-62 is the opposite absolute configuration compared to the compounds 2-54 to 2-57. The other enantiomer can be synthesized by using (R)-phenylglycine.

![Scheme 2-11. Cyclohexyl amine synthesis](image)

2.4.3 **Fused Cyclohexyl Substituted Amine Synthesis**

To increase the steric bulk around the ligand, a cyclohexyl ring fused to the BIQ core was proposed. Using Chem3D, the *trans* configuration 2-63 was rejected while the *cis* 2-64 was preferred because the cyclohexyl ring seemed to sterically intrude more in this conformation (Figure 2-3).

**Rac-2-65** was first synthesized to make sure this pathway could work (Scheme 2-12). Phenyl cuprate, made *in situ*, was added to cyclohexene oxide 2-66 which gave the *trans* alcohol rac-2-67. Then this alcohol was replaced by an amine with an inversion of stereocenter using Gabriel synthesis.\(^{76}\) Mitsonobu reaction\(^{77}\) was used to replace the secondary alcohol rac-2-67 with phthalimide in a S\(_{N}\)2 pathway, and then rac-2-68 was reduced to the *cis* amine rac-2-65 using ethylene diamine.
Figure 2-3. Fused cyclohexyl BIQ (trans 2-63 and cis 2-64 configuration) calculated with Chem3D

Scheme 2-12. Racemic synthesis of the fused Cy amine rac-2-65

To resolve this racemic amine, the two diastereomers resulting of the amide coupling with mandelic acid were synthesized (Scheme 2-13). Both compounds 2-69 and 2-70 could be
separated by column chromatography unfortunately the cleavage of the amide moiety to recover
the chiral amine was too harsh and the compound could not be isolated. Resolving at the alcohol
stage would be more economical thus we decided to study rac-2-67.

Scheme 2-13. Amide synthesis for chiral resolution

The two esters 2-72 and 2-73 were first synthesized (Scheme 2-14), but unfortunately they
were not separable by chromatography.

Scheme 2-14. Ester synthesis for chiral resolution

Then using kinetic resolution,78 the pure chiral alcohol (1R,2S)-2-67 could be obtained by
replacing the alcohol moiety by a chloride 2-74 using Mitsonobu conditions (Scheme 2-15). This
reaction was very efficient but it used a large amount of chiral BINAP (2,2'-
bis(diphenylphosphino)-1,1'-binaphthyl) which made this process expensive for a large scale
synthesis.

Scheme 2-15. Non enzymatic kinetic resolution of secondary alcohol
Following this kinetic resolution example, other similar methodologies were researched. Many studies reported enzymatic kinetic resolution for secondary alcohol using different lipases such as CALB, PS30 and AK. Because CAL-B (Candida antarctica lipase B) also known as Novozym 435 was widely used, this enzyme was chosen and different conditions were screened (Table 2-1).

Table 2-1. Optimization of the enzymatic kinetic resolution of rac-2-67 using lipase CALB

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent and conditions</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBuOMe at 40 °C</td>
<td>80% ee</td>
<td>93% ee</td>
<td>96% ee</td>
</tr>
<tr>
<td>2</td>
<td>nPrOH at 40 °C</td>
<td>1% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DCM at 40 °C</td>
<td>1% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>THF at 40 °C</td>
<td>20% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Hexane at rt</td>
<td>22% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>tBuOMe at rt after 24 h add 0.5 eq Et3N and heat at 40 °C</td>
<td>34% ee</td>
<td>85% ee</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1,2 dimethoxyethane after 24 h add 0.5 eq Et3N and heat at 40 °C</td>
<td>40% ee</td>
<td>72% ee</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1,4 dioxane</td>
<td>13% ee</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After careful screening, tBuOMe (MTBE) was chosen as the solvent and 40 °C for the temperature and this reaction could be done on a large scale. The enzyme coated on acrylic resin could be reused by simple filtration and there was no need for careful buffering or temperature control. No yields were reported for this table because the reactions were realized on a small scale and only the enantioselectivity of the crude reaction mixture was monitored. Then it was
tried on a larger scale and the same enzyme was filtered and reused four times with only 1% ee loss (Scheme 2-16).

Scheme 2-16. Scale up of the kinetic resolution of secondary alcohol with reused enzyme

Following the previous plan (Scheme 2-12), the single enantiomer (1S,2R)-2-67 was converted to 2-65.

2.4.4 Phenyl Substituted Amine Synthesis

The previously reported synthesis of amines 2-39 (Scheme 2-10) could not be used because the regioselectivity of the phenyl cuprate addition would be opposite (Scheme 2-17). With alkyl substituents, the addition takes place on the least hindered carbon but with aryl substituents the benzylic position is more reactive and electronic effects are more important than steric effects in this case.

Scheme 2-17. Reverse regioselectivity with phenyl substituted aziridine

Different strategies were envisioned (Scheme 2-18). We decided to take advantage of the existing chirality in 2-78 and find a way to remove the alcohol. First, the amine 2-78 was protected with a tosylate group then Et₃SiH associated with a Lewis acid was used to reduce the
benzylic alcohol 2-79. Unfortunately, only the starting material was isolated. Then, the aziridine 2-80 was made using Mitsonobu conditions and allowed for the formation of a more reactive C<sub>2</sub>-symmetric benzylic position. Polymethylhydrosiloxane and Pd/C were used to ring open the aziridine. The desired tosylated amine 2-82 was synthesized in 70% yield. Even though this reaction worked well, four steps total are needed. A shorter path would be a good upgrade in order to make more material.

Scheme 2-18. Synthesis of (S)-1,2-diphenylethanamine

As seen previously, a ring structure was more reactive toward hydrogenation. Using diethyl carbonate, the oxazolidinone 2-81 was formed in a quantitative yield. Using an autoclave for the hydrogenation, the desired amine 1-46 was produced in 77% yield. This pathway was two steps shorter and gave an overall yield of 76%.
All the desired chiral phenethylamines 2-39 have been synthesized, now they can be used in the synthesis of the $C_2$-symmetric BIQ based carbene ligands 2-36. In chapter 4, the same chiral phenethylamines could also be used in the synthesis of the $C_1$-symmetric MIQ (monoisoquinoline) based carbene ligand 4-2.

### 2.4.5 Biisoquinoline Based Carbene Synthesis from Chiral Amine

Bisamides 2-38 could serve as precursors for a double Bischler-Napieralski cyclization (Scheme 2-9). Following previous work (Scheme 2-6), we used diethyl oxalate as the coupling agent (Table 2-2).

Table 2-2. Optimization of bisamide coupling using diethyl oxalate

![Scheme 2-9](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>solvent</th>
<th>$T ; ^\circ \text{C}$</th>
<th>time</th>
<th>bisamide yield</th>
<th>monoamide yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>toluene</td>
<td>125</td>
<td>36 h</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cy</td>
<td>1,4 dioxane</td>
<td>130</td>
<td>5 d</td>
<td>18%</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>$i$-Pr</td>
<td>1,4 dioxane</td>
<td>130</td>
<td>5 d</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cy</td>
<td>1,4 dioxane + 4 A MS</td>
<td>130</td>
<td>1 d</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$i$-Pr</td>
<td>1,4 dioxane + 4 A MS</td>
<td>130</td>
<td>1 d</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$i$-Pr</td>
<td>neat</td>
<td>120</td>
<td>12 h</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cy</td>
<td>neat</td>
<td>120</td>
<td>12 h</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

Typical conditions gave only the monoamide product 2-83 (entry 1). A more polar solvent was used and the temperature was increased (entry 2) but only small amount of bisamide was formed and the monoamide stayed predominant. Molecular sieves were also added to the
reaction mixture to trap the released ethanol but the yields stayed low (entries 4 and 5). When neat conditions were used (entry 6), the yield was increased drastically for \(2-86\). Unfortunately, \(2-87\) with more bulky substituents still gave low yield using neat conditions (entry 7). For \(2-86\), the neat condition was chosen but a better procedure was still needed for more bulky substituent such as Cy. If the reactivity of the nucleophile is decreased by steric effects, then a more reactive electrophile could be used such as oxalyl chloride (Scheme 2-19). This new reagent was more efficient than diethyl oxalate but it required a quick column chromatography instead of a simple filtration.

Scheme 2-19. Bisamide synthesis using oxalyl chloride

With the bisamides in hand, the double Bischler-Napieralski cyclization could be attempted (Table 2-3). This reaction consists of a double intramolecular electrophilic aromatic substitution.

Scheme 2-20. Double Bischler-Napieralski cyclization
In a first stage, the amide moiety is converted to an imidoyl chloride 2-92 which subsequently is transformed into a nitrilium ion 2-93. Then the aromatic ring will attack this carbocation (Scheme 2-20).

Different dehydrating agents have been used (most common are POCl₃, P₂O₅ and Tf₂O) to convert the amide into the nitrilium ion. Usually this reaction works best with electron donating group on the aromatic ring. Few reports exist on the biscyclization and none describes a successful biscyclization with absence of substituents on the phenyl rings. The main issue of the double cyclization is the vicinal proximity of the two carbocations. Even if the reaction involves a step wise process, each nitrilium ion will be destabilized by either an amide group or an imine. Following reported conditions for the cyclization of mono amido-ester,⁸⁰ a non chiral bisamide 2-94 was reacted with POCl₃ and ZnCl₂ to give no product (entry 1). The use of a Lewis acid seems necessary to activate the nitrilium ion for an attack from the benzene ring. ZnCl₂ was replaced by a stronger Lewis acid Zn(OTf)₂ which gave product in 38% yield (entry 2). Then those conditions were tried out on different substituted chiral bisamide (entries 3-5). The bisamide 2-87 gave no reaction (entry 5), which was probably due to increased steric effects. Previously, a bis(imidoyl) chloride (Scheme 2-6) was synthesized using PCl₅ as the dehydrating agent, to make the precursor for bisimidazoline based carbene ligand. The latter reagent is stronger than POCl₃ and was used in combination with Zn(OTf)₂ in the Bischler-Napieralski cyclization to yield the bisimine 2-98 in good yields (entries 8, 9, 11 and 12). The fused Cy substituted bisamide gave a compound similar to the product by ¹H NMR but the ¹³C NMR did not show the characteristic imine peak around 160 ppm seeing in similar compounds (Figure 2-5).
Table 2-3. Optimization of the double Bischler-Napieralski cyclization

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>dehydrating agent (eq)</th>
<th>Lewis acid (eq)</th>
<th>T °C</th>
<th>bisimine yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>POCl₃ (14)</td>
<td>ZnCl₂ (7)</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>POCl₃ (14)</td>
<td>Zn(OTf)₂ (7)</td>
<td>110</td>
<td>38%</td>
</tr>
<tr>
<td>3</td>
<td>i-Bu</td>
<td>POCl₃ (14)</td>
<td>Zn(OTf)₂ (7)</td>
<td>110</td>
<td>54%</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>POCl₃ (14)</td>
<td>Zn(OTf)₂ (7)</td>
<td>110</td>
<td>41%</td>
</tr>
<tr>
<td>5</td>
<td>Cy</td>
<td>POCl₃ (14)</td>
<td>Zn(OTf)₂ (7)</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Cy</td>
<td>POCl₃ (14)</td>
<td>Zn(OTf)₂ (7)</td>
<td>85</td>
<td>12% monoimine</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>POCl₃ (14)</td>
<td>Zn(OTf)₂ (7)</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Cy</td>
<td>PCl₅ (6)</td>
<td>Zn(OTf)₂ (3)</td>
<td>85</td>
<td>61%</td>
</tr>
<tr>
<td>9</td>
<td>i-Pr</td>
<td>PCl₅ (6)</td>
<td>Zn(OTf)₂ (3)</td>
<td>85</td>
<td>83%</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>PCl₅ (6)</td>
<td>Zn(OTf)₂ (3)</td>
<td>85</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>CH₂Cy</td>
<td>PCl₅ (6)</td>
<td>Zn(OTf)₂ (3)</td>
<td>85</td>
<td>91%</td>
</tr>
<tr>
<td>12</td>
<td>i-Bu</td>
<td>PCl₅ (6)</td>
<td>Zn(OTf)₂ (3)</td>
<td>85</td>
<td>90%</td>
</tr>
<tr>
<td>13</td>
<td>Fused Cy</td>
<td>PCl₅ (6)</td>
<td>Zn(OTf)₂ (3)</td>
<td>85</td>
<td>NR</td>
</tr>
</tbody>
</table>

On the other hand, the bisamide 2-88 reacted with major consumption of the starting material to yield in the various conditions tried (Tf₂O/DMAP, POCl₃/Zn(OTf)₂) a non polar product. The latter could not be clearly identified but according to a reported paper, it could be stilbene 2-102 (Scheme 2-21). This fragmentation may be driven by the formation of cyanogen gas in the decomposition of 2-93.
Scheme 2-21. Fragmentation of phenyl substituted bisnitrilium

The standard reaction of the bisimine with chloromethyl ethyl ether produced the $C_2$-symmetric BIQ imidazolium salts (Scheme 2-22). There was no problem with the closing of the ring for this compound which enforced the hypothesis made about the electronics of this new ligand being similar to typical NHC. The tert-butyl substituted BIQ-imidazolium compound was synthesized by Dr Hwimin Seo.

Scheme 2-22. Imidazolium synthesis from chiral amine

2.4.6 Formation of Metal Complexes

Two main methods can be used to make NHC metal complexes. First, the imidazolium can be deprotonated with a base to make the aminocarbene and a metal is added to produce the metal
complex. Also a transmetallation route can be used where a carbene silver complex is synthesized from the imidazolium salt and this silver complex is exchanged with another metal. The latter was used in our project because this reaction was proved to be more efficient and cleaner than the deprotonation route.

A NHC palladium complex 2-103 was synthesized by Dr Hwimin Seo (Scheme 2-23) and its X-ray crystal structure was obtained to look at the orientation of the chiral groups (Figure 2-4).

![Scheme 2-23. Synthesis of Pd-BIQ-cinnamyl complex 2-103](image)

In this structure, the chiral groups seem to be located in the axial position of the ring structure which allows a wider coverage of the metal sphere. Also, the phenyl rings at the back are twisted like atropoisomers. If this ring twist equilibrates in solution, two diastereomers should be formed and two sets of peaks should be visible by $^1$H NMR. The imidazolium 2-104 only showed one set of peaks (see supporting information) which implied either only one diastereomer exists in solution or the ring flip was too quick for the NMR time scale.

Interestingly, the solid state of this structure showed the chiral groups pointing in the same direction of the phenyl rings. This BIQ-Pd complex was used in the synthesis of oxindoles by amide α-arylation\textsuperscript{19,20,24} but only racemic product was obtained.
Figure 2-4. X-ray structure of Pd-carbene complex 2-103

After making the palladium complex, the synthesis of copper carbene complexes was realized. Using the transmetallation route with Ag₂O, five copper complexes were synthesized in good yields (Scheme 2-24).

Scheme 2-24. Copper complexes from C₂-symmetric BIQ carbene ligands
2.4.7 Application: Copper-Catalyzed Asymmetric Allylic Alkylation

As a reminder, two types of products can be obtained from the allylic alkylation. The branched compound 1-118 which gives two enantiomers and the linear product 1-119 (Scheme 2-25).

![Scheme 2-25. General scheme for allylic alkylation catalyzed by copper complexes using Grignard reagents as nucleophiles.]

The initial optimization of the reaction conditions was mostly performed with 3 mol% of catalyst 2-109 on naphthyl substrates 2-114. The reaction protocol consisted of adding the Grignard reagent to 2-109 to generate the cuprate complex \( \text{in situ} \). Then the allylic substrate 2-114 was added dropwise over 10 minutes. For the different solvents array, the acetate leaving group was chosen and EtMgBr was used as a nucleophile (Table 2-4). THF gave inverse regioselectivity (entry 6) as reported previously.\(^{55c}\) DCM gave surprisingly a low \( \gamma:\alpha \) ratio (entry 4) compared to Alexakis’ results.\(^{60}\) Et\( _2 \)O gave the best results at 0 °C (entry 1). Decreasing further the temperature had a negative effect on the reaction yield (entries 2 and 3). MTBE gave good regioselectivity but the yield dropped to 61% (entry 5). After this quick survey, Et\( _2 \)O was chosen as the optimum solvent.

Different leaving groups were also used in the reaction conditions (Table 2-5). First, the chloride leaving group 2-117 was tried (entry 1) to compare it with the results obtained with phosphoramidite ligands.\(^{56}\) Surprisingly, the enantioselectivity was greatly decreased as well as the regioselectivity. Then the phosphonate leaving group 2-118 was used (entry 2) because it gives good results when bidentate carbene ligands are used for zinc reagent alkylations.\(^{58}\)
Then a pyridyl leaving group 2-120 was used (entry 4) to compare with the best results using another monodentate carbene ligand. This time the regioselectivity was good but the enantioselectivity was similar to phosphonate leaving groups. This new BIQ ligand 2-109 seems to be a good match for ester based leaving groups (entries 5-7) which was in contrast to the previous reported papers. Benzoyl 2-121 and pivaloyl 2-122 substrates are bulkier (entries 6 and 7) which increased the desired regioselectivity. Benzoyl is also a better leaving group than pivaloyl which seemed to decrease the enantioselectivity; similar trend was seen between acetate 2-114 and methyl carbonate 2-119.

Acetate and pivaloyl leaving groups were chosen as the best candidates for the ligand structure screening (Table 2-6). For pivaloyl leaving group, the cyclohexyl complex 2-111 (entry 5) gave the best yield (99%) and enantioselectivity (72% ee). Interestingly, any other substitutions such as tert-butyl 2-112, cyclohexyl alanine 2-113 and iso-butyl 2-109 gave similar results (entries 4, 6 and 7).
Table 2-5. Leaving group optimization for the asymmetric allylic alkylation

![Chemical structure of the reaction](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
<th>γ : α</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X = Cl</td>
<td>2-117</td>
<td>98</td>
<td>66:34</td>
</tr>
<tr>
<td>2</td>
<td>O[PO(OMe)]</td>
<td>2-118</td>
<td>98</td>
<td>53:47</td>
</tr>
<tr>
<td>3</td>
<td>O[POCMe]</td>
<td>2-119</td>
<td>98</td>
<td>50:50</td>
</tr>
<tr>
<td>4</td>
<td>O[POCPh]</td>
<td>2-120</td>
<td>80</td>
<td>74:26</td>
</tr>
<tr>
<td>5</td>
<td>O[POCCH₃]</td>
<td>2-114</td>
<td>98</td>
<td>77:23</td>
</tr>
<tr>
<td>6</td>
<td>O[POCPh]</td>
<td>2-121</td>
<td>99</td>
<td>84:16</td>
</tr>
<tr>
<td>7</td>
<td>O[POCt-Bu]</td>
<td>2-122</td>
<td>68</td>
<td>88:12</td>
</tr>
</tbody>
</table>

For acetate leaving group, 2-111 and 2-109 gave similar enantioselectivity (entries 1 and 3) but the regioselectivity was superior for bulkier cyclohexyl. Once again, the iso-propyl 2-110 gave similar results as the other substitutions (entry 2). Other copper catalysts were synthesized using CuBr and CuTC but the reaction results were indifferent to those changes. As a result from all those optimizations, 2-111 was chosen in combination with pivaloyl leaving group in Et₂O at 0 °C.

Other alkyl Grignard reagents can be used without significantly decreasing reaction yield, regio-, or enantioselectivity (Table 2-7). However, use of phenyl Grignard reagent afforded the S_N2 product exclusively (entry 4).
Table 2-6. Ligand structure optimization for the asymmetric allylic alkylation

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>yield (%)</th>
<th>γ : α</th>
<th>% ee (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X = -OOCCH₃</td>
<td>2-109</td>
<td>98</td>
<td>77:23</td>
<td>70 (S)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2-110</td>
<td>98</td>
<td>77:23</td>
<td>62 (S)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2-111</td>
<td>98</td>
<td>83:17</td>
<td>73 (R)</td>
</tr>
<tr>
<td>4</td>
<td>OCl-Bu</td>
<td>2-109</td>
<td>68</td>
<td>88:12</td>
<td>61 (S)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2-111</td>
<td>99</td>
<td>90:10</td>
<td>72 (R)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2-112</td>
<td>80</td>
<td>85:15</td>
<td>62 (S)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2-113</td>
<td>98</td>
<td>84:16</td>
<td>62 (S)</td>
</tr>
</tbody>
</table>

Table 2-7. Grignard reagent survey for the asymmetric allylic alkylation

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>RMgBr</th>
<th>yield (%)</th>
<th>γ:α</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtMgBr</td>
<td>2-115</td>
<td>99</td>
<td>88:12</td>
</tr>
<tr>
<td>2</td>
<td>nHexylMgBr</td>
<td>2-123</td>
<td>91</td>
<td>85:15</td>
</tr>
<tr>
<td>3</td>
<td>CyclopentylMgBr</td>
<td>2-124</td>
<td>91</td>
<td>84:16</td>
</tr>
<tr>
<td>4</td>
<td>PhenylMgBr</td>
<td>2-125</td>
<td>95</td>
<td>&lt;2:98</td>
</tr>
</tbody>
</table>
Then the substrate scope was explored (Table 2-8). The reaction was effective for the formation of a quaternary chiral center (entry 5). The aryl substrates also tolerate electron donating (entry 2) and electron withdrawing substituents (entry 3), as well as ortho-substituents (entry 4).

Table 2-8. Substrate scope

![Chemical Reaction Image]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>RMgBr</th>
<th>yield (%)</th>
<th>γ:α</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="2-122" alt="Image" /></td>
<td>Et</td>
<td>99</td>
<td>88:12</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td><img src="2-126" alt="Image" /></td>
<td>Et</td>
<td>66</td>
<td>86:14</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td><img src="2-127" alt="Image" /></td>
<td>n-Hex</td>
<td>60</td>
<td>77:23</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td><img src="2-128" alt="Image" /></td>
<td>n-Hex</td>
<td>77</td>
<td>75:25</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td><img src="2-129" alt="Image" /></td>
<td>Et</td>
<td>91</td>
<td>85:15</td>
<td>76</td>
</tr>
</tbody>
</table>

### 2.4.8 Proposed Mechanism for The Copper-Catalyzed Allylic Alkylation

To explain the regioselectivity and the enantioselectivity, a mechanism was proposed (Scheme 2-26). This mechanism showed only monomeric copper species. Before adding the substrate, the copper carbene complex was premixed with ethyl magnesium bromide which was likely to form a cuprate (I) complex with two ethyl groups because using different copper sources gave similar results. The cuprate complex could attack the allylic substrate in a $S_N2'$
fashion to generate a copper (III) species 2-130. Then a reductive elimination could take place to form the desired branched product 1-118. The copper (III) species 2-130 can also be isomerized to the α position through a π-allyl complex 2-131, then another reductive elimination can happen from the other intermediate 2-132 to produce the linear product 1-119. The regioselectivity probably came from this isomerization. In this proposed mechanism, the leaving group came back on the catalyst to replace one of the ethyl substituent. The active σ-complex 2-130 could be ligated to the carbene ligand, the ethyl group, the substrate and the leaving group. This species would go to the π-allyl complex 2-131 by a precomplexation of the alkene. The nature of the leaving group seemed to play a crucial role in the regioselectivity of the reaction (Table 2-5).

Scheme 2-26. Proposed mechanism for the asymmetric allylic alkylation

In the first σ-complex 2-130, the leaving group could influence a lot the coordination of the alkene, which would change the ratio of linear: branched. To support this hypothesis, a bidentate leaving group was used to minimize the coordination of the alkene which should yield a single branched product. The trisubstituted allylic substrate 2-133 was protected with thiophene
carboxylate (TC) leaving group which can coordinate with the ester part as well as the thiophene moiety. As expected, only one regioisomer 2-134 was isolated (Scheme 2-27).

Scheme 2-27. Allylic alkylation using TC leaving group

To further support the first stage of this proposed mechanism ($S_N{2'}$), a secondary alcohol substrate 2-136 was used and the linear substitution product 2-116 was obtained as a major product (Scheme 2-28).

Scheme 2-28. Asymmetric allylic alkylation from a secondary alcohol pivalate

The phenyl Grignard reagent gave mostly the linear compound which could be explained by an increase stability of the bisphenylcuprate complex. If this species was more stable, it would isomerize more readily to the least hindered $\sigma$-complex 2-132 and deliver mostly the linear compound 1-119.

During the course of this study, it was found out that premixing of the imidazolium, the Grignard reagent and the copper source gave similar results to the preformed copper complex (Scheme 2-29).
The current best example of the tricyclic chiral diaminocarbene ligand gave up to 78% ee for the asymmetric allylic alkylation of trisubstituted alkenes. But in order to use this new chiral catalyst in the total synthesis of a natural product, the enantioselectivity should reach at least 85-90% ee. That is why more structural changes were attempted on the ligand design.

2.4.9 Further Optimization of The Ligand Structure

As a first simple change, the electronics of the ligand were modified by putting OMe substituents on the two phenyl moieties at the back of the structure (Scheme 2-30). Starting from the aziridine 2-47, the anisole Grignard reagent was used to give the tosylated amine 2-137. Then it was deprotected using the combination of Li/naphthalene. Using oxalyl chloride, the bisamide 2-139 was formed in 87% yield. A milder procedure was used for the Bischler-Napieralski cyclization because some product decomposition was observed when using the PCl₅/Zn(OTf)₂ procedure. DMAP and Tf₂O converted the amide 2-139 into the desired nitrilium ion by basic conditions and yielded the bisimine 2-140 in 40% yield. 2-140 was cyclized into the imidazolium 2-141 using conventional procedure.
This new ligand was tested in the allylic alkylation. The branched compound was obtained in 58% ee same as 2-109. More donating substituents on the aromatic rings seemed to have no effect on the enantioselectivity for the allylic alkylation (Scheme 2-31).

Scheme 2-31. Allylic alkylation using 2-141

85% yield, \( \gamma:\alpha \approx 99:1 \)
58% ee
Electron withdrawing substituents were not attempted because the Bischler-Napieralski cyclization might be difficult with electron withdrawing groups on the phenyl rings. As it was discussed earlier, the phenyl rings at the back are twisted due to a common repulsion of the hydrogen atoms. If some substituents were to replace those hydrogen atoms, the rings would be even more twisted and the chiral groups at the front will be even more extended. The same synthesis was attempted with 3,5-dimethoxyphenyl Grignard reagent, but the synthesis of 2-146 was not successful (Scheme 2-32). It was probably due to steric effects, which were too large to overcome.

Scheme 2-32. Synthesis of the bis-OMe substituted BIQ carbene ligand 2-146
While working on the fused cyclohexyl 2-63, we also tried to synthesize ligands with chiral groups in α and β position. Commercially available D-(+)-norephedrine 2-147 was used as a cheap model compound. Even though, the α position was only substituted with a methyl substituent, the β position was functional and there was a phenyl group for the Bischler-Napieralski cyclization. The amine 2-147 was reacted with diethyl oxalate to give the bisamide 2-148 in excellent yields (Scheme 2-33).

![Scheme 2-33. Bisamide synthesis of norephedrine](image)

The alcohol 2-148 had to be protected to resist the harsh conditions of the Bischler-Napieralski cyclization (Table 2-9). First, silicon reagent was used but with little or no success (entries 1-2). DCM increased the reactivity of the starting material but only the monoprotected bisamide was isolated (entry 2). The poor formation of bis-protected 2-149 was probably due to the steric bulk of the tert-butyl diphenylsilyl groups. This large protecting group was used to serve as a bulky chiral substituent. On the other hand, the alcohol was successfully protected with an acetyl group (entry 3).

In order to protect the alcohol with a silicone group, the order of addition was reversed (Scheme 2-34). Norephedrine 2-147 was protected with tert-butyl diphenylsilyl group then the bisamide 2-149 formation needed oxalyl chloride as a coupling partner instead of diethyl oxalate.
Table 2-9. Protection of the β alcohol of the bisamide compound

<table>
<thead>
<tr>
<th>entry</th>
<th>protective agent</th>
<th>solvent</th>
<th>additives</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBu-Si-Cl</td>
<td>DMF</td>
<td>Et₃N</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>tBu-Si-Cl</td>
<td>DCM</td>
<td>imidazole DMAP</td>
<td>monoprotected</td>
</tr>
<tr>
<td>3</td>
<td>Ac₂O</td>
<td>DCM</td>
<td>Et₃N DMAP</td>
<td>80%</td>
</tr>
</tbody>
</table>

Scheme 2-34. Synthesis of the silylated bisamide

The Bischler-Napieralski cyclization was attempted using various methods (Table 2-10). The milder condition using Tf₂O/DMAP gave only decomposed products (entry 1). In the case of
the typical procedure PCl₅/Zn(OTf)₂, the starting materials decomposed also (entries 2 and 4). The Lewis acid was removed to decrease the harshness of the reaction conditions, but even though the starting material did not decompose only monocyclized product 2-155 was obtained (entry 3). The O-acetyl protected amide only gave a product 2-156 very similar to bis(imidoyl) chloride 2-92 (entry 5). The latter was stuck at this stage and would not cyclize. If some Lewis acid was added afterward, it led to decomposed products.

Table 2-10. Bisimine optimization for β substituted bisamides

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>cyclizing agents</th>
<th>yield</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph/Si/tBu</td>
<td>Tf₂O, DMAP</td>
<td>N/A</td>
<td>decomposed</td>
</tr>
<tr>
<td>2</td>
<td>Ph/Si/tBu</td>
<td>PCl₅/Zn(OTf)₂</td>
<td>N/A</td>
<td>decomposed</td>
</tr>
<tr>
<td>3</td>
<td>Ph/Si/tBu</td>
<td>PCl₅</td>
<td>81%</td>
<td>monocyclized</td>
</tr>
<tr>
<td>4</td>
<td>Ph/Si/tBu</td>
<td>PCl₅/Zn(OTf)₂</td>
<td>N/A</td>
<td>decomposed</td>
</tr>
<tr>
<td>5</td>
<td>Ph/Si/tBu</td>
<td>PCl₅</td>
<td>68%</td>
<td>bisimidoyl chloride</td>
</tr>
</tbody>
</table>

The characterization of those compounds can be rather difficult sometimes, but a general trend can be seen among them. The main difference between bisamide 2-150, bis(imidoyl) halide 2-156 and bisimine 2-100 is their \(^{13}\)C NMR. Their respective characteristic peaks are 160 ppm (Figure 2-5), 139 ppm \(^{73}\) (Figure 2-6) and 164 ppm (Figure 2-7). This general trend was seen for most of the compounds synthesized so far.
Figure 2-5. $^{13}$C NMR of bisamide 2-150

Figure 2-6. $^{13}$C NMR of bis(imidoyl) halide 2-156
Those results marked the end of the trials for β-substituted BIQ based carbene ligands. This substitution seemed to be too reactive and only lead to decomposition or synthesis of an intermediate in the formation of the product.
CHAPTER 3
IN SITU GENERATION OF ACYCLIC DIAMINOCARBENE COPPER COMPLEX

3.1 Introduction: Discovery of The In Situ Generation of Aminocarbene Copper Complex from Chloroimidazolium

In the previous chapter, the synthesis of a new chiral carbene ligand was reported as well as its application in the copper-catalyzed allylic alkylation using Grignard reagent as a nucleophile. The X-ray of the Pd carbene complex 2-103 was obtained by Dr. Hwimin Seo, but a X-ray of the Cu carbene complex 2-110 would be more relevant in our copper catalyzed research. Several trials were attempted with the complex 2-110 but with no success. In order to increase the stability of this complex, the copper (II) complex 3-1 was attempted following the same transmetallation procedure (Scheme 3-1).

![Scheme 3-1. Attempted synthesis of copper(II) BIQ-carbene complex 3-1](image)

But unexpectedly chloroimidazolium salt 3-2 was isolated and characterized by X-ray crystallography (Figure 3-1). The silver complex was synthesized but instead of exchanging with copper (II) chloride, it generated this BIQ chloroimidazolium 3-2.

Before obtaining the X-ray structure, this supposed complex 3-1 was used in the allylic alkylation to compare with copper (I) complex 2-110 (Scheme 3-2). At that time, it was not surprising to get similar results based on the fact that copper(II) can be reduced to copper(I) complex in the presence of Grignard reagent. When the result of the X-ray came back and the
supposed copper (II) complex was found to be the chloroimidazolium 3-2, the results from the allylic alkylation were now intriguing (Scheme 3-2).

Figure 3-1. X-Ray structure of chloroimidazolium-CuCl₂ salt 3-2

Scheme 3-2. Comparison between catalysts 2-110 and 3-2 in the allylic alkylation of naphthyl substrate 2-114

It seemed a Cu-carbene species was generated in situ from 3-2 and EtMgBr under the allylic alkylation conditions. This new in situ generation is not useful for NHCs because their
imidazoliums can be easily synthesized and they can also be readily deprotonated to generate various NHC-metal complexes. On the other hand, acyclic carbene metal complexes are more challenging to synthesize (1.3 Acyclic Carbene and Methods of Preparation).

3.2 New In Situ Generation of ADC-Cu Complex and Application in Allylic Alkylation

Commercially available chloroamidinium 1-112 was used as a potential acyclic carbene precursor (Table 3-1). To follow as closely as possible the procedure described previously (Scheme 3-2), the chloroamidinium 1-112 was first stirred with a copper salt to generate an intermediate 3-3 which would be similar to chloroimidazolium 3-2. Then it was combined with the Grignard reagent to generate the hypothetical acyclic aminocarbene-copper species.

Table 3-1. Allylic alkylation using chloroamidinium premixed with copper salt

<table>
<thead>
<tr>
<th>entry</th>
<th>CuX</th>
<th>3-3</th>
<th>yield</th>
<th>γ : α</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂</td>
<td>Yes</td>
<td>85%</td>
<td>46 : 54</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>Yes</td>
<td>75%</td>
<td>48 : 52</td>
</tr>
<tr>
<td>3</td>
<td>CuCl₂</td>
<td>No</td>
<td>10%</td>
<td>35 : 65</td>
</tr>
</tbody>
</table>

The reaction yielded products in good yields, but with poor regioselectivity. Different copper oxidation states could be used in this reaction (entries 1 and 2). The absence of
chloroamidinium gave low yield and poorer regioselectivity (entry 3). Even though the linear:
 branched ratio was lower than seen with 3-2, the proof of concept was a success.

In order to increase the regioselectivity, the substrate was varied. It was found that alkyl
based substrates gave good regioselectivity (Table 3-2). The substrate 3-4 carried a PMB
protecting group to facilitate HPLC conditions in future chiral experiments.

Table 3-2. S_N2' allylic alkylation catalyzed by copper carbene complexes

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand precursor</th>
<th>Cu salt</th>
<th>solvent</th>
<th>yield</th>
<th>γ : α</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-112</td>
<td>CuCl_2</td>
<td>Et_2O</td>
<td>82%</td>
<td>93:7</td>
</tr>
<tr>
<td>2</td>
<td>1-112</td>
<td>CuCl</td>
<td>Et_2O</td>
<td>81%</td>
<td>93:7</td>
</tr>
<tr>
<td>3</td>
<td>1-112</td>
<td>CuTC</td>
<td>Et_2O</td>
<td>83%</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td>1-112</td>
<td>CuTC</td>
<td>THF</td>
<td>37%</td>
<td>68:32</td>
</tr>
<tr>
<td>5</td>
<td>1-112</td>
<td>CuTC</td>
<td>DCM</td>
<td>13%</td>
<td>50:50</td>
</tr>
<tr>
<td>6</td>
<td>1-112</td>
<td>none</td>
<td>Et_2O</td>
<td>25%</td>
<td>94:6</td>
</tr>
<tr>
<td>7</td>
<td>none</td>
<td>CuTC</td>
<td>Et_2O</td>
<td>9%</td>
<td>19:81</td>
</tr>
<tr>
<td>8</td>
<td>3-7 (10 mol%)</td>
<td>CuTC</td>
<td>Et_2O</td>
<td>71%</td>
<td>90:10</td>
</tr>
<tr>
<td>9</td>
<td>3-8</td>
<td>CuTC</td>
<td>Et_2O</td>
<td>57%</td>
<td>92:8</td>
</tr>
</tbody>
</table>

The premixing of chloroamidinium 1-112 with a copper source was not required (entries 1-
6). Cu(I) salts such as CuCl (entry 2) or CuTC (entry 3) also gave identical results to those with
CuCl₂. Changing the solvent to THF (entry 4) or DCM (entry 5) significantly decreased yield and regioselectivity. Both the copper salt and the chloroamidinium were necessary for good yields (entries 6 and 7). However, 1-112 without CuTC (entry 6) still managed to give high γ selectivity (γ : α = 94:6) whereas CuTC without 1-112 (entry 7) showed very different selectivity (γ : α = 13:87).¹⁸⁴ Commercially available 3-8 showed similarly high γ selectivity (γ : α = 94:6) despite the slightly reduced yield (entry 9). Acyclic carbene 3-7 prepared by the reported deprotonation protocol (Scheme 3-4) also gave a similar result (entry 8), which was consistent with the idea of in-situ carbene generation.

Acyclic diaminocarbene 3-7 was made in situ from amidinium 3-11 following Alder’s procedure (Scheme 3-3).⁴⁵b Pyrrolidine was first reacted with ethyl formate in neat conditions to yield quantitatively the formamide 3-9. Then the imidoyl chloride 3-10 was formed using POCl₃ and it was subsequently mixed with another equivalent of pyrrolidine. This reaction gave rise to a mixture of amidiniums due to different counterions being present (Cl⁻, PO₂Cl₂). All those ions were exchanged with hexafluorophosphate to yield the desired product 3-11 which precipitated from the solvent media.

The amidinium 3-11 was then reacted with fresh LDA to give a stock solution of free carbene in THF which was used immediately (Scheme 3-4). Only 65 µL of this solution was used in the following allylic alkylation which contained 2 mL of Et₂O, so the THF present was almost negligible. To compare with ADC, chloroimidazolium 3-2 was reacted with the substrate 3-4 (Scheme 3-5).
Scheme 3-3. Bispyrrolidine amidinium preparation

\[
\text{NH} \quad \xrightarrow{\text{HCOEt}} \quad \text{3-9} \quad \xrightarrow{\text{POCl}_3} \quad \text{3-10} \quad \xrightarrow{\text{Et}_3\text{N}} \quad \text{3-11}
\]

neat, 80 °C, 6 h, 99%\)

\[
\text{3-11} \quad + \text{fresh LDA}
\]

-20 °C, 30 min, stock solution of carbene was made in THF

71% yield, \( \gamma : \alpha = 90:10 \)

Scheme 3-4. Allylic alkylation using free carbene (Table 3-2, entry 8)

\[
\text{PMBO-} \quad \xrightarrow{\text{EtMgBr/CuTC}} \quad \text{PMBO-} \quad + \text{PMBO-}
\]

\[3-4\]

\[3-5 \gamma (S_{N2}')\]

\[3-6 \alpha (S_{N2})\]

5 mol% catalyst\)

\[
\text{PMBO-} \quad \xrightarrow{\text{EtMgBr}} \quad \text{PMBO-} \quad + \text{PMBO-}
\]

\[3-4\]

\[3-5 \gamma (S_{N2}')\]

\[3-6 \alpha (S_{N2})\]

Catalyst = \(2-110\) : 78% yield, \( \gamma : \alpha = 94:6, (50\% \text{ ee}) \)

Catalyst = \(3-2\) : 69% yield, \( \gamma : \alpha = 97:3, (50\% \text{ ee}) \)

Scheme 3-5. Comparison between catalysts \(2-110\) and \(3-2\) in the allylic alkylation of alkyl substrate
The enantioselectivity dropped to 50% probably due to decreased steric effects from the substrate. The results were still similar between the isolated copper carbene complex \( \text{2-110} \) and the chloroimidazolium \( \text{3-2} \).

This reaction was also tested with a chiral ADC \( \text{3-12} \) synthesized by Dr. David Snead (Scheme 3-6). The enantioselectivity was good for a preliminary result. Unfortunately the major compound was linear. Attempts to increase this ratio in favor of branched products did not succeed.

Scheme 3-6. Enantioselective allylic alkylation using chiral ADC \( \text{3-12} \)

We decided to focus on achiral catalyst to study the scope of this reaction. This ADC-Cu catalyst (\( \text{1-112} \) with CuTC) showed excellent \( \gamma \) selectivity for various allylic substrates (Table 3-3). Symmetrical dibenzoate substrate \( \text{3-13} \) could be used owing to high \( \gamma \) selectivity (entry 1), and quaternary centers could be generated from tri-substituted alkene substrates in high yields (entries 3-5). E and Z substrates \( \text{3-15} \) and \( \text{3-16} \) reacted both efficiently (entries 2-4). The reaction with piperidine substrate \( \text{3-17} \) was sluggish and 15 mol% of catalyst loading was required (entry 5). However, this ADC-Cu catalyst appears to be more reactive than the NHC-Cu catalyst\(^8\) \( \text{3-22} \) which gave 24% yield of \( \text{3-21} \) under identical conditions (Scheme 3-7).
Table 3-3. Substrate scope

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMPCO=CH-OCMPM</td>
<td>PMPCO-CH-Et</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>MeO-CH=CH-OAc</td>
<td>MeO-CH-Et</td>
<td>97%</td>
</tr>
<tr>
<td>3</td>
<td>CH-CH-CH-OAc</td>
<td>CH-CH-Et</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>Ts-CH-CH-OAc</td>
<td>Ts-CH-Et</td>
<td>96%</td>
</tr>
<tr>
<td>5</td>
<td>Ts-NHPHCH-CH-OAc</td>
<td>Ts-piperidine-CH-Et</td>
<td>93%</td>
</tr>
</tbody>
</table>

[a] 15 mol % of chloroamidinium/CuTC

Scheme 3-7. Allylic alkylation of piperidine substrate with IMesCuCl catalyst 3-22
3.3 NMR Experiments

Several $^{13}$C NMR experiments were performed to characterize the copper species and collect some indication that the copper carbene complex was really synthesized in situ (Table 3-4). The experiments consisted of mixing the chloroamidinium 1-112, a copper (I) source and Grignard reagent in CD$_2$Cl$_2$ for some time. The premixing at room temperature (entry 1) showed mostly decomposition of the starting material. Then it was stirred at 0 °C same as in the reaction procedure for a short time and then cooled to -78 °C to trap the newly formed species and the NMR was checked at -60 °C (entry 2). This time the chloroamidinium peak was visible but no carbene peak was present. Those conditions were repeated with CuCl and phenyl Grignard which has been reported to give stable cuprate complexes (entry 3). In this case the chloroamidinium peak disappeared which meant it was completely converted into the metal carbene species or something else, unfortunately no peak was observed in the >200 ppm region.

<table>
<thead>
<tr>
<th>entry</th>
<th>CuX</th>
<th>Grignard reagent</th>
<th>temperature/time</th>
<th>$^{13}$C NMR at °C</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>EtMgBr</td>
<td>rt / 10 min</td>
<td>rt</td>
<td>weak peaks, decomposition</td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>EtMgBr</td>
<td>0 °C / 2 min</td>
<td>-60 °C</td>
<td>chloroamidinium peak still present no carbene peak</td>
</tr>
<tr>
<td>3</td>
<td>CuCl</td>
<td>PhMgBr</td>
<td>0 °C / 5 min</td>
<td>-60 °C</td>
<td>chloroamidinium peak gone but no carbene peak</td>
</tr>
<tr>
<td>4</td>
<td>CuCl</td>
<td>EtMgBr</td>
<td>0 °C / 5 min</td>
<td>-60 °C</td>
<td>chloroamidinium peak still present no carbene peak</td>
</tr>
</tbody>
</table>

Those experiments were fruitful but not conclusive. The absence of carbene peak did not necessarily mean the compound was not present; the acyclic aminocarbene bound to copper can
sometimes be rather weak in intensity. The solvent was replaced by THF-\textit{d}_8 which would be more similar in nature to the solvent used in the reaction. Also it is less reactive with free carbene than CD\textsubscript{2}Cl\textsubscript{2} which can sometimes be acidic. The main issue to address was the weak intensity of the carbene peak; it was resolved using \textsuperscript{13}C-labeled chloroamidinium precursor 3-25 (Scheme 3-8). The pyrrolidine was reacted with \textsuperscript{13}C-labeled phosgene to yield the desired urea 3-24. It was then mixed with oxalyl chloride to give the \textsuperscript{13}C-labeled chloroamidinium 3-25 which was synthesized by Dr David Snead. \textsuperscript{13}C-labeled chloroamidinium 3-25, CuCl and Grignard reagent were mixed in THF-\textit{d}_8 and monitored by \textsuperscript{13}C NMR at low temperature (Figure 3-2).

![Scheme 3-8. Preparation of \textsuperscript{13}C-labeled chloroamidinium precursor 3-25](image)

When a mixture of chloroamidinium 3-25 and CuCl was treated with PhMgBr, the starting material 3-25 was fully converted to two species showing typical metal-carbene sp\textsuperscript{2} carbon resonances at 206 and 217 ppm (Figure 3-2a).\textsuperscript{46} The 161 and 168 ppm resonances are assigned to aryl and alkyl amidinium compounds, 3-28 and 3-25 respectively.\textsuperscript{88,89} We speculated that the signals at 206 ppm and 217 ppm might be assigned to Cu-carbene complex 3-27\textsuperscript{90} and Mg-carbene complex 3-26 respectively.\textsuperscript{91} These tentative assignments are supported by the following observations: When chloroamidinium 3-25 was treated with PhMgBr in the absence of CuCl (Figure 3-2b), the 216 ppm resonance appeared as the only carbene species 3-26. When this mixture was further treated with CuCl (Figure 3-2c), the 216 ppm resonance was completely converted to the resonance at 206 ppm 3-27. When a mixture of 3-25 and CuCl was treated with
EtMgBr (Figure 3-2d), the Cu-carbene resonance at 207 ppm 3-27 was again observed while the 216 ppm resonance was not detected in this case.

Figure 3-2. Direct \(^{13}\)C NMR monitoring (at -60°C) of carbene-metal complex generation using \(^{13}\)C-labeled chloroamidinium precursor 3-25

In order to further support those findings, the \(^{13}\)C-labeled formamidinium ion 3-32 was synthesized. The pyrrolidine was reacted with \(^{13}\)C-labeled ethyl formate, followed by POCl\(_3\) and another pyrrolidine to give the desired product (Scheme 3-9).
It would be useful for this work to generate the free carbene \textbf{3-33} with reported conditions and then subject it to Grignard reagent as well as copper. The carbene peak would be expected to shift downfield and be close to the values found before (Figure 3-2). When \textsuperscript{13}C-labeled formamidinium \textbf{3-32} was reacted with fresh LDA in a NMR tube, a resonance peak at 235 ppm appeared (Figure 3-3a) which was close to the reported value for free lithiated acyclic carbene \textbf{3-33}. When this mixture was further treated with PhMgBr, the 235 ppm peak was completely converted to the resonance at 214 ppm (Figure 3-3b) which was very similar to the observed resonance (Figure 3-2b). When this new mixture was treated with CuCl, the resonance at 214 ppm was fully converted to a new peak at 207 ppm (Figure 3-3c) which was in accordance with the previous value (Figure 3-2c). Those findings further support the \textit{in situ} generation of copper carbene complex from chloroamidinium precursor.

One of the plausible mechanistic scenarios might involve metal-halide exchange between chloroamidinium \textbf{1-112} and R\textsubscript{2}CuMgBr (Scheme 3-10).\textsuperscript{92} This process could involve first an oxidative addition of the cuprate reagent into the carbon-chloride bond to form a copper(III) complex \textbf{3-34} which upon reductive elimination would generate the copper(I) carbene complex \textbf{3-35}. Another scenario could involve a two-step sequence of magnesium-chloride exchange\textsuperscript{93a} followed by transmetallation (Scheme 3-11).\textsuperscript{92b}

Scheme 3-9. Preparation of \textsuperscript{13}C-labeled formamidinium precursor \textbf{3-32}
Figure 3-3. Direct $^{13}$C NMR monitoring at room temperature of carbene-metal complex generation using $^{13}$C-labeled formamidinium 3-32.

Scheme 3-10. Copper carbene complex generation involving cuprate-chloride exchange.

Scheme 3-11. Copper carbene complex generation involving Grignard-chloride exchange.
This transformation allowed the conversion from easily synthesized chloroamidinium to their respective copper complexes. While this project was studied, Dr David Snead developed a similar concept but more general using lithium-halogen exchange (1.3Acyclic Carbene and Methods of Preparation).\textsuperscript{53}
4.1 Introduction: Ligand Design for $C_1$-Symmetric Ligands

The enantiomeric excess in the asymmetric allylic alkylation was limited to 75% with biisoquinoline-based carbene ligands 2-2 developed in Chapter 2, which is why these ligands have to be improved. In this first design, we observed that the chiral carbene ligand 2-1 developed by Grubbs$^{11}$ positioned the aryl groups at the front orthogonal to the plane by transfer from the backbone chirality. We thought it would be interesting to bring the chiral groups closer to the metal center using a tricyclic structure 2-2. It was clear that the BIQ ligand was rather open on the other available quadrants compared to ligand 2-1 which included those trans phenyl substituents at the back. In order to fill more efficiently the remaining quadrants, we conceived a $C_1$-symmetric version of this ligand which was built on the same chiral isoquinoline core 4-1 (Figure 4-1).

Figure 4-1. Increasing bulk around metal center by switching from $C_2$-symmetric BIQ 2-2 to $C_1$-symmetric MIQ 4-1 carbene ligands

The imidazolium 4-2 could be synthesized from bisimine 4-3 which resulted from imine coupling of the ketone 4-4. The Bischler-Napieralski cyclization could be used to convert the
ketoamide 4-5 into the monoimine 4-4. This process should be easier than the previously reported one because it involved only one ring closing. To finish, chiral phenethylamines 2-39 developed in Chapter 2 could be used to form the monoamide 4-5 (Scheme 4-1).

Scheme 4-1. Retrosynthesis of the $C_1$-symmetric monoisoquinoline ligand

4.2 First Attempt Using $R_2=\text{Me}$

The first design consisted on using isobutyl chiral substituents 4-6 which showed good results in the allylic alkylation (Figure 4-2).

Figure 4-2. First design of the $C_1$-symmetric isoquinoline ligand 4-6

The chiral phenethylamine 2-55 was coupled with pyruvic acid to give the monoamide 4-7 using EDCI and HOBT (Table 4-1). DCM was used as a solvent but only 50% yield was obtained (entry 1). To increase the yield, bases were added into the reaction conditions (entries 2-3) but the yield dropped because of an unknown byproduct which appeared in the reaction. The bases
were removed and a more polar solvent such as DMF was used instead of DCM (entry 4) with better results.

Table 4-1. Monoamide optimization

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No base</td>
<td>DCM</td>
<td>51%</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N</td>
<td>DCM</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>DMAP</td>
<td>DCM</td>
<td>30%</td>
</tr>
<tr>
<td>4</td>
<td>No base</td>
<td>DMF</td>
<td>74%</td>
</tr>
</tbody>
</table>

To form the mono dihydroisoquinoline 4-8 (Table 4-2), the current best conditions developed previously were used (entry 1) but only decomposition of product was observed. The PCl₅ was replaced with weaker POCl₃ (entry 2) but the same result was obtained. Using a 5:3 combination of Tf₂O and DMAP, the monoimine 4-9 was obtained in good yield (entry 3).

Table 4-2. Optimization of the Bischler-Napieralski cyclization

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents</th>
<th>solvent</th>
<th>T °C/time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PCl₅ / Zn(OTf)₂</td>
<td>toluene</td>
<td>85 °C / 8 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>POCl₃ / Zn(OTf)₂</td>
<td>toluene</td>
<td>85 °C / 8 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Tf₂O / DMAP</td>
<td>DCM</td>
<td>60 °C / 6 h</td>
<td>57%</td>
</tr>
</tbody>
</table>
With aryl amines (Table 4-3), different acid catalysts were used in combination with dehydrating reagents, but only the starting material was isolated (entries 1-4). With aliphatic amines, same result was obtained but the main issue in this case remained the bad solubility of the protonated aliphatic amines (entries 5-9). As a last resort, more nucleophilic amines such as methoxyamine or substituted hydrazine were used (entries 10-11). Only methoxyamine gave the product **4-9** but in poor yield (entry 10). Yields could not be increased by longer reaction times because the product was decomposing with excess heating. The methyl ketone moiety in the compound **4-8** seemed unreactive which might result from enolization under acidic conditions.

Table 4-3. Optimization of imine formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>NH₂R</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Solvent</th>
<th>T °C/time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4,6-trimethylaniline</td>
<td>pTsOH</td>
<td>4 Å MS</td>
<td>toluene</td>
<td>reflux / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>2,4,6-trimethylaniline</td>
<td>HCO₂H</td>
<td>no additive</td>
<td>methanol</td>
<td>reflux / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>2,4,6-trimethylaniline</td>
<td>TiCl₄</td>
<td>MgSO₄</td>
<td>toluene</td>
<td>reflux / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>4</td>
<td>2,4,6-trimethylaniline</td>
<td>H₂SO₄</td>
<td>no additive</td>
<td>Si(OEt)₄</td>
<td>160 °C / 12 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>diphenylmethanamine</td>
<td>pTsOH</td>
<td>4 Å MS</td>
<td>toluene</td>
<td>reflux / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>6</td>
<td>diphenylmethanamine</td>
<td>HCO₂H</td>
<td>no additive</td>
<td>ethanol</td>
<td>70 °C / 48 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>7</td>
<td>adamantylamine</td>
<td>HCO₂H</td>
<td>no additive</td>
<td>toluene</td>
<td>rt / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>8</td>
<td>adamantylamine</td>
<td>TiCl₄ (1 eq)</td>
<td>Et₃N</td>
<td>Et₂O</td>
<td>rt / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>9</td>
<td>(R)-2-phenylglycinol</td>
<td>no catalyst</td>
<td>MgSO₄</td>
<td>DCM</td>
<td>rt / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>10</td>
<td>methoxyamine·HCl</td>
<td>no catalyst</td>
<td>K₂CO₃</td>
<td>ethanol</td>
<td>85 °C / 1 h</td>
<td>17%</td>
</tr>
<tr>
<td>11</td>
<td>1,1-diphenylhydrazine</td>
<td>no catalyst</td>
<td>K₂CO₃</td>
<td>ethanol</td>
<td>85 °C / 1 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>
4.3 Second Attempt Using R₂=Ph

This issue could be easily fixed by replacing pyruvic acid with phenylglyoxylic acid (Scheme 4-2). Starting from the amine 2-55, it was coupled with 2-oxo-2-phenylacetic acid to yield the desired monoamide 4-10. The Bischler-Napieralski cyclization went smoothly to give the monoimine 4-11 in 85% yield.

Scheme 4-2. Monoimine synthesis from chiral isobutyl phenethylamine

This imino-ketone 4-11 was non-enolizable and was submitted to the imine condensation (Table 4-4). The typical conditions using pTsOH as a catalyst and molecular sieves or a Dean-Stark apparatus to trap the water were first used but with no success (entries 1 and 2). Then the stronger TiCl₄ was used stoichiometrically in combination with Et₃N to give excellent yield of the desired product 4-12 (entry 3).³⁴

Table 4-4. Optimization of the imine condensation from the non-enolizable ketone

<table>
<thead>
<tr>
<th>entry</th>
<th>NH₂R</th>
<th>catalyst</th>
<th>additive</th>
<th>solvent</th>
<th>T °C/time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4,6-trimethylaniline</td>
<td>pTsOH</td>
<td>4 Å MS</td>
<td>toluene</td>
<td>reflux / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>diphenylmethanamine</td>
<td>pTsOH</td>
<td>Dean-Stark</td>
<td>toluene</td>
<td>reflux / 12 h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>2,4,6-trimethylaniline (5 eq)</td>
<td>TiCl₄ (1.2 eq)</td>
<td>Et₃N (2 eq)</td>
<td>toluene</td>
<td>rt / 12 h</td>
<td>98%</td>
</tr>
</tbody>
</table>
Following this success, the bisimine was converted to the imidazolium 4-14 using typical procedure and it was converted to the corresponding copper complex 4-15, by transmetallation with silver, in good yield (Scheme 4-3).

Scheme 4-3. Imidazolium and copper complex synthesis for mesityl substituted imine

This complex was used in the allylic alkylation developed previously in order to compare its efficiency with the BIQ based carbene copper complex (Scheme 4-4). Using the same conditions, the \( C_1 \)-symmetric copper complex 4-15 gave excellent regioselectivity compared to the respective \( C_2 \)-symmetric copper complex 2-109. Unfortunately the enantioselectivity dropped drastically.

Scheme 4-4. Asymmetric allylic alkylation using 4-15

In order to increase the enantioselectivity, the bulky side of this new ligand was modified by changing the aryl amine in the imine condensation step (Table 4-5). Bulkier 2,6-diisopropylaniline (entry 1) and meta substituted 3,5-dimethylaniline (entry 2) were successfully
condensed with the ketone moiety. Then they were converted to imidazolium and copper complexes in good yields. 3,5-Dimethoxyaniline gave decomposed products (entry 3) as well as very bulky triphenylaniline (entry 4).

### 4.4 Achiral Side Variation

Table 4-5. Synthesis of disubstituted MIQ-NHC copper complexes

<table>
<thead>
<tr>
<th>entry</th>
<th>NH₂R</th>
<th>A yield</th>
<th>B yield</th>
<th>C yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂N-</td>
<td>70%, 4-16</td>
<td>77%, 4-20</td>
<td>70%, 4-22</td>
</tr>
<tr>
<td>2</td>
<td>H₂N-</td>
<td>45%, 4-17</td>
<td>86%, 4-21</td>
<td>74%, 4-23</td>
</tr>
<tr>
<td>3</td>
<td>H₂N-</td>
<td>decomposed, 4-18</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>H₂N-</td>
<td>SM recovered, 4-19</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

The two new complexes 4-22 and 4-23 were used in the allylic alkylation (Table 4-6). Using more bulky substituents at the ortho position decreased the enantioselectivity from 35% to 23% (entry 1). Meta substitution gave results similar to those obtained with bulky diisopropyl groups (entry 3). The carbene copper complex could also be synthesized in situ as it was observed for the BIQ carbene ligand (Scheme 2-29); only the yield was slightly reduced (entry...
2). The $C_1$-symmetric ligand 4-1 seemed to be optimum for this reaction with substituents smaller than isopropyl and positioned at the ortho position.

Table 4-6. Allylic alkylation with disubstituted MIQ-NHC copper complexes

```
Table 4-6. Allylic alkylation with disubstituted MIQ-NHC copper complexes

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield</th>
<th>$\gamma : \alpha$</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-22</td>
<td>85%</td>
<td>99 : 1</td>
<td>23%</td>
</tr>
<tr>
<td>2a</td>
<td>4-22</td>
<td>77%</td>
<td>99 : 1</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td>4-23</td>
<td>95%</td>
<td>99 : 1</td>
<td>20%</td>
</tr>
</tbody>
</table>

[a] The copper carbene complex was synthesized in situ from premixing of $C_1$-symmetric imidazolium precursor, EtMgBr and CuTC for 10 minutes prior addition of the substrate.
```

Monosubstituted aryl amines should be less bulky and may give better enantioselectivity (Table 4-7). Coordinating substituents such as pyridine 4-27 and sulfonic acid 4-29 failed to form any products (entries 4 and 6). The synthesis of the monosubstituted isopropyl imidazolium 4-30 gave a mixture of diastereomers by NMR (entry 1) which was surprising considering that the disubstituted isopropyl imidazolium 4-20 gave only one isomer. This diastereomeric mixture
issue would be discussed later in the chapter. Only 2-methyl and 2-methoxy aniline gave the desired imidazolium as a single product (entries 2 and 5).

Table 4-7. Synthesis of monosubstituted MIQ-NHCs

![Synthesis of monosubstituted MIQ-NHCs](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>NH₂R</th>
<th>A yield</th>
<th>B yield</th>
<th>diastereomeric ratio of imidazolium</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>91%, 4-24</td>
<td>77%, 4-30</td>
<td>54:46</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>87%, 4-25</td>
<td>66%, 4-31</td>
<td>one isomer</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>89%, 4-26</td>
<td>68%, 4-32</td>
<td>40:60</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>SM recovered, 4-27</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>crude used in next step, 4-28</td>
<td>95% after 2 steps, 4-33</td>
<td>one isomer</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>decomposed, 4-29</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

The imidazoliums 4-31 and 4-33 were tested in the allylic alkylation (Table 4-8). The regioselectivity stayed excellent but the enantioselectivity almost nullified which meant that this monosubstitution was not intruding efficiently within the metal sphere (entries 1 and 2).
Table 4-8. Allylic alkylation using monosubstituted MIQ-NHCs

\[
\text{2-122} \xrightarrow{\text{EtMgBr, Et}_2\text{O, 0 °C, 1 h}} \text{CuTC (3 mol%)} \xrightarrow{\text{3 mol%}} \text{2-115} (\text{S}) + \text{2-116} \alpha \text{ product (S}_n{2})
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield</th>
<th>γ : α</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>4-31</td>
<td>82%</td>
<td>99 : 1</td>
</tr>
<tr>
<td>2</td>
<td>MeO</td>
<td>4-33</td>
<td>82%</td>
<td>99 : 1</td>
</tr>
</tbody>
</table>

The achiral side of the ligand was locked with 2,4,6-trimethylanilnine which gave the best results so far. The chiral side was then modified using other chiral phenethylamines developed previously in Chapter 2.

### 4.5 Chiral Side Variation

The (S)-1,2-diphenylethanamine 1-46 was reacted with phenylglyoxylic acid to give the monoamide 4-34 (Scheme 4-5). Then the cyclization procedure gave the same non polar product 2-102 as the BIQ synthesis (Scheme 2-21).

Scheme 4-5. Attempted synthesis of the phenyl substituted isoquinoline 4-35
The cyclohexyl phenethylamine 2-62 was reacted with the carboxylic acid to give the corresponding monoamide 4-36 in 60% yield. Then it was cyclized in quantitative yield using toluene as a solvent instead of DCM. The bisimine 4-38 was obtained using mesitylamine (Scheme 4-6).

Scheme 4-6. Synthesis of 4-38

When the cyclization from bisimine 4-38 to imidazolium 4-39 was attempted at different temperatures (Table 4-9), different ratios of α and β were observed (entries 1 and 2). The same results were observed previously (Table 4-7, entries 1 and 3). When the product mixture was further heated in toluene at 120 °C for 2 hours, the ratio stayed unchanged.

Table 4-9. Dependence between temperature and imidazolium ratio

<table>
<thead>
<tr>
<th>entry</th>
<th>T °C</th>
<th>α : β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>84 : 16</td>
</tr>
<tr>
<td>2</td>
<td>35 °C</td>
<td>51 : 49</td>
</tr>
</tbody>
</table>
The evidence of this mixture was obtained from the $^1$H NMR (Figure 4-3 and Figure 4-4). The characteristic imidazolium signal area showed 2 peaks at 10.5 ppm and 11.8 ppm with different ratio. Even though those peaks are acidic and may exchange, they are the only peaks not overlapping in the spectrum.

![Figure 4-3. $^1$H NMR of the 4-39 (84:16) (Scheme 4-6, entry 1).](image1)

![Figure 4-4. $^1$H NMR of 4-39 (51:49) (Scheme 4-6, entry 2)](image2)

At first glance, the compound 4-39 possesses only one chiral center but an unexpected atropoisomerism between the isoquinoline moiety and the imidazolium ring could explain this
phenomenon. With an opposite twist of the two phenyls at the back of the molecule, two diastereomers could be synthesized and would be hard to separate. The bulk increase on the isoquinoline moiety seemed to be responsible for the appearance of this mixture.

The fused Cy amine 2-65 failed to give $C_2$-symmetric bisimine 2-101 but it could work in this $C_1$-symmetric ligand. The bisimine 4-42 was successfully synthesized in good overall yield (Scheme 4-7). The imidazolium synthesis gave again a mixture of diastereomers 4-43α and 4-43β but this time they could be both isolated by column chromatography (separated spots).

Unfortunately, when this reaction was scaled up, only 4-43β was isolated.

Scheme 4-7. Imidazolium synthesis of 4-43

When looking at their respective NMR (Figure 4-5), the main difference is their imidazolium peaks ($\alpha = 9.65$ ppm, $\beta = 10.34$ ppm). The mass spectroscopy gave the same molecular weight for both of them. X-ray could not be obtained so their structural difference remain a mystery.
Figure 4-5. $^1$H NMR of the two diastereomers of 4-43
4-43α and 4-43β were tested in the allylic alkylation (Table 4-10) and gave different enantioselectivities. This result proves that those two compounds are different and the various ratio obtained for 4-39 (α:β) would probably lead to different enantioselectivities.

Table 4-10. Allylic alkylation with two different isomers of 4-43

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield</th>
<th>γ : α</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-43α</td>
<td>90%</td>
<td>99 : 1</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>4-43β</td>
<td>90%</td>
<td>99 : 1</td>
<td>40%</td>
</tr>
</tbody>
</table>

4.6 Gold BIQ and MIQ Metal Complexes

All of the reactions studied involved copper complexes. Unfortunately X-ray of those complexes could never be obtained. Considering another metal complex in the same row, gold was chosen as an alternative to obtain an X-ray structure. MIQ and BIQ gold complexes 4-44 and 4-45 were synthesized by transmetallation from silver complex (Scheme 4-8). Those complexes could be purified by column chromatography.

X-ray structures were obtained for both complexes (Figure 4-7 and Figure 4-8). Looking at the front view of the complexes, it was clear that 4-44 was more demanding than 4-45. It was interesting to note that the chiral substituents in both complexes were pointing in the axial position. To further compare the ligand steric effects, the buried volumes were calculated (Figure 4-6). This new parameter has been developed recently to quantify the steric effects resulting from NHC when compared to phosphine ligand which used the Tolman cone angle. The buried volume gives a measure of the space occupied by the NHC ligand in the first coordination sphere of the metal centre.
Scheme 4-8. Synthesis of BIQ and MIQ gold complexes

It is defined by two parameters being R (the radii of the coordination sphere) and d (the atomic radii). The best correlation between \( \% V_{Bur} \) and DFT calculations was found for \( R = 3.5 \) Å. Recently, Nolan and co-workers disclosed a review on \( \% V_{Bur} \) for an extensive list of NHC and phosphine ligands.\(^{95c}\) In this paper, they used \( d = 2 \) Å for the atomic radii. For further comparison with known complexes, we decided to use the same parameters.

Amount of Ligand Intruding into Radius of Coordination

\[ R = 3.5 \text{ Å} \]
\[ d = 2 \text{ Å} \]

Figure 4-6. Buried volume for NHC ligand
We found 42.8% for 4-44 and 33.2% for 4-45. Au-MIQ 4-44 was more demanding than Au-BIQ 4-45 by 10%. This finding supported our design expressed by three quadrants around the metal being occupied (Figure 4-1).

Figure 4-7. X-ray structure of 4-44

98
Figure 4-8. X-ray structure of 4-45$^{99}$
4.7 Application: Copper-Catalyzed β-Borylation of α,β-Unsaturated Carbonyl Compounds

The allylic alkylation seems to give limited results with this new ligand design. Copper is definitely a good choice for this ligand so the effort into finding a new application was directed toward reactions catalyzed by this metal. After a few attempts, the copper-catalyzed β-borylation of α,β-unsaturated carbonyl compounds was selected. An in situ catalyst generation was chosen for ease of access. It consisted of a premixing of an imidazolium, a CuCl salt and NaOtBu in THF at room temperature for 30 minutes. The base would deprotonate the imidazolium to form an aminocarbene which would complex with CuCl followed by substitution of the halide to form an alkoxide carbene-copper complex 1-187 which would be our active catalyst (Figure 1-6). From previous work by Yun,\textsuperscript{69b} methanol was used to regenerate the active complex in the catalytic cycle (Figure 4-9).

\[
\text{CuCl} + \text{NaOtBu} \rightarrow \text{CuOt-Bu}
\]

\[
\text{L = phosphine}
\]

\[
\text{B}_2\text{pin}_2
\]

\[
\text{1-188}
\]

\[
\text{1-171}
\]

\[
\text{1-189}
\]

\[
\text{1-190}
\]

\[
\text{1-172}
\]

Figure 4-9. Proposed mechanism by Yun for β-borylation of unsaturated substrates
The boron ester addition product 4-47 was found to be hard to isolate. Without any purification, this intermediate was further treated with NaBO₃ to give the β-alcohol substrate 4-48. The yields and enantioselectivities reported would be for two consecutive steps. The preliminary result was encouraging with 86% yield and 50% ee (Table 4-11, entry 1). KOrBu and NaOtBu were equally efficient (entries 1 and 3). Polar, non polar solvents and other copper salts did not affect the outcome of the reaction (entries 3-7). Decreasing the temperature did not increase the enantioselectivity but the yield was decreased (entry 2). Absence of ligand gave reduced yield (entries 8-10).

Table 4-11. Optimization of β-borylation for cinnamonitrile

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>copper salt</th>
<th>base</th>
<th>solvent</th>
<th>T °C</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-14</td>
<td>CuCl</td>
<td>NaOtBu</td>
<td>THF</td>
<td>rt</td>
<td>86</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>4-14</td>
<td>CuCl</td>
<td>NaOtBu</td>
<td>THF</td>
<td>-70</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>4-14</td>
<td>CuCl</td>
<td>KOrBu</td>
<td>THF</td>
<td>rt</td>
<td>84</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>4-14</td>
<td>CuCl</td>
<td>KOrBu</td>
<td>Et₂O</td>
<td>rt</td>
<td>84</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>4-14</td>
<td>CuBr.Me₂S</td>
<td>KOrBu</td>
<td>THF</td>
<td>rt</td>
<td>86</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>4-14</td>
<td>CuBr.Me₂S</td>
<td>KOrBu</td>
<td>DCM</td>
<td>rt</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>4-14</td>
<td>CuBr.Me₂S</td>
<td>KOrBu</td>
<td>toluene</td>
<td>rt</td>
<td>85</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>CuCl</td>
<td>NaOtBu</td>
<td>THF</td>
<td>rt</td>
<td>76</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td>none</td>
<td>CuCl</td>
<td>NaOtBu</td>
<td>THF</td>
<td>-20</td>
<td>50</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>none</td>
<td>CuCl</td>
<td>NaOtBu</td>
<td>THF</td>
<td>-70</td>
<td>30</td>
<td>N/A</td>
</tr>
</tbody>
</table>

The various C₁-symmetric ligands developed previously were tested in this reaction (Table 4-12). Fused cyclohexyl substitution 4-43β gave lower ee than isobutyl 4-14 (entries 2 and 1) which was the inverse of the allylic alkylation results. Increased bulk on the achiral side 4-20
decreased the enantioselectivity (entry 5) as was observed in the allylic alkylation. Surprisingly, the BIQ ligand 2-108 gave mostly racemic products which reinforced the need of this new C\textsubscript{1}-symmetric ligand (entries 3 and 4). When using DCM, the yield was decreased resulting probably from trace amount of hydrochloric acid present in the solvent (entries 5 and 6).

Table 4-12. Ligand scope for cinnaminitrile

From this small study, 4-14 gave the best results. The electron withdrawing groups from the substrate 1-171 were varied to study their effect on this reaction (Table 4-13). The reaction worked well for quaternary substrates 4-49 and 4-52 (entries 1 and 5). Ketone 4-49 gave lower ee than nitrile 4-50 (entries 1 and 2). On the other hand, amide 4-55 increased the ee significantly compared to nitriles and esters (entries 4, 5 and 8). Thioester 4-53 was unreactive toward this reaction (entry 6).
Table 4-13. Substrate scope

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁EWG</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1-49" alt="Image" /></td>
<td>82</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td><img src="4-46" alt="Image" /></td>
<td>86</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td><img src="4-50" alt="Image" /></td>
<td>No reaction SM recovered</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td><img src="4-51" alt="Image" /></td>
<td>83</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td><img src="4-52" alt="Image" /></td>
<td>93</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td><img src="4-53" alt="Image" /></td>
<td>No reaction SM recovered</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td><img src="4-54" alt="Image" /></td>
<td>No reaction SM recovered</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td><img src="4-55" alt="Image" /></td>
<td>60</td>
<td>76</td>
</tr>
</tbody>
</table>
A trend between the enantioselectivity and the functional group of the substrate seemed to appear. The more electronegative the oxygen atom becomes the better the enantioselectivity is. This is probably due to a stronger and tighter binding of the copper with the oxygen atom which would be responsible for a closer transition state (Figure 4-10).

Figure 4-10. Proposed transition state with amide functionality

The amide functionality was the most promising. Thus substituents off the nitrogen atom were varied to further increase the enantioselectivity (Table 4-14). Bigger groups such as Cy 4-56 gave better yields but the same enantioselectivity (entry 2). The Weinreb amide 4-57 was tested and gave excellent yields with satisfactory selectivity (entry 3).

Table 4-14. Amide substrate optimization

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Me</td>
<td>60</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>Cy</td>
<td>Cy</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>OMe</td>
<td>99</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>4-OMeBn</td>
<td>4-OMeBn</td>
<td>95</td>
<td>86</td>
</tr>
</tbody>
</table>
The latter would be interesting for further derivatization. The benzyl substrates for the first time gave an enantioselectivity over 80% (entry 4) with excellent yields for PMB substituents (entry 5).

In a recent report by Hoveyda,\textsuperscript{71} it was shown that carbene-copper complexes did not need methanol to be regenerated in the catalytic cycle with $\alpha,\beta$-unsaturated ketones (Figure 4-11). This probably resulted from higher reactivity of copper enolate $\textit{1-190}$ bearing strong $\sigma$-donor NHC compared to the less Lewis basic phosphine-based ligands.

![Figure 4-11. Proposed mechanism for $\beta$-borylation with NHC ligand](image)

New optimizations were realized with the benzyl amide substrate $\textit{4-58}$ (Table 4-15). The reaction proceeded very well without methanol (entries 1 and 2) which reinforced the advantage of NHC over phosphine ligands. Other polar and apolar solvents increased slightly the ee but the yield dropped a lot (entries 3-6 and 8). This was probably due to lower solubility. When using a mixture of THF/Et$_2$O, the enantioselectivity stayed the same as when pure Et$_2$O was used but the
yield was similar to pure THF (entry 7). The THF might coordinate to B$_2$pin$_2$ and facilitate the σ bond metathesis. Copper (II) salts were similarly effective in this reaction (entries 9 and 10).

Table 4-15. Reaction condition optimization for N,N-dibenzylcinnamamide

<table>
<thead>
<tr>
<th>entry</th>
<th>copper salt</th>
<th>MeOH</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>Yes</td>
<td>THF</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>No</td>
<td>THF</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>No</td>
<td>Et$_2$O</td>
<td>46</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>No</td>
<td>toluene</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>No</td>
<td>fBuOMe</td>
<td>33</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>No</td>
<td>DME</td>
<td>63</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>No</td>
<td>Et$_2$O/THF (1:1)</td>
<td>87</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>CuBr$\cdot$Me$_2$S</td>
<td>No</td>
<td>1,4-dioxane</td>
<td>41</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)$_2$</td>
<td>No</td>
<td>THF</td>
<td>78</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)$_2$</td>
<td>No</td>
<td>THF</td>
<td>72</td>
<td>85</td>
</tr>
</tbody>
</table>

The optimization results with amide substrates were similar to those with cinnamonic acid which showed the robustness of this new C$_1$-symmetric catalyst 4-14. For mechanistic studies, the Z unsaturated amide 4-59 was synthesized and submitted to the Borylation reaction (Table 4-16). The catalyst favored the other enantiomer but in lower enantioselectivity (entries 1 and 2).

New imidazoliums were synthesized for further studies of the effect of the achiral moiety (Table 4-17). 4-70 was synthesized for comparison with 4-14 (entry 2). Those two ligands differ by the methyl in para position.
Table 4-16. β-borylation with different alkene configuration

<table>
<thead>
<tr>
<th>entry</th>
<th>Z/E configuration</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>95</td>
<td>86 (S)</td>
</tr>
<tr>
<td>2</td>
<td>Z</td>
<td>80</td>
<td>-66 (R)</td>
</tr>
</tbody>
</table>

Lower ee for 4-70 would mean the methyl is needed in the para position and bigger groups could be incorporated for improvement. Similar ee would suggest that the para position does not interfere with the reaction. Higher ee would imply the para position obstructs the reaction. 4-69 was formed to increase the bulk between methyl and isopropyl (entry 1). 4-71 was made to study inductive effect on the catalyst (entry 3). Anthracene substituted 4-72 would be interesting as a facial bulk (entry 4). Aliphatic amines could also be used in the synthesis of this ligand (entry 5).

Those new imidazoliums were used in the copper-catalyzed borylation (Table 4-18). 4-70 gave slight better enantioselectivity than 4-14 which proved the additional methyl is decreasing the ee (entries 1 and 3). The slight increase in bulk with ethyl substitution 4-69 gave the same results (entry 4). A large increase in bulk with isopropyl in 4-20 decreased the enantioselectivity (entry 2). Interestingly, the electron withdrawing substituents in 4-71 contributed to a 13% drop in ee (entries 5 and 6). 4-33 and 4-72 did not improve the enantioselectivity in the borylation reaction (entries 7 and 8).
This amide substrate may give a better transition state considering that BIQ based carbene ligand 2-104 obtained 36% ee with 4-59 (entry 12) and 7% ee with 4-46 (Table 4-12, entry 3). Two mixtures of 4-39 were tested in this reaction (entries 10 and 11). The difference in ee supported the formation of two diastereomers. The three best ligands are the unhindered ortho substituted ones (entries 1, 3 and 4).
Table 4-18. Ligand scope for N,N-bis(4-methoxybenzyl)cinnamamide

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-14</td>
<td>95</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>4-20</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>4-70</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>4-69</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>4-21</td>
<td>97</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>4-71</td>
<td>90</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>4-33</td>
<td>99</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>4-72</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>4-43β</td>
<td>90</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>4-39 (51:49)</td>
<td>88</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>4-39 (84:16)</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>2-104</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>13</td>
<td>4-73</td>
<td>80</td>
<td>62</td>
</tr>
</tbody>
</table>

Over the course of this study, inconsistencies were observed in the yields of this reaction.

After a careful screening of the reaction parameters, the temperature of the reaction was put at fault (Table 4-19). From fall to winter, the room temperature decreased by 6 ºC and this small drop had a dramatic effect on the yields (entries 1 and 3). To palliate this variation in yields, the reaction temperature was increased to 40 ºC. Better yields were obtained without a drop in the enantioselectivity (entries 4 and 5). Additionally, the reaction could be completed in 6 hours instead of 12 hours (entries 5 and 6). Unfortunately, 4-69 only gave 85% ee (entries 1-3) instead of 88% reported previously (Table 4-18, entry 4).
For reproducibility reasons, we decided to choose 4-14 as our ligand of choice for the substrate scope (Table 4-20). The reaction tolerated electron-donating (entries 2 and 3), electron withdrawing (entry 5) and meta substituents (entry 6), as well as aliphatic substituents (entries 6 and 7). Surprisingly, low yield and ee was obtained with ortho fluorine substitution (entry 4).

Combining our results and observations, we envisioned a working transition state responsible for our selectivity (Figure 4-12). Using the X-ray structure 4-44, gold and chloride atoms were replaced by copper and boron using reported bond lengths for similar complexes. Considering that MIQ carbene ligand blocks the three quadrants around the metal center and giving the absolute configuration of the product, the substrate should approach from the bottom left corner. The model i with Si-face attack by the boryl group is most likely to form the major enantiomer (S) (Table 4-14, entry 1) where as model ii with attack on the Re-face would encounter steric repulsion from the aryl substituents.
Table 4-20. Substrate scope

<table>
<thead>
<tr>
<th>entry</th>
<th>SM/P</th>
<th>R</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-59/64</td>
<td><a href="#">苯</a></td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>4-74/81</td>
<td><a href="#">甲基苯</a></td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>4-75/82</td>
<td><a href="#">甲氧基苯</a></td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>4-76/83</td>
<td><a href="#">氟苯</a></td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>4-77/84</td>
<td><a href="#">氟苯</a></td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>4-78/85</td>
<td><a href="#">苯</a></td>
<td>94</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>4-79/86</td>
<td><a href="#">环己基</a></td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>4-80/87</td>
<td><a href="#">甲基</a></td>
<td>99</td>
<td>75</td>
</tr>
</tbody>
</table>

Figure 4-12. Proposed transition-state model for the asymmetric borylation. B = pinB-
4.8 Further Directions for MIQ or BIQ Ligands

Over the course of this study, several BIQ or MIQ substituted carbene ligands were synthesized. The pursuit of more bulky substitution is still needed to increase selectivity. β-Substitution prevented the formation of the bisimine moiety as seen in fused cyclohexyl and norephedrine. Ligands with only α-substitution should be pursued but a few substituents raise issues. Aryl groups decompose the bisamide into cyanogens and stilbene (Scheme 2-21). Benzyl substituents can also participate in the Bischler-Napieralski cyclization which can scramble the chiral centers. Interesting results could be obtained by incorporation of quaternary centers at the α position.
Bisoxazoline and bisimidazoline based carbene ligand synthesis revealed some issues either in the metal complex or the imidazolium formation. Concluding that the proximal heteroatom next to the imidazolium rings were detrimental for N-heterocyclic carbene reactivity, new all carbon based amino carbene ligands were synthesized with success.

New $C_2$- (BIQ) and $C_1$-symmetric (MIQ) aminocarbene ligands were developed from the same chiral phenethylamines which were synthesized in four steps from amino acids. Both synthesis involved amide formation followed by Bischler-Napieralski cyclization. BIQ based carbene ligands could accommodate any alkyl chirality $\alpha$ to the nitrogen atoms (isopropyl, isobutyl, tert-butyl, cyclohexyl, cyclohexyl alanine). Fused cyclohexyl with $\beta$ chirality could not be installed on this ligand. On the other hand, MIQ based carbene ligands could accept both types of chirality as long as they possessed CH$_2$ groups next to it (fused cyclohexyl and isobutyl). Other groups such as cyclohexyl and tert-butyl gave mixture of diastereomers resulting from hindered rotation.

BIQ based carbene ligands were successfully applied in the copper-catalyzed allylic alkylation using Grignard reagent as nucleophiles. The highlight of this transformation was the formation of an all carbon quaternary center in 91% yield, 85:15 (S$_N$2' vs S$_N$2) selectivity and 76% ee. MIQ based carbene ligands were used in the copper-catalyzed borylation of $\alpha,\beta$ unsaturated amides with an average of 85% ee for alkyl and aryl substrates. The ligands gave opposite results in those two reactions: BIQ gave 36% ee for the borylation and MIQ gave 35% ee in the allylic alkylation. Those two results proved the need for diversity in ligand structure. These ligands can be accessed readily from the same intermediate and used accordingly for future applications.
While working on the BIQ copper complex characterization, we observed an \textit{in situ} carbene copper complex formation from chloroimidazolium. As our group was interested in the development of new acyclic carbene ligands, we applied the methodology to this field. Using the same copper-catalyzed allylic alkylation with Grignard reagent, we generated \textit{in situ} the first acyclic carbene copper complex which catalyzed efficiently the latter reaction. The carbene cuprate complex was observed by low temperature NMR and based on characteristic metal-carbene $^{13}$C NMR chemical shifts. This project was a typical example of serendipity in organic chemistry.
CHAPTER 6
EXPERIMENTAL SECTION

6.1 General Remarks

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon. THF, CH₂Cl₂, Et₂O and toluene were purified under positive pressure of dry nitrogen by Meyer Solvent Dispensing System prior to use. All the chemicals used were purchased from Sigma-Aldrich Co., Acros Organics and Strem Chemicals Inc. and were used as received without further purification. NMR spectra were recorded using a Mercury-300 FT-NMR, operating at 300 MHz for ¹H NMR and at 75.4 MHz for ¹³C NMR. All chemical shifts for ¹H and ¹³C NMR spectroscopy were referenced to residual signals from CDCl₃ (¹H ) 7.27 ppm and (¹³C ) 77.23 ppm. High resolution mass spectra were recorded on a GC/MS spectrometer or a TOF-LC/MS spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Enantiomer ratios were determined by chiral HPLC analysis (Shimadzu) using Chiral Technologies Chiralcel OJ-H, Chiralpak IA and IB columns and Regis Technologies Whelk-01 column.

6.2 C₂-Symmetric NHC Ligands

6.2.1 Bisoxazoline Derived NHC Ligand

\[ \text{N1,N2-bis((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)oxalamide (2-11)} \]

In a flame dried Schlenk flask, 194 µL (1.42 mmol) of diethyl oxalate was added to a suspension of 445 mg (2.98 mmol) of (1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol in toluene (10 mL). The reaction mixture was stirred at reflux for 12 h. It was cooled at room temperature
and hexane (5 mL) was added. The product was isolated by filtration on Buchner funnel and it was washed with hexane (3 x 5 mL) to yield 478 mg (1.36 mmol, 95.5%) of \( \text{N}_1,\text{N}_2\)-bis((1\(R\),2\(R\))-2-hydroxy-2,3-dihydro-1H-inden-1-yl)oxalamide.

\(^1\)H NMR (300MHz, DMSO-\(d_6\)) \( \delta = 9.08\) (d, \( J = 9.1\) Hz, 2 H), 7.26 - 7.04 (m, 8 H), 5.36 (d, \( J = 5.9\) Hz, 2 H), 5.15 - 5.05 (m, 2 H), 4.57 - 4.45 (m, 2 H), 3.16 (dd, \( J = 7.3, 15.2\) Hz, 2 H), 2.72 (dd, \( J = 7.6, 15.5\) Hz, 2 H)

\(^{13}\)C NMR (75MHz, CHLOROFORM-d) \( \delta = 166.0, 146.6, 145.2, 133.1, 132.1, 130.1, 129.0, 82.3, 66.9, 44.2 \)

\( \text{N}_1,\text{N}_2\)-bis((1\(R\),2\(R\))-2-methanesulfonate-2,3-dihydro-1H-inden-1-yl)oxalamide (2-13)

\[
\begin{array}{c}
\text{MsO} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{HN} \\
\text{O} \\
\text{QMs}
\end{array}
\end{array}
\]

In a flame dried Schlenk flask, 55.0 \( \mu \)L of mesylate chloride (0.712 mmol) was added to a suspension of 100 mg of \( \text{N}_1,\text{N}_2\)-bis((1\(R\),2\(R\))-2-hydroxy-2,3-dihydro-1H-inden-1-yl)oxalamide (0.284 mmol) and 158 \( \mu \)L (1.14 mmol) of Et\(_3\)N in THF (2 mL) at 0 \(^\circ\)C. The suspension was stirred at room temperature for 4 h. 4 mL of H\(_2\)O was added and the solid was isolated by filtration on Buchner funnel. It was washed with H\(_2\)O (3 x 2 mL) to yield 117 mg (0.230 mmol, 82.0%) of \( \text{N}_1,\text{N}_2\)-bis((1\(R\),2\(R\))-2-methanesulfonate-2,3-dihydro-1H-inden-1-yl)oxalamide.

\(^1\)H NMR (300MHz, DMSO-\(d_6\)) \( \delta = 9.51\) (d, \( J = 8.5\) Hz, 2 H), 7.35 - 7.24 (m, 6 H), 7.18 (s, 2 H), 5.52 - 5.40 (m, 4 H), 3.49 (dd, \( J = 6.9, 16.0\) Hz, 2 H), 3.24 (s, 6 H), 3.16 - 3.03 (m, 2 H)

\(^{13}\)C NMR (75MHz, DMSO-\(d_6\)) \( \delta = 160.9, 139.5, 138.8, 129.2, 128.1, 125.5, 124.3, 85.1, 59.5, 38.3, 37.1 \)
(3aR,3'aR,8aS,8'aS)-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole (2-10)

To a flame-dried Schlenk flask was added 268 mg (0.527 mmol) of \( N_1,N_2\)-bis((1R,2R)-2-methanesulfonate-2,3-dihydro-1H-inden-1-yl)oxalamide, 440 mg (7.90 mmol) of potassium hydroxide and 25 mL of methanol. The suspension was heated at 70 °C for 1 h. The reaction mixture was concentrated under vacuum. The residue was extracted with DCM (10 mL) and washed with \( \text{H}_2\text{O} \) (2 x 10 mL), dried over anhydrous \( \text{MgSO}_4 \), and the solvent was removed under reduced pressure to yield 156 mg (0.494 mmol, 94.0%) of (3aR,3'aR,8aS,8'aS)-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole.

\(^1\text{H} \text{NMR} \) (299 MHz, CHLOROFORM-d) \( \delta = 7.57 - 7.43 \) (m, 1 H), 7.36 - 7.12 (m, 3 H), 5.73 (d, \( J = 7.9 \) Hz, 1 H), 5.55 - 5.40 (m, 1 H), 3.54 - 3.23 (m, 2 H)

\(^{13}\text{C} \text{NMR} \) (75 MHz, CHLOROFORM-d) \( \delta = 155.3, 140.5, 139.6, 129.0, 127.6, 125.8, 125.4, 84.6, 77.2, 39.5 \)

\text{IBiox\[(R,S)-indanol\]-HOTf} \ (2-19)

IBiox[(\( R,S \))-indanol]-HOTf (2-19)

To a flame-dried Schlenk flask was added 460 mg (1.46 mmol) of (3aR,3'aR,8aS,8'aS)-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole, 449 mg (1.75 mmol) of silver
triflate and 5 mL of DCM. The reaction mixture was wrapped in aluminum foil to protect it from the light and stirred for 5 min. 306 µL (2.11 mmol) of chloromethyl pivalate was then added. The mixture was stirred at 40 °C for 16 h. It was cooled to room temperature and DCM (10 mL) followed by methanol (10 mL) were added to the flask. The suspension was filtered and concentrated under vacuum. Silicagel column chromatography with a 98:2 mixture of DCM and methanol as the eluent gave 230 mg (0.480 mmol, 32.9%) of IBiox[(R,S)-indanol]-HOTf.

\[ \begin{align*}
\text{1H NMR (299MHz, CHLOROFORM-d)} & \quad \delta = 9.38 \text{ (s, 1 H)}, 7.75 \text{ (d, } J = 7.6 \text{ Hz, 2 H)}, 7.38 - 7.15 \text{ (m, 6 H)}, 6.26 \text{ (d, } J = 6.5 \text{ Hz, 2 H)}, 6.07 - 5.97 \text{ (m, 2 H)}, 3.54 - 3.33 \text{ (m, 4 H)} \\
\text{13C NMR (75MHz, CHLOROFORM-d)} & \quad \delta = 139.9, 135.1, 131.0, 129.1, 126.2, 125.5, 125.1, 114.5, 95.4, 67.1, 38.5
\end{align*} \]

### 6.2.2 Bisimidazoline Derived NHC Ligand

\[ \text{N1,N2-bis((S)-1-chloro-3-methylbutan-2-yl)oxalamide (2-26)} \]

To a flame-dried Schlenk flask was added 100 mg (0.384 mmol) of N1,N2-bis((S)-1-hydroxy-3-methylbutan-2-yl)oxalamide, 61.3 µL (0.845 mmol) of thionyl chloride and 2 mL of toluene. The reaction mixture was stirred at 90 °C for 12 h. After cooling at room temperature, the solution was poured onto cold 20% potassium hydroxide (4 mL). The mixture was extracted with DCM (3 X 5 mL), washed with a saturated NaHCO₃ solution (10 mL) and dried over anhydrous sodium sulfate. The reaction mixture was concentrated under vacuum to yield 111 mg (0.373 mmol, 97.2%) of N1,N2-bis((S)-1-chloro-3-methylbutan-2-yl)oxalamide (2-26).
$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 7.54$ (d, $J = 9.1$ Hz, 2 H), 3.93 (ddt, $J = 4.2$, 8.2, 9.6 Hz, 2 H), 3.78 - 3.60 (m, 4 H), 2.06 (dq, $J = 6.8$, 14.8 Hz, 2 H), 0.98 (d, $J = 6.7$ Hz, 6 H), 1.02 (d, $J = 6.7$ Hz, 6 H)

(4S,4'S)-1,1'-dibenzyl-4,4'-diisopropyl-4',5',5'-tetrahydro-1H,1'H-2,2'-bimidazole (2-28)

To a flame-dried Schlenk flask was added 100 mg (0.336 mmol) of $N_1,N_2$-bis((S)-1-chloro-3-methylbutan-2-yl)oxalamide, 175 mg (0.840 mmol) of PCl$_5$ and 5 mL of toluene. The reaction mixture was stirred for 5 h at 85 °C. After cooling to room temperature, the solution was concentrated under vacuum and under inert atmosphere to give the crude imidoyl chloride as a yellow oil. 5 mL of acetonitrile and 281 µL (2.02 mmol) of Et$_3$N were added to the residue and the mixture was stirred for 5 min. 81 µL (0.730 mmol) of benzylamine was then added and the reaction mixture was stirred at reflux for 12 h. After cooling to room temperature, 25 mL of water was added. The mixture was extracted with DCM (3 X 10 mL), and dried over anhydrous sodium sulfate. The reaction mixture was concentrated under vacuum. Silicagel column chromatography with a 95:5 mixture of ethyl acetate and methanol as the eluent gave 54 mg (0.134 mmol, 40%) of (4S,4'S)-1,1'-dibenzyl-4,4'-diisopropyl-4',5',5'-tetrahydro-1H,1'H-2,2'-bimidazole.
1H NMR (300MHz, CHLOROFORM-d) \( \delta = 7.44 - 7.12 \text{ (m, 10 H)}, 4.67 - 4.40 \text{ (m, 4 H)}, \\
3.87 \text{ (td, } J = 6.7, 10.4 \text{ Hz, 2 H)}, 3.33 \text{ (dd, } J = 9.4, 10.8 \text{ Hz, 2 H)}, 2.92 \text{ (t, } J = 9.7 \text{ Hz, 2 H)}, \\
1.75 \text{ (dq, } J = 6.7, 13.3 \text{ Hz, 2 H)}, 0.94 \text{ (d, } J = 6.7 \text{ Hz, 6 H)}, 0.84 \text{ (d, } J = 6.7 \text{ Hz, 6 H)}

13C NMR (75MHz, CHLOROFORM-d) \( \delta = 156.5, 137.9, 128.8, 128.1, 127.6, 71.5, 52.4, \\
51.6, 33.5, 19.4, 18.9 \\
(4S,4'S)-4,4'-diisopropyl-1,1'-diphenyl-4,4',5,5'-tetrahydro-1H,1'H-2,2'-biimidazole

(2-29)

To a flame-dried Schlenk flask was added 313 mg (1.05 mmol) of \( N1,N2 \)-bis((S)-1-chloro-3-methylbutan-2-yl)oxalamide, 550 mg (2.63 mmol) of \( \text{PCl}_5 \) and 15 mL of toluene. The reaction mixture was stirred for 5 h at 85 °C. After cooling to room temperature, the solution was concentrated under vacuum and under inert atmosphere to give the crude imidoyl chloride as a yellow oil. 15 mL of acetonitrile and 880 µL (6.32 mmol) of \( \text{Et}_3\text{N} \) were added to the residue and the mixture was stirred for 5 min. 215 µL (2.32 mmol) of aniline was then added and the reaction mixture was stirred at reflux for 12 h. After cooling to room temperature, 75 mL of water was added. The mixture was extracted with DCM (3 X 30 mL), and dried over anhydrous sodium sulfate. The reaction mixture was concentrated under vacuum. Silicagel column chromatography with ethyl acetate as the eluent gave 70 mg (0.187 mmol, 17.7%) of (4S,4'S)-4,4'-diisopropyl-1,1'-diphenyl-4,4',5,5'-tetrahydro-1H,1'H-2,2'-biimidazole.
$^1$H NMR (299MHz, CHLOROFORM-d) δ = 7.71 - 7.58 (m, 4 H), 7.50 (d, J = 7.1 Hz, 2 H), 7.29 - 7.18 (m, 4 H), 4.71 - 4.53 (m, J = 11.3 Hz, 1 H), 4.24 (t, J = 9.5 Hz, 2 H), 4.12 (dd, J = 9.2, 11.5 Hz, 2 H), 2.65 - 2.48 (m, 1 H), 1.70 (d, J = 6.8 Hz, 6 H), 1.61 (d, J = 6.5 Hz, 6 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) δ = 153.6, 139.9, 128.4, 123.3, 119.5, 71.2, 53.8, 32.9, 19.6, 19.1, 1.2

6.2.3 Biisoquinoline Derived NHC Ligand

$(S)$-2-isobutyl-1-tosylaziridine (2-47).

To a flame-dried Schlenk flask was added 4.60 g (39.2 mmol) of $(S)$-2-amino-4-methylpentan-1-ol 2-43, 22.0 mL (157 mmol) of triethylamine and 50 mL of CH$_2$Cl$_2$. The reaction mixture was cooled to -25 °C, and 8.40 g (44.0 mmol) of p-toluenesulfonyl chloride was added. The cooled mixture was stirred for 2 h at -30 °C and then for 1 h at room temperature. The stirred mixture was cooled to -25 °C, and 3.20 mL (41.5 mmol) of methanesulfonyl chloride was added. After stirring for 2 h at -30 °C, the reaction mixture was stirred for 10 h at room temperature. The reaction solution was washed with 200 mL of 1 M aqueous HCl solution and then 100 mL of a saturated NaHCO$_3$ solution. The organic solution was dried over anhydrous MgSO$_4$, and the solvent was removed under reduced pressure. Silicagel column chromatography with a 6:1 solution of hexane and ethyl acetate as the eluent afforded 8.00 g (31.6 mmol, 80.5%) of 2-47.

$(S)$-2-isopropyl-1-tosylaziridine (2-46)
6.50 g (27.2 mmol, 79.4 %) of 2-46 was obtained from 3.50 g (34.0 mmol) of (S)-2-amino-3-methylbutan-1-ol 2-43.

(S)-4-methyl-1-phenylpentan-2-amine (2-55).

To a flame-dried Schlenk flask was added 1.90 g (10.0 mmol) of CuI and 20 mL of THF. The reaction mixture was cooled to -30 °C, and 33.0 mL of PhMgCl solution (2.0 M in THF) was slowly added. After 30 min stirring at -30 °C, 8.00 g (31.6 mmol) of 2-47 was added, and the reaction temperature was slowly increased to room temperature. After 3 h, the reaction was cautiously quenched by 50 mL of a saturated NH₄Cl aqueous solution. The organic layer was separated and dried over anhydrous MgSO₄. All volatiles were removed in vacuo. Silicagel column chromatography with a 3:1 mixture of hexane and ethyl acetate as the eluent gave 8.60 g (25.9 mmol, 82.1 %) of 2-51.

To a flame-dried Schlenk flask was added 1.45 g (210.0 mmol) of Li and 30 mL of THF. To the reaction mixture was added 0.190 g of naphthalene at room temperature. After 30 min, the solution turned dark blue. 5.50 g (16.6 mmol) of (S)-4-methyl-N-(4-methyl-1-phenylpentan-2-yl) benzenesulfonamide 2-51 was added at -78 °C, and the reaction temperature was slowly warmed to room temperature. After 12 h, the solution was transferred through a canula to another flask to remove the unreacted Li. The solution was quenched by a saturated NH₄Cl solution and rinsed with water. To the organic solution was added 30 mL of 1 M HCl aqueous...
solution, and the organic layer was discarded. To the acidic aqueous solution was added 20 mL of 20% NaOH aqueous solution. Crude 2-55 was extracted by 60 mL of Et₂O and dried over anhydrous MgSO₄. Evaporation of the solvent gave 2.80 g (15.8 mmol, 95.1%) of 2-55.

(R)-3-methyl-1-phenylbutan-2-amine (2-54).

1.40 g (8.60 mmol, 83%) of 2-54 was obtained from 2.50 g (10.4 mmol) of 2-46.

(S)-1-cyclohexyl-3-phenylpropan-2-amine (2-57)

600 mg (2.76 mmol, 57%) of (S)-1-cyclohexyl-3-phenylpropan-2-amine was obtained from 1.42g (4.84 mmol) of (S)-2-(cyclohexylmethyl)-1-tosylaziridine.

¹H NMR (300MHz, CHLOROFORM-d) δ = 7.39 - 7.02 (m, 5 H), 3.10 (br. s., 1 H), 2.78 (dd, J = 4.3, 13.3 Hz, 1 H), 2.41 (dd, J = 8.8, 13.5 Hz, 1 H), 1.80 - 1.62 (m, 4 H), 1.34 - 1.04 (m, 7 H), 1.04 - 0.76 (m, 2 H)

¹³C NMR (75MHz, CHLOROFORM-d) δ = 140.0, 129.5, 128.6, 126.3, 49.9, 45.9, 45.5, 34.7, 34.4, 33.2, 26.9, 26.6, 26.5

(S)-1-cyclohexyl-2-phenylethanamine (2-62)

A flame-dried Schlenk flask was charged with 6.20 g (45.0 mmol) of (S)-2-amino-2-phenylethanol 2-59, 9.00 g of MgSO₄ and 50 mL of CH₂Cl₂. To the reaction mixture was added
5.00 mL (42.0 mmol) of cyclohexyl carboxaldehyde at room temperature. After stirring for 2 h, the reaction mixture was filtered through a pad of celite. All volatiles were removed in vacuo. To another flame-dried schlenk flask was added the filtrate and 20 ml of THF. 100 mL of benzylmagnesium chloride solution (2.0 M in THF) was added to the reaction flask at -30 °C. The reaction mixture was slowly warmed to room temperature, and stirred for 4 h. The reaction was quenched with 50 mL of a saturated NH₄Cl solution, and the organic layer was separated and dried over anhydrous MgSO₄. After removal of the solvent under reduced pressure, silicagel column chromatography with a 4:1 mixture of hexane and ethyl acetate as the eluent gave 9.70 g (29.9 mmol, 66.4 %) of (S)-2-((S)-1-cyclohexyl-2-phenylethlamino)-2-phenylethanol 2-61.

A mixture of 9.70 g (29.9 mmol) of 2-61, 2.50 g of 10% Pd/C in 100 mL of ethanol was stirred at 75 °C for 48 h under 800 psi pressure of H₂. The reaction solution was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silicagel column chromatography using 5 % MeOH solution in CH₂Cl₂ as the eluent to give 3.66 g (18.0 mmol, 60.2%) of 2-62.

*trans*-2-phenylcyclohexanol (rac-2-67)

To a cooled (0 °C), magnetically stirred solution of PhMgBr (89.0 mL, 89.0 mmol) and 40 mL of THF, 5.64 g (29.65 mmol) of CuI was added under argon followed by dropwise addition of a solution of 5.0 mL (49.4 mmol) of cyclohexene oxide in 30 mL of THF. The reaction mixture was stirred at room temperature for 12 h. A saturated solution of ammonium chloride (20 mL) was slowly added and the mixture was extracted with diethyl ether (3 X 30mL), dried with MgSO₄ and concentrated under vacuum. The residue was purified by flash column
chromatography (silica gel, 1:4 ethyl acetate/hexane) to afford 7.90 g (44.8 mmol, 90.7%) of trans-2-phenylcyclohexanol.  

\begin{center}
\textbf{(1S,2R)-2-phenylcyclohexanol (1S,2R-2-67)}
\end{center}

To a flame-dried pressur vessel was added 2.00 g (11.4 mmol) of trans-2-phenylcyclohexanol, 5.3 mL (57.1 mmol) of vinyl acetate, 2.5 g of CALB and 57 mL of tBuOMe. The reaction mixture was heated at 45 °C and stirred for 2 d. The enzyme CALB was filtered off and could be reused while the solution was concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 2.5:97.5 ethyl acetate/hexane) to afford 720 mg (4.11 mmol, 71.8% yield, 99.4% ee) of (1S,2R)-2-phenylcyclohexanol.  

\begin{center}
\textbf{2-((1R,2R)-2-phenylcyclohexyl)isoindoline-1,3-dione (2-68)}
\end{center}

To a flame-dried Schlenk flask was added 500 mg (2.85 mmol) of (1S,2R)-2-phenylcyclohexanol, 630 mg (4.28 mmol) of phthalimide, 1.12 g (4.28 mmol) of PPh$_3$, 876 µL (4.42 mmol) of DIAD and 10 mL (0.3M) of THF. The reaction mixture was stirred at room temperature for 12 h and concentrated under vacuum. Silicagel column chromatography with a 97.5:2.5 mixture of hexane and ethyl acetate as the eluent gave 634 mg (2.08 mmol, 72.8%) of 2-((1R,2R)-2-phenylcyclohexyl)isoindoline-1,3-dione.
(1R,2R)-2-phenylcyclohexanamine (2-65)

To a flame dried Schlenk flask was added 585 mg (1.916 mmol) of 2-((1R,2R)-2-phenylcyclohexyl)isoindoline-1,3-dione, 642 µL (9.58 mmol) of ethylene diamine and 10 mL of ethanol. The reaction mixture was stirred at 90 °C for 12 h. The suspension was filtered and the solution was concentrated under reduced pressure. The residue was diluted in Et₂O (20 mL) and to the resulting organic solution was added 15 mL of 1 M HCl aqueous solution, and the organic layer was discarded. To the acidic aqueous solution was added 20 mL of 20% NaOH aqueous solution. The latter was extracted by 60 mL of Et₂O and dried over anhydrous MgSO₄. Evaporation of the solvent gave 275 mg (1.57 mmol, 82.2%) of (1R,2R)-2-phenylcyclohexanamine.

$^1$H NMR (300MHz, CHLOROFORM-d) δ = 7.44 - 7.04 (m, 5 H), 3.66 (td, J = 4.5, 10.0 Hz, 1 H), 2.49 - 2.38 (m, 1 H), 2.18 - 2.05 (m, 1 H), 1.92 - 1.72 (m, 3 H), 1.62 - 1.35 (m, 4 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) δ = 143.5, 129.0, 128.1, 127.0, 74.6, 53.4, 34.7, 33.5, 26.3, 25.3

(2R,3R)-2,3-diphenyl-1-tosylaziridine (2-80)

To a flame dried Schlenk flask was added 500 mg (1.36 mmol) of N-((1R,2S)-2-hydroxy-1,2-diphenylethyl)-4-methylbenzenesulfonamide, 535 mg (2.04 mmol) of PPh₃, 416 µL (2.10 mmol) of DIAD and 10 mL of THF. The reaction mixture was stirred at room temperature for 12 h. The suspension was concentrated under vacuum. Silicalgel chromatography with a 5:1
mixture of hexane and ethyl acetate as eluent gave 400 mg (1.14 mmol, 84.2% yield) of
(2R,3R)-2,3-diphenyl-1-tosylaziridine.

$^1$H NMR (300MHz,CHLOROFORM-d) $\delta$ = 7.63 (d, $J$ = 8.5 Hz, 1 H), 7.47 - 7.31 (m, 10
H), 7.20 (d, $J$ = 8.2 Hz, 1 H), 4.27 (s, 2 H), 2.39 (s, 3 H)

(4R,5S)-4,5-diphenyloxazolidin-2-one (2-81)

To a flame dried Schlenk flask was added 2.00 g (9.38 mmol) of (1S,2R)-2-amino-1,2-
diphenylethanol, 152 mg (2.80 mmol) of sodium methoxide and 36 mL (300 mmol) of diethyl
carbonate. The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was
concentrated under vacuum and the solid was washed with hexane (2 X 40 mL) to yield 2.24 g
(9.377 mmol, 99%) of (4R,5S)-4,5-diphenyloxazolidin-2-one.

$^1$H NMR (299MHz,CHLOROFORM-d) $\delta$ = 7.23 - 7.01 (m, 6 H), 7.01 - 6.80 (m, 4 H),
5.94 (d, $J$ = 8.2 Hz, 1 H), 5.64 (br. s., 1 H), 5.17 (d, $J$ = 8.2 Hz, 1 H)

$^{13}$C NMR (75MHz,CHLOROFORM-d) $\delta$ = 151.9, 128.5, 128.3, 128.1, 127.1, 126.3, 82.5,
61.7

(S)-1,2-diphenylethanamine (1-46)

7.83 g (32.7 mmol) of (4R,5S)-4,5-diphenyloxazolidin-2-one, 2.3g of 10% Pd/C and 175
mL of methanol were stirred at room temperature for 60 h under 400 psi pressure of H$_2$. The
reaction solution was filtered through a pad of celite, and the filtrate was concentrated under
reduced pressure. The residue was diluted in Et$_2$O (20 mL) and to the resulting organic solution was added 15 mL of 1 M HCl aqueous solution, and the organic layer was discarded. To the acidic aqueous solution was added 20 mL of 20 % NaOH aqueous solution. The latter was extracted by 60 mL of Et$_2$O and dried over anhydrous MgSO$_4$. Evaporation of the solvent gave 4.20 g (21.3 mmol, 65%) of (S)-1,2-diphenylethanamine.

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 7.44 - 7.19$ (m, 10 H), 4.23 (dd, $J = 4.9$, 8.8 Hz, 1 H), 3.06 (dd, $J = 5.0$, 13.4 Hz, 1 H), 2.87 (dd, $J = 8.9$, 13.3 Hz, 1 H), 1.50 (br. s., 2 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 146.0$, 139.4, 129.7, 128.7, 127.4, 126.7, 126.7, 57.9, 46.8

(S)-1-(4-methoxyphenyl)-4-methylpentan-2-amine (2-138)

82 mg (0.395 mmol, 48.2%) of (S)-1-(4-methoxyphenyl)-4-methylpentan-2-amine was obtained from 208 mg (0.825 mmol) of (S)-2-isobutyl-1-tosylaziridine.

$^1$H NMR (299MHz ,CHLOROFORM-d) $\delta = 7.17 - 6.99$ (m, $J = 8.5$ Hz, 2 H), 6.89 - 6.72 (m, $J = 8.5$ Hz, 2 H), 3.76 (s, 3 H), 3.00 (br. s., 1 H), 2.70 (dd, $J = 4.5$, 13.6 Hz, 1 H), 2.48 - 2.26 (m, 1 H), 1.74 (tt, $J = 6.5$, 13.4 Hz, 1 H), 1.24 (t, $J = 6.9$ Hz, 2 H), 0.86 (d, $J = 6.5$ Hz, 3 H), 0.90 (d, $J = 6.8$ Hz, 3 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 158.3$, 131.8, 130.4, 114.0, 55.5, 50.7, 47.1, 44.2, 25.0, 23.7, 22.2

(S)-1-(3,5-dimethoxyphenyl)-4-methylpentan-2-amine (2-143)
163 mg (0.686 mmol, 43.2%) of (S)-1-(3,5-dimethoxyphenyl)-4-methylpentan-2-amine was obtained from 75 mg (0.296 mmol) of (S)-2-isobutyl-1-tosylaziridine

\[ \text{\( ^1\text{H NMR (299MHz ,CHLOROFORM-d) \( \delta = 6.44 - 6.19 \text{ (m, 3 H)}, 3.76 \text{ (s, 6 H)}, 3.10 - 2.97 \text{ (m, 1 H)}, 2.72 \text{ (dd, } J = 4.2, 13.3 \text{ Hz, 1 H)}, 2.39 - 2.23 \text{ (m, 1 H)}, 1.74 \text{ (dt, } J = 6.8, 13.9 \text{ Hz, 1 H)}, 1.31 - 1.22 \text{ (m, 2 H)}, 0.88 \text{ (d, } J = 6.5 \text{ Hz, 3 H)}, 0.92 \text{ (d, } J = 6.5 \text{ Hz, 3 H)} \) \} \]

\[ \text{\( ^13\text{C NMR (75MHz ,CHLOROFORM-d) \( \delta = 161.0, 142.3, 107.5, 98.3, 55.5, 50.4, 47.3, 45.6, 25.1, 23.6, 22.3 \) \) \} \]

\[ N_1, N_2\text{-bis((S)-4-methyl-1-phenylpentan-2yl)oxalamide (2-90).} \]

In a flame-dried schlenk flask, 2.60 g (14.7 mmol) of 2-55 and 0.82 mL (6.00 mmol) of diethyl oxalate were stirred at 120 °C for 12h under Ar. After cooling to room temperature, the solid residue was purified by column chromatography using silicagel (CH\text{\textsubscript{2}}Cl\text{\textsubscript{2}}) to afford 1.13 g (2.77 mmol, 46.2 %) of 2-90.

\[ \text{\( ^1\text{H NMR (300 MHz, CDCl}_3\) \( \delta ppm 7.31 - 7.12 \text{ (m, 12H)}, 4.18 \text{ (m, 2H)}, 2.79 \text{ (d, } J = 4.8 \text{ Hz, 2H)}, 2.77 \text{ (d, } J = 4.8 \text{ Hz, 2H)}, 1.59 \text{ (m, 2H)}, 1.34 \text{ (m, 4H)}, 0.88 \text{ (d, } J = 6.6 \text{ Hz, 6H)}, 0.87 \text{ (d, } J = 6.6 \text{ Hz, 6H)} \) \} \]

152
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 159.44, 137.65, 129.64, 128.64, 126.75, 49.38, 43.41, 41.65, 25.03, 23.36, 22.06

HRMS Calcd. for C\(_{26}\)H\(_{37}\)N\(_2\)O\(_2\) [M+H]\(^+\): 409.2850, Found: 409.2826

\([\alpha]_D^{24}\) -27.7° (c 2.76, CHCl\(_3\))

\(\text{N1, N2-bis((R)-3-methyl-1-phenylbutan-2yl)oxalamide (2-86).}\)

0.88 g (2.30 mmol, 80.0 %) of 2-86 was obtained from 0.988 g (6.05 mmol) of 2-54 and 0.394 ml (2.88 mmol) of diethyl oxalate.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.28 – 7.12 (m, 12H), 3.98 (m, 2H), 2.85 (dd, \(J = 5.8, 14.2\) Hz, 2H), 2.67 (dd, \(J = 8.4, 14.1\) Hz, 2H), 1.80 (m, 2H), 0.96 (d, \(J = 7.2\) Hz, 6H), 0.94 (d, \(J = 6.9\) Hz, 6H)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 159.66, 138.18, 129.31, 128.64, 126.64, 56.60, 38.47, 31.02, 19.85, 17.62

HRMS Calcd. for C\(_{24}\)H\(_{33}\)N\(_2\)O\(_2\) [M+H]\(^+\): 381.2537, Found: 381.2518

\([\alpha]_D^{25}\) +16.5 (c 2.71, CHCl\(_3\))

\(\text{N1, N2-bis((S)-1-cyclohexyl-2-phenylethyl)oxalamide (2-87).}\)

153
To a cooled, magnetically stirred solution of 2-62 (0.458 g, 2.25 mmol) and triethylamine (0.350 mL, 2.53 mmol) in THF (28 mL) under argon, oxalyl chloride (0.096 mL, 1.09 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was then stirred for 12 h. The reaction mixture was cooled to 0 °C before quenching with water (10 mL). The mixture was extracted with CHCl₃ (3 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3:1 chloroform/hexane) to afford 2-87 (0.349 g, 0.778 mmol, 70.7% yield).

¹H NMR (300 MHz, CDCl₃) δ ppm 7.27 – 7.09 (m, 12H), 3.95 (m, 2H), 2.88 (dd, J = 5.6, 14.0 Hz, 2H), 2.66 (dd, J = 8.3, 14.0 Hz, 2H), 1.78 – 1.58 (m, 10H), 1.44 (m, 2H), 1.24 – 1.02 (m, 10H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 159.54, 138.20, 129.34, 128.61, 126.59, 56.05, 40.98, 38.15, 30.31, 28.28, 26.45, 26.29, 26.24

HRMS Calcd. for C₃₀H₄₁N₂O₂ [M+H]⁺: 461.3163, Found: 461.3164

[α]D²⁴ -24.4 (c 4.78, CHCl₃)

N₁,N₂-bis((S)-1-cyclohexyl-3-phenylpropan-2-yl)oxalamide (2-91)
90 mg (0.184 mmol, 91.1%) of \(N_1,N_2\)-bis((\(S\))-1-cyclohexyl-3-phenylpropan-2-yl)oxalamide was obtained from 90 mg (0.414 mmol) of (\(S\))-1-cyclohexyl-3-phenylpropan-2-amine, 65 \(\mu\)L (0.460 mmol) of Et\(_3\)N, 17.6 \(\mu\)L (0.202 mmol) of oxalyl chloride and 4 mL of THF.

\([\text{H} \text{NMR (300MHz ,CHLOROFORM-d)} \delta = 7.33 - 7.10 \text{ (m, 11 H), 4.32 - 4.11 (m, 2 H), 2.78 (d, } J = 6.4 \text{ Hz, 4 H), 1.89 - 1.49 (m, 11 H), 1.43 - 1.05 (m, 11 H), 1.01 - 0.63 (m, 4 H)\)]

\([\text{C} \text{NMR (75MHz ,CHLOROFORM-d)} \delta = 159.4, 137.7, 129.6, 128.6, 126.7, 48.7, 41.9, 41.6, 34.5, 34.0, 32.8, 26.7, 26.4, 26.3\)]

\(N_1,N_2\)-bis((\(1R,2R\))-2-phenylcyclohexyl)oxalamide (2-89)

260 mg (0.642 mmol, 91.0%) of \(N_1,N_2\)-bis((\(1R,2R\))-2-phenylcyclohexyl)oxalamide was obtained from 255 mg (1.45 mmol) of (\(1R,2R\))-2-phenylcyclohexanamine, 216 \(\mu\)L (1.56 mmol) of Et\(_3\)N, 62 \(\mu\)L (0.709 mmol) of oxalyl chloride and 3 mL of THF.

\([\text{H} \text{NMR (300MHz ,CHLOROFORM-d)} \delta = 7.50 \text{ (d, } J = 9.1 \text{ Hz, 2 H), 7.37 - 6.99 (m, 10 H), 4.27 (dq, } J = 3.1, 9.4 \text{ Hz, 2 H), 2.93 (dt, } J = 3.9, 11.9 \text{ Hz, 2 H), 2.02 - 1.63 (m, 12 H), 1.53 - 1.38 (m, 4 H)\)]

\([\text{C} \text{NMR (75MHz ,CHLOROFORM-d)} \delta = 159.1, 142.7, 128.5, 127.5, 126.7, 50.5, 45.8, 31.1, 25.8, 25.7, 20.6\)]
**N1,N2-bis((S)-1,2-diphenylethyl)oxalamide (2-88)**

![Chemical Structure](image1)

320 mg (0.713 mmol, 68.8%) of N1,N2-bis((S)-1,2-diphenylethyl)oxalamide was obtained from 419 mg (2.13 mmol) of (S)-1,2-diphenylethanamine, 330 µL (2.39 mmol) of Et₃N, 90.0 µL (1.037 mmol) of oxalyl chloride and 15 mL of THF.

**1H NMR (300MHz ,CHLOROFORM-d)**

δ = 7.76 (d, J = 8.2 Hz, 2 H), 7.34 - 7.11 (m, 16 H), 7.08 - 6.95 (m, 4 H), 5.12 (q, J = 7.4 Hz, 2 H), 3.11 (d, J = 7.0 Hz, 4 H)

**13C NMR (75MHz ,CHLOROFORM-d)**

δ = 159.0, 140.5, 136.9, 129.5, 128.8, 128.7, 127.9, 127.0, 126.8, 55.5, 42.8

**N1,N2-bis((S)-1-(4-methoxyphenyl)-4-methylpentan-2-yl)oxalamide (2-139)**

![Chemical Structure](image2)

480 mg (1.02 mmol, 87.1%) of N1,N2-bis((S)-1-(4-methoxyphenyl)-4-methylpentan-2-yl)oxalamide was obtained from 512 mg (2.47 mmol) of (S)-1-(4-methoxyphenyl)-4-methylpentan-2-amine, 375 µL (2.76 mmol) of Et₃N, 102 µL (1.18 mmol) of oxalyl chloride and 8 mL of THF.
$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 7.19$ (d, $J = 9.7$ Hz, 2 H), 7.07 - 6.99 (m, 4 H), 6.84 - 6.78 (m, 4 H), 4.13 (tq, $J = 6.1$, 9.1 Hz, 2 H), 3.76 (s, 6 H), 2.75 - 2.66 (m, 4 H), 1.65 - 1.51 (m, 2 H), 1.38 - 1.22 (m, 4 H), 0.86 (d, $J = 5.0$ Hz, 6 H), 0.84 (d, $J = 4.7$ Hz, 6 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 159.5, 158.5, 130.6, 129.6, 114.0, 55.4, 49.4, 43.3, 40.7, 25.0, 23.4, 22.1$

$N_1,N_2$-bis((S)-1-(3,5-dimethoxyphenyl)-4-methylpentan-2-yl)oxalamide (2-144)

96.8 mg (0.183 mmol, 56.0%) of $N_1,N_2$-bis((S)-1-(3,5-dimethoxyphenyl)-4-methylpentan-2-yl)oxalamide was obtained from 163 mg (0.686 mmol) of (S)-1-(3,5-dimethoxyphenyl)-4-methylpentan-2-amine, 105 µL (0.751 mmol) of Et$_3$N, 28.8 µL (0.327 mmol) of oxalyl chloride and 4 mL of THF.

$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 7.23$ (d, $J = 9.7$ Hz, 2 H), 6.34 - 6.26 (m, 6 H), 4.26 - 4.08 (m, 2 H), 3.74 (s, 12 H), 2.79 - 2.62 (m, 2 H), 1.67 - 1.50 (m, 2 H), 1.32 (ddd, $J = 2.6, 5.5, 8.6$ Hz, 4 H), 0.87 (d, $J = 5.0$ Hz, 6 H), 0.84 (d, $J = 4.7$ Hz, 6 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 161.0, 159.5, 139.9, 107.5, 99.0, 55.5, 49.2, 43.2, 41.9, 25.0, 23.4, 22.0$

$(3S, 3'S)$-3,3'-diisobutyl-3,3’,4,4’-tetrahydro-1,1'-biisoquinoline (2-96).
To a flame dried schlenk flask was added 1.20 g (2.94 mmol) of 2-90 and 30 mL of toluene. To this flask under nitrogen atmosphere was added 3.20 g (8.80 mmol) of Zn(OTf)$_2$ and 3.70 g (18.0 mmol) of PCl$_5$. The reaction mixture was heated at 85 °C for 12 h. After cooling to room temperature, the reaction was quenched with 20mL of 30% aqueous ammonium hydroxide solution. The solution was diluted with 100 mL of diethyl ether. The organic layer was separated and dried over anhydrous MgSO$_4$. After all volatiles were evaporated under reduced pressure, 0.930 g (2.50 mmol, 85.0 %) of 2-96 was purified by silicagel column chromatography with a 7:1 mixture of hexane and ethyl acetate as the eluent.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.35 – 7.14 (m, 8H), 3.84 (m, 2H), 2.93 (dd, $J = 5.4$, 15.9 Hz, 2H), 2.65 (dd, $J = 11.2$, 15.9 Hz, 2H), 1.98 – 1.79 (m, 4H), 1.53 (m, 2H), 0.97 (d, $J = 6.0$ Hz, 6H), 0.95 (d, $J = 6.6$ Hz, 6H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 164.06, 137.51, 131.13, 128.67, 128.03, 127.08, 126.98, 55.28, 44.99, 31.59, 25.08, 23.39, 22.60

HRMS Calcd. for C$_{26}$H$_{32}$N$_2$ [M$^+$]: 372.2560, Found: 372.2581

[$\alpha$]$_D^{23}$ -72.7 (c 1.73, CHCl$_3$)

(3R, 3’R)-3,3’-diisopropyl-3,3’,4,4’-tetrahydro-1,1’-biisoquinoline (2-97).
2.10 g (6.10 mmol, 82.7%) of 2-97 was obtained from 2.81 g (7.38 mmol) of 2-86, 8.1 g (22.3 mmol) of Zn(OTf)₂ and 9.2 g (44.2 mmol) of PCl₅.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.33 – 7.13 (m, 8H), 3.48 (m, 2H), 2.78 – 2.74 (m, 4H), 2.23 (m, 2H), 1.13 (d, J = 6.9 Hz, 6H), 1.08 (d, J = 6.6 Hz, 6H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 164.15, 138.26, 131.00, 128.68, 127.98, 126.98, 126.87, 62.81, 33.07, 27.62, 19.94, 19.02

HRMS Calcd. for C₂₄H₂₈N₂ [M⁺]: 344.2247, Found: 344.2213

[α]D²⁵ +32.4 (c 2.43, CHCl₃)

(3S,3’S)-3,3’-dicyclohexyl-3,3’,4,4’-tetrahydro-1,1′-biisoquinoline (2-98).

0.357 g (0.841 mmol, 60.9%) of 2-98 was obtained from 0.619 g (1.38 mmol) of 2-87.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.26 – 7.05 (m, 8H), 3.40 (m, 2H), 2.69 (m, 4H), 1.93 – 1.54 (m, 12H), 1.29 – 1.09 (m, 10H)

¹³C NMR (75 MHz, CDCl₃), δ ppm 163.86, 138.16, 130.85, 128.47, 127.79, 62.03, 42.92, 30.35, 29.18, 27.88, 26.81, 26.70, 26.57
HRMS Calcd. for C_{30}H_{37}N_{2} [M+H]^+: 425.2951, Found: 425.2957

[\alpha]_D^{24} +6.2^\circ (c 2.64, CHCl_3)

(3S,3'S)-3,3'-bis(cyclohexylmethyl)-3,3',4,4'-tetrahydro-1,1'-biisoquinoline (2-101)

380 mg (0.839 mmol, 91.0%) of (3S,3'S)-3,3'-bis(cyclohexylmethyl)-3,3',4,4'-tetrahydro-1,1'-biisoquinoline was obtained from 450 mg (0.921 mmol) of N1,N2-bis((S)-1-cyclohexyl-3-phenylpropan-2-yl)oxalamide, 1.15 g (5.52 mmol) of PCl_5, 1.00 g (2.76 mmol) of Zn(OTf)_2 and 45 mL of toluene.

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 7.44$ - 7.04 (m, 8 H), 3.98 - 3.75 (m, 2 H),
2.93 (dd, $J = 5.6$, 15.8 Hz, 2 H), 2.64 (dd, $J = 11.1$, 15.8 Hz, 2 H), 1.98 - 1.48 (m, 16 H), 1.38 - 1.06 (m, 6 H), 1.06 - 0.75 (m, 4 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 164.0$, 137.5, 131.1, 128.6, 128.0, 127.1,
126.9, 54.5, 43.5, 34.6, 34.1, 33.3, 31.6, 26.9, 26.6

(3S,3'S)-3,3'-diisobutyl-7,7'-dimethoxy-3,3',4,4'-tetrahydro-1,1'-biisoquinoline (2-140)
To a flame dried schlenk flask was added 105 mg (0.224 mmol) of \textit{N}1,\textit{N}2-bis((\textit{S})-1-(4-methoxyphenyl)-4-methylpentan-2-yl)oxalamide and 4 mL of toluene. To this flask under argon atmosphere was added 82 mg (0.672 mmol) of DMAP and 186 µL (1.34 mmol) of Tf\textsubscript{2}O. The reaction mixture was heated at 95 °C for 12 h. After cooling to room temperature, the reaction was quenched with 10mL of a saturated solution of sodium carbonate. The solution was diluted with 20 mL of DCM. The organic layer was separated and dried over anhydrous MgSO\textsubscript{4}. After all volatiles were evaporated under reduced pressure, 38.0 mg (0.0878 mmol, 39.2 %) of (3\textit{S},3'\textit{S})-3,3'-diisobutyl-7,7'-dimethoxy-3,3',4,4'-tetrahydro-1,1'-biisoquinoline was purified by silicagel column chromatography with a 99:1 mixture of DCM and methanol as the eluent.

\textsuperscript{1}H NMR (300MHz ,CHLOROFORM-d) δ = 7.12 - 7.06 (m, 2 H), 6.94 - 6.81 (m, 4 H), 3.85 - 3.75 (m, 2 H), 3.67 (s, 6 H), 2.84 (dd, \textit{J} = 5.4, 15.7 Hz, 2 H), 2.55 (dd, \textit{J} = 11.1, 15.5 Hz, 2 H), 2.00 - 1.85 (m, 2 H), 1.79 (dt, \textit{J} = 7.1, 13.7 Hz, 2 H), 1.48 (ddd, \textit{J} = 6.6, 7.5, 13.5 Hz, 2 H), 0.92 (d, \textit{J} = 3.5 Hz, 6 H), 0.94 (d, \textit{J} = 3.5 Hz, 6 H)

\textsuperscript{13}C NMR (75MHz ,CHLOROFORM-d) δ = 163.7, 158.4, 129.6, 129.2, 128.8, 116.8, 112.6, 55.6, 55.5, 44.9, 30.7, 25.0, 23.3, 22.6

(3\textit{S},3'\textit{S})-3,3'-diisobutyl-6,6',8,8'-tetramethoxy-3,3',4,4'-tetrahydro-1,1'-biisoquinoline (2-145)
144 mg (0.292 mmol, 86.9%) of (3S,3'S)-3,3'-diisobutyl-5,6',8,8'-tetramethoxy-3,3',4,4'-tetrahydro-1,1'-biisoquinoline was obtained from 177 mg (0.336 mmol) of N1,N2-bis((S)-1-(3,5-dimethoxyphenyl)-4-methylpentan-2-yl)oxalamide, 246 mg (2.02 mmol) of DMAP, 470 µL (3.36 mmol) of Tf2O and 17 mL of toluene.

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 6.29$ (s, 2 H), 6.15 - 6.04 (m, 2 H), 3.85 - 3.67 (m, 8 H), 3.35 - 3.27 (m, 6 H), 2.74 (dd, $J = 4.5$, 15.4 Hz, 2 H), 2.41 (dd, $J = 11.7$, 15.2 Hz, 2 H), 1.89 - 1.74 (m, 4 H), 1.51 - 1.37 (m, 2 H), 0.90 (t, $J = 6.2$ Hz, 12 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 164.4$, 161.8, 157.9, 142.4, 113.4, 104.7, 97.0, 55.5, 55.1, 54.2, 44.5, 32.9, 25.0, 23.6, 22.5

[6(S),8(S)-Diisobutyl-5,6,8,9-tetrahydro-6a,7a-diaza dibenzo[c,g]fluorenium] chloride (2-104)

A flame dried Schlenk flask was charged with 0.250 g (0.670 mmol) of 2-96, 0.140 mL (1.49 mmol) of chloromethyl ethyl ether and 3 mL of THF. After 12 h, all volatiles were evaporated in vacuo. The sticky residue was purified by silicagel column chromatography with a 10:1 mixture of CH2Cl2 and methanol as the eluent to afford 0.260 g (0.619 mmol, 92.4%) of 2-104.

$^1$H NMR (300 MHz, CDCl3) $\delta$ ppm 11.22 (s, 1H), 7.94 (d, $J = 8.1$ Hz, 2H), 7.43 – 7.31 (m, 6H), 5.21 (m, 2H), 3.42 (m, 2H), 3.01 (d, $J = 15.9$ Hz, 2H), 1.59 (m, 4H), 1.28 (m, 2H), 0.96 (d, $J = 6.3$ Hz, 6H), 0.94 (d, $J = 6.3$ Hz, 6H)
\(^{13}\text{C} \text{NMR} (75 \text{ MHz}, \text{CDCl}_3) \ \delta \ \text{ppm} \ 135.33, 132.20, 130.76, 130.18, 127.95, 124.55, \\
124.06, 53.60, 41.36, 33.15, 25.08, 23.22, 22.12

\text{HRMS Calcd. for } C_{27}H_{33}N_2 [M-\text{Cl}]^+: 385.2638, \text{ Found: } 385.2637

\left[\alpha\right]_{D}^{24} -290.5 \ (c \ 1.38, \text{CHCl}_3)

\text{[6(R),8(R)-Diisopropyl-5,6,8,9-tetrahydro-6a,7a-diaza[6a,7a]-dibenzo[c,g]fluorenium] chloride (2-105)}

\begin{center}
\includegraphics[width=0.2\textwidth]{diisopropyl_dibenzo_fluorenium_chloride}
\end{center}

0.091 g (0.230 mmol, 60.5 \%) of 2-105 was obtained from 0.130 g (0.380 mmol) of 2-97.

\(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3): \ \delta \ \text{ppm} \ 11.23 \ (s, 1\text{H}), 7.94 \ (d, J = 7.8 \text{ Hz}, 2\text{H}), 7.43 - 7.26 \\
(m, 6\text{H}), 4.86 \ (m, 2\text{H}), 3.41 \ (dd, J = 4.8, 15.9 \text{ Hz}, 2\text{H}), 3.20 \ (d, J = 15.9 \text{ Hz}, 2\text{H}), 1.68 \ (m, 2\text{H}), \\
1.04 \ (d, J = 6.9 \text{ Hz}, 6\text{H}), 0.94 \ (d, J = 6.6 \text{ Hz}, 6\text{H})

\(^{13}\text{C} \text{NMR} (75 \text{ MHz}, \text{CDCl}_3): \ \delta \ \text{ppm} \ 136.52, 132.61, 130.78, 129.82, 127.90, 124.44, \\
124.06, 123.90, 60.86, 31.91, 29.62, 19.83, 19.15

\text{HRMS Calcd. for } C_{25}H_{29}N_2 [M-\text{Cl}]^+: 357.2325, \text{ Found: } 357.2309

\left[\alpha\right]_{D}^{25} -228.9 \ (c \ 0.88, \text{CHCl}_3)

\text{[6(R),8(R)-Dicyclohexyl-5,6,8,9-tetrahydro-6a,7a-diaza[6a,7a]-dibenzo[c,g]fluorenium] chloride (2-106)}
0.0750 g (0.159 mmol, 81.9 %) of 2-106 was obtained from 0.0822 g (0.194 mmol) of 2-98.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 11.31 (s, 1H), 7.92 (d, $J = 7.2$ Hz, 2H), 7.39 – 7.32 (m, 6H), 7.17 (m, 2H), 3.34 (dd, $J = 5.5$, 16.1 Hz, 2H), 3.20 (d, $J = 15.9$ Hz, 2H), 1.73 – 0.82 (m, 20H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 137.15, 132.78, 130.72, 129.89, 127.87, 124.50, 124.09, 123.98, 60.07, 38.31, 31.58, 29.52, 29.42, 25.87, 25.68, 25.55

HRMS Calcd. for C$_{31}$H$_{37}$N$_2$ [M-Cl]$^+$: 437.2957, Found: 437.2971

$[\alpha]_D^{25} +212.1$ (c 2.44, CHCl$_3$)

[6(R),8(R)- bis(cyclohexylmethyl)-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluorenium] chloride (2-108)

300 mg (0.598 mmol, 90.3%) of [6(R),8(R)- bis(cyclohexylmethyl)-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluorenium] chloride was obtained from 300 mg (0.662 mmol) of
(3S,3’S)-3,3’-bis(cyclohexylmethyl)-3,3’,4,4’-tetrahydro-1,1’-biisoquinoline, 400 µL (4.04 mmol) of chloromethyl ethylether and 33 mL of THF.

$^1$H NMR (500MHz ,CHLOROFORM-d) $\delta = 11.18$ (br. s., 1 H), $7.96$ (d, $J = 7.7$ Hz, 2 H), $7.49 - 7.32$ (m, 6 H), $5.27$ (br. s., 2 H), $3.43$ (d, $J = 14.8$ Hz, 2 H), $3.05$ (d, $J = 15.5$ Hz, 2 H), $1.99$ (br. s., 2 H), $1.79 - 1.56$ (m, 12 H), $1.37 - 1.06$ (m, 12 H)

$^{13}$C NMR (126MHz ,CHLOROFORM-d) $\delta = 135.4, 132.2, 130.7, 130.2, 127.9, 124.5, 124.1, 123.9, 53.1, 40.1, 34.4, 33.8, 33.0, 32.5, 26.4, 26.3, 26.2

[6(R),8(R)- diisobutyl-7,7’-dimethoxy -5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluorenium] chloride (2-141)

16.9 mg (0.0351 mmol, 80.0%) of 6(R),8(R)- diisobutyl-7,7’-dimethoxy -5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluorenium] chloride was obtained from 19.0 mg (0.439 mmol) of (3S,3’S)-3,3’-diisobutyl-7,7’-dimethoxy-3,3’,4,4’-tetrahydro-1,1’-biisoquinoline, 25.0 µL (0.267 mmol) of chloromethyl ethylether and 2 mL of THF.

[6(S),8(S)-Diisobutyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoren-5-ylidene)-(η³-cinnamyl)chloropalladium(0) (2-103)
To a flame-dried Schlenk flask was added 0.250 g (0.450 mmol) of $2$-104, 0.063 g (0.270 mmol) of Ag$_2$O and 15 mL of CH$_2$Cl$_2$. The reaction mixture was stirred for 12 h at room temperature and filtered through a pad of celite. The solvent of the filtrate was removed under reduced pressure. To another flame-dried Schlenk flask was added the filtered silver complex, 0.110 g (0.220 mmol) of [Pd(cinnamyl)Cl]$_2$ and 20 mL of CH$_2$Cl$_2$. The reaction mixture was stirred for 3 h at room temperature and filtered through a pad of celite. The solvent was removed under reduced pressure, and the residue was purified by silicagel column chromatography with CH$_2$Cl$_2$ as the eluent to yield 0.150 g (0.240 mmol, 53.3 %) of $2$-103. Four possible isomers can exist according to the orientation of cinnamyl group. Crystals of an isomer were obtained by slow diffusion of CH$_2$Cl$_2$ solution of $2$-103 into hexanes, but the NMR spectra of the crystals showed that there were at least two isomers in solution.

$^1$H NMR of the major isomer (300 MHz, CDCl$_3$) $\delta$ ppm 7.86 - 7.76 (m, 2H) 7.47 (d, $J = 7.5$ Hz, 2H), 7.33 – 7.06 (m, 9H), 6.12 – 6.01 (m, 1H), 5.75 – 5.64 (m, 1H), 4.85 (d, $J=12.6$Hz, 1H), 4.55 (d, $J = 11.4$ Hz, 1H), 4.29 (d, $J = 8.1$ Hz, 1H), 3.51 – 3.34 (m, 2H), 3.02 – 2.93 (m, 2H), 2.32 (d, $J = 14.7$ Hz, 1H), 1.93 – 0.79 (m, 18H)

$^{13}$C NMR of mixture of isomers (75 MHz, CDCl$_3$) $\delta$ ppm 176.15, 175.15, 140.4, 140.28, 138.05, 133.21, 132.44, 132.19, 129.85, 129.73, 129.48, 129.35, 129.0, 128.87, 128.63, 128.52, 128.38, 127.48, 127.38, 127.05, 126.94, 126.86, 126.77, 126.59, 126.47, 126.43, 126.37, 124.97,
124.69, 123.95, 123.84, 123.6, 111.53, 110.38, 109.3, 91.73, 69.93, 69.63, 69.14, 68.95, 52.99, 52.67, 44.13, 42.92, 41.83, 41.62, 33.92, 33.83, 33.36, 32.47, 25.41, 25.3, 25.2, 25.16, 24.17, 23.99, 23.84, 23.65, 22.97, 22.54, 22.32, 21.72

Anal. Calcd. for C\textsubscript{36}H\textsubscript{41}ClN\textsubscript{2}Pd: C, 67.18; H, 6.42; N, 4.35, Found: C, 66.83; H, 6.49; N, 4.27

[\alpha]_D^{23} -90 (c 1.12, CHCl\textsubscript{3})

\textbf{X-ray experimental for 2-103}

Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK\textsubscript{\alpha} radiation (\( \lambda = 0.71073 \) Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the \( \omega \)-scan method (0.3° frame width). The first 50 frames were re-measured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in \textit{SHELXTL6}, and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. The C27 methyl group was disordered and refined in two parts with their site occupation factors dependently refined. Its isopropyl counter methyl group was not significantly disordered and could not be resolved. The major disorder is in the C28-C36 ligand. It is completely disordered and was refined with anisotropic displacement parameters and with the phenyl ring treated as an idealized hexagon rigid body. A total of 338 parameters were refined in the final cycle of
refinement using 5574 reflections with $I > 2\sigma(I)$ to yield $R_1$ and $wR_2$ of 3.77\% and 8.40\%, respectively. Refinement was done using $F^2$.

*SHELXTL6* (2000). Bruker-AXS, Madison, Wisconsin, USA.

**Crystal data and structure refinement for 2-103**

Identification code 2-103

Empirical formula C36 H41 Cl N2 Pd

Formula weight 643.56

Temperature 173(2) K

Wavelength 0.71073 Å

Crystal system Orthorhombic

Space group P2(1)2(1)2(1)

Unit cell dimensions

\[ a = 5.6873(4) \, \text{Å} \quad \alpha = 90^\circ. \]

\[ b = 23.3061(18) \, \text{Å} \quad \beta = 90^\circ. \]

\[ c = 23.7168(18) \, \text{Å} \quad \gamma = 90^\circ. \]

Volume 3143.6(4) Å³

Z 4

Density (calculated) 1.360 Mg/m³

Absorption coefficient 0.702 mm⁻¹

F(000) 1336

Crystal size 0.19 x 0.19 x 0.15 mm³

Theta range for data collection 1.72 to 27.50°.

Index ranges $-7 \leq h \leq 7, -30 \leq k \leq 26, -30 \leq l \leq 28$
Reflections collected  20343
Independent reflections  7185 [R(int) = 0.0463]
Completeness to theta = 27.50° 99.7%
Absorption correction  Integration
Max. and min. transmission  0.9057 and 0.8827
Refinement method  Full-matrix least-squares on F²
Data / restraints / parameters  7185 / 1 / 338
Goodness-of-fit on F²  0.972
Final R indices [I>2sigma(I)]  R1 = 0.0377, wR2 = 0.0840 [5574]
R indices (all data)  R1 = 0.0532, wR2 = 0.0877
Absolute structure parameter  -0.02(3)
Largest diff. peak and hole  0.526 and -0.314 e.Å⁻³

R1 = Σ(|F₀| - |Fᵣ|) / Σ|F₀|

wR2 = [Σ[w(F₀² - Fᵣ²)²] / Σ[w(F₀²)²]]¹/²

S = [Σ[w(F₀² - Fᵣ²)²] / (n-p)]¹/²

w= 1/[σ²(F₀²)+m*p²+n*p], p = [max(F₀²,0)+ 2* Fᵣ²]/3, m & n are constants.

[6(S),8(S)-Diisobutyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoren-5-ylidene]-
chlorocopper(I) (2-109).
A flame dried Schlenk flask was charged with 0.200 g (0.360 mmol) of 2-104, 0.046 g (0.200 mmol) of Ag\textsubscript{2}O and 5 mL of CH\textsubscript{2}Cl\textsubscript{2}. After stirring for 12 h, the reaction mixture was filtered through a pad of celite. The solvent of the filtrate was removed under reduced pressure. To another flame-dried Schlenk flask was added the filtered silver complex and 0.0340 g (0.340 mmol) of CuI. The reaction mixture was stirred for 2 h at room temperature. The reaction solution was filtered through a pad of celite and evaporated to dryness. The residue was purified quickly by silicagel column chromatography with CH\textsubscript{2}Cl\textsubscript{2} as the eluent to yield 0.210 g (0.340 mmol, 94.4 %) of 2-109.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 7.9 (dd, \(J = 1.8, 6.6\) Hz, 2H), 7.32 – 7.24 (m, 6H), 4.78 (m, 2H), 3.36 (dd, \(J = 5.0, 15.5\) Hz, 2H), 2.95 (d, \(J = 15.3\) Hz, 2H), 1.74 (m, 2H), 1.38 (m, 2H), 1.27 (m, 2H), 0.97 (d, \(J = 6.6\) Hz, 6H), 0.94 (d, \(J = 6.6\) Hz, 6H)

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 132.49, 129.79, 127.4, 125.96, 124.10, 54.79, 42.82, 34.20, 25.00, 23.56, 22.40

Anal. Calcd. for C\textsubscript{27}H\textsubscript{32}ClCuN\textsubscript{2}: C, 67.06; H, 6.67; N, 5.79, Found: C, 67.13; H, 6.43; N, 5.71

[\([\alpha]_D\)\textsuperscript{23} -283.4 (c 0.48, CHCl\textsubscript{3})]

[6(R),8(R)-Diisopropyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoren-5-ylidene]chlorocopper(I) (2-110)
0.096 g (0.16 mmol, 55.2 %) of 2-110 was obtained from 0.150 g (0.290 mmol) of 2-105.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.88 (d, $J = 7.4$ Hz, 2H), 7.31 – 7.23 (m, 6H), 4.40 (m, 2H), 3.28 (dd, $J = 4.2$, 15.3 Hz, 2H), 3.15 (d, $J = 15.6$ Hz, 2H), 1.61 (m, 2H), 1.02 (d, $J = 6.6$ Hz, 6H), 0.88 (D, $J = 6.9$ Hz, 6H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 174.23, 133.24, 129.43, 129.18, 127.38, 126.22, 124.09, 124.01, 62.60, 33.07, 30.29, 21.45, 19.67

Anal Calcd. for C$_{25}$H$_{28}$ClCuN$_2$: C, 65.92; H, 6.20; N, 6.15. Found: C, 66.38; H, 6.22; N, 5.98

$[\alpha]_D^{23}$ -251.5 (c 2.20, CHCl$_3$)

[6(R),8(R)-Dicyclohexyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoren-5-ylidene]chlorocopper(I) (2-111)

0.240 g (0.450 mmol, 71.4 %) of 2-111 was obtained from 0.300 g (0.630 mmol) of 2-106.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.88 (dd, $J = 2.3$, 6.2 Hz, 2H), 7.29 – 7.23 (m, 6H), 4.43 (m, 2H), 3.26 (dd, $J = 5.0$, 15.8 Hz, 2H), 3.16 (dd, $J = 1.8$, 15.6 Hz, 2H), 1.73 – 0.89 (m, 22H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 133.36, 129.42, 129.09, 127.29, 126.32, 124.11, 124.00, 61.68, 38.15, 32.73, 31.43, 29.95, 26.09, 26.00, 25.89
Anal. Calcd. for C$_{31}$H$_{36}$ClCuN$_2$: C, 69.51; H, 6.77; N, 5.23; Found: C, 69.42; H, 6.75; N, 4.83

[α]$_D^{23} +173.6$ (c 0.78, CHCl$_3$).

[6(R),8(R)- bis(cyclohexylmethyl)-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoren-5-ylidene]chlorocopper(I) (2-113)

36.5 mg (0.0648 mmol, 65.0%) of [6(R),8(R)- bis(cyclohexylmethyl)-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoren-5-ylidene]chlorocopper(I) was obtained from 50 mg (0.0997 mmol) of [6(R),8(R)- bis(cyclohexylmethyl)-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluorenium] chloride, 13.9 mg (0.0598 mmol) of silver oxide, 10.9 mg (0.109 mmol) of copper chloride and 10 mL of DCM.

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 7.90$ (d, $J = 7.0$ Hz, 2 H), 7.54 - 7.03 (m, 6 H), 4.84 (q, $J = 6.2$ Hz, 2 H), 3.35 (dd, $J = 5.3$, 15.2 Hz, 2 H), 3.10 - 2.79 (m, 2 H), 1.85 (d, $J = 12.3$ Hz, 2 H), 1.76 - 1.55 (m, 8 H), 1.46 - 1.09 (m, 12 H), 1.07 - 0.81 (m, 4 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta =$ 171.9, 132.5, 129.8, 129.1, 127.3, 126.0, 124.1, 54.0, 41.4, 34.3, 34.0, 33.1, 26.5, 26.2

6.2.4 Synthesis of the Substrates for The Copper-Catalyzed Allylic Alkylation

(E)-3-(2-methoxyphenyl)allyl pivalate (2-128)
Synthesis of (E)-ethyl 3-(2-methoxyphenyl)acrylate:

A flame-dried Schlenk flask was charged with 0.440 g (11.0 mmol) of NaH (60% in mineral oil) and 20 mL of toluene. To this solution was added 2.0 mL (10.0 mmol) of triethyl phosphonoacetate at 0 °C. The temperature was slowly increased to room temperature for 30 min. To the reaction solution was added 1.2 mL (10.0 mmol) of o-anisole, and the solution was heated to 60 °C for 4 h. After cooling to room temperature, 20 mL of a saturated NH₄Cl solution was added to quench the reaction. The organic layer was extracted with 30 mL of Et₂O, and all the volatiles were evaporated under reduced pressure to give crude (E)-ethyl 3-(2-methoxyphenyl)acrylate.

Synthesis of (E)-3-(2-methoxyphenyl)prop-2-en-1-ol:

To a flame-dried Schlenk flask was added the crude (E)-ethyl 3-(2-methoxyphenyl)acrylate and 20 mL of Et₂O. 20 mL of DIBALH (1.0 M solution in toluene) was slowly added to the reaction solution at 0 °C. The temperature was slowly increased to room temperature. After 3 h, 30 mL of 1M HCl aqueous solution was added and the organic layer was separated. All volatiles were removed under reduced pressure to give crude (E)-3-(2-methoxyphenyl)prop-2-en-1-ol.

Synthesis of (E)-3-(2-methoxyphenyl)allyl pivalate:

A flame-dried Schlenk flask was charged with 1.25 g (8.00 mmol) of the crude (E)-3-(2-methoxyphenyl)allyl pivalate, 0.100 g (0.800 mmol) of 4-dimethylamino pyridine, 1.4 mL (10.0 mmol) of triethyl amine and 20 mL of CH₂Cl₂. To the reaction flask was added 1.0 mL (8.00 mmol) of pivaloyl chloride at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 2 h. The reaction mixture was poured to a 20 mL of saturated
NaHCO₃ aqeous solution, and the organic layer was separated. After evaporation of the solvent, the residue was purified by silicagel column chromatography with a 5:1 mixture of hexane and Et₂O as the eluent to give 1.80 g (7.2 mmol, 65.5 %) of the pure product.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.49 (dd, J = 7.5, 1.6 Hz, 1 H), 7.24 - 7.32 (m, 1 H), 6.86 - 7.10 (m, 3 H), 6.35 (dt, J = 16.1, 6.3 Hz, 1 H), 4.79 (dd, J = 6.2, 1.4 Hz, 2 H), 3.88 (s, 3 H), 1.29 (s, 9 H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 178.21, 156.70, 128.95, 128.59, 128.33, 126.91, 125.23, 124.00, 120.53, 110.75, 65.35, 55.31, 38.70, 27.15


(E)-3-(naphthalen-2-yl)allyl benzoate (2-121)

(¹H NMR (300 MHz, CDCl₃) δ ppm 8.13 - 8.19 (m, 2 H), 7.82 (dd, J = 7.92, 4.69 Hz, 4 H), 7.56 - 7.68 (m, 2 H), 7.44 - 7.54 (m, 4 H), 6.93 (d, J = 15.8 Hz, 1 H), 6.56 (dt, J = 15.8, 6.30 Hz, 1 H), 5.08 (dd, J = 6.5, 1.5 Hz, 2 H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 166.35, 134.23, 133.64, 133.47, 133.16, 132.96, 130.17, 129.64, 128.34, 128.25, 128.01, 127.63, 126.84, 126.29, 126.06, 123.57, 123.47, 65.54

HRMS Calcd. for C₂₀H₁₆O₂ [M⁺]: 288.1150, Found : 288.1141

(E)-3-(naphthalen-2-yl)allyl pivalate (2-122)
$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.74 - 7.89 (m, 4 H), 7.62 (dd, $J = 8.5$, 1.7 Hz, 1 H), 7.42 - 7.54 (m, 2 H), 6.83 (d, $J = 15.9$ Hz, 1 H), 6.44 (dt, $J = 15.9$, 6.2 Hz, 1 H), 4.81 (dd, $J = 6.2$, 1.13 Hz, 2 H), 1.30 (s, 9 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 178.31, 133.74, 133.59, 133.45, 133.10, 128.21, 127.98, 127.62, 126.69, 126.28, 126.00, 123.89, 123.47, 64.95, 38.80, 27.21

HRMS Calcd. for C$_{18}$H$_{20}$NaO$_2$ [M+Na]$^+$: 291.1355, Found: 291.1318

*(E)-3-(naphthalen-2-yl)but-2-enyl pivalate (2-129)*

![naphthalen-2-yl](image)

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.77 - 7.95 (m, 4 H), 7.61 (dd, $J = 8.6$, 1.86 Hz, 1 H), 7.41 - 7.55 (m, 2 H), 6.08 (td, $J = 6.7$, 1.2 Hz, 1 H), 4.86 (d, $J = 6.9$ Hz, 2 H), 2.25 (d, $J = 0.6$ Hz, 3 H), 1.26 (s, 9 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 178.48, 139.65, 139.46, 133.26, 132.71, 128.09, 127.72, 127.43, 126.11, 125.80, 124.52, 124.07, 122.23, 61.68, 38.76, 27.18, 16.16

HRMS Calcd. for C$_{19}$H$_{22}$NaO$_2$ [M+Na]$^+$: 305.1512, Found: 305.1473

*(E)-3-(4-methoxyphenyl)allyl pivalate (2-126)*

![4-methoxyphenyl](image)

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.33 (m, 2 H), 6.86 (m, 2 H), 6.59 (d, $J = 16.1$ Hz, 1 H), 6.15 (dt, $J = 15.8$, 6.5 Hz, 1 H), 4.70 (dd, $J = 6.5$, 1.2 Hz, 2 H), 3.80 (s, 3 H), 1.24 (s, 9 H)
$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 178.27, 159.43, 133.31, 128.99, 127.72, 121.15, 113.90, 65.11, 55.12, 38.69, 27.12

HRMS Calcd. for C$_{15}$H$_{20}$O$_3$ [M]$^+$: 248.1407, Found: 248.1410

*(E)-3-(4-chlorophenyl)allyl pivalate (2-127)*

\[ \text{Cl} \]
\[ \text{C} \]
\[ \text{O} \]
\[ \text{H} \]

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.28 - 7.35 (m, 4 H), 6.60 (d, $J = 15.8$ Hz, 1 H), 6.20 - 6.34 (m, $J = 16.1$, 6.2, 6.2 Hz, 1 H), 4.73 (dd, $J = 6.2$, 1.5 Hz, 2 H), 1.26 (s, 9 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 178.07, 134.75, 133.49, 132.07, 128.63, 127.67, 124.23, 64.56, 38.70, 27.12

HRMS Calcd. for C$_{14}$H$_{17}$ClO$_2$ [M]$^+$: 252.0917, Found: 252.0914

*(E)-2-(3-(naphthalen-2-yl)allyloxy)pyridine (2-120)*

\[ \text{N} \]
\[ \text{C} \]
\[ \text{O} \]
\[ \text{H} \]

*(E)-2-(3-(naphthalen-2-yl)allyloxy)pyridine was prepared from *(E)-3-(naphthalen-2-yl)prop-2-en-1-ol by using a literature method$^{15}$.*

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.21 (dd, $J = 5.0$, 2.1 Hz, 1 H), 7.74 - 7.91 (m, 4 H), 7.56 - 7.70 (m, 2 H), 7.40 - 7.53 (m, 2 H), 6.87 - 6.97 (m, 2 H), 6.83 (d, $J = 8.2$ Hz, 1 H), 6.62 (ddd, $J = 16.0$, 6.0, 5.9 Hz, 1 H), 5.08 (dd, $J = 6.0$, 1.0 Hz, 2 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 146.85, 138.65, 134.09, 133.52, 133.13, 128.17, 127.99, 127.64, 126.63, 126.23, 125.91, 125.11, 123.59, 116.85, 111.25, 66.33
HRMS Calcd. for C₁₈H₁₆NO [M+H]^+: 262.1226, Found: 262.1232

1-(naphthalen-6-yl)allyl pivalate (2-136)

1H NMR (300 MHz, CDCl₃) δ ppm 7.81 - 7.90 (m, 4 H), 7.44 - 7.55 (m, 3 H), 6.42 (d, J = 5.6 Hz, 1 H), 6.10 (ddd, J = 17.2, 10.5, 5.7 Hz, 1 H), 5.25 - 5.43 (m, 2 H), 1.27 (s, 9 H)

13C NMR (75 MHz, CDCl₃) δ ppm 177.27, 136.56, 136.46, 133.16, 133.03, 128.33, 128.05, 127.64, 126.19, 126.14, 126.02, 124.71, 116.65, 75.83, 40.17, 27.13

HRMS Calcd. for C₁₈H₂₀O₂ [M]^+: 268.1458, Found: 268.1465

6.2.5 Products from The Copper-Catalyzed Allylic Alkylation

Typical procedure for asymmetric Cu-heterocyclic carbene catalyzed allylic substitution:

A flame-dried Schlenk flask was charged with a substrate (0.5 mmol), a copper catalyst (3 mol %) and 3 ml of a solvent. To this solution was added a Grignard reagent (0.75 mmol in Et₂O) at a specified temperature. After 1 hr, the reaction was quenched by a saturated aqueous NH₄Cl solution and diluted by 20 mL of Et₂O. The organic layer was separated and the solvent was evaporated under reduced pressure. Silicagel column chromatography with hexane as the eluent gave a pure product. The regioselectivity was calculated by the integration ratio of the protons shown on the two regioisomers by NMR spectra.
A racemic product was synthesized using IMes-Cu-Cl complex as the catalyst.

2-(pent-1-en-3-yl)naphthalene (2-115)

![Chemical Structure]

Ee was measured by chiral HPLC with a Whelk-01 column (UV 254 nm, 100% pentane, 0.2 mL/min). $t_S$: 25.5, $t_R$: 26.9

2-(non-1-en-3-yl)naphthalene (2-123-product)

![Chemical Structure]

$^1$H NMR (300 MHz, CDCl₃) δ ppm 7.72 - 7.89 (m, 3 H), 7.63 (s, 1 H), 7.39 - 7.51 (m, 2 H), 7.35 (dd, $J = 8.5$, 1.7 Hz, 1 H), 5.97 - 6.11 (m, 1 H), 4.98 - 5.16 (m, 2 H), 3.42 (q, $J = 7.6$ Hz, 1 H), 1.81 (q, $J = 7.5$ Hz, 2 H), 1.24 - 1.35 (m, 8 H), 0.84 - 0.90 (m, 3 H)

$^{13}$C NMR (75 MHz, CDCl₃) δ ppm 142.42, 142.07, 133.62, 132.21, 127.96, 127.57, 126.28, 125.82, 125.19, 114.07, 49.96, 35.30, 31.77, 29.30, 27.55, 22.65, 14.09


Ee was measured by chiral HPLC with a Whelk-01 column (UV 254 nm, 100% pentane, 0.2 ml/min). $t_1$: 26.0, $t_2$: 28.2

2-(1-cyclopentylallyl)naphthalene (2-124-product)
$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.81 - 7.92 (m, 2 H), 7.69 (s, 1 H), 7.39 - 7.56 (m, 3 H), 6.17 (ddd, $J = 17.0, 10.2, 8.2$ Hz, 1 H), 5.03 - 5.19 (m, 2 H), 3.23 (t, $J = 9.3$ Hz, 1 H), 2.30 - 2.47 (m, 1 H), 1.88 - 2.06 (m, 1 H), 1.38 - 1.78 (m, 6 H), 1.06 - 1.29 (m, 1 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 142.45, 142.23, 133.94, 132.49, 128.21, 127.89, 126.76, 126.45, 126.11, 125.46, 114.65, 57.07, 44.92, 31.76, 25.61

HRMS Calcd. for C$_{18}$H$_{20}$ [M]$^+$: 236.1560, Found: 236.1552

Ee was measured by chiral HPLC with a Whelk-01 column (UV 254 nm, 100% pentane, 0.2 mL/min). $t_1$: 30.9, $t_2$: 34.0

(\textit{E})-2-(3-phenylprop-1-enyl)naphthalene (2-125-product)

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.66 - 7.82 (m, 4 H), 7.58 (dd, $J = 8.5, 1.8$ Hz, 1 H), 7.37 - 7.48 (m, 2 H), 7.18 - 7.37 (m, 5 H), 6.61 (d, $J = 15.8$ Hz, 1 H), 6.48 (dt, $J = 15.8, 6.5$ Hz, 1 H), 3.61 (d, $J = 6.5$ Hz, 2 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 140.11, 134.91, 133.63, 132.74, 131.12, 129.69, 128.69, 128.50, 128.06, 127.83, 127.60, 126.20, 126.14, 125.71, 125.56, 123.55, 39.45

HRMS Calcd. for C$_{19}$H$_{16}$ [M]$^+$: 244.1252, Found: 244.1245

2-(3-methylpent-1-en-3-yl)naphthalene (2-129-product)
Ee was measured by chiral HPLC with a Whelk-01 column (UV 254 nm, 100% pentane, 0.2 mL/min). $t_1$: 32.8, $t_2$: 35.4

**1-methoxy-4-(pent-1-en-3-yl)benzene (2-126-product)**

Ee was measured by chiral HPLC with a Chiralcel OJ-H column (UV 254 nm, hexane: iPrOH = 99.5:0.5, 0.5 mL/min). $t_1$: 15.6, $t_2$: 16.7

**1-chloro-4-(non-1-en-3-yl)benzene (2-127-product)**

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.26 (m, 2 H), 7.10 (m, 2 H), 5.89 (ddd, $J = 16.7$, 10.6, 7.5 Hz, 1 H), 4.94 - 5.07 (m, 2 H), 3.20 (q, $J = 7.4$ Hz, 1 H), 1.57 - 1.74 (m, 2 H), 1.19 - 1.31 (m, 8 H), 0.83 - 0.90 (m, 3 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 143.07, 142.00, 131.68, 128.94, 128.46, 114.19, 49.22, 35.35, 31.74, 29.21, 27.40, 22.63, 14.06

HRMS Calcd. for C$_{15}$H$_{22}$Cl [M+H]$^+$: 237.1405, Found: 237.1408

Ee was measured by chiral HPLC with a Chiralcel OJ-H column (UV 215 nm, 100% pentane, 0.2 mL/min). $t_1$: 21.4, $t_2$: 22.4

**1-methoxy-2-(non-1-en-3-yl)benzene (2-128-product)**
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.10 - 7.22 (m, 2 H), 6.80 - 6.95 (m, 2 H), 5.98 (ddd, \(J\) = 17.1, 10.3, 7.6 Hz, 1 H), 4.93 - 5.06 (m, 2 H), 3.80 (s, 3 H), 3.73 (q, \(J\) = 7.5 Hz, 1 H), 1.60 - 1.73 (m, 2 H), 1.15 - 1.36 (m, 8 H), 0.80 - 0.91 (m, 3 H) 

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 157.23, 142.35, 133.37, 128.02, 127.10, 120.86, 113.93, 110.96, 55.69, 42.37, 34.84, 32.07, 29.57, 27.78, 22.94, 14.37 

HRMS Calcd. for C\(_{16}\)H\(_{25}\)O [M+H]\(^+\): 233.1900, Found: 233.1892 

Ee was measured by chiral HPLC with a Chiralpak IA column (UV 254 nm, 100% pentane, 0.2 mL/min). \(t_1\): 21.5, \(t_2\): 22.4 

6.3 In Situ Generation of Acyclic Diaminocarbene-Copper Complex 

6.3.1 Substrates and Catalysts Synthesis 

\([6(R),8(R)]-\)Diisopropyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoreniumchloride] copper (II) chloride (3-2). 

A flame dried Schlenk flask was charged with 0.100 g (0.254 mmol) of \([6(R),8(R)]-\)Diisopropyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluorenium chloride (2-105), 0.036 g (0.153 mmol) of Ag\(_2\)O and 10 mL of CH\(_2\)Cl\(_2\). After stirring for 12 h, the reaction mixture was
filtered through a pad of celite. The solvent of the filtrate was removed under reduced pressure. To another flame-dried Schlenk flask was added the filtered silver complex and 0.038 g (0.279 mmol) of CuCl$_2$. The reaction mixture was stirred for 5 h at room temperature. The reaction solution was filtered through a pad of celite and evaporated to dryness. The residue was purified by recrystallization using a mixture of CH$_2$Cl$_2$:hexane to yield 0.090 g (0.182 mmol, 71.6 \%) of 3-2.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.97 (d, $J=7.6$ Hz, 1 H), 7.30 - 7.56 (m, 3 H), 4.56 - 4.75 (m, 1 H), 3.68 (dd, $J=15.9$, 5.4 Hz, 1 H), 3.27 (d, $J=16.1$ Hz, 1 H), 1.74 - 2.00 (m, 1 H), 1.03 (d, $J=6.8$ Hz, 3 H), 0.87 (d, $J=6.8$ Hz, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 132.8, 131.4, 129.7, 128.1, 126.1, 124.9, 123.3, 61.2, 31.7, 30.6, 20.6, 19.2

**X-ray experimental for 3-2**

Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK$_\alpha$ radiation ($\lambda = 0.71073$ Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the $\omega$-scan method (0.3° frame width). The first 50 frames were re-measured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 \%). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in SHELXTL6, and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of
280 parameters were refined in the final cycle of refinement using 4548 reflections with $I > 2\sigma(I)$ to yield $R_1$ and $wR_2$ of 3.45% and 7.82%, respectively. Refinement was done using $F^2$.

*SHELXTL6* (2000). Bruker-AXS, Madison, Wisconsin, USA.

**Crystal data and structure refinement for 3-2**

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Reflections collected 9852

Independent reflections 5109 [R(int) = 0.0340]

Completeness to theta = 28.03° 92.7%

Absorption correction  Integration

Max. and min. transmission 0.8961 and 0.7376

Refinement method Full-matrix least-squares on F^2

Data / restraints / parameters 5109 / 0 / 280

Goodness-of-fit on F^2 1.014

Final R indices [I>2sigma(I)]  R1 = 0.0345, wR2 = 0.0782 [4548]

R indices (all data) R1 = 0.0408, wR2 = 0.0807

Absolute structure parameter 0.020(11)

Largest diff. peak and hole 0.314 and -0.275 e Å^-3

R1 = Σ(||Fo| - |Fc||) / Σ|Fo|

wR2 = [Σ[w(Fo^2 - Fc^2)^2]] / [Σ[w(Fo^2)]^1/2

S = [Σ[w(Fo^2 - Fc^2)^2] / (n-p)]^1/2

w = 1/[σ^2(Fo^2)+(m*p)^2+n*p], p = [max(Fo^2,0)+ 2* Fc^2]/3, m & n are constants.

(Z)-4-(4-methoxybenzyloxy)but-2-en-1-ol

To a flame-dried Schlenk flask were added 1.25 g (14.16 mmol) of (Z)-2-buten-1,4-diol and 5 mL (0.06 mmol) of a solution of TfOH in Et_2O (10 μL in 10 mL of Et_2O). The reaction mixture was cooled to 0 °C and a solution of 4-methoxybenzyl-2,2,2-trichloroacetimidate (0.67
g, 2.36 mmol) in DCM (1.2 mL) was added dropwise. After stirring over 2 hours at 0 °C, it was quenched with 4 mL of a saturated solution of NaHCO₃. The aqueous layer was extracted with Et₂O (3 x 5mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, from 2.3:1 to 1:1 Hexanes/EtOAc) to yield 0.40 g (1.90 mmol, 80%) of (Z)-4-(4-methoxybenzyloxy)but-2-en-1-ol.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.26 (d, J=8.21 Hz, 2 H), 6.88 (d, J=8.78 Hz, 2 H), 5.65 - 5.85 (m, 2 H), 4.45 (s, 2 H), 4.14 (d, J=5.95 Hz, 2 H), 4.05 (d, J=5.66 Hz, 2 H), 3.79 (s, 3 H), 2.32 (br. s, 1 H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 159.5, 132.6, 130.1, 129.7, 128.4, 114.1, 72.4, 65.6, 58.8, 55.5

HRMS Calcd. for C₁₂H₁₆O₃ [M+Na]⁺: 231.0992, Found: 231.0991

(Z)-4-(4-methoxybenzyloxy)but-2-enyl acetate (3-4)

To a flame-dried Schlenk flask were added 356 mg (1.71 mmol) of (Z)-4-(4-methoxybenzyloxy)but-2-en-1-ol, 755 μL (5.42 mmol) of Et₃N, 44 mg (0.36 mmol) of DMAP, 205 μL (2.17 mmol) of Ac₂O, and 18 mL of DCM. The reaction mixture was stirred at room temperature over 12 hours. It was quenched with 10 mL of H₂O and extracted with DCM (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 1:1 Hexanes/EtOAc) to yield 400 mg (1.60 mmol, 93%) of (Z)-4-(4-methoxybenzyloxy)but-2-enyl acetate.

185
$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.27 (d, $J=8.80$ Hz, 2 H), 6.88 (d, $J=8.80$ Hz, 2 H), 5.76 - 5.86 (m, 1 H), 5.64 - 5.75 (m, 1 H), 4.62 (dd, $J=6.45$, 0.88 Hz, 2 H), 4.45 (s, 2 H), 4.09 (dd, $J=6.16$, 1.17 Hz, 2 H), 3.80 (s, 3 H), 2.06 (s, 3 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 170.8, 159.3, 130.9, 130.1, 129.4, 126.6, 113.8, 72.1, 65.3, 60.3, 55.2, 20.9

HRMS Calcd. for C$_{14}$H$_{18}$O$_4$ [M+Na]$^+$: 273.1097, Found: 273.1104

(Z)-but-2-ene-1,4-diyl bis(4-methoxybenzoate) (3-13)

![Chemical structure](image)

To a flame-dried Schlenk flask were added 54 mg (0.61 mmol) of (Z)-2-buten-1,4-diol, 212 μL (1.52 mmol) of Et$_3$N, 15 mg (0.12 mmol) of DMAP, 10 mL of DCM, and dropwise 206 μL (1.52 mmol) of 4-methoxybenzoyl chloride. The reaction mixture was stirred at room temperature over 17 hours. It was quenched with 6 mL of 30% NaOH solution and extracted with DCM (3 x 8 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 1:1 Hexanes/EtOAc) to yield 217 mg (0.61 mmol, quantitative yield) of 3-13.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.00 (d, $J=8.91$ Hz, 4 H), 6.91 (d, $J=8.91$ Hz, 4 H), 5.93 (ddd, $J=5.22$, 3.98, 1.17 Hz, 2 H), 4.97 (d, $J=5.26$ Hz, 4 H), 3.86 (s, 6 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 166.2, 163.6, 131.8, 128.5, 122.5, 113.8, 60.5, 55.6

HRMS Calcd. for C$_{20}$H$_{20}$O$_4$ [M+Na]$^+$: 379.1152, Found: 379.1185

Ethyl 2-(1-tosylpiperidin-4-ylidene)acetate
To a flame-dried Schlenk flask was added 177 mg of NaH (60% in mineral oil, 4.42 mmol) in 12 mL of toluene. To this suspension at 0 °C was added dropwise 790 μL (3.95 mmol) of triethyl phosphonoacetate. The reaction mixture was stirred 30 min at room temperature then 1.00 g (3.95 mmol) of 1-tosylpiperidin-4-one was added portionwise. It was stirred at 60 °C over a day. The reaction mixture was quenched by 10 mL of H₂O and extracted with Et₂O (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, from 1:0 to 4:1 Hexanes/EtOAc) to give 940 mg (2.9 mmol, 74%) of ethyl 2-(1-tosylpiperidin-4-ylidene)acetate.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.64 (d, J=8.20 Hz, 2 H), 7.31 (d, J=8.65 Hz, 2 H), 5.64 (s, 1 H), 4.11 (q, J=7.16 Hz, 2 H), 2.99 - 3.18 (m, 6 H), 2.42 (s, 2 H), 2.38 (t, J=6.34 Hz, 3 H), 1.24 (t, J=7.09 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 166.0, 153.4, 143.7, 133.1, 129.7, 127.6, 115.9, 59.9, 47.3, 46.8, 35.8, 28.5, 21.5, 14.2


2-(1-tosylpiperidin-4-ylidene)ethanol
To a flame-dried Schlenk flask were added 1.14 g (3.52 mmol) of ethyl 2-(1-tosylpiperidin-4-ylidene)acetate and 38 mL of DCM. The reaction mixture was cooled at -78 °C and 10.6 mL (10.55 mmol) of DIBAL (1M in toluene) was added dropwise. It was stirred at -78 °C for 2 hours. It was quenched with 20 mL of a saturated solution of NH₄Cl and extracted with DCM (3 x 30 mL). The combined organic extracts were filtered on a celite pad, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, from 1:1.5 to 1:2.3 Hexanes/EtOAc) to yield 0.89 mg (3.17 mmol, 90%) of 2-(1-tosylpiperidin-4-ylidene)ethanol.

\[ \text{1H NMR (300 MHz, CDCl₃)} \delta \text{ ppm 7.62 (d, J=8.21 Hz, 2 H), 7.31 (d, J=8.49 Hz, 2 H), 5.42 (t, J=6.94 Hz, 1 H), 4.09 (d, J=6.79 Hz, 2 H), 2.98 - 3.09 (m, 4 H), 2.42 (s, 3 H), 2.37 (t, J=5.80 Hz, 2 H), 2.29 (t, J=5.80 Hz, 2 H), 1.36 (br. s., 1 H)} \]

\[ \text{13C NMR (75 MHz, CDCl₃)} \delta \text{ ppm 143.55, 137.41, 133.08, 129.61, 127.58, 123.52, 58.08, 47.64, 47.08, 35.05, 27.76, 21.47} \]

HRMS Calcd. for C₁₄H₁₉NO₃S [M+Na]⁺: 304.0978, Found: 304.0984

2-(1-tosylpiperidin-4-ylidene)ethyl acetate (3-17)

To a flame-dried Schlenk flask were added 489 mg (1.74 mmol) of 2-(1-tosylpiperidin-4-ylidene)ethanol, 740 μL (5.31 mmol) of Et₃N, 43 mg (0.36 mmol) of DMAP, 201 μL (2.13 mmol) of Ac₂O, and 18 mL of DCM. The reaction mixture was stirred at room temperature over 17 hours. It was quenched with 10 mL of H₂O and extracted with DCM (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure.
pressure. The residue was purified by flash column chromatography (silica gel, 1:1 Hexanes/EtOAc) to yield 548 mg (1.69 mmol, 97%) of 3-17.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta ppm 7.64 (d, } J=8.21 \text{ Hz, 2 H), 7.31 (d, } J=8.78 \text{ Hz, 2 H), 5.36 (t, } J=6.94 \text{ Hz, 1 H), 4.51 (d, } J=7.36 \text{ Hz, 2 H), 3.06 (q, } J=6.23 \text{ Hz, 4 H), 2.37 - 2.49 (m, 5 H), 2.31 (t, } J=5.52 \text{ Hz, 2 H), 2.01 (s, 3 H) }\]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \delta ppm 171.1, 143.8, 140.1, 133.5, 129.9, 127.8, 118.9, 60.2, 47.7, 47.1, 35.3, 28.2, 21.7, 21.2 }\]

HRMS Calcd. for C_{16}H_{21}NO_4S [M+Na]^+: 346.1084, Found: 346.1080

**Pyrrolidine-1-carbaldehyde-13C (3-30)**

![Pyrrolidine-1-carbaldehyde-13C](image)

To a flame-dried pressurized vessel were added 1.42 mL (17.29 mmol) of pyrrolidine and 1000 mg (16.38 mmol) of methyl formate-\(^{13}\)C. The reaction mixture was stirred at 80 °C for 12 hours. It was warmed to room temperature and concentrated under reduced pressure to yield 1640 mg (16.38 mmol, 99%) of pyrrolidine-1-carbaldehyde-\(^{13}\)C

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta ppm 8.2 (d, } J=188.8 \text{ Hz, 1 H), 3.4 (m, 4 H), 1.9 (m, 4 H) }\]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \delta ppm 160.7, 45.9, 43.0, 24.8, 24.1 }\]

HRMS Calcd. for C_{4}^{13}CH_{9}NO [M+H]^+: 101.0790, Found: 101.0793

**Piperidin-1-ylmethyldenepiperidinium hexafluorophosphate-13C (3-32)**

![Piperidin-1-ylmethyldenepiperidinium hexafluorophosphate-13C](image)
To a flame-dried Schlenk flask were added 467 μL (5.01 mmol) of phosphorus oxychloride and 5 mL of DCM. To the reaction mixture at -78 °C in a dry ice-acetone bath was added a solution of 502 mg (5.01 mmol) of pyrrolidine-1-carbaldehyde\textsuperscript{13}C 3-30 in 2 mL of DCM. It was warmed up to room temperature and stirred for 2 hours. Then it was cooled at 0 °C and a solution of 693 μL (5.01 mmol) of triethyl amine and 412 μL (5.01 mmol) of pyrrolidine in 2.5 mL of DCM was added dropwise. It was stirred at room temperature for 2 hours. The reaction mixture was extracted with cold H\textsubscript{2}O (3 x 2.5 mL), the combined aqueous layer was added to a cold solution of 1600 mg (10.02 mmol) of ammonium hexafluorophosphate in 5 mL of H\textsubscript{2}O. The precipitate was filtered and washed with H\textsubscript{2}O (2 x 3 mL) and Et\textsubscript{2}O (2 x 5 mL). The yellowish solid was dried under reduced pressure to yield 1000 mg (3.34 mmol, 67% yield) of piperidin-1-ylmethylidene piperidinium hexafluorophosphate\textsuperscript{13}C 3-32.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 7.81 (d, J=190.0 Hz, 1 H), 3.81 (dt, J=14.0, 7.0 Hz, 4 H), 2.01 (dt, J=13.2, 7.0 Hz, 4 H)

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ ppm 151.0, 54.2, 48.2, 25.8, 23.8

HRMS Calcd. for C\textsubscript{8}\textsuperscript{13}CH\textsubscript{17}F\textsubscript{6}N\textsubscript{2}P [M+H]\textsuperscript{+}: 154.1420, Found: 154.1432

6.3.2 Products from The Copper-Catalyzed Allylic Alkylation

Typical procedure for the allylic alkylation:

A flame-dried Schlenk flask was charged with a copper source (5 mol %), 1-(chloro(pyrrolidin-1-yl)methylene)pyrrolidinium tetrafluoroborate (5 mol%) and 1 mL of a solvent. To this solution was added a Grignard reagent (0.22 mmol in Et\textsubscript{2}O) at 0 °C. The mixture reaction was stirred for 5 min at 0 °C. Then a solution of substrate (0.15 mmol) in 1 mL of Et\textsubscript{2}O was added over a 15 min period. After 1 hr, the reaction was quenched by a saturated aqueous NH\textsubscript{4}Cl solution and extracted with Et\textsubscript{2}O (3 x 5 mL). The combined organic extracts were dried
over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give a pure product.

1-((2-ethylbut-3-nyloxy)methyl)-4-methoxybenzene (3-5)

\[
\begin{equation*}
\text{MeO}
\end{equation*}
\]

\(^1\)H NMR (300 MHz, CDCl₃) \(\delta \) ppm 7.20 - 7.37 (m, 2 H), 6.87 (d, \(J=8.4\) Hz, 2 H), 5.54 - 5.79 (m, 1 H), 4.98 - 5.23 (m, 2 H), 4.44 (s, 2 H), 3.80 (s, 3 H), 3.36 (d, \(J=6.4\) Hz, 2 H), 2.12 - 2.42 (m, 1 H), 1.45 - 1.71 (m, 1 H), 1.13 - 1.37 (m, 1 H), 0.86 (t, \(J=7.4\) Hz, 3 H)

\(^1^3\)C NMR (75 MHz, CDCl₃) \(\delta \) ppm 159.1, 140.0, 130.7, 129.1, 115.5, 113.7, 73.2, 72.6, 55.2, 45.7, 24.0, 11.4


2-ethylbut-3-enyl 4-methoxybenzoate (3-18)

\[
\begin{equation*}
\text{MeO}
\end{equation*}
\]

\(^1\)H NMR (300 MHz, CDCl₃) \(\delta \) ppm 7.91 (d, \(J=8.78\) Hz, 2 H), 6.83 (d, \(J=9.06\) Hz, 2 H), 5.62 (ddd, \(J=17.06, 10.40, 8.21\) Hz, 1 H), 5.00 - 5.09 (m, 2 H), 4.15 (dd, \(J=6.51, 1.98\) Hz, 2 H), 3.77 (s, 3 H), 2.25 - 2.41 (m, 1 H), 1.44 - 1.60 (m, 1 H), 1.23 - 1.39 (m, 1 H), 0.86 (t, \(J=7.36\) Hz, 3 H)

\(^1^3\)C NMR (75 MHz, CDCl₃) \(\delta \) ppm 166.52, 163.50, 139.18, 131.76, 123.07, 116.68, 113.79, 67.37, 55.61, 45.13, 24.23, 11.61
HRMS Calcd. for C\textsubscript{14}H\textsubscript{18}O \textsuperscript{[M+Na]+}: 257.1148, Found: 257.1142

1-(2-ethylbut-3-enyl)-4-methoxybenzene (3-19)

\[
\begin{array}{c}
\text{MeO} \\
\end{array}
\]

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.06 (d, \textit{J}=9 Hz, 2 H), 6.81 (d, \textit{J}=9 Hz, 2 H), 5.47 - 5.72 (m, 1 H), 4.73 - 5.04 (m, 2 H), 3.79 (s, 3 H), 2.43 - 2.70 (m, 2 H), 2.05 - 2.27 (m, 1 H), 1.36 - 1.52 (m, 1 H), 1.17 - 1.36 (m, 1 H), 0.87 (t, \textit{J}=8 Hz, 3 H)

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 157.9, 142.6, 133.0, 130.3, 114.8, 113.7, 55.4, 47.7, 40.8, 27.0, 11.9

HRMS Calcd. for C\textsubscript{13}H\textsubscript{18}O \textsuperscript{[M+H]+}: 191.1430, Found: 191.1436

2,6-dimethyl-6-vinyldodec-2-ene (3-20)

\[
\begin{array}{c}
\end{array}
\]

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 5.71 (dd, \textit{J}=17.6, 10.9 Hz, 1 H), 5.05 - 5.15 (m, 1 H), 4.84 - 5.02 (m, \textit{J}=15.9, 11.0, 1.6 Hz, 2 H), 1.82 - 1.94 (m, 2 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.21 - 1.34 (m, 12 H), 0.96 (s, 3 H), 0.86 - 0.92 (m, 3 H)

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ ppm 147.5, 130.9, 125.2, 111.3, 40.9, 40.8, 39.5, 32.0, 30.2, 25.7, 24.0, 22.9, 22.7, 22.6, 17.6, 14.1

HRMS Calcd. for C\textsubscript{16}H\textsubscript{30} \textsuperscript{[M]+}: 222.2348, Found: 223.2342

4-ethyl-1-tosyl-4-vinylpiperidine (3-21)
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.58 (m, $J=8$ Hz, 2 H) 7.26 (m, $J=8$ Hz, 2 H), 5.36 (dd, $J=18$, 11 Hz, 1 H), 5.04 (d, $J=11$ Hz, 1 H), 4.77 (d, $J=18$ Hz, 1 H), 3.17 - 3.35 (m, 2 H), 2.55 - 2.71 (m, 2 H), 2.38 (s, 3 H), 1.59 - 1.76 (m, 2 H), 1.41 - 1.59 (m, 2 H), 1.22 (q, $J=7$ Hz, 2 H), 0.68 (t, $J=7$ Hz, 3 H)

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.4, 133.8, 129.8, 127.8, 115.1, 42.9, 38.1, 34.1, 33.6, 21.8, 7.7

HRMS Calcd. for C$_{16}$H$_{23}$NO$_2$S [M+H]$^+$: 294.1522, Found: 294.1499

6.3.3 NMR Experiments

Figure 3-2. Experiment (a)

To a flame-dried Schlenk flask was added 20 mg (0.089 mmol) of 1-(chloro-1-pyrrolidinylmethylene)-pyrrolidinium chloride, 8.9 mg (0.089 mmol) of copper (I) chloride and 750 $\mu$L of THF-$d_8$. The reaction mixture was cooled to 0 °C and phenylmagnesium bromide (0.36 mmol in THF) was added. It was stirred at 0 °C for 5 min then it was transferred to a flame-dried NMR tube under argon via syringe. The NMR tube was cooled to -78 °C in a dry ice-acetone bath before being analyzed in the NMR instrument at -60 °C.

Figure 3-2. Experiment (b)
To a flame-dried Schlenk flask was added 10 mg (0.045 mmol) of 1-(chloro-1-pyrrolidinylmethylene)-pyrrolidinium chloride and 750 μL of THF-\(d_8\). The reaction mixture was cooled to 0 °C and phenylmagnesium bromide (0.18 mmol in THF) was added. It was stirred at 0 °C for 5 min, and then it was transferred to a flame-dried NMR tube under argon via syringe. The NMR tube was cooled to -78 °C in a dry ice-acetone bath before being analyzed in the NMR instrument at -60 °C.

**Figure 3-2. Experiment (c)**

To the NMR tube from experiment 2 was added 4.5 mg (0.045 mmol) of copper (I) chloride at 0 °C. Then it was stirred at 0 °C for 5 min and cooled at -78 °C in a dry ice-acetone bath before being analyzed in the NMR instrument at -60 °C.

**Figure 3-2. Experiment (d)**
To a flame-dried Schlenk flask was added 10 mg (0.045 mmol) of 1-(chloro-1-pyrrolidinylmethylene)-pyrrolidinium chloride, 4.4 mg (0.045 mmol) of copper (I) chloride and 750 μL of THF-$d_8$. The reaction mixture was cooled to 0 °C, and ethylmagnesium bromide (0.18 mmol in THF) was added. It was stirred at 0 °C for 5 min, and then it was transferred to a flame-dried NMR tube under argon via syringe. The NMR tube was cooled to -78 °C in a dry ice-acetone bath before being analyzed in the NMR instrument at -60 °C.

Figure 3-3. Experiment (a)

![Diagram](attachment:3-32.png)

3-32

Figure 3-3. Experiment (b)

To a flame-dried NMR tube was added 41.4 mg (0.138 mmol) of piperidin-1-ylmethylidenepiperidinium hexafluorophosphate-$^{13}$C. Then it was cooled at -78 °C in a dry ice-acetone bath and 147 μL (0.94 M) of LDA followed by 750 μL of THF-$d_8$. It was stirred at room temperature for 5 min until dissolution of the suspension before being analyzed in the NMR experiment at room temperature.

Figure 3-3. Experiment (b)

![Diagram](attachment:3-33.png)
To the NMR tube from experiment 5 at -78 °C in a dry ice-acetone bath was added 548 μL (1 M in THF) of phenyl magnesiumbromide and the reaction mixture was stirred for 5 min at room temperature before being analyzed in the NMR experiment at room temperature.

**Figure 3-3. Experiment (c)**

![Chemical structure]

To the NMR tube from experiment 6 at -78 °C in a dry ice-acetone bath was added 14 mg (0.138 mmol) of copper chloride and the reaction mixture was stirred for 5 min at room temperature before being analyzed in the NMR experiment at room temperature.

### 6.3.4 Additional Experiments from Table 3-2

**Table 3-2.Entry 8**

![Chemical structure]

To a flame-dried Schlenk flask were added 201 mg (0.674 mmol) of piperidin-1-ylmethylideneepiperidinium hexafluorophosphate to a solution of 0.674 mmol (3 M in THF) of LDA. The reaction mixture was stirred at -20 °C for 30 min. 65 μL (0.022 mmol) of this carbene solution generated in situ was added to a flame-dried Schlenk flask at 0 °C containing 110 μL (3
M in Et₂O) of ethyl magnesiumbromide, 4.2 mg (0.022 mmol) of copper thiophene-2-carboxylate and 1 mL of Et₂O. The reaction mixture was stirred for 5 min then a solution of 55 mg (0.221 mmol) of (Z)-4-(4-methoxybenzyl)oxy)but-2-enyl acetate in 1 mL of Et₂O was added dropwise. After 1 hr, the reaction was quenched by a saturated aqueous NH₄Cl solution and extracted with Et₂O (3 x 5 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 1:0.05 Hexanes/EtOAc) to yield 33.9 mg (0.154 mmol, 71%, γ:α 90:10) of 1-((2-ethylbut-3-enyloxy)methyl)-4-methoxybenzene.

Table 3.2. Entry 9

To a flame-dried Schlenk flask were added 3.5 mg (0.011 mmol) of 1,3-Bis(2,4,6-trimethyl-phenyl)imidazol-2-ylidene, 2.1 mg (0.011 mmol) of copper thiophene-2-carboxylate, 116 μL (3 M in Et₂O) of ethyl magnesiumbromide and 1 mL of Et₂O. The reaction mixture was stirred for 5 min at 0 °C then a solution of 58 mg (0.231 mmol) of (Z)-4-(4-methoxybenzyloxy)but-2-enyl acetate in 1 mL of Et₂O was added dropwise. After 1 hr, the reaction was quenched by a saturated aqueous NH₄Cl solution and extracted with Et₂O (3 x 5 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 1:0.05
Hexanes/EtOAc) to yield 29 mg (0.131 mmol, 60%, γ:α 92:8) of 1-((2-ethylbut-3-enyloxy)methyl)-4-methoxybenzene.

6.4 C$_1$-Symmetric Monoisoquinoline NHC Ligands

6.4.1 Ligands Synthesis

(S)-N-(4-methyl-1-phenylpentan-2-yl)-2-oxo-2-phenylacetamide (4-10)

To a flame-dried Schlenk flask was added 2.21 g (12.5 mmol) of (S)-4-methyl-1-phenylpentan-2-amine, 2.18 g (16.1 mmol) of HOBt, 3.09 g (16.2 mmol) of EDCI, 2.05 g (13.7 mmol) of 2-oxo-2-phenylacetic acid and 33 mL (0.377 M) of DMF. The reaction mixture was stirred at room temperature for 12 h. It was quenched by 40 mL of water. The reaction mixture was extracted with ethyl acetate (2 x 40 mL), washed with water (2 x 40 mL) and dried over anhydrous MgSO$_4$. All volatiles were removed in vacuo. Silicagel column chromatography with a 95:5 mixture of hexane and ethyl acetate as the eluent gave 2.91 g (9.41 mmol, 75.3%) of (S)-N-(4-methyl-1-phenylpentan-2-yl)-2-oxo-2-phenylacetamide.

$^1$H NMR (299 MHz, CHLOROFORM-d) $\delta$ = 8.18 - 8.29 (m, 2 H), 7.56 - 7.67 (m, 1 H), 7.41 - 7.51 (m, 2 H), 7.16 - 7.36 (m, 5 H), 6.79 (d, $J$=9.3 Hz, 1 H), 4.30 - 4.46 (m, $J$=9.1, 6.0, 6.0, 3.0 Hz, 1 H), 2.75 - 2.97 (m, $J$=13.9, 6.2 Hz, 2 H), 1.67 (td, $J$=13.7, 6.7 Hz, 1 H), 1.43 (ddd, $J$=8.9, 5.4, 3.5 Hz, 2 H), 0.93 (dd, $J$=6.5, 1.4 Hz, 6 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-d) $\delta$ = 161.2, 137.5, 134.3, 131.1, 129.5, 128.4, 126.5, 48.6, 43.3, 41.6, 25.0, 23.2, 21.9
HRMS Calcd. for C_{20}H_{23}NO_2 [M+H]^+: 310.1802, Found: 310.1826

[α]^{20}_{D} - 22.2° (c 1.33, CHCl₃)

(S)-N-(1,2-diphenylethyl)-2-oxo-2-phenylacetamide (4-34)

265 mg (0.805 mmol, 71.9%) of (S)-N-(1,2-diphenylethyl)-2-oxo-2-phenylacetamide was obtained from 200 mg (1.014 mmol) of (S)-1,2-diphenylethanamine, 167 mg (1.12 mmol) of 2-oxo-2-phenylacetic acid, 253 mg (1.32 mmol) of EDCI, 180 mg (1.32 mmol) of HOBt and 2.5 mL of DMF.

^1H NMR (300MHz, CHLOROFORM-d) δ = 8.41 - 8.08 (m, 2 H), 7.89 - 7.51 (m, 2 H), 7.51 - 7.11 (m, 12 H), 5.38 (q, J = 7.5 Hz, 1 H), 3.38 - 3.06 (m, 2 H)

^13C NMR (75MHz, CHLOROFORM-d) δ = 187.9, 161.3, 140.9, 137.2, 134.6, 133.5, 131.4, 129.6, 129.0, 128.7, 128.0, 126.9, 55.0, 42.9

(R)-N-(1-cyclohexyl-2-phenylethyl)-2-oxo-2-phenylacetamide (4-36)

460 mg (1.37 mmol, 54.0%) of (R)-N-(1-cyclohexyl-2-phenylethyl)-2-oxo-2-phenylacetamide was obtained from 517 mg (2.54 mmol) of (R)-1-cyclohexyl-2-
phenylethanolamine, 400 mg (2.66 mmol) of 2-oxo-2-phenylacetic acid, 634 mg (3.31 mmol) of EDCI, 447 mg (3.31 mmol) of HOBt and 6.4 mL of DMF.

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 8.24 - 8.12$ (m, 2 H), 7.70 - 7.56 (m, 1 H), 7.53 - 7.40 (m, 2 H), 7.38 - 7.17 (m, 5 H), 6.86 (d, $J = 9.7$ Hz, 1 H), 4.29 - 4.13 (m, 1 H), 3.04 (dd, $J = 5.3$, 14.1 Hz, 1 H), 2.76 (dd, $J = 8.8$, 13.8 Hz, 1 H), 1.86 (t, $J = 14.2$ Hz, 4 H), 1.76 - 1.67 (m, 1 H), 1.65 - 1.51 (m, 1 H), 1.34 - 1.04 (m, 5 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 188.4$, 161.6, 138.3, 134.5, 133.5, 131.3, 129.4, 128.7, 128.6, 126.6, 55.3, 41.3, 38.3, 30.4, 28.4, 26.5, 26.3

2-oxo-2-phenyl-N-((1R,2R)-2-phenylcyclohexyl)acetamide (4-40)

270 mg (0.878 mmol, 75.7%) of 2-oxo-2-phenyl-N-((1R,2R)-2-phenylcyclohexyl)acetamide was obtained from 204 mg (1.16 mmol) of (1R,2R)-2-phenylcyclohexanamine, 183 mg (1.22 mmol) of 2-oxo-2-phenylacetic acid, 290 mg (1.51 mmol) of EDCI, 204 mg (1.51 mmol) of HOBt and 2.8 mL of DMF.

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 8.06 - 7.96$ (m, 2 H), 7.66 - 7.48 (m, 1 H), 7.48 - 7.14 (m, 8 H), 4.60 (dq, $J = 3.2$, 9.4 Hz, 1 H), 3.06 (dt, $J = 4.0$, 11.6 Hz, 1 H), 2.12 (d, $J = 15.0$ Hz, 1 H), 2.06 - 1.66 (m, 5 H), 1.64 - 1.46 (m, 2 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 188.7$, 161.7, 142.9, 134.4, 133.3, 131.2, 128.6, 128.5, 127.7, 126.7, 50.0, 45.6, 31.3, 25.9, 25.7, 20.8

(S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone (4-11)
To a flame-dried Schlenk flask was added 400 mg (1.29 mmol) of (S)-N-(4-methyl-1-phenylpentan-2-yl)-2-oxo-2-phenylacetamide, 472 mg (3.87 mmol) of DMAP and 50 mL (0.025 M) of toluene. The reaction mixture was cooled to 0 °C, and 1.09 mL (6.45 mmol) of Tf₂O was slowly added. After 10 min stirring at 0 °C, the reaction mixture was stirred at 90 °C for 8 h. It was quenched by 10 mL of a saturated Na₂CO₃ aqueous solution. The reaction mixture was extracted with DCM (3 x 40 mL) and dried over anhydrous MgSO₄. All volatiles were removed in vacuo. Silicagel column chromatography with a 95:5 mixture of hexane and ethyl acetate as the eluent gave 370 mg (1.27 mmol, 98.4%) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone.

¹H NMR (300 MHz, CHLOROFORM-d) δ = 8.01 - 8.14 (m, 2 H), 7.54 - 7.69 (m, 1 H), 7.20 - 7.53 (m, 6 H), 3.84 - 3.98 (m, 1 H), 2.94 (dd, J=16.1, 5.6 Hz, 1 H), 2.68 (dd, J=16.0, 11.0 Hz, 1 H), 1.88 - 2.04 (m, J=13.5, 6.7, 6.7, 6.7 Hz, 1 H), 1.70 - 1.84 (m, 1 H), 1.50 (ddd, J=13.6, 7.0, 6.9 Hz, 1 H), 0.98 (dd, J=6.6, 2.2 Hz, 6 H)

¹³C NMR (75 MHz, CHLOROFORM-d) δ =194.08, 164.15, 137.16, 135.74, 134.05, 131.72, 130.69, 128.71, 128.33, 127.33, 126.95, 126.62, 55.34, 44.50, 31.43, 25.03, 23.08, 22.80

HRMS Calcd. for C₂₀H₂₁NO [M+H]⁺: 291.1696, Found: 291.1700

[α]²⁰D - 13.9° (c 1.21, CHCl₃)

(R)-(3-cyclohexyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone (4-37)
280 mg (0.882 mmol, 98.7%) of \((R)\)-(3-cyclohexyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone was obtained from 300 mg (0.894 mmol) of \(2(R)\)-N-(1-cyclohexyl-2-phenylethyl)-2-oxo-2-phenylacetamide, 327 mg (2.68 mmol) of DMAP, 752 µL (4.47 mmol) of Tf₂O and 36 mL of toluene.

\(^1\)H NMR (300MHz ,CHLOROFORM-d) \(\delta = 8.34 - 7.97\) (m, 2 H), 7.82 - 7.56 (m, 1 H), 7.56 - 7.34 (m, 4 H), 7.34 - 6.96 (m, 2 H), 3.53 (dt, \(J = 6.3, 12.4\) Hz, 1 H), 2.96 - 2.70 (m, 2 H), 2.05 (d, \(J = 11.4\) Hz, 1 H), 1.94 - 1.62 (m, 5 H), 1.49 - 1.12 (m, 5 H)

\(^13\)C NMR (75MHz ,CHLOROFORM-d) \(\delta = 194.0, 164.1, 138.0, 135.8, 134.0, 131.6, 130.7, 128.7, 128.3, 127.2, 127.1, 126.5, 62.4, 42.9, 30.1, 29.7, 28.2, 26.8, 26.7

\(((4aR,10bR)-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl)(phenyl)methanone (4-41)

80 mg (0.276 mmol, 94.7%) of \(((4aR,10bR)-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl)(phenyl)methanone was obtained from 90 mg (0.292 mmol) of 2-oxo-2-phenyl-N-((1R,2R)-2-phenylcyclohexyl)acetamide, 107 mg (0.878 mmol) of DMAP, 246 µL (1.46 mmol) of Tf₂O and 12 mL of toluene.
$^1$H NMR (299 MHz, CHLOROFORM-d) $\delta = 8.17 - 8.03$ (m, 2 H), 7.67 - 7.13 (m, 7 H), 3.90 (q, $J = 4.7$ Hz, 1 H), 2.96 - 2.80 (m, 1 H), 2.18 (d, $J = 10.2$ Hz, 1 H), 1.97 - 1.35 (m, 7 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-d) $\delta = 194.3, 165.4, 142.4, 135.7, 134.2, 132.1, 130.6, 128.8, 127.5, 127.2, 126.9, 125.8, 57.1, 37.6, 30.9, 29.0, 24.4, 22.3

$(S,E)$-$(3$-isobutyl-$3,4$-dihydroisoquinolin-1-yl)(phenyl)methylene-3,5-bis(trifluoromethyl)aniline (4-67)

![Chemical Structure](image)

37.0 mg (0.0736 mmol, 79.5%) of $(S,E)$-$(3$-isobutyl-$3,4$-dihydroisoquinolin-1-yl)(phenyl)methylene-3,5-bis(trifluoromethyl)aniline was obtained from 27.0 mg (0.0926 mmol) of $(S)$-$(3$-isobutyl-$3,4$-dihydroisoquinolin-1-yl)(phenyl)methanone, 25.6 µL (1.85 mmol) of Et$_3$N, 71.3 µL (0.460 mmol) of 3,5-bis(trifluoromethyl)aniline and 110 µL of TiCl$_4$ (1 M in toluene).

$^1$H NMR (300 MHz, CHLOROFORM-d) $\delta = 7.95$ (d, $J = 7.4$ Hz, 2 H), 7.55 - 7.34 (m, 4 H), 7.34 - 7.20 (m, 3 H), 7.20 - 7.01 (m, 3 H), 3.78 - 3.55 (m, 1 H), 2.63 (dd, $J = 5.5, 16.0$ Hz, 1 H), 1.88 - 1.65 (m, 1 H), 1.57 (dt, $J = 6.7, 13.3$ Hz, 1 H), 1.40 - 1.15 (m, 1 H), 0.85 (d, $J = 6.5$ Hz, 3 H), 0.88 (d, $J = 6.8$ Hz, 3 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-d) $\delta = 163.0, 151.9, 136.3, 136.1, 132.0, 131.7, 131.1, 128.7, 128.0, 127.1, 125.7, 124.9, 121.3, 120.7, 116.9, 54.9, 44.2, 30.7, 24.5, 22.6, 22.4

HRMS Calcd. for C$_{28}$H$_{24}$F$_{6}$N$_{2}$ [M+H]$^+$: 503.1916, Found: 503.1919
$[\alpha]^{32}_D - 43.4^\circ$ (c 0.78, CHCl$_3$)

$(S,E)$-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-1,1-diphenylmethanamine (4-13)

46.0 mg (0.100 mmol, 72.9%) of $(S,E)$-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-1,1-diphenylmethanamine was obtained from 40.0 mg (0.137 mmol) of $(S)$-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 37.9 µL (0.274 mmol) of Et$_3$N, 118 µL (0.685 mmol) of diphenylmethanamine and 165 µL of TiCl$_4$ (1 M in toluene).

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 7.96$ (d, $J = 10.0$ Hz, 2 H), 7.52 - 7.12 (m, 15 H), 6.94 (br. s., 1 H), 6.89 - 6.55 (m, 1 H), 5.91 - 5.73 (m, 1 H), 4.09 - 3.85 (m, 1 H), 3.13 - 2.89 (m, 1 H), 2.83 - 2.65 (m, 1 H), 2.12 - 1.66 (m, 2 H), 1.58 - 1.41 (m, 1 H), 0.97 (d, $J = 6.4$ Hz, 6 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 164.5, 144.2, 137.9, 137.7, 136.6, 136.0, 131.6, 130.6, 128.4, 128.3, 127.5, 127.4, 126.9, 70.0, 54.9, 44.8, 31.9, 31.6, 24.8, 23.0

HRMS Calcd. for C$_{33}$H$_{32}$N$_2$ [M+H]$^+$: 457.2638, Found: 457.2638

$[\alpha]^{32}_D - 88.8^\circ$ (c 1.08, CHCl$_3$)

$(S,E)$-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)anthracen-9-amine (4-68)
36.0 mg (0.0773 mmol, 75.0%) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)anthracen-9-amine was obtained from 30.0 mg (0.103 mmol) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 100 µL (0.723 mmol) of Et₃N, 100 mg (0.435 mmol) of anthracen-9-aminium chloride and 125 µL of TiCl₄ (1 M in toluene).

¹H NMR (300MHz, CHLOROFORM-d) δ = 8.27 (d, J = 6.7 Hz, 2 H), 8.14 - 7.86 (m, 3 H), 7.86 - 7.65 (m, 2 H), 7.65 - 7.45 (m, 3 H), 7.45 - 7.12 (m, 4 H), 7.03 (d, J = 7.6 Hz, 1 H), 6.95 - 6.76 (m, 1 H), 6.76 - 6.52 (m, 2 H), 3.29 (s, 1 H), 1.94 - 1.72 (m, J = 7.3 Hz, 1 H), 1.67 - 1.47 (m, 1 H), 1.19 (dt, J = 7.1, 13.7 Hz, 1 H), 0.99 - 0.82 (m, 2 H), 0.76 (t, J = 7.0 Hz, 6 H)

¹³C NMR (75MHz, CHLOROFORM-d) δ = 168.0, 163.7, 143.7, 137.2, 131.8, 131.6, 131.4, 130.2, 129.2, 128.9, 127.8, 127.3, 126.9, 126.1, 125.4, 125.3, 125.2, 123.9, 121.7, 54.7, 30.8, 29.9, 24.5, 22.8, 22.7

HRMS Calcd. for C₃₄H₃₀N₂ [M+H]⁺: 467.2482, Found: 467.2487

[α]²⁸D = 252.9° (c 0.5, CHCl₃)

(S)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,6-diisopropylaniline (4-16)
217 mg (0.482 mmol, 70.6%) of (S)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,6-diisopropylaniline was obtained from 200 mg (0.686 mmol) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 190 µL (1.37 mmol) of Et₃N, 647 µL (3.43 mmol) of 2,6-diisopropylaniline and 820 µL of TiCl₄ (1 M in toluene).

¹H NMR (300 MHz, CHLOROFORM-d) δ = 8.07 (d, J=6.5 Hz, 2 H), 7.42 - 7.58 (m, 3 H), 7.19 - 7.26 (m, 1 H), 6.80 - 7.15 (m, 6 H), 3.54 (br. s., 1 H), 3.00 - 3.15 (m, 1 H), 2.78 (br. s., 1 H), 2.38 (dd, J=15.5, 4.7 Hz, 1 H), 1.84 (dt, J=13.1, 6.8 Hz, 2 H), 1.55 (dt, J=13.7, 7.1 Hz, 1 H), 0.80 - 1.30 (m, 19 H)

¹³C NMR (75MHz ,CHLOROFORM-d) δ = 163.5, 163.2, 146.2, 137.4, 137.1, 136.7, 135.6, 131.0, 130.4, 128.6, 128.3, 127.5, 126.6, 125.7, 123.1, 121.7, 54.7, 44.2, 31.2, 28.5, 28.4, 24.5, 24.0, 23.0, 22.6, 20.9, 20.8


[α]²₀D - 8.7° (c 0.96, CHCl₃)

(S)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4,6-trimethylaniline (4-12)
To a flame-dried Schlenk flask was added 204 mg (0.700 mmol) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 194 µL (1.40 mmol) of Et₃N, 492 µL (3.50 mmol) of mesitylamine and 8 mL (0.1 M) of toluene. The reaction mixture was cooled to 0 °C, and 840 µL of TiCl₄ solution (1 M in toluene) was slowly added. After 10 min stirring at 0 °C, the reaction mixture was stirred at room temperature for 12 h. It was quenched by 4 mL of a saturated NH₄Cl aqueous solution. The reaction mixture was extracted with DCM (3 x 20 mL) and dried over anhydrous MgSO₄. All volatiles were removed in vacuo. Silicagel column chromatography with a 99:1 mixture of hexane and ethyl acetate as the eluent gave 280 mg (0.685 mmol, 97.8%) of (S)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4,6-trimethylaniline.

¹H NMR (300 MHz, CHLOROFORM-d) δ = 7.95 - 8.14 (m, 2 H), 7.40 - 7.58 (m, 3 H), 7.19 - 7.27 (m, 1 H), 7.01 - 7.14 (m, 3 H), 6.67 (br. s., 1 H), 6.55 (br. s., 1 H), 3.56 (dd, J=11.9, 5.4 Hz, 1 H), 2.46 (dd, J=15.5, 5.0 Hz, 1 H), 2.17 (s, 3 H), 2.10 (br. s., 3 H), 1.75 - 2.00 (m, 4 H), 1.52 - 1.63 (m, 1 H), 1.23 - 1.34 (m, 2 H), 0.91 (dd, J=10.7, 6.6 Hz, 6 H)

¹³C NMR (75MHz, CHLOROFORM-d) δ = 165.6, 163.2, 145.7, 137.3, 136.9, 131.8, 131.0, 130.6, 128.6, 128.3, 127.9, 127.6, 127.4, 126.2, 126.0, 54.7, 44.4, 31.3, 30.3, 29.7, 24.5, 22.8, 22.6, 20.6

HRMS Calcd. for C₂₉H₃₂N₂ [M+H]⁺: 409.2638, Found: 409.2640

[α]²⁰°D - 28.2° (c 0.97, CHCl₃)
(S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-3,5-dimethylaniline (4-17)

69.0 mg (0.175 mmol, 45.1%) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-3,5-dimethylaniline was obtained from 113 mg (0.388 mmol) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 107 µL (0.776 mmol) of Et₃N, 242 µL (1.94 mmol) of 3,5-dimethylaniline and 465 µL of TiCl₄ (1 M in toluene).

¹H NMR (300MHz ,CHLOROFORM-d) δ = 8.25 - 7.99 (m, 1 H), 7.93 (br. s., 1 H), 7.59 (d, J = 7.3 Hz, 1 H), 7.51 - 7.20 (m, 4 H), 7.17 - 7.04 (m, 2 H), 6.79 - 6.25 (m, 3 H), 3.99 - 3.61 (m, 1 H), 3.08 - 2.46 (m, 2 H), 2.39 - 2.04 (m, 6 H), 1.94 (dd, J = 6.7, 13.5 Hz, 1 H), 1.85 - 1.61 (m, 1 H), 1.50 (dd, J = 6.9, 13.6 Hz, 1 H), 1.03 - 0.77 (m, 6 H)

¹³C NMR (75MHz ,CHLOROFORM-d) δ = 164.3, 150.6, 137.7, 137.5, 136.4, 134.0, 131.7, 131.2, 130.7, 128.6, 128.3, 127.9, 127.3, 127.1, 126.5, 125.5, 118.5, 113.3, 55.3, 44.5, 31.4, 25.0, 24.8, 23.1, 22.8, 21.4

[α]²⁹D = 27.4° (c 1.58, CHCl₃)


(S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,6-dimethylaniline (4-66)
99.0 mg (0.234 mmol, 68.2%) of \((S,E)-N-((3\text{-isobutyl-3,4-dihydroisoquinolin-1-yl})(phenyl)methylene)-2,6\text{-dimethylaniline\) was obtained from 100 mg (0.343 mmol) of \((S)-(3\text{-isobutyl-3,4-dihydroisoquinolin-1-yl})(phenyl)methanone, 94.9 \mu L (0.686 mmol) of Et\text{3}N, 210 \mu L (1.72 mmol) of 2,6-dimethylaniline and 410 \mu L of TiCl\text{4} (1 M in toluene).

\(^1\)H NMR (300MHz ,CHLOROFORM-d) \(\delta = 8.05\) (d, \(J = 7.0\) Hz, 1 H), 7.62 - 7.39 (m, 3 H), 7.35 - 7.17 (m, 2 H), 7.16 - 6.93 (m, 3 H), 6.91 - 6.60 (m, 3 H), 3.53 (td, \(J = 6.4, 12.2\) Hz, 1 H), 2.41 (dd, \(J = 5.0, 15.5\) Hz, 1 H), 2.22 - 2.04 (m, 3 H), 2.01 - 1.74 (m, 4 H), 1.63 - 1.50 (m, 1 H), 1.39 - 1.18 (m, 2 H), 0.89 (d, \(J = 10.3\) Hz, 3 H), 0.91 (d, \(J = 10.6\) Hz, 3 H)

\(^{13}\)C NMR (75MHz ,CHLOROFORM-d) \(\delta = 165.7, 163.3, 148.4, 137.4, 131.3, 130.9, 128.9, 128.5, 127.8, 127.5, 126.5, 126.1, 123.0, 54.9, 44.9, 31.5, 24.8, 23.0, 22.9, 19.2, 18.5

HRMS Calcd. for C\text{28}H\text{30}N\text{2} [M+H]\text{+}: 395.2482, Found: 395.2487

\([\alpha]^{32}_D = -25.3^\circ\) (c 1.58, CHCl\text{3})

\((S,E)-2,6\text{-diethyl-N-((3\text{-isobutyl-3,4-dihydroisoquinolin-1-yl})(phenyl)methylene)aniline\) (4-65)
26.0 mg (0.0615 mmol, 71.7%) of (S,E)-2,6-diethyl-\(N\)-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)aniline was obtained from 25.0 mg (0.0857 mmol) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 23.6 \(\mu\)L (0.171 mmol) of Et\(_3\)N, 66.6 \(\mu\)L (0.428 mmol) of 2,6-diethylaniline and 103 \(\mu\)L of TiCl\(_4\) (1 M in toluene).

\(^1\)H NMR (300MHz ,CHLOROFORM-d) \(\delta = 8.04\) (d, \(J = 6.7\) Hz, 2 H), 7.59 - 7.39 (m, 3 H), 7.25 - 7.18 (m, 1 H), 7.14 - 6.97 (m, 3 H), 6.95 - 6.69 (m, 3 H), 3.48 (dd, \(J = 5.1, 11.9\) Hz, 1 H), 2.60 (dt, \(J = 7.6, 15.2\) Hz, 1 H), 2.49 - 2.32 (m, 3 H), 1.95 - 1.70 (m, 1 H), 1.63 - 1.41 (m, 2 H), 1.34 - 1.04 (m, 5 H), 1.03 - 0.78 (m, 9 H)

\(^{13}\)C NMR (75MHz ,CHLOROFORM-d) \(\delta = 164.9, 163.3, 137.4, 137.3, 132.6, 131.7, 131.3, 130.8, 128.9, 128.6, 127.7, 126.5, 126.0, 124.9, 123.2, 54.8, 31.5, 29.9, 25.2, 24.7, 24.5, 23.0, 22.8, 13.5, 13.2

HRMS Calcd. for C\(_{30}\)H\(_{44}\)N\(_2\) [M+H]\(^+\): 423.2795, Found: 423.2795

\([\alpha]\)^{29}_D - 18.4° (c 0.79, CHCl\(_3\))

(S,E)-\(N\)-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2-isopropylaniline (4-24)

![Diagram](image)

42.0 mg (0.102 mmol, 71.7%) of (S,E)-\(N\)-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2-isopropylaniline was obtained from 33.0 mg (0.113 mmol) of (S)-(3-
isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 31.0 µL (0.226 mmol) of Et₃N, 80.0 µL (0.560 mmol) of 2-isopropylaniline and 136 µL of TiCl₄ (1 M in toluene).

¹H NMR (299MHz, CHLOROFORM-d) δ = 8.00 (d, J = 6.2 Hz, 2 H), 7.54 - 7.37 (m, 3 H), 7.33 - 7.23 (m, 1 H), 7.21 - 7.05 (m, 4 H), 7.00 - 6.77 (m, 2 H), 6.63 (br. s., 1 H), 3.80 - 3.62 (m, 1 H), 3.23 (br. s., 1 H), 2.67 (dd, J = 4.5, 14.7 Hz, 1 H), 1.88 - 1.65 (m, 1 H), 1.56 (dd, J = 6.4, 12.9 Hz, 1 H), 1.40 - 1.04 (m, 8 H), 1.02 - 0.72 (m, 6 H)

¹³C NMR (75MHz, CHLOROFORM-d) δ = 164.1, 148.0, 140.0, 137.5, 136.6, 131.2, 130.7, 128.7, 128.0, 127.1, 126.3, 125.2, 124.5, 119.0, 54.8, 53.7, 44.5, 31.4, 28.4, 24.7, 23.0, 22.7

(S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4-dimethylaniline (4-25)

41.0 mg (0.104 mmol, 71.7%) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4-dimethylaniline was obtained from 35.0 mg (0.120 mmol) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 33.0 µL (0.240 mmol) of Et₃N, 75.0 µL (0.600 mmol) of 2,4-dimethylaniline and 144 µL of TiCl₄ (1 M in toluene).

¹H NMR (300MHz, CHLOROFORM-d) δ = 8.04 - 7.90 (m, 2 H), 7.54 - 7.34 (m, 3 H), 7.32 - 7.21 (m, 1 H), 7.19 - 7.02 (m, 3 H), 6.83 (s, 1 H), 6.73 - 6.51 (m, 2 H), 3.84 - 3.62 (m, 1 H), 2.79 - 2.57 (m, 1 H), 2.34 - 2.07 (m, 7 H), 1.67 - 1.48 (m, 1 H), 1.39 - 1.19 (m, 2 H), 0.94 - 0.80 (m, 6 H)
\[ ^{13}\text{C NMR (75MHz ,CHLOROFORM-d)} \delta = 164.4, 146.6, 137.4, 136.6, 134.1, 133.4, 131.1, 130.8, 129.4, 128.7, 128.6, 128.1, 127.1, 126.3, 126.0, 118.8, 55.3, 54.9, 44.5, 31.3, 24.8, 23.0, 21.0, 18.5 \]

\((S,E)-N-((3\text{-isobutyl-3,4-dihydroisoquinolin-1-yl})(phenyl)methylene)biphenyl-2-amine (4-26)\)

\[
\begin{align*}
\text{42.0 mg (0.0948 mmol, 71.7%)} & \text{ of (S,E)-N-((3\text{-isobutyl-3,4-dihydroisoquinolin-1-yl})(phenyl)methylene)biphenyl-2-amine was obtained from 31.4 mg (0.107 mmol) of (S)-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 30.0 µL (0.215 mmol) of Et}_3\text{N, 91.0 mg (0.535 mmol) of biphenyl-2-amine and 129 µL of TiCl}_4 (1 \text{ M in toluene}).}
\end{align*}
\]

\[ ^{1}\text{H NMR (299MHz ,CHLOROFORM-d)} \delta = 7.86 (d, J = 7.1 \text{ Hz, } 2 \text{ H}), 7.59 - 7.51 (m, 2 \text{ H}), 7.49 - 7.29 (m, 5 \text{ H}), 7.28 - 7.00 (m, 6 \text{ H}), 6.93 - 6.76 (m, 2 \text{ H}), 6.58 (d, J = 7.4 \text{ Hz, } 1 \text{ H}), 3.77 - 3.58 (m, 1 \text{ H}), 2.68 (dd, J = 3.8, 16.0 \text{ Hz, } 1 \text{ H}), 1.97 - 1.70 (m, 1 \text{ H}), 1.70 - 1.49 (m, 1 \text{ H}), 1.40 - 1.18 (m, 2 \text{ H}), 1.02 - 0.64 (m, 6 \text{ H}) \]

\[ ^{13}\text{C NMR (75MHz ,CHLOROFORM-d)} \delta = 164.7, 163.8, 148.3, 140.3, 137.2, 136.4, 132.8, 131.1, 130.9, 130.7, 130.1, 129.8, 129.3, 129.0, 128.6, 128.0, 127.8, 127.4, 127.2, 126.7, 126.5, 124.4, 120.7, 115.8, 54.8, 44.5, 31.4, 24.7, 23.1, 22.7 \]

\((R,E)-N-((3\text{-cyclohexyl-3,4-dihydroisoquinolin-1-yl})(phenyl)methylene)-2,4,6\text{-trimethylaniline (4-38)}\)
204 mg (0.470 mmol, 99.6%) of (R,E)-N-((3-cyclohexyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4,6-trimethylaniline was obtained from 150 mg (0.472 mmol) of (R)-(3-cyclohexyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone, 130 µL (0.945 mmol) of Et₃N, 332 µL (2.36 mmol) of 2,4,6-trimethylaniline and 570 µL of TiCl₄ (1 M in toluene).

$^{1}$H NMR (299MHz ,CHLOROFORM-d) $\delta = 8.07$ (dd, $J = 1.4$, 7.9 Hz, 2 H), 7.63 - 7.39 (m, 3 H), 7.35 - 6.99 (m, 4 H), 6.71 (br. s., 1 H), 6.55 (br. s., 1 H), 3.22 (dt, $J = 5.3$, 13.9 Hz, 1 H), 2.44 (dd, $J = 4.8$, 15.6 Hz, 1 H), 2.19 (s, 6 H), 2.14 - 1.98 (m, 1 H), 1.89 (br. s., 1 H), 1.86 - 1.46 (m, 8 H), 1.40 - 1.00 (m, 5 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 165.7$, 163.3, 145.8, 137.9, 137.6, 131.7, 131.0, 130.5, 128.6, 128.3, 128.0, 127.6, 126.7, 126.2, 125.4, 62.1, 42.6, 29.6, 29.4, 28.0, 26.7, 26.5, 20.7, 19.2, 18.2

(E)-N-(((4aR,10bR)-1,2,3,4a,10b-hexahydropyridin-6-yl)(phenyl)methylene)-2,4,6-trimethylaniline (4-42)

67.0 mg (0.164 mmol, 95.3%) of (E)-N-(((4aR,10bR)-1,2,3,4a,10b-hexahydropyridin-6-yl)(phenyl)methylene)-2,4,6-trimethylaniline was obtained from 50
mg (0.172 mmol) of ((4aR,10bR)-1,2,3,4,4a,10b-hexahydrophenanthridin-6-
yl)(phenyl)methanone, 48.0 µL (0.345 mmol) of Et₃N, 121 µL (0.860 mmol) of 2,4,6-
trimethylaniline and 206 µL of TiCl₄ (1 M in toluene).

¹H NMR (300MHz ,CHLOROFORM-d) δ = 8.10 - 8.02 (m, 2 H), 7.57 - 7.41 (m, 3 H),
7.33 - 7.23 (m, 1 H), 7.18 - 7.02 (m, 3 H), 6.74 (br. s., 1 H), 6.50 (s, 1 H), 3.71 - 3.63 (m, 1 H),
2.50 - 2.38 (m, 1 H), 2.32 - 2.11 (m, 8 H), 1.78 - 1.57 (m, 4 H), 1.55 - 1.43 (m, 1 H), 1.42 - 1.20
(m, 3 H), 1.14 (d, J = 12.3 Hz, 1 H)

¹³C NMR (75MHz ,CHLOROFORM-d) δ = 166.2, 165.2, 146.4, 143.3, 137.8, 132.1,
131.5, 131.4, 128.9, 128.5, 128.2, 127.9, 127.5, 127.3, 126.3, 125.9, 125.1, 56.7, 38.0, 31.9, 27.1,
22.9, 20.8, 19.7, 18.2, 14.4

(S)-2-(3,5-bis(trifluoromethyl)phenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-
imidazo[5,1-a]isoquinolin-4-iium chloride (4-71)

![Chemical Structure](image)

21.0 mg (0.0381 mmol, 70.9%) of (S)-2-(3,5-bis(trifluoromethyl)phenyl)-5-isobutyl-1-
phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-iium chloride was obtained from 27.0 mg
(0.0537 mmol) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-3,5-
bis(trifluoromethyl)aniline and 29.8 µL (0.322 mmol) of chloromethyl ethyl ether.
$^1$H NMR (299MHz, CHLOROFORM-d) $\delta = 10.88$ (br. s., 1 H), 8.32 - 6.48 (m, 12 H), 5.33 (br. s., 1 H), 3.56 (d, $J = 16.7$ Hz, 1 H), 3.06 (d, $J = 15.6$ Hz, 1 H), 2.03 - 1.61 (m, 3 H), 1.20 - 0.76 (m, 6 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 136.7, 134.7, 133.5, 133.1, 131.8, 131.8, 131.3, 131.0, 130.6, 129.9, 129.7, 127.8, 126.9, 124.7, 124.5, 124.0, 123.9, 114.3, 54.4, 41.6, 32.5, 24.9, 22.9, 21.7

HRMS Calcd. for C$_{29}$H$_{25}$F$_6$N$_2$ [M$^+$]: 515.1916, Found: 515.1932

$[\alpha]^{32}_D -11.8^\circ$ (c 0.65, CHCl$_3$)

$(S)$-2-benzhydryl-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-$a$]isoquinolin-4-ium chloride (4-73)

30.0 mg (0.0594 mmol, 90.3%) of $(S)$-2-benzhydryl-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-$a$]isoquinolin-4-ium chloride was obtained from 30.0 mg (0.0658 mmol) of $(S,E)$-$N$-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-1,1-diphenylmethanamine and 36.5 $\mu$L (0.394 mmol) of chloromethyl ethyl ether.

$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 9.96$ (s, 1 H), 7.85 - 7.49 (m, 2 H), 7.49 - 7.11 (m, 14 H), 7.11 - 6.88 (m, 2 H), 6.78 (d, $J = 7.6$ Hz, 1 H), 6.31 (s, 1 H), 5.68 (br. s., 1 H), 3.59 (br. s., 1 H), 2.97 (d, $J = 16.1$ Hz, 1 H), 1.64 - 1.37 (m, 3 H), 0.96 - 0.82 (m, 6 H)
\[^{13}\text{C NMR (75MHz ,CHLOROFORM-d)} \delta = 136.1, 135.8, 132.0, 131.3, 130.3, 129.9, 129.8, 129.4, 128.8, 128.5, 127.6, 125.8, 124.4, 122.9, 66.3, 53.8, 41.9, 32.5, 25.3, 23.2, 22.2\]

HRMS Calcd. for C\(_{34}\)H\(_{33}\)N\(_2\) [M]: 469.2638, Found: 469.2641

[\(\alpha\)]\(^{29}\)\(_D\) + 36.6° (c 0.73, CHCl\(_3\))

\((S)-2\)-(anthracen-9-yl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-\(\alpha\)]isoquinolin-4-ium chloride (4-72)

20.0 mg (0.0388 mmol, 90.4%) of (\(S\))-2-(anthracen-9-yl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-\(\alpha\)]isoquinolin-4-ium chloride was obtained from 20.0 mg (0.0429 mmol) of (\(S,E\))-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)anthracen-9-amine and 24.5 µL (0.264 mmol) of chloromethyl ethyl ether.

\[^{1}\text{H NMR (300MHz ,CHLOROFORM-d)} \delta = 10.51 (\text{br. s., 1 H}), 8.59 (\text{s, 1 H}), 8.09 (\text{d, } J = 8.5 \text{ Hz, 1 H}), 7.96 (\text{d, } J = 8.5 \text{ Hz, 1 H}), 7.73 - 7.33 (\text{m, 8 H}), 7.23 - 6.93 (\text{m, 7 H}), 5.94 (\text{br. s., 1 H}), 3.86 (\text{br. s., 1 H}), 3.19 (\text{d, } J = 11.7 \text{ Hz, 1 H}), 1.85 (\text{br. s., 1 H}), 1.73 (\text{br. s., 2 H}), 1.06 (\text{d, } J = 5.6 \text{ Hz, 3 H}), 1.09 (\text{d, } J = 5.6 \text{ Hz, 3 H})\]

\[^{13}\text{C NMR (75MHz ,CHLOROFORM-d)} \delta = 138.5, 132.4, 131.9, 131.3, 130.9, 130.8, 130.6, 130.1, 129.5, 129.4, 129.1, 128.7, 127.8, 126.6, 126.1, 125.3, 124.8, 123.7, 123.0, 121.9, 120.6, 54.3, 42.3, 33.0, 25.5, 23.3, 22.4\]
HRMS Calcd. for C$_{35}$H$_{31}$N$_2$ [M]$^+$: 479.2482, Found: 479.2488

$[\alpha]^{28}_D +19.2^\circ$ (c 0.7, CHCl$_3$)

(S)-2-(2,6-diisopropylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-$a$]isoquinolin-4-ium chloride (4-20)

60.0 mg (0.120 mmol, 75.5%) of (S)-2-(2,6-diisopropylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-$a$]isoquinolin-4-ium chloride was obtained from 72.0 mg (0.159 mmol) of ((S)-N-((3-isobutyl-3,4-dihyridoisoquinolin-1-yl)(phenyl)methylene)-2,6-diisopropylaniline and 83.5 µL (0.954 mmol) of chloromethyl ethyl ether.

$^1$H NMR (300 MHz, CHLOROFORM-d) $\delta$ = 10.63 (s, 1 H), 7.16 - 7.50 (m, 6 H), 6.79 - 7.16 (m, 6 H), 5.74 - 6.00 (m, 1 H), 3.70 (dd, $J$=16.1, 4.7 Hz, 1 H), 3.01 (d, $J$=16.4 Hz, 1 H), 2.53 (br. s., 1 H), 2.42 (dt, $J$=13.7, 6.8 Hz, 1 H), 2.27 (dt, $J$=13.3, 6.5 Hz, 1 H), 1.41 - 1.61 (m, 2 H), 0.41 - 1.36 (m, 18 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta$ = 145.9, 145.4, 137.2, 131.9, 131.5, 130.6, 130.3, 129.9, 129.7, 129.1, 128.1, 127.3, 125.6, 125.0, 124.7, 124.5, 124.0, 122.3, 53.1, 41.8, 32.9, 31.4, 29.1, 28.8, 26.0, 25.5, 24.8, 22.5, 22.3, 22.1

HRMS Calcd. for C$_{33}$H$_{30}$ClN$_2$ [M]$^+$: 463.3108, Found: 463.3108

$[\alpha]^{29}_D -38.1^\circ$ (c 0.90, CHCl$_3$)
(S)-5-isobutyl-2-mesityl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride (4-14)

To a flame-dried Schlenk flask was added 225 mg (0.551 mmol) of (S)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4,6-trimethylaniline, 256 µL (2.75 mmol) of chloromethyl ethyl ether and 28 mL (0.02M) of THF. After 48 h, all volatiles were removed in vacuo. Silicagel column chromatography with a 95:5 mixture of DCM and methanol as the eluent gave 220 mg (0.481 mmol, 87.3%) of (S)-5-isobutyl-2-mesityl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride.

$^1$H NMR (299 MHz, CHLOROFORM-d) $\delta = 10.35$ (s, 1 H), 7.30 - 7.48 (m, 5 H), 7.04 - 7.24 (m, 4 H), 6.93 (s, 1 H), 6.76 (s, 1 H), 5.63 (br. s., 1 H), 3.64 (dd, $J=16.0, 4.1$ Hz, 1 H), 3.07 (d, $J=15.9$ Hz, 1 H), 2.18 (s, 3 H), 2.23 (s, 3 H), 1.90 (s, 3 H), 1.47 - 1.72 (m, 3 H), 0.99 (dd, $J=9.1, 6.2$ Hz, 3 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 140.8, 136.8, 135.1, 134.4, 131.7, 130.6, 130.2, 129.8, 129.7, 129.3, 129.2, 128.9, 127.4, 125.8, 125.3, 124.4, 122.6, 53.5, 41.8, 32.7, 25.0, 22.8, 22.0, 21.0, 17.9

HRMS Calcd. for C$_{30}$H$_{33}$N$_2$ [M]: 421.2638, Found: 421.2646

$[\alpha]^{29}_D - 23^\circ$ (c 1.06, CHCl$_3$)

(S)-2-(3,5-dimethylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride (4-21)
37.0 mg (0.0835 mmol, 84.5%) of \((S)-2-(3,5\text{-dimethylphenyl})-5\text{-isobutyl}-1\text{-phenyl}-5,6\text{-dihydro-2H-imidazo[5,1-}
\text{a]}\text{isoquinolin-4-ium chloride was obtained from 39.0 mg (0.0988 mmol) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-3,5-
\text{dimethylaniline and 91.6 \mu L (0.988 mmol) of chloromethyl ethyl ether}.

\(^1\)H NMR (299MHz, CHLOROFORM-d) \(\delta = 10.59 \text{ (s, 1 H), 7.51 - 7.34 (m, 3 H), 7.31 - 7.21 \text{ (m, 4 H), 7.11 - 6.93 (m, 3 H), 6.85 (s, 2 H), 5.69 - 5.58 (m, 1 H), 3.53 (dd, } J = 4.8, 16.1 \text{ Hz, 1 H), 3.02 (d, } J = 15.6 \text{ Hz, 1 H), 2.18 (s, 6 H), 1.80 - 1.61 \text{ (m, 2 H), 1.56 - 1.44 (m, 1 H), 0.99 (d, } J = 6.2 \text{ Hz, 6 H)}.

\(^{13}\)C NMR (75MHz, CHLOROFORM-d) \(\delta = 139.9, 135.9, 133.1, 132.0, 131.0, 130.8, 130.3, 129.8, 129.5, 129.1, 127.7, 126.1, 125.7, 124.5, 123.7, 122.9, 53.7, 41.9, 32.7, 25.2, 23.2, 22.0, 21.2

HRMS Calcd. for \(C_{29}H_{31}N_2 [M]^+\): 407.2482, Found: 407.2487

\([\alpha]^{29}_D \text{ - 24.2}^\circ \text{ (c 0.7, CHCl}_3\)

\((S)-2-(2,6\text{-dimethylphenyl})-5\text{-isobutyl}-1\text{-phenyl}-5,6\text{-dihydro-2H-imidazo[5,1-}
\text{a]}\text{isoquinolin-4-ium chloride (4-70)}

219
40.0 mg (0.0903 mmol, 47.8%) of (S)-2-(2,6-dimethylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride was obtained from 80.0 mg (0.189 mmol) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,6-dimethylaniline and 105 µL (1.14 mmol) of chloromethyl ethyl ether.

$^1$H NMR (299MHz ,CHLOROFORM-d) $\delta = 10.60$ (s, 1 H), 7.48 - 7.30 (m, 5 H), 7.26 - 7.07 (m, 6 H), 7.00 (d, $J = 7.4$ Hz, 1 H), 5.83 - 5.72 (m, 1 H), 3.75 - 3.61 (m, 1 H), 3.10 (dd, $J = 2.0$, 16.1 Hz, 1 H), 2.26 (s, 3 H), 1.99 (s, 3 H), 1.80 - 1.49 (m, 3 H), 1.04 (dd, $J = 6.2$, 8.5 Hz, 6 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 137.2$, 136.0, 135.1, 132.2, 131.8, 131.1, 131.0, 130.6, 130.0, 129.5, 129.0, 127.7, 126.2, 125.6, 124.7, 122.9, 53.9, 42.1, 33.0, 29.9, 25.4, 23.2, 22.4, 18.4

HRMS Calcd. for $C_{29}H_{31}N_2$ [M$^+$]: 407.2482, Found: 407.2490

$[\alpha]_{D}^{29} = 38.8^\circ$ (c 0.77, CHCl$_3$)

(S)-2-(2,6-diethylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride (4-69)
14.0 mg (0.0297 mmol, 85%) of ((S)-2-(2,6-diethylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-α]isoquinolin-4-ium chloride was obtained from 15.0 mg (0.0355 mmol) of (S,E)-2,6-diethyl-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)aniline and 19.7 µL (0.213 mmol) of chloromethyl ethyl ether.

$^1$H NMR (299MHz, CHLOROFORM-d) δ = 10.75 (s, 1 H), 7.47 - 7.29 (m, 6 H), 7.28 - 7.03 (m, 6 H), 5.95 (d, J = 4.5 Hz, 1 H), 3.71 (dd, J = 4.2, 16.1 Hz, 1 H), 3.10 (d, J = 16.1 Hz, 1 H), 2.63 - 2.33 (m, 2 H), 2.05 (dd, J = 7.4, 15.3 Hz, 1 H), 1.83 - 1.41 (m, 4 H), 1.42 - 1.17 (m, 5 H), 1.15 - 0.94 (m, 7 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) δ = 141.2, 140.8, 137.3, 132.1, 131.4, 130.9, 130.5, 130.3, 130.0, 129.6, 129.4, 127.6, 126.9, 126.7, 126.0, 125.4, 124.7, 122.8, 53.6, 42.0, 33.0, 25.3, 24.6, 23.9, 23.1, 22.5, 15.0, 13.8

HRMS Calcd. for C$_{31}$H$_{35}$N$_2$ [M]$^+$: 435.2795, Found: 435.2801

$[α]^{29}_D$ - 34.0° (c 0.92, CHCl$_3$)

((S)-5-isobutyl-2-(2-isopropylphenyl)-1-phenyl-5,6-dihydro-2H-imidazo[5,1-α]isoquinolin-4-ium chloride (4-30)
25.0 mg (0.0547 mmol, 85.0%) of (S)-5-isobutyl-2-(2-isopropylphenyl)-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride was obtained from 30.0 mg (0.0744 mmol) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2-isopropylaniline and 65.0 µL (0.744 mmol) of chloromethyl ethyl ether.

**(S)-2-(2,4-dimethylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride (4-31)**

22.0 mg (0.0497 mmol, 66.7%) of (S)-2-(2,4-dimethylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride was obtained from 30.0 mg (0.0744 mmol) of (S,E)-N-((3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methylene)-2,4-dimethylaniline and 65.0 µL (0.744 mmol) of chloromethyl ethyl ether.

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 10.49$ (br. s., 1 H), 7.53 - 7.17 (m, 8 H), 7.17 - 6.78 (m, 4 H), 5.66 (br. s., 1 H), 3.68 - 3.54 (m, 1 H), 3.06 (d, $J = 15.8$ Hz, 1 H), 2.27 (s, 6 H), 1.81 - 1.60 (m, 2 H), 1.58 - 1.46 (m, 1 H), 1.08 - 0.88 (m, 6 H)
$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 141.4, 136.9, 132.4, 132.1, 130.8, 130.6, 130.5, 130.0, 129.5, 128.9, 128.0, 127.7, 125.9, 125.7, 124.6, 123.0, 53.9, 42.0, 32.9, 25.3, 23.3, 22.2, 21.4, 17.9

$(S)$-5-isobutyl-2-(2-methoxyphenyl)-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride (4-33)

23.0 mg (0.0517 mmol, 66.7%) of $(S)$-5-isobutyl-2-(2-methoxyphenyl)-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium chloride was obtained from 15.8 mg (0.0544 mmol) of $(S)$-(3-isobutyl-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone.

$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 10.44$ (s, 1 H), 7.52 - 7.16 (m, 9 H), 7.16 - 6.98 (m, 2 H), 6.98 - 6.68 (m, 2 H), 5.78 - 5.59 (m, 1 H), 3.68 (s, 3 H), 3.59 (dd, $J = 4.8, 16.3$ Hz, 1 H), 3.04 (d, $J = 15.0$ Hz, 1 H), 1.85 - 1.63 (m, 2 H), 1.60 - 1.43 (m, 1 H), 0.99 (d, $J = 6.2$ Hz, 3 H), 1.03 (d, $J = 6.4$ Hz, 3 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 153.9, 137.2, 132.5, 132.0, 130.6, 130.3, 129.9, 129.2, 128.9, 127.7, 126.0, 125.6, 124.5, 123.2, 122.0, 121.3, 112.3, 56.0, 53.9, 42.0, 33.1, 25.2, 23.4, 22.3

$(4aR,8aR)$-2-mesityl-1-phenyl-4a,5,6,7,8,8a-hexahydro-2H-imidazo[1,5-f]phenanthridin-4-ium chloride (4-43)
15.0 mg (0.0357 mmol, 36.5%) of (4aR,8aR)-2-mesityl-1-phenyl-4a,5,6,7,8,8a-hexahydro-2H-imidazo[1,5-f]phenanthridin-4-ium chloride (**4-43a**) and 15.0 mg (0.0357 mmol, 36.5%) of (4aR,8aR)-2-mesityl-1-phenyl-4a,5,6,7,8,8a-hexahydro-2H-imidazo[1,5-f]phenanthridin-4-ium chloride (**4-43b**) were obtained from 40.0 mg (0.0980 mmol) of (E)-N-(((4aR,10bR)-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl)(phenyl)methylene)-2,4,6-trimethylaniline and 55.0 µL (0.590 mmol) of chloromethyl ethyl ether.

**(4-43a):**

$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 9.65$ (s, 1 H), 7.53 - 7.15 (m, 7 H), 7.15 - 6.98 (m, 2 H), 6.88 (s, 2 H), 5.20 - 5.01 (m, 1 H), 3.55 - 3.38 (m, 1 H), 2.26 (s, 3 H), 2.19 - 1.89 (m, 8 H), 1.89 - 1.70 (m, 2 H), 1.70 - 1.44 (m, 4 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 141.4, 136.3, 135.7, 134.5, 131.0, 130.8, 130.0, 129.6, 129.1, 127.9, 127.5, 126.9, 125.6, 125.2, 122.6, 56.1, 38.9, 29.9, 28.0, 27.6, 22.1, 21.3, 18.1, 17.9

HRMS Calcd. for C$_{30}$H$_{31}$N$_2$ [M$^+$]: 419.2482, Found: 419.2517

$[\alpha]^{20}_D = -0.7^\circ$ (c 1.08, CHCl$_3$)

**(4-43b)**

$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 10.39$ (s, 1 H), 7.48 - 7.29 (m, 5 H), 7.20 (d, $J = 7.0$ Hz, 2 H), 7.09 (d, $J = 3.2$ Hz, 2 H), 6.86 (s, 2 H), 5.27 - 5.06 (m, 1 H), 3.51 - 3.29 (m, 1 H), 2.24 (s, 3 H), 2.16 - 1.91 (m, 9 H), 1.89 - 1.68 (m, 2 H), 1.67 - 1.51 (m, 3 H)
$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 141.2, 137.0, 136.4, 135.5, 134.6, 130.9,$  
130.6, 130.0, 129.7, 129.6, 129.3, 127.9, 127.5, 126.6, 125.8, 125.1, 122.7, 56.1, 38.9, 28.2, 27.6,  
22.4, 22.2, 21.3, 18.3, 18.0

HRMS Calcd. for C$_{30}$H$_{31}$N$_2$ [M]$^+$: 419.2482, Found: 419.2516

[α]$^2_0$ D $– 5.4^\circ$ (c 1.08, CHCl$_3$)

6.4.2 Gold Complexes Synthesis

$(S)$-choloro(2-(2,6-diisopropylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1- 
a]isoquinolin-4-ium-3-yl)aurate(I) (4-44)

To a flame-dried Schlenk flask was added 33.0 mg (0.0661 mmol) of $(S)$-2-(2,6-
diisopropylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-a]isoquinolin-4-ium 
chloride, 9.20 mg (0.0396 mmol) of Ag$_2$O and 1.3 mL (0.05M) of DCM. After stirring for 12 h, 
the reaction mixture was filtered through a pad of celite. The solvent of the filtrate was removed 
under reduced pressure. To another flame-dried Schlenk flask was added the filtered silver 
complex, 22.0 mg (0.0747 mmol) of AuCl•Me$_2$S and 1.3 mL (0.05M) of DCM. The reaction 
mixture was stirred for 12 h at room temperature. The reaction solution was filtered through a 
pad of celite and evaporated to dryness. The residue was dissolved in ether and the solid was 
discarded. Then the ethereal solution was concentrated and additional impurities were washed 
away with hexane to yield 40.0 mg (0.0574 mmol, 86.8 %) of $(S)$-chloro(2-(2,6-
diisopropylphenyl)-5-isobutyl-1-phenyl-5,6-dihydro-2H-imidazo[5,1-α]isoquinolin-4-ium-3-yl)aurate(I).

$^1$H NMR (300MHz, DICHLOROMETHANE-d$_2$) δ = 7.41 - 6.80 (m, 12 H), 5.08 (q, $J$ = 6.2 Hz, 1 H), 3.47 (dd, $J$ = 5.6, 15.8 Hz, 1 H), 2.99 (d, $J$ = 16.1 Hz, 1 H), 2.71 - 2.50 (m, 1 H), 2.29 (dt, $J$ = 6.6, 13.4 Hz, 1 H), 1.77 (dt, $J$ = 6.5, 13.3 Hz, 1 H), 1.56 - 0.53 (m, 20 H)

$^{13}$C NMR (75MHz, DICHLOROMETHANE-d$_2$) δ = 170.7, 147.1, 146.7, 133.4, 132.5, 131.0, 131.0, 130.8, 130.2, 130.1, 129.4, 129.3, 128.4, 128.4, 127.6, 125.6, 125.3, 124.8, 124.7, 55.1, 43.5, 34.1, 29.3, 29.1, 26.6, 26.1, 25.2, 23.7, 23.6, 22.9, 22.6

HRMS Calcd. for C$_{33}$H$_{39}$ClN$_2$Au [M+NH$_4$]$^+$: 712.2727, Found: 712.2739

$[^{29}\text{D}]$ - 12.8$^\circ$ (c 0.84, CHCl$_3$)

X-ray experimental for 4-44

Data were collected at 100 K on a Bruker DUO system equipped with an APEX II area detector and a graphite monochromator utilizing MoK$_\alpha$ radiation ($\lambda$ = 0.71073 Å). Cell parameters were refined using up to 9999 reflections. A hemisphere of data was collected using the ω-scan method (0.5$^\circ$ frame width). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in SHELXTL6, and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. The asymmetric unit consists of two chemically equivalent but crystallographically independent. The data was checked for higher symmetry, in specific checked for the possibility of the space group being P2$_1$/m. No possible solution was found. Additionally, the two molecules in the asymmetric unit do not have neither a mirror symmetry nor an inversion symmetry. A total of 679 parameters
were refined in the final cycle of refinement using 11154 reflections with I > 2σ(I) to yield R₁ and wR₂ of 2.32% and 4.24%, respectively. Refinement was done using F².


**Crystal data and structure refinement for 4-44**

Identification code **4-44**

Empirical formula C₃₃ H₃₈ Au Cl N₂

Formula weight 695.07

Temperature 100(2) K

Wavelength 0.71073 Å

Crystal system Monoclinic

Space group P2(1)

Unit cell dimensions

a = 12.074(12) Å  \(\alpha = 90^\circ\).

b = 11.168(12) Å  \(\beta = 93.82(2)^\circ\).

c = 22.31(2) Å  \(\gamma = 90^\circ\).

Volume 3002(5) Å³

Z 4

Density (calculated) 1.538 Mg/m³

Absorption coefficient 5.013 mm⁻¹

F(000) 1384

Crystal size 0.15 x 0.13 x 0.03 mm³

Theta range for data collection 1.69 to 27.50°.

Index ranges  -15 ≤ h ≤ 15, -14 ≤ k ≤ 13, -28 ≤ l ≤ 28
Reflections collected  31564
Independent reflections 12574 [R(int) = 0.0246]
Completeness to theta = 27.50° 100.0 %
Absorption correction  Numerical
Max. and min. transmission  0.8642 and 0.5221
Refinement method  Full-matrix least-squares on F^2
Data / restraints / parameters  12574 / 1 / 679
Goodness-of-fit on F^2  0.919
Final R indices [I>2sigma(I)]  R1 = 0.0232, wR2 = 0.0424 [11154]
R indices (all data)  R1 = 0.0300, wR2 = 0.0442
Absolute structure parameter  0.006(4)
Largest diff. peak and hole  1.341 and -0.688 e.Å^-3

\[
R1 = \frac{\sum(||F_0| - |F_c||)}{\sum|F_0|}
\]

\[
wR2 = \left[ \frac{\sum[w(F_o^2 - F_c^2)^2]}{\sum[w(F_o^2)^2]} \right]^{1/2}
\]

\[
S = \left[ \frac{\sum[w(F_o^2 - F_c^2)^2]}{(n-p)} \right]^{1/2}
\]

w = 1/[σ^2(F_o^2)+(m*p)^2+n*p], p = [max(F_o^2,0)+ 2* F_c^2]/3, m & n are constants.

[6(S),8(S)-Diisobutyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo[c,g]fluoren-5-ylidene]-chloroaurate(I) (4-45)
To a flame-dried Schlenk flask was added 15.0 mg (0.0356 mmol) of \([6(S),8(S)]\)-diisobutyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo\([c,g]\)fluorenium] chloride, 4.80 mg (0.0207 mmol) of Ag\(_2\)O and 700 µL (0.05M) of DCM. After stirring for 12 h, the reaction mixture was filtered through a pad of celite. The solvent of the filtrate was removed under reduced pressure. To another flame-dried Schlenk flask was added the filtered silver complex, 12.0 mg (0.0407 mmol) of AuCl•Me\(_2\)S and 1.3 mL (0.05M) of DCM. The reaction mixture was stirred for 12 h at room temperature. The reaction solution was filtered through a pad of celite and evaporated to dryness. The residue was purified by silicagel column chromatography with a 70:30 mixture of hexane and ethyl acetate as the eluent gave 17.0 mg (0.0275 mmol, 77.2%) of \([6(S),8(S)]\)-diisobutyl-5,6,8,9-tetrahydro-6a,7a-diazadibenzo\([c,g]\)fluoren-5-ylidene- chloroaurate(I).

\(^1\)H NMR (300MHz ,CHLOROFORM-d) \(\delta = 7.87\) (d, \(J = 7.0\) Hz, 2 H), 7.39 - 7.12 (m, 6 H), 5.02 - 4.78 (m, 2 H), 3.29 (dd, \(J = 5.4, 15.4\) Hz, 2 H), 2.94 (d, \(J = 15.2\) Hz, 2 H), 1.83 - 1.60 (m, 1 H), 1.49 - 1.36 (m, 2 H), 1.31 - 1.23 (m, 2 H), 0.95 (dd, \(J = 6.7, 9.7\) Hz, 12 H)

\(^{13}\)C NMR (75MHz ,CHLOROFORM-d) \(\delta = 166.3, 132.3, 129.6, 129.2, 127.2, 125.5, 124.0, 123.7, 54.5, 41.9, 33.3, 24.9, 23.5, 21.9\)

HRMS Calcd. for \(C_{27}H_{33}ClN_2Au \ [M]^+\): 616.1920, Found: 616.1959

\([\alpha]^{29}_D\) - 266.5° (c 0.32, CHCl\(_3\))

**X-ray experimental for 4-45**

Data were collected at 100 K on a Bruker DUO system equipped with an APEX II area detector and a graphite monochromator utilizing MoK\(_\alpha\) radiation (\(\lambda = 0.71073\) Å). Cell parameters were refined using up to 9999 reflections. A hemisphere of data was collected using the \(\omega\)-scan method (0.5° frame width). Absorption corrections by integration were applied based on measured indexed crystal faces.
The structure was solved by the Direct Methods in SHELXTL6, and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. The asymmetric unit consists of the complex and a disordered dichloromethane solvent molecule. The latter molecule was disordered and could not be modeled properly, thus program SQUEEZE, a part of the PLATON package of crystallographic software, was used to calculate the solvent disorder area and remove its contribution to the overall intensity data. Judging by the total count of electrons calculated by program SQUEEZE, it looks like the solvent exists in about 80% occupancy and disordered by the 2\_1 screw axis of symmetry along the a-axis. A total of 281 parameters were refined in the final cycle of refinement using 6106 reflections with I > 2\_σ(I) to yield \( R_1 \) and \( wR_2 \) of 2.01% and 5.62%, respectively. Refinement was done using \( F^2 \).


SHELXTL6 (2000). Bruker-AXS, Madison, Wisconsin, USA.


Crystal data and structure refinement for 4-45

Identification code 4-45

Empirical formula C27 H32 Au Cl N2

Formula weight 616.96

Temperature 100(2) K

Wavelength 0.71073 Å

Crystal system Orthorhombic

Space group P2(1)2(1)2(1)

Unit cell dimensions
a = 9.4129(6) Å  \quad \alpha = 90^\circ.

b = 16.7290(11) Å  \quad \beta = 90^\circ.

c = 17.6201(12) Å  \quad \gamma = 90^\circ.

Volume 2774.6(3) Å³

Z 4

Density (calculated) 1.477 Mg/m³

Absorption coefficient 5.413 mm⁻¹

F(000) 1216

Crystal size 0.28 x 0.17 x 0.13 mm³

Theta range for data collection 1.68 to 27.50°.

Index ranges -12 ≤ h ≤ 12, -21 ≤ k ≤ 21, -20 ≤ l ≤ 22

Reflections collected 43949

Independent reflections 6356 [R(int) = 0.0281]

Completeness to theta = 27.50° 100.0%

Absorption correction Numerical

Max. and min. transmission 0.5441 and 0.3165

Refinement method Full-matrix least-squares on $F^2$

Data / restraints / parameters 6356 / 0 / 281

Goodness-of-fit on $F^2$ 0.849

Final R indices [I>2\sigma(I)] R1 = 0.0201, wR2 = 0.0562 [6106]

R indices (all data) R1 = 0.0216, wR2 = 0.0569

Absolute structure parameter 0.009(6)

Largest diff. peak and hole 1.156 and -1.026 e.Å⁻³
\[ R1 = \sum(||F_o| - |F_c||) / \sum|F_o| \]
\[ wR2 = [\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]]^{1/2} \]
\[ S = [\sum[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2} \]
\[ w= 1/\left[\sigma^2(F_o^2) + (m*p)^2 + n*p\right], \quad p = [\max(F_o^2, 0) + 2*F_c^2]/3, \quad m \& n \text{ are constants.} \]

### 6.4.3 Synthesis of The Substrates for The Copper-Catalyzed β-Borylation

**2-chloro-\(N,N\)-bis(4-methoxybenzyl)acetamide**

![Chemical Structure](image)

To a flame-dried Schlenk flask was added 618 µL (7.77 mmol) of 2-chloroacetyl chloride and 16 mL (0.5 M) of THF. The reaction mixture was cooled to 0 °C and 2.00 g (7.77 mmol) of bis(4-methoxybenzyl)amine was added dropwise followed by 1.08 mL (7.77 mmol) of Et\(_3\)N. The reaction mixture was stirred at room temperature for 12 h. It was diluted with 20 mL of Et\(_2\)O and washed with 1N HCl (2 x 15 mL) followed by a saturated NaHCO\(_3\) aqueous solution (2 x 15 mL). It was dried over anhydrous MgSO\(_4\). All volatiles were removed in vacuo to yield 2.55 g (7.62 mmol, 98.1%) of 2-chloro-\(N,N\)-bis(4-methoxybenzyl)acetamide.

\(^1\)H NMR (300MHz, CHLOROFORM-d) \(\delta = 7.22 - 6.97\) (m, 4 H), 6.84 (d, \(J = 8.5\) Hz, 2 H), 6.88 (d, \(J = 8.5\) Hz, 2 H), 4.50 (s, 2 H), 4.40 (s, 2 H), 4.12 (s, 2 H), 3.78 (s, 3 H), 3.80 (s, 3 H)
$^{13}$C NMR (75MHz, CHLOROFORM-d) δ = 167.2, 159.6, 129.9, 128.8, 128.1, 127.8, 114.7, 114.3, 55.6, 55.5, 49.8, 48.0, 41.7

HRMS Calcd. for C$_{18}$H$_{20}$ClNO$_3$ [M+H]$^+$: 334.1204, Found: 334.1208

**Diethyl 2-(bis(4-methoxybenzyl)amino)-2-oxoethylphosphonate**

![Chemical Structure](image)

To a flame-dried Schlenk flask was added 970 mg (2.90 mmol) of 2-chloro-N,N-bis(4-methoxybenzyl)acetamide and 1.26 mL (7.25 mmol) of triethyl phosphite. The reaction mixture was stirred at 100 °C for 60 h. After cooling at room temperature, it was washed with hexane (3 x 5 mL) and concentrated in vacuo to yield 1.13 g (2.59 mmol, 89.3%) of diethyl 2-(bis(4-methoxybenzyl)amino)-2-oxoethylphosphonate.

$^1$H NMR (300MHz, CHLOROFORM-d) δ = 7.19 - 7.11 (m, 2 H), 7.06 (d, $J = 8.8$ Hz, 2 H), 6.93 - 6.73 (m, 4 H), 4.52 (d, $J = 5.6$ Hz, 4 H), 4.24 - 4.06 (m, 4 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 3.13 (s, 1 H), 3.06 (s, 1 H), 1.39 - 1.22 (m, 6 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) δ = 165.7, 159.4, 159.2, 129.6, 129.2, 128.4, 128.3, 127.9, 114.6, 114.2, 62.9, 62.8, 55.6, 50.4, 48.0, 34.8, 33.1, 16.6, 16.5

HRMS Calcd. for C$_{22}$H$_{30}$NO$_6$P [2M+H]$^+$: 871.3616, Found: 871.3720

(Z)-N,N-bis(4-methoxybenzyl)-3-phenylacrylamide (Z-4-59)
To a flame-dried Schlenk flask was added 150 mg (1.012 mmol) of (Z)-cinnamic acid, 137 mg (1.012 mmol) of HOBt and 7 mL (0.14 M) of DCM. The reaction mixture was stirred 30 minutes at room temperature. 12.0 mg (0.100 mmol) of DMAP and 260 mg (1.012 mmol) of bis(4-methoxybenzyl)amine were then added. The reaction mixture was cooled to 0 ºC and a solution of 209 mg (1.012 mmol) of DCC in 5 mL (0.2 M) of DCM was added dropwise. The reaction was stirred 1 h at 0 ºC and 12 h at room temperature. The reaction mixture was concentrated and 15 mL of ethyl acetate was added and the white solid was filtered off. The ethyl acetate solution was concentrated. Silicagel column chromatography with a 75:25 mixture of hexane and ethyl acetate as the eluent gave 245 mg (0.633 mmol, 62.5%) of (Z)-N,N-bis(4-methoxybenzyl)-3-phenylacrylamide.

\[ \text{HRMS Calcd. for } C_{25}H_{25}NO_3 [M+H]^+: 388.1907, \text{ Found: 388.1905} \]

\[ \text{N-methoxy-N-methylcinnamamide (4-57)} \]
940 mg (4.92 mmol, 95.9%) of \(N\)-methoxy-\(N\)-methylcinnamamide was obtained from 1.25 g (10.3 mmol) of DMAP, 1.37 g (6.66 mmol) of DCC, 500 mg (5.13 mmol) of \(N,O\)-dimethylhydroxylammonium chloride and 986 mg (6.66 mmol) of \(trans\)-cinnamic acid.

\[ ^1H \text{NMR (300MHz ,CHLOROFORM-d)} \delta = 7.74 (d, J = 15.8 Hz, 1 H), 7.62 - 7.52 (m, 2 H), 7.45 - 7.29 (m, 3 H), 7.04 (d, J = 15.8 Hz, 1 H), 3.76 (s, 3 H), 3.30 (s, 3 H) \]

\[ ^{13}C \text{NMR (75MHz ,CHLOROFORM-d)} \delta = 167.2, 143.6, 135.4, 130.0, 129.0, 128.2, 116.0, 62.1, 32.7 \]

HRMS Calcd. for \(C_{11}H_{13}NO_2\) [M+H]+: 192.1019, Found: 192.1024

\(N,N\)-dicyclohexylcinnamamide (4-56)

400 mg (1.28 mmol, 37.9%) of \(N,N\)-dicyclohexylcinnamamide was obtained from 42 mg (0.344 mmol) of DMAP, 765 mg (3.71 mmol) of DCC, 455 mg (3.37 mmol) of HOBt, 670 µL (3.37 mmol) of dicyclohexylamine and 500 mg (3.37 mmol) of \(trans\)-cinnamic acid.

\[ ^1H \text{NMR (300MHz ,CHLOROFORM-d)} \delta = 7.80 - 7.43 (m, 3 H), 7.43 - 7.15 (m, 3 H), 6.84 (d, J = 15.2 Hz, 1 H), 3.56 (br. s., 2 H), 2.26 (br. s., 2 H), 1.80 (br. s., 6 H), 1.64 (br. s., 6 H), 1.48 - 1.21 (m, 4 H), 1.18 (br. s., 2 H) \]
To a flame-dried Schlenk flask was added 60.2 mg (2.51 mmol) of sodium hydride and 2 mL (1.3 M) of DMF. A solution of 100 mg (0.679 mmol) of trans-cinnamide in 2 mL (0.33 M) of DMF was then added dropwise at room temperature. The reaction mixture was heated to 70 °C for 1 h. Then 276 µL (2.04 mmol) of 1-(chloromethyl)-4-methoxybenzene was added dropwise to the reaction mixture. It was stirred at 70 °C for 2 h. It was cooled to room temperature and quenched by 10 mL of water. The reaction mixture was extracted with Et₂O (2 x 15 mL), washed with water (2 x 15 mL) and dried over anhydrous MgSO₄. All volatiles were removed in vacuo. Silicagel column chromatography with a 80:20 mixture of hexane and ethyl acetate as the eluent gave 260 mg (0.671 mmol, 98.8%) of \( N,N\)-bis(4-methoxybenzyl)cinnamamide.

\( ^{1}H\) NMR (300MHz, CHLOROFORM-d) \( \delta = 7.84 \) (d, \( J = 15.2 \) Hz, 1 H), 7.55 - 7.40 (m, 2 H), 7.40 - 7.07 (m, 7 H), 7.02 - 6.76 (m, 5 H), 4.62 (s, 2 H), 4.52 (s, 2 H), 3.80 (s, 6 H)

\( ^{13}C\) NMR (75MHz, CHLOROFORM-d) \( \delta = 167.2, 159.4, 159.2, 143.8, 135.5, 130.0, 129.9, 129.8, 129.0, 128.9, 128.1, 117.7, 114.6, 114.2, 55.5, 49.5, 48.2 \)

HRMS Calcd. for \( C_{25}H_{25}NO_3 \) \([M+H]^+\): 388.1907, Found: 388.1926

\( N,N\)-dibenzylcinnamamide (4-58)
197 mg (0.602 mmol, 88.7%) of \(N, N\)-dibenzylcinnamamide was obtained from 60.2 mg (2.51 mmol) of sodium hydride, 100 mg (0.679 mmol) of \(trans\)-cinnamide and 242 µL (2.04 mmol) of benzyl bromide.

\[
^1H\text{ NMR (300MHz ,CHLOROFORM-d)} \delta = 7.87 (d, J = 15.2 Hz, 1 H), 7.56 - 7.17 (m, 15 H), 6.92 (d, J = 15.2 Hz, 1 H), 4.73 (s, 2 H), 4.62 (s, 2 H)
\]

\[
^{13}C\text{ NMR (75MHz ,CHLOROFORM-d)} \delta = 167.4, 144.1, 137.6, 137.0, 135.4, 129.9, 129.2, 129.0, 128.9, 128.6, 128.1, 128.0, 127.7, 126.8, 117.5, 50.3, 49.1
\]

HRMS Calcd. for C_{23}H_{21}NO [M+H]^+: 328.1696, Found: 328.1704

\(N, N\)-dimethylcinnamamide (4-55)

90.0 mg (0.514 mmol, 75.7%) of \(N, N\)-dimethylcinnamamide was obtained from 60.2 mg (2.51 mmol) of sodium hydride, 100 mg (0.679 mmol) of \(trans\)-cinnamide and 127 µL (2.04 mmol) of methyl iodide.

\[
^1H\text{ NMR (300MHz ,CHLOROFORM-d)} \delta = 7.67 (d, J = 15.2 Hz, 1 H), 7.59 - 7.46 (m, 2 H), 7.46 - 7.22 (m, 3 H), 6.89 (d, J = 15.5 Hz, 1 H), 3.17 (s, 3 H), 3.06 (s, 3 H)
\]

\[
^{13}C\text{ NMR (75MHz ,CHLOROFORM-d)} \delta = 166.9, 142.5, 135.6, 129.7, 129.0, 128.0, 117.7, 37.6, 36.1
\]

HRMS Calcd. for C_{11}H_{13}NO [M+H]^+: 176.1070, Found: 176.1068
General procedure for the Horner-Wadsworth-Emmons olefination for aryl substrates

To a flame-dried Schlenk flask was added 1.10 mmol of sodium hydride and 1.6 mL (0.7 M) of THF. The reaction was cooled to 0 °C and a solution of 0.919 mmol of diethyl 2-(bis(4-methoxybenzyl)amino)-2-oxoethylphosphonate in 1.6 mL (0.7 M) of THF was added dropwise. The reaction mixture was stirred at room temperature for 1 h. 1.10 mmol of aryl aldehyde was then added and the mixture was stirred for 12 h at room temperature. It was quenched by 4 mL of water. The reaction mixture was extracted with Et₂O (2 x 10 mL), washed several times with water (2 x 5 mL) and dried over anhydrous MgSO₄. All volatiles were removed in vacuo.

Silicagel column chromatography with a mixture of hexane and ethyl acetate as the eluent gave the desired \((E)-\alpha,\beta\)-unsaturated amide.

\((E)-N,N\text{-bis}(4\text{-methoxybenzyl})-3-(4\text{-methoxyphenyl})\text{acrylamide (4-74)}\)

\[
\begin{align*}
\text{H NMR (300MHz ,CHLOROFORM-d) } & \delta = 7.79 \text{ (d, } J = 15.2 \text{ Hz, 1 H), 7.40 \text{ (d, } J = 7.9 \text{ Hz, 2 H), 7.30 - 7.00 \text{ (m, 4 H), 7.00 - 6.70 \text{ (m, 7 H), 4.60 \text{ (s, 2 H), 4.50 \text{ (s, 2 H), 3.92 - 3.64 \text{ (m, 9 H) }]} } } } \\
\text{C NMR (75MHz ,CHLOROFORM-d) } & \delta = 167.5, 161.1, 159.3, 159.2, 143.5, 130.0, 129.6, 129.0, 128.1, 115.2, 114.5, 114.4, 114.2, 55.5, 49.4, 48.1 \\
\text{HRMS Calcd. for } & C_{26}H_{27}NO_4 [M+H]^+: 418.2013, \text{ Found: 418.2009} \\
\text{(E)-N,N\text{-bis}(4\text{-methoxybenzyl})-3-(2\text{-methoxyphenyl})\text{acrylamide (4-75)}}
\end{align*}
\]
$^1$H NMR (299MHz, CHLOROFORM-d) $\delta = 8.08$ (d, $J = 15.3$ Hz, 1 H), 7.40 (d, $J = 7.6$ Hz, 1 H), 7.30 - 7.01 (m, 6 H), 6.95 - 6.80 (m, 6 H), 4.61 (s, 2 H), 4.50 (s, 2 H), 3.85 - 3.74 (m, 9 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 167.6$, 159.0, 158.9, 158.2, 139.1, 130.7, 129.8, 129.2, 128.9, 127.9, 124.3, 120.6, 118.5, 114.2, 113.9, 111.1, 55.4, 55.3, 49.2, 47.9

HRMS Calcd. for C$_{26}$H$_{27}$NO$_4$ [M+H]$^+$: 418.2013, Found: 418.2008

$(E)$-3-(4-fluorophenyl)-N,N-bis(4-methoxybenzyl)acrylamide (4-77)

$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 7.78$ (d, $J = 15.5$ Hz, 1 H), 7.43 (dd, $J = 5.6$, 8.5 Hz, 2 H), 7.31 - 7.06 (m, 4 H), 7.00 (t, $J = 8.5$ Hz, 2 H), 6.93 - 6.68 (m, 5 H), 4.60 (s, 2 H), 4.50 (s, 2 H), 3.78 (s, 3 H), 3.78 - 3.75 (m, 3 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 167.0$, 165.4, 162.0, 159.4, 159.2, 142.5, 131.7, 130.0, 129.9, 129.8, 129.7, 128.8, 128.0, 117.5, 116.2, 115.9, 114.6, 114.2, 55.5, 49.5, 48.2

HRMS Calcd. for C$_{25}$H$_{24}$FNO$_3$ [M+H]$^+$: 406.1813, Found: 406.1818

$(E)$-N,N-bis(4-methoxybenzyl)-3-m-tolylacrylamide (4-78)
$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 7.85$ (d, $J = 15.2$ Hz, 1 H), 7.40 - 7.05 (m, 8 H), 7.05 - 6.77 (m, 5 H), 4.64 (s, 2 H), 4.55 (s, 2 H), 3.79 (s, 6 H), 2.34 (s, 3 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 167.3, 159.4, 159.3, 144.0, 138.6, 135.5, 130.8, 130.1, 129.8, 128.9, 128.8, 128.2, 125.3, 117.5, 114.6, 114.2, 55.5, 49.5, 48.1, 21.6

HRMS Calcd. for C$_{26}$H$_{27}$NO$_3$ [M+H]$^+$: 402.2064, Found: 402.2045

(E)-3-cyclohexyl-N,N-bis(4-methoxybenzyl)acrylamide (4-79)

To a flame-dried Schlenk flask was added 200 mg (0.459 mmol) of diethyl 2-(bis(4-methoxybenzyl)amino)-2-oxoethylphosphonate, 146 µL (0.834 mmol) of Hunig’s base, 36.0 mg (0.834 mmol), 51.0 µL (0.417 mmol) of cyclohexanecarbaldehyde and 3 mL (0.15 M) of acetonitrile. It was stirred at room temperature for 12 h. The reaction mixture was extracted with ethyl acetate (2 x 10 mL), washed with water (2 x 10 mL) and dried over anhydrous MgSO$_4$. All volatiles were removed in vacuo. Silicagel column chromatography with a 70:30 mixture of
hexane and ethyl acetate as the eluent gave 140 mg (0.356 mmol, 85.4%) of \((E)-3\text{-cyclohexyl-}
N,N\text{-bis(4-methoxybenzyl)acrylamide.}\)

\(^1\text{H NMR (300MHz ,CHLOROFORM-d) } \delta = 7.12 \text{ (t, } J = 7.6 \text{ Hz, 4 H), 6.97 (dd, } J = 7.0, 15.0 \text{ Hz, 1 H), 6.84 (dd, } J = 8.4, 12.2 \text{ Hz, 4 H), 6.22 (d, } J = 15.0 \text{ Hz, 1 H), 4.52 (s, 2 H), 4.40 (br. s., 2 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 2.18 - 2.03 \text{ (m, 1 H), 1.81 - 1.58 \text{ (m, 5 H), 1.30 - 1.05 \text{ (m, 5 H)}}

\(^{13}\text{C NMR (75MHz ,CHLOROFORM-d) } \delta = 167.7, 159.3, 159.1, 152.9, 130.0, 128.9, 128.1, 118.0, 114.4, 114.1, 55.4, 49.3, 47.8, 41.0, 32.2, 26.1, 25.9

HRMS Calcd. for C\text{\textsubscript{25}}H\text{\textsubscript{31}}NO\text{\textsubscript{3}} [M+H]\textsuperscript{+}: 394.2377, Found: 394.2393

\((E)-N,N\text{-bis(4-methoxybenzyl)but-2-enamide (4-80)}\)

\(^1\text{H NMR (300MHz ,CHLOROFORM-d) } \delta = 7.16 \text{ (d, } J = 7.6 \text{ Hz, 2 H), 7.12 - 6.93 \text{ (m, 3 H), 6.82 (d, } J = 8.2 \text{ Hz, 2 H), 6.87 (d, } J = 8.5 \text{ Hz, 2 H), 6.30 (d, } J = 15.0 \text{ Hz, 1 H), 4.53 (br. s., 2 H), 4.40 (br. s., 2 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 1.85 (d, } J = 6.7 \text{ Hz, 3 H)}}

\(^{13}\text{C NMR (75MHz ,CHLOROFORM-d) } \delta = 167.3, 159.3, 159.2, 142.9, 129.9, 128.9, 128.0, 122.0, 114.5, 114.1, 55.5, 49.2, 47.7, 18.5

HRMS Calcd. for C\text{\textsubscript{20}}H\text{\textsubscript{23}}NO\text{\textsubscript{3}} [M+H]\textsuperscript{+}: 326.1751, Found: 326.1735
6.4.4 Products from The Copper-Catalyzed Borylation

General procedure for copper-catalyzed borylation of α,β-unsaturated substrates:

To a flame-dried Schlenk flask was added copper (I) bromide-dimethylsulfide complex (3 mol%), NHC ligand (3.5 mol%), potassium tert-butoxide (9 mol%) and THF (0.16 M). The reaction mixture was stirred for 30 minutes at room temperature. Then bis(pinacolato)diboron (0.178 mmol) was added followed by substrate (0.162 mmol) and methanol (0.324 mmol) when used. Then the reaction mixture was stirred at room temperature for 12 h or at 40 ºC for 6 h. NaBO_3•(H_2O)_4 (0.810 mmol) and water (0.16 M) were added and the reaction mixture was stirred an additional 3 h at room temperature. The suspension was then extracted with Et_2O (3 x 10 mL), dried with MgSO_4 and concentrated in vacuo. Silicagel column chromatography with a mixture of hexane and ethyl acetate as the eluent gave the chiral β alcohol.

The racemic compound was obtained by using IMes as racemic NHC ligand.

3-hydroxy-3-phenylpropanenitrile (4-48)

\[
\begin{align*}
\text{OH} & \quad \text{CN} \\
\text{C} & \quad \text{H}
\end{align*}
\]

^1^H NMR (300MHz ,CHLOROFORM-d) \(\delta = 7.53 - 7.24 \text{ (m, 5 H)}, 4.98 \text{ (t, } J = 6.3 \text{ Hz, 1 H)}, \) 3.10 (br. s., 1 H), 2.71 (d, \( J = 6.2 \text{ Hz, 2 H)})

^13^C NMR (75MHz ,CHLOROFORM-d) \(\delta = 141.3, 129.1, 129.0, 125.8, 117.7, 70.1, 28.1\)

HRMS Calcd. for C_9H_9NO \([M+H]^+: 148.0757\), Found: 148.0753

Ee was measured by chiral HPLC with a OJ-H column (UV 215 nm, 10% isopropanol/hexane, 1.0 ml/min). \( t_1: 25.6, t_2: 30.4 \)

Ethyl 3-hydroxy-3-phenylpropanoate (4-51-product)
$\text{H NMR (299MHz, CHLOROFORM-d): } \delta = 7.49 - 7.17 \text{ (m, 5 H), } 5.13 \text{ (dd, } J = 4.2, 8.2 \text{ Hz, 1 H), } 4.18 \text{ (q, } J = 7.1 \text{ Hz, 2 H), } 3.34 \text{ (br. s., 1 H), } 2.83 - 2.62 \text{ (m, 2 H), 1.26 (t, } J = 7.1 \text{ Hz, 3 H).}

$\text{C NMR (75MHz, CHLOROFORM-d): } \delta = 172.6, 142.7, 128.7, 128.0, 125.9, 70.5, 61.1, 43.6, 14.4$

HRMS Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_3 [M+Na]^+: 217.0835$, Found: 217.0830

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 10% isopropanol/hexane, 1.0 ml/min). $t_1: 7.69, t_2: 8.92$

**3-hydroxy-$N,N$-dimethyl-3-phenylpropanamide (4-60)**

$\text{H NMR (299MHz, CHLOROFORM-d): } \delta = 7.47 - 7.17 \text{ (m, 5 H), } 5.13 \text{ (dd, } J = 3.1, 9.1 \text{ Hz, 1 H), } 4.79 \text{ (br. s., 1 H), } 2.93 \text{ (s, 3 H), } 2.97 \text{ (s, 3 H), } 2.73 - 2.58 \text{ (m, 2 H).}$

$\text{C NMR (75MHz, CHLOROFORM-d): } \delta = 172.5, 143.2, 128.7, 127.7, 125.9, 70.6, 42.1, 37.3, 35.4$

HRMS Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_2 [M+H]^+: 194.1176$, Found: 194.1172

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 30% isopropanol/hexane, 1.5 ml/min). $t_1: 7.58, t_2: 10.4$

**3-hydroxy-$N$-methoxy-$N$-methyl-3-phenylpropanamide (4-62)**
^1^H NMR (300MHz, CHLOROFORM-d) δ = 7.55 - 7.18 (m, 5 H), 5.15 (d, J = 9.1 Hz, 1 H), 4.29 - 4.22 (m, 1 H), 3.62 (s, 3 H), 3.20 (s, 3 H), 2.92 - 2.75 (m, 2 H)

^13^C NMR (75MHz, CHLOROFORM-d) δ = 173.5, 143.3, 128.7, 127.8, 126.0, 70.4, 61.5, 40.7, 32.1

HRMS Calcd. for C_{11}H_{15}NO_3 [M+Na]^+: 232.0944, Found: 232.0948

Ee was measured by chiral HPLC with a IB column (UV 215 nm, 5% isopropanol/hexane, 1.4 ml/min). t_1: 12.2, t_2: 14.5

N,N-dicyclohexyl-3-hydroxy-3-phenylpropanamide (4-61)

^1^H NMR (300MHz, CHLOROFORM-d) δ = 7.54 - 7.23 (m, 5 H), 5.12 (d, J = 9.1 Hz, 1 H), 4.99 (br. s., 1 H), 3.34 (t, J = 11.6 Hz, 1 H), 3.13 - 2.81 (m, 1 H), 2.78 - 2.49 (m, 2 H), 2.45 (br. s., 2 H), 1.92 - 1.69 (m, 4 H), 1.61 (br. s., 4 H), 1.49 (t, J = 12.5 Hz, 4 H), 1.33 - 0.98 (m, 6 H)

^13^C NMR (75MHz, CHLOROFORM-d) δ = 171.6, 143.5, 128.6, 127.6, 126.1, 70.8, 57.8, 56.4, 43.7, 31.2, 30.5, 30.1, 26.8, 26.0, 25.6, 25.4

HRMS Calcd. for C_{21}H_{31}NO_2 [M+H]^+: 330.2428, Found: 330.2423
Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 10% isopropanol/hexane, 1.0 ml/min). $t_1$: 11.8, $t_2$: 22.4

$N,N$-dibenzyl-3-hydroxy-3-phenylpropanamide (4-63)

\[
\text{OH} \quad \text{O} \\
\text{N} \quad \text{CH} \quad \text{N} \\
\text{Ph} \quad \text{Ph} \quad \text{Ph} \\
\text{Ph} \quad \text{Ph} \quad \text{Ph}
\]

$^1$H NMR (299MHz, CHLOROFORM-d) $\delta = 7.49 - 7.17$ (m, 13 H), 7.17 - 7.05 (m, 2 H), 5.29 - 5.20 (m, 1 H), 4.84 (d, $J = 2.8$ Hz, 1 H), 4.75 (d, $J = 14.7$ Hz, 1 H), 4.54 (d, $J = 15.0$ Hz, 1 H), 4.48 - 4.33 (m, 2 H), 2.88 - 2.77 (m, 2 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 173.2, 143.1, 137.0, 136.0, 129.3, 129.0, 128.7, 128.5, 128.1, 127.8, 127.8, 126.6, 126.0, 70.9, 50.1, 48.4, 41.9

HRMS Calcd. for C$_{23}$H$_{23}$NO$_2$ [M+H]$^+$: 346.1802, Found: 346.1802

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 30% isopropanol/hexane, 1.5 ml/min). $t_1$: 12.2, $t_2$: 19.0

3-hydroxy-$N,N$-bis(4-methoxybenzyl)-3-phenylpropanamide (4-64)

\[
\text{OH} \quad \text{O} \\
\text{O} \quad \text{N} \quad \text{CH} \quad \text{N} \\
\text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph}
\]

$^1$H NMR (300MHz, CHLOROFORM-d) $\delta = 7.45 - 7.23$ (m, 5 H), 7.14 (d, $J = 8.5$ Hz, 2 H), 7.01 (d, $J = 8.8$ Hz, 2 H), 6.95 - 6.79 (m, 4 H), 5.22 (br. s., 1 H), 4.87 (d, $J = 2.9$ Hz, 1 H),
4.61 (d, $J = 14.7$ Hz, 1 H), 4.45 (d, $J = 14.4$ Hz, 1 H), 4.30 (d, $J = 4.1$ Hz, 2 H), 3.81 (s, 3 H), 3.81 - 3.79 (m, 3 H), 2.87 - 2.75 (m, 2 H)

$^1$H NMR (299MHz, CHLOROFORM-d) $\delta = 7.36 - 7.29$ (m, 2 H), 7.17 (d, $J = 8.5$ Hz, 2 H), 7.05 (d, $J = 8.8$ Hz, 2 H), 6.99 - 6.83 (m, 6 H), 5.20 (t, $J = 5.5$ Hz, 1 H), 4.84 (br. s., 1 H), 4.65 (d, $J = 14.4$ Hz, 1 H), 4.48 (d, $J = 14.7$ Hz, 1 H), 4.34 (d, $J = 4.2$ Hz, 2 H), 3.97 - 3.76 (m, 9 H), 2.81 (d, $J = 6.2$ Hz, 2 H)

$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 172.9, 159.3, 159.2, 159.2, 135.3, 129.9, 129.1, 127.8, 127.2, 114.6, 114.2, 114.0, 70.5, 55.5, 49.2, 47.4, 41.9

HRMS Calcd. for $C_{26}H_{29}NO_5$ [M+H]$^+$: 436.2118, Found: 436.2105

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 40% isopropanol/hexane, 1.5 ml/min). $t_1$: 26.6, $t_2$: 47.2

3-hydroxy-$N,N$-bis(4-methoxybenzyl)-3-(2-methoxyphenyl)propanamide (4-82)
$^1$H NMR (299 MHz, CHLOROFORM-d) $\delta = 7.59$ (d, $J = 7.6$ Hz, 1 H), 7.36 - 6.68 (m, 11 H), 5.47 (d, $J = 8.5$ Hz, 1 H), 5.03 (d, $J = 3.4$ Hz, 1 H), 4.66 (d, $J = 14.4$ Hz, 1 H), 4.47 - 4.15 (m, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 2.99 (dd, $J = 2.4$, 16.0 Hz, 1 H), 2.69 (dd, $J = 8.8$, 15.9 Hz, 1 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-d) $\delta = 173.5$, 159.3, 159.2, 155.7, 131.3, 129.8, 129.2, 128.3, 128.0, 127.9, 126.7, 121.0, 114.5, 114.2, 110.2, 66.1, 55.5, 55.3, 49.1, 47.2, 39.6

HRMS Calcd. for C$_{26}$H$_{29}$NO$_5$ [M+H]$^+$: 436.2118, Found: 436.2108

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 40% isopropanol/hexane, 1.5 ml/min). $t_1$: 27.5, $t_2$: 54.3

3-(4-fluorophenyl)-3-hydroxy-$N,N$-bis(4-methoxybenzyl)propanamide (4-84)

$^1$H NMR (300 MHz, CHLOROFORM-d) $\delta = 7.38$ - 7.20 (m, 2 H), 7.19 - 6.80 (m, 10 H), 5.15 (dd, $J = 4.3$, 7.8 Hz, 1 H), 4.90 (br. s., 1 H), 4.58 (d, $J = 14.4$ Hz, 1 H), 4.43 (d, $J = 14.7$ Hz, 1 H), 4.28 (d, $J = 2.3$ Hz, 2 H), 3.79 (d, $J = 2.1$ Hz, 6 H), 2.77 - 2.69 (m, 2 H)
$^{13}$C NMR (75 MHz, CHLOROFORM-d) $\delta = 172.7, 159.4, 159.3, 138.9, 129.9, 129.0, 127.8, 127.7, 127.6, 115.6, 115.3, 114.6, 114.3, 70.3, 55.5, 55.5, 49.3, 47.5, 41.8

HRMS Calcd. for C$_{25}$H$_{26}$FNO$_4$ [M+H]$^+$: 424.1919, Found: 424.1916

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 40% isopropanol/hexane, 1.5 ml/min). $t_1$: 12.3, $t_2$: 16.4

3-hydroxy-$N,N$-bis(4-methoxybenzyl)-3-m-tolylpropanamide (4-85)

3-cyclohexyl-3-hydroxy-$N,N$-bis(4-methoxybenzyl)propanamide (4-86)

$^1$H NMR (300 MHz, CHLOROFORM-d) $\delta = 7.34 - 6.95$ (m, 8 H), 6.95 - 6.72 (m, 4 H), 5.18 (br. s., 1 H), 4.83 (d, $J = 2.9$ Hz, 1 H), 4.61 (d, $J = 14.7$ Hz, 1 H), 4.45 (d, $J = 14.4$ Hz, 1 H), 4.30 (d, $J = 3.8$ Hz, 2 H), 3.81 (d, $J = 2.1$ Hz, 6 H), 2.85 - 2.73 (m, 2 H), 2.34 (s, 3 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-d) $\delta = 173.0, 159.4, 159.3, 143.1, 138.3, 129.9, 129.1, 128.6, 128.5, 127.9, 126.6, 123.0, 114.6, 114.3, 70.9, 55.6, 55.5, 49.3, 47.4, 42.0, 21.7

HRMS Calcd. for C$_{26}$H$_{29}$NO$_4$ [M+H]$^+$: 344.1856, Found: 344.1859

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 40% isopropanol/hexane, 1.5 ml/min). $t_1$: 15.1, $t_2$: 23.9
$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 7.22 - 6.98$ (m, 4 H), 6.98 - 6.69 (m, 4 H), 4.66 - 4.41 (m, 2 H), 4.36 (d, $J = 4.4$ Hz, 2 H), 4.25 (d, $J = 2.6$ Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.58 (d, $J = 2.1$ Hz, 1 H), 2.48 (d, $J = 9.7$ Hz, 1 H), 1.87 (br. s., 1 H), 1.81 - 1.58 (m, 4 H), 1.43 - 1.10 (m, 4 H), 1.10 - 0.98 (m, 2 H)

$^{13}$C NMR (75MHz ,CHLOROFORM-d) $\delta = 173.8, 159.4, 159.3, 129.9, 129.3, 128.1, 127.9, 114.6, 114.2, 72.6, 55.6, 55.5, 49.3, 47.4, 43.2, 36.8, 29.2, 28.6, 26.7, 26.4, 26.3

HRMS Calcd. for C$_{25}$H$_{33}$NO$_4$ [M+H]$^+$: 412.2482, Found: 412.2482

Ee was measured by chiral HPLC with a Whelk-01 column (UV 215 nm, 5% isopropanol/hexane, 1.5 ml/min). t$_1$: 84.9, t$_2$: 94.5

3-hydroxy-$N,N$-bis(4-methoxybenzyl)butanamide (4-87)

$^1$H NMR (300MHz ,CHLOROFORM-d) $\delta = 7.20 - 6.98$ (m, 4 H), 6.96 - 6.78 (m, 4 H), 4.58 (d, $J = 14.7$ Hz, 1 H), 4.43 (d, $J = 14.4$ Hz, 2 H), 4.38 - 4.22 (m, 3 H), 3.80 (s, 6 H), 2.57 (dd, $J = 2.6, 16.4$ Hz, 1 H), 2.42 (dd, $J = 9.4, 16.7$ Hz, 1 H), 1.23 - 1.18 (m, 3 H)
$^{13}$C NMR (75MHz, CHLOROFORM-d) $\delta = 173.4, 159.4, 159.3, 129.9, 129.2, 128.0, 127.9, 114.7, 114.3, 64.7, 55.6, 55.5, 49.2, 47.3, 41.2, 22.5

Ee was measured by chiral HPLC with a IA column (UV 215 nm, 10% isopropanol/hexane, 1.2 ml/min). $t_1$: 16.6, $t_2$: 23.1
LIST OF REFERENCES


(81) Thermal ellipsoids are drawn at the 50% probability level. Inserted structure (PdClC$_9$H$_9$ omitted) shows the front view of the tricyclic carbene ligand. Selected bond lengths (Å) and angles (°): Pd-C1 2.031(3), Pd-C1 2.359(8), Pd-C28 2.053(8), Pd-C29 2.086(7), Pd-C30 2.267(6), N1-C1-N2 104.3(2), C9-C4-C2-C3 26.6.

(83) Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (°): Cl1-C1 1.680(2), Cu1-Cl2 2.1069(8), Cu1-Cl3 2.0963(9), N1-C1-N2 109.6(2), C20-C15-C3-C2 21.6

(84) The alpha selectivity with CuTC alone (without a donating ligand) has been reported. Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147-4149.


(96) The calculations used SambVca with the following parameters: radius of sphere, 3.5 Å; distance from sphere, 2 Å; mesh step, 0.05 Å.

(98) Thermal ellipsoids are drawn at the 50% probability level. The inserted structure shows the front view of the complex. Selected bond lengths (Å) and angles (°): Au1-Cl1 2.289(2), Au1-C1 1.988(4), N2-C1-N1 105.0(3), C8-C9-C10-C11 21.0, C28-C18-N1-C1 80.6.

(99) Thermal ellipsoids are drawn at the 50% probability level. The inserted structure shows the front view of the complex. Selected bond lengths (Å) and angles (°): Au1-Cl1 2.2829(10), Au1-C1 1.985(4), N2-C1-N1 104.6(3), C8-C9-C10-C11 23.3.

Dimitri Hirsch-Weil was born in Paris, France in 1982, and grew up in Nîmes, France. After graduating from Alphonse Daudet High School in 2000, he spent two years in preparatory classes for chemistry school entry’s exam at Alphonse Daudet High School. He then joined the Ecole Supérieure de Chimie Physique Electronique de Lyon (CPE), France where he spent two years majoring in organic chemistry. For his one year internship, he was hired by GlaxoSmithKline in Upper Merrion, Pennsylvania to work in their medicinal chemistry department. This rich experience led him to pursue a PhD in organic chemistry under the supervision of Sukwon Hong at the University of Florida.