Enantioselective Synthesis of Substituted Polycyclic Heterocycles by Rhodium-Catalyzed Ring-Opening Reactions of Aryne Diels-Alder adducts

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Department of Chemistry
University of Toronto

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Abstract

We report the application of our rhodium-catalyzed nucleophilic ring-opening methodology to the enantioselective synthesis of nitrogen-substituted polycyclic heterocycles. By using a cationic Rh(I) triflate catalyst in the presence of the chiral Josiphos ligand PPF-PBu₂, the ring opening reactions on dihydrooxaquinoline and dihydrooxaisoquinoline using different nucleophiles afford access to multiple dihydroquinolines and dihydroisoquinolones in high yield and high enantioselectivity (up to 99% total yield and >99%ee.) A variety of nucleophiles were shown to be compatible with the catalytic system.

The electronic effects in the new ring opening reactions were investigated using a variety of nucleophiles. It was found that reactivity and enantioselectivity of the ring opening products depends on the electronic effects as well as the position of the substituents on the substrates. Good yields and high ee of regioisomeric products are obtained using electron donating substituents, whereas electron withdrawing substituents decelerate the reactions.
Acknowledgements

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I grateful acknowledge Rob Webster for giving me my research idea, for proofreading my thesis, and for all his help and advices given to me during my study. He was always there to discuss my research and for making good suggestions. I would also like to give a special thanks to the members of the Lautens group for their help in times of need as well as for their friendship.

My thank also goes to Dr. Vy Maria Dong for reviewing this thesis.

This work is dedicated to my family, for their support and encouragement have always brought optimism into my life no matter what task lies ahead.

“None of my inventions came by accident. I see a worthwhile need to be met and I make trial after trial until it comes. What it boils down to is one per cent inspiration and ninety-nine per cent perspiration.”

- Thomas Alva Edison
# Table of Contents

Acknowledgements........................................................................................................... iii

Table of Contents.................................................................................................................. iv

List of Abbreviations ........................................................................................................ vii

List of Tables ......................................................................................................................... ix

1 Introduction ....................................................................................................................... 1

1.1 Asymmetric Ring Opening of Oxy-bridged Bicylic Alkenes in Organic Synthesis ........ 1

1.1.1 Nickel Catalysis ......................................................................................................... 2

1.1.2 Copper catalysis ........................................................................................................ 3

1.1.3 Palladium Catalysis .................................................................................................. 5

1.1.4 Rhodium Catalysis .................................................................................................. 7

2 Goals and Targets ............................................................................................................ 18

3 Results and Discussion .................................................................................................... 20

3.1 Preparation of Starting Materials .................................................................................. 20

3.2 Synthesis and Asymmetric Ring-Opening Reactions of 5,8-Dihydro-5,8-epoxyquinoline ......................................................................................................................... 22

3.2.1 Synthesis of 5,8-dihydro-5,8-epoxyquinoline........................................................... 22

3.2.2 Initial Investigation ................................................................................................... 23

3.2.3 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 5,8-dihydro-5,8-epoxyquinoline ....................................................................................... 26

3.3 Synthesis and Asymmetric Ring-Opening Reactions of 5,8-Dihydro-5,8-epoxyisoquinoline .......................................................................................................................... 29

3.3.1 Synthesis of 5,8-dihydro-5,8-epoxyisoquinoline......................................................... 29

3.3.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 5,8-Dihydro-5,8-epoxyisoquinoline................................................................. 31
3.4 Synthesis and Asymmetric Ring-Opening Reactions of Substituted Epoxyisoquinoline and Epoxyquinoline ................................................................. 34

3.4.1 Synthesis and Asymmetric Ring-Opening Reactions of 1-Ethoxy-5,8-epoxy-5,8-dihydro-isoquinoline ................................................................. 34

3.4.2 Synthesis and Asymmetric Ring-Opening Reactions of 1-Chloro-5,8-epoxy-5,8-dihydro-isoquinoline ................................................................. 39

3.4.3 Synthesis of 8-Hydro-5-methyl-5,8-epoxyisoquinoline and 5-Hydro-8-methyl-5,8-epoxyisoquinoline ................................................................. 43

3.4.4 Synthesis and Asymmetric Ring-Opening Reactions of 8-Hydro-5-methyl-5,8-epoxyquinoline and 5-Hydro-8-methyl-5,8-epoxyquinoline ............... 44

3.4.5 Synthesis and Asymmetric Ring-Opening Reactions of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide ................................................................. 47

3.5 Discussion ........................................................................................................... 50

3.5.1 Effects of Nitrogen Position on the Pyridine Ring Core ........................................ 50

3.5.2 Substitution effects in reactivity ...................................................................... 50

3.5.3 Substituents of the aromatic ring ...................................................................... 51

3.5.4 Substitution on the bridgehead ........................................................................ 52

3.5.5 Enantioselectivity ............................................................................................. 53

3.5.6 Proposed mechanism ....................................................................................... 54

3.6 Synthesis and Asymmetric Ring-Opening Reactions of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline ........................................................................ 56

3.6.1 Synthesis of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline ............... 56

3.6.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]-quinoline ........... 57

3.7 Synthesis and Asymmetric Ring-Opening Reactions of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole .................................................. 59

3.7.1 Synthesis of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole ....... 60

3.7.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole ....... 62

3.8 Synthesis of 7-oxabicyclo[2.2.1]hept-5-eno-2,3-[c]thiophene ................................. 63
4 Future work and Conclusion ................................................................. 65
5 Experimental ........................................................................................ 66
Appendix: Selected $^1$H and $^{13}$C NMR Spectra and X-Ray Crystallographic Data ................. 139
List of Abbreviations

[a]D  Specific Rotation measured at 589nm
ARO  Asymmetric Ring Opening
BuLi  Butyl Lithium
COD  1,5-cyclooctadiene
CsF  Cesium Fluoride
DCM  Dichloromethane
dppf  1,1'-Bis(diphenylphosphino)ferrocene
dppp  1,3-Bis(diphenylphosphino)propane
ee  Enantiomeric Excess
equiv  Equivalent
EtOH  Ethanol
HMDS  Hexamethyldisilazane
HRMS  High Resolution Mass Spectrum
IR  Infared
LDA  Lithium Diisopropyl Amine
mCPBA  meta-Chloroperoxybenzoic acid
MeOH  Methanol
NMR  Nuclear Magnetic Resonance
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>nOe</td>
<td>nuclear Overauser effect</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>TESCl</td>
<td>Triethylsilyl Chloride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMSCl</td>
<td>Trimethylsilyl Chloride</td>
</tr>
</tbody>
</table>
List of Tables

Table 3.1. Catalyst screening of ring opening reactions .......................................................... 23
Table 3.2. Rh-Catalyzed Divergent Enatioselective Ring Opening of 5, 8-Dihydro-5, 8-epoxyquinoline .................................................................................................................. 26
Table 3.3. Competition reaction of methanol and phenol ......................................................... 28
Table 3.4. Rh-Catalyzed Divergent Enatioselective Ring Opening of 5,8-dihydro-5,8-epoxyisoquinoline .......................................................................................................................... 31
Table 3.5 Optimization of the Rhodium-Catalyzed ARO reactions ...................................... 32
Table 3.6. Effect of the bases in the synthesis of 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline . 35
Table 3.7. Rh-Catalyzed Divergent Enatioselective Ring Opening of 1-ethoxy-5,8-epoxy-5,8-dihydro-isoquinoline ................................................................................................................. 36
Table 3.8. Rh-Catalyzed Divergent Enatioselective Ring Opening of 1-chloro-5,8-epoxy-5,8-dihydro-isoquinoline ......................................................................................................................... 40
Table 3.9. Effects of temperature in ARO reactions ................................................................ 41
Table 3.10. Effects of additives in ARO reactions .................................................................... 42
Table 3.11. Rh-Catalyzed Divergent Enatioselective Ring Opening of 5-hydro-8-methyl-5,8-epoxyquinoline .......................................................................................................................... 45
Table 3.12. Rh-Catalyzed Ring Opening of 8-hydro-5-methyl-5,8-epoxyquinoline ............... 46
Table 3.13. Rh-Catalyzed Divergent Enatioselective Ring Opening of 8-hydro-5-methyl-5,8-epoxyquinoline N-Oxide .................................................................................................................. 48
Table 3.14. Nucleophilic scope comparison of substrates ......................................................... 51
Table 3.15. Rh-Catalyzed Divergent Enatioselective Ring Opening of 5-chloro-7,10-dihydro-7,10-epoxy-benzo[h]-quinoline ........................................................................................................ 57
Table 3.16. Rh-Catalyzed Divergent Enatioselective Ring Opening of 4,5-(Bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole.......................................................... 62
1 Introduction

1.1 Asymmetric Ring Opening of Oxy-bridged Bicyclic Alkenes in Organic Synthesis

Oxabicyclic alkenes are valuable intermediates in organic synthesis. The large number of selective transformations possible with the oxabicyclic system has created interest in many research groups. A crucial synthetic transformation employing these intermediates involves the cleavage of the oxygen bridge to produce functionalized cyclohexene derivatives. Different approaches have been developed such as the use of strong acids\(^1\), alkylative bridge cleavage\(^2\) and ring opening reactions. Transition-metal-catalyzed ring-opening reactions of oxabicyclic alkene systems emerged as one of the most powerful methods, since the combination of a strained bicyclic structure and a carbon-carbon double bond in the bicyclic framework of these bicyclic alkenes allows them to be easily activated by transition-metal catalysts and allows for the formation of several stereocenters in a single step. Various transition metals such as nickel, palladium, rhodium, copper, iron and zirconium were found to be effective catalysts in the ring-opening reactions of oxabicyclic alkenes.


1.1.1 Nickel Catalysis

Nickel has enjoyed less success than other metals in catalytic asymmetric ring opening reactions due to the requirement of harsher conditions such as air-sensitive catalysts as well as the sensitivity of the substrates under investigation. Lautens and coworkers reported the use DIBAL-H in the presence of a catalytic amount of Ni(COD)$_2$ and BINAP that results in a highly enatioselective reductive ring opening of oxabicyclo[2.2.1]heptenes (Scheme 1.1.) Later they applied this methodology to the total synthesis of the clinically important antidepressant agent Sertraline.

![Scheme 1.1](image)

**Scheme 1.1**

The methodology was extended to [3.2.1] oxabicycles, even though harsher conditions required (Scheme 1.2.)

![Scheme 1.2](image)

**Scheme 1.2**

In 2003, Cheng described a nickel-catalyzed reductive ring opening of oxabenzonorbornadienes with organic acids to furnish 1,2-hydronaphth-1-ols in good yields and high enantiomeric excess (Scheme 1.3).

---


1.1.2 Copper catalysis

Copper was also found to be an effective catalyst in the ring-opening reactions of heterobicyclic alkenes. Recently, Feringa reported a copper-catalyzed addition of alkylzinc reagents to oxabicyclic alkenes by using monophosphorus ligand, and high \textit{anti}-stereoselectivity and enantioselectivity were obtained\textsuperscript{6} (Scheme 1.4).

---


The use of copper catalysts with Grignard reagents has been used in non asymmetric ring-opening reactions, providing very high to complete anti-stereocontrol under mild conditions (Scheme 1.5).

Zhou reported\textsuperscript{8,9} simple Grignard reagents react in copper-catalyzed asymmetric ring-opening reactions of oxabenzenorbornadienes derivatives using spiro phosphoramidite ligands. Excellent anti-stereoselectivities and good enantioselectivities were achieved (Scheme 1.6).

1.1.3 Palladium Catalysis

The Pd-catalyzed carbanionic alkylative ring opening of oxabicyclic [3.2.1]-, [2.2.1]-, and oxabenzonorbornene systems to give substituted tetrahydronaphthalenes is a well established reaction which has been extensively studied by Lautens and co-workers. They reported the first efficient, enatioselective carbanionic ring opening of several oxabenzonorbornenes with different dialkylzinc reagents (Scheme 1.7).\(^{10,11}\)

![Scheme 1.7](image)

The alkylative enantioselective ring opening could also be achieved with [3.2.1] and [2.2.1] oxabicyclic compounds by changing the solvent to dichloroethane, increasing the temperature and modifying the chiral ligand (Scheme 1.8).\(^{12}\) The mechanism was also studied suggesting an enantioselective carbopalladation as the key step in the process.\(^{13}\)

![Scheme 1.8](image)

---

Good results were also obtained for asymmetric ring-opening studies of azabicyclic systems (Scheme 1.9) despite the attenuated reactivity of those systems.

Scheme 1.9

In 2005, Carretero reported another highly efficient catalyst system\textsuperscript{14} for the alkylative ring opening of oxa- and azabiclyclic alkenes with dialkylzinc reagents, showing a broad scope with regard to both the bicyclic substrate and the dialkylzinc reagent, used low catalyst loadings, and affording ring-opened products in good yields and enantioselectivities (Scheme 1.10.)

Scheme 1.10

1.1.4 Rhodium Catalysis

Since the first report in 1973, rhodium has emerged as one of the most effective catalysts in the ring-opening reactions of heterobicyclic alkenes.\(^\text{15}\) Since the early 1990s, a significant advancement in the ring-opening chemistry of oxabicyclic compounds has occurred as a result of the work of Lautens and coworkers. In particular, the use of rhodium catalysts allowed the addition of various nucleophiles such as alcohols,\(^{16a,b}\) amines,\(^{16a,c}\) carboxylates,\(^{16d}\) thiols,\(^{16e}\) and arylboronic acids\(^{16f}\) to oxabicyclic alkenes with good control of region-, stereo-, and enantioselectivities.

1.1.4.1 Asymmetric Ring Opening with Heteroatom Nucleophiles

In 2000, Lautens and coworkers reported the first rhodium-catalyzed asymmetric ring opening reaction of oxabenzenonorbornadienes using alcohol and phenol nucleophiles.\(^{4a}\) This reaction produces a new carbon – oxygen bond via an intermolecular allylic displacement of the bridgehead oxygen with inversion providing the 1,2-trans product. The reaction proceeds with very high regio- and diastereoselectivity (>99:1), and excellent enantioselectivities (up to 99\% ee). It is noteworthy that the formation of the 1,2-trans product is atypical for ring opening reactions of oxabicyclic alkenes using this catalyst system. This research team further expanded the scope of the methodology to include anilines\(^{4g}\), simple amines\(^{4b}\), malonates, carboxylates\(^{4d}\) and sulfur\(^{4e}\) as nucleophiles (Scheme 1.11.)

---


Based on the mechanistic and ligand studies, they proposed the sequence outlined in Scheme 1.12. The process involves the cleavage of the dimeric rhodium complex to give monomer rhodium complex (step a). Reversible exo coordination of the substrate is followed by oxidative insertion with retention into the bridgehead C-O bond (b & c) to give two rhodium intermediates. These complexes are protonated by nucleophiles to generate a cationic rhodium complex. Protonation enhances the electrophilicity of the Rh-substrate complex, hence it is more likely to involve in SN2’ substitution. Nucleophilic attack with inversion to the alkoxy group then follows, and the product is liberated, followed by regeneration of the rhodium monomer.

---

Scheme 1.12
1.1.4.2 Asymmetric Ring Opening with Arylboronic acids

Catalytic asymmetric carbon-carbon bond forming reactions is of fundamental importance in organic chemistry. Among the asymmetric carbon–carbon bond forming reactions catalyzed by chiral transition metal complexes, the asymmetric 1,4-addition is one of the most promising reactions because its non-asymmetric version is an important carbon-carbon formation reaction in organic chemistry. The use of metal catalysis in the enantioselective addition of organometallic reagents has been highly successful. One of the examples is the addition of organozinc reagents by use of copper (I) catalysts coordinated with chiral phosphorus ligands.\(^{18}\)

Since Miyaura reported the first non-asymmetric 1,4-addition of aryl- and alkenyl-boronic acids to α,β-unsaturated ketones in high yield\(^{19}\) in 1997, tremendous success has been achieved in rhodium-catalyzed carbon-carbon bond forming reactions by the use of organometallic reagents, which include the 1,4-conjugate addition of organoboronic acids to electron-deficient olefins of both non-asymmetric and asymmetric versions.\(^{20}\)

Lautens reported the asymmetric ring-opening reaction of oxanorbonadinene derivatives with arylboronic acids or arylboronate esters catalyzed by a chiral rhodium complex.\(^{8,21}\) (Scheme 1.13)

---


They also demonstrated that the ring-opening of oxabicycle proceeded in a higher yield and enantioselectivity by slight modification of the arylboronic acid to the corresponding ethylene boronic ester (Scheme 1.14.)

At the same time, Murakami reported the facile racemic addition reaction of boronic acids to oxabenzonorbornadienes using a catalytic amount of [Rh(COD)Cl]$_2$ with P(OEt)$_3$ ligands (Scheme 1.15.)$^{22}$

---

It is noteworthy that the cis-isomer was formed exclusively. This stereochemical outcome parallels the Lautens results in ARO with arylboronic acids but is opposite to those of the rhodium-catalyzed ARO with heteroatom nucleophiles.\textsuperscript{16,17}

The catalytic cycle has been suggested\textsuperscript{17,22} to involve a $\beta$-oxygen elimination as a key step. The rhodium catalyst reacts with the organoboronic acid to generate an aryl-rhodium complex. Insertion of the double bond of oxabenzonorbornadiene into the aryl-rhodium bond forms the intermediate. Beta-oxygen elimination then follows to generate an alkoxy-rhodium intermediate, leading to the formation of the product and regeneration of the catalyst upon hydrolysis (Scheme 1.16.)

\begin{center}
Scheme 1.16
\end{center}
1.1.4.3 Asymmetric Ring Opening with Unsymmetrical substrates

Lautens and coworkers have extended the application of the rhodium-catalyzed nucleophilic ring opening methodology to unsymmetrically bridgehead/arene substituted oxabenzonorbornadienes (Scheme 1.17.) In MeOH:TFE (1:1) and catalytic [Rh(CO)₂Cl]₂, only regioisomer 1.17a and 1.17c are produced, indicating that C-O bond cleavage occurs at the position most able to stabilize positive charge at the bridgehead. The result is suggestive of an ionization pathway where insertion is occurring at the more substituted C-O bond and this Rh-catalyzed addition is under complete substrate control.

Scheme 1.17

Further investigation by this group revealed that good to excellent regioselectivities could be obtained using strongly π-donating substituents, whereas σ-donating and electron-withdrawing functionalities have a minimal effect.

---

Recently, the Lautens group reported the use of the cationic catalyst [Rh(cod)$_2$OTf]$^{24}$ to resolve racemic bridgehead substituted oxabicyclic alkenes into pairs of regioisomeric products with high enantioselectivity, demonstrating powerful reagent control. The process provides a quick and simple access to multiple 1,2-dihydronapthalene products in high enantioselectivity from simple starting materials.

Scheme 1. 18

Selected examples of AR0

---

1.1.4.4 Asymmetric Ring Opening of Azabicyclic Alkenes in Organic Synthesis

Asymmetric ring-openings of azabicyclic alkenes are very useful methodologies in organic synthesis. These reactions allow for the efficient access to the cyclohexyl-1,2-diamine moiety which has been found to be an important class of compounds with interesting biological activity\(^{16c}\). The development of nucleophilic ring opening reactions of azabicycles, however, has not enjoyed as much success as its cousin, despite the fact that azabicyclic alkenes are very similar to oxabicyclic alkenes. It is found that azabicycles are far less reactive than the corresponding oxabicycles because nitrogen functionalities are often poorer leaving groups. A nucleophilic nitrogen anion is also generated during the ring-opening process, which could compete with the desired nucleophiles.

Lautens and coworkers first reported the rhodium-catalyzed asymmetric ring opening reaction of azabicyclic alkenes with aliphatic amine nucleophiles and its application in the total synthesis of an analgesic compound (Scheme 1.20.)\(^{25}\)

\[
\begin{align*}
\text{NHBOC} & \quad \text{NHBOC} \\
\text{C}_2\text{-Ferriphos (1 equiv. to Rh)} & \quad \text{R}_2\text{N}_2 \\
\text{Amine Nucleophile} & \quad \text{THP / 100°C} \\
\text{Additives} & \quad \text{4 steps} \\
\text{>70% yield} & \quad \text{k-opioid analgesic}
\end{align*}
\]

Scheme 1.20

A full description of the catalytic asymmetric ring-opening reaction of azabenzonorbornadienes with aliphatic and aromatic amines were later reported.\(^{14,26}\) In the presence of a rhodium catalyst


(5 mol %) generated in situ from [Rh(cod)Cl]₂ and \((S,S')-(R,R')-C_2\)-ferrophos (4a), the asymmetric ring-opening reaction of azabenzonorbornadienes (1a–m) with various aliphatic and aromatic amines (2a–l) proceeded with high enantioselectivity (up to >99% ee) to give the corresponding 1,2-diamine derivatives 3 in high yields. It was found that the nature of the activating group strongly influences both the reaction yield and the enantioselectivity of the product. N-acetamide is the most enatioselective while N-methyl is not effective. In some cases, the addition of Et₃NHCl is necessary for good reactivity and enantioselectivity. It is also found that the nature of the chiral phosphine ligand strongly influence the reaction yield and the stereochemical outcome of the ring-opening.

![Scheme 1](image)

**Scheme 1. 21**

The Lautens group also reported the rhodium-catalyzed ring-opening of azabenzonorbornadienes with chiral amine nucleophiles easily derived from amino acids such as \((S)\)-proline and \((R)\)-phenylglycine in the presence of a readily available achiral rhodium phosphine catalyst²⁷ (Scheme 1.22.) The desired products were obtained as a mixture of diastereomers, which could be easily separated in high yield. Enantiomerically pure ring-fused nitrogen heterocycles and 1,2-diamines were also obtained by further transformation of the ring-opened products.

---

Scheme 1. 22
2 Goals and Targets

Over the past decade, nucleophilic ring opening of oxa- and azabicyclic alkenes has received considerable attention. Many metal-catalyzed asymmetric ring cleaving reactions have been developed in our group that generate ring-opened products in high yield and selectivity. Some examples are ring opening with hydride using a Ni catalyst, ring opening with dialkyl zinc using a palladium catalyst, and ring opening with heteroatom nucleophiles using rhodium catalyst and ring opening with boronic acids using Rh/Pd catalysts (Scheme 2.1.)\textsuperscript{2-4,10-13,20-26}

![Scheme 2.1](image)

The ring opening chemistry with heteroatom nucleophiles has been explored under rhodium catalysis with many substrates by the Lautens group. However, there has been no report so far of successful asymmetric ring opening of oxabicyclic substrates with the backbone fused with a heterocycle containing nitrogen, sulphur or oxygen (Scheme 2.2.) Given the prevalence of biologically interesting compounds containing these heteroatom backbones, we sought to investigate the reactivity and selectivity of asymmetric ring opening reaction of some relevant compounds.
The substrates of interest are nitrogen-based oxapolylicyclic compounds such as quinoline, isoquinoline and indole-cored polycyclic alkenes. Our goal was to synthesize these substrates and examine the reactivity of these heteroaryl fused bicycles toward asymmetric ring opening reactions using Rhodium or Pd catalysts (Scheme 2.3.)
3 Results and Discussion

3.1 Preparation of Starting Materials

Oxabicyclic alkenes are typically prepared via [4+2] cycloaddition reactions between furans and arynes. Because arynes are highly reactive and not isolable, they must be prepared in situ and reacted immediately with the dienophiles.

Different approaches to the arynes were considered and carried out to access to the starting materials in large scale (Scheme 3.1.) In general, two methods were utilized: the fluoride induced desilylation of trialkylsilylpyridyl triflate method and lithiation of halide substituted substrates using nBuLi/ tBuLi/ LDA method.

It is also known that the regiochemistry of ARO of oxabicyclic alkenes can be controlled by the inductive and/or steric effect of a substituent. To test whether this effect could improve the regioselectivity of the ARO reactions of those selected heteroaryl fused compounds, we carried out the synthesis of the oxabicyclic alkenes derived from pyridines and investigated the reactivity of these compounds toward ARO (Scheme 3.2). The directing groups of chloro-, ethoxy- and methyl- were selected due to their relatively straightforward/feasible synthesis.
Scheme 3.2
3.2 Synthesis and Asymmetric Ring-Opening Reactions of 5,8-Dihydro-5,8-epoxy-quinoline

3.2.1 Synthesis of 5,8-dihydro-5,8-epoxyquinoline

The synthesis of 5, 8-dihydro-5, 8-epoxyquinoline was synthesized as outlined in Scheme 3.4. 3-Trimethylsilyl-2-pyridyl trifluoromethanesulfonate 10 was prepared by a three-step process based on the method of Carroll. 28 2-Hydroxypyridine was treated with 2.0 equivalents of LDA in THF and then 1.1 equivalent of TMSCl at 0°C. 3-Trimethylsilyl-2-hydroxy-2-pyridine 9 was converted to the desired intermediate 10 (91% from 9) by reaction of it with triflic anhydride. The standard Diels Alder condition developed in our lab was then employed utilizing CsF as the desilylating agent. 2,3-pyridyne formation and trapping was successfully carried out by dropwise addition of a solution of 10 in CH$_3$CN to a mixture of CsF and freshly distilled furan in CH$_3$CN overnight. Purification of the reaction gave the desired product 5, 8-dihydro-5, 8-epoxy-quinoline 11 in racemic form in 30% yield.

Scheme 3.3

---

3.2.2 Initial Investigation

Having the starting material, we explored the ring opening reaction with 5, 8-dihydro-5, 8-epoxyquinoline. Different catalyst systems, previously successful in the asymmetric ring opening studies of oxabicyclic alkenes, were chosen for screening against new substrate (Table 3.1).

Table 3.1. Catalyst screening of ring opening reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Nucleophile</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Results$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(COD)Cl]$\text{2}$</td>
<td>—</td>
<td>MeOH</td>
<td>TFE</td>
<td>80</td>
<td>N.R</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(COD)Cl]$\text{2}$</td>
<td>dppf 5 mol%</td>
<td>MeOH</td>
<td>THF</td>
<td>80</td>
<td>N.R</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(COD)Cl]$\text{2}$</td>
<td>dppf 10 mol%</td>
<td>MeOH</td>
<td>THF</td>
<td>80</td>
<td>N.R</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(COD)Cl]$\text{2}$</td>
<td>dppf 5 mol%</td>
<td>MeOH</td>
<td>NH$_3$.HCl (1 eq.)</td>
<td>THF</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(COD)Cl]$\text{2}$</td>
<td>dppf 5 mol%</td>
<td>N-Methylaniline</td>
<td>THF</td>
<td>80</td>
<td>N.R</td>
</tr>
<tr>
<td>6</td>
<td>Rh(COD)$_2$OTf</td>
<td>dppf 10 mol%</td>
<td>MeOH</td>
<td>THF</td>
<td>80</td>
<td>Messy</td>
</tr>
<tr>
<td>7</td>
<td>PdCl$_2$</td>
<td>dppp 5 mol%</td>
<td>Phenylboronic acid (1.2 eq.)</td>
<td>MeOH</td>
<td>r.t</td>
<td>5% yield$^b$</td>
</tr>
<tr>
<td>7</td>
<td>Rh(COD)$_2$OTf</td>
<td>Josiphos 6.0 mol%</td>
<td>Bn$_2$NH (1.5 eq.)</td>
<td>THF</td>
<td>60</td>
<td>62% yield$^b$ (2 isomers)</td>
</tr>
</tbody>
</table>

$^a$ N.R: no reaction. $^b$ Isolated yields.
Methanol was chosen as the standard nucleophile, since it can easily used in large excess while being small enough not to dominate the Rf in the ring-opened products. Preliminary screening revealed that many catalyst systems were either unreactive or showed little conversion under the reaction conditions. Previously, earlier work in our group showed that Rh halide complexes give the best yields and enantioselectivities in these types of reactions\textsuperscript{17}. However, when 1 was subjected to well-established condition of Rh halide catalyst, no conversion of the starting material was observed on TLC (Table 3.1, entry 1). The use of rhodium dimer with achiral ligand gave no desired products (entry 2). Increasing the catalyst loading from 2.5 mol% to 5 mol% (entry 3), adding various additives (NH\textsubscript{3}.HCl) (entry 4) as well as changing the nucleophile from methanol to N-Methyl aniline gave no ring opening products. Changing the counterion from halide to triflate resulted in a messy reaction. This result is expected as azabicycles are generally less sensitive to the ARO as mentioned in 1.1.4.4.

The ring opening products were observed in the last two conditions (entries 6 &7). The first successful condition is with Pd catalyst. The ring opening using PdCl\textsubscript{2} with 1,3-bis(diphenylphosphino)propane (dppp) (figure 3.1) and phenylboronic acid gave one regiosomer with cis- configuration (Scheme 3.2.) However the yield of the desired product is quite low.

\[
\text{Scheme 3. 4}
\]

\[
\text{Figure 3.1}
\]
The second successful condition is with a rhodium catalyst when a more electrophilic catalyst system was employed. Using Rh(cod)$_2$OTf and Josiphos ligand PPF-PtBu$_2$ (Figure 3.1) gave the corresponding ring-opening products A and B in relatively good yield (76% yield in 1.5:1 ratio) (Scheme 3.3.) The diastereomers A and B could easily be isolated by conventional column chromatography. The NMR spectrum of each regiosiomer is very diagnostic with the allylic protons in the region of 5-6 ppm. The stereochemistry of both products was proven to be trans by NMR experiment and later by X-ray crystallography.

We therefore attempted to use rhodium triflate catalyst in the presence of Josiphos ligand to study the scope on epoxyquinoline.
3.2.3 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 5,8-dihydro-5,8-epoxyquinoline

Table 3.2. Rh-Catalyzed Divergent Enantioselective Ring Opening of 5, 8-Dihydro-5, 8-epoxyquinoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>MeOH</td>
<td>29</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>Bn₂NH</td>
<td>32</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>PhNHCH₃</td>
<td>43</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Tetrahydroquinoline</td>
<td>37</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Et₂NH</td>
<td>Inseparable products</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Morpholine</td>
<td>Inseparable products</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Indole</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Phenol</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>TsNH₂</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Phthalimide</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>MeOH + (nBu)₄NI (20 mol %)</td>
<td>No reaction</td>
<td></td>
</tr>
</tbody>
</table>

a Isolated yields. b Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section.

As shown in Scheme 3.4, nucleophiles (1.5-5 equiv.) along with substrate in THF was added to pre-mixed catalyst system consisting of 5 mol% of [Rh(cod)₂OTf] and 6 mol% of Josiphos ligand. The reaction was arbitrarily heated to 60°C for 12-18 hours, quenched and purified. It was found that the ring-opening reaction works with amines as well as methanol to give
relatively good yield and selectivities (Table 3.2). As a general trend, product type A has moderate to good ee and product type B has excellent ee (>99%). The reaction using methanol gave moderate yield (63% total yield) and excellent enantioselectivity (>99% ee) (entry 1.) Aromatic amines also showed high reactivity and good to excellent enantioselectivity in the asymmetric ring-opening (entries 2-4.) The reaction of 1 using N-methylaniline proceeded to give good yield (86%) and good to excellent enantioselectivity (75% ee and >99% ee for each regioisomer). The reaction using dibenzylamine or tetrahydroquinoline gave moderate yield and good to excellent enantioselectivity. The conversion was also observed using linear amines and morpholine (entries 5-6). The products detected by $^1$H NMR, however, are inseparable. We next attempted to expand the scope by the use of nitrogen nucleophiles and phenol. It has been previously shown that benzene sulfonamides as well as phthalimide react with oxanorbonadienes$^{17,20}$ under rhodium catalysis to give retention of absolute configuration in good yield. In our case all four failed to induce any reaction (entries 7-10.)

It is interesting to note that the presence of halide poisons the catalyst. When reaction with methanol was performed with the standard catalyst system and addition of (nBu)$_4$NI, no products were observed (entry 11). The fact that with the epoxyquinoline, the ARO reaction works well with triflates as the only counterion is remarkable since previous studies shows that the use of triflates is not as mild or general as the use of iodide counterions. It suggests that the epoxyquinoline is less sensitive to well-established ARO protocol and requires a more powerful catalyst system. In conclusion, although the halide ligands have previously reported to play positive roles in overcoming catalyst poisoning, improving the enantioselectivity and increasing the reactivity in the rhodium-catalyzed ARO reaction, no such effect was observed on the ARO reaction in the under-investigated epoxyquinoline system.
An important factor to determine was whether the lack of reactivity with phenol was a consequence of poorer nucleophilicity or if it reacted with rhodium catalyst and poisoned the reaction. A competition experiment was carried out involving a good nucleophile (methanol) and a poor nucleophile (phenol). When run independently, methanol results in complete consumption of 1 in 4 hours (Table 3.3, entry 1), while phenol fails to react after 24 hours (entry 2). When both nucleophiles are added to the reaction mixture, only methanol adds (entry 3), indicating that the addition of phenol does not deactivate the catalyst and the poor reactivity of phenol resides solely with a problem of nucleophilicity.

### Table 3.3. Competition reaction of methanol and phenol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Yield(%)(^a)</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methanol</td>
<td></td>
<td>29%</td>
<td>34%</td>
</tr>
<tr>
<td>2</td>
<td>Phenol</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>3</td>
<td>Methanol/Phenol(^b)</td>
<td>28%</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields. \(^b\) Only ARO products of MeOH were observed.
3.3 Synthesis and Asymmetric Ring-Opening Reactions of 5,8-Dihydro-5,8-epoxyisoquinoline

3.3.1 Synthesis of 5,8-dihydro-5,8-epoxyisoquinoline

The 3,4-pyridyne-ring-based analogue 2 was first synthesized by a procedure similar to that for 1 (Scheme 3.6). 3-Hydroxypyridine was protected by treating with diethylcarbamoyl chloride in pyridine. The protected alcohol was treated with LDA, followed by TESCl to give 4-(triethylsilyl)pyridin-3-yl diethylcarbamate. Carbamate removal of 15 proved to be a challenging step, resulting in a very low yield for the whole process. Several attempts including reduction method (LAH/THF/reflux) or hydrolysis (NaOMe/MeOH) and heating/adding extra base afforded 4-(triethylsilyl)pyridin-3-ol 16 with only 40% yield. Pyridone 16 was converted to the desired silylpyridyl triflate 17 (54% from 16) by reaction of it with triflic anhydride. 3-Pyridyne, generated by treating 4-triethylsilylpyridin-3-yl trifluoromethanesulfonate 17 with cesium fluoride in acetonitrile, was trapped with furan to give 2 (55% from 17.)
Given the difficulties in preparation of 5,8-dihydro-5,8-epoxyisoquinoline 2 using the fluoride induced desilylation of trialkylsilylpyridyl triflate method (low yield and multi-step synthesis); a different synthetic approach was sought to allow easier and scalable access to the desired product. Treatment of 3-chloropyridine with LDA, generated in situ at -100°C results in regioselective lithiation at the C-4 position to give the corresponding 3-chloro-4-lithiopyridine. The intermediate was trapped with freshly distilled furan in a Diels-Alder reaction to give the desired 5,8-epoxy-5,8-dihydroisoquinoline 2 in 15% yield. The competing products were insoluble polymeric products, derived from addition of the lithium intermediate and addition of diisopropylamine to the aryne.

Scheme 3.7

---

3.3.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 5,8-Dihydro-5,8-epoxyisoquinoline

Table 3.4. Rh-Catalyzed Divergent Enantioselective Ring Opening of 5,8-dihydro-5,8-epoxyisoquinoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>25&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Bn&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>29&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>PhNHCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>40&lt;sup&gt;c&lt;/sup&gt;</td>
<td>41&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Tetrahydroquinoline</td>
<td>48&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>Inseparable products&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Morpholine</td>
<td>Inseparable products&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Allyl alcohol</td>
<td>No reaction&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pyrrole</td>
<td>No reaction&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Indole&lt;sup&gt;g&lt;/sup&gt;</td>
<td>No reaction&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Phenol&lt;sup&gt;g&lt;/sup&gt;</td>
<td>No reaction&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>TsNH&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;g&lt;/sup&gt;</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Phthalimide</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Tetrahydroquinoline/dppf</td>
<td>No reaction</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section. <sup>c</sup> Yield measured by <sup>1</sup>H NMR. <sup>d</sup> Measured as a mixture of two regioisomers. <sup>e</sup> Products identified by <sup>1</sup>H NMR. <sup>f</sup> Trace amount of products. <sup>g</sup> Variation of the conditions was applied (Table 3.5)
The scope of the ring-opening of 5,8-dihydro-5,8-epoxyisoquinoline was also explored using the same catalyst system (Table 3.4). Similar to the scope of epoxyquinoline, amines and methanol worked well to give the desired products (entries 1-4). A slight difference in reactivity between 1 and 2 was observed. The reaction using allyl alcohol, pyrrole, indole and phenol gave trace amounts of desired products as detected by $^1$H NMR (entries 7-10) while p-toluenesulfonamide and phthalimide failed (entries 11-12.) The reaction using methanol or aliphatic amines gave the corresponding products in equal or better enantioselectivity and higher yield compared to substrate 1 (entries 1-4). The combined yield of the products are in the range of 90%. In terms of selectivity, both products have excellent ee’s (>90%ee.)

As observed, in the reaction of 2 with tetrahydroquinoline, the use of Josiphos gave 93% total yield while the reaction using dppf did not proceed (entry 13). The nature of the phosphine ligand strongly influenced the reaction yield in the present reaction.

Table 3.5 Optimization of the Rhodium-Catalyzed ARO reactions

<table>
<thead>
<tr>
<th>Variables</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature ($^{\circ}$C)</td>
<td>60, 80, 100</td>
</tr>
<tr>
<td>Solvent</td>
<td>THF, DME</td>
</tr>
<tr>
<td>Time (h)</td>
<td>24 – 84</td>
</tr>
<tr>
<td>Equivalence of nucleophiles</td>
<td>1.5, 3, 4, 5</td>
</tr>
<tr>
<td>Addition of additives</td>
<td>CSA-Bu$_4$NI, acetic acid, NH$_4$I, NH$_3$HCl</td>
</tr>
</tbody>
</table>

In order to improve the scope of the nucleophiles, some conditions have been varied such as temperature, time, and equivalent of nucleophiles and also addition of some additives to the ring opening of 2 with indole, phenol and p-toluenesulfonamide (these nucleophiles showed no conversion in initial results). It was, however, rather disappointing that none of the conditions significantly improved the results from the initial test reaction (Table 3.5). The increase in temperature to 80°C, and increase in equivalence of nucleophile that participates in the reaction (3 equiv) only increased the yield slightly. Any further increase had a negative effect on the
reactivity. As previously reported\textsuperscript{16g}, the effects of halide ligands and protic additives on enantioselectivity and reactivity plays an important role in rhodium-catalyzed asymmetric ring-opening reactions. The screening of additives was carried out in order to increase the rate of the reaction. In all cases, the use of additives was not beneficial in these cases and a significant reduction of reactivity or no reactivity was observed when CSA-Bu\textsubscript{4}NI, acetic acid, NH\textsubscript{4}I, NH\textsubscript{3}.HCl were used.
3.4 Synthesis and Asymmetric Ring-Opening Reactions of Substituted Epoxyisoquinoline and Epoxyquinoline

Two different substrate modifications were considered to determine if a directing effect was present: aromatic ring substitution and bridgehead substitution.

In the first case, the effects of aromatic ring substitution were examined by choosing aryl substituents with differing electronic properties. The substitution on the aromatic ring is more remote from the active site of the substrates, thus the steric influence can be minimized while creating an electronic bias that could direct the ring opening event.

In the second case, the effect of bridgehead substitution was investigated by reaction of methyl substituted 7 and 8.

3.4.1 Synthesis and Asymmetric Ring-Opening Reactions of 1-Ethoxy-5,8-epoxy-5,8-dihydro-isoquinoline

In order to investigate the effects that substituents on the aromatic ring of substrate 2, substrate 5 was prepared and reacted under the standard conditions.

3.4.1.1 Synthesis of 1-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline

\[ \text{Scheme 3.8} \]

1-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline 5 was synthesized as outlined in Scheme 3.8.\(^{30}\) 2-Ethoxy-3-chloropyridine 20 was generated from 2, 3-dichloropyridine using sodium ethoxide in ethanol. Pyridyne was then generated from 20 using \(n\)- or tert-butyllithium as the lithiating reagent with 10 equivalents of furan. In contrast to the reported result\(^{30}\), use of \(t\)-BuLi with 2-\(n\)BuLi, -78°C

\[ \text{Overall yield: 35\%} \]

---

ethoxypyridine to generate the corresponding aryne gave a messy reaction and resulted in a very low yield of the desired product upon purification. Use of $n$-BuLi gave a clean reaction with a moderate yield of the trapped product.

Table 3.6. Effect of the bases in the synthesis of 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline

<table>
<thead>
<tr>
<th>Base</th>
<th>Yield (%)</th>
<th>Reported yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t$-BuLi</td>
<td>19</td>
<td>71</td>
</tr>
<tr>
<td>$n$-BuLi</td>
<td>40</td>
<td>29</td>
</tr>
</tbody>
</table>
3.4.1.2 Nucleophilic scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 1-Ethoxy-5,8-epoxy-5,8-dihydro-isooquinoline

Table 3.7. Rh-Catalyzed Divergent Enantioselective Ring Opening of 1-Ethoxy-5,8-epoxy-5,8-dihydro-isooquinoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>MeOH</td>
<td>49</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>51</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Allyl alcohol</td>
<td>47</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>PhNHCH(_3)</td>
<td>39</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>Tetrahydroquinoline</td>
<td>43</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Indole</td>
<td>48</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>Phenol</td>
<td>37</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>TsNH(_2)</td>
<td>36</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>MsNH(_2)</td>
<td>Inseparable products(^d)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Phthalimide</td>
<td>Inseparable products(^d)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Bn(_2)NH</td>
<td>Inseparable products(^d)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>MeOH/dppf</td>
<td>Incomplete reaction after 72 hours (presence of 2 regioisomers 33% &amp; 17%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields. \(^b\) Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section. \(^c\) Yield measured by \(^1\)H NMR. \(^d\) Products identified by \(^1\)H NMR.
The ring-opening 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline was examined with the [Rh(cod)\(_2\)OTf]/PPF-P\(^3\)Bu\(_2\) catalyst and THF. The ee’s obtained from the ring-opening of ethoxy-substituted substrate 5 on the aromatic moiety are summarized in Table 3.7. A wide variety of alcohol and amine nucleophiles react, all in good yields and good to excellent ee. A difference in reactivity between 2 and the more electron rich 5 was observed. As an ethoxy group is introduced into the ring, the scope of the reaction was expanded. The catalyst system works with all the nucleophiles which failed to add with the previous substrates including indole, phenol, p-toluenesulfonamide and phthalimide (entries 6-10).

Several alcohols also successfully added to 5 and therefore expanded the scope of the ARO (entries 1-3). The ratio of product A and B shifts from 1:1 to 2:1 for alkyl alcohols. Surprisingly, the reaction using dppf and MeOH in the reaction of 5 proceeded (entry 12). However, the conversion rate was very low even after prolonged heating (3 days).

In term of enantioselectivity, product B has excellent ee’s (all >99%ee) while enantioselectivity of product A varies from moderate to high. ARO product A using alcohols have only moderate enantioselectivity (58-61%ee) and other nucleophiles gave good ee’s (74-89%ee.)

Indole was also found to be a good nucleophile and to react exclusively at the C-3 position of the indole ring, rather than through N-1 (Scheme 3.10). The structure of the indole ring-opening product was assigned by \(^1\)H-\(^{13}\)C coupled NMR experiments and identification of the N-H indole peak at 7.8 ppm. A similar pattern was also observed in the asymmetric ring-opening reaction of oxabenzonorbornadienes with indole.\(^{16f,g}\)

---

Scheme 3.9
The X-ray crystal structures of the two ARO products with p-toluenesulfonamide were also determined and they proved the regiochemistry, the relative stereochemistry and provided the absolute configuration of the ring opened products (Figure 3.2.)

We observed significant differences in the relative rates of reaction. All reactions are complete within 2 h, confirming that the presence of an electron-donating group on the aromatic ring accelerates the rate of addition and expands the range of nucleophiles.
3.4.2 Synthesis and Asymmetric Ring-Opening Reactions of 1-Chloro-5,8-epoxy-5,8-dihydro-isoquinoline

3.4.2.1 Synthesis of 1-Chloro-5,8-epoxy-5,8-dihydroisoquinoline

![Scheme 3.10](image)

1-Chloro-5,8-epoxy-5,8-dihydroisoquinoline 6 was prepared from the corresponding o-trimethylsilyl triflate as shown in Scheme 3.10. Precursor of pyridine was synthesized by reported method through 3 steps. 2-Chloro-3-hydroxypyridine was transformed into the corresponding trimethylsilyl derivative 23 by treatment with HMDS. Metalation of 23 by using LDA in THF was followed by the migration of the trimethylsilyl group from the oxygen atom to position 4, affording pyridinol 24. Treatment of pyridinol 24 with triflic anhydride yielded the corresponding pyridyne precursor 25. The key Diels Alder cycloaddition between 25 and furan was carried out by subjecting the pyridyne precursor to the standard Diels Alder condition with CsF. The desired product was obtained in 30% yield.

---

3.4.2.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 1-Chloro-5,8-epoxy-5,8-dihydro-isoquinoline

Table 3.8. Rh-Catalyzed Divergent Enantioselective Ring Opening of 1-chloro-5,8-epoxy-5,8-dihydro-isoquinoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>MeOH</td>
<td>40</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>Bn&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>PhNHCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>38</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>Tetrahydroquinoline</td>
<td>34</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>Piperidine</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>Morpholine</td>
<td>40</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>Indole</td>
<td>38</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>Phenol</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>TsNH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Phthalimide</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>MeOH/dppf</td>
<td>Incomplete reaction after 72 hours (presence of 2 regioisomers)</td>
<td></td>
</tr>
</tbody>
</table>

a Isolated yields. b Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section.

We next examined the effect of electron-withdrawing substitution on the reactivity of ring-opening reactions and the results obtained from the ring-opening of 6 are summarized in Table 3.8. Although longer reaction time (over 36h) was required, generally amines and methanol react...
in good to excellent yield and enantioselectivity. Similar to 2, amines and methanol react while phenol, p-toluenesulfonamide and phthalimide fail to proceed. Indole, however, was found to react with 6 to give good yield and excellent enantioselectivity for both ARO products. The basic amine piperidine showed a dramatic loss in yield and enantioselectivity (entry 5) which is in line with previously reported results\textsuperscript{16c,f}.

Examination of the enantioselectivity of the products from the ring openings revealed an interesting result – the enantioselectivity of product A and B is equal for each nucleophile. This is contrast to previously observed results in ARO of substrates 1, 2 and 5 where one of the regioisomers is produced with very high ee (>99% ee, product type B), while the other is formed in lower selectivity (Table 3.2, 3.4 and 3.7.)

Table 3.9. Effects of temperature in ARO reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophiles</th>
<th>ee% at 60°C</th>
<th>ee% at 80°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Product A</td>
<td>Product B</td>
</tr>
<tr>
<td>1</td>
<td>Bn,NH</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Indole</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

Note: Yields of the isolated products at both temperatures are quite constant.

We found that the enantioselectivity of ring-opening of 6 was sensitive to the temperature of the reaction (Table 3.9.) This unexpected result was discovered when two sets of different enantiomeric ligands were run at different temperature (60°C and 80°C). TLC of the crude product run at 80°C was not as clean as that at 60°C. The enantioselectivity of the ARO products decreased when the temperature was increased from 60°C to reflux (80°C). Lautens and Webster previously reported that running the reaction at either 60°C or 80°C had no major effect on the enantioselectivity of the products.
The unusual low reactivity and selectivity of piperidine prompted us to further investigate that nucleophile. As any interaction of the amine with the rhodium catalyst should be affected by the presence of other species in solution capable of binding to the metal, the effect of additives was examined. Previous studies have shown that the reactivity and enantioselectivity of the substrate toward rhodium-catalyzed ARO was improved in the presence of zinc triflate\textsuperscript{11-12} or tetraammonium tetraborofluorate\textsuperscript{32}. Addition of these additives to the reactions, however, slowed the rate of the reactions down (Table 3.10.) After 84 hour observation, the substrates were not fully converted and the catalyst appeared to be no longer active. The isolated ARO products and enantioselectivity measurement showed slightly higher enantioselectivity.

\textsuperscript{32} Intramolecular ARO studies with oxabenzonorbornadienes by Rob Webster in Lautens group.
3.4.3 Synthesis of 8-Hydro-5-methyl-5,8-epoxyisoquinoline and 5-Hydro-8-methyl-5,8-epoxyisoquinoline

![Scheme 3.11](image)

We also attempted to make methyl substituted epoxyisoquinoline analogues 28 and 29. Using the analogous method used to make 2, the lithium intermediate was treated with 2-methylfuran to give the desired products. The capture of 2-methylfuran as a Diels Alder adduct gave no preference in regioselectivity. The products were obtained in equal amounts (1:1 ratio). Unfortunately, any attempts to separate the regioisomers failed; the cycloadducts were isolated as an inseparable mixture in 70% yield.
3.4.4 Synthesis and Asymmetric Ring-Opening Reactions of 8-Hydro-5-methyl-5,8-epoxyquinoline and 5-Hydro-8-methyl-5,8-epoxyquinoline

3.4.4.1 Synthesis of 8-Hydro-5-methyl-5,8-epoxyquinoline and 5-Hydro-8-methyl-5,8-epoxyquinoline

As any attempt to make methyl substituted epoxyisoquinoline analogue failed to give separable products, attention was shifted to the synthesis of methyl substituted epoxyquinoline. The synthesis required 3 steps (Scheme 3.12). Reaction of 2,3-pyridine formed in the fashion described in 3.1.1 with 2-methylfuran gave a 21% yield of a 2:1 ratio of 8-hydro-5-methyl-5,8-epoxyquinoline 7 and 5-hydro-8-methyl-5,8-epoxyquinoline 8, this ratio being in agreement with that reported previously for this cycloaddition reaction. \(^{33}\)

3.4.4.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 5-Hydro-8-methyl-5,8-epoxyquinoline

The asymmetric ring-opening of 5-hydro-8-methyl-5,8-epoxyquinoline with various nucleophiles was investigated. The results are summarized in table 3.10 and show that the introduction of methyl group on the bridgehead of epoxyquinoline brought an increase in the reactivity of ring opening.

Table 3.11. Rh-Catalyzed Divergent Enantioselective Ring Opening of 5-hydro-8-methyl-5,8-epoxyquinoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>MeOH</td>
<td>43</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>Bn₂NH</td>
<td>49</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>Tetrahydroquinoline</td>
<td>43</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Piperidine</td>
<td>38</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>Morpholine</td>
<td>46</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>Phenol</td>
<td>33</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>Indole</td>
<td>Inseparable products⁶</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>TsNH₂</td>
<td>Inseparable products⁶</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Phthalimide</td>
<td>Inseparable products⁶</td>
<td></td>
</tr>
</tbody>
</table>

---

† Isolated yields.  
‡ Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section.  
§ Products identified by ¹H NMR.
ARO products were observed with all the nucleophiles tested in this experiment with excellent enantioselectivity (95 to >99%ee). Product A is formed in higher yield than product B. High total yield and excellent enantioselectivity were observed for nitrogen-based nucleophiles, including the basic amine piperidine (entries 2-5). Methanol and phenol were also shown to be good nucleophiles (entries 1 and 6). Phthalimide, indole and p-toluenesulfonamide, previously shown to be unreactive toward substrates 1 and 2 reacted with the 8. TLC and $^1$H NMR analysis of the crude products showed a complete consumption of the starting materials and presence of the desired ARO products. Unfortunately, the product mixture was not separable. The broader scope and higher enantioselectivity in the ring-opening reactions of methyl-substituted substrate 8 suggests that the methyl group might act as a directing group and an electronic effect of the substituent might play an important role in ARO of 1 and 2.

3.4.4.3 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 8-Hydro-5-methyl-5,8-epoxyquinoline

Table 3.12. Rh-Catalyzed Ring Opening of 8-hydro-5-methyl-5,8-epoxyquinoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>N.R</td>
</tr>
<tr>
<td>2</td>
<td>Bn$_2$NH</td>
<td>N.R</td>
</tr>
<tr>
<td>3</td>
<td>Tetrahydroquinoline</td>
<td>N.R</td>
</tr>
<tr>
<td>4</td>
<td>Morpholine</td>
<td>N.R</td>
</tr>
<tr>
<td>5</td>
<td>Indole</td>
<td>N.R</td>
</tr>
<tr>
<td>6</td>
<td>Phenol</td>
<td>N.R</td>
</tr>
<tr>
<td>7</td>
<td>TsNH$_2$</td>
<td>N.R</td>
</tr>
<tr>
<td>8</td>
<td>Phthalimide</td>
<td>N.R</td>
</tr>
</tbody>
</table>
Interestingly, the ARO of 8-hydro-5-methyl-5,8-epoxyquinoline using the same ARO standard conditions did not proceed. A variety of nucleophiles were tried unsuccessfully. The results suggest that changing on the electronic properties of the bridgehead has great influence on the reactivity. The presence of electron-donating group methyl on the opposite side of electron rich nitrogen of pyridine core might be a hindering factor.

3.4.5 Synthesis and Asymmetric Ring-Opening Reactions of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide

3.4.5.1 Synthesis of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide

![Scheme 3.13](image)

The electronic effects of the nitrogen atom in the aromatic ring and the methyl group on the bridgehead might cancel each other and result in the substrate being inert toward ARO. In order to minimize this, a slightly modified structure was prepared. One method to test whether this effect is a hindering factor is to take some electron density away from the electronic rich pyridine ring. Thus, if the substitution is not symmetric, one bridgehead carbon should preferentially stabilize the positive charge of the rhodium intermediate complex more than the other and the ARO might proceed. This was accomplished by the synthesis of 8-hydro-5-methyl-5,8-epoxyquinoline N-oxide 32 nitrogen group on the pyridine ring was oxidized with mCPBA at room temperature to give N-oxide 32. The reaction was complete overnight with 78% yield.
3.4.5.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide

Table 3.13. Rh-Catalyzed Divergent Enantioselective Ring Opening of 8-hydro-5-methyl-5,8-epoxyquinoline N-Oxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>Bn₂NH</td>
<td>43</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>PhNHCH₃</td>
<td>58</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Tetrahydroquinoline</td>
<td>38</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>Piperidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>MeOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Indole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Phenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>TsNH₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Phthalimide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Isolated yields. b Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section. c Yield measured by ¹H NMR. d Products identified by ¹H NMR.

Having the starting material in hand, the reactivity of the substrate toward ARO was investigated. The high polarity of the starting materials and products proved to be the hindering
factor in purification and isolation of the desired ARO products. Only three examples were successfully separated. In general, the scope of nucleophiles is similar to that of substrate 2. Phthalimide, phenol, indole and p-toluenesulfonamide showed no conversion while amines and methanol worked well (entries 1-4). In term of regioselectivity, the ratio (product A to B) of ARO products shifts from 1:1 as observed in ARO of substrate 2 to 2:1. The enantioselectivity of the ARO products is excellent. The results suggest that the electronic effects of the nitrogen in the aromatic ring and the methyl group on the bridgehead indeed interfere with each other and upon manipulating the electronic properties of the aromatic ring; the ARO reactivity of the substrate increased and resembled those results observed previously.
3.5 Discussion

3.5.1 Effects of Nitrogen Position on the Pyridine Ring Core

![Figure 3.3](image)

The effect of nitrogen position on the pyridine ring core toward ARO was investigated through the ARO reactions of substrates 1 and 2. Examination of the scope of the reactions The scope of nucleophiles are similar in both cases. Amines and alcohols worked well while indole, phenol and p-toluenesulfonamide showed no activity. There is no clear regioselectivity of the ARO products. The ratio of products varies from 1:1 to 2:1. The results emphasize that changing the position of nitrogen on the aromatic ring has little influence on the reactivity and regioselectivity of the rhodium-catalyzed ring opening of 1 and 2 using Josiphos and Rh(cod)$_2$OTf. However, changing the position of nitrogen has a positive influence in term of enantioselectivity. ARO products with MeOH and product B with amines in both cases have excellent ee’s (>99%ee). Amine-induced ARO product A of 1 has relatively moderate ee’s (60-75%ee) while those of isoquinoline has excellent ee’s (91-94%ee).

3.5.2 Substitution effects in reactivity

An understanding of the effects of different substitution on 1 and 2 on the reactivity of ring opening reactions would provide useful information on the nature of reactive intermediates as well as allowing for the preparation of synthetically useful isoquinoline/quinoline core products.

The mechanism of the ARO in symmetrical substrates was previously proposed by Lautens and coworkers. They suggest the ionization of the C-O bond as a key step in the catalytic cycle and any factor being able to stabilize the ionic nature of the cycle can facilitate the rate of the reaction and also influence the regiochemistry of the reaction.
3.5.3 Substituents of the aromatic ring

We observed significant differences in the relative rates of reaction, with the more electron rich ring 5 adding faster (1-2h reaction time) and less electron ring 6 (>24 h reaction time) being the lowest.

Scheme 3.14. Rate of the Rhodium-catalyzed ARO reaction

The scope of nucleophilic ring opening reactions follows a similar trend where electron rich 5 has a very broad scope while less electron chloro-substituted ring 6 and unsubstituted ring 2’s nucleophilic scopes are similar.

Table 3.14. Nucleophilic scope comparison of substrates

<table>
<thead>
<tr>
<th>Nucleophiles</th>
<th>MeOH</th>
<th>EtOH</th>
<th>Allyl alcohol</th>
<th>Amines</th>
<th>Morpholine</th>
<th>Indole</th>
<th>Phenol</th>
<th>Sulfonamide</th>
<th>Phthalimide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
</tr>
</tbody>
</table>
The results indicate that the remote substitution effects the ring opening step and show that the formation of the stabilized ionic intermediate is the key step in determining whether a nucleophile adds or not. The presence of electron-donating group stabilizes the cationic intermediate and facilitates the reaction rate as well as makes the ARO more tolerant to a variety of nucleophiles while the presence of electron-withdrawing groups deactivate the epoxydihydroisoquinoline system toward reaction with the rhodium catalyst.

3.5.4 Substitution on the bridgehead

When methyl is present at the bridgehead, at the position (number) on the opposite side of the nitrogen, no conversion was observed (Table 3.2.) The results suggest that although breaking the C-O bond at the more highly substituted carbon seems to be favored by the methyl substituent on the bridgehead, this effect is cancelled by the electronic effect on the nitrogen on the aromatic ring, leading to the inactivity of the substrate. In order to minimize the interference of two directing groups and to test whether the interference is the hindering factor, a slightly modified structure was synthesized. Ring opening reactions with 32 supported our predictions. Indeed, by taking some electron density away from the pyridine ring in the form of an N-oxide, reactivity of ARO was improved. The nucleophilic scope and enantioselectivity is similar to unsubstituted epoxyisoquinoline, indicating it is possible to override the electronic effect of nitrogen. The nitrogen electron density is shifted away from the aromatic ring and the methyl group dominates and controls the reactivity. The ratio of the ring opening regioisomers (Table 3.12) also showed that the formation of product A formed from the C-O cleavage at the more highly substituted carbon is more favoured (Scheme 3.15).
Methyl substitution at the bridgehead position on the same side has a positive influence on the reactivity and enantioselectivity. Many different nucleophiles are reactive with this substrate providing the products in good to excellent yield. We were surprised to find that piperidine was a good nucleophile for this transformation. Poor reactivity and enantioselectivity for piperidine induced ring opening was detected when it was used in the ring opening reaction of substrates 1, 2 and 6.

The results showed that appropriate substitution on the bridgehead proved critical to the success of the ring opening reactions.

More work is needed as many questions remain unanswered. For example, the effect of other substituents needs to be investigated to validate the hypothesis. However, the results obtained from the study of substitution effects in this project further validate the proposal that the reaction proceeds through an ionic or charge separated intermediate. It seems that any substituents being able to stabilize any cationic character present along the reaction pathway will facilitate the rate of the reactions and have a positive influence on the enantioselectivity.

3.5.5 Enantioselectivity

The results show that the degree of enantioselectivity depends on the identity of the substituent. The epoxyquinoline 1 gives product A in moderate to good ee and type B in very high ee. Adding a methyl group to the bridgehead leads to an increase in enantioselectivity, the methyl-substituted substrate 8 gives both product A and B in excellent ee (96- >99%ee). Addition of substituents on the aromatic ring has either a positive or negative effect depending on the nature of the substituent. Ethoxy- substituted epoxyisoquinoline gives product type A in moderate ee (lower compared to epoxyisoquinoline 2) and type B in very high ee (>99%ee).
Product type A typically has lower ee than product type B. As recently discussed in the work of Rob Webster, a matched/mismatched effect during the oxidative insertion of the Rh ligand complex into the C-O bond is operative and responsible for the observed stereoselectivity (Scheme 3.16). For substrate B, both substrate and catalyst favour the same C-O bond. Product type A arises from nucleophilic addition via pathway a, while pathway b is inactive. For the S version, the starting material interacts with the chiral catalyst in a mismatched manner. The substrate controlled pathway a’ leads to product A with lower ee while ligand control gives rise to product B with high ee.

3.5.6 Proposed mechanism

The proposed catalytic pathway for the rhodium-catalyzed ring-opening of epoxyquinoline/isoquinoline follows closely that put forward regarding simple oxabenzonorbornenes (Scheme 3.17). Beginning with the chiral rhodium complex, exo-binding can occur to the
oxygen and the olefin on the substrate 2 to give the intermediate B. At this point, oxidative insertion of rhodium catalyst into the C-O bond of 2 forms either C or C’ and an S\textsubscript{N}2’ displacement of the rhodium catalyst by the nucleophile gives product A and B and regenerates the catalyst. Nucleophilic attack with inversion from the \textit{endo}-direction provides the 1,2-trans-product, in an S\textsubscript{N}2’ fashion relative to the rhodium metal. The oxidative insertion of the catalyst into a bridgehead carbon-oxygen bond is considered as the enantiodiscriminating step in the catalytic cycle. The formation of aromatized side product in the ARO supports oxidative insertion occurs prior to nucleophilic attack.

Scheme 3.17. Proposed catalytic pathway for the rhodium-catalyzed ring opening of epoxyisoquinolines.
3.6 Synthesis and Asymmetric Ring-Opening Reactions of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline

Given the success obtained with epoxyquinoline and epoxisoquinoline, we sought to expand the studies of this rhodium catalysed ARO to other nitrogen based polycyclic substrates. Quick access to ARO products of chloro substituted tricycles such as 5-chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline is highly attractive, as its scaffold provides a facile access to a broad range of enantioenriched products which could be further transformed into substituted benzoquinoline which are themselves pharmaceutically interesting compounds.

3.6.1 Synthesis of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline

Scheme 3.18

5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline 37 was synthesized as outlined in Scheme 3.16 according to the procedure modified from Knochel.\textsuperscript{34} Commercially available 5-chloro-7-iodo-8-quinolinol was readily converted into the corresponding arylsulfonate 36 using 4-chlorobenzenesulfonyl chloride. Compound 36 was treated with \textit{i}-PrMgCl at -78°C, which underwent iodine-magnesium exchange to form a corresponding Grignard reagent. After warming to room temperature, the functionalized heterocyclic aryne was formed and trapped

\textsuperscript{34}Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. \textit{Angew. Chem. Int. Ed.} 2004, 43, 4364-4366.
with furan to give the desired product 37 in 74% yield. It is worth noting that the various functionalities like chlorine were readily tolerated on the quinoline intermediates which might undergo further transformation and be useful in synthetic applications.

3.6.2  Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]-quinoline

Table 3.15. Rh-Catalyzed Divergent Enantioselective Ring Opening of 5-chloro-7,10-dihydro-7,10-epoxy-benzo[h]-quinoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>MeOH</td>
<td>Inseparable products c</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>2</td>
<td>Bn₂NH</td>
<td>Inseparable products c</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>3</td>
<td>Tetrahydroquinoline</td>
<td>Inseparable products c</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>4</td>
<td>PhNHCH₃</td>
<td>36  98  13  &gt;99</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>5</td>
<td>Morpholine</td>
<td>36  98  13  &gt;99</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>6</td>
<td>iPrNH₂</td>
<td>33  96  23  99</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>7</td>
<td>Piperidine</td>
<td>32  95  35  &gt;99</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>8</td>
<td>Indole</td>
<td>No reaction</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>9</td>
<td>Phenol</td>
<td>No reaction</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>10</td>
<td>TsNH₂</td>
<td>No reaction</td>
<td>Inseparable products c</td>
</tr>
<tr>
<td>11</td>
<td>Phthalimide</td>
<td>No reaction</td>
<td>Inseparable products c</td>
</tr>
</tbody>
</table>

a Isolated yields. b Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section. c Products identified by ¹H NMR.
We have conducted the studies on the ARO of 37 with various nucleophiles and obtained encouraging results (Table 3.14.) The reactivity of the nucleophiles is similar to that observed for 1 and 2 which suggests that the catalytically active complex is the same in each case. Nucleophiles can added in moderate yield moderate yield (>60% yield) and excellent ee’s (>95%ee). Some nucleophiles such as phthalimide, phenol, indole and p-toluenesulfonamide fail to induce ring opening.
3.7 Synthesis and Asymmetric Ring-Opening Reactions of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole

The indole heterocyclic core is found in an astonishing number of natural products and medicinal agents. More than 10000 biologically active indole derivatives have been discovered to date, with over 200 of these currently being marketed as pharmaceuticals or undergoing clinical trials. No example has ever been reported in enantioselective ring-opening of bicyclic [2.2.1] alkenes with an indole backbone (Scheme 3.16). The absence of these studies was surprising given the potential utility of these intermediates. Therefore it would be interesting to synthesize and explore the ARO of this core as the asymmetric ring opening of these substrates would provide an attractive entry into complex natural products.

Scheme 3.19

---

3.7.1 Synthesis of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole

Synthesis of desired indole 44 was first attempted using the method described by Garg\textsuperscript{36} (Scheme 3.18.) Commercially available 5-benzyloxyindole was converted to hydroxyindole 40 through two-step sequence. Hydroxyindole 40 was reacted with isopropyl isocyanate in the presence of a catalytic amount of Et\textsubscript{3}N to afford carbamate 41. However, attempts to convert carbamate 41 to silyl carbamate 42 were unsuccessful and the final desired product could not be achieved.

A second attempt to synthesize the desired product 50 employed the use of ortho dihalides in the indole system. The attempt began with the synthesis of 4,5-dibromoindole (Scheme 3.19). Nitration of commercially available 2,3-dibromobenzene with HNO₃ in H₂SO₄ gave a mixture of two regioisomers 43 and 44. After careful separation, the 4-nitro isomer 43 was reduced with either iron in ethanol or stannous chloride in ethanol to the corresponding aniline. The aniline was diazotized and reduced with stannous chloride to give the hydrazine 46 in 80% yield. Condensation of 46 with phenylacetaldehyde under Fischer conditions with polyphosphoric acid afforded a separable mixture of 5,6-dibromoindole 47 and 4,5-dibromoindole 48. Methylation of 4,5-dibromoindole gave the N-methyl indole 49 in 92% yield. The use of 1.2 equivalents of n-butyllithium in ether at -78°C in the presence of 20 equivalents of furan gave the desired product 50 in 89% yield.

3.7.2 Nucleophilic Scope of Rh-Catalyzed Divergent Enantioselective Ring Opening of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole

Table 3.16. Rh-Catalyzed Divergent Enantioselective Ring Opening of 4,5-\((\text{bicycle[2.2.1]\text{hept-5-ene}\text{-1-methyl-3-phenyl-1H-indole}})\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield(^a)</td>
<td>ee(^b)</td>
</tr>
<tr>
<td>1</td>
<td>Morpholine</td>
<td>31</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>Phenol</td>
<td>30</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>Phthalimide</td>
<td>43</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>Inseperable products(^c)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Bn(_2)NH</td>
<td>Inseperable products(^c)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PhNHCH(_3)</td>
<td>Inseperable products(^c)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Tetrahydroquinoline</td>
<td>Inseperable products(^c)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Piperidine</td>
<td>Inseperable products(^c)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Indole</td>
<td>Inseperable products(^c)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>TsNH(_2)</td>
<td>Inseperable products(^c)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields. \(^b\) Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Experimental section. \(^c\) Products identified by \(^1\)H NMR.

As shown in Table 3.14, various heteroatom nucleophiles undergo smooth ARO reaction with indole 50 to give ring opening products with good to high ee’s and moderate to good yields (entries 1-3). The ARO nucleophilic scope of indole 50 was very broad and the reactions were
complete within an hour. This substrate was the most reactive one investigated in this project. Due to similar polarities, the ARO products were not easily separated by column chromatography. By careful choosing the nucleophiles, that problem could be overcome. The ring opened products of 50 should be useful for further transformations such as coupling reactions and cyclization. The indole skeleton can be found in several biologically interesting pharmaceutical agents and such reactions provide a facile and attractive route to these skeletons in enantioenriched form.

3.8 Synthesis of 7-oxabicyclo[2.2.1]hept-5-eno-2,3-[c]thiophene

Thiophenes occur frequently as structural units in many natural and non-natural molecules and enjoy potential applications in pharmaceutical industry. Moreover, in the preparation of a wide range of cyclic and acyclic thiophene molecules, thiophene derivatives are excellent synthetic intermediates because of the unique electronic properties of sulfur. Therefore, it would be interesting to synthesize the (oxabicyclic substituted with thiophene backbone).

Scheme 3.22 Retrosynthesis of 7-oxabicyclo[2.2.1]hept-5-eno-2,3-[c]thiophene

The synthesis of 4 was envisioned to start from 3,4-bis(trimethylsilyl)thiophene (Scheme 3.17). Attempts to prepare 3,4-bis(trimethylsilyl)thiophene by dilithiation of 3,4-dibromothiophene with n-butyl/t-butyllithium followed by disilylation proved unsuccessful (Scheme 3.20.) The reaction yielded an inseparable mixture of mono- and bis(trimethylsilyl)-thiophene.

Scheme 3.23
Another possible method is to employ the sonochemical cross-coupling of 3, 4-dibromo-thiophene with Me₃SiCl (Scheme 3.19). However, when a mixture of 2, 3-dibromothiophene, Me₃SiCl, and magnesium powder in THF in a sealed tube was kept under ultrasonication, the reaction took place very slowly and was not complete after 7 days.

\[ \text{Inseparable mixture of starting material and product.} \]

**Scheme 3.24**

Given the difficulty encountered to access 4, no investigation of the asymmetric ring opening was carried out.

---

4 Future work and Conclusion

We have explored a new rhodium catalysed ring opening of nitrogen containing polycyclic substrates. Even though it does not proceed with complete regioselectivity, it resolves racemic nitrogen containing oxygen bridged polycyclic alkenes into pairs of regioisomeric products with excellent enantioselectivity (up to 99% ee). To the best of our knowledge, this constitutes the first example of rhodium catalyzed enantioselective ring opening of nitrogen containing polycyclic substrates.

Although resolutions may offer convenient access to enantiomerically pure materials, the maximum yield for a resolution process is 50%. Therefore, by using this new methodology, it is possible to get higher yields if oxabicyclic systems are enantiomerically pure to begin with.

The diverse range of nucleophiles demonstrates the potential to utilize epoxyquinoline/epoxyisoquinoline as a common precursor to a library of highly enantiomerically enriched substituted nitrogen containing polycyclic derivatives which would not be readily accessible by conventional means. The alcohol and double bonds as well as the substituent on the bridgehead and aromatic ring present in all products could be easily functionalized to provide more complicated products. The ring-opened products derived from this system can undergo hydrolysis, hydrogenation and Friedel Craft alkylation. This methodology can be utilized for use in library development as well as in the total synthesis of nitrogen-containing polycyclic alkaloid natural products.
5 Experimental

5.1 General experimental procedure

Unless otherwise noted, all reactions were carried out under an argon atmosphere with magnetic stirring. Air- or water-sensitive reactions were performed using standard inert gas atmosphere handling techniques. Unless otherwise noted, reagents were obtained from Aldrich and used as received. All solvents were dried and distilled prior to use.

Analytical thin layer chromatography was performed with EMD Silica Gel 60 F254 0.25mm glass-backed TLC plates. Visualization was accomplished with 254 nm UV light and a p-Anisaldehyde or a KMnO$_4$ TLC-stain solution. Purification of reaction products was generally done by flash chromatography with Silicycle flash silica gel (40-63 µm). NMR spectra were measured at room temperature on Varian 300, 400 or 500 MHz spectrometers. Chemical shifts are given relative to TMS (0 ppm) using the solvent signals as internal reference. NMR multiplet analysis was done by applying first-order rules. IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR or a Shimadzu 8400s FT-IR spectrometer with the substance as a neat film on a NaCl plate. Mass spectra were obtained using a Waters GCT Premier Time of Flight (ToF) mass spectrometer (EI) or a Sciex API 4000 triple quadrupole mass spectrometer (ESI). Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured in a 10 cm cell with a Rudolph Autopol IV polarimeter and are reported as follows: $[\alpha]_D^T$ (c = g/100 mL, solvent).
5.2 Synthesis and asymmetric ring opening of 5,8-dihydro-5,8-epoxyquinoline

5.2.1 Synthesis of 5,8-dihydro-5,8-epoxyquinoline (11)

The procedure for the preparation of the title compound was modified from reported method\textsuperscript{28}

3-Trimethylsilyl-2-hydroxypyridine (9)

\( nBuLi \) (14.3 ml, 1.62M in hexanes) was added slowly to a solution of distilled diisopropylamine (3.27 ml, 23.5 mmol) in THF (11.75 ml) at 0°C. The mixture was stirred at 0°C for 1.5 hours. To a dry flask, cooled under nitrogen, 2-hydroxypyridine (1.14g, 11.6 mmol) was dissolved in anhydrous THF (15.85 ml). The solution was transferred by cannula to the flask of newly-made LDA placed in an ice-bath. After 5 minute stirring, the solution was allowed to warm to room temperature over an hour. The solution was again placed in an ice bath, chlorotrimethylsilane (1.5 ml, 11.6 mmol) was added over 10 min to the solution. After stirring 5 min at 0°C, the solution was allowed to stir overnight at room temperature. The solvent was evaporated and ethyl acetate was added. The ethyl acetate was filtered and evaporated. Flash chromatography over silica gel (EtOAc/Hex, 1:1) yields 3-trimethylsilyl-2-hydroxypyridine as a white solid (1.28g, 66 %). The \( ^1H \)-NMR spectrum was in agreement with the literature reported spectrum\textsuperscript{28}.

\[ ^1H \text{-NMR (CDCl}_3, \text{400 MHz): } \delta = 13.06 \text{ (br s, 1H), 7.54 (dd, 1H, } J = 6.4, 2.0 \text{ Hz), 7.35 (dd, 1H, } J = 6.4, 2.0 \text{ Hz), 6.23 (t, 1H, } J = 6.4 \text{ Hz.), 0.28 (s, 9H).} \]

\[ ^13C \text{-NMR (CDCl}_3, \text{100 MHz): } \delta = 167.9, 147.3, 135.6, 131.4, 106.5, 18.1. \]
3-Trimethylsilyl-2-pyridyl Trifluoromethanesulfonate (10)

\[
\begin{align*}
\text{TMS} & \quad \text{OTf} \\
\text{H} & \quad \text{N}
\end{align*}
\]

To a stirred, ice-cold solution of 3-trimethylsilyl-2-hydroxypyridine (0.56 g, 3.3 mmol) in 3.3 ml of pyridine under argon was added dropwise trifluoromethanesulfonic anhydride (0.62 ml, 3.63 mmol). The solution was allowed to stir at room temperature overnight. The solvent was evaporated; diethyl ether and water were added. The ether extracts were washed with brine, dried with anhydrous MgSO\textsubscript{4} and evaporated. Flash chromatography over silica gel (EtOAc/Hex, 5:95) yielded 899 mg (91%) of 10 as a clear oil. The \textsuperscript{1}H-NMR spectrum was in agreement with the literature reported spectrum\textsuperscript{28}.  

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\ ppm = 8.32\) (dd, 1H, \(J = 2.0, 4.8\) Hz), 7.92 (dd, 1H, \(J = 2.0, 7.2\) Hz), 7.30 (dd, 1H, \(J = 4.8, 7.2\) Hz), 0.37 (s, 9H).

\textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\ ppm = 160.8, 148.7, 146.9, 125.2, 123.2, 118.5\) (d, \(J_{\text{CF}} = 319\) Hz), 113.7, -1.6.

5,8-dihydro-5,8-epoxyquinoline (11)

\[
\begin{align*}
\text{O} & \quad \text{N}
\end{align*}
\]

To a 50 ml round bottom flask was added CsF (687 mg, 4.52 mmol). The flask was flame dried under vacuum and switched to Argon. Acetonitrile (8 ml) and furan (2.23 ml, 30.11 mmol) were added to the flask. In a separate flask, 10 (451 mg, 1.51 mmol) was dissolved in acetonitrile (7 ml). Using a syringe pump, the aryne solution was added to the flask containing CsF very slowly and stirred overnight. Water and diethyl ether were added. The aqueous layer extracted with ether and the organic layers were combined and dried over anhydrous MgSO\textsubscript{4}. The solvent was removed in vacuo and the crude product was flash chromatographed (EtOAc/Hex, 40:60) to yield 11 as a red oil (65 mg, 30%). The \textsuperscript{1}H-NMR spectrum was in agreement with the literature reported spectrum\textsuperscript{33}.  
\[ \text{H-NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ ppm } = 7.96 \text{ (dd, } 1\text{H, } J = 1.2 \text{ and } 5.4 \text{ Hz), } 7.34 \text{ (dd, } 1\text{H, } J = 1.2 \text{ and } 7.2 \text{ Hz), } 7.06 \text{ (dd, } 1\text{H, } J = 2.0 \text{ and } 5.6 \text{ Hz), } 7.01 \text{ (dd, } 1\text{H, } J = 2.0 \text{ and } 5.6 \text{ Hz), } 6.77 \text{ (dd, } 1\text{H, } J = 5.6 \text{ and } 7.2 \text{ Hz), } 5.71 \text{ (d, } 1\text{H, } J = 1.6 \text{ Hz), } 5.53 \text{ (d, } 1\text{H, } J = 1.6 \text{ Hz) } \]

\[ \text{C-NMR (CDCl}_3, 100 \text{ MHz): } \delta \text{ ppm } = 172.7, 143.7, 143.4, 142.2, 141.9, 126.3, 119.1, 82.6, 81.6. \]

5.2.2 ARO reactions of 5,8-dihydro-5,8-epoxyquinoline

**General procedure**

Rh(cod)\(_2\)OTf (8.0mg, 0.017 mmol, 5% equiv) and Josiphos (11.2 mg, 0.021 mmol, 6% equiv) were added in flame dried microwave vial, sealed and purged with Argon and dissolved in anhydrous THF (0.5ml). Substrate 1 (50 mg, 0.344 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, others: 1.5 eq.) were dissolved in THF in a separated vial and added to the catalyst vial. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction was complete (typically 12-18 hours), the solvent was removed in vacuo and the crude products were purified by flash chromatography.

6-Methoxy-5,6-dihydroquinolin-5-ol (12.1) and 7-Methoxy-7,8-dihydroquinolin-8-ol (13.1)

Obtained from oxabicycle 1 (50 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu):; Product 12.1 isolated as a white solid (17.8 mg, 29% yield, >99%ee); Product 13.1 was isolated as a white solid (20.9 mg, 34% yield, >99% ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 10% → 20% → 40%.

6-Methoxy-5,6-dihydroquinolin-5-ol (12.1)

\[ \text{H-NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ ppm } = 8.35 \text{ (dd, } 1\text{H, } J = 5.0, 1.5 \text{ Hz, } 1\text{H), } 7.34 \text{ (dd, } 1\text{H, } J = 7.6, 1.5 \text{ Hz, } 1\text{H), } 7.16 \text{ (ddd, } J = 7.6, 5.0, 0.7 \text{ Hz, } 1\text{H), } 6.38 \text{ (dd, } J = 10.1, 2.4 \text{ Hz, } 1\text{H), } 6.06 \text{ (dd, } J = 10.1, 2.0 \text{ Hz, } 1\text{H), } 4.94 \text{ (d, } J = 11.1 \text{ Hz, } 1\text{H), } 4.63 \text{ (s, } 1\text{H), } 4.29 \text{ (dt, } J = 11.1, 2.2 \text{ Hz, } 1\text{H), } 3.60 \text{ (s, } 3\text{H). } \]
$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 155.7, 146.9, 133.0, 131.1, 127.5, 125.2, 123.3, 82.9, 73.5, 57.8

IR (neat): $\nu_{\text{max}}$ = 702, 818, 1111, 1343, 1443, 1574, 2824, 2924, 3048, 3171, 3410 (br) cm$^{-1}$.


$[\alpha]_{D}^{25} = -97.9^\circ\cdot$cm$^2$g (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralcel OJ, hexanes + 3% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 35.752 min, 41.646 min.

7-Methoxy-7,8-dihydroquinolin-8-ol (13.1)

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.54 – 8.26 (m, 1H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.14 (dd, $J = 7.7$, 5.0 Hz, 1H), 6.61 (dd, $J = 10.2$, 2.2 Hz, 1H), 6.32 (dd, $J = 10.2$, 2.0 Hz, 1H), 4.96 (d, $J = 10.8$ Hz, 1H), 4.15 (dt, $J = 11.1$, 2.1 Hz, 1H), 3.51 (s, 3H), 2.86 (d, $J = 2.9$ Hz, 1H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 151.4, 148.4, 132.7, 132.3, 132.0, 130.0, 122.6, 82.5, 72.3, 57.2.

IR (neat): $\nu_{\text{max}}$ = 802, 1042, 1111, 1188, 1443, 1574, 2361, 2824, 2924, 3333 (br) cm$^{-1}$.


$[\alpha]_{D}^{25} = +45.4^\circ\cdot$cm$^2$g (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralcel OJ, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 13.2 min, 14.8 min.

6-(Dibenzylamino)-5,6-dihydroquinolin-5-ol (12.2) and 7-(dibenzylamino)-7,8-dihydroquinolin-8-ol (13.2)

Obtained from oxabicycle 1 (50 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 12.2 isolated as a yellow oil (38.0 mg, 32% yield, 67% ee); Product 13.2 was isolated as a yellow oil (35.6 mg, 30% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 10% $\rightarrow$ 20% $\rightarrow$ 40%.
6-(Dibenzylamino)-5,6-dihydroquinolin-5-ol (12.2)

\[
\begin{align*}
\text{Chemical Structure Image}
\end{align*}
\]

\(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta \text{ ppm} = 8.32 \text{ (dd, } J = 4.9, 1.4 \text{ Hz, 1H}), 7.44 \text{ (d, } J = 7.1 \text{ Hz, 4H)}, 7.35 - 7.25 \text{ (m, 8H)}, 7.10 \text{ (dd, } J = 7.5, 5.0 \text{ Hz, 1H}), 6.41 \text{ (dd, } J = 10.0, 2.8 \text{ Hz, 1H}), 6.06 \text{ (dd, } J = 9.9, 2.5 \text{ Hz, 1H)}, 5.23 \text{ (d, } J = 11.5 \text{ Hz, 1H}), 4.01 \text{ (d, } J = 13.7 \text{ Hz, 2H}), 3.91 - 3.83 \text{ (m, 3H)}.
\]

\(^13\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta \text{ ppm} = 156.8, 146.9, 140.2, 134.3, 132.7, 129.1, 128.4, 127.7, 127.1, 126.5, 123.0, 70.8, 61.7, 54.8.

IR (neat): \(\nu_{\text{max}} = 702, 741, 772, 1451, 2338, 2808, 2847, 2916, 3024, 3426 \text{ (br) cm}^{-1}.

HR-MS (EI): Calc. for [M+H]\(^+\): 343.1804, found: 343.1814.

\([\alpha]_D^{25} = +18.3^\circ \text{cm}^2\text{g} \text{ (c = 1.0, 67\% ee, CHCl}_3\).

HPLC: Chiralcel OD-H, hexanes + 3\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 30.7 min, 35.0 min.

7-(Dibenzylamino)-7,8-dihydro-quinolin-8-ol (13.2)

\[
\begin{align*}
\text{Chemical Structure Image}
\end{align*}
\]

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta \text{ ppm} = 8.29 \text{ (ddd, } J = 4.9, 1.5, 0.9 \text{ Hz, 1H}), 7.69 \text{ (d, } J = 7.6 \text{ Hz, 1H)}, 7.26 - 7.16 \text{ (m, 10H)}, 7.01 \text{ (dd, } J = 7.6, 4.9 \text{ Hz, 1H}), 6.65 \text{ (dd, } J = 10.2, 2.7 \text{ Hz, 1H}), 6.37 \text{ (dd, } J = 10.2, 2.2 \text{ Hz, 1H}), 4.98 \text{ (d, } J = 12.3 \text{ Hz, 1H}), 3.93 \text{ (d, } J = 13.6 \text{ Hz, 2H}), 3.64 \text{ (dt, } J = 12.3, 2.5 \text{ Hz, 1H}), 3.55 \text{ (d, } J = 13.6 \text{ Hz, 2H}), 3.06 \text{ (s, 1H)}.
\]

\(^13\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta \text{ ppm} = 151.12, 148.14, 138.99, 132.92, 132.64, 131.77, 130.74, 129.15, 128.85, 127.69, 122.54, 68.76, 62.64, 55.15.

IR (neat): \(\nu_{\text{max}} = 702, 748, 1072, 1435, 2338, 2361, 2855, 2924, 3217 \text{ (br) cm}^{-1}.

HR-MS (EI): Calc. for [M+H]\(^+\): 343.1804, found: 343.1815.
[\alpha]_D^{25} = -56.3^\circ \cdot \text{cm}^2 \cdot \text{g} (c = 1.0, >99\% \text{ ee}, \text{CHCl}_3).

**HPLC:** Chiralcel OD-H, hexanes + 10\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 14.0 min, 16.8 min.

**6-(Methyl(phenyl)amino)-5,6-dihydroquinolin-5-ol (12.3) and 7-(methyl(phenyl)amino)-7,8-dihydro-quinolin-8-ol (13.3)**

Obtained from oxabicycle 1 (50 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 12.3 isolated as a white solid (35.1 mg, 43\% yield, 75\% ee); Product 13.3 was isolated as a yellow solid (35.7 mg, 43\% yield, >99\% ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 10\% → 20\% → 40\%.

**6-(Methyl(phenyl)amino)-5,6-dihydroquinolin-5-ol (12.3) and 7-(methyl(phenyl)amino)-7,8-dihydro-quinolin-8-ol (13.3)**

![Chemical Structure](image)

**$^1$H-NMR** (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.37 (dd, $J = 5.0$, 1.5 Hz, 1H), 7.38 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.27 – 7.16 (m, 3H), 6.96 (dd, $J = 10.1$, 2.1 Hz, 2H), 6.75 (t, $J = 7.3$ Hz, 1H), 6.51 (dd, $J = 9.9$, 2.8 Hz, 1H), 6.05 (dd, $J = 9.9$, 2.5 Hz, 1H), 5.22 (d, $J = 11.6$ Hz, 1H), 4.90 (dt, $J = 11.6$, 2.6 Hz, 1H), 4.54 (s, 1H), 3.02 (s, 3H).

**$^{13}$C-NMR** (CDCl$_3$, 100 MHz): $\delta$ ppm = 156.6, 150.3, 147.1, 133.1, 133.0, 129.3, 127.7, 126.7, 123.2, 117.8, 114.7, 70.3, 64.4, 34.4.

**IR** (neat): $\nu_{\text{max}} = 748, 818, 1103, 1211, 1265, 1366, 1435, 1505, 1597, 2886, 3040, 3179$ (br) cm$^{-1}$.


$[\alpha]_D^{25} = +75.7^\circ \cdot \text{cm}^2 \cdot \text{g} (c = 1.0, 75\% \text{ ee}, \text{CHCl}_3)$.

**HPLC:** Chiralcel OJ, hexanes + 10\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 19.9 min, 24.7 min.

**7-(Methyl(phenyl)amino)-7,8-dihydro-quinolin-8-ol (13.3)**
**H-NMR** (CDCl₃, 400 MHz): \( \delta \text{ ppm} = 8.33 \) (dd, \( J = 4.9 \) Hz, 1H), 7.81 (d, \( J = 7.6 \) Hz, 1H), 7.22 – 7.14 (m, 2H), 7.09 (dd, \( J = 7.6 \) Hz, 1H), 6.88 (d, \( J = 8.0 \) Hz, 2H), 6.74 (t, \( J = 7.3 \) Hz, 1H), 6.65 (dd, \( J = 10.0 \) Hz, 1H), 6.15 (dd, \( J = 10.0 \) Hz, 2H), 5.16 (d, \( J = 11.2 \) Hz, 1H), 4.73 (dt, \( J = 11.2 \) Hz, 2H), 2.90 (d, \( J = 3.0 \) Hz, 1H), 2.84 (s, 3H).

**13C-NMR** (CDCl₃, 100 MHz): \( \delta \text{ ppm} = 151.4, 150.4, 148.6, 133.4, 133.1, 132.8, 131.6, 129.6, 122.7, 118.9, 115.2, 69.9, 64.5, 34.0 \).

**IR** (neat): \( \nu_{\text{max}} = 748, 810, 1042, 1219, 1345, 1505, 1597, 2338, 2816, 3179 \text{ (br)} \) cm\(^{-1} \).


**\([\alpha]_D^{25}\)** = +95.4°·cm\(^2\)g (c = 1.0, >99% ee, CHCl₃).

**HPLC**: Chiralcel OJ, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 16.0 min, 23.0 min.

**6-(3,4-dihydro-1(2H)-quinolinyl)-5,6-dihydroquinolin-5-ol (12.4) and 7-(3,4-dihydro-1(2H)-quinolinyl)-7,8-dihydro-quinolin-8-ol (13.4)**

Obtained from oxabicycle 1 (50 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 12.4 isolated as a yellow oil (35.5 mg, 37% yield, 60% ee); Product 13.4 was isolated as a yellow oil (36.4 mg, 38% yield, >99 % ee).

**Flash Chromatography Eluent**: ethyl acetate in hexanes: 40%.

**6-(3,4-dihydro-1(2H)-quinolinyl)-5,6-dihydroquinolin-5-ol (12.4)**

**H-NMR** (CDCl₃, 400 MHz): \( \delta \text{ ppm} = 8.42 \) (d, \( J = 5.0 \) Hz, 1H), 7.50 (dd, \( J = 7.6 \) Hz, 1H), 7.35 – 7.29 (m, 1H), 7.02 (dd, \( J = 9.8 \) Hz, 7.9 Hz, 2H), 6.86 (d, \( J = 8.1 \) Hz, 1H), 6.62 (td, \( J = 7.3 \) Hz, 0.9 Hz, 1H), 6.56 (dd, \( J = 9.9 \) Hz, 2.8 Hz, 1H), 6.13 (dd, \( J = 9.9 \) Hz, 2.5 Hz, 1H), 5.42 (d, \( J = 11.4 \) Hz, 1H), 4.91 (d, \( J = 11.3 \) Hz, 1H), 4.60 (s, 1H), 3.54 – 3.35 (m, 2H), 2.83 (t, \( J = 6.4 \) Hz, 2H), 2.12 – 1.92 (m, 2H).
$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ ppm = 156.8, 147.0, 145.2, 133.6, 133.2, 129.6, 127.8, 126.9, 126.6, 124.0, 123.3, 116.5, 112.8, 69.7, 62.4, 45.9, 28.5, 22.8.

IR (neat): $\nu_{max}$ = 748, 818, 1188, 1458, 1497, 2338, 2886, 2932, 3194, 3426 (br) cm$^{-1}$.

HR-MS (EI): Calc. for [M$^+$]: 278.1419, found: 278.1422.

$[a]_D^{25}$ = $+14.7^\circ$ cm$^2$ g$^{-1}$ (c = 1.0, 60% ee, CHCl$_3$).

HPLC: Chiralcel OD-H, hexanes + 8% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 16.7 min, 25.0 min.

7-(3,4-dihydro-1(2H)-quinolinyl))-7,8-dihydro-quinolin-8-ol (13.4)

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ ppm = 8.42 (dd, $J$ = 4.9, 0.9 Hz, 1H), 7.86 (d, $J$ = 7.6 Hz, 1H), 7.17 (dd, $J$ = 7.6, 5.0 Hz, 1H), 7.09 – 6.97 (m, 2H), 6.88 (d, $J$ = 8.2 Hz, 1H), 6.76 (dd, $J$ = 10.0, 2.6 Hz, 1H), 6.66 (t, $J$ = 7.3 Hz, 1H), 6.23 (dd, $J$ = 10.0, 2.8 Hz, 1H), 5.42 – 5.16 (m, 1H), 4.83 (dt, $J$ = 10.6, 2.6 Hz, 1H), 3.50 – 3.12 (m, 2H), 2.80 (dd, $J$ = 10.1, 6.2 Hz, 2H), 2.01 – 1.85 (m, 2H), 1.72 (s, 1H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ ppm = 151.5, 148.6, 145.3, 134.1, 133.4, 133.0, 131.6, 129.9, 127.3, 124.5, 122.7, 117.4, 112.7, 69.4, 62.2, 45.1, 28.3, 22.8.

IR (neat): $\nu_{max}$ = 748, 1042, 1304, 1435, 1497, 1597, 2847, 2924, 3225 (br) cm$^{-1}$.

HR-MS (EI): Calc. for [M$^+$]: 278.1419, found: 278.1414.

$[a]_D^{25}$ = $+18.0^\circ$ cm$^2$ g$^{-1}$ (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralcel OD-H, hexanes + 8% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 17.2 min, 22.6 min.
5.3 Synthesis and ARO of 5,8-dihydro-5,8-epoxyisoquinoline

5.3.1 Synthesis of 5,8-dihydro-5,8-epoxyisoquinoline

Method 1:
Pyridine-3-yl diethylcarbamate (14)

In a 500 ml flask, 3-hydroxypyridine (20 g, 0.21 mol) was dissolved in 105 ml of pyridine and placed in an ice bath at 0°C. Diethylcarbamoyl chloride (30 ml, 0.22 mol) was added. The solution was then warmed to room temperature overnight. Water was added and the mixture was extracted with ether. The organic layers were dried with anhydrous MgSO₄, filtered and evaporated to yield 14 as a yellow oil (38.7 g, 95%). The ¹H-NMR spectrum was in agreement with the literature reported spectrum.²⁸

¹H-NMR (CDCl₃, 400 MHz): δ ppm = 8.42 (m, 2H), 7.51 (m, 1H), 7.29 (m, 1H), 3.37 (q, 2H, J = 7.2 Hz), 3.43 (q, 1H, J = 7.2 Hz), 1.19 (t, 3H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.2 Hz).

¹³C-NMR (CDCl₃, 100 MHz): δ ppm = 153.4, 148.1, 146.0, 143.5, 129.3, 123.6, 42.4, 42.0, 14.2, 13.2.

4-(triethylsilyl)pyridin-3-yl diethylcarbamate (15):

ₙBuLi (142 ml, 1.62M in hexanes) was added slowly to a solution of distilled diisopropylamine (33 ml, 234 mmol) in THF (117.75 ml) at 0°C. The mixture was stirred at 0°C for 1.5 hours. To a dry flask, cooled under nitrogen, pyridine-3-yl diethylcarbamate (30 g, 154 mmol) was dissolved in anhydrous THF (309 ml). The solution was transferred by cannula to the flask of newly-made LDA placed in an ice-bath. After 25 minute stirring, trimethylsilyl trifluoromethanesulfonate (52.2 ml, 231 mmol) was added over 15 min to the solution. The solution was allowed to stir overnight at room temperature. Water was added, and the mixture was extracted with ether. The
organic layers were washed with brine, dried with magnesium sulfate, filtered and evaporated. Flash chromatography over silica gel (EtOAc/Hex, 1:1) yielded 15 as a white solid (33.8 g, 71 %). The $^1$H-NMR spectrum was in agreement with the literature reported spectrum.$^{28}$

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.38 (d, 1H, $J$ = 4.8 Hz), 8.32 (s, 1H), 7.32 (d, 1H, $J$ = 4.8 Hz), 3.48 (q, 2H, $J$ = 7.2 Hz), 3.40 (q, 2H, $J$ = 7.2 Hz), 1.26 (t, 3H, $J$ = 7.2 Hz), 1.20 (t, 3H, $J$ = 7.2 Hz), 0.94 (t, 9H, $J$ = 7.2 Hz), 0.83 (m, 6H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 153.8, 152.9, 145.0, 144.0, 138.7, 129.5, 42.0, 41.7, 14.2, 13.2, 7.2, 3.0.

4-(Triethylsilyl)pyridin-3-ol (16)

Methanol (3.08 ml) was added to a solution of 4-(triethylsilyl)pyridin-3-yl diethylcarbamate (2.45 g, 7.93 mmol) in 30 ml of 25% sodium methoxide in methanol. The solution was heated at reflux overnight. Hydrochloric acid (10%) was added dropwise, and the mixture was extracted with ether, washed with brine, dried with anhydrous MgSO$_4$ and evaporated. The crude product was flash chromatographed to yield 16 as a white solid (663.4 mg, 40%). The $^1$H-NMR spectrum was in agreement with the literature reported spectrum$^{28}$.

4-(Triethylsilyl)pyridin-3-yl Trifluoromethanesulfonate (17):

To a stirred, ice-cold solution of 4-(triethylsilyl)pyridin-3-ol (300 mg, 1.43 mmol) in 1.43 ml of pyridine under Argon was added dropwise trifluoromethanesulfonic anhydride (0.267 ml, 1.58 mmol). The solution was allowed to stir at room temperature overnight. The solvent was evaporated; diethyl ether and water were added. The ether extracts were washed with brine, dried with anhydrous MgSO$_4$ and evaporated. Flash chromatography over silica gel (EtOAc/Hex, 5:95
(40:60) yielded 263 mg of 17 as a clear oil. The 1H-NMR spectrum was in agreement with the literature reported spectrum.\(^{28}\)

1H-NMR (CDCl\(_3\), 400 MHz): \(\delta \text{ ppm} = 8.60 \) (s, 1H), 8.56 (d, 1H, \(J = 4.8 \) Hz), 8.56 (d, 1H, \(J = 4.8 \) Hz), 0.94 (m, 15H).

13C-NMR (CDCl\(_3\), 100 MHz): \(\delta \text{ ppm} = 149.3, 145.1, 138.3, 137.4, 128.0, 115.6 \) (q, \(J = 319 \) Hz, CF\(_3\)), 4.2, 0.0.

5,8-dihydro-5,8-epoxyisoquinoline (2):

![Diagram](https://via.placeholder.com/150)

To a 50 ml round bottom flask was added CsF (290 mg, 1.92 mmol). The flask was flame dried under vacuum and switched to Argon. Acetonitrile (3.36 ml) and furan (0.94 ml, 12.80 mmol) were added to the flask. In a separate flask, 17 (217 mg, 0.64 mmol) was dissolved in acetonitrile (3 ml). Using a syringe pump, the solution of 7 in MeCN was added to the flask containing CsF very slowly and stirred overnight. Water and diethyl ether were added. The aqueous layer extracted with ether and the organic layers were combined and dried over anhydrous MgSO\(_4\). The solvent was removed in vacuo and the crude product was flash chromatographed (EtOAc/Hex, 40:60) to yield 2 as a yellow brown oil that solidified upon drying under vacuo (50.6 mg, 55%). The 1H-NMR spectrum was in agreement with the literature reported spectrum.\(^{29}\)

1H NMR (CDCl\(_3\), 400 MHz): \(\delta \text{ ppm} = 8.38 \) (1 H, s), 8.22 (1 H, d, \(J = 4.56 \) Hz), 7.16 (1 H, d, \(J = 4.56 \) Hz), 6.98 (1 H, dd, \(J = 5.57, 1.84 \) Hz), 6.92 (1 H, dd, \(J = 5.56, 1.89 \) Hz), 5.77-5.73 (1 H, m), 5.67-5.65 (1 H, m)

13C-NMR (CDCl\(_3\), 100 MHz): \(\delta \text{ ppm} = 158.8, 147.4, 144.1, 143.4, 141.9, 139.8, 116.1, 81.7, 80.6.\)

**Method 2:** The title compound was prepared by the reported method.\(^{29}\)

5,8-dihydro-5,8-epoxyisoquinoline (2): to an oven dried 100 ml 3-neck round-bottomed flask with an internal thermometer, septum, nitrogen adapter and stirring bar was added dry THF (20
ml) and dry isopropyl amine (3.7 ml, 26.4 mmol) at -100°C under N₂. To this was added nBuLi (16.5 ml, 1.6 M in hexanes) dropwise via syringe. This was stirred at -100°C for 30 minutes and to this solution of LDA was added over 15 min 3-chloropyridine (2.51 ml, 26.4 mmol) in THF (5 ml) using a cannula. The mixture was stirred for 20 min at -100°C then was added freshly distilled furan (19.2 ml, 264 mmol) via a syringe. The mixture was allowed to warm to room temperature overnight. The insoluble polymer material was filtered and washed well with diethyl ether. The washings were combined and concentrated in vacuo, taken up in CHCl₃, washed with 10% NaHCO₃, H₂O and brine. The organic layer was dried by anhydrous MgSO₄ and the solvent was removed in vacuo. The crude product was purified by flash chromatography twice (first with EtOAc, then EtOAc/Hex, 40:60.) to yield 2 as a red solid (573.2 mg, 15%). The ¹H-NMR spectrum was in agreement with the literature reported spectrum.²⁹

5.3.2  ARO of 5,8-dihydro-5,8-epoxyisoquinoline

Rh(cod)₂OTf (8.0 mg, 0.017 mmol, 5% equiv) and Josiphos (11.2 mg, 0.021 mmol, 6% equiv) were added in flame dried microwave vial, sealed and purged with argon and dissolved in anhydrous THF (0.5 ml). Epoxyquinoline 2 (50 mg, 0.344 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, others: 1.5 eq.) were dissolved in THF in a separated vial and added to the catalyst vial. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction was complete (typically 1.5-12 hours), the solvent was removed in vacuo and the crude products were purified by flash chromatography.

6-(Dibenzylamino)-5,6-dihydroisoquinolin-5-ol (18.2) and 7-(dibenzylamino)-7,8-dihydroisoquinolin-8-ol (19.2)

Obtained from oxabicycle 2 (50 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 18.2 isolated as a yellow oil (34.8 mg, 30% yield, 94% ee); Product 19.2 was isolated as a yellow oil (34.3 mg, 29% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 80%.

6-(Dibenzylamino)-5,6-dihydroquinolin-5-ol (18.2)
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.34 (d, $J = 4.9$ Hz, 1H), 8.18 (s, 1H), 7.35 (d, $J = 4.9$ Hz, 1H), 7.29 – 7.16 (m, 10H), 6.50 (dd, $J = 10.0$, 2.8 Hz, 1H), 6.18 (dd, $J = 10.0$, 2.1 Hz, 1H), 4.90 (d, $J = 12.8$ Hz, 1H), 3.93 (d, $J = 13.6$ Hz, 2H), 3.63 (dt, $J = 12.8$, 2.5 Hz, 1H), 3.54 (d, $J = 13.6$ Hz, 2H), 3.14 (s, 1H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 149.5, 146.3, 145.6, 138.9, 129.1, 128.9, 128.0, 127.7, 127.6, 126.6, 119.7, 68.4, 62.5, 55.1.

IR (neat): $\nu_{\text{max}}$ = 702, 748, 849, 1373, 1589, 2847, 2924, 3032, 3194 (br) cm$^{-1}$.


$[\alpha]_D^{25}$ = +99.6°·cm$^2$·g$^{-1}$ (c = 1.0, 94% ee, CHCl$_3$).

HPLC: Chiralcel OD-H, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 13.1 min, 17.9 min.

7-(dibenzylamino)-7,8-dihydro-isoquinolin-8-ol (19.2)

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.60 (s, 1H), 8.38 (d, $J = 4.7$ Hz, 1H), 7.43 – 7.11 (m, 11H), 6.84 (d, $J = 4.9$ Hz, 1H), 6.45 (dd, $J = 9.9$, 2.6 Hz, 1H), 6.30 (dd, $J = 9.9$, 2.5 Hz, 1H), 5.01 (d, $J = 11.2$ Hz, 1H), 3.87 (d, $J = 13.6$ Hz, 2H), 3.64 (dt, $J = 11.2$, 2.5 Hz, 1H), 3.54 (d, $J = 13.6$ Hz, 2H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 149.8, 146.9, 1389.0, 138.9, 132.0, 131.2, 129.1, 128.8, 128.1, 127.7, 120.0, 67.3, 62.6, 55.0.

IR (neat): $\nu_{\text{max}}$ = 702, 748, 849, 1026, 1072, 1451, 1597, 2855, 2924, 3024, 3194 (br) cm$^{-1}$.


$[\alpha]_D^{25}$ = +135.6°·cm$^2$·g$^{-1}$ (c = 1.0, >99% ee, CHCl$_3$).
HPLC: Chiracel OJ, hexanes + 2% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 42.1 min, 48.2 min.

6-(Methyl(phenyl)amino)-5,6-dihydroquinolin-5-ol (18.3) and 7-(methyl(phenyl)amino)-7,8-dihydro-quinolin-8-ol (19.3)

Obtained from oxabicycle 2 (50 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 18.3 isolated as a yellow solid (33.0 mg, 40 % yield, 94% ee); Product 19.3 was isolated as a yellow oil (33.7 mg, 41 % yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 10% → 40%.

6-(Methyl(phenyl)amino)-5,6-dihydroquinolin-5-ol (18.3)

\[
\begin{align*}
\text{H-NMR (CDCl}_3, 400 \text{ MHz): } & \delta \text{ ppm } = 8.47 (d, J = 4.9 \text{ Hz, 1H}), 8.28 (s, 1H), 7.52 (d, J = 4.7 \text{ Hz, 1H}), 7.27 - 7.22 (m, 2H), 6.94 (dd, J = 8.8, 0.8 \text{ Hz, 2H}), 6.87 - 6.71 (m, 1H), 6.55 (dd, J = 9.8, 2.8 \text{ Hz, 1H}), 6.02 (dd, J = 9.8, 2.4 \text{ Hz, 1H}), 5.16 (d, J = 12.0 \text{ Hz, 1H}), 4.77 (dt, J = 12.0, 2.6 \text{ Hz, 1H}), 2.92 (s, 3H), 2.76 (d, J = 9.5 \text{ Hz, 1H}). \\
\text{C-NMR (CDCl}_3, 100 \text{ MHz): } & \delta \text{ ppm } = 150.5, 149.8, 146.5, 145.5, 130.8, 129.6, 127.9, 126.4, 119.9, 119.0, 115.4, 69.4, 64.6, 34.0. \\
\text{IR (neat): } & \nu_{\text{max}} = 748, 849, 1103, 1211, 1420, 1505, 1597, 2816, 2886, 3163 (\text{br}) \text{ cm}^{-1}. \\
\text{HR-MS (EI): } & \text{Calc. for } [\text{M}^+]: 252.1263, \text{found: 252.1270}. \\
[a]_D^{25} & = -104.4^\circ \text{-cm}^2\text{-g (c }= 1.0, 94% \text{ ee, CHCl}_3). \\
\text{HPLC: Chiralcel OD-H, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 20.8 min, 31.7 min.} \\
7-(Methyl(phenyl)amino)-7,8-dihydro-quinolin-8-ol (19.3)

\[
\begin{align*}
\text{H-NMR (CDCl}_3, 400 \text{ MHz): } & \delta \text{ ppm } = 8.76 (s, 1H), 8.54 (d, J = 4.9 \text{ Hz, 1H}), 7.38 - 7.20 (m, 4H), 6.98 (dd, J = 11.8, 6.7 \text{ Hz, 2H}), 6.83 (t, J = 7.3 \text{ Hz, 1H}), 6.56 (dd, J = 9.8, 2.5 \text{ Hz, 1H}), 6.20
\end{align*}
\]
(dd, \( J = 9.8, 2.9 \) Hz, 1H), 5.21 (d, \( J = 10.0 \) Hz, 1H), 4.79 (dt, \( J = 10.0, 2.7 \) Hz, 1H), 2.86 (s, 3H), 2.48 (s, 1H).

\(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz): \( \delta \text{ ppm} = 150.1, 150.1, 147.3, 139.2, 134.2, 131.3, 129.6, 127.9, 120.3, 118.7, 115.0, 68.2, 63.9, 33.9.\)

IR (neat): \( \nu_{\text{max}} = 748, 910, 1103, 1366, 1505, 1597, 2816, 2886, 3055, 3163 \text{ cm}^{-1}.\)

HR-MS (EI): Calc. for [M\(^{+}\)]: 252.1263, found: 252.1261.

\([\alpha]_D^{25} = +8.9^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} (c = 1.0, >99\% \text{ ee, CDCl}_3).\)

HPLC: Chiralpak AD-H, hexanes + 17% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 10.9 min, 19.3 min.

6-(3,4-dihydro-1(2H)-quinolinyl)-5,6-dihydroisoquinolin-5-ol (18.4) and 7-(3,4-dihydro-1(2H)-quinolinyl))-7,8-dihydro-isoquinolin-8-ol (19.4)

Obtained from oxabicycle 2 (45.5 mg, 0.31 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)_2; Product 18.4 isolated as a white solid (41.8 mg, 48% yield, 91% ee); Product 19.4 was isolated as a white solid (39 mg, 45% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 40%.

6-(3,4-dihydro-1(2H)-quinolinyl)-5,6-dihydroisoquinolin-5-ol (18.4)

\(^1\text{H-NMR}\) (CDCl\(_3\), 400 MHz): \( \delta \text{ ppm} = 8.46 (d, \( J = 4.9 \) Hz, 1H), 8.28 (s, 1H), 7.51 (d, \( J = 5.0 \) Hz, 1H), 7.01 (dd, \( J = 13.3, 6.9 \) Hz, 2H), 6.84 (d, \( J = 8.2 \) Hz, 1H), 6.65 (t, \( J = 7.3 \) Hz, 1H), 6.58 (dd, \( J = 9.8, 2.7 \) Hz, 1H), 6.03 (dd, \( J = 9.8, 2.5 \) Hz, 1H), 5.22 (d, \( J = 11.6 \) Hz, 1H), 4.81 (dt, \( J = 11.6, 2.5 \) Hz, 1H), 3.40 – 3.18 (m, 2H), 2.91 – 2.72 (m, 3H), 2.00 – 1.89 (m, 2H).

\(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz): \( \delta \text{ ppm} = 149.7, 146.6, 145.7, 145.3, 131.6, 130.0, 128.0, 127.3, 126.5, 124.6, 120.1, 117.6, 112.9, 68.9, 62.3, 45.4, 28.3, 22.8.

IR (neat): \( \nu_{\text{max}} = 741, 1188, 1304, 1350, 1458, 1497, 1559, 1597, 2839, 2932, 3171 \text{ cm}^{-1}.\)

HR-MS (EI): Calc. for [M\(^{+}\)]: 278.1419, found: 278.1425.

\([\alpha]_D^{25} = +36.8^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} (c = 1.0, 91\% \text{ ee, CDCl}_3).\)
**HPLC:** Chiralcel OD-H, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 16.8 min, 24.5 min.

7-(3,4-dihydro-1(2H)-quinolinyl)-7,8-dihydro-isoquinolin-8-ol (19.4)

\[
\text{\includegraphics[width=0.2\textwidth]{structure.png}}
\]

\[^1\text{H-NMR} (\text{CDCl}_3, 400 \text{ MHz}): \delta \text{ ppm} = 8.69 \text{ (s, 1H)}, 8.50 \text{ (d, } J = 4.9 \text{ Hz, 1H)}, 7.15 - 7.03 \text{ (m, 1H)}, 7.01 \text{ (dd, } J = 5.0, 3.3 \text{ Hz, 2H)}, 6.90 \text{ (d, } J = 8.2 \text{ Hz, 1H)}, 6.67 \text{ (td, } J = 7.3, 1.0 \text{ Hz, 1H)}, 6.60 \text{ (dd, } J = 9.8, 2.4 \text{ Hz, 1H}), 6.26 - 6.16 \text{ (m, 1H)}, 5.22 \text{ (d, } J = 8.9 \text{ Hz, 1H)}, 4.81 \text{ (dt, } J = 8.9, 2.8 \text{ Hz, 1H)}, 3.17 \text{ (ddt, } J = 54.4, 11.5, 5.8 \text{ Hz, 2H)}, 2.88 \text{ (s, 1H)}, 2.78 \text{ (t, } J = 6.0 \text{ Hz, 2H)}, 1.98 - 1.82 \text{ (m, 2H)}.\]

\[^{13}\text{C-NMR} (\text{CDCl}_3, 100 \text{ MHz}): \delta \text{ ppm} = 150.3, 147.5, 145.1, 139.3, 134.5, 131.2, 130.0, 128.0, 127.3, 124.5, 120.4, 117.5, 112.6, 67.8, 61.6, 45.0, 28.3, 22.8.\]

**IR** (neat): \(\nu_{\text{max}} = 748, 1188, 1304, 1458, 1497, 1597, 2855, 2924, 3040, 3179 \text{ cm}^{-1}.\)

**HR-MS** (EI): Calc. for \([\text{M}^+]\): 278.1419, found: 278.1427.

\[\left[a\right]_{D}^{25} = -105.3^\circ \text{ cm}^{-1} \text{g (c = 1.0, >99% ee, CHCl}_3].\]

**HPLC:** Chiralpak AD-H, hexanes + 12% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 16.5 min, 35.5 min.
5.4 Synthesis and ARO of 1-ethoxy-5,8-epoxy-5,8-
dihydroisoquinoline

5.4.1 Synthesis of 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline

2-Ethoxy-3-chloropyridine (20)

\[ \text{\text{\textbullet\text{Cl}}\text{\textbullet\text{Et}}} \]

To a 500 ml round-bottomed flask at 0°C, sodium metal (~5.5 g), was added to absolute ethanol (220 ml) and the resulting suspension was stirred until the sodium had disappeared and hydrogen liberation ceased. 2,3-Dichloropyridine (9.65 g, 65.7 mmol) was added and the mixture was refluxed overnight. The reaction vessel was allowed to cool to room temperature, quenched with saturated aqueous NH₄Cl (150 ml) and extracted with chloroform (4 x 250 ml). The organic extracts were combined and dried by anhydrous MgSO₄. The solvent was removed in vacuo and the residue was flash chromatographed (EtOAc/Hex = 10/90) to give the product 20 as a colorless liquid (9.01 g, 88%). The ¹H-NMR spectrum was in agreement with the literature spectrum.³⁰

¹H-NMR (CDCl₃, 400 MHz): δ ppm = 8.03 (m, 1H), 7.61 (dd, 1H, J = 1.6 and 7.6 Hz), 6.80 (m, 1H), 4.45 (q, 2H, J = 7.1 Hz), 1.44 (t, 3H, J = 7.1 Hz).

¹³C-NMR (CDCl₃, 100 MHz): δ ppm = 159.1, 144.6, 138.1, 118.2, 117.0, 62.6, 14.5.

1-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline (5)

The title compound was synthesized by a modification of the reported method.³⁰ To an oven dried 250 ml round-bottomed flask under nitrogen fitted with a stirring bar and a septum was charged with a solution of 2-ethoxy-3-chloropyridine (4.03 g, 25.6 mmol) in dry THF (50 ml) and cooled to -78°C. After 20 minutes at -78°C, nBuLi (17.3 ml, 1.62 M in hexanes, 28.1 mmol) was added slowly with stirring to give cloudy bright yellow solution. After 60 minutes at -78°C,
freshly distilled furan (18.6 ml, 256 mmol) was added. The mixture was allowed to warm to room temperature overnight, concentrated in vacuo, taken up in chloroform, washed with saturated NaHCO₃, water, brine and dried by anhydrous MgSO₄. The solvent was removed in vacuo and the crude product was purified by flash chromatography (EtOAc/Hex, 3/97 →10/90) to give the desired product as a yellow oil (1.93 g, 40%). The ¹H-NMR spectrum was in agreement with the literature reported spectrum.

¹H-NMR (CDCl₃, 400 MHz): δ ppm = 7.90 (d, J = 4.8 Hz, 1H), 7.12 (dd, J = 5.5, 1.9 Hz, 1H), 7.01 (dd, J = 5.5, 1.9 Hz, 1H), 6.93 (d, J = 4.8 Hz, 1H), 5.90 (m, 1H), 5.71 (m, 1H), 4.38 (q, J = 7.04, 2H), 1.39 (t, J = 7.06, 3H)

¹³C-NMR (CDCl₃, 100 MHz): δ ppm = 163.9, 157.6, 146.0, 143.5, 142.1, 129.3, 110.4, 82.1, 78.6, 61.3, 15.3,

5.4.2 ARO of 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline

General procedure for ARO

Rh(cod)₂OTf (8.0 mg, 0.017 mmol, 5% equiv) and Josiphos (11.2 mg, 0.021 mmol, 6% equiv) were added to a flame dried microwave vial which was sealed and purged with argon and dissolved in anhydrous THF (0.5 ml). Substrate 5 (50 mg, 0.344 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, tetrahydroquinoline/N-Methyl aniline: 1.5 eq.) were dissolved in THF (0.5 ml) in a separated vial and added to the catalyst vial. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction was complete (typically 1.5-4 hours), the solvent was removed in vacuo and the crude products were purified by flash chromatography.

1-Ethoxy-6-methoxy-5,6-dihydroisoquinolin-5-ol (21.1) and 1-Ethoxy-7-methoxy-7,8-dihydroisoquinolin-8-ol (22.1)

Obtained from oxabicycle 5 (65 mg, 0.34 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 21.1 was isolated as a white solid (36.9 mg, 49% yield, 58% ee); Product 22.1 was isolated as a yellow oil (18.6 mg, 25% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 20% → 30%.
1-Ethoxy-6-methoxy-5,6-dihydroisoquinolin-5-ol (21.1)

\[
\begin{align*}
\text{MeO}, & \quad \text{OEt} \\
\end{align*}
\]

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta \ ppm = 8.03 \ (d, J = 5.2 \ Hz, 1H)\), 7.18 – 6.93 (m, 1H), 6.70 (dd, \(J = 10.0, 2.1 \ Hz, 1H\)), 6.06 (dd, \(J = 10.1, 2.1 \ Hz, 1H\)), 4.82 (dd, \(J = 11.5, 3.1 \ Hz, 1H\)), 4.36 (q, \(J = 7.1 \ Hz, 2H\)), 4.11 (dt, \(J = 11.6, 2.2 \ Hz, 1H\)), 3.48 (d, \(J = 10.4 \ Hz, 3H\)), 2.61 (d, \(J = 3.4 \ Hz, 1H\)), 1.53 (s, 1H), 1.37 (t, \(J = 7.1 \ Hz, 3H\)).

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta \ ppm = 159.1, 146.8, 146.5, 127.2, 122.0, 114.8, 113.3, 82.3, 72.4, 62.1, 57.0, 14.9\).

IR (neat): \(\nu_{\text{max}} = 710, 1042, 1111, 1304, 1343, 1381, 1427, 1566, 2824, 2932, 2978, 3410 \ (\text{br}) \ cm^{-1}\).

HR-MS (EI): Calc. for [M\(^+\)]: 221.1052, found: 221.1048.

[\(\alpha\)\]\(_D\)\(^{25}\) = +157.7°·cm\(^2\)·g\(^{-1}\) (c = 1.0, 58% ee, CHCl\(_3\)).

HPLC: Chiralcel OD-H, hexanes + 0.9% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 20.6 min, 23.5 min

1-Ethoxy-7-methoxy-7,8-dihydroisoquinolin-8-ol (22.1)

\[
\begin{align*}
\text{MeO}, & \quad \text{OEt} \\
\end{align*}
\]

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta \ ppm = 8.04 \ (d, J = 5.1 \ Hz, 1H)\), 6.66 (d, \(J = 5.1 \ Hz, 1H\)), 6.48 (dd, \(J = 9.8, 1.1 \ Hz, 1H\)), 6.27 (dd, \(J = 9.8, 4.2 \ Hz, 1H\)), 5.12 (t, \(J = 3.5 \ Hz, 1H\)), 4.57 – 4.31 (m, 2H), 4.12 (td, \(J = 4.2, 1.1 \ Hz, 1H\)), 3.54 – 3.41 (m, 3H), 2.98 (d, \(J = 3.2 \ Hz, 1H\)), 1.40 (t, \(J = 7.1 \ Hz, 3H\)).

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta \ ppm = 61.9, 147.3, 140.6, 130.7, 127.3, 116.2, 115.8, 78.7, 66.4, 62.4, 57.1, 15.0\).

IR (neat): \(\nu_{\text{max}} = 841, 957, 1080, 1319, 1427, 1559, 1597, 2932, 2979, 3372 \ (\text{br}) \ cm^{-1}\).

HR-MS (EI): Calc. for [M\(^+\)]: 221.1052, found: 221.1046.

[\(\alpha\)\]\(_D\)\(^{25}\) = +256.6°·cm\(^2\)·g\(^{-1}\) (c = 1.0, >99% ee, CHCl\(_3\)).
HPLC: Chiracel OD-H, hexanes + 0.9% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 32.5 min, 40.8 min

1,6-Diethoxy-5,6-dihydroisoquinolin-5-ol (21.2) and 1,7-diothoxy-7,8-dihydroquinolin-8-ol (22.2)

Obtained from oxabicycle 5 (65 mg, 0.34 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)_2; Product 21.2 isolated as a white solid (41.1 mg, 51% yield, 61% ee); Product 22.2 was isolated as a yellow oil (19.5 mg, 24% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 20% → 30%.

1,6-Diethoxy-5,6-dihydroisoquinolin-5-ol (21.2)

\[
\begin{align*}
\text{EtOH} & \quad \text{OH} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\(^1\text{H-NMR}\) (CDCl\(_3\), 400 MHz): \(\delta\) ppm = 8.02 (d, \(J = 5.1\) Hz, 1H), 7.12 (d, \(J = 5.1\) Hz, 1H), 6.67 (dd, \(J = 10.1, 2.3\) Hz, 1H), 6.04 (dd, \(J = 10.1, 2.0\) Hz, 1H), 4.81 (dd, \(J = 11.8, 3.0\) Hz, 1H), 4.36 (q, \(J = 7.0\) Hz, 2H), 4.19 (dt, \(J = 11.8, 2.2\) Hz, 1H), 3.80 (dq, \(J = 9.3, 7.0\) Hz, 1H), 3.55 (dq, \(J = 9.3, 7.0\) Hz, 1H), 2.66 (d, \(J = 3.1\) Hz, 1H), 1.37 (t, \(J = 7.1\) Hz, 3H), 1.27 (t, \(J = 7.0\) Hz, 3H).

\(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) ppm = 159.0, 147.0, 146.4, 128.3, 121.7, 114.8, 113.3, 80.7, 72.5, 65.0, 62.0, 15.7, 14.9.

IR (neat): \(\nu_{\text{max}} = 710, 833, 910, 988, 1042, 1103, 1312, 1381, 1427, 1566, 1589, 1628, 2870, 2978, 3055, 3410\) cm\(^{-1}\).

HR-MS (EI): Calc. for [M\(^+\)]: 235.1208, found: 235.1211.

\([\alpha]\)\(_D\)\(^{25}\) = -194.4°·cm\(^2\)g (c = 1.0, 61% ee, CHCl\(_3\)).

HPLC: Chiracel OD-H, hexanes + 8% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 5.8 min, 7.8 min.
1,7-Diethoxy-7,8-dihydroquinolin-8-ol (22.2)

\[
\text{\includegraphics[width=1cm]{image.png}}
\]

\(^1\text{H-NMR}\) (CDCl\(_3\), 400 MHz): \(\delta\) ppm = 8.06 (d, \(J = 5.1\) Hz, 1H), 6.68 (d, \(J = 5.1\) Hz, 1H), 6.48 (dd, \(J = 9.8\), 1.2 Hz, 1H), 6.27 (dd, \(J = 9.8\), 4.3 Hz, 1H), 5.23 – 4.99 (m, 1H), 4.63 – 4.34 (m, 2H), 4.24 (td, \(J = 4.2\), 1.2 Hz, 1H), 3.78 (dq, \(J = 9.3\), 7.0 Hz, 1H), 3.67 (dq, \(J = 9.3\), 7.0 Hz, 1H), 2.99 (d, \(J = 3.2\) Hz, 1H), 1.43 (t, \(J = 7.1\) Hz, 3H), 1.24 (t, \(J = 7.0\) Hz, 3H).

\(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) ppm = 161.89, 147.23, 140.64, 131.35, 126.90, 116.28, 115.78, 104.98, 66.96, 64.97, 62.34, 15.82, 14.98.

IR (neat): \(\nu_{\text{max}}\) = 841, 1003, 1080, 1258, 1312, 1427, 1559, 1597, 2870, 2978, 3040, 3379 cm\(^{-1}\).

HR-MS (EI): Calc. for [M\(^+\)]: 235.1208, found: 235.1204.

\([\alpha]_D^{25}\) = -355.2\(^\circ\)-cm\(^2\)-g (c = 1.0, >99\% ee, CHCl\(_3\)).

HPLC: Chiralcel OD-H, hexanes + 8\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 10.5 min, 12.4 min.

1-Ethoxy-6-(2-propen-1-yloxy)-5,6-dihydroisoquinolin-5-ol (21.3) and 1-ethoxy-7-(2-propen-1-yloxy)-7,8-dihydroisoquinolin-8-ol (22.3)

Obtained from oxabicycle 5 (65 mg, 0.34 mmol); reaction run at 60\(^\circ\)C using (R,S)-PF-P(t-Bu)\(_2\); Product 21.3 was isolated as a yellow oil (40.1 mg, 47\% yield, 60\%ee); Product 22.3 was isolated as a yellow oil (39.7 mg, 47\% yield, >99\%ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 10\%.

1-Ethoxy-6-(2-propen-1-yloxy)-5,6-dihydroisoquinolin-5-ol (21.3)

\[
\text{\includegraphics[width=1cm]{image.png}}
\]

\(^1\text{H-NMR}\) (CDCl\(_3\), 300 MHz): \(\delta\) ppm = 8.04 (d, \(J = 5.2\) Hz, 1H), 7.13 (d, \(J = 5.2\) Hz, 1H), 6.70 (dd, \(J = 10.1\), 2.2 Hz, 1H), 6.11 – 6.02 (m, 1H), 6.02 – 5.89 (m, 1H), 5.34 (dq, \(J = 17.2\), 1.5 Hz,
$^1$H-NMR (CDCl$_3$, 400 MHz): δ ppm = 8.05 (d, $J = 5.1$ Hz, 1H), 7.39 – 7.18 (m, 2H), 7.12 (d, $J = 5.1$ Hz, 1H), 6.94 (d, $J = 8.1$ Hz, 2H), 6.86 – 6.73 (m, 2H), 5.95 (dd, $J = 10.0$, 2.6 Hz, 1H), 5.15 – 5.00 (m, 1H), 4.74 (dt, $J = 11.9$, 2.6 Hz, 1H), 4.39 (q, $J = 7.0$ Hz, 2H), 2.90 (s, 3H), 2.57 (d, $J = 8.3$ Hz, 1H), 1.39 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ ppm = 159.1, 150.5, 147.5, 146.5, 129.5, 128.5, 123.5, 118.7, 115.2, 114.8, 113.7, 69.8, 64.0, 62.1, 33.9, 14.9.
IR (neat): $\nu_{\text{max}} = 748, 1042, 1111, 1312, 1343, 1427, 1505, 1597, 2924, 3395 \text{ (br) cm}^{-1}$.

HR-MS (EI): Calc. for [M$^+$]: 296.1525, found: 296.1523.

$[\alpha]_D^{25} = -39.0^\circ\text{cm}^2\text{g (c = 1.0, 89% ee, CHCl}_3$).

HPLC: Chiralcel OD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 56.2 min, 63.7 min.

1-Ethoxy-7-(methyl(phenyl)amino)-7,8-dihydro-isoquinolin-8-ol (22.4)

1H-NMR (CDCl$_3$, 400 MHz): $\delta \text{ ppm} = 8.09 (d, J = 5.1 \text{ Hz, 1H}), 7.32 – 7.26 (m, 2H), 7.05 – 6.90 \text{ (m, 2H)}, 6.85 – 6.76 (m, 1H), 6.73 (d, J = 5.1 \text{ Hz, 1H}), 6.63 (dd, J = 9.7, 1.9 \text{ Hz, 1H}), 6.16 (dd, J = 9.7, 4.3 \text{ Hz, 1H}), 5.17 (t, J = 3.1 \text{ Hz, 1H}), 4.82 – 4.68 \text{ (m, 1H)}, 4.54 – 4.29 (m, 2H), 2.84 (d, J = 3.1 \text{ Hz, 1H}), 2.62 (s, 3H), 1.39 (t, J = 7.1 \text{ Hz, 4H})$.

13C-NMR (CDCl$_3$, 100 MHz): $\delta \text{ ppm} = 161.7, 149.4, 147.3, 140.8, 132.1, 129.5, 127.2, 117.9, 116.7, 115.7, 114.2, 65.7, 62.3, 60.7, 33.6, 15.0$.

IR (neat): $\nu_{\text{max}} = 748, 1011, 1103, 1335, 1505, 1597, 2338, 2361, 2924, 3364 \text{ (br) cm}^{-1}$.


$[\alpha]_D^{28} = -198.7^\circ\text{cm}^2\text{g (c = 1.0, >99% ee, CHCl}_3$).

HPLC: Chiralcel OD-H, hexanes + 11% 2-propanol, flow 0.3 ml/min, 220, 254, 280 nm, retention times: 29.7 min, 32.5 min.

1-Ethoxy-6-(3,4-dihydro-1(2H)-quinolinyl)-5,6-dihydroisoquinolin-5-ol (21.5) and 1-ethoxy-7-(3,4-dihydro-1(2H)-quinolinyl)-7,8-dihydroisoquinolin-8-ol (22.5)

Obtained from oxabicycle 5 (65 mg, 0.34 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 21.5 was isolated as a yellow oil (47.6 mg, 43% yield, 88% ee); Product 22.5 was isolated as a brown solid (46.9 mg, 42% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 10% $\rightarrow$ 20%.

1-Ethoxy-6-(3,4-dihydro-1(2H)-quinolinyl)-5,6-dihydroisoquinolin-5-ol (21.5)
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.04 (d, $J = 5.1$ Hz, 1H), 7.09 (d, $J = 5.1$ Hz, 1H), 7.02 (ddd, $J = 13.4$, 7.9, 3.9 Hz, 2H), 6.88 – 6.80 (m, 2H), 6.64 (td, $J = 7.3$, 1.0 Hz, 1H), 5.96 (dd, $J = 10.0$, 2.8 Hz, 1H), 5.12 (dd, $J = 11.3$, 3.1 Hz, 1H), 4.77 (dt, $J = 11.3$, 2.6 Hz, 1H), 4.47 – 4.31 (m, 2H), 3.38 – 3.17 (m, 2H), 2.89 – 2.73 (m, 2H), 2.40 (d, $J = 3.5$ Hz, 1H), 2.01 – 1.89 (m, 2H), 1.39 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 159.1, 147.6, 146.5, 145.4, 129.9, 129.1, 127.3, 124.6, 123.6, 117.4, 114.9, 113.9, 112.7, 69.2, 62.1, 61.7, 44.9, 28.4, 22.8, 14.9.

IR (neat): $\nu_{\text{max}}$ = 748, 1042, 1312, 1343, 1427, 1474, 1597, 2932, 3395 (br) cm$^{-1}$.


$[\alpha]_D^{25}$ = -75.6°·cm$^2$·g$^{-1}$ (c = 1.0, 88% ee, CHCl$_3$).

HPLC: Chiralcel OD-H, hexanes + 2% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 25.9 min, 29.4 min.

1-Ethoxy-7-(3,4-dihydro-1(2H)-quinolinyl)-7,8-dihydroisoquinolin-8-ol (22.5)

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.08 (d, $J = 5.1$ Hz, 1H), 7.11 – 7.04 (m, 1H), 7.01 – 6.93 (m, 2H), 6.70 (d, $J = 5.1$ Hz, 1H), 6.63 (ddd, $J = 5.4$, 4.5, 1.4 Hz, 2H), 6.14 (dd, $J = 9.7$, 4.4 Hz, 1H), 5.19 (t, $J = 3.1$ Hz, 1H), 4.81 – 4.67 (m, 1H), 4.56 – 4.28 (m, 2H), 3.22 – 3.04 (m, 1H), 2.85 – 2.66 (m, 4H), 1.80 (td, $J = 6.5$, 5.8, 3.3 Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 159.1, 147.6, 146.5, 145.4, 129.9, 129.1, 127.3, 124.6, 123.6, 117.4, 114.9, 113.9, 112.7, 69.2, 62.1, 61.7, 44.9, 28.4, 22.8, 14.9.

IR (neat): $\nu_{\text{max}}$ = 748, 1080, 1312, 1335, 1474, 1497, 1597, 2338, 2361, 2924, 3379 (br) cm$^{-1}$.


$[\alpha]_D^{25}$ = -40.8°·cm$^2$·g$^{-1}$ (c = 1.0, >99% ee, CHCl$_3$).
HPLC: Chiralcel OD-H, hexanes + 3% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 19.3 min, 22.7 min.

Procedure for ARO of 5 using phenol/indole/p-toluenesulfonamide:

Nucleophile (1.7 mmol, 5 equiv), Rh(cod)$_2$OTf (8.0 mg, 0.017 mmol, 5% equiv), Josiphos (11.2 mg, 0.021 mmol, 6% eq.) were added to a microwave vial which was sealed and purged with argon. Substrate 5 (65 mg, 0.344 mmol, 1 equiv) was dissolved in THF (2ml) in a separate vial and added to the vial containing the catalyst. The reaction was stirred for 24 hours at 60°C. The reaction mixture was then poured into H$_2$O, extracted with EtOAc three times. Organic layers were combined, washed with brine, dried with MgSO$_4$ and concentrated. The crude was purified by flash chromatography.

1-Ethoxy-6-(1H-indol-3-yl)-5,6-dihydroisoquinolin-5-ol (21.6) and 1-ethoxy-7-(1H-indol-3-yl)-7,8-dihydroisoquinolin-8-ol (22.6)

Obtained from oxabicycle 5 (65 mg, 0.34 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 21.6 was isolated as a brown oil (50.7 mg, 48% yield, 75% ee); Product 22.6 was isolated as a white solid (43.0 mg, 41% yield, >99 % ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 30%.

1-Ethoxy-6-(1H-indol-3-yl)-5,6-dihydroisoquinolin-5-ol (21.6)

![](image)

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.18 (s, 1H), 8.04 (d, $J = 5.1$ Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 1H), 7.30 – 7.20 (m, 1H), 7.18 – 7.11 (m, 1H), 7.08 (s, 1H), 7.03 (d, $J = 5.1$ Hz, 1H), 6.92 (dd, $J = 9.8$, 2.5 Hz, 1H), 6.20 (dd, $J = 9.8$, 3.2 Hz, 1H), 4.98 (dd, $J = 10.7$, 4.3 Hz, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 4.01 (dt, $J = 10.7$, 2.9 Hz, 1H), 2.26 – 2.11 (m, 1H), 1.43 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 159.2, 146.9, 146.2, 137.1, 130.9, 126.7, 123.0, 122.7, 121.2, 119.9, 119.9, 115.6, 114.6, 114.2, 111.7, 72.5, 62.1, 41.2, 15.0.
IR (neat): \( \nu_{\text{max}} = 718, 748, 1042, 1103, 1258, 1312, 1427, 1566, 2870, 2978, 3055, 3287 \) (br) cm\(^{-1}\).


\([a]_D^{25} = -26.7^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} \) (c = 1.0, 75% ee, CHCl\(_3\)).

HPLC: Chiralcel OD-H, hexanes + 9% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 32.7 min, 42.9 min.

1-Ethoxy-7-(1H-indol-3-yl)-7,8-dihydroisoquinolin-8-ol (22.6)

\( ^1\text{H-NMR} \) (CDCl\(_3\), 400 MHz): \( \delta \text{ ppm} = 8.05 \) (d, \( J = 5.2 \) Hz, 1H), 7.91 (s, 1H), 7.76 – 7.67 (m, 1H), 7.36 – 7.30 (m, 1H), 7.22 – 7.17 (m, 1H), 7.17 – 7.11 (m, 1H), 6.77 (d, \( J = 2.0 \) Hz, 1H), 6.71 (d, \( J = 5.2 \) Hz, 1H), 6.58 (dd, \( J = 9.6, 1.4 \) Hz, 1H), 6.42 (ddd, \( J = 9.6, 5.2, 0.8 \) Hz, 1H), 5.30 – 5.22 (m, 1H), 4.38 (dq, \( J = 10.5, 7.1 \) Hz, 1H), 4.26 (ddt, \( J = 14.1, 10.5, 4.2 \) Hz, 2H), 2.54 (d, \( J = 4.2 \) Hz, 1H), 1.30 (t, \( J = 7.1 \) Hz, 3H).

\( ^13\text{C-NMR} \) (CDCl\(_3\), 100 MHz): \( \delta \text{ ppm} = 162.1, 147.1, 141.4, 136.8, 134.6, 126.6, 124.1, 122.5, 122.1, 119.9, 119.2, 115.8, 115.4, 114.0, 111.5, 105.0, 66.3, 62.1, 40.2, 14.9.

IR (neat): \( \nu_{\text{max}} = 733, 849, 910, 1011, 1080, 1096, 1312, 1335, 1427, 1551, 1597, 2924, 2978, 3279 \) (br) cm\(^{-1}\).


\([a]_D^{25} = -306.7^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} \) (c = 1.0, >99% ee, CHCl\(_3\)).

HPLC: Chiralcel OD-H, hexanes + 8.5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 35.7 min, 63.9 min.

1-Ethoxy-6-(phenoxy)-5,6-dihydroisoquinolin-5-ol (21.7) and 1-ethoxy-7-(phenoxy)-7,8-dihydroisoquinolin-8-ol (22.7)

Obtained from oxabicycle 5 (65 mg, 0.34 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)\(_2\);
Product 21.7 was isolated as a yellow solid (35.7 mg, 37% yield, 89% ee); Product 22.7 was isolated as a white solid (29.2 mg, 30% yield, >99% ee).
Flash Chromatography Eluent: ethyl acetate in hexanes: 30%.

1-Ethoxy-6-(phenoxy)-5,6-dihydroisoquinolin-5-ol (21.7)

![Chemical structure](image)

\[
\begin{align*}
1^H-NMR \text{ (CDCl}_3, \text{ 400 MHz): } & \delta \text{ ppm } = 8.07 \text{ (d, } J = 5.1 \text{ Hz, 1H), 7.33 – 7.25 (m, 2H), 7.18 (d, } J = 5.1 \text{ Hz, 1H), 7.02 – 6.96 (m, 1H), 6.95 – 6.90 (m, 2H), 6.74 (d, } J = 9.4 \text{ Hz, 1H), 6.02 (d, } J = 9.9 \text{ Hz, 1H), 5.12 (d, } J = 1.2 \text{ Hz, 2H), 4.56 – 4.31 (m, 2H), 2.77 – 2.65 (m, 1H), 1.38 (t, } J = 7.1 \text{ Hz, 3H).} \\
13^C-NMR \text{ (CDCl}_3, \text{ 100 MHz): } & \delta \text{ ppm } = 159.1, 157.4, 146.8, 146.6, 130.0, 126.6, 122.7, 121.9, 116.0, 114.8, 113.4, 105.0, 79.0, 72.4, 62.2, 14.9. \\
IR \text{ (neat): } & \nu \text{ max } = 694, 710, 1049, 1234, 1311, 1381, 1427, 1489, 1589, 2346, 2924, 2978, 3318 \text{ (br) cm}^{-1}. \\
HR-MS \text{ (EI): } & \text{ Calc. for } [M+H]^+: 284.1281, \text{ found: 284.1284.} \\
[a]_D^{25} & = +270.6^\circ \cdot \text{cm}^2 \cdot \text{g} \text{ (c = 1.0, 89% ee, CHCl}_3). \\
HPLC \text{: Chiralcel OD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 39.2 min, 46.1 min.}
\end{align*}
\]

1-Ethoxy-7-(phenoxy)-7,8-dihydroisoquinolin-8-ol (22.7)

![Chemical structure](image)

\[
\begin{align*}
1^H-NMR \text{ (CDCl}_3, \text{ 400 MHz): } & \delta \text{ ppm } = 8.09 \text{ (d, } J = 5.1 \text{ Hz, 1H), 7.34 – 7.26 (m, 2H), 7.06 – 7.01 (m, 2H), 7.01 – 6.94 (m, 1H), 6.71 (d, } J = 5.1 \text{ Hz, 1H), 6.57 (dd, } J = 9.7, 1.1 \text{ Hz, 1H), 6.31 (dd, } J = 9.7, 4.3 \text{ Hz, 1H), 5.26 (t, } J = 3.4 \text{ Hz, 1H), 5.18 – 5.03 (m, 1H), 4.55 – 4.32 (m, 2H), 3.02 (d, } J = 3.2 \text{ Hz, 1H), 1.39 (t, } J = 7.1 \text{ Hz, 3H).} \\
13^C-NMR \text{ (CDCl}_3, \text{ 100 MHz): } & \delta \text{ ppm } = 161.9, 157.5, 147.5, 140.3, 129.9, 129.3, 128.0, 121.7, 116.2, 115.9, 104.7, 75.4, 66.2, 62.4, 15.0. \\
IR \text{ (neat): } & \nu \text{ max } = 756, 841, 1011, 1080, 1227, 1319, 1427, 1489, 1559, 1597, 2924, 2978, 3364 \text{ (br) cm}^{-1}. 
\end{align*}
\]
**HR-MS** (EI): Calc. for [M-H$_2$O]: 265.1076, found: 265.1074.

[α]$_D^{25} = -48.9°·cm^2·g$ (c = 1.0, >99% ee, CHCl$_3$).

**HPLC**: Chiralcel OD-H, hexanes + 2% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 26.4 min, 40.7 min.

(1-Ethoxy-5-hydroxy-5,6-dihydro-isoquinolin-6-yl)-methylbenzene sulfonamide (21.8) and (1-ethoxy-8-hydroxy-7,8-dihydro-isoquinolin-7-yl)-methylbenzene sulfonamide (22.8)

Obtained from oxabicycle 5 (65 mg, 0.34 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 21.8 isolated as a white solid (44.4 mg, 36% yield, 74% ee); Product 22.8 was isolated as a white solid (35.8 mg, 29% yield, >99% ee).

**Flash Chromatography Eluent**: ethyl acetate in hexanes: 25%.

(1-Ethoxy-5-hydroxy-5,6-dihydro-isoquinolin-6-yl)-methylbenzene sulfonamide (21.8)

1H-NMR (CDCl$_3$, 400 MHz): δ ppm = 8.05 (d, $J = 5.2$ Hz, 1H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 2H), 7.07 (d, $J = 5.2$ Hz, 1H), 6.67 (dd, $J = 9.9$, 2.2 Hz, 1H), 5.49 (dd, $J = 9.9$, 2.8 Hz, 1H), 4.91 (d, $J = 8.3$ Hz, 1H), 4.73 (dd, $J = 10.8$, 4.2 Hz, 1H), 4.35 (q, $J = 7.0$ Hz, 2H), 4.13 – 4.02 (m, 1H), 2.96 (d, $J = 4.5$ Hz, 1H), 2.44 (s, 3H), 1.36 (t, $J = 7.1$ Hz, 3H).

13C-NMR (CDCl$_3$, 100 MHz): δ ppm = 159.1, 147.1, 146.1, 144.3, 137.0, 130.2, 129.9, 127.5, 126.7, 126.4, 123.6, 114.3, 114.1, 72.1, 62.2, 57.0, 21.8, 14.9.

**IR** (neat): $\nu_{\max} = 710, 1042, 1096, 1157, 1319, 1427, 1566, 2855, 2924, 3264$ cm$^{-1}$.

**HR-MS** (EI): Calc. for [M+H]: 361.1216, found: 361.1225.

[α]$_D^{25} = +35.1°·cm^2·g$ (c = 1.0, 74% ee, CHCl$_3$).

**HPLC**: Chiralcel OD-H, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 35.2 min, 53.4 min.
(1-Ethoxy-8-hydroxy-7,8-dihydro-isoquinolin-7-yl)-methylbenzene sulfonamide (22.8)

\[
\begin{array}{c}
\text{TsHNN} \\
\text{OEt} \\
\text{OH}
\end{array}
\]

\[^1H\text{-NMR (CDCl}_3, 400 MHz): \delta \text{ ppm} = 8.05 (d, J = 5.1 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.31 (dd, J = 8.5, 0.6 Hz, 2H), 6.61 (d, J = 5.1 Hz, 1H), 6.41 (dd, J = 9.6, 1.1 Hz, 1H), 6.01 (ddd, J = 9.6, 5.1, 0.7 Hz, 1H), 4.96 (t, J = 3.9 Hz, 1H), 4.47 (d, J = 7.9 Hz, 1H), 4.42 – 4.29 (m, 2H), 4.19 – 4.11 (m, 1H), 2.58 (d, J = 4.1 Hz, 1H), 2.43 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H).
\]

\[^{13}C\text{-NMR (CDCl}_3, 100 MHz): \delta \text{ ppm} = 162.0, 147.9, 143.9, 140.4, 137.7, 130.2, 130.1, 127.4, 115.5, 114.6, 66.0, 62.4, 53.5, 21.8, 14.9, 14.4.
\]

\[\text{IR (neat): } \nu_{\text{max}} = 756, 887, 1018, 1080, 1157, 1258, 1327, 1435, 1559, 1597, 2855, 2924, 2978, 3063, 3264 \text{ (br) cm}^{-1}
\]

\[\text{HR-MS (EI): Calc. for [M-H}_2\text{O]}^+: 342.1038, \text{ found: 342.1041.}
\]

\[\left[\alpha\right]_D^{25} = -66.8^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} \text{ (c = 1.0, >99% ee, CHCl}_3\right).
\]

\[\text{HPLC: Chiralcel OD-H, hexanes + 7\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 34.3 min, 41.4 min.}\]
5.5 Synthesis of 1-chloro-5,8-epoxy-5,8-dihydroisoquinoline

5.5.1 Synthesis of 1-chloro-5,8-epoxy-5,8-dihydroisoquinoline

2-Chloro-3-(trimethylsilyloxy)pyridine (23)

HMDS (2.42 ml, 11.36 mmol) was added to 2-chloro-3-pyridinol (1.47 g, 11.36 mmol). The mixture was heated at 80°C for 3 hours under a mild stream of nitrogen. Evaporation of excess HMDS in vacuo yielded 23 as a yellow oil, which was used for the next reaction without purification. The \(^1\)H-NMR spectrum was in agreement with the literature reported spectrum.\(^{31}\)

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta \text{ ppm } = 7.97 \text{ (m, 1H)}, 7.15-7.07 \text{ (m, 2H)}, \ 0.27 \text{ (s, 9H)}.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta \text{ ppm } = 148.0, 143.8, 141.7, 128.1, 123.0, 0.14.

2-Chloro-3-hydroxy-4-(trimethylsilyl)pyridine (24)

\(n\)-BuLi (3.3 ml, 1.68M in hexanes) was added slowly to a solution of distilled diisopropylamine (0.85 ml, 6.11 mmol) in THF (3 ml) at -78°C. The mixture was stirred at -78°C for 2 hours. A solution of 23 (0.8625 g, 4.28 mmol) in dry THF (10.4 ml) was slowly added at -78°C through a cannula to a solution of prepared LDA and the temperature of the bath was then allowed to increase slowly to room temperature. The mixture was poured into a saturated NaHCO\(_3\) solution (20 ml), extracted with CH\(_2\)Cl\(_2\) (3 x 20 ml) and dried with anhydrous MgSO\(_4\). Evaporation of solvent in vacuo afforded a residue that was purified by flash chromatography (Et\(_2\)O/hex, 1:2), giving 24 (671 mg, 78%) as a white solid. The \(^1\)H-NMR was in agreement with the literature reported spectrum.\(^{31}\)

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta \text{ ppm } = 7.93 \text{ (d, 1H, } J = 4.4 \text{ Hz)}, 7.19 \text{ (d, 1H, } J = 4.4 \text{ Hz)}, 5.75\text{ (br, s, 1H)}, 0.33 \text{ (s, 9H)}.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta \text{ ppm } = 153.6, 142.4, 139.3, 138.6, 130.6, 0.13.\)
2-Chloro-3-(trifluoromethanesulfonyloxy)-4-(trimethylsilyl)pyridine (25)

![Chemical Structure](image)

Compound 24 was dissolved in dry CH$_2$Cl$_2$ (9.4 ml) and cooled to -80°C. iPr$_2$EtN (585 µl, 3.34 mmol) and then, slowly Tf$_2$O (764 µl, 4.45 mmol) were added. The solution was stirred for 1 hour at -80°C. The cool bath was then removed and let warm to room temperature. When the reaction mixture had reached room temperature, it was poured into a dilute NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The organic phase was dried with anhydrous MgSO$_4$ and the solvent was evaporated in vacuo. Hexane was added and the remaining solid was filtered. Evaporation of solvent in vacuo afforded a residue that was purified by flash chromatography (Hex/Et$_2$O, 100:0 → 95:5) to yield 25 (0.590 g, 80%) as yellow oil that solidified upon drying in vacuo. The $^1$H-NMR was in agreement with the literature reported spectrum.$^{31}$

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.32 (d, 1H, $J = 4.4$ Hz), 7.37 (d, 1H, $J = 4.4$ Hz), 0.41 (s, 9H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 148.5, 147.5, 145.2, 144.6, 129.4, 118.5 (q, $J = 320$ Hz, CF$_3$), -0.73.

1-Chloro-5,8-dihydro-5,8-epoxyisoquinoline (6)

![Chemical Structure](image)

A 25 ml round bottom flask was charged with CsF (465 mg, 3.03 mmol) and flame dried under vacuum. Argon was added then acetonitrile (5 ml) and furan (750 µl, 10.1 mmol). In a separate flask, substrate 25 (336 mg, 1.01 mmol) was dissolved in acetonitrile (5 ml). Using a syringe pump, the aryne precursor was added to the flask containing CsF very slowly and stirred overnight. Water and diethyl ether were added. The aqueous layer extracted with ether and the organic layers were combined and dried over anhydrous MgSO$_4$. The solvent was removed in
vacuo and the crude product was purified by flash chromatography (EtOAc/Hex, 10:90 → 40:60) to yield 6 as yellow oil (51 mg, 28%).

$^1$H-NMR (CDCl$_3$, 400 MHz): δ ppm = 8.09 (d, 1H, J = 6 Hz), 7.17 (d, 1H, J = 6 Hz), 7.08 (m, 2H), 5.85 (m, 1H), 5.77 (m, 1H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ ppm = 162.6, 148.1, 143.5, 143.0, 142.4, 141.9, 115.3, 82.5, 80.7.

IR (neat): ν$_{max}$ = 3022, 1607, 1570, 1404, 1186, 1128, 856, 717 cm$^{-1}$.


5.5.2 ARO of 1-chloro-5,8-epoxy-5,8-dihydroisoquinoline

**General procedure:**

Rh(cod)$_2$OTf (7.8 mg, 0.017 mmol, 5% equiv) and Josiphos (10.9 mg, 0.0210 mmol, 6% eq.) were added to a flame dried microwave vial which was sealed and purged with argon and dissolved in anhydrous THF (0.5ml). 1-chloro-5,8-epoxy-5,8-dihydroisoquinoline (60 mg, 0.334 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, others: 1.5 eq.) were dissolved in THF (1 ml) in a separate vial and added to the catalyst vial. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction was complete (typically 24-36 hours), the solvent was removed in vacuo and the crude products were purified by flash chromatography.

**1-Chloro-6-methoxy-5,6-dihydroisoquinolin-5-ol (26.1) and 1-chloro-7-methoxy-7,8-dihydroisoquinolin-8-ol (27.1)**

Obtained from oxabicycle 6 (61 mg, 0.340 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 26.1 was isolated as a colorless oil (28.8 mg, 40% yield, 94% ee); Product 27.1 was isolated as a colorless oil (28.1 mg, 39% yield, >99 % ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 30%.

**1-Chloro-6-methoxy-5,6-dihydroisoquinolin-5-ol (26.1)**
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.26 (m, 1H), 7.51 (d, $J$ = 4.9 Hz, 1H), 6.74 (dd, $J$ = 10.2, 2.3 Hz, 1H), 6.24 (dd, $J$ = 10.2, 1.9 Hz, 1H), 4.87 (d, $J$ = 11.2 Hz, 1H), 4.14 (td, $J$ = 11.9, 2.1, 1H), 3.53 (s, 1H)

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 148.5, 148.0, 147.4, 130.7, 126.0, 123.0, 118.9, 81.4, 72.0, 57.0.

IR (neat): $\nu_{\text{max}}$ = 694, 849, 980, 1119, 1188, 1366, 1582, 2824, 2932, 3248 (br) cm$^{-1}$.

HR-MS (EI): Calc. for [M+]: 211.0400, found: 211.0397.

$[^a]D^{25}$ = -202.7°·cm$^2$·g$^{-1}$ (c = 1.0, 94% ee, CHCl$_3$).

HPLC: Chiralpak AD-H, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 13.5 min, 15.5 min.

1-Chloro-7-methoxy-7,8-dihydroisoquinolin-8-ol (27.1)

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

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.30 (d, $J$ = 4.92 Hz, 1H), 7.03 (d, $J$ = 4.92 Hz, 1H), 6.65 (d, $J$ = 9.64 Hz, 1H), 6.44 (ddd, $J$ = 9.62, 5.37, 1.03 Hz, 1H), 5.15 (s, 1H), 4.08 (dd, $J$ = 5.37, 1.77 Hz, 1H), 3.44 (s, 1H), 2.40 (s, 1H)

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 152.0, 150.2, 141.6, 131.1, 128.1, 127.8, 121.2, 76.1, 65.4, 57.1,

IR (neat): $\nu_{\text{max}}$ = 980, 1119, 1188, 1258, 13656, 1458, 1551, 1636, 3410 (broad) cm$^{-1}$.

HR-MS (EI): Calc. for [M-H$_2$O]: 193.0294, found: 193.0297.

$[^a]D^{25}$ = -300.5°·cm$^2$·g$^{-1}$ (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralcel OJ, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 12.9 min, 18.3 min.

1-Chloro-6-(dibenzylamino)-5,6-dihydroisoquinolin-5-ol (26.2) and 1-chloro-7-(dibenzylamino)-7,8-dihydroisoquinolin-8-ol (27.2)

Obtained from oxabicycle 6 (62.1 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 26.2 isolated as a yellow oil (56.8 mg, 45% yield, 80% ee); Product 27.2 was isolated as a yellow oil (54.7 mg, 43% yield, 81% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 20%.
1-Chloro-6-(dibenzylamino)-5,6-dihydroisoquinolin-5-ol (26.2)

![Chemical Structure]

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta \text{ ppm } = 8.19 \text{ (d, } J = 4.9 \text{ Hz, } 1\text{H}), 7.40 \text{ (d, } J = 4.7 \text{ Hz, } 1\text{H}), 7.35 - 7.30 \text{ (m, } 10\text{H}), 6.84 \text{ (dd, } J = 10.2, 2.8 \text{ Hz, } 1\text{H}), 6.36 \text{ (dd, } J = 10.2, 2.1 \text{ Hz, } 1\text{H}), 4.92 \text{ (d, } J = 13.2 \text{ Hz, } 1\text{H}), 4.00 \text{ (d, } J = 13.6 \text{ Hz, } 2\text{H}), 3.81 \text{ (s, } 1\text{H}), 3.72 - 3.65 \text{ (m, } 1\text{H}), 3.62 \text{ (d, } J = 13.6 \text{ Hz, } 2\text{H}).

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta \text{ ppm } = 149.0, 148.7, 147.6, 138.6, 129.7, 129.1, 128.9, 127.8, 127.2, 125.2, 119.2, 68.5, 61.8, 55.0.

IR (neat): \(\nu_{\text{max}} = 841, 964, 1026, 1072, 1119, 1188, 1358, 1451, 1543, 1620, 1859, 2083, 3032, 3410 \text{ (broad) cm}^{-1}.


\([\alpha]_D^{25} = +80.2^\circ \text{cm}^2 \text{g} \ (c = 1.0, 80\% \text{ ee, CHCl}_3).

HPLC: Chiracel OJ, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 18.7 min, 23.3 min.

1-Chloro-7-(dibenzylamino)-7,8-dihydroisoquinolin-8-ol (27.2)

![Chemical Structure]

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta \text{ ppm } = 8.27 \text{ (d, } J = 4.9 \text{ Hz, } 1\text{H}), 7.33 - 7.26 \text{ (m, } 8\text{H}), 7.24 - 7.19 \text{ (m, } 2\text{H}), 6.99 \text{ (d, } J = 4.9 \text{ Hz, } 1\text{H}), 6.68 \text{ (dd, } J = 9.7, 1.4 \text{ Hz, } 1\text{H}), 6.30 \text{ (ddd, } J = 9.7, 5.3, 1.0 \text{ Hz, } 1\text{H}), 5.31 \text{ (s, } 1\text{H}), 3.75 \text{ (dt, } J = 5.3, 1.2 \text{ Hz, } 1\text{H}), 3.53 \text{ (d, } J = 13.7 \text{ Hz, } 2\text{H}), 3.39 \text{ (d, } J = 13.7 \text{ Hz, } 2\text{H}), 2.09 \text{ (s, } 1\text{H}).

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta \text{ ppm } = 151.4, 149.9, 142.4, 139.4, 133.3, 128.8, 128.5, 128.4, 127.4, 126.4, 121.0, 64.1, 59.2, 54.0.

IR (neat): \(\nu_{\text{max}} = 694, 725, 1018, 1119, 1188, 1242, 1327, 1366, 1451, 1535, 1582, 1636, 2083, 2716, 3410 \text{ (broad) cm}^{-1}.

$[\alpha]D^{25} = +254.5^\circ\cdot\text{cm}^2\cdot\text{g} \ (c = 1.0, \ 81\% \ ee, \ \text{CHCl}_3)$.

**HPLC**: Chiralcel OJ, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 14.4 min, 18.7 min.

1-Chloro-6-(methyl(phenyl)amino)-5,6-dihydroisoquinolin-5-ol (26.3) and 1-Chloro-7-(methyl(phenyl)amino)-7,8-dihydro-isoquinolin-8-ol (27.3)

Obtained from oxabicycle 6 (63.5 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 26.3 was isolated as a yellow solid (38.6 mg, 38% yield, 98% ee); Product 27.3 was isolated as a yellow solid (38.7 mg, 38% yield, >99 % ee).

**Flash Chromatography Eluent**: ethyl acetate in hexanes: 10% → 20% → 40%.

1-Chloro-6-(methyl(phenyl)amino)-5,6-dihydroisoquinolin-5-ol (26.3)

![Structure of 1-Chloro-6-(methyl(phenyl)amino)-5,6-dihydroisoquinolin-5-ol](image)

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.27 (d, $J = 4.9$ Hz, 1H), 7.56 – 7.49 (m, 1H), 7.31 – 7.24 (m, 2H), 6.95 (dd, $J = 8.8$, 0.8 Hz, 2H), 6.88 – 6.82 (m, 2H), 6.16 (dd, $J = 10.1$, 2.3 Hz, 1H), 5.16 (d, $J = 12.6$ Hz, 1H), 4.76 (dt, $J = 12.6$, 2.6 Hz, 1H), 2.96 (s, 3H), 2.73 (s, 1H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 150.3, 149.0, 148.9, 147.8, 132.5, 129.6, 126.2, 125.1, 119.4, 119.3, 115.6, 69.6, 64.1, 34.1.

**IR** (neat): $\nu_{\text{max}} = 772, 1188, 1350, 1505, 1582, 2361, 3017, 3055, 3264$ (br) cm$^{-1}$.

**HR-MS** (EI): Calc. for [M$^+$]: 286.0873, found: 286.0861.

$[\alpha]D^{25} = -9.5^\circ\cdot\text{cm}^2\cdot\text{g} \ (c = 1.0, \ 98\% \ ee, \ \text{CHCl}_3)$.

**HPLC**: Chiralcel OJ, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 19.1 min, 23.1 min.

1-Chloro-7-(methyl(phenyl)amino)-7,8-dihydro-isoquinolin-8-ol (27.3)

![Structure of 1-Chloro-7-(methyl(phenyl)amino)-7,8-dihydro-isoquinolin-8-ol](image)
\(^{1}\text{H-NMR}\) (CDCl\(_3\), 400 MHz): \(\delta\) ppm = 8.35 (d, \(J = 4.9\) Hz, 1H), 7.36 – 7.27 (m, 2H), 7.12 (t, \(J = 12.9\) Hz, 1H), 6.97 (d, \(J = 8.0\) Hz, 2H), 6.90 – 6.81 (m, 1H), 6.79 (dd, \(J = 9.6, 1.4\) Hz, 1H), 6.29 (ddd, \(J = 9.6, 5.4, 1.0\) Hz, 1H), 5.11 (s, 1H), 4.78 (d, \(J = 5.4\) Hz, 1H), 2.43 (s, 3H), 2.38 (d, \(J = 3.8\) Hz, 1H).

\(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) ppm = 151.2, 149.9, 148.8, 141.8, 131.9, 129.4, 128.1, 126.8, 120.9, 118.4, 114.4, 66.2, 59.3, 32.3.

IR (neat): \(\nu_{\text{max}}\) = 694, 748, 1026, 1204, 1505, 1589, 2361, 3284, 3318 (br) cm\(^{-1}\).

HR-MS (EI): Calc. for [M\(^{+}\)]: 286.0873, found: 286.0875.

[a]\(^{25}\)D = +147.9°·cm\(^2\)g (c = 1.0, >99% ee, CHCl\(_3\)).

HPLC: Chiralcel OJ, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 50.5 min, 55.7 min.

1-Chloro-6-(3,4-dihydro-1(2H)-quinoliny1)-5,6-dihydroisoquinolin-5-ol (26.4) and 1-chloro-7-(3,4-dihydro-1(2H)-quinoliny1)-7,8-dihydroisoquinolin-8-ol (27.4)

Obtained from oxabicycle 6 (60 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu); Product 26.4 was isolated as a yellow gum (35.7 mg, 34% yield, >99% ee); Product 27.4 was isolated as a yellow solid (33.1 mg, 32% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 20% \(\rightarrow\) 30%.

1-Chloro-6-(3,4-dihydro-1(2H)-quinoliny1)-5,6-dihydroisoquinolin-5-ol (26.4)

\(^{1}\text{H-NMR}\) (CDCl\(_3\), 400 MHz): \(\delta\) ppm = 8.24 (d, \(J = 4.9\) Hz, 1H), 7.52 – 7.46 (m, 1H), 7.05 – 6.98 (m, 2H), 6.90 – 6.84 (m, 1H), 6.80 (d, \(J = 8.2\) Hz, 1H), 6.67 (td, \(J = 7.4, 1.0\) Hz, 1H), 6.15 (dd, \(J = 10.1, 2.4\) Hz, 1H), 5.21 (d, \(J = 12.3\) Hz, 1H), 4.80 (dt, \(J = 12.3, 2.5\) Hz, 1H), 3.39 – 3.22 (m, 2H), 2.91 – 2.72 (m, 2H), 2.67 (s, 1H), 2.05 – 1.89 (m, 2H).

\(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) ppm = 149.2, 148.9, 147.9, 145.1, 133.4, 130.0, 127.3, 126.3, 125.2, 124.8, 119.5, 117.8, 112.9, 69.1, 61.9, 45.3, 28.3, 22.8.

IR (neat): \(\nu_{\text{max}}\) = 1018, 1188, 1342, 1451, 1551, 1636, 3410 (broad) cm\(^{-1}\).

HR-MS (EI): Calc. for [M+H]\(^{+}\): 313.1102, found: 313.1087.
\[ \text{[a]} \beta_{25} = -21.7^\circ \cdot \text{cm}^2 \cdot \text{g} \ (c = 1.0, >99\% \text{ ee, CHCl}_3). \]

**HPLC:** Chiracel OJ, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 40.2 min, 49.8 min.

1-Chloro-7-(3,4-dihydro-1(2H)-quinolinyl))-7,8-dihydroisoquinolin-8-ol (27.4)

![Chemical Structure](image)

**\(^1\text{H-NMR} \) (CDCl\(_3\), 400 MHz):** \( \delta \text{ ppm} = 8.34 \ (d, J = 5.0 \text{ Hz, } 1\text{H}), 7.14 \ (dt, J = 8.3, 1.7\text{Hz, } 1\text{H}), 7.09 \ (d, J = 5.0 \text{ Hz, } 1\text{H}), 7.01 \ (m, 2\text{H}), 6.79 \ (dd, J = 9.6, 1.4 \text{ Hz, } 1\text{H}), 6.70 \ (dt, J = 7.3, 1.0 \text{ Hz, } 1\text{H}), 6.27 \ (ddd, J = 9.6, 5.5, 1 \text{ Hz, } 1\text{H}), 5.13 \ (s, 1\text{H}), 4.84 \ (dd, J = 5.5, 1.0 \text{ Hz, } 1\text{H}), 2.89 \ (m, 1\text{H}), 2.70 \ (dd, J = 11.4, 6.2 \text{ Hz, } 2\text{H}), 2.52 \ (m, 2\text{H}), 1.74 \ (m, 2\text{H}), 1.64 \ (s, 1\text{H})

**\(^{13}\text{C-NMR} \) (CDCl\(_3\), 100 MHz):** \( \delta \text{ ppm} = 151.1, 149.8, 144.1, 141.9, 131.5, 129.7, 128.2, 127.2, 127.0, 124.1, 120.9, 117.3, 111.4, 66.2, 57.2, 42.6, 27.9, 22.4.

**IR (neat):** \( \nu_{\text{max}} = 702, 748, 1026, 1188, 1342, 1381, 1450, 1581, 2847, 2924, 3333 \text{ (broad) cm}^{-1}. \)

**HR-MS (EI):** Calc. for [M+H]: \( 313.1102, \) found: 313.1101.

\[ \text{[a]} \beta_{25} = -441.6^\circ \cdot \text{cm}^2 \cdot \text{g} \ (c = 1.0, >99\% \text{ ee, CHCl}_3). \]

**HPLC:** Chiracel OJ, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 15.2 min, 24.5 min.

1-Chloro-6-(1-piperidinyl)-5,6-dihydroisoquinolin-5-ol (26.5) and 1-chloro-7-(1-piperidinyl)-7,8-dihydroisoquinolin-8-ol (27.5)

Obtained from oxabicycle 6 (60 mg, 0.33 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)\(_2\); Product 26.5 was isolated as a yellow oil (22.4 mg, 25% yield, 55% ee); Product 27.5 was isolated as a yellow oil (22.5 mg, 25% yield, 53 % ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 50% → 70%.
1-Chloro-6-(1-piperidinyl)-5,6-dihydroisoquinolin-5-ol (26.5)

![Chemical structure of 1-Chloro-6-(1-piperidinyl)-5,6-dihydroisoquinolin-5-ol](image)

\[\text{H-NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ ppm} = 8.18 (d, J = 4.9 \text{ Hz}, 1H), 7.43 (d, J = 4.9 \text{ Hz}, 1H), 6.74 (dd, J = 10.2, 2.8 \text{ Hz}, 1H), 6.28 (dd, J = 10.2, 2.1 \text{ Hz}, 1H), 4.77 (d, J = 13.5 \text{ Hz}, 1H), 3.57 (s, 1H), 3.39 (dt, J = 13.5, 2.3 Hz, 1H), 2.77 (ddd, J = 10.8, 7.0, 3.4 Hz, 2H), 2.42 (ddd, J = 10.7, 6.9, 3.5 Hz, 2H), 1.70 – 1.50 (m, 5H), 1.52 – 1.33 (m, 3H).

\[\text{C-NMR (CDCl}_3, 100 \text{ MHz): } \delta \text{ ppm} = 149.6, 148.7, 147.7, 128.7, 125.9, 124.7, 119.1, 67.7, 67.2, 50.7, 29.9, 26.5, 26.2, 24.6.

\[\text{IR (neat): } \nu_{\text{max}} = 1111, 1188, 1358, 1451, 1528, 1636, 2932, 3410 \text{ (broad) cm}^{-1}.

\[\text{HR-MS (EI): } \text{Calc. for [M+H]}^+ : 265.1102, \text{found: } 265.1095.

\[\text{[a]}_D^{25} = +94.5^\circ \text{cm}^2 \text{g} (c = 1.0, 55 \% \text{ ee, CHCl}_3).

\[\text{HPLC: } \text{Chiralcel OJ, hexanes + 1\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: } 14.9 \text{ min, 17.1 min}.

1-Chloro-7-(1-piperidinyl)-7,8-dihydroisoquinolin-8-ol (27.5)

![Chemical structure of 1-Chloro-7-(1-piperidinyl)-7,8-dihydroisoquinolin-8-ol](image)

\[\text{H-NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ ppm} = 8.24 (d, J = 4.9 \text{ Hz}, 1H), 6.96 (d, J = 4.9 \text{ Hz}, 1H), 6.64 (dd, J = 9.7, 0.8 \text{ Hz}, 1H), 6.23 (dd, J = 9.7, 4.7 Hz, 1H), 5.18 (s, 1H), 4.17 – 3.99 (m, 1H), 3.57 (d, J = 5.0 Hz, 1H), 2.49 (dd, J = 10.6, 5.4 Hz, 2H), 2.30 – 2.16 (m, 2H), 1.44 (d, J = 4.6 Hz, 4H), 1.31 (dt, J = 13.9, 7.1 Hz, 2H).

\[\text{C-NMR (CDCl}_3, 100 \text{ MHz): } \delta \text{ ppm} = 151.1, 149.9, 142.3, 132.3, 129.0, 126.5, 121.0, 65.4, 63.8, 50.0, 26.5, 24.4.

\[\text{IR (neat): } \nu_{\text{max}} = 702, 733, 895, 1265, 1420, 2307, 2986, 3055, 3588 \text{ cm}^{-1}.

\[\text{HR-MS (EI): } \text{Calc. for [M+H]}^+ : 265.1102, \text{found: } 265.1092.

\[\text{[a]}_D^{25} = +196.5^\circ \text{cm}^2 \text{g} (c = 1.0, 53 \% \text{ ee, CHCl}_3).
HPLC: Chiralcel OJ, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 21.5 min, 24.5 min.

1-Chloro-6-morpholin-5,6-dihydroisoquinolin-5-ol (26.6) and 1-chloro-7-morpholin-7,8-dihydroisoquinolin-8-ol (27.6)

Obtained from oxabicycle 6 (61.8 mg, 0.34 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 26.6 was isolated as a yellow gum (36.4 mg, 40% yield, 85% ee); Product 27.6 was isolated as a yellow gum (41.2 mg, 45% yield, 87% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 50% → 70%.

1-Chloro-6-morpholin-5,6-dihydroisoquinolin-5-ol (26.6)

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{H}
\end{array} \\
\text{Cl}
\quad \text{N} \\
\text{O}
\]

\(^1\)H-NMR (CDCl₃, 400 MHz): \(\delta\) ppm = 8.27 (d, \(J = 4.9\) Hz, 1H), 7.51 (d, \(J = 4.9\) Hz, 1H), 6.85 (dd, \(J = 10.2, 2.8\) Hz, 1H), 6.36 (dd, \(J = 10.2, 2.2\) Hz, 1H), 4.84 (d, \(J = 13.4\) Hz, 1H), 3.88 – 3.74 (m, 4H), 3.57 (s, 1H), 3.46 (dt, \(J = 13.4, 2.5\) Hz, 1H), 2.93 – 2.81 (m, 2H), 2.57 (ddd, \(J = 9.5, 5.8, 3.2\) Hz, 2H).

\(^{13}\)C-NMR (CDCl₃, 100 MHz): \(\delta\) ppm = 148.98, 148.55, 147.51, 128.15, 125.56, 124.78, 118.81, 67.23, 66.82, 49.26, 29.65, 21.01, 14.16.

IR (neat): \(\nu\) max = 1111, 1188, 1358, 1451, 2338, 2855, 2916, 3379 (broad) cm⁻¹.


\([\alpha]_D\)^{25} = -160.6°·cm⁻²·g⁻¹ (c = 1.0, 85% ee, CHCl₃).

HPLC: Chiralcel OJ, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 23.9 min, 27.3 min.

1-Chloro-7-morpholin-7,8-dihydroisoquinolin-8-ol (27.6)

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{H}
\end{array} \\
\text{Cl}
\quad \text{N} \\
\text{O}
\]
1H-NMR (CDCl3, 400 MHz): δ ppm = 8.30 (d, J = 4.9 Hz, 1H), 7.04 (d, J = 4.9 Hz, 1H), 6.71 (dd, J = 9.7, 1.0 Hz, 1H), 6.39 – 6.18 (m, 1H), 5.22 (s, 1H), 3.70 – 3.52 (m, 5H), 2.70 – 2.51 (m, 3H), 2.41 – 2.23 (m, 2H).

13C-NMR (CDCl3, 100 MHz): 151.13, 149.99, 142.18, 131.47, 128.70, 126.91, 121.00, 67.32, 64.62, 63.66, 49.15, 21.23, 14.38.

IR (neat): νmax = 1111, 1250, 1327, 1543, 1582, 2338, 2762, 2823, 2855, 2924, 3055, 3364 (broad) cm⁻¹.


[a]D 25 = -69.6°·cm²·g⁻¹ (c = 1.0, 87% ee, CHCl₃).

HPLC: Chiralcel OJ, hexanes + 7% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 28.1 min, 39.9 min.

1-Chloro-6-(1H-indol-3-yl)-5,6-dihydroisoquinolin-5-ol (26.7) and 1-chloro-7-(1H-indol-3-yl)-7,8-dihydroisoquinolin-8-ol (27.7)

Obtained from oxabicycle 6 (60 mg, 0.33 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 26.7 was isolated as a yellow oil (37.7 mg, 38% yield, 97% ee); Product 27.7 was isolated as a yellow solid (33.4 mg, 34% yield, 97% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 10% → 20% → 40%.

1-Chloro-6-(1H-indol-3-yl)-5,6-dihydroisoquinolin-5-ol (26.7)

1H-NMR (CDCl3, 400 MHz): δ ppm = 8.38 – 8.11 (m, 2H), 7.71 (t, J = 10.3 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.31 – 7.22 (m, 1H), 7.19 – 7.11 (m, 2H), 6.97 (dt, J = 9.9, 2.9 Hz, 1H), 6.38 (dt, J = 9.9, 3.2 Hz, 1H), 5.05 (dd, J = 11.6, 2.4 Hz, 1H), 4.01 (dq, J = 11.6, 2.9 Hz, 1H), 3.81 – 3.63 (m, 1H).

13C-NMR (CDCl3, 100 MHz): δ ppm = 148.7, 148.6, 147.8, 137.1, 134.7, 127.0, 127.0, 123.0, 123.1, 122.9, 120.1, 119.8, 119.7, 113.9, 111.9, 77.6, 77.2, 76.9, 72.4, 41.1.

IR (neat): νmax = 733, 910, 1011, 1188, 1357, 1543, 1636, 2338, 2854, 2924, 3410 (broad) cm⁻¹.

$[\alpha]_D^{25} = -7.2^\circ \text{cm}^2 \text{g} (c = 1.0, \text{97% ee, CHCl}_3)$.

**HPLC**: Chiralpak AD-H, hexanes + 20% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 14.7 min, 16.2 min.

1-Chloro-7-(1H-indol-3-yl)-7,8-dihydroisoquinolin-8-ol (27.7)

![Chemical Structure](image)

**$^1$H-NMR** (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.31 (d, $J = 4.9$ Hz, 1H), 7.92 (s, 1H), 7.73 (d, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.4$ Hz, 1H), 7.21 (ddd, $J = 16.2, 10.6, 4.2$ Hz, 2H), 7.07 (d, $J = 5.0$ Hz, 1H), 6.67 (t, $J = 7.0$ Hz, 2H), 6.59 (dd, $J = 9.0, 5.1$ Hz, 1H), 5.35 (d, $J = 4.3$ Hz, 1H), 4.43 (d, $J = 5.7$ Hz, 1H), 2.29 (d, $J = 5.5$ Hz, 1H).

**$^{13}$C-NMR** (CD$_3$OD, 75 MHz): $\delta$ ppm = 153.0, 150.4, 145.3, 138.7, 137.6, 129.4, 127.7, 124.8, 123.2, 122.9, 122.1, 120.2, 119.1, 112.8, 111.4, 68.7, 42.4.

**IR** (neat): $\nu_{\text{max}}$ = 964, 1026, 1111, 1026, 1404, 1458, 1535, 1589, 1636, 2338, 2855, 2924, 3264, 3410 (broad) cm$^{-1}$.

**HR-MS** (EI): Calc. for [M+H$^+$]: 297.0789, found: 297.0785.

$[\alpha]_D^{25} = +122.0^\circ \text{cm}^2 \text{g} (c = 1.0, \text{97% ee, CHCl}_3)$.

**HPLC**: Chiralpak AD-H, hexanes + 30% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 7.8 min, 10.3 min.
5.6 Synthesis of 8-hydro-5-methyl-5,8-epoxyisoquinoline and 5-hydro-8-methyl-5,8-epoxyisoquinoline

8-hydro-5-methyl-5,8-epoxyisoquinoline (28) and 5-hydro-8-methyl-5,8-epoxyisoquinoline (29)

![Structures 28 and 29]

To an oven dried 100 ml 3-neck round-bottomed flask with an internal thermometer, septum, nitrogen adapter and stirring bar was added dry THF (10 ml) and dry isopropyl amine (1.85 ml, 13.2 mmol) at -78°C under N₂. To this solution was added nBuLi (8.57 ml, 1.62 M in hexanes) dropwise via syringe. The solution was stirred at -78°C for 30 minutes and a solution of 3-chloropyridine (1.26 ml, 13.2 mmol) in THF (2.5 ml) was added over 15 min using a cannula. The mixture was stirred for 20 min at -100°C prior to addition of freshly distilled 2-methylfuran (11.83 ml, 132 mmol) via a syringe. The mixture was allowed to warm to room temperature overnight. The insoluble polymeric material was filtered and washed well with diethyl ether. The washings were combined and concentrated in vacuo, taken up in CHCl₃, washed with saturated NaHCO₃, H₂O and brine. The organic layer was dried by anhydrous MgSO₄ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (EtOAc/Hex, 50:50 → 70:30) to yield 28 and 29 as inseparable red oil (147 mg, 70%).

5.7 Synthesis and ARO of 8-hydro-5-methyl-5,8-epoxyquinoline and 5-hydro-8-methyl-5,8-epoxyquinoline

5.7.1 Synthesis of 8-hydro-5-methyl-5,8-epoxyquinoline and 5-hydro-8-methyl-5,8-epoxyquinoline

8-hydro-5-methyl-5,8-epoxyquinoline (7) and 5-hydro-8-methyl-5,8-epoxyquinoline (8).

To a 250 ml round-bottomed flask was added CsF (6.04 g, 39.4 mmol). The flask was flame dried under vacuum and switched to argon. Acetonitrile (97 ml) and 2-methylfuran (11.8 ml, 131.2 mmol) were added to the flask. In a separate flask, 10 (3.93 g, 13.1 mmol) was dissolved in acetonitrile (32.3 ml). Using a syringe pump, the aryne precursor was added to the flask
containing CsF dropwise and stirred overnight. The solvent was removed in vacuo. Water was added and the aqueous layer extracted with CH$_2$Cl$_2$ and the organic layers were combined, washed with brine, and dried over anhydrous MgSO$_4$. The solvent was removed in vacuo and the crude product was purified by flash chromatography twice (first with EtOAc/Hex, 50:50, then second with EtOAc/Hex, 10/90) to yield 7 as a red solid (300 mg, 14%) and 8 as a red oil (145 mg.) The $^1$H-NMR spectrum was in agreement with the literature reported spectrum.$^{33}$

8-hydro-5-methyl-5,8-epoxyquinoline (7)

![Diagram of 7]

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 7.99 (dd, 1H, $J = 5.4$, 1.3 Hz,), 7.32 (ddd, 1H, $J = 7.2$ and 1.3 Hz), 7.10 (dd, 1H, $J = 5.4$ and 1.9 Hz), 6.84 (dd, 1H, $J = 7.2$ and 5.4 Hz), 6.79 (d, 1H, $J = 5.4$ Hz), 5.52 (d, 1H, $J = 1.9$ Hz), 1.91 (s, 1H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 173.9, 146.1, 144.3, 143.4, 143.0, 124.8, 119.1, 89.0, 82.4, 15.2.

5-hydro-8-methyl-5,8-epoxyquinoline (8)

![Diagram of 8]

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.03 (dd, 1H, $J = 5.4$, 1.1 Hz), 7.38 (dd, 1H, $J = 7.1$, 1.1 Hz,), 7.06 (dd, 1H, $J = 5.4$, 1.9 Hz), 6.84 (d, 1H, $J = 5.4$ Hz), 6.83 (dd, 1H, $J = 7.1$, 5.4 Hz), 5.67 (d, 1H, $J = 1.9$ Hz,), 1.93 (s, 1H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 173.6, 145.2, 145.1, 143.4, 143.4, 126.3, 119.1, 89.5, 80.9, 14.0.
5.7.2 ARO of 5-hydro-8-methyl-5,8-epoxyquinoline

General procedure for ARO of 5-hydro-8-methyl-5,8-epoxyquinoline

Rh(cod)₂OTf (7.8 mg, 0.017 mmol, 5% equiv) and Josiphos (10.9 mg, 0.0210 mmol, 6% eq.) were added to a flame dried microwave vial which was sealed and purged with argon and dissolved in anhydrous THF (0.5ml). 1-chloro-5,8-epoxy-5,8-dihydroisoquinoline (50 mg, 0.31 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, amines: 1.5 eq., phenol: 5 eq.) were dissolved in THF (1 ml) in a separate vial and added to the vial containing the catalyst. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction was complete (typically 8-12 hours), the solvent was removed in vacuo and the crude products were purified by flash chromatography.

6-Methoxy-8-methyl-5,6-dihydroisoquinolin-5-ol (30.1) and 7-Methoxy-8-methyl-7,8-dihydroisoquinolin-8-ol (31.1)

Obtained from oxabicycle 8 (67.7 mg, 0.43 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 30.1 was isolated as a white solid (35 mg, 43% yield, >99% ee); Product 31.1 was isolated as a white solid (25 mg, 31% yield, >99% ee).  

Flash Chromatography Eluent: ethyl acetate in hexanes: 30%

6-Methoxy-8-methyl-5,6-dihydroisoquinolin-5-ol (30.1)

\[
\text{HOCH}_3\quad \text{C}_9\text{H}_7
\]

\(^1\text{H-NMR}\) (CDCl₃, 400 MHz): \(\delta \text{ ppm} = 8.34 \text{ (dd, } J = 4.9, 1.5 \text{ Hz, 1H), 7.30 (dd, } J = 7.6, 1.6 \text{ Hz, 1H), 7.13 (dd, } J = 7.6, 4.9 \text{ Hz, 1H), 6.33 (dd, } J = 10.0, 2.7 \text{ Hz, 1H), 6.00 (dd, } J = 10.0, 1.9 \text{ Hz, 1H), 4.75 (s, 1H), 4.42 – 4.28 (m, 1H), 3.61 (s, 3H), 1.36 (s, 3H).}

\(^{13}\text{C-NMR}\) (CDCl₃, 100 MHz): \(\delta \text{ ppm} = 160.35, 147.11, 133.18, 133.14, 126.66, 124.71, 123.10, 85.12, 76.15, 59.03, 21.60.

\(\text{IR (neat): } \nu_{\text{max}} = 779, 818, 957, 1111, 1196, 1358, 1435, 2824, 2932, 2978, 3441 \text{ (br) cm}^{-1}.

\(\text{HR-MS (EI): Calc. for } [M+H]^+: 192.1019, \text{ found: 192.1022.}

\([\alpha]_D^{25} = +53.1^\circ \text{cm}^2 \text{g} \text{ (c = 1.0, >99% ee, CHCl}_3)).
HPLC: Chiralcel OD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 9.4 min, 11.2 min.

7-Methoxy-8-methyl-7,8-dihydroisoquinolin-8-ol (31.1)

![Chemical Structure]

$^1$H-NMR (CDCl$_3$, 400 MHz): 8.48 (ddd, $J =$ 4.9, 1.7, 0.9 Hz, 1H), 7.97 – 7.77 (m, 1H), 7.17 (dd, $J =$ 7.6, 4.9 Hz, 1H), 6.12 (dd, $J =$ 3.3, 1.6 Hz, 1H), 4.90 (d, $J =$ 10.8 Hz, 1H), 4.18 – 3.98 (m, 1H), 3.52 (s, 3H), 3.02 (s, 1H), 2.25 – 2.12 (m, 3H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): 152.39, 148.06, 136.11, 132.39, 132.18, 127.43, 122.40, 82.25, 72.40, 57.09, 18.18.

IR (neat): $\nu_{\text{max}} =$ 787, 972, 1026, 1065, 1126, 1188, 1373, 1435, 1566, 2824, 2924, 3379 cm$^{-1}$.


$[\alpha]_{D}^{25} =$ -86.4°·cm$^2$g (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralcel OD-H, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 10.5 min, 13.2 min.

6-(Dibenzylamino)-8-methyl-5,6-dihydro-isoquinolin-5-ol (30.2) and 7-(dibenzylamino)-8-methyl-7,8-dihydro-isoquinolin-8-ol (31.2)

Obtained from oxabicycle 8 (51.3 mg, 0.32 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 30.2 isolated as a yellow oil (56.2 mg, 49% yield, >99% ee); Product 31.2 was isolated as a yellow oil (51.5 mg, 45% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 40%.

6-(Dibenzylamino)-8-methyl-5,6-dihydro-isoquinolin-5-ol (30.2)

![Chemical Structure]
\[ ^1H\text{-NMR} (\text{CDCl}_3, 400 MHz): \delta ppm = 8.42 (dd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.40 – 7.25 (m, 10H), 7.10 (dd, J = 7.6, 4.9 Hz, 1H), 6.22 (s, 1H), 4.97 (d, J = 12.2 Hz, 1H), 4.01 (d, J = 13.6 Hz, 2H), 3.62 (d, J = 13.6 Hz, 3H), 3.13 (s, 1H), 2.18 (dd, J = 2.2, 1.5 Hz, 3H). \]

\[ ^13C\text{-NMR} (\text{CDCl}_3, 100 MHz): \delta ppm = 152.1, 147.7, 139.2, 137.7, 133.1, 132.2, 129.2, 128.8, 127.6, 125.8, 122.4, 68.8, 62.2, 55.1, 18.5. \]

\[ \text{IR (neat): } \nu_{\text{max}} = 702, 748, 1026, 1134, 1373, 1451, 2338, 2839, 3024, 3487 \text{ (br) cm}^{-1}. \]

\[ \text{HRMS (EI): Calc. for } [M]^{+}: 356.1889, \text{ found: } 356.1884. \]

\[ [\alpha]_D^{25} = -77.2^\circ\cdot \text{cm}^2\cdot \text{g}^{-1} \text{ (c = 1.0, >99% ee, CHCl}_3). \]

\[ \text{HPLC: Chiralpak AD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 21.3 min, 25.2 min.} \]

7-(Dibenzylationamo)-8-methyl-7,8-dihydro-isoquinolin-8-ol (31.2)

\[ \text{Obtained from oxabicycle } 8 \text{ (50 mg, 0.31 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu); Product } 30.3 \text{ was isolated as a red solid (38.5 mg, 43% yield, 96% ee); Product } 31.3 \text{ was isolated as a red solid (26.9 mg, 30% yield, 98% ee).} \]

\[ \text{Flash Chromatography Eluent: ethyl acetate in hexanes: 30%}. \]
6-(3,4-dihydro-1(2H)-quinolinyl)-8-methyl-5,6-dihydroisoquinolin-5-ol (30.3)

\[ \text{\textbf{1H-NMR (CDCl}_3, 400 MHz): } \delta \text{ ppm } = 8.51 \text{ (dd, } J = 5.0, 0.9 \text{ Hz, } 1H), 7.90 \text{ (d, } J = 7.3 \text{ Hz, } 1H), 7.20 \text{ (dd, } J = 7.5, 5.1 \text{ Hz, } 1H), 7.07 - 6.95 \text{ (m, } 2H), 6.83 \text{ (d, } J = 8.2 \text{ Hz, } 1H), 6.65 \text{ (td, } J = 7.3, 0.9 \text{ Hz, } 1H), 6.02 \text{ (s, } 1H), 5.20 \text{ (d, } J = 10.5 \text{ Hz, } 1H), 4.80 - 4.73 \text{ (m, } 1H), 3.39 - 3.16 \text{ (m, } 2H), 2.87 - 2.71 \text{ (m, } 2H), 2.47 \text{ (s, } 1H), 2.20 \text{ (s, } 3H), 2.01 - 1.87 \text{ (m, } 2H). \]

\[ \text{\textbf{13C-NMR (CDCl}_3, 100 MHz): } \delta \text{ ppm } = 152.4, 148.2, 145.5, 137.9, 133.2, 132.9, 129.9, 129.3, 127.3, 124.6, 122.5, 117.4, 112.6, 69.4, 61.7, 44.7, 28.4, 22.9, 18.3. \]

\[ \text{\textbf{IR (neat): } } \nu_{\text{max}} = 748, 1057, 1188, 1211, 1304, 1458, 1497, 1605, 2847, 2924, 3325 \text{ cm}^{-1}. \]

\[ \text{\textbf{HR-MS (EI): } } \text{Calc. for } [M]^+ : 292.1576, \text{ found: } 292.1572. \]

\[ [a]_D^{25} = -57.3 ^\circ \text{cm}^{-1} \text{g (c = 1.0, 95% ee, CHCl}_3). \]

\[ \text{HPLC: Chiralpak AD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 57.5 min, 62.4 min.} \]

7-(3,4-dihydro-1(2H)-quinolinyl)-8-methyl-7,8-dihydro-isoquinolin-8-ol (31.3)

\[ \text{\textbf{1H-NMR (CDCl}_3, 400 MHz): } \delta \text{ ppm } = 8.46 - 8.37 \text{ (m, } 1H), 7.42 \text{ (d, } J = 6.8 \text{ Hz, } 1H), 7.22 \text{ (dd, } J = 7.6, 5.1 \text{ Hz, } 1H), 7.16 \text{ (d, } J = 8.4 \text{ Hz, } 1H), 7.03 \text{ (t, } J = 7.3 \text{ Hz, } 1H), 6.94 \text{ (d, } J = 6.9 \text{ Hz, } 1H), 6.59 \text{ (t, } J = 7.3 \text{ Hz, } 1H), 6.53 \text{ (dd, } J = 9.9, 2.4 \text{ Hz, } 1H), 6.10 \text{ (dd, } J = 9.9, 3.2 \text{ Hz, } 1H), 4.99 \text{ (s, } 1H), 3.84 \text{ (s, } 1H), 3.42 - 3.31 \text{ (m, } 1H), 3.12 \text{ (ddd, } J = 11.8, 8.5, 3.0 \text{ Hz, } 1H), 2.78 \text{ (t, } J = 6.4 \text{ Hz, } 2H), 1.94 - 1.73 \text{ (m, } 2H), 1.56 \text{ (s, } 3H). \]

\[ \text{\textbf{13C-NMR (CDCl}_3, 75 MHz): } \delta \text{ ppm } = 159.4, 147.5, 146.1, 133.9, 130.7, 129.7, 127.2, 126.8, 126.2, 123.4, 122.8, 116.6, 113.3, 64.7, 46.6, 29.9, 28.6, 24.0, 22.7. \]

\[ \text{\textbf{IR (neat): } } \nu_{\text{max}} = 741, 1188, 1288, 1451, 1497, 1574, 1597, 2338, 2924, 3364 \text{ cm}^{-1}. \]

\[ \text{\textbf{HR-MS (EI): } } \text{Calc. for } [M]^+ : 292.1756, \text{ found: } 292.1581. \]

\[ [a]_D^{25} = -33.4 ^\circ \text{cm}^{-1} \text{g (c = 1.0, 98% ee, CHCl}_3). \]
**HPLC:** Chiralpak AD-H, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 16.6 min, 19.7 min.

**6-(1-piperidinyl)-8-methyl-5,6-dihydroisoquinolin-5-ol (30.4) and 7-(1-piperidinyl)-8-methyl-7,8-dihydroisoquinolin-8-ol (31.4)**

Obtained from oxabicycle 8 (50.4 mg, 0.32 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)_2; Product 30.4 was isolated as a red oil (29.6 mg, 38% yield, >99% ee); Product 31.4 was isolated as a yellow gum (27.3 mg, 35% yield, 97% ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 60% → 80%.

**6-(1-piperidinyl)-8-methyl-5,6-dihydroisoquinolin-5-ol (30.4)**

![Chemical Structure](image)

**^1H-NMR** (CDCl₃, 400 MHz): δ ppm = 8.39 (dd, J = 4.9, 1.6 Hz, 1H), 7.34 (dd, J = 7.6, 1.6 Hz, 1H), 7.14 (dd, J = 7.6, 4.9 Hz, 1H), 6.52 (dd, J = 10.0, 2.3 Hz, 1H), 6.23 (dd, J = 10.0, 3.3 Hz, 1H), 3.62 (dd, J = 3.1, 2.5 Hz, 1H), 3.46 (s, 1H), 2.79 – 2.57 (m, 4H), 1.63 – 1.48 (m, 7H), 1.47 – 1.36 (m, 2H).

**^13C-NMR** (CDCl₃, 100 MHz): δ ppm = 160.00, 147.50, 133.44, 129.76, 127.06, 126.17, 122.98, 75.58, 70.42, 52.70, 27.10, 24.69, 23.18.

**IR** (neat): ν_max = 1088, 1273, 1373, 1435, 1566, 1651, 2747, 2801, 2855, 2932, 3048, 3379 cm⁻¹.

**HR-MS** (EI): Calc. for [M]^+: 244.1576, found: 244.1574.

[a]_D^25 = +226.5°·cm²·g⁻¹ (c = 1.0, >99% ee, CHCl₃).

**HPLC:** Chiralcel OD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 15.8 min, 17.7 min.

**7-(1-piperidinyl)-8-methyl7,8-dihydroisoquinolin-8-ol (31.4)**

![Chemical Structure](image)
$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.46 (ddd, $J = 4.9$, 1.6, 0.9 Hz, 1H), 7.89 – 7.79 (m, 1H), 7.16 (dd, $J = 7.6$, 4.9 Hz, 1H), 6.30 – 6.08 (m, 1H), 4.86 (d, $J = 12.6$ Hz, 1H), 3.90 (s, 1H), 3.50 – 3.32 (m, 1H), 2.99 – 2.73 (m, 2H), 2.56 – 2.42 (m, 2H), 2.16 (dd, $J = 2.4$, 1.6 Hz, 3H), 1.71 – 1.57 (m, 4H), 1.56 – 1.47 (m, 2H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 152.12, 147.59, 136.88, 133.75, 131.90, 125.28, 122.31, 68.05, 67.48, 50.54, 26.61, 24.80, 18.38.

IR (neat): $\nu_{\text{max}}$ = 988, 1111, 1273, 1373, 1443, 1566, 2338, 2754, 2855, 2932, 3348 cm$^{-1}$.

HR-MS (EI): Calc. for [M+H$^+$]: 245.1648, found: 245.1642.

[a]$^D_{25}$ = +84.1°·cm$^{2}$ g (c = 1.0, 97% ee, CHCl$_3$).

HPLC: Chiralcel OJ, hexanes +1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 7.8 min, 11.0 min.

6-Morpholin-8-methyl-5,6-dihydroisoquinolin-5-ol (30.5) and 7-morpholin-8-methyl-7,8-dihydroisoquinolin-8-ol (31.5)

Obtained from oxabicycle 8 (50.4 mg, 0.32 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 30.5 was isolated as a red oil (36.3 mg, 46% yield, >99% ee); Product 31.5 was isolated as a yellow solid (29.1 mg, 37% yield, 99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 50% → 70%.

6-Morpholin-8-methyl-5,6-dihydroisoquinolin-5-ol (30.5)

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.38 (dd, $J = 4.9$, 1.6 Hz, 1H), 7.35 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.15 (dd, $J = 7.6$, 4.9 Hz, 1H), 6.55 (dd, $J = 10.0$, 2.2 Hz, 1H), 6.19 (dd, $J = 10.0$, 3.3 Hz, 1H), 3.81 (s, 1H), 3.69 (dd, $J = 5.2$, 3.6, 1.4 Hz, 4H), 3.58 (dd, $J = 3.2$, 2.4 Hz, 1H), 2.79 (ddd, $J = 9.2$, 7.3, 2.4 Hz, 2H), 2.74 – 2.56 (m, 2H), 1.53 (s, 3H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 159.8, 147.6, 133.6, 128.8, 126.9, 126.7, 123.2, 75.4, 69.9, 67.8, 51.7, 23.1.

IR (neat): $\nu_{\text{max}}$ = 802, 826, 1011, 1111, 1258, 1327, 1373, 1451, 1651, 2924, 3372 cm$^{-1}$.

[α]D<sup>25</sup> = -258.3°·cm<sup>2</sup>g (c = 1.0, >99% ee, CHCl<sub>3</sub>).

**HPLC**: Chiralpak AD-H, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 22.3 min, 24.9 min.

7-morpholin-8-methyl-7,8-dihydroisoquinolin-8-ol (31.5)

![Chemical Structure](image)

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ ppm = 8.48 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 8.06 – 7.68 (m, 1H), 7.18 (dd, J = 7.6, 4.9 Hz, 1H), 6.29 – 6.07 (m, 1H), 4.87 (d, J = 12.4 Hz, 1H), 3.83 – 3.72 (m, 4H), 3.54 – 3.32 (m, 2H), 2.85 (ddd, J = 10.7, 5.8, 3.2 Hz, 2H), 2.58 (ddd, J = 9.5, 5.7, 3.3 Hz, 2H), 2.18 (dd, J = 2.4, 1.6 Hz, 3H).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100 MHz): δ ppm = 152.0, 147.8, 137.5, 133.2, 132.0, 124.7, 122.4, 67.7, 67.6, 67.3, 49.5, 18.4.

**IR** (neat): ν<sub>max</sub> = 795, 1003, 1111, 1258, 1451, 1566, 2338, 2855, 2924, 3379 cm<sup>-1</sup>.


[a]<sub>D</sub><sup>25</sup> = -74.2°·cm<sup>2</sup>g (c = 1.0, 99% ee, CHCl<sub>3</sub>).

**HPLC**: Chiralcel OD-H, hexanes + 5% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 12.7 min, 15.3 min.

8-Methyl-6-(phenoxy)-5,6-dihydroisoquinolin-5-ol (30.6) and 8-methyl-7-(phenoxy)-7,8-dihydroisoquinolin-8-ol (31.6)

Obtained from oxabicycle 8 (52 mg, 0.33 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)<sub>2</sub>; Product 30.6 was isolated as a white solid (27.2 mg, 33% yield, >99% ee); Product 31.6 was isolated as a white solid (25.5 mg, 31% yield, >99 % ee).

**Flash Chromatography Eluent**: ethylacetate in dichloromethane: 5%.

8-Methyl-6-(phenoxy)-5,6-dihydroisoquinolin-5-ol (30.6)

![Chemical Structure](image)
$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ ppm = 8.43 – 8.31 (m, 1H), 7.38 (dd, $J = 7.6$, 1.1 Hz, 1H), 7.34 – 7.23 (m, 2H), 7.20 (dd, $J = 7.6$, 5.0 Hz, 1H), 7.09 – 7.01 (m, 2H), 7.00 – 6.90 (m, 1H), 6.44 (dd, $J = 10.0$, 2.6 Hz, 1H), 6.10 (dd, $J = 10.0$, 1.6 Hz, 1H), 5.40 (t, $J = 2.0$ Hz, 1H), 4.76 (s, 1H), 1.57 (s, 3H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ ppm = 160.1, 158.2, 147.44, 133.5, 131.8, 129.7, 126.7, 125.7, 123.3, 121.5, 116.5, 81.7, 75.3, 22.0.

IR (neat): $\nu_{\text{max}}$ = 756, 818, 964, 1018, 1096, 1227, 1288, 1358, 1427, 1450, 1489, 1597, 2847, 2916, 3448 (broad) cm$^{-1}$.


$[\alpha]_D^{25}$ = -36.4°·cm$^2$·g$^{-1}$ (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralpak AD-H, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 6.6 min, 8.7 min.

8-Methyl-7-(phenoxy)-7,8-dihydroisoquinolin-8-ol (31.6)

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ ppm = 8.51 (d, $J = 4.9$ Hz, 1H), 7.93 (d, $J = 7.6$ Hz, 1H), 7.32 (dd, $J = 16.3$, 8.5 Hz, 2H), 7.19 (dd, $J = 7.6$, 4.9 Hz, 1H), 6.97 (dd, $J = 19.3$, 7.7 Hz, 3H), 6.07 (s, 1H), 5.13 (ddd, $J = 12.6$, 10.8, 5.9 Hz, 2H), 2.72 (dd, $J = 7.5$, 4.4 Hz, 1H), 2.15 (s, 3H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ ppm = 160.1, 158.2, 147.4, 133.5, 131.8, 129.7, 126.7, 125.7, 123.3, 121.5, 116.5, 81.7, 75.3, 22.0.

IR (neat): $\nu_{\text{max}}$ = 756, 1011, 1065, 1180, 1227, 1458, 1489, 1589, 2916, 3264 cm$^{-1}$.


$[\alpha]_D^{25}$ = -36.4°·cm$^2$·g$^{-1}$ (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralpak AD-H, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 10.8 min, 20.6 min.
5.8 Synthesis and ARO of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide

5.8.1 Synthesis of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide

8-hydro-5-methyl-5,8-epoxyquinoline N-Oxide (32)

In a 100-ml round-bottomed flask, mCPBA (2.32 g) was added to a solution of 8-hydro-5-methyl-5,8-epoxyquinoline 7 (1.57 g) in CH₂Cl₂ (60 ml) at 0°C. The flask was stirred at room temperature overnight during which time precipitation of m-chlorobenzoic acid was observed. The resulting suspension was washed with cold 10% NaOH solution. The layers were separated and the aqueous portion extracted with CHCl₃. The combined organic extracts were dried over anhydrous MgSO₄, and the solvent was removed in vacuo to give 32 as a white solid (1.35 g, 78%).

¹H-NMR (CDCl₃, 400 MHz):  δ ppm = 7.73 (d, 1H, J = 6.5 Hz), 7.17 (d, 1H, J = 5.0 Hz), 7.00 (d, 1H, J = 7.1 Hz), 6.92 (t, 1H, J = 6.8 Hz), 6.85 (d, 1H, J = 5.0 Hz), 6.04 (s, 1H), 1.92 (s, 1H).

¹³C-NMR (CDCl₃, 100 MHz):  δ ppm = 150.5, 146.7, 142.6, 136.6, 124.9, 123.1, 116.7, 90.3, 78.5, 15.3.

IR (neat): νₘₐₓ = 1454, 2872, 2947, 3071, 3347 cm⁻¹.


5.8.2 ARO of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide

General procedure for ARO

Rh(cod)₂OTf (6.7 mg, 0.014 mmol, 5% eq.), Josiphos (9.3 mg, 0.017 mmol, 6% eq.), 8-hydro-5-methyl-5,8-epoxyquinoline N-Oxide (50 mg, 0.29 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, amines: 1.5 eq., others: 5 eq.) were added to a flame dried microwave vial which was sealed and purged with argon. Anhydrous THF (1.5 ml) was added to the vial containing the catalyst. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction
was complete (typically 2-12 hours), the solvent was removed in vacuo and the crude products were purified by flash chromatography.

6-(Dibenzylamino)-5-methyl-5,6-dihydro-isoquinolin-5-ol N-oxide (33.1) and 7-(dibenzylamino)-5-methyl-7,8-dihydro-isoquinolin-8-ol N-oxide (34.1)

Obtained from oxabicycle 32 (50 mg, 0.29 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)_2; Product 33.1 was isolated as a yellow oil (45.9 mg, 43% yield, >99% ee); Product 34.1 was isolated as a yellow oil (31.3 mg, 29% yield, 99% ee).

Flash Chromatography Eluent: methanol in ethylacetate: 5%.

7-(dibenzylamino)-5-methyl-7,8-dihydro-isoquinolin-8-ol N-oxide (33.1)

![Chemical Structure of 7-(dibenzylamino)-5-methyl-7,8-dihydro-isoquinolin-8-ol N-oxide (33.1)]

\(^1\text{H-NMR}\) (CDCl\(_3\), 400 MHz): \(\delta\) ppm = 8.12 (dd, \(J = 4.8, 2.7\) Hz, 1H), 7.47 – 7.36 (m, 4H), 7.33 – 7.26 (m, 4H), 7.25 – 7.18 (m, 4H), 5.97 – 5.93 (m, 1H), 5.90 (s, 1H), 5.61 (d, \(J = 4.5\) Hz, 1H), 3.75 – 3.62 (m, 4H), 2.13 – 1.97 (m, 3H).

\(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) ppm = 146.9, 139.8, 138.1, 133.1, 130.6, 129.2, 129.1, 128.4, 127.2, 124.7, 122.1, 64.2, 60.1, 54.2, 19.34.

\(\text{IR}\) (neat): \(\nu_{\text{max}}\) = 702, 741, 1026, 1180, 1258, 1350, 1435, 2924, 3024, 3264 cm\(^{-1}\).

\(\text{HR-MS}\) (EI): Calc. for [M-OH]\(^+\): 355.1810, found: 355.1812.

\([\alpha]_D^{25}\) = +119.3°·cm\(^2\)·g\(^{-1}\) (c = 1.0, >99% ee, CHCl\(_3\)).

\(\text{HPLC}\): Chiracel OJ, hexanes + 10% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 15.1 min, 28.6 min.

6-(Dibenzylamino)-5-methyl-5,6-dihydro-isoquinolin-5-ol N-oxide (34.1)

![Chemical Structure of 6-(Dibenzylamino)-5-methyl-5,6-dihydro-isoquinolin-5-ol N-oxide (34.1)]
\textbf{\textsuperscript{1}H-NMR} (CDCl\textsubscript{3}, 400 MHz): $\delta_{ppm} =$ \textsuperscript{1}H NMR (400 MHz, cdcl\textsubscript{3}) $\delta$ 8.04 (dd, $J = 6.5$, 1.1 Hz, 1H), 7.47 (dd, $J = 10.5$, 2.4 Hz, 1H), 7.41 – 7.32 (m, 9H), 7.32 – 7.22 (m, 3H), 7.04 (dd, $J = 7.8$, 6.5 Hz, 1H), 6.59 (dd, $J = 10.5$, 3.1 Hz, 1H), 3.86 (t, $J = 2.9$ Hz, 1H), 3.82 (d, $J = 13.9$ Hz, 2H), 3.67 (d, $J = 14.0$ Hz, 2H), 1.48 (s, 3H).

\textbf{\textsuperscript{13}C-NMR} (CDCl\textsubscript{3}, 75 MHz): $\delta_{ppm} =$ 141.9, 141.3, 138.8, 138.1, 133.5, 128.9, 128.9, 127.8, 124.2, 122.1, 120.8, 74.0, 64.2, 56.9, 24.3.

\textbf{IR} (neat): $\nu_{\text{max}} = 702$, 895, 1026, 1072, 1204, 1250, 1381, 1636, 2338, 2855, 2924, 3395 cm\textsuperscript{-1}.


\textbf{[a$]_D$}$^{25} = +239.3 \degree \cdot \text{cm}^2 \cdot \text{g}^{-1} (c = 1.0, 99\% \text{ ee}, \text{CHCl}_3).

\textbf{HPLC}: Chiralpak AD-H, hexanes + 10\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 13.3 min, 16.3 min.

\textbf{6-(Methyl(phenyl)amino)-5-methyl-5,6-dihydro-isoquinolin-5-ol N-oxide (33.1) and 7-(methyl(phenyl)amino)-5-methyl-7,8-dihydro-isoquinolin-8-ol N-oxide (34.1)}

Obtained from oxabicycle 32 (50.4 mg, 0.29 mmol); reaction run at 60\(^\circ\)C using (R,S)-PPF-(t-Bu)$_2$; Product 33.2 was isolated as a white solid (47.2 mg, 58\% yield, 63\% ee); Product 34.2 was isolated as a yellow solid (23.6 mg, 29\% yield, >99\% ee).

\textbf{Flash Chromatography Eluent}: methanol in ethyl acetate: 5%.

\textbf{7-(Methyl(phenyl)amino)-5-methyl-7,8-dihydro-isoquinolin-8-ol N-oxide (33.2)}

\begin{center}
\includegraphics[width=0.2\textwidth]{molecule.png}
\end{center}

\textbf{\textsuperscript{1}H-NMR} (CDCl\textsubscript{3}, 400 MHz): $\delta_{ppm} =$ 8.13 (dd, $J = 5.6$, 1.5 Hz, 1H), 7.32 – 7.22 (m, 4H), 6.97 (d, $J = 8.1$ Hz, 2H), 6.78 (t, $J = 7.3$ Hz, 1H), 6.16 (d, $J = 1.6$ Hz, 1H), 6.02 – 5.80 (m, 1H), 5.45 (d, $J = 4.2$ Hz, 1H), 4.91 (s, 1H), 2.76 (s, 3H), 2.32 – 2.10 (m, 3H).

\textbf{\textsuperscript{13}C-NMR} (CDCl\textsubscript{3}, 100 MHz): $\delta_{ppm} =$ 149.4, 146.8, 138.3, 132.9, 129.7, 129.4, 129.0, 124.9, 122.2, 118.1, 114.7, 67.2, 62.1, 34.5, 19.4.

\textbf{IR} (neat): $\nu_{\text{max}} = 748$, 934, 1034, 1188, 1258, 1350, 1427, 1505, 1597, 2361, 3094, 3263 cm\textsuperscript{-1}.

$[\alpha]_D^{25} = +89.4^\circ \text{cm}^2 \text{g} \ (c = 1.0, \ 63\% \ ee, \ \text{CHCl}_3)$.

**HPLC:** Chiralpak AD-H, hexanes + 20% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 11.7 min, 14.4 min.

6-(Methyl(phenyl)amino)-5-methyl-5,6-dihydro-isoquinolin-5-ol N-oxide (34.2)

![Chemical Structure](image)

$^1\text{H-NMR}$ (CDCl$_3$, 300 MHz): $\delta \text{ ppm} = 8.05$ (d, $J = 5.6$ Hz, 1H), 7.48 (dd, $J = 15.0$, 9.1 Hz, 2H), 7.26 (t, $J = 8.0$ Hz, 3H), 7.10 (t, $J = 7.2$ Hz, 1H), 6.99 (d, $J = 8.2$ Hz, 2H), 6.79 (t, $J = 7.2$ Hz, 1H), 6.38 (dd, $J = 10.4$, 3.4 Hz, 1H), 4.98 (s, 1H), 2.80 (s, 3H), 1.53 (s, 3H).

$^{13}\text{C-NMR}$ (CDCl$_3$, 75 MHz): $\delta \text{ ppm} = 150.3$, 142.2, 140.5, 138.3, 134.8, 129.5, 124.2, 122.4, 119.9, 118.1, 113.5, 75.2, 64.8, 35.3, 24.7.

**IR** (neat): $\nu_{\text{max}} = 748$, 988, 1088, 1204, 1250, 1427, 1505, 1597, 3225 cm$^{-1}$.


$[\alpha]_D^{25} = +80.7^\circ \text{cm}^2 \text{g} \ (c = 1.0, >99\% \ ee, \ \text{CHCl}_3)$.

**HPLC:** Chiralpak AD-H, hexanes + 10% 2-propanol, flow 1.2 ml/min, 220, 254, 280 nm, retention times: 16.7 min, 21.8 min.

6-(3,4-dihydro-1(2H)-quinoliny1)-5-methyl-5,6-dihydro-isoquinolin-5-ol N-oxide (33.3) and 7-(3,4-dihydro-1(2H)-quinoliny1)-5-methyl-7,8-dihydro-isoquinolin-8-ol N-oxide (34.3)

Obtained from oxabicycle 32 (50 mg, 0.29 mmol); reaction run at 60$^\circ$C using (R,S)-PPF-P(t-Bu)$_2$; Product 33.3 was isolated as a white solid (33.7 mg, 38% yield, 91% ee); Product 34.3 was isolated as a yellow oil (22.6 mg, 26% yield, >99% ee).

**Flash Chromatography Eluent:** methanol in ethyl acetate: 5% $\rightarrow$ 10%.
7-(3,4-dihydro-1(2H)-quinolinyl)-5-methyl-7,8-dihydro-isooquinolin-8-ol N-oxide (33.3)

\[
\text{IR (neat): } \nu_{\text{max}} = 702, 1026, 1150, 1188, 1443, 1497, 2731, 2847, 2932, 3086, 3148, 3973 \text{ cm}^{-1}.
\]
\[
\text{HR-MS (EI): Calc. for [M-H_2O]^+: 290.1419, found: 290.1416.}
\]
\[
[a]_D^{25} = -204.9^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} (c = 1.0, 91\% ee, \text{CHCl}_3).
\]

\[
\text{HPLC: Chiralpak AD-H, hexanes + 20\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 11.2 min, 14.6 min.}
\]

6-(3,4-dihydro-1(2H)-quinolinyl)-5-methyl-5,6-dihydro-isooquinolin-5-ol N-oxide (34.3)

\[
\text{IR (neat): } \nu_{\text{max}} = 748, 1188, 1250, 1304, 1427, 1497, 1597, 2855, 2924, 3225 \text{ cm}^{-1}.
\]
\[
\text{HR-MS (EI): Calc. for [M+H]^+: 290.1419, found: 290.1421.}
\]
\[
[a]_D^{25} = -110.0^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} (c = 1.0, >99\% ee, \text{CHCl}_3).
\]

\[
\text{HPLC: Chiralpak AD-H, hexanes + 20\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 6.702 min, 8.412 min.}
\]
5.9 Synthesis and ARO of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline

5.9.1 Synthesis of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline

4-Chloro-benzenesulfonic acid 5-chloro-7-iodo-quinolin-8-yl ester (36)

To a 500 ml round-bottomed flask, was added with 5-chloro-7-iodo-8-quinolinol (15.28 g, 50 mmol) and anhydrous pyridine (50 ml). To the mixture was added 4-chlorobenzenesulfonyl chloride (13.06 g, 60 mmol) portion-wise. After the addition was complete, the reaction mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and 75 ml of water was added to the mixture residue. The mixture was diluted with CH$_2$Cl$_2$ (250 ml) and washed with saturated NaHCO$_3$ (250 ml) and brine (250 ml), then dried over MgSO$_4$. After filtration, the solvent was evaporated in vacuo. The residue was re-crystallized from absolute ethanol to yield 21.02 g (88%) of the desired product as a green solid. (m.p: 127-128 °C)

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta$ ppm = 8.75 (dd, 1H, $J$ = 4.2 and 1.6 Hz), 8.50 (dd, 1H, $J$ = 8.6 and 1.6 Hz), 8.02 (m, 2H), 7.55 (m, 3H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 151.5, 148.1, 142.3, 141.0, 136.9, 135.6, 133.4, 130.6, 129.3, 127.4, 123.1, 105.0, 91.5.

IR (neat): $\nu_{\max}$ = 3684, 3615, 3019, 2399, 1558, 1514, 1477, 1443, 1385, 1871, 1350, 1188, 1174, 1060, 1041.6, 929, 669 cm$^{-1}$


Preparation of $i$PrMgCl:

Magnesium granule were placed in a 250 ml argon-flushed round-bottomed flask and THF (50 ml) was added. A solution of $i$PrCl (9.24 ml, 100 mmol) in THF (50 ml) was slowly added at room temperature. The reaction mixture was gently heated by heat gun. The reaction started within a few minutes. The reaction mixture was stirred for 18 hours at room temperature. The
grey solution of iPrMgCl was added via a cannula to another flask under Argon and removed in this from excess of magnesium. The iPrMgCl solution is titrated prior to use by the method of Paquette.³⁹

5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline:

To a dry and argon flushed 25 ml round-bottomed flask equipped with a magnetic stirrer and a septum, was charged with a solution of 4-chloro-benzenesulfonyl acid 5-chloro-7-iodo-quinolin-8-yl ester (480 mg, 1 mmol) in dry THF (6 ml). iPrMgCl (1.23 ml, 1.01 mmol, 0.82 M in THF) was then added dropwise at -78°C. After 30 minutes, freshly distilled furan was then added slowly at -78°C and the resulting mixture was warmed to room temperature and stirred until the TLC showed the starting material was completed. Saturated NH₄Cl was added and the resulting mixture was extracted with CH₂Cl₂. The organic extracts were dried over anhydrous MgSO₄ and concentrated. Purification by flash chromatography (hexanes/ether, 2:1) yielded the final product (170 mg, 74%) as a yellow solid.

¹H-NMR (CDCl₃, 400 MHz): δ ppm = 8.80 (dd, 1H, J = 4.1 and 1.5 Hz), 8.41 (dd, 1H, J = 8.7 and 1.5 Hz), 7.60 (s, 1H), 7.30 (dd, 1H, J = 8.7 and 4.1 Hz), 7.20 (dd, 1H, J = 5.5 and 1.8 Hz), 7.09 (dd, 1H, J = 5.5 and 1.8 Hz), 6.43 (d, 1H, J = 0.8 Hz), 5.84 (m, 1H).

¹³C-NMR (CDCl₃, 100 MHz): δ ppm = 153.6, 151.6, 148.6, 144.5, 144.3, 142.4, 133.4, 128.5, 123.1, 121.6, 121.0, 83.4, 81.4.

IR (neat): νmax = 3404, 3073, 3026.4, 1603, 1585, 1568, 1508.4, 1446, 1391, 1341, 1277, 1223, 1194, 1055, 1013, 966, 926, 912, 842 cm⁻¹.


5.9.2 ARO of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline

General procedure for ARO

Rh(cod)₂OTf (8.2 mg, 0.017 mmol, 5% eq.), Josiphos (11.4 mg, 0.020 mmol, 6% eq.), 5-chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline (80 mg, 0.35 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, amines: 1.5 eq., others: 5 eq.) were added to a flame dried microwave vial which was sealed and purged with argon. Anhydrous THF (1.5 ml) was added to the vial containing the catalyst. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction was complete (typically 2-12 hours), the solvent was removed in vacuo and the crude products were purified by flash chromatography.

9-Morpholin-9,10-dihydro-benzo[h]quinolin-10-ol (38.5) and 8-Morpholin-7,8-dihydro-benzo[h]quinolin-7-ol (39.5)

Obtained from oxabicycle 37 (80 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 38.5 was isolated as a brownish oil (39.6 mg, 36% yield, 98% ee); Product 39.5 was isolated as a brownish oil (13.9 mg, 13% yield, >99% ee).

Flash Chromatography Eluent: ethyl acetate in hexanes: 80% → 100%, then methanol in ethylacetate: 5%.

9-Morpholin-9,10-dihydro-benzo[h]quinolin-10-ol (38.5)

\[
\text{\textsuperscript{1}H-NMR (CDCl}_3, 400 MHz): \delta ppm = 8.92 (dd, J = 4.1, 1.7 Hz, 1H), 8.53 (dd, J = 8.5, 1.7 Hz, 1H), 7.95 (s, 1H), 7.80 (dd, J = 10.2, 2.6 Hz, 1H), 7.46 (dd, J = 8.5, 4.2 Hz, 1H), 6.35 (dd, J = 10.2, 2.4 Hz, 1H), 5.05 (d, J = 12.8 Hz, 1H), 3.87 – 3.70 (m, 4H), 3.58 (d, J = 12.8 Hz, 2H), 2.96 – 2.83 (m, 2H), 2.73 – 2.56 (m, 2H).} 
\]
\( ^{13}\text{C-NMR} \text{ (CDCl}_3, \text{ 100 MHz): } \delta \text{ ppm} = 150.6, 144.6, 138.4, 133.2, 130.8, 128.1, 125.7, 125.2, 125.0, 124.2, 121.8, 68.4, 67.9, 67.4, 49.7. \)
\( \text{IR (neat): } v_{\text{max}} = 741, 934, 1111, 1451, 2338, 2847, 2916, 3441 \text{ (br) cm}^{-1}. \)
\( \text{HR-MS (EI): Calc. for [M-H}_2\text{O}^+]^+: 298.0873, \text{ found: } 298.0878. \)
\( [\alpha]_D^{25} = +279.0^\circ \text{ cm}^2 \text{ g} \text{ (c = 1.0, 98\% ee, CHCl}_3). \)
\( \text{HPLC: Chiralpak AD-H, hexanes + 10\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: } 11.3 \text{ min, 13.3 min.} \)

8-Morpholin-7,8-dihydro-benzo[h]quinolin-7-ol (39.5)

\[
\text{O} \quad \text{N} \quad \text{O} \quad \text{N} \\
\text{HO} \quad \text{Cl} \\
\text{N} \quad \text{N} \quad \text{Cl}
\]

\( ^1\text{H-NMR} \text{ (CDCl}_3, \text{ 400 MHz): } \delta \text{ ppm} = 8.87 \text{ (dd, } J = 4.2, 1.7 \text{ Hz, 1H), 8.53 \text{ (dd, } J = 8.5, 1.7 \text{ Hz, 1H), 7.46 \text{ (dd, } J = 8.5, 4.2 \text{ Hz, 1H), 7.42 \text{ (s, 1H), 6.62 \text{ (dd, } J = 9.8, 2.0 \text{ Hz, 1H), 6.19 \text{ (dd, } J = 9.8, 4.0 \text{ Hz, 1H), 5.97 \text{ (d, } J = 5.9 \text{ Hz, 1H), 5.37 \text{ (s, 1H), 3.79 \text{ (ddd, } J = 6.0, 4.0, 2.1 \text{ Hz, 1H), 3.73 – 3.60 \text{ (m, 4H), 2.86 – 2.71 \text{ (m, 2H), 2.63 – 2.46 \text{ (m, 2H).} \}
\( \text{IR (neat): } v_{\text{max}} = 772, 1034, 1111, 1219, 2338, 2855, 2916, 3457 \text{ (br) cm}^{-1}. \)
\( \text{HR-MS (EI): Calc. for [M]^+: 316.0979, \text{ found: } 316.0977. \)
\( [\alpha]_D^{25} = +310.4^\circ \text{ cm}^2 \text{ g} \text{ (c = 1.0, >99\% ee, CHCl}_3). \)
\( \text{HPLC: Chiralpak AD-H, hexanes + 1\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: } 37.5 \text{ min, 44.7 min.} \)
9,10-dihydro-9-(diisopropyl)-benzo[h]quinolin-10-ol (38.6) and 7,8-dihydro-8-(diisopropyl)-benzo[h]quinolin-7-ol (39.6)

Obtained from oxabicycle 37 (80 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 38.6 was isolated as a red solid (37.9 mg, 33% yield, 96% ee); Product 39.6 was isolated as a dark brown solid (37.7 mg, 33% yield, 99% ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 0% → 10%.

9,10-dihydro-9-(diisopropyl)-benzo[h]quinolin-10-ol (38.6)

\[
\text{\includegraphics[width=0.5\textwidth]{structure.png}}
\]

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ ppm = 8.91 (dd, $J = 4.2$, 1.7 Hz, 1H), 8.53 (dd, $J = 8.5$, 1.7 Hz, 1H), 7.96 (s, 1H), 7.66 (dd, $J = 10.2$, 2.9 Hz, 1H), 7.45 (dd, $J = 8.6$, 4.1 Hz, 1H), 6.37 (dd, $J = 10.2$, 2.1 Hz, 1H), 4.95 (d, $J = 13.7$ Hz, 1H), 3.79 (dt, $J = 13.7$, 2.5 Hz, 1H), 3.57 (s, 1H), 3.48 – 3.26 (m, 2H), 1.14 (dd, $J = 12.6$, 6.6 Hz, 12H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 150.5, 144.5, 139.3, 133.2, 130.3, 128.3, 125.5, 124.3, 124.1, 121.6, 69.7, 59.3, 46.3, 25.1, 21.4.

**IR** (neat): $\nu_{\text{max}}$ = 787, 934, 1142, 1258, 1281, 1397, 1451, 1505, 1613, 2338, 2361, 2847, 2916, 2970, 3410 cm$^{-1}$.


$[\alpha]_D^{25} = +132.0^\circ$ cm$^2$ g$^{-1}$ (c = 1.0, 96% ee, CHCl$_3$).

**HPLC:** Chiralpak AD-H, hexanes + 3% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 5.4 min, 6.0 min.
7,8-dihydro-8-(diisopropyl)-benzo[h]quinolin-7-ol (39.6)

\[
\begin{align*}
\text{H-NMR (CDCl}_3, 300 MHz): & \quad \delta \text{ ppm } = 8.89 (dd, J = 4.2, 1.1 Hz, 1H), 8.51 (dd, J = 8.5, 1.1 Hz, 1H), 7.47 - 7.38 (m, 2H), 6.57 (dd, J = 9.6, 1.2 Hz, 1H), 6.15 (dd, J = 9.6, 4.7 Hz, 1H), 5.86 (d, J = 3.1 Hz, 1H), 3.93 - 3.79 (m, 1H), 3.69 (br s, 1H), 2.89 (dt, J = 13.2, 6.6 Hz, 2H), 1.02 (t, J = 6.4 Hz, 12H).
\end{align*}
\]

\[
\begin{align*}
\text{C-NMR (CDCl}_3, 100 MHz): & \quad \delta \text{ ppm } = 150.8, 147.3, 135.2, 133.5, 133.5, 131.6, 131.2, 126.6, 125.8, 125.3, 121.3, 69.6, 55.6, 46.2, 23.5.
\end{align*}
\]

\[
\begin{align*}
\text{IR (neat): } & \quad \nu_{\text{max}} = 1358, 1397, 1466, 1574, 1637, 2338, 3410 \text{ cm}^{-1}.
\end{align*}
\]

\[
\begin{align*}
\text{HR-MS (EI): } & \quad \text{Calc. for [M-H}_2\text{O]}^+ : 312.1393, \text{found: 312.1398.}
\end{align*}
\]

\[
\begin{align*}
[a]_D^{25} = +98.5^\circ \cdot \text{cm}^2 \cdot \text{g} \quad (c = 1.0, >99\% \text{ ee, CHCl}_3).
\end{align*}
\]

\[
\begin{align*}
\text{HPLC: } & \quad \text{Chiralpak AD-H, hexanes + 3% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 11.0 min, 12.8 min.}
\end{align*}
\]

9-(1-piperidinyl)-9,10-dihydro-benzo[h]quinolin-10-ol (38.7) and 8-(1-piperidinyl)-7,8-dihydro-benzo[h]quinolin-7-ol (39.7)

Obtained from oxabicycle 37 (80 mg, 0.35 mmol); reaction run at 60°C using (R,S)-PPF-\((t\)-Bu)\(_2\); Product 38.7 was isolated as a yellow solid (34.6 mg, 32% yield, 95% ee); Product 39.7 was isolated as a yellow solid (38.7 mg, 35% yield, >99% ee).

\[
\begin{align*}
\text{Flash Chromatography Eluent: } & \quad \text{ethyl acetate in hexanes: 50%}.
\end{align*}
\]
9-(1-piperidinyl)-9,10-dihydro-benzo[h]quinolin-10-ol (38.7)

1H-NMR (CDCl3, 400 MHz): δ ppm = 8.91 (dd, J = 4.2, 1.7 Hz, 1H), 8.53 (dd, J = 8.5, 1.7 Hz, 1H), 7.96 (s, 1H), 7.74 (dd, J = 10.2, 2.7 Hz, 1H), 7.45 (dd, J = 8.5, 4.2 Hz, 1H), 6.39 (dd, J = 10.2, 2.3 Hz, 1H), 5.02 (d, J = 13.5 Hz, 1H), 3.51 (d, J = 13.2 Hz, 1H), 2.92 – 2.76 (m, 2H), 2.51 (t, J = 7.1 Hz, 2H), 1.75 – 1.46 (m, 7H).

13C-NMR (CDCl3, 100 MHz): δ ppm = 150.5, 144.6, 139.1, 133.2, 128.3, 126.6, 125.6, 124.3, 124.1, 121.6, 68.6, 68.2, 50.8, 26.8, 24.9.

IR (neat): νmax = 941, 1126, 1227, 1389, 1451, 1505, 1559, 1613, 1883, 1998, 2338, 2700, 2808, 2932, 3387 cm⁻¹.


[a]D²⁵ = -267.2°·cm²·g⁻¹ (c = 1.0, 95% ee, CHCl₃).

HPLC: Chiralpak AD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 20.3 min, 23.8 min.

8-(1-piperidinyl)-7,8-dihydro-benzo[h]quinolin-7-ol (39.7)

1H-NMR (CDCl3, 400 MHz): δ ppm = 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.53 (dd, J = 8.5, 1.7 Hz, 1H), 7.53 – 7.37 (m, 2H), 6.60 (dd, J = 9.8, 2.1 Hz, 1H), 6.21 (dd, J = 9.8, 4.1 Hz, 1H), 5.98 (d, J = 5.5 Hz, 1H), 3.89 – 3.68 (m, 2H), 2.73 (dt, J = 10.9, 5.4 Hz, 2H), 2.57 – 2.41 (m, 2H), 1.55 (dt, J = 11.0, 5.5 Hz, 4H), 1.41 (dd, J = 11.4, 6.0 Hz, 2H).
$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ ppm = 150.3, 147.4, 133.8, 133.3, 131.7, 131.6, 131.3, 127.1, 126.5, 126.0, 121.5, 66.6, 64.8, 50.4, 26.7, 24.7.

IR (neat): $\nu_{\text{max}}$ = 739, 934, 1038, 1107, 1385, 1402, 1452, 1585, 2810, 2853, 2934, 3028, 3048, 3069, 3302 cm$^{-1}$.


$[\alpha]_D^{25}$ = -249.0$^\circ$·cm$^2$·g$^{-1}$ (c = 1.0, >99% ee, CHCl$_3$).

HPLC: Chiralpak AD-H, hexanes + 1% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 34.8 min, 40.1 min.
5.10 Synthesis and ARO of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole and 6,7-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole

5.10.1 Synthesis of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole and 6,7-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole

2,3-Dibromonitrobenzene (43) and 3,4-Dibromonitrobenzene (44): 

![Structure of 2,3-Dibromonitrobenzene and 3,4-Dibromonitrobenzene]

To 50 ml round-bottomed flask containing 1,2-dibromobenzene (6.84 g, 29 mmol) in a was added a mixture of concentrated HNO$_3$ (18 ml) and H$_2$SO$_4$ (9 ml) at 0°C. The mixture was stirred at 0°C for 30 min and at room temperature overnight and then poured into 200 g of ice water. The precipitate was filtered and washed with cold water. Recrystallization 5 times from MeOH yielded some of the 3,4-isomer. All remaining material was purified by flash chromatography (10% ethylacetate in hexanes) to yield 2,3-isomer and 3,4-isomer as yellow solids. 2,3-dibromonitrobenzene (1.1 g, 14%) and 3,4-dibromonitrobenzene (5.1 g, 63%). The products were identical to those reported.

3,4-Dibromoaniline (45)

![Structure of 3,4-Dibromoaniline]

Method 1:

Iron powder (2.2 g, 38.4 mmol, 3 equiv) was added to a solution of 50% EtOH/H$_2$O (24 ml) then the mixture was added to starting material. The mixture was heated to 90°C for 2.5 hr, cooled to room temperature, filtered through Celite and washed with EtOH and EtOAc. A small quantity of NaHCO$_3$ was added to convert all the aniline salt to basic aniline. The mixture was extracted with EtOAc, concentrated and purified by flash chromatography (10% EtOAc in hexanes) to
yield the final product (2.51 g, 78%) as an off white solid. The products were previously characterized\(^{40}\).

**Method 2:**

3,4-dibromonitrobenzene (2.0 g, 7.12 mmol) was dissolved in 40 ml of absolute EtOH. SnCl\(_2\cdot2\)H\(_2\)O (8 g, 35.6 mmol) was added and the mixture was heated at 70°C for 2 hours and then poured into 250 g of ice. The aqueous phase was adjusted to pH 9 with 2N NaOH and extracted with ether. The organic layers were dried over MgSO\(_4\), concentrated and flash chromatographed (10% EtOAc in hexanes) to yield the final product 45 (1.59 g, 89%) as a white solid.

The following compounds were synthesized by a modification of the reported method.\(^{37}\)

**3,4-Dibromophenylhydrazine (46)**

![3,4-Dibromophenylhydrazine](image)

In a 250 ml round-bottom flask was added 3,4-dibromoaniline (5.62 g, 22.4 mmol) and 90 ml of MeOH. To the solution was added 15 ml concentrated hydrochloric acid. The mixture was stirred for 10 min and evaporated under reduced pressure. 2N HCl (25 ml) was added to the flask. A solution of NaNO\(_2\) (1.71 g, 24.8 mmol, 1.1 equiv) in 15 ml H\(_2\)O was then added at 0°C. The solution was stirred for 30 min and then added dropwise a solution of SnCl\(_2\cdot2\)H\(_2\)O (20.24g in 85 ml concentrated HCl). The mixture was stirred overnight and filtered. The collected precipitate was added to 300 ml of 10% aqueous NaOH and 400 ml ether and stirred for 1 hour after which the phases were separated. The aqueous layer was washed with ether. The combined organic layers were dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (30% EtOAc in hexanes) to give 4.77 g of the final product.
4,5-Dibromo-3-phenyl-1H-indole (48)

![Chemical Structure](image)

To a 500 ml round bottom flask under nitrogen, 3,4-dibromophenylhydrazine (7.32 g, 27.5 mmol) was dissolved in anhydrous THF (300 ml), then added phenylacetaldehyde (4.05 g, 30.3 mmol) and polyphosphoric acid (44 g). The mixture was heated at reflux for 3 hours and concentrated under vacuum. Water and CH$_2$Cl$_2$ were added and the aqueous layer was washed with CH$_2$Cl$_2$. The organic layers were combined, dried over MgSO$_4$ and concentrated. The crude product was first purified by flash chromatography (5% EtOAc in hexane) to yield a mixture of 2 products (6.73 g, 70%). Further separation by flash chromatography (twice with 20% EtOAc in hexanes) afforded some of 4,5-dibromo-3-phenyl-1H-indole 48.

4,5-Dibromo-1-methyl-3-phenyl-1H-indole (49)

![Chemical Structure](image)

In a 250 ml flask under nitrogen, 4,5-dibromo-3-phenyl-1H-indole (1.97 g, 5.6 mmol) was dissolved in 72 ml THF and 95% NaH (0.17 g, 6.72 mmol, 1.2 equiv) was added. The solution was stirred at room temperature for 30 min, and then MeI (0.7 ml, 11.2 mmol, 2 equiv) was added dropwise. The resulting solution was stirred overnight, then quenched with water. The aqueous mixture was extracted with diethyl ether. Combined organic layers were washed with brine and dried over MgSO$_4$. Evaporation of the solvent under reduced pressure and flash chromatography of the crude mixture (hexanes/ethylacetate, 9/1) afforded the final product (1.87 g, 92%) as a yellow oil.
4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1\textit{H}-indole (50)

![Chemical Structure](image)

To a flame-dry 300 ml round bottomed flask under argon was added 4,5-dibromo-1-methyl-3-phenyl-1\textit{H}-indole (1.81 g 5.0 mmol, 1 equiv), anhydrous diethyl ether (170 ml) and freshly distilled furan (7.42 ml, 100 mmol, 20 equiv). The mixture was cooled to -78°C and \textit{n}BuLi (5.34 ml, 5.5 mmol, 1.03 M in hexanes) was added dropwise over 2 hours. The solution was allowed to warm slowly to room temperature overnight. Water was added, the mixture was extracted with diethyl ether, the combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethylacetate/hexanes, 1/9 $\rightarrow$ 2/8) to give the final product (1.21 g, 89%) as a grey solid.

5.10.2 ARO of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1\textit{H}-indole

**General procedure for ARO**

Rh(cod)$_2$OTf (6.0 mg, 0.013 mmol, 5% eq.), Josiphos (8.3 mg, 0.015 mmol, 6% eq.), 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1\textit{H}-indole (70 mg, 0.26 mmol, 1 eq.) and the nucleophile (alcohol: 1 ml, amines: 1.5 eq., others: 5 eq.) were added to a flame dried microwave vial which was sealed and purged with Argon. Anhydrous THF (1.5 ml) was added to the catalyst vial. The reaction was stirred at 60°C and monitored by thin layer chromatography. After the reaction was complete (1 hour), the solvent was removed in \textit{vacuo} and the crude products were purified by flash chromatography.

**Ring opening product 51.1 and 52.1**

Obtained from oxabicycle 50 (69.5 mg, 0.26 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)$_2$; Product 51.1 was isolated as a yellow solid (27.9 mg, 31% yield, >99% ee); Product 52.1 was isolated as a white solid (26.7 mg, 30% yield, 94 % ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 60%.
Ring opening product 51.1

\[
\begin{align*}
&\text{\textsuperscript{1}H-NMR (CDCl}_3, 400 MHz): \delta ppm = 7.58 - 7.26 (m, 7H), 7.01 (s, 1H), 6.83 (dd, J = 10.2, 2.2 Hz, 1H), 5.95 (dd, J = 10.1, 3.1 Hz, 1H), 4.96 (d, J = 10.0 Hz, 1H), 3.81 (d, J = 5.2 Hz, 3H), 3.78 - 3.66 (m, 4H), 3.43 (dt, J = 4.9, 2.7 Hz, 1H), 2.84 - 2.69 (m, 2H), 2.66 - 2.53 (m, 2H). \\
&\text{\textsuperscript{13}C-NMR (CDCl}_3, 100 MHz): \delta ppm = 137.6, 136.8, 130.5, 129.3, 128.8, 128.3, 127.3, 126.7, 124.4, 123.2, 123.1, 120.1, 117.8, 109.0, 68.5, 67.6, 67.4, 49.6, 33.1. \\
&\text{IR (neat): } \nu_{\text{max}} = 702, 756, 818, 941, 995, 1111, 1219, 1343, 1381, 1543, 1597, 2855, 2916, 3410 \text{ (br) cm}^{-1}. \\
&\text{HR-MS (EI): Calc. for [M-H}_2\text{O}]^+: 342.1732, \text{ found: 342.1729.} \\
&[\alpha]_D^{25} = +131.0^\circ\text{-cm}^2\text{-g} (c = 1.0, >99\% ee, CHCl}_3). \\
&\text{HPLC: Chiralpak AD-H, hexanes + 15\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, } \\
&\text{retention times: 21.5 min, 46.4 min.}
\end{align*}
\]
Ring opening product 51.2

\[ \text{\textsuperscript{1}H-NMR (CDCl}_3, 300 \text{ MHz): } \delta \text{ ppm} = 7.57 \text{ (d, } J = 8.4 \text{ Hz, 1H)}, \text{ 7.36 (ddd, } J = 18.3, 12.5, 8.7, 3.8 \text{ Hz, 9H)}, \text{ 7.03 (s, 1H)}, \text{ 6.97 (dd, } J = 7.7, 4.1 \text{ Hz, 3H)}, \text{ 6.78 (dd, } J = 10.1, 1.6 \text{ Hz, 1H)}, \text{ 5.89 (dd, } J = 10.1, 2.5 \text{ Hz, 1H)}, \text{ 5.26 – 5.18 (m, 1H)}, \text{ 5.09 (dt, } J = 9.5, 2.1 \text{ Hz, 1H)}, \text{ 3.82 (s, 3H)}. \]

\[ \text{\textsuperscript{13}C-NMR (CDCl}_3, 75 \text{ MHz): } \delta \text{ ppm} = 157.5, 137.6, 136.4, 130.3, 129.6, 129.3, 128.1, 127.1, 126.8, 126.5, 124.5, 124.4, 123.2, 121.2, 119.9, 117.6, 115.9, 108.9, 78.5, 72.6, 32.9. \]

IR (neat): \( \nu_{\max} = 748, 957, 1250, 1497, 1597, 2855, 2924, 3017, 3364 \text{ (br) cm}^{-1}. \]

HR-MS (EI): Calc. for [M-H\textsubscript{2}O\textsuperscript{+}]: 349.1467, found: 349.1466.

[\text{[a]}]_D^{25} = +287.3^\circ \cdot \text{cm}^2 \cdot \text{g}^{-1} (c = 1.0, >99\% ee, \text{CHCl}_3). \]

HPLC: Chiralpak AD-H, hexanes + 40\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 9.5 min, 20.4 min.

Ring opening product 52.2

\[ \text{\textsuperscript{1}H-NMR (CDCl}_3, 300 \text{ MHz): } \delta \text{ ppm} = 7.41 – 7.09 \text{ (m, 10H)}, \text{ 6.95 (dd, } J = 10.7, 4.0 \text{ Hz, 1H)}, \text{ 6.85 (dd, } J = 9.0, 5.8 \text{ Hz, 3H)}, \text{ 6.03 (dd, } J = 9.6, 5.3 \text{ Hz, 1H)}, \text{ 5.24 (d, } J = 5.7 \text{ Hz, 1H)}, \text{ 4.80 (dd, } J = 5.3, 1.8 \text{ Hz, 1H}), \text{ 3.80 (s, 3H)}, \text{ 1.54 (s, 1H)}. \]
The text contains chemical and physical data, as well as information about the preparation and analysis of a compound. The data includes NMR and IR spectra, HRMS, and optical rotation values. There are also mentions of HPLC retention times and chromatography eluents.

**13C-NMR (CDCl₃, 75 MHz):** δ ppm = 157.6, 137.9, 136.1, 132.6, 129.7, 128.4, 127.3, 127.1, 125.9, 123.4, 123.2, 121.1, 119.9, 117.4, 116.1, 109.9, 77.4, 73.1, 64.2, 33.1.

**IR (neat):** νmax = 702, 756, 810, 988, 1227, 1296, 1489, 1597, 2916, 3040, 3426 (br) cm⁻¹.

**HR-MS (EI):** Calc. for [M-H₂O]⁺: 349.1467, found: 349.1464.

[a]D²⁵ = +42°·cm²·g⁻¹ (c = 1.0, 87% ee, CHCl₃).

**HPLC:** Chiralpak AD-H, hexanes + 40% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 9.8 min, 21.6 min.

**Ring opening product 51.3 and 52.3**

Obtained from oxabicycle 50 (63.5 mg, 0.23 mmol); reaction run at 60°C using (R,S)-PPF-P(t-Bu)₂; Product 51.3 isolated as a yellow oil (41.6 mg, 43% yield, 93% ee); Product 52.3 was isolated as a red oil (3.4.4 mg, 35% yield, 70% ee).

**Flash Chromatography Eluent:** ethyl acetate in hexanes: 15%.

**Ring opening product 51.3**

![Chemical Structure Image]

**1H-NMR (CDCl₃, 400 MHz):** δ ppm = 7.76 (dd, J = 5.3, 3.2 Hz, 2H), 7.66 (dd, J = 5.6, 3.0 Hz, 2H), 7.45 – 7.37 (m, 2H), 7.32 (d, J = 8.3 Hz, 1H), 7.25 (dt, J = 4.7, 2.5 Hz, 3H), 7.18 (d, J = 8.3 Hz, 1H), 7.00 (s, 1H), 6.84 (dd, J = 9.6, 1.7 Hz, 1H), 5.70 (dd, J = 9.6, 4.7 Hz, 1H), 5.31 (d, J = 3.4 Hz, 1H), 5.03 (ddd, J = 5.3, 3.7, 1.7 Hz, 1H), 3.81 (s, 3H), 1.72 (s, 1H).

**13C-NMR (CDCl₃, 100 MHz):** δ ppm = 167.7, 138.2, 136.7, 134.1, 132.2, 131.5, 130.0, 129.8, 128.5, 128.4, 127.2, 124.2, 123.9, 123.5, 122.9, 118.6, 117.3, 109.6, 67.2, 51.3, 33.1.

**IR (neat):** νmax = 718, 764, 810, 995, 1088, 1173, 1219, 1381, 1543, 1605, 1713, 2924, 3024, 3472 (br) cm⁻¹.


[a]D²⁵ = +127.1°·cm²·g⁻¹ (c = 1.0, 93% ee, CHCl₃).

**HPLC:** Chiralpak AD-H, hexanes + 40% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm, retention times: 7.2 min, 11.4 min.
Ring opening product 52.3

\[
\begin{align*}
\text{H-NMR (CDCl}_3, 400 MHz): & \delta \text{ ppm } = 7.87 - 7.80 \text{ (m, 2H), 7.73 - 7.66 (m, 2H), 7.54 (d, } J = 8.4 \\
& \text{Hz, 1H), 7.45 (dt, } J = 8.0, 1.7 \text{ Hz, 2H), 7.42 - 7.35 (m, 2H), 7.35 - 7.24 \text{ (m, 2H), 7.02 (s, 1H),} \\
& 6.80 (dd, } J = 10.0, 3.0 \text{ Hz, 1H), 5.75 (dd, } J = 10.0, 2.4 \text{ Hz, 1H), 5.56 (dd, } J = 12.3, 6.4 \text{ Hz, 1H),} \\
& 5.17 (dt, } J = 12.8, 2.8 \text{ Hz, 1H), 3.81 (s, 3H), 1.65 (s, 1H).\end{align*}
\]

\[
\begin{align*}
\text{C-NMR (CDCl}_3, 100 MHz): & \delta \text{ ppm } = 168.7, 137.8, 136.7, 134.2, 132.3, 130.5, 129.5, 129.1, \\
& 128.3, 126.7, 126.5, 125.5, 125.2, 123.6, 123.4, 118.7, 117.8, 108.9, 71.9, 55.6, 33.1.\end{align*}
\]

\[
\begin{align*}
\text{IR (neat): } & \nu_{\text{max}} = 718, 810, 926, 1072, 1173, 1304, 1389, 1543, 2924, 3024, 3464 \text{ cm}^{-1}.\end{align*}
\]

\[
\begin{align*}
\text{HR-MS (EI): Calc. for } [M-H_2O]^+: 402.1368, \text{ found: 402.1365.} \\
[a]_D^{25} & = +173.1^\circ \cdot \text{cm}^2 \cdot \text{g} \quad (c = 1.0, 70\% \text{ ee, CHCl}_3). \\
\text{HPLC: Chiralpak AD-H, hexanes + 15\% 2-propanol, flow 1.0 ml/min, 220, 254, 280 nm,} \\
\text{retention times: 21.4 min, 56.1 min.} \end{align*}
\]
Appendix: Selected $^1$H and $^{13}$C NMR Spectra and X-Ray Crystallographic Data
ARO of 5,8-dihydro-5,8-epoxyquinoline
ARO of 5,8-dihydro-5,8-epoxyisoquinoline
ARO of 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline
ARO of 1-chloro-5,8-epoxy-5,8-dihydroisoquinoline
No text provided in the image.
ARO of 5-hydro-8-methyl-5,8-epoxyquinoline
ARO of 8-Hydro-5-methyl-5,8-epoxyquinoline N-Oxide
ARO of 5-Chloro-7,10-dihydro-7,10-epoxy-benzo[h]quinoline
ARO of 4,5-(bicycle[2.2.1]hept-5-ene)-1-methyl-3-phenyl-1H-indole
ORTEP Diagram of 21.8
Table 1. Crystal data and structure refinement for k0916.

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<td>Wavelength</td>
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<td>Space group</td>
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<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>b = 5.6946(2) Å, (\beta = 91.521(3)^\circ)</td>
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<td></td>
<td>c = 13.6545(10) Å, (\gamma = 90^\circ)</td>
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<td>Volume</td>
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<td>Density (calculated)</td>
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<td>Theta range for data collection</td>
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<td>Index ranges</td>
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<td>Completeness to theta = 27.49°</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F(^2)</td>
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<tr>
<td>Goodness-of-fit on F(^2)</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
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<td>Absolute structure parameter</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.268 and -0.411 e.Å(^{-3})</td>
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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for k0916. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

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<th>y</th>
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Table 3. Bond lengths [Å] and angles [°] for k0916.

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Symmetry transformations used to generate equivalent atoms:
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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^{-3}) for k0916.

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<th>U(eq)</th>
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<td>37</td>
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<td>1786</td>
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<td>H(8A)</td>
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<td>710</td>
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<td>H(10A)</td>
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<td>H(11B)</td>
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<td>3477</td>
<td>69</td>
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<tr>
<td>H(1O)</td>
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<td>3380(110)</td>
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Table 6. Hydrogen bonds for k0916 [Å and °].

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<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
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Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+1    #2 x,y-1,z
ORTEP Diagram of 22.8
Table 1. Crystal data and structure refinement for k0922.

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<td>β</td>
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<tr>
<td>γ</td>
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<td>Semi-empirical from equivalents</td>
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<td>Full-matrix least-squares on F²</td>
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Table 2. Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\AA^2 \times 10^3)\) for k0922. \(U(\text{eq})\) is defined as one third of the trace of the orthogonalized \(U^{ij}\) tensor.

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for k0922. The anisotropic displacement factor exponent takes the form: 
\[-2\pi² [ h² a² U^{11} + ... + 2 h k a* b* U^{12} ] \]

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Table 6. Hydrogen bonds for k0922 [Å and °].

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Symmetry transformations used to generate equivalent atoms:

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