DESIGN, SYNTHESIS AND EVALUATION OF CHIRAL AUXILIARIES, LIGANDS AND CATALYSTS FOR ASYMMETRIC SYNTHESIS

by

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ABSTRACT

A series of chiral acetals were prepared from 7-hydroxyindan-1-one and a variety of substituted chiral nonracemic C_2-symmetric 1,2-ethanediols [R = Me, Ph, CH_2OMe, CH_2OBn, $CH_2O(1\text{-Np})$, *i*-Pr] in an experimentally simple acid-catalyzed condensation reaction. These acetals were evaluated as chiral auxiliaries for use in asymmetric synthesis. Saturated and α,β-unsaturated substrates were attached to the chiral acetals and alkylation, cyclopropanation, 1,3-dipolar cycloaddition as well as Diels-Alder reactions were performed. A high degree of stereochemical induction was observed in the diethylaluminum chloride-promoted Diels-Alder reaction of an acrylate derivative (R = *i*-Pr) with cyclopentadiene (91:9 diastereomeric ratio). This result demonstrated that these acetals could serve as effective chiral directors in asymmetric synthesis.

A chiral bidentate 1,2-amino alcohol and several chiral tridentate Schiff bases were synthesized in one or two steps from the chiral auxiliary (R = Ph). These novel acetals were evaluated as chiral ligands in metal-catalyzed sulfoxidation, Diels-Alder and hetero Diels-Alder reactions as well as in alkylzinc addition reactions. The chromium(III)-complex of a tridentate Schiff base was found to catalyze the hetero Diels-Alder reaction of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene and benzaldehyde in good yield (88%) and enantioselectivity (74:26 enantiomeric ratio).

Heterocyclic analogs of the chiral acetals were also prepared for evaluation as chiral catalysts in a variety of asymmetric transformations. Chiral pyridine and *N,N*-pyrrolidinopyridine-derived acetals were synthesized in three and twelve steps, respectively. These chiral pyridine and substituted pyridine derivatives were evaluated as chiral catalysts in the kinetic resolution of a racemic secondary alcohol under a variety of reaction conditions. These structures were found to be ineffective catalysts in these asymmetric processes. The two chiral substituted pyridine derivatives (R = Me, Ph) were

examined in several other catalytic asymmetric reactions. A modest level of asymmetric induction was observed in the dihydroxylation reaction of (*E*)-stilbene involving catalytic quantities of both osmium tetroxide and the chiral substituted pyridine (R = Ph , 54:46 enantiomeric ratio).

In a related study, a series of chiral tetrahydroquinolines were synthesized by experimentally simple acid-catalyzed three-component imino Diels-Alder reactions of cyclopentadiene with substituted aldehydes and anilines. The racemic tetrahydroquinolines were resolved and the absolute stereochemical configurations were determined by X-ray crystallography. The chiral nonracemic tetrahydroquinolines were evaluated as secondary amine catalysts in the iminium ion-promoted Diels-Alder reaction of cinnamaldehyde and cyclopentadiene and good levels of stereochemical induction were observed (79:21 enantiomeric ratio).

DEDICATION

To my parents, Lois and Swaresh, and my brothers, Sacha and Anil.

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I would like to thank my mentor and friend, Pete Wilson.

He has taught me many things about chemistry... and much more.

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LIST OF ABBREVIATIONS

°	degree(s)
1D	one dimensional
^{13}C NMR	carbon nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
aq.	aqueous
Ac	acetate
acac	acetoacetate
AD	asymmetric dihydroxylation
Anal.	analytical
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
c	concentration
Calcd	calculated
CI	chemical ionization
COD	1,5-cyclooctadiene
COSY	^{1}H-^{1}H correlation NMR spectroscopy
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
D	deuterium
DA	Diels-Alder
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMSO	dimethylsulfoxide
$E^{\oplus}$	electrophile
ef	evaporative film
EI	electron impact
ent	enantiomer
equiv	equivalent(s)
er	enantiomeric ratio
Et	ethyl
ether	diethyl ether
EtOAc	ethyl acetate

FAB	fast atom bombardment
GC	gas chromatography
h	hour
HFIA	high resolution
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HR	high resolution
IR	infrared
J	coupling constant
MALDI-TOF	matrix-assisted laser desorption/ionization time-of-flight
MAO	methylalumoxane
Me	methyl
MeOH	methanol
min	minute
mL	milliliter
mol	mole(s)
MS	mass spectrometry
m/z	mass to charge ratio
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NOE	nuclear Overhauser effect
Np	naphthyl
[O]	oxidation
Ph	phenyl
pKa	acid dissociation constant
pp.	page(s)
p.s.i.	pounds per square inch
PPTS	pyridinium *p*-toluenesulfonate
PPY	4-pyrrolidinopyridine
rac	racemic
rel	relative stereochemical configuration
rt	room temperature
rxn.	reaction
$S_{Ar}E$	electrophilic aromatic substitution
$S_{Nu}Ar$	nucleophilic aromatic substitution
SOI	secondary orbital interactions
t	tertiary
TADDOL	α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol

TBME	*t*-butylmethyl ether
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
THQ	tetrahydroquinoline
TMS	trimethylsilyl
p-TsOH	*p*-toluenesulfonic acid
TS	transition state
UV	ultraviolet
wt.	weight

CHAPTER 1: INTRODUCTION

DESIGN, SYNTHESIS AND EVALUATION OF CHIRAL AUXILIARIES, LIGANDS AND CATALYSTS FOR ASYMMETRIC SYNTHESIS

1.1 General Overview

This thesis describes the design, synthesis and evaluation of 7-hydroxyindan-1-one-derived chiral acetals and their heterocyclic counterparts as chiral auxiliaries, chiral mono-, bi- and tridentate ligands and chiral catalysts for use in a variety of stoichiometric and catalytic asymmetric reactions. A series of chiral tetrahydroquinolines were synthesized, resolved and evaluated as secondary amine catalysts in the iminium ion-promoted Diels-Alder reaction. In all of the studies, experimentally simple and modular two- or three-component acid-catalyzed condensation reactions were employed. This allowed for a large number of different chiral auxiliaries and reagents to be prepared.

1.2 Asymmetric Synthesis

The development and evaluation of new chiral auxiliaries, ligands and catalysts for use in asymmetric synthesis is a central focus of modern synthetic organic chemistry. In 1971, Morrison and Mosher reviewed important studies in asymmetric synthesis compiling information from 850 research publications going back through the history of organic chemistry.[1] Over the next single decade, approximately the same number of reports pertaining to asymmetric synthesis could be found in the literature indicating that interest in this field was increasing.[2] Since the early 1980's, the study of asymmetric synthesis has intensified and as Ojima states: "the number of publications on asymmetric synthesis has been increasing exponentially every year."[2]

The total synthesis of natural products has served many roles through the history of organic chemistry.[3] This pursuit has played an important role in the structural assignment of compounds isolated from natural sources. It has provided, in some cases, access to practical quantities of these target compounds for biological and medical studies as well as a means to modify the structures that Nature has created. Natural product synthesis has also helped to reveal the underlying of principles of chemical reactivity. One facet is a greater understanding of the requisite structural features of reagents and substrates to achieve diastereoselective and enantioselective control in chemical reactions. The pursuit of natural product total syntheses has led to the development of new synthetic methods. In turn, the application of asymmetric synthetic methods to natural product synthesis has provided a testing ground and has allowed for the scope and limitations of particular methods to be evaluated.

Asymmetric synthesis, defined by Marckwald at the beginning of the 20th century as "reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active material but with the exclusion of all analytical processes", is not the only procedure by which chiral nonracemic compounds can be accessed.[4] The spontaneous crystallization of tartaric acid into enantiomorphous crystals allowed Pasteur to physically separate the racemate into its single enantiomers and dates back to the origins of the concept of chirality in chemistry.[5] More practically, many racemates can be resolved into their enantiomeric components by the formation of diastereomeric salts or derivatives with chiral nonracemic resolving agents.

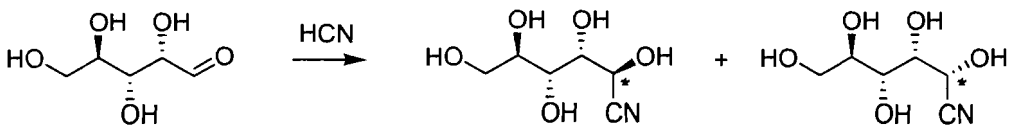
Nature can also provide compounds for the synthetic chemist in chiral nonracemic form. Many amino acids, carbohydrates and terpenes, which constitute the "chiral pool", have been used as chiral scaffolds around which complex chiral natural products have been prepared as single stereoisomers.[3] Chiral auxiliaries, ligands and catalysts have also

been synthesized from "chiral pool" precursors.[6,2] Isolated natural, chemically- and genetically-modified enzymes and bacteria have provided an extension to the natural source of chiral nonracemic compounds.[7] However, with some inspiration from Nature and the need to do what Nature is unable to do in many cases, synthetic chemists have devoted much effort to the development of stoichiometric and catalytic asymmetric methods. This has allowed for broad classes of compounds to be prepared, and, in the best case scenarios, as single stereoisomers. The modern requirement of the pharmaceutical industry illustrates the importance of asymmetric synthesis: the enantiomer of a chiral drug can be considered to be an impurity.[8]

1.3 Strategies for Asymmetric Induction: Substrate, Auxiliary and Reagent Control

The strategies for the creation of new stereogenic centres in molecules can be broadly grouped into three categories: (i) substrate control, (ii) auxiliary control and (iii) reagent control. In a substrate-controlled reaction, an asymmetric centre(s) in the reaction substrate directs the selective formation of a new stereogenic centre(s) during the chemical reaction with an achiral reagent. Substrate-controlled reactions lie at the origin of asymmetric synthesis. In 1890, Fischer observed that hydrogen cyanide added to D-arabinose **1** to form D-gluconononitrile diastereoselectively (**2**:**3** = 66:34) (Scheme 1.3.1).[9] The control of the relative stereochemical orientation of asymmetric centres in the racemic or enantioselective synthesis of natural products often relies upon existing chirality within the synthetic precursors and intermediates.

Scheme 1.3.1 Diastereoselective Addition of Hydrogen Cyanide to D-Arabinose



1 **2** **3**

The selective replacement of one prochiral substituent or the addition of a reagent (**NuH**) to a prochiral face of a molecule leads to the formation a new stereogenic centre (Figure 1.3.1). Stereogenic elements within a substrate (*i.e.* R or R^1 contain a stereogenic centre) render the prochiral substituents or faces diastereotopic and the reaction of the substrate with an achiral reagent can result in the preferential formation of one diastereomer of the product.

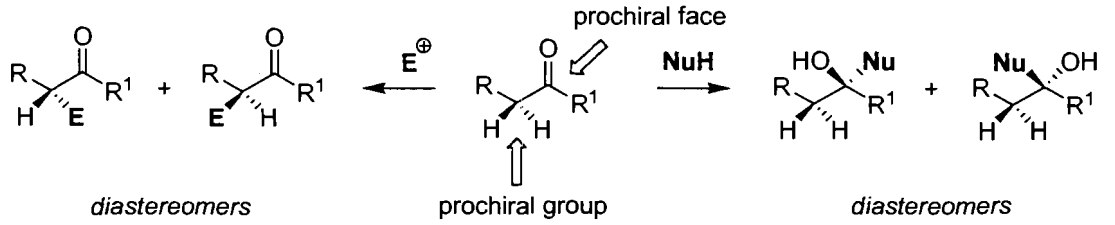


Figure 1.3.1 Selective formation of diastereomers in the reaction of prochiral groups and faces with achiral reagents.

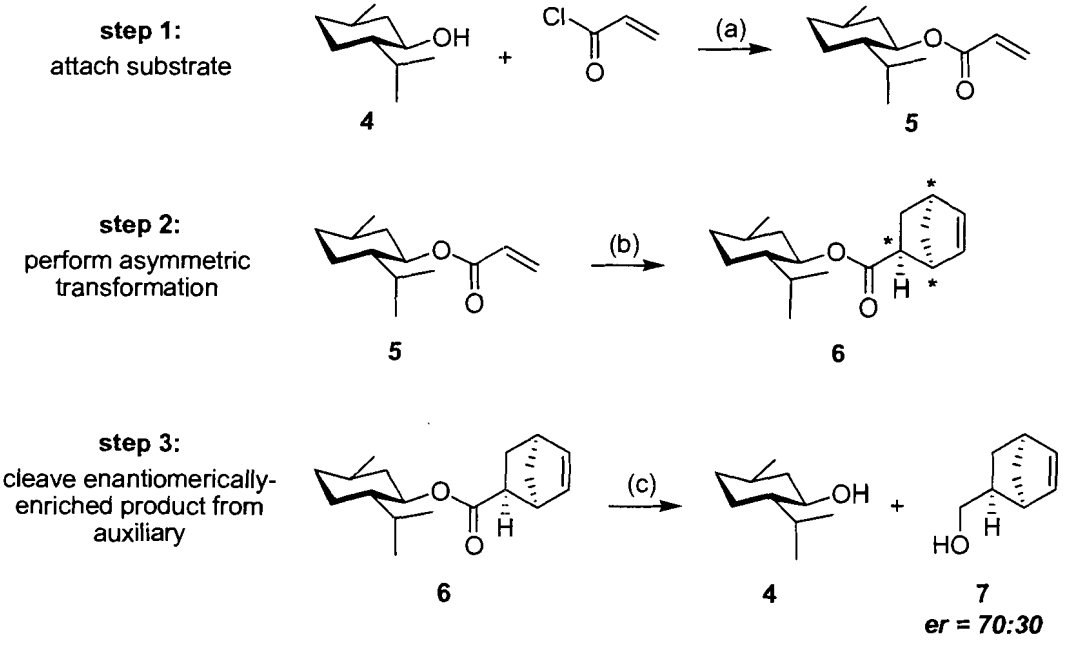
The advent of the chiral auxiliary approach to introduce chirality into organic compounds is more recent. This method involves the temporary covalent attachment of a chiral nonracemic compound to a substrate prior to the desired stereoselective chemical transformation. The temporary chiral environment imposed on the substrate by the auxiliary can result in the transfer of stereochemical information upon reaction with an achiral reagent. In the final step of the three-step reaction sequence, the chiral nonracemic product is removed from the chiral auxiliary. The auxiliary can be recovered for use in additional asymmetric transformations. For example, L-menthol **4** has been used as a chiral auxiliary in the asymmetric Lewis acid-promoted Diels-Alder reaction (Scheme 1.3.2).[10]

L-menthol was reacted with acryloyl chloride to afford the acrylate **5** that was then reacted with cyclopentadiene in the presence of the Lewis acid catalyst, tin tetrachloride, to form the cycloadduct **6** diastereoselectively (* indicates the new stereogenic centres that were formed). It is sometimes possible to remove the minor diastereomeric impurity

by chromatography or recrystallization at this stage. In this case, the crude reaction product was reduced with lithium aluminum hydride to afford the major *endo*-adduct **7**, as a mixture of enantiomers (70:30) and the L-menthol auxiliary.

Of note, the ester linkage is commonly used in chiral auxiliary chemistry because the chiral nonracemic products can be cleaved efficiently from the auxiliary by reduction and by acid- or base-catalyzed hydrolysis reactions. The chiral auxiliary approach adds two extra steps to a synthetic sequence; namely, attachment to the substrate and removal of the product from the auxiliary. However, the use of a chiral auxiliary can serve simultaneously to protect sensitive functional groups during the asymmetric transformation or during subsequent synthetic steps prior to its removal.

Scheme 1.3.2 L-Menthol as a Chiral Auxiliary in an Asymmetric Diels-Alder Reaction

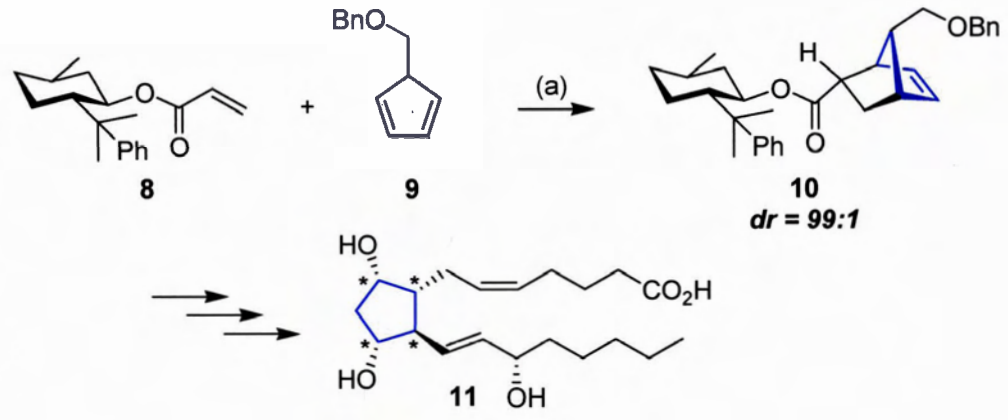


Reagents and conditions: (a) Et_3N, ether, reflux, 30 min, 85%. (b) $SnCl_4$ (1 equiv), toluene, cyclopentadiene, 3 to 8 °C, 45 min. (c) $LiAlH_4$, ether, 10 h, **7** (76% over two steps, *endo*:*exo* = 95:5).

The chiral auxiliary concept described above was adapted by Corey and co-workers as a key step in the asymmetric total synthesis of prostaglandin $F_{2\alpha}$ **11**

(Scheme 1.3.3).[11] Using the related chiral auxiliary, 8-phenylmenthol, an aluminum trichloride-promoted asymmetric Diels-Alder reaction of an acrylate **8** and a substituted cyclopentadiene **9** was performed. The resultant Diels-Alder *endo*-adduct **10** was isolated as a 99:1 mixture of diastereomers. The ability of the synthetic auxiliary, 8-phenylmenthol, to produce high diastereoselectivities in this reaction and others, has been attributed to the ability of the phenyl substituent to effectively shield one of the diastereotopic π-faces of the substrate.[12] In a series of subsequent synthetic steps, the chirality of the cycloadduct **10** was used to control the selective formation of the new stereogenic centres in the prostaglandin product **11** (* indicates the new stereogenic centres that were formed).

Scheme 1.3.3 The Use of 8-Phenylmenthol as a Chiral Auxiliary in the Asymmetric Synthesis of Prostaglandin $F_{2\alpha}$

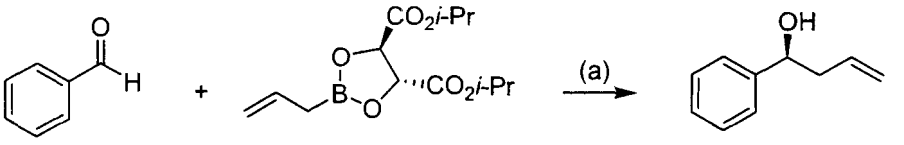


Reagents and conditions: (a) $AlCl_3$ (0.7 equiv), -55 °C, CH_2Cl_2, 1 h, 89%.

Chiral reagents can be subdivided into two types: chiral compounds used in a stoichiometric quantity and those used in a sub-stoichiometric quantity; namely, chiral catalysts and ligands. In this area of asymmetric synthesis, the selectivity in the formation of a new asymmetric centre in a chemical reaction is governed by the chiral reagent in its reaction with a prochiral substrate. For example, the reaction of a stoichiometric amount of the chiral boronate **12**, derived from (2*R*,3*R*)-diisopropyltartrate

and developed by Roush and co-workers, with benzaldehyde afforded the homoallylic alcohol **13** in 72% yield. The reaction was found to be highly enantioselective (er = 85:15).

Scheme 1.3.4 Stoichiometric Asymmetric Allylation Reaction of Benzaldehyde

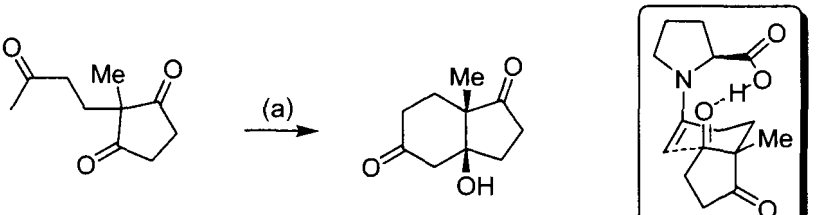


12 **13**
er = 85:15

Reagents and conditions: (a) toluene, -78 °C, 20 h, 78%.

Chiral catalysts can be defined as species that in the absence of other additives such as metal salts, promote an asymmetric transformation between a prochiral substrate and an achiral reagent. The chiral reagent, L-proline is a particularly interesting example as it has been found to catalyze a broad range of reactions with exceptional enantioselectivities. In 1974, L-proline was shown to be a highly effective metal-free chiral catalyst for the intramolecular aldol reaction of the triketone **14** (Scheme 1.3.5).[13]

Scheme 1.3.5 Proline-Catalyzed Asymmetric Intramolecular Aldol Reaction



14 **15** **16**
er = 96:4

Reagents and conditions: (a) L-proline (3 mol %), CH_3CN, rt, 6 days, 100%.

The bicyclic aldol product **15** was formed from the achiral triketone precursor **14** in quantitative yield and in excellent enantioselectivity (er = 96:4). L-proline has been postulated to act as a bifunctional catalyst and Bahmanyar and Houk have proposed the transition state **16** based upon theoretical studies.[14,15] Similar transition states and

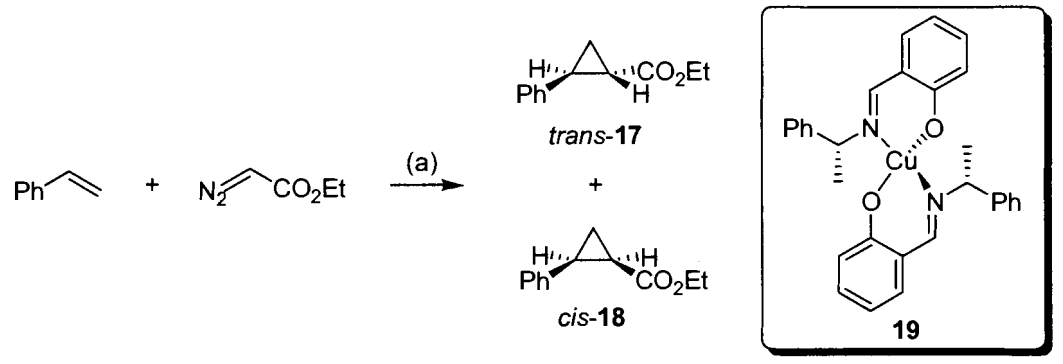
reaction mechanisms have been invoked to rationalize the stereochemical outcome of other L-proline-catalyzed reactions.[16] In this proposed mechanism, condensation of L-proline with the acyclic ketone affords the enamine **16**. The enamine then reacts nucleophilically with one of the cyclic ketone moieties, which is activated through the formation of an intramolecular hydrogen bond with the carboxylate group of L-proline. Only recently has the potential of L-proline been realized.[17] It has been used to catalyze a variety of asymmetric reactions such as intermolecular aldol reactions and Mannich reactions in high enantioselectivities. The use of L-proline and other secondary amines as well as tertiary amines and phosphines, to promote reactions has been termed "organocatalysis" because these structures do not contain metallic elements.[18]

Metal complexes generated from chiral ligands can be used to catalyze the asymmetric reactions of achiral substrates. Asymmetric induction occurs when the substrate and/or reagent interacts with the chiral metal complex during the chemical transformation. Through the 1990's to the present day, the vast majority of work in the field of asymmetric synthesis has involved the preparation of chiral ligands for use in metal-catalyzed reactions.[2] Chiral catalysts and ligands have certain advantages over chiral auxiliaries and stoichiometric chiral reagents. In particular, they can reduce the total number of steps by two as compared to the auxiliary approach. As well, their use can reduce the quantities of the chiral nonracemic material needed to facilitate a given asymmetric process.

In 1966, Nozaki and co-workers reported the first example of the use of a chiral metal complex in asymmetric synthesis.[19] The copper complex **19** of a chiral bidentate ligand, which was derived from salicylaldehyde and (*R*)-α-phenylethylamine, was found to catalyze the reaction of styrene and ethyl diazoacetate to form the diastereomeric *trans*- and *cis*-cyclopropanes, albeit in low enantioselectivity (*trans*-**17**, er = 53:47; *cis*-**18**, er = 53:47, Scheme 1.3.6). The copper complex **19** presumably reacts with the

diazoester to form a copper-carbenoid complex which then reacts with styrene. Thereby, the copper complex **19** is regenerated for re-entry into the catalytic cycle.

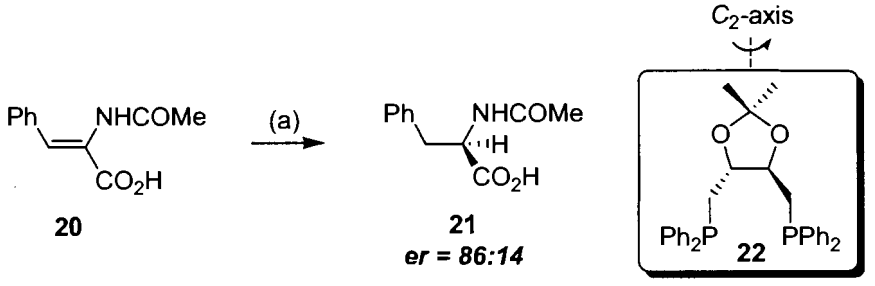
Scheme 1.3.6 The First Metal-Catalyzed Asymmetric Reaction: A Copper(I)-Catalyzed Cyclopropanation Reaction



Reagents and conditions: (a) complex **19** (*cat.*), 58-60 °C, 72% (combined yield, *trans*:*cis* = 70:30).

Kagan and Dang's work in the field of metal-catalyzed asymmetric synthesis is pioneering for several reasons.[20] The bidentate phosphine ligand, DIOP **22**, was the first chiral ligand to show high levels of stereochemical induction in a catalytic process (Scheme 1.3.1).

Scheme 1.3.7 Asymmetric Hydrogenation Reaction of *N*-Acetylaminoacrylic Acid **21**

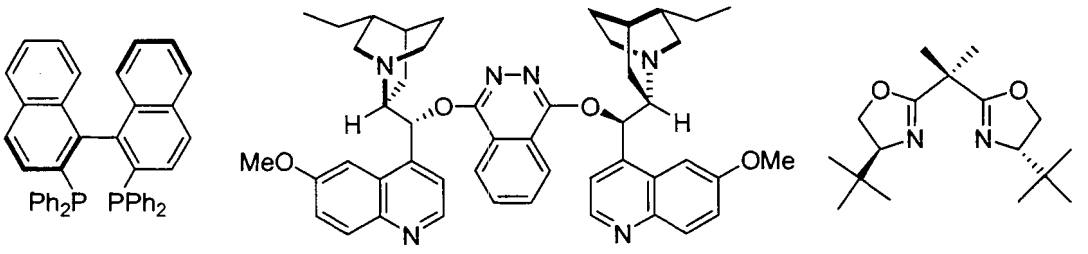


Reagents and conditions: (a) H_2, $[RhCl(COD)_2]_2$ (0.2 mol %), phosphine **22** (0.2 mol %), EtOH:benzene (4:1), rt, 95%.

A chiral rhodium complex, formed between the phosphine **22** and a rhodium(I) source, efficiently catalyzed the asymmetric hydrogenation reaction of *N*-acetylaminoacrylic acid **20** to form the D-phenylalanine derivative **21**. These studies

showed that bidentate (phosphine) ligands were more catalytically active and granted higher levels of asymmetric induction than their monodentate counterparts. Kagan and Dang incorporated a C_2-axis of symmetry into the phosphine ligand **22** which has been shown to be intimately linked to the high levels of stereochemical induction that this structure could impart.

Since the pioneering studies of Nozaki and Kagan, the field of chiral metal complex-catalyzed asymmetric synthesis has evolved into a sophisticated technology. In 1985, Noyori and co-workers developed the chiral diphosphine ligand **23** (BINAP) for use in ruthenium-catalyzed asymmetric hydrogenation reactions (Figure 1.3.2).[21] The cinchona alkaloid-based ligand, quinidine derivative **24**, reported by Sharpless and co-workers in 1991, remains as the most broadly applicable structure for osmium-catalyzed asymmetric dihydroxylation reactions.[22] The bis(oxazoline) **25**, readily synthesized from a chiral 1,2-amino alcohol, was described by Evans and co-workers in 1991 for use in the copper-catalyzed cyclopropanation reaction.[23] These chiral ligands are able to impart high levels of asymmetric induction (er > 95:5) in reactions involving a wide range of substrates. Of note, these three structurally-diverse ligands share a common element: they are all C_2-symmetric.



23 *hydrogenations* **24** *dihydroxylations* **25** *cyclopropanations*

Figure 1.3.2 Phosphine, quinidine and oxazoline ligands for use in metal-catalyzed asymmetric synthesis.

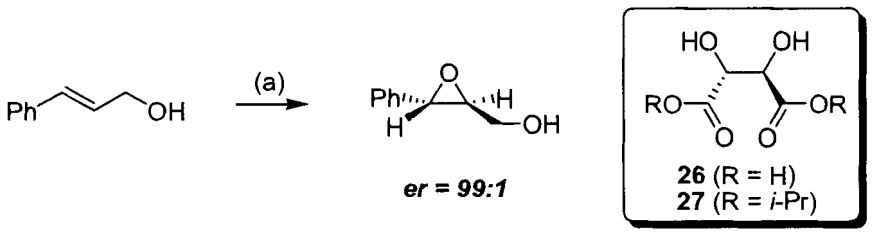
1.4 C_2-Symmetry in Chiral Auxiliary and Reagent Design

Whitesell states: "it might appear that the introduction of a symmetry element within a chiral auxiliary would be antithetical to the stated objective of achieving stereochemical induction in a chemical transformation".[24] However, the introduction of a two-fold (or higher) axis of symmetry into a chiral ligand can reduce the number of competing diastereomeric transition states in an asymmetric process and, thus, afford higher levels of asymmetric induction. As well, the stereochemical outcome of a reaction involving a C_2-symmetric chiral ligand is often easier to rationalize or predict.

1.4.1 Chiral C_2-Symmetric 1,2-Diols

Chiral C_2-symmetric 1,2-diols have received much attention mainly due to the ease with which a variety of structures can be prepared from tartaric acid **26** (R = H), which is commercially available in both enantiomeric forms (Scheme 1.4.1). Chiral C_2-symmetric 1,2-diols have been used directly as chiral auxiliaries and ligands.[6,2] As well, they have served as building blocks to construct further chiral auxiliaries and reagents. The Sharpless asymmetric epoxidation exemplifies the use a chiral 1,2-diol in asymmetric synthesis. The diisopropylester **27** of (2*R*,3*R*)-tartaric acid forms a catalytic species upon reaction with titanium(IV) isopropoxide which has the ability to epoxidize allylic alcohols, using *t*-butyl hydroperoxide as an achiral co-oxidant, in high yields and enantioselectivities (Scheme 1.4.1).[25]

Scheme 1.4.1 Sharpless Catalytic Asymmetric Epoxidation Reaction of an Allylic Alcohol



Reagents and conditions: (a) Ti(*i*-OPr)$_4$ (5 mol %), tartrate **27** (R = *i*-Pr, 7.5 mol %), *t*-BuOOH (2 equiv), 4 Å molecular sieves, -20 °C, CH_2Cl_2, 3 h, 89%.

Seebach's tetraaryl diols **28** are a further example of the use of a group of C_2-symmetric diols that are readily derived from tartaric acid using simple Grignard chemistry. These compounds have been used extensively in catalytic and stoichiometric asymmetric synthesis (Figure 1.4.1).[26] The C_2-symmetric 1,2-diol, (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29**, has also been prepared and used as a chiral ligand in, for example, the titanium(IV) isopropoxide-catalyzed oxidation of sulfides.[27] Moreover, the diol **29** can be readily prepared in both enantiomeric forms *via* the Sharpless asymmetric dihydroxylation reaction of (*E*)-stilbene.[28]

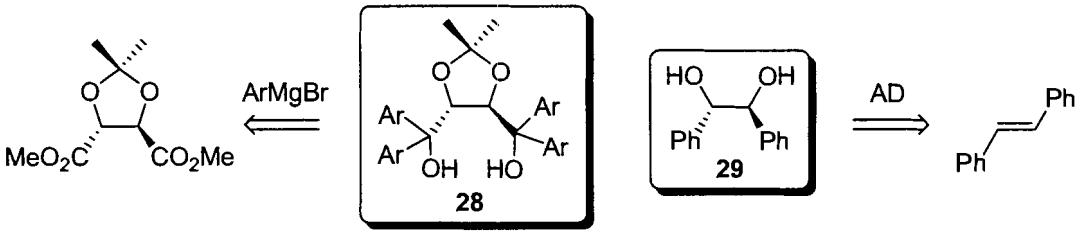
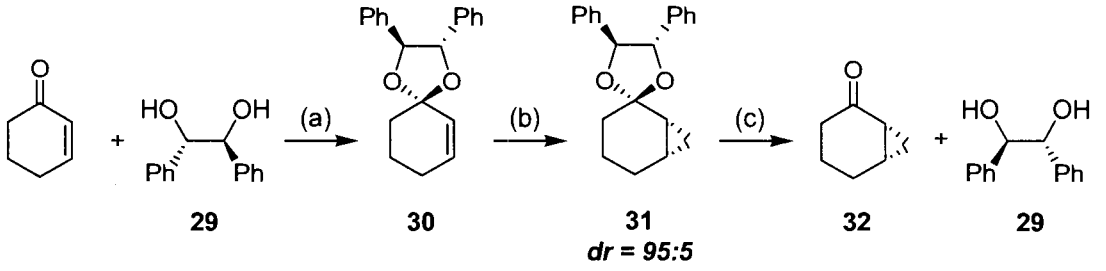


Figure 1.4.1 Chiral C_2-symmetric 1,2-diols for use in asymmetric synthesis (from natural and unnatural sources).

Mash and co-workers used the diol **29** as a chiral auxiliary and attached it to 2-cyclohexen-1-one *via* an acid-catalyzed condensation reaction, which formed the chiral cyclic acetal **30**. This acetal was then subjected to a highly diastereoselective Simmons-Smith reaction to afford the tricyclic adduct **31** (Scheme 1.4.2).[29] The cyclopropane product **32**, in turn, could be cleaved from the diol auxiliary **29** in an acid-catalyzed hydrolysis reaction and both were recovered in good yield. Of note, the chiral auxiliary **29** provided simultaneous protection of the ketone moiety while also modifying the reactivity of the substrate: the achiral electron-deficient enone precursor was unreactive in the Simmons-Smith cyclopropanation reaction while the more-electron rich acetal readily reacted.

Scheme 1.4.2 Asymmetric Cyclopropanation Reaction Using the Chiral C_2-Symmetric Diol **29** as a Chiral Auxiliary



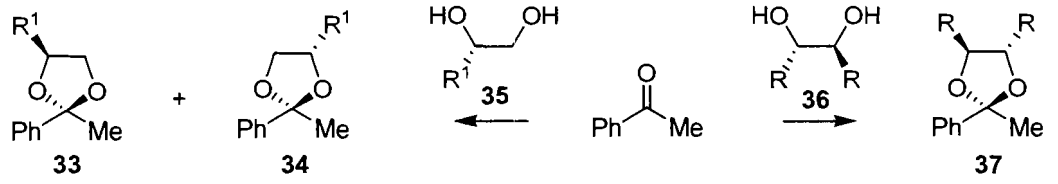
Reagents and conditions: (a) PPTS, benzene, reflux, 87%. (b) CH_2I_2, Zn/Cu couple, ether, rt, 90%. (c) HCl, MeOH, rt, 1.5 h, **32** (75%), **29** (90%).

1.5 Chiral Cyclic Acetals in Asymmetric Synthesis

Cyclic acetals can be formed in a simple acid-catalyzed condensation reaction of an aldehyde or ketone and a 1,2- or 1,3-diol. The resultant 1,3-dioxolane and 1,3-dioxane heterocycles are stable under a variety of reaction conditions and, thus, have served as common protecting groups for the aldehyde and ketone functional groups.[30] More recently, chiral cyclic acetals have found use in synthetic chemistry for the preparation of a variety of chiral nonracemic compounds.[31] For example, in the presence of strong Lewis acids, chiral cyclic acetals can be ring-opened with nucleophiles.[32] As well, chiral cyclic acetals have been installed in proximity to prochiral centres to direct subsequent asymmetric transformations.

The use of chiral nonracemic C_2-symmetric 1,2-diols **36** to prepare cyclic acetals ensures that only a single diastereomer **37** is produced in the condensation reaction with an unsymmetrical ketone (*e.g.* acetophenone, Scheme 1.5.1). The use of an unsymmetrical diol **35** results in the formation of a diastereomeric mixture of acetals **33** and **34**.

Scheme 1.5.1 Unsymmetrical and C_2-Symmetrical 1,2-Diols in Condensation Reactions with a Ketone



It has been stated that, "the rigid stereochemistry characterizing the heterocyclic acetal ring" is an important feature of the acetal functional group.[33] Thus, the acetal subunit has the ability to provide conformational constraint within a substrate or reagent and reduce the number of competing diastereomeric transition states in an asymmetric transformation. For example, the isopropylidene acetal subunit of Seebach's TADDOLs **28** forces the two diarylcarbinol substituents into a rigid and proximal relationship (see: Figure 1.4.1). The pre-organization imparted by the acetal moiety in the TADDOLs has an added effect: the entropic barrier in the chelation process with a metal centre is reduced.[34] Rate enhancements have also been observed as a result of the restricted geometry that an acetal moiety can impose. In a "tether-controlled" intramolecular Diels-Alder reaction, both *trans*- and *cis*-isopropylidene acetals have been found to increase the rate of the reaction by orienting the diene and dienophile in a reactive conformation.[35] As Nógradí states, "perhaps influenced by the knowledge of how enzymes work, it slowly became clear that for high stereoselectivity it was necessary to immobilize the substrate in a suitable conformation".[36] Chiral cyclic acetal subunits can satisfy this important issue.

1.6 Proposed Studies: Indan-1-one Derived Cyclic Acetals for Use as Chiral Auxiliaries, Ligands and Catalysts in Asymmetric Synthesis

The goal of this research project was to prepare and evaluate a series of chiral cyclic acetals **38**, which represent a general class of chiral auxiliaries, ligands and catalysts (Figure 1.6.1). Using the achiral parent ketones **39** and chiral C_2-symmetric

diols **36** as synthetic precursors, a structurally diverse series of novel chiral auxiliaries and reagents could be prepared by experimentally simple acid-catalyzed condensation reactions. The fused bicyclic ketones **39** incorporate a site **X** at which a substrate could be attached, in the case of a chiral auxiliary, or to which a metal could bind, in the case of a chiral ligand. The position **X** of the chiral cyclic acetals could also serve as a catalytic site.

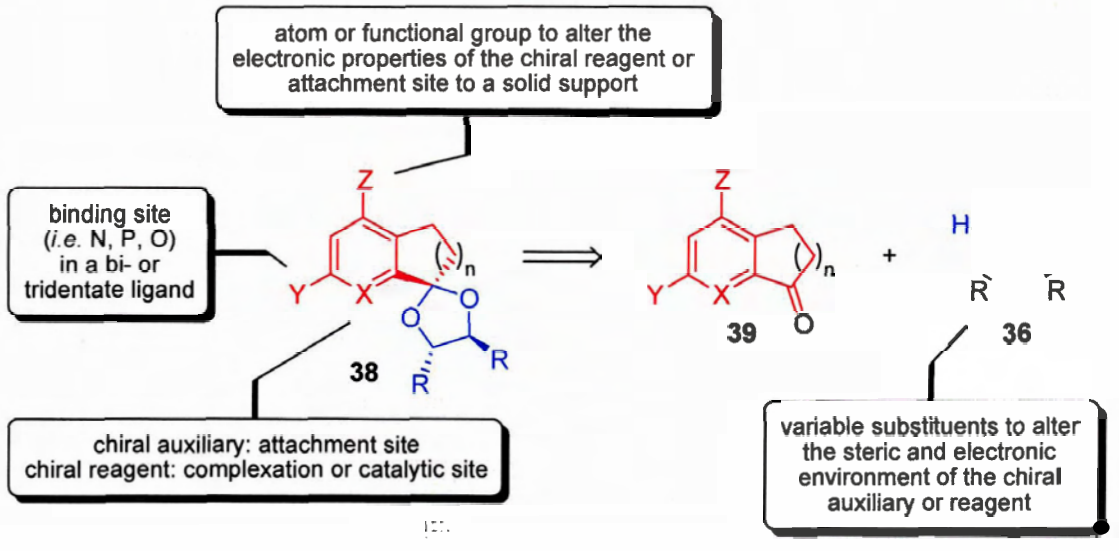


Figure 1.6.1 7-Hydroxyindan-1-one-derived chiral auxiliaries, ligands and catalysts.

The spiro ring junction inherent to cyclic acetals prepared from cyclic ketones necessitates that the planes of the ketone and diol portions of the auxiliary/reagent **38** are in an approximately orthogonal arrangement. One of the two substituents of the acetal (**R**) is oriented such that it would occupy the "interior" region of the acetal. This effectively shields one diastereotopic face of the auxiliary/reagent **38**. The steric and electronic environment imposed by the substituents (**R**) of the acetals **38** could be varied by condensing a variety of chiral C_2-symmetric 1,2-diols with the ketone **39**. The substituent **Z** could be introduced into certain structures, particularly chiral ligands and catalysts, so that their catalytic activity could be modified. As well, the acetal **38** could be attached to a solid support at this site. The site **Y** could be introduced as an additional

coordination site so that chiral polydentate ligands could be constructed.

1.7 Proposed Studies: Chiral Tetrahydroquinolines as Secondary Amine Catalysts

An additional study involving the use of tetrahydroquinolines as chiral catalysts was also considered. The chiral tetrahydroquinolines **43** were targeted because they represent a rigid template and a variety of structures should be available using the experimentally simple acid-catalyzed imino Diels-Alder reaction of anilines **42**, aldehydes **41** and alkenes **40**. In similarity to the chiral acetals **38**, the modular nature of the synthesis, in which three simple components could be varied to produce diversity, would allow for the structure of the catalyst to be optimized.

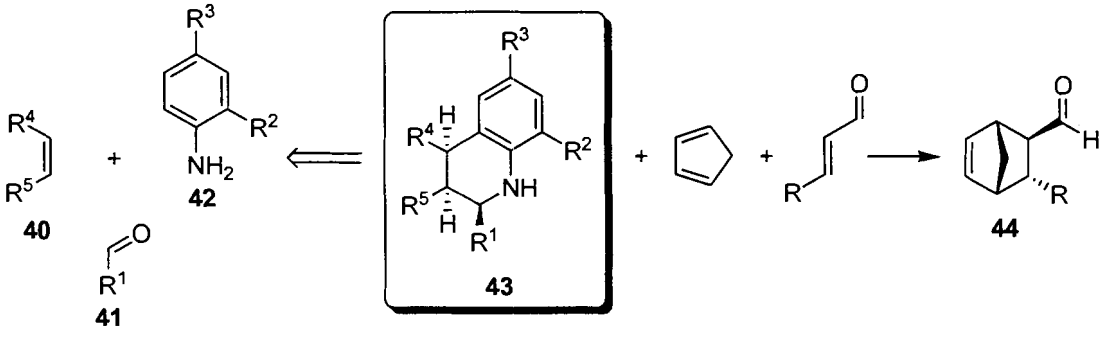


Figure 1.7.1 Modular synthesis of chiral tetrahydroquinolines and their use in the iminium ion-promoted Diels-Alder reaction.

The racemic synthesis and resolution of several tetrahydroquinolines **43** was proposed. These chiral nonracemic tetrahydroquinolines **43** would be evaluated as chiral secondary-amine catalysts in the iminium ion-promoted Diels-Alder reaction of α,β-unsaturated aldehydes and cyclopentadiene to afford the cycloadducts **44**.

1.8 Thesis Overview

In *Chapter 2*, the synthesis of 7-hydroxyindan-1-one-derived chiral auxiliaries prepared from six C_2-symmetric 1,2-diols is described. These auxiliaries were evaluated in asymmetric alkylation, cyclopropanation, 1,3-dipolar cycloaddition and Diels-Alder

reactions. Of these reactions, the Diels-Alder reaction was studied in most detail. The substituents of the chiral acetal subunit were varied to determine their effect on the diastereoselectivities of each reaction.

In *Chapter 3*, a 7-hydroxyindan-1-one derived chiral auxiliary was used as a precursor to prepare several chiral ligands. Two classes of chiral ligands, bidentate 1,3-amino alcohols and tridentate Schiff bases, were synthesized in one or two steps. Each class of ligand was evaluated in two metal-catalyzed asymmetric reactions.

In *Chapter 4*, the synthesis of chiral pyridines and pyrrolidinopyridines based upon the general chiral acetal **38** is described. These structures were evaluated primarily as chiral (nucleophilic) catalysts for use in the kinetic resolution of a racemic secondary alcohol. The pyrrolidinopyridine was also examined as a potential chiral general acid and base catalyst as well as a chiral monodentate ligand in two metal-catalyzed reactions.

In *Chapter 5*, the synthesis of a series of racemic tetrahydroquinolines is described. These compounds were resolved with a chiral nonracemic L-proline derivative and their absolute stereochemical configurations were assigned by X-ray crystallography. The chiral nonracemic tetrahydroquinolines were examined as metal-free secondary amine catalysts in the iminium ion-promoted Diels-Alder reaction of cinnamaldehyde and cyclopentadiene.

In *Chapter 6*, a general conclusion of the results obtained in this thesis is provided.

In *Chapter 7*, experimental procedures and characterization data for all compounds that were prepared is detailed. In addition, an *Appendix* is provided that lists experimental procedures and tables of bond lengths and angles for the X-ray crystallographic analysis studies.

CHAPTER 2: RESULTS AND DISCUSSION

THE SYNTHESIS AND EVALUATION OF 7-HYDROXYINDAN-1-ONE-DERIVED CYCLIC ACETALS FOR USE AS CHIRAL AUXILIARIES IN ASYMMETRIC SYNTHESIS

2.1 Introduction

In this chapter, the synthesis of a series of chiral auxiliaries **45** based upon the general chiral acetal structure **38** is described. The chiral auxiliary structure **45** incorporated a phenol moiety at the site **X** of the general structure **38** to serve as a site at which substrates could be covalently attached *via* an ester or ether linkage. The synthesis of the chiral auxiliaries **45** involved an acid-catalyzed condensation reaction of 7-hydroxyindan-1-one **46** and a variety of chiral nonracemic 1,2-diols **36** (Figure 2.1.1).

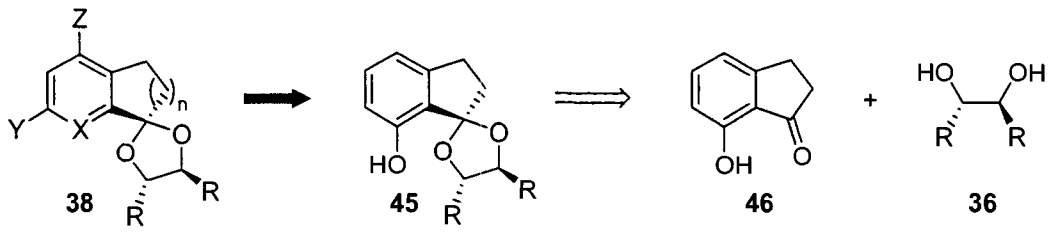


Figure 2.1.1 7-Hydroxyindan-1-one-derived chiral auxiliaries **45**.

A series of structurally distinct chiral auxiliaries were prepared, in which the substituents (R) of the chiral 1,2-diol **36** were varied. Substituents of different size were selected to determine the optimum steric environment of the chiral auxiliary that was required for high levels of stereochemical induction. As well, diol substituents that contained heteroatoms or aromatic groups were selected to allow for the possibility of chelation control or π-π-interactions to be exploited.

The series of auxiliaries were screened in a variety of reaction types, each involving a series of substrates, in order to provide further insight into the important structural features of the chiral auxiliaries as well as to determine the versatility of these

structures. Saturated substrates **47** of the 7-hydroxyindan-1-one-derived auxiliaries were prepared and these substrates were subjected to alkylation reactions (Figure 2.1.2). As well, α,β-unsaturated substrates **49** were synthesized and a variety of cycloaddition reactions such as the Diels-Alder reaction were performed. The respective alkylation and cycloaddition products **48** and **50** were hydrolyzed to determine the stereochemical outcome of these reactions and to recover the chiral auxiliaries **45** for further use.

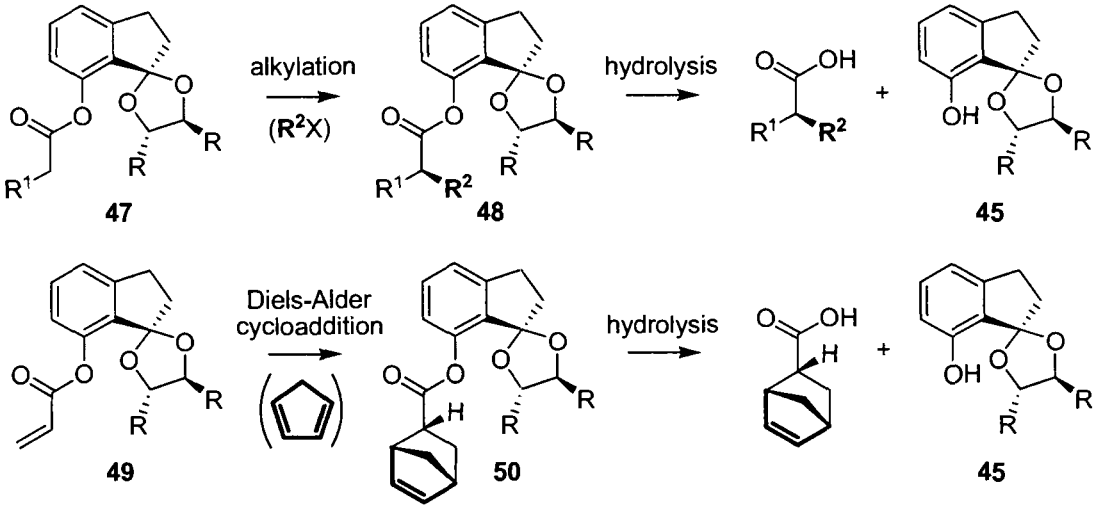
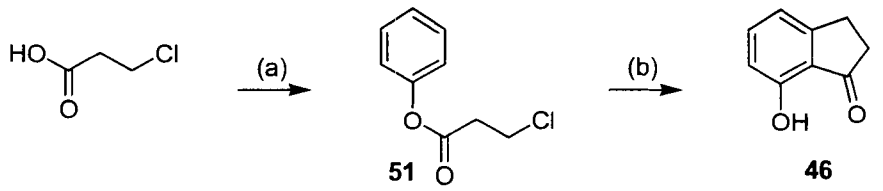


Figure 2.1.2 Alkylation and Diels-Alder cycloaddition reactions of saturated and α,β-unsaturated substrates **47** and **49**.

2.2 Synthesis of 7-Hydroxyindan-1-one (46)

7-Hydroxyindan-1-one **46** was prepared in multi-gram quantities using a three-step sequence following literature procedures (Scheme 2.2.1).[37] 3-Chloropropanoic acid was converted to the phenyl ester **51**, which was heated with aluminum trichloride to afford 7-hydroxyindan-1-one **46**. The product was isolated by direct steam distillation from the reaction flask and obtained as a pale yellow crystalline solid of adequate purity for subsequent use. Recrystallization of the indanone **46** following steam distillation afforded material that was analytically pure. In the ^{1}H NMR spectrum of the indanone **46**, as a result of intramolecular hydrogen bonding, the signal for the phenolic hydrogen was a sharp singlet at δ 9.1 ppm.

Scheme 2.2.1 Synthesis of 7-Hydroxyindan-1-one **46**



Reagents and conditions: (a) PCl_3, 110-120 °C, 3 h; phenol, toluene, reflux, 3 h, 54%. (b) $AlCl_3$, 90-100 °C, 3 h; 100-180 °C, 4 h; 180 °C, 1 h, 41%.

The formation of 7-hydroxyindan-1-one **46** from the phenyl ester **51** involved a tandem Fries rearrangement and Friedel-Crafts alkylation reaction.[38] The mechanism involves coordination of aluminum trichloride to the carbonyl oxygen of the ester **51** followed by migration of the activated acyl group onto the aromatic ring (Figure 2.2.1). Subsequently, an intramolecular Friedel-Crafts alkylation reaction, again facilitated by the Lewis acid, installs the aliphatic ring of 7-hydroxyindan-1-one **46**.

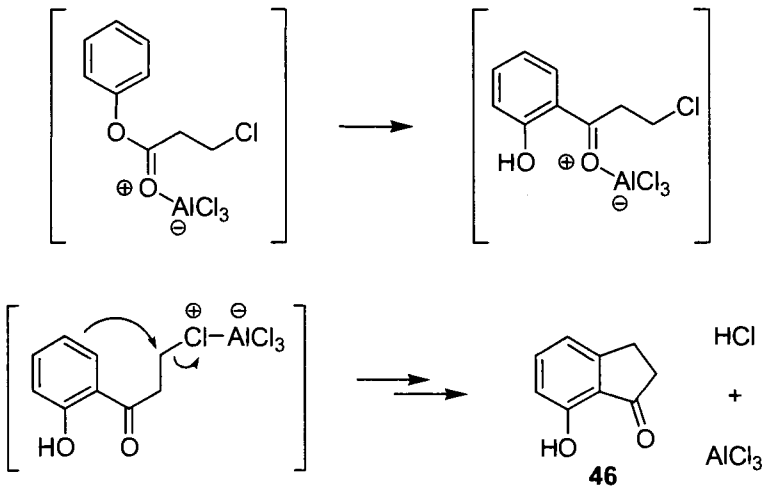


Figure 2.2.1 Mechanism of the tandem Fries/Friedel-Crafts reaction to form 7-hydroxyindan-1-one **46**.

2.3 Chiral C_2-Symmetric 1,2-Diols

A variety of C_2-symmetric chiral 1,2-diols are commercially-available or easily prepared from inexpensive chiral nonracemic precursors (Figure 2.3.1). The diols

52 (R = Me) and **29** (R = Ph)* are commercially-available in both enantiomeric forms and the enantiomers shown were purchased. The remaining four diols **53** (R = CH_2OMe), **54** (R = CH_2OBn), **55** [R = CH_2O(1-Np)] and **56** (R = *i*-Pr) were prepared from (2*R*,3*R*)-(+)-tartaric acid by short known syntheses that were divergent (*i.e.* a key intermediate could be converted into several of the diols) and were amenable to large-scale synthesis.[39, ,31]

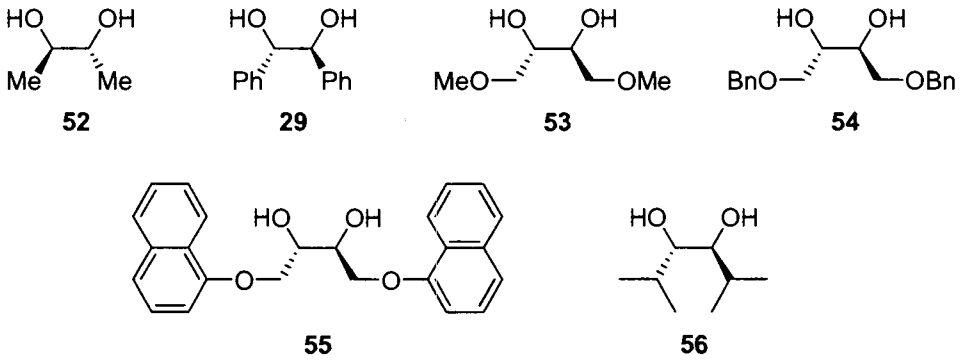


Figure 2.3.1 Chiral C_2-symmetric 1,2-diols.

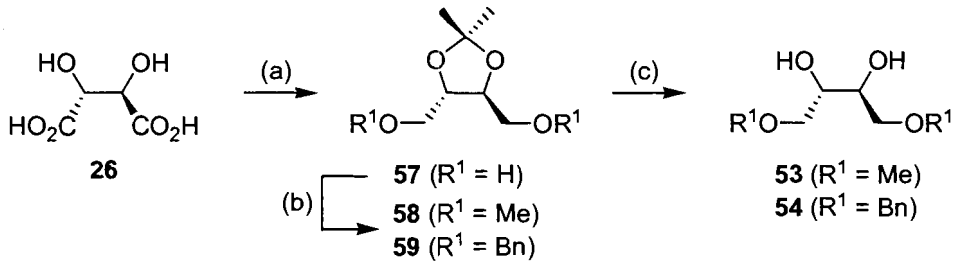
(+)-Tartaric acid **26** was reacted with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid which protected the 1,2-diol function as an isopropylidene acetal (Scheme 2.3.1).[40] This also converted the carboxylic acid groups into their methyl esters. The resultant diester was then reduced with lithium aluminum hydride to afford the diol **57**†, which was alkylated with either methyl iodide or benzyl bromide using sodium hydride as a base to afford the diethers **58** and **59**. Finally, the diethers **58** and **59** were deprotected in a hydrochloric acid-catalyzed hydrolysis reaction

* Initially, when the diol **29** (R = Ph) was unavailable from a commercial source, it was prepared in the Sharpless asymmetric dihydroxylation reaction of (*E*)-stilbene (Chapter 7: Experimental Section).

† Not optimized.

to afford the desired 1,2 diols **53** ($R^1 = CH_2OMe$) and **54** ($R^1 = CH_2OBn$).*

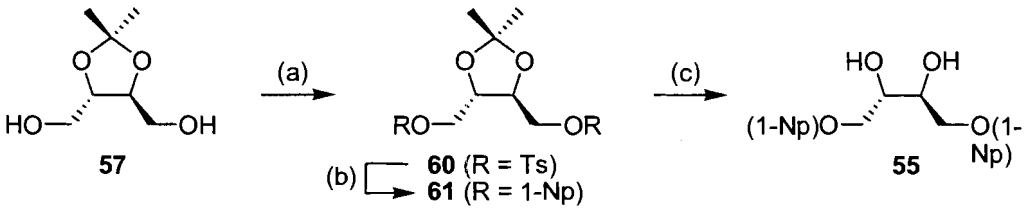
Scheme 2.3.1 Synthesis of (2*S*,3*S*)-Dimethoxy- and Dibenzyloxy-2,3-Butanediols **53** and **54**



Reagents and conditions: (a) (i) 2,2-dimethoxypropane, *p*-TsOH, MeOH, cyclohexane, reflux, 2 days, 78%. (ii) $LiAlH_4$, ether, rt, 3 h; reflux, 3 h, 24%. (b) NaH, MeI *or* BnBr, THF, rt, 18 to 19 h. (c) 1 M HCl, MeOH, 2 h, 9%, **53** (R^1 = Me), 64%, **54** (R^1 = Bn).

To prepare the 1-naphthyl substituted diol **55**, the protected diol **57** was reacted with *p*-toluenesulfonyl chloride and the resultant tosylate **60** was converted to the protected diether **61** upon reaction with the sodium salt of 1-naphthol.[41] The acetal moiety was then deprotected in a hydrochloric acid-catalyzed hydrolysis reaction to afford the diol **55**. (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol was prepared in our laboratory by Mr. Michael P. A. Lyle in a six-step sequence from the diethyl ester of (+)-tartaric acid.[42]

Scheme 2.3.2 Synthesis of (2*S*,3*S*)-Bis(1-Naphthyloxy)-2,3-Butanediol **55**



Reagents and conditions: (a) *p*-toluenesulfonyl chloride, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 16 h, 42%. (b) 1-naphthol, DMF, NaH, 0 °C to rt, 1.5 h; ditosylate **60**, DMF, rt, 40 h. (c) HCl, EtOH:water (1:1), reflux, 16 h, 58% (over two steps).

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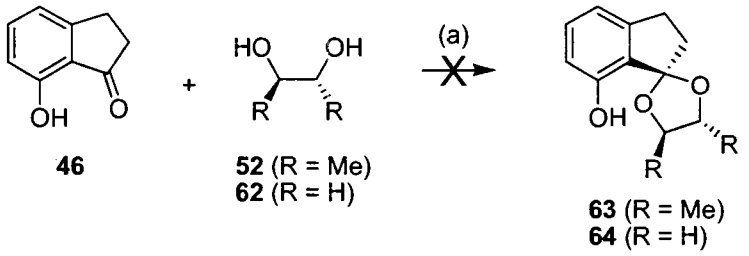
* The yield for the hydrolysis reaction leading to the diol **53** (R = CH_2OMe) was particularly low. However, sufficient quantities of material for this study were produced; therefore, efforts to optimize the reaction were not undertaken. It is postulated that the diol product was relatively volatile and steam distilled from the aqueous reaction mixture during the reaction or workup step (see: Chapter 7: Experimental Section).

2.4 Synthesis of 7-Hydroxyindan-1-one-Derived Chiral Auxiliaries

The direct synthesis of the chiral auxiliary **63** (R = Me) by an acid-catalyzed condensation reaction of 7-hydroxyindan-1-one **46** and (2*R*,3*R*)-2,3-butanediol **52** was unsuccessful: no condensation product was observed after several days at reflux in either benzene or toluene (Scheme 2.4.1). To determine if this was a steric phenomenon, an attempted condensation reaction of the indanone **46** and 1,2-ethanediol **62** (R = H) was performed under *p*-toluenesulfonic acid-catalysis. However, the condensation product **64** was not formed.

Scheme 2.4.1 Attempted Condensation Reactions of 7-Hydroxyindan-1-one **46** and Diols **62** (R = H) and **52** (R = Me)

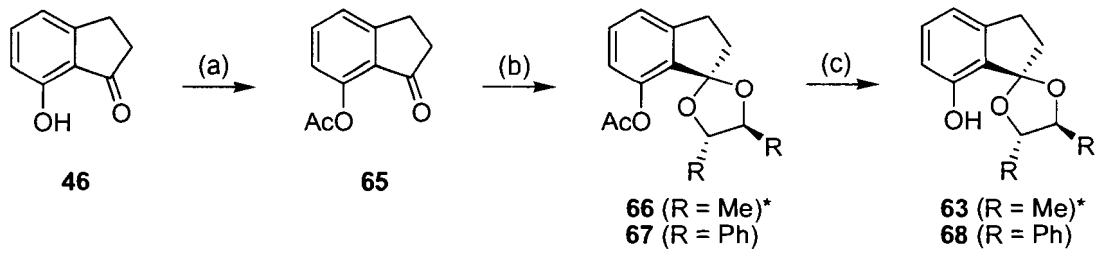


46 **52** (R = Me) **62** (R = H) **63** (R = Me) **64** (R = H)

Reagents and conditions: (a) (2*R*,3*R*)-2,3-butanediol *or* 1,2-ethanediol, *p*-TsOH, benzene *or* toluene, reflux, 6 h to 3 days.

Therefore, 7-hydroxyindan-1-one was protected by reaction with acetyl chloride and triethylamine to form the acetate **65** (Scheme 2.4.2). The acetate **65** reacted readily with (2*R*,3*R*)-2,3-butanediol **52** and (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29** under *p*-toluenesulfonic acid-catalysis to form the acetals **66** (R = Me) and **67** (R = Ph) in excellent yield.

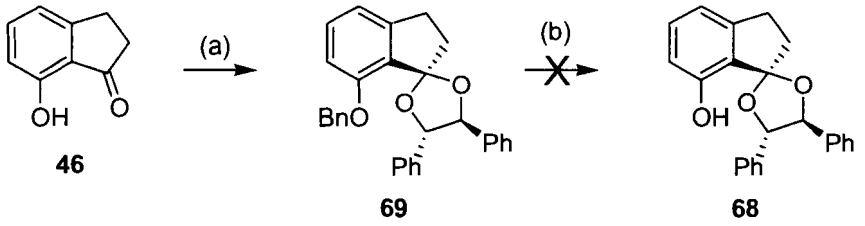
Scheme 2.4.2 Synthesis of 7-Hydroxyindan-1-one-Derived Chiral Auxiliaries **63** (R = Me) and **68** (R = Ph)



Reagents and conditions: (a) acetyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 19 h, 89%. (b) diols **52** (R = Me), **29** (R = Ph), *p*-TsOH, benzene, reflux, 16 h to 40 h, 90%, **66** (R = Me), 83%, **67** (R = Ph). (c) LiOH, THF:H_2O (3:1), rt, 16-40 h, 84%, **63** (R = Me), 91%, **68** (R = Ph). *The enantiomer of that indicated in the reaction scheme was prepared.

The indan-1-one **46** could also be efficiently converted to its corresponding benzyl ether, which condensed with the diol **29** (R = Ph) to afford the acetal **69** (R = Bn) (Scheme 2.4.3). However, deprotection of the benzyl ether moiety of compound **69** by hydrogenolysis using palladium on activated carbon as a catalyst did not proceed at atmospheric pressure and, at elevated pressure (50 p.s.i.), partial decomposition of the acetal occurred.

Scheme 2.4.3 Attempted Synthesis of the Chiral Auxiliary **68** *via* the Benzyl Ether **69**



Reagents and conditions: (a) (i) benzyl bromide, K_2CO_3, DMF, rt, 5 h, 82%. (ii) diol **29** (R = Ph), *p*-TsOH, benzene, reflux, 4 days, 90%. (b) H_2, Pd/C, rt, up to 50 p.s.i.

A possible explanation for the failure of the direct acid-catalyzed condensation reaction of 7-hydroxyindan-1-one **46** was that under acidic conditions, this compound rapidly tautomerized to the enol form **70** (Figure 2.4.1). The presence of an intramolecular hydrogen bond in the enol form **70** may have made this tautomer more thermodynamically-stable. Highly enolized ketones are known to react less readily with

nucleophiles.[43] Thus, it is likely that this pre-equilibration slowed the overall rate of the acetal formation reaction. Interestingly, Wipf and co-workers were unable to condense 1,2-ethanediol with an 8-hydroxytetral-1-one derivative during a natural product synthesis and found that protection of the hydroxyl substituent was necessary for the desired acetal condensation reaction to proceed.[44]

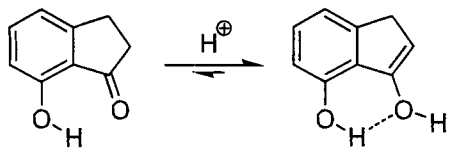


Figure 2.4.1 Acid-catalyzed keto-enol tautomerization of 7-hydroxyindan-1-one **46**.

Alternatively, the failure of the acetal condensation reaction involving 7-hydroxyindan-1-one can be explained if the phenol group (pKa ~ 10 in water) acted as an intramolecular acid-catalyst and facilitated an acetal hydrolysis reaction. However, when a few drops of water were added to an NMR sample of the auxiliary **68** (R = Ph) in deuterated benzene, after several hours, no decomposition of the auxiliary to its corresponding diol and ketone components was observed. Once formed, the chiral auxiliaries **63** (R = Me) and **68** (R = Ph) were stable compounds that could be stored in a capped vial at 4 °C for several months without any sign of decomposition. In addition, the aforementioned auxiliaries were stable in a variety of organic solvents for prolonged periods of time.

2.5 Synthesis of Saturated Substrates for Enolate Alkylation Reactions

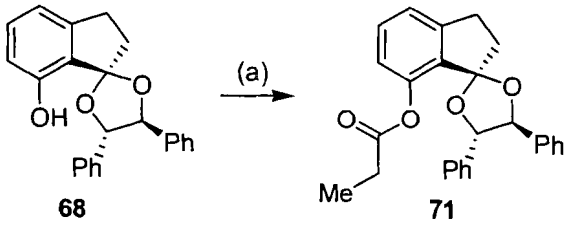
Saturated substrates were attached to the chiral auxiliaries **63** (R = Me) and **68** (R = Ph) by two methods. The first synthetic method involved attachment of the substrates onto the auxiliary and the second, more direct route, involved attachment of the substrates onto 7-hydroxyindan-1-one prior to the acetal condensation reactions. Two substrates of different steric and electronic properties were selected for study: a

propanoate and a phenylacetate. Of additional note, the two auxiliaries **63** (R = Me) and **68** (R = Ph) were selected because the acetal component of each differed in both steric and electronic properties. As well, both were easily prepared from commercially-available diols.

2.5.1 Synthesis of Saturated Substrates from the Chiral Auxiliary 68 (R = Ph)

The chiral auxiliary **68** (R = Ph) was converted to the propanoate **71** on reaction with propanoic anhydride, triethylamine and a catalytic quantity of *N*,*N*-dimethyl-4-aminopyridine in good yield (Scheme 2.5.1). The propanoate **71** displayed a strong sharp band at 1764 cm^{-1} characteristic of an ester carbonyl group.

Scheme 2.5.1 Synthesis of the Propanoate **71** (R = Ph)



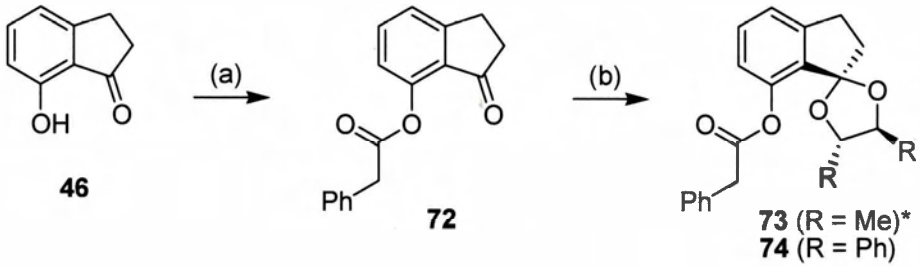
68 **71**

Reagents and conditions: (a) propanoic anhydride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1.5 h, 87%.

2.5.2 Synthesis of Saturated Substrates from 7-Hydroxyindan-1-one (46)

In order to prepare the substrates by a more direct method, 7-hydroxyindan-1-one **46** was converted to the ketoester **72** in 94% yield by reaction with phenylacetyl chloride, pyridine and *N*,*N*-dimethyl-4-aminopyridine (Scheme 2.5.2). The ketoester was then condensed with the diols **52** (R = Me) and **29** (R = Ph) on reaction with catalytic quantities of either *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate to afford the phenylacetates **73** (R = Me) and **74** (R = Ph) in 79 and 88% yield, respectively.

Scheme 2.5.2 Direct Synthesis of the Phenylacetates **73** (R = Me) and **74** (R = Ph)



Reagents and conditions: (a) phenylacetyl chloride, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 3 days; reflux, 2 days, 94%. (b) diols **52** (R = Me), **29** (R = Ph), *p*-TsOH *or* PPTS, benzene, reflux, 3 to 4 days, 79%, **73** (R = Me), 88%, **74** (R = Ph). *The enantiomer of that indicated in the reaction scheme was prepared.

2.5.3 X-Ray Crystallographic Analysis of the Phenylacetates 73 (R = Me) and 74 (R = Ph)

X-ray crystallographic analysis of the phenylacetates **73** (R = Me) and **74** (R = Ph) confirmed that the orthogonal relationship of the indanone and acetal ring systems resulted in shielding of one of the diastereotopic faces of the phenylacetate substituent (Figure 2.5.1, Figure 2.5.2). In both structures, the phenylacetate subunit adopted a *pseudo*-orthogonal relationship to the indanone ring system (torsion angle ~ 65°).

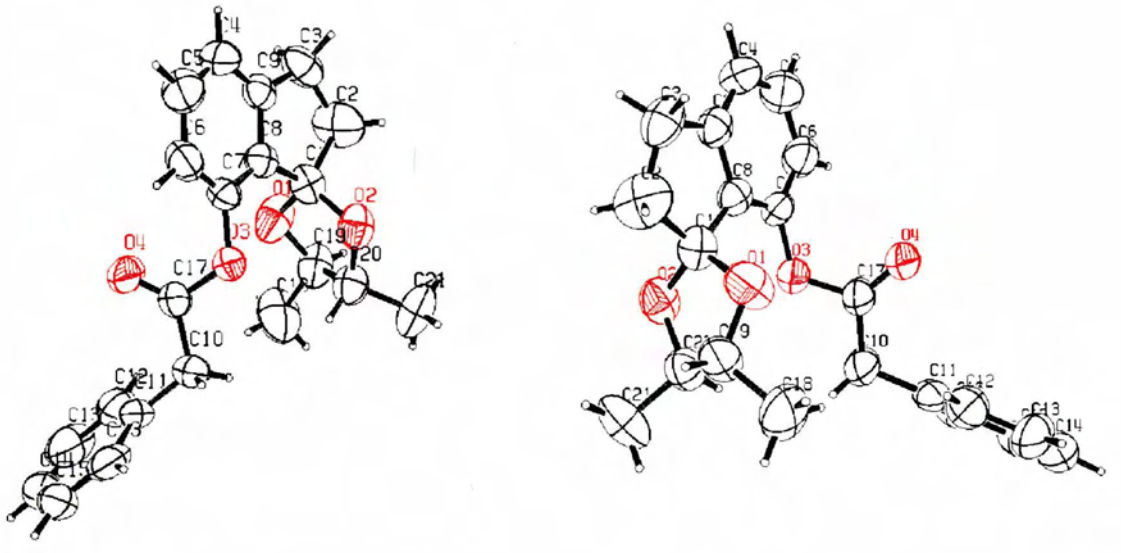


Figure 2.5.1 Two Ortep views of the molecular structure of the phenylacetate **73** (R = Me) (with thermal ellipsoids drawn at a 50% probability level).

For the phenylacetate **74** (R = Ph), the edge of the distal acetal phenyl group and the face of the phenyl of the substrate were 3 Å apart, indicative of an edge-to-face π-π interaction in the solid state.[45]

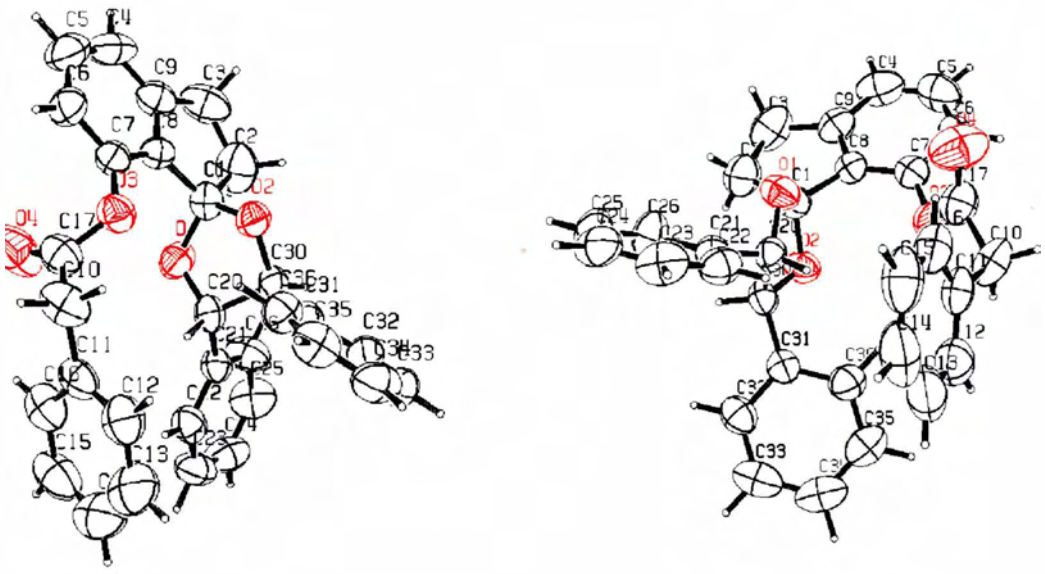


Figure 2.5.2 Two Ortep views of the molecular structure of the phenylacetate **74** (R = Ph) (with thermal ellipsoids drawn at a 50% probability level).

2.6 Synthesis of Unsaturated Substrates for Cycloaddition Reactions

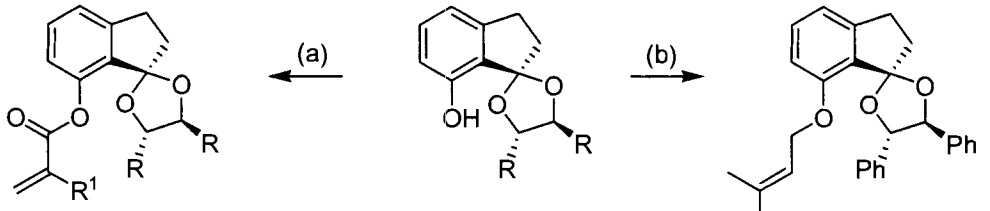
As above, the substrates could be synthesized from the chiral auxiliary, or from 7-hydroxyindan-1-one prior to the acetalization reaction. Auxiliaries derived from all six chiral nonracemic 1,2-diols **52** (R = Me), **29** (R = Ph), **53-56** [R = CH_2OMe, CH_2OBn, CH_2O(1-Np) and *i*-Pr] were prepared for study in cycloaddition reactions. Several unsaturated substrates that varied in size and electronic properties were also attached to the auxiliaries.

2.6.1 Synthesis of α,β-Unsaturated Substrates from the Chiral Auxiliaries

The chiral auxiliaries **63** (R = Me) and **68** (R = Ph) were converted into the acrylates **75** (R = Me) and **76** (R = Ph) as well as the methacrylate **77** (R = Ph) upon reaction with acryloyl chloride or methacryloyl chloride in 88, 85 and 75% yield, respectively (Scheme 2.6.1). As well, the reaction of the auxiliary **68** (R = Ph) with

4-bromo-2-methyl-2-butene and potassium carbonate afforded the ether **78** in 78% yield.

Scheme 2.6.1 Synthesis of the Acrylates **75**, **76** and **77** and the Ether **69** from the Auxiliaries **63** (R = Me) and **78** (R = Ph)



75 (R^1 = H, R = Me)*
76 (R^1 = H, R = Ph)
77 (R^1 = Me, R = Ph)

63 (R = Me)*
68 (R = Ph)

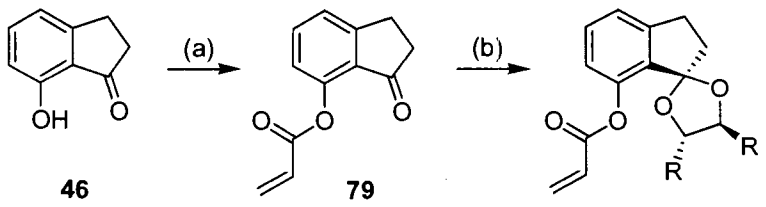
78

Reagents and conditions: (a) acryloyl chloride, Et_3N, benzene, 0 °C to rt, 2 to 2.5 h, 88%, **75** (R^1 = H, R = Me), 85%, **76** (R^1 = H, R = Ph) *or* methacryloyl chloride, Et_3N, benzene, rt, 12 h; reflux, 1 h, 75%, **77** (R^1 = Me, R = Ph). (b) 4-bromo-2-methyl-2-butene, K_2CO_3, DMF, 55 °C, 3 h, 78%. *The enantiomer of that indicated in the reaction scheme was prepared.

2.6.2 Synthesis of α,β-Unsaturated Substrates from 7-Hydroxyindan-1-one (46)

Using the more direct route, 7-hydroxyindan-1-one **46** was reacted with acryloyl chloride and triethylamine to afford the ketoester **79** (Scheme 2.6.2). The acetals **75**, **76** and **80-83** were typically formed in greater than 80% yield by heating solutions of the ketoester **79** and the chiral 1,2-diols **29**, **52-56** in the presence of catalytic amounts of *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate.

Scheme 2.6.2 Direct Synthesis of the Acrylates **75** (R = Me), **76** (R = Ph) and **80-83** [R = CH_2OMe, CH_2OBn, CH_2O(1-Np) and i-Pr]



46

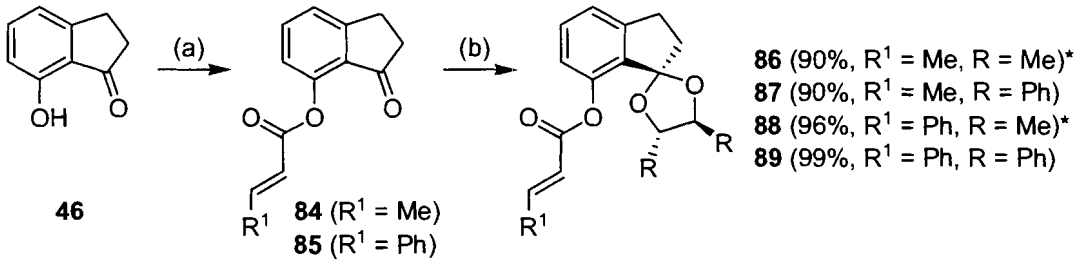
79

75 (93%, R = Me)*
76 (92%, R = Ph)
80 (82%, R = CH_2OMe)
81 (80%, R = CH_2OBn)
82 [55%, R = CH_2O(1-Np)]
83 (80%, R = *i*-Pr)

Reagents and conditions: (a) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h. (b) diols **52**, **29**, **53-56**, *p*-TsOH and/or PPTS, benzene, reflux, 4 h to 4 days. *The enantiomer of that indicated in the reaction scheme was prepared.

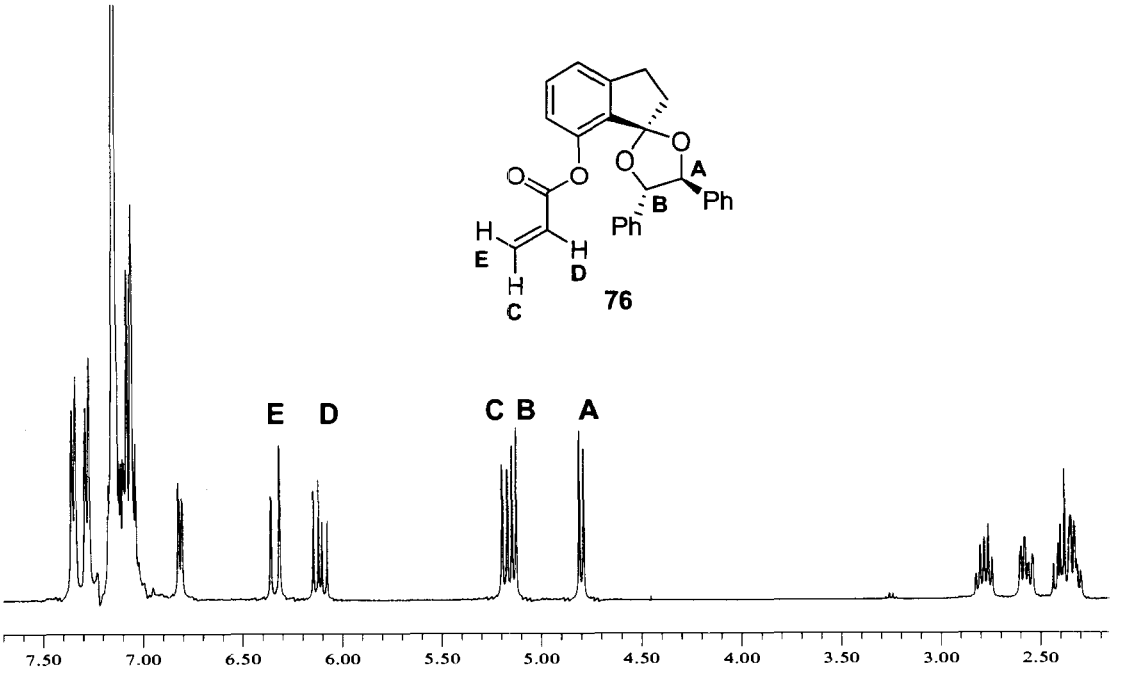
In addition, 7-hydroxyindan-1-one **46** was reacted with (*E*)-crotonyl chloride and (*E*)-cinnamoyl chloride and the resultant ketoesters **84** (R^1 = Me) and **85** (R^1 = Ph) were each condensed with the diols **52** (R = Me) and **29** (R = Ph) to afford the crotonates **86** (R^1 = R = Me) and **87** (R^1 = Me, R = Ph) as well as the cinnamates **88** (R^1 = Ph, R = Me) and **89** (R^1 = Ph, R = Ph) (Scheme 2.6.3).

Scheme 2.6.3 Direct Synthesis of the Crotonates **86** (R = Me), **87** (R = Ph) and Cinnamates **88** (R = Me), **89** (R = Ph)



Reagents and conditions: (a) (*E*)-crotonoyl chloride *or* (*E*)-cinnamoyl chloride, Et_3N, CH_2Cl_2, 45 min to 2 h, 90%, **84** (R^1 = Me), 87%, **85** (R^1 = Ph). (b) diols **52** (R = Me) *or* **29** (R = Ph), *p*-TsOH *and/or* PPTS, benzene, reflux, 4 to 5 days.

The ^{1}H NMR spectrum of the acrylate **76** (R = Ph) indicated that the two faces of the acetal moiety were in distinct chemical environments: the signal for the "interior" hydrogen (**B**) was shifted downfield, with respect to the "exterior" hydrogen (**A**), likely as a result of its proximity to the acrylate moiety (Figure 2.6.1).



76

Figure 2.6.1 ^{1}H NMR (400 MHz, C_6D_6) spectrum of 7-acryloyloxyindan-1-one (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol acetal **76**.

2.7 Asymmetric Enolate Alkylation Reactions

2.7.1 Introduction

The asymmetric alkylation reactions of ester enolates have been extensively studied.[46] The mechanism is well understood, which has allowed for the rational design of many chiral auxiliaries. These structures have incorporated control elements that involve both steric and stereoelectronic effects and high levels of asymmetric induction have been achieved. It is often possible to selectively generate one geometrical isomer of an enolate (see below) and so the efficiency of an alkylation reaction (*e.g.* to form the chiral ester **90**) is usually determined by the ability of the chiral auxiliary to effectively render one of the diastereotopic faces of the enolate more accessible to electrophilic attack (Figure 2.7.1). The enolate alkylation reaction could be used to evaluate the ability of the 7-hydroxyindan-1-one-derived chiral auxiliaries to differentiate the π-faces of an ester enolate

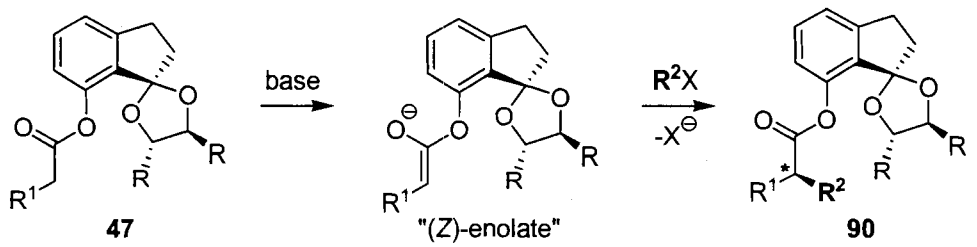
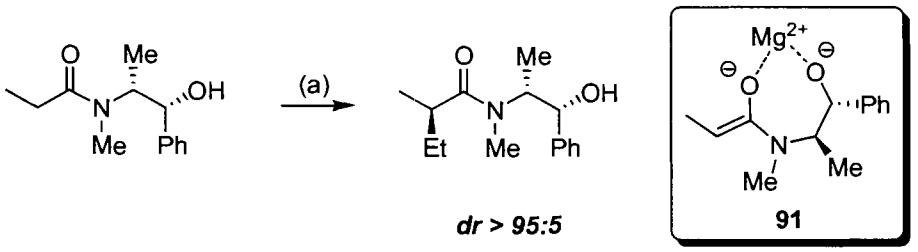


Figure 2.7.1 Stereoselective enolate formation and subsequent reaction with an electrophile.

2.7.2 Background

The first asymmetric enolate alkylation reaction was developed by Larcheveque and co-workers using (2*R*,3*S*)-ephedrine as a chiral auxiliary (Scheme 2.7.1).[47] The authors suggested that the magnesium chelate **91** was responsible for the high diastereoselectivities obtained. However, when the reactions were performed using lithium *N*,*N*-diisopropylamide, the diastereoselectivities obtained were much lower (dr = 76:24). This was presumably due to the reduced ability of the lithium ion to form chelates.

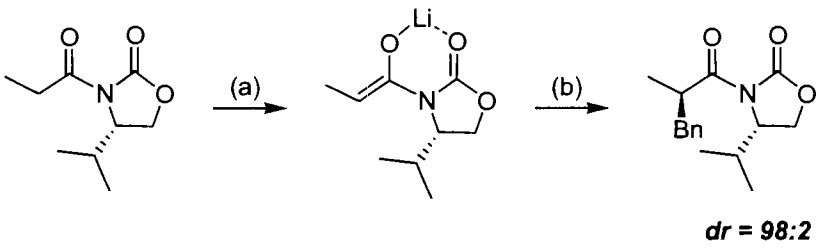
Scheme 2.7.1 The First Asymmetric Enolate Alkylation Reaction: Using (2*R*,3*S*)-Ephedrine as a Chiral Auxiliary



Reagents and conditions: (a) Mg(*i*-Pr$_2$N)$_2$, EtI, ether:HMPA, 20 °C, 75%.

In 1982, Evans and co-workers reported the use of a chiral auxiliary derived from L-valinol in an asymmetric enolate alkylation reaction that showed high diastereoselectivities and remains to date one of the best auxiliaries for this reaction (Scheme 2.7.2). [48] This is also coupled with the relatively simple means of its construction.

Scheme 2.7.2 Asymmetric Enolate Alkylation Reaction Using an Amino Acid-Derived Chiral Oxazolidinone

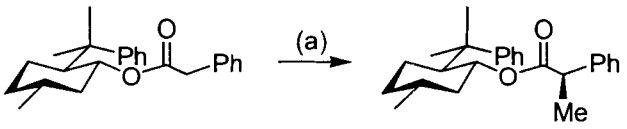


***dr* = 98:2**

Reagents and conditions: (a) LDA, THF, -78 °C. (b) BnBr (3 equiv), 0 °C, 3 h, 78%.

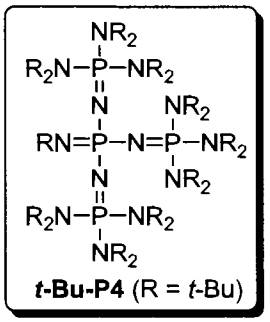
More recently, 8-phenylmenthol has been used in the asymmetric alkylation of a phenylacetate derivative **92** (Scheme 2.7.3).[49] Diastereoselectivities up to 80:20 could be obtained using lithium *N*,*N*-diisopropylamide in tetrahydrofuran/*N*,*N*-dimethylpropyleneurea. However, the alkylation product **93** was formed in significantly increased diastereoselectivity (dr = 93:7) when the strong hindered cation-free phosphorus base, *t*-Bu-P4, was used ($pKa_{conjugate\ acid}$ = 28 in THF).

Scheme 2.7.3 Asymmetric Enolate Alkylation Reaction Using the Hindered Cation-Free Phosphazene Base *t*-Bu-P4



92

93
***dr* = 93:7**



***t*-Bu-P4** (R = *t*-Bu)

Reagents and conditions: (a) *t*-Bu-P4, Me_2SO_4, -100 °C to rt, 2 h, 80%.

The diastereotopic *Re* and *Si* π-faces of a chiral enolate (R* represents a substituent with a stereogenic centre and/or some other element of chirality; *e.g.* a chiral auxiliary) will react with an electrophile ($\mathbf{R^2X}$) to form diastereomeric products **94** and

95 (Figure 2.7.2).*

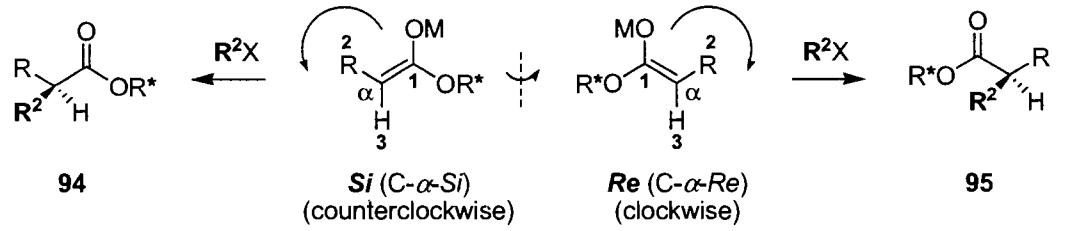


Figure 2.7.2 Reaction of diastereotopic faces of an enolate leads to diastereomeric alkylation products.

In addition, the reaction of an electrophile at a given face of the geometrical (*E*)- or (*Z*)-enolates will lead to the diastereomeric alkylation products **96** and **97**, respectively (Figure 2.7.3).† Therefore, the diastereoselectivity in an alkylation reaction "will be *no greater* than the enolate ratio."[46‡]

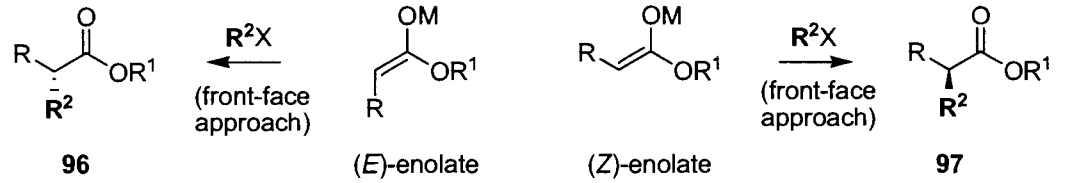


Figure 2.7.3 Reaction of geometrical (*E*)- and (*Z*)-enolates leads to diastereomeric alkylation products.

Ireland has rationalized the selective formation of (*E*)- and (*Z*)-enolates.[50] When hindered lithium amide bases such as lithium *N*,*N*-diisopropylamide are used, Ireland's proposed mechanism of enolate formation involves a cyclic, six-membered, chair-like transition state in which lithium ion transfer and proton abstraction occur simultaneously

---

* Applying the Cahn-Ingold-Prelog priority rules, the enolate face is denoted as *Re* (*rectus* from Latin = right, C-α-*Re*) if the three substituents surrounding the trigonal α-carbon decrease in priority in a clockwise direction. The *Si* (*sinister* from Latin = left, C-α-*Si*) enolate face has the substituents oriented in a counterclockwise direction.

† Based upon the *E*/*Z* stereochemical descriptors used for alkene geometrical isomers, for ester enolates, the OM (M = Li, Na, K) group is assigned the highest priority irrespective of the metal component.[46]

‡ This presupposes that the alkylation reaction goes to completion so that a kinetic resolution process does not occur. As well, the rate of the alkylation reaction must be significantly faster than the rate of enolate interconversion.

(Figure 2.7.4). Of note, due to the significant difference in acidity between *N,N*-diisopropylamine (pKa ~ 36 in water) and esters (pKa ~ 22-24 in water), lithium *N,N*-diisopropylamide is commonly used to rapidly and irreversibly form the enolate of an ester (*i.e.* a kinetic deprotonation).

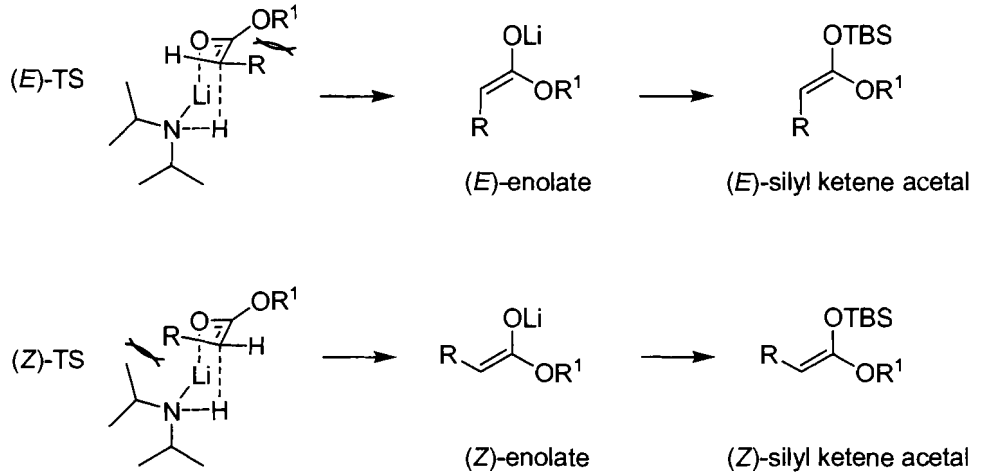


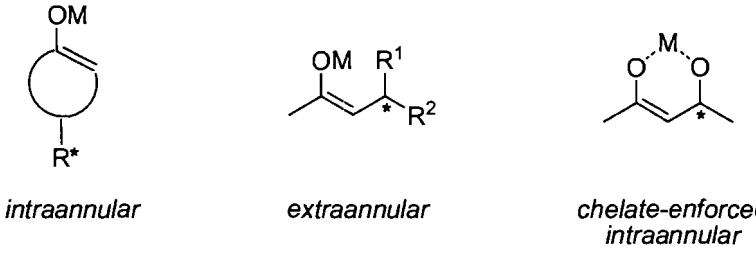
Figure 2.7.4 Ireland's postulated six-membered cyclic transition state in the lithium *N,N*-diisopropylamide deprotonation of esters.

The formation of the (*E*)-enolate involves destabilizing 1,2-eclipsing interactions between the R and OR^1 groups. The formation of the (*Z*)-enolate involves repulsive steric interactions between the substituent (R) and isopropyl groups; namely, 1,3-diaxial interactions. (*E*)-enolates are formed predominantly in the reaction of acyclic esters with lithium *N,N*-diisopropylamide in ethereal solvents (*e.g.* tetrahydrofuran, ether, 1,2-dimethoxyethane). This suggests that 1,3-diaxial interactions are more destabilizing than 1,2-eclipsing interactions. The selective formation of the isomeric (*Z*)-ester enolate can be achieved by performing the deprotonation reaction in the presence of polar, aprotic solvents such as hexamethylphosphoramide, hexamethylphosphorous triamide, *N,N*-dimethylpropyleneurea or *N,N,N',N'*-tetramethylethylenediamine. Solvation of the lithium cation by the polar aprotic solvent reduces coordination between the lithium and carbonyl oxygen and leads to a more "open" or even acyclic transition state. This

reduces or eliminates 1,3-diaxial interactions in the transition state that leads to the (*Z*)-enolate. However, 1,2-eclipsing interactions are retained in the (*E*)-enolate transition state.

Ester enolates are often reacted with silylating agents such as trimethylsilyl chloride or *t*-butyldimethylsilyl chloride, to form the corresponding silylketene acetals, so that the ratio and stereochemistry of the major enolate isomer can be determined (Figure 2.7.4). 1D-^{1}H NMR and NOESY experiments can then be used to determine the selectivity and stereochemistry.

Evans has subdivided the methods by which chiral enolates induce asymmetry into three general classes (Figure 2.7.5).[46]



intraannular *extraannular* *chelate-enforced intraannular*

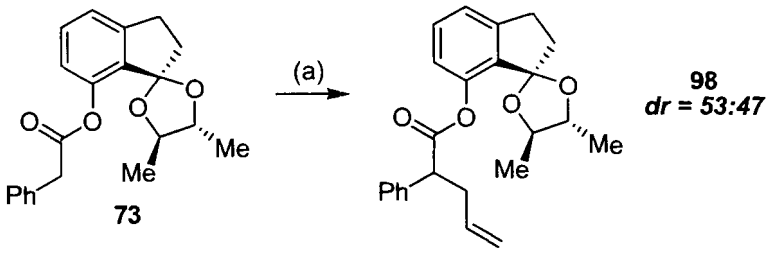
Figure 2.7.5 Classes of stereochemical induction in ester enolate alkylation reactions.

The first method involves the transfer of chirality to the enolate from a stereogenic centre when both ends of the enolate are connected together in a ring composed of all covalent bonds (*intraannular*). Secondly, asymmetric induction can occur if a stereogenic centre is appended to the enolate *via* a single bond (*extraannular*). In analogy to the first and second cases, in the final class, transfer of chirality can occur when the stereogenic centre and the enolate become organized *via* the formation of a chelate (*chelate-enforced intraannular*). The majority of chiral auxiliaries rely on the latter two methods of stereochemical induction.

2.7.3 Enolate Alkylation Reaction of the Phenylacetate [73 (R = Me)]

The phenylacetate **73** (R = Me) was deprotonated with lithium *N,N*-diisopropylamide in tetrahydrofuran at -78 °C and reacted with allyl iodide (Scheme 2.7.4). The desired alkylation products **98** were obtained in 76% yield. As determined from the ^{1}H NMR spectrum of the crude reaction product, the diastereomeric ratio was 53:47. The absolute stereochemical configuration of the alkylation products were not determined because the diastereoselectivity in this reaction was low. Of note, this auxiliary directed enolate alkylation is an example of extraannular (stereochemical) control.

Scheme 2.7.4 Enolate Alkylation Reaction of the Phenylacetate **73** (R = Me)

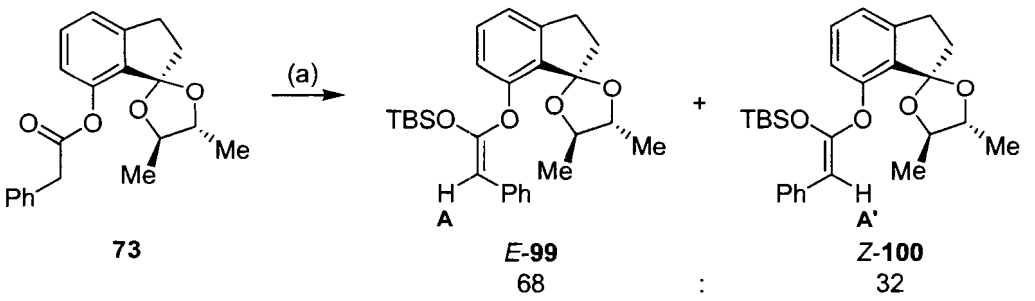


Reagents and conditions: (a) LDA, THF, -78 °C, 30 min; allyl iodide, -78 °C, 1 h 45 min, 76%.

2.7.4 Determination of the Enolate Ratio and Geometry for the Phenylacetate [73 (R = Me)]

The phenylacetate **73** (R = Me) was deprotonated with lithium *N,N*-diisopropylamide in tetrahydrofuran and the resultant enolate was reacted with *t*-butyldimethylsilyl chloride. The (*E*)-and (*Z*)-silylketene acetals *E*-**99** and *Z*-**100** were formed in a 68:32 ratio as determined from the ^{1}H NMR spectrum of the crude reaction product (Scheme 2.7.5)

Scheme 2.7.5 Determination of the Enolate Ratio and Geometry for the Phenylacetate **73** (R = Me)



Reagents and conditions: (a) LDA, THF, -78 °C, 30 min; TBSCl, -78 °C, 2.5 h, ~ 100%.

The stereochemistry of the silylketene acetals **99** and **100** was determined by a NOESY experiment on the crude reaction product (Figure 2.7.6). In the major isomer, a crosspeak was observed between the methyl groups of the *t*-butyldimethylsilyl ether (δ 0.9 ppm) and the olefinic hydrogen (**A**, δ 5.5 ppm) suggesting a *trans*-relationship of the *t*-butyldimethylsilyl and phenyl groups which is consistent with the (*E*)-silylketene acetal structure **99**.

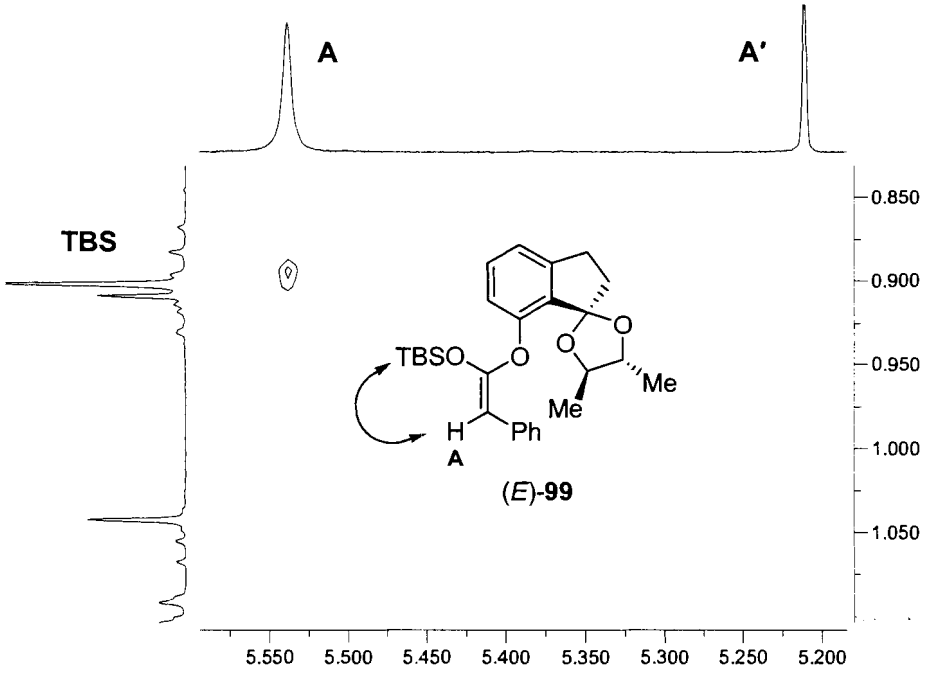
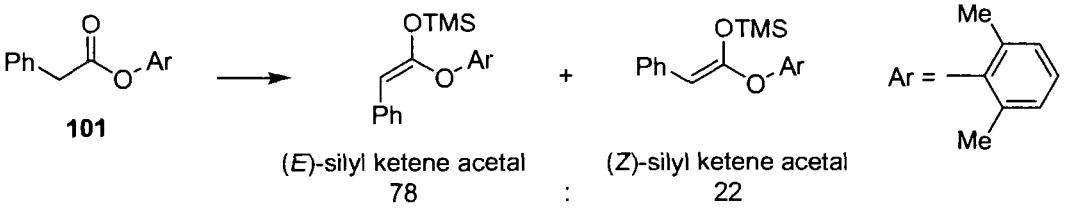


Figure 2.7.6 NOESY spectrum of the silylketene acetal mixture *E*-**99** and *Z*-**100**.

The (*Z*)-silylketene acetal **100** did not display a crosspeak between its olefinic hydrogen ($\mathbf{H_a}$, δ 5.2 ppm) and its corresponding *t*-butylsilyl group. Geometrical silylketene acetals can degrade at different rates, thus, compromising estimation of the enolate ratio; however, no starting material **73** (R = Me) or auxiliary **63** (R = Me) were present in the crude reaction product.[51] This suggested that no decomposition of the silylketene acetals **99** and **100** had occurred prior to NMR analysis of the crude mixture. Flash chromatography of the crude reaction product, however, resulted in complete degradation of the silylketene acetals to afford the auxiliary **63**.

Both Fuji and co-workers as well as Solladié-Cavallo and co-workers have determined the enolate ratios and geometries for several phenylacetates and found that (*E*)-lithium enolates could *not* be formed in high selectivity using lithium *N*,*N*-diisopropylamide in tetrahydrofuran at -78 °C.[52,53] As an example, Fuji and co-workers found the (*E*)/(*Z*)-silylketene acetal ratio to be 78:22 for the enolate generated from 2,6-dimethylphenyl phenylacetate **101** and trapped with trimethylsilyl chloride (Figure 2.7.7).



Reagents and Conditions: LDA, -78 °C, 30 min; TMSCl, -78 °C to rt, 1 h.

Figure 2.7.7 Determination of (*E*)/(*Z*)-geometry in the lithium *N*,*N*-diisopropylamide deprotonation of an aryl phenylacetate **101**.

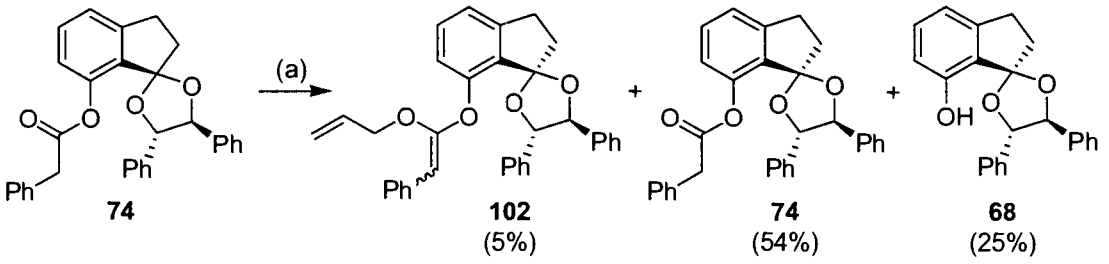
The low diastereoselectivity in the enolate alkylation reaction of the phenylacetate **73** (R = Me) with allyl iodide using lithium *N*,*N*-diisopropylamide in tetrahydrofuran was, therefore, likely a combination of lack of control of enolate geometry as well as a lack of significant facial selectivity in the subsequent alkylation reaction. Further studies

involving the phenylacetate **73** (R = Me) were not undertaken due to the near complete lack of diastereoselection that was observed.

2.7.5 Enolate Alkylation Reaction of the Phenylacetate [74 (R = Ph)]

The phenylacetate **74** (R = Ph) was deprotonated with lithium *N*,*N*-diisopropylamide and subsequently reacted with allyl iodide (Scheme 2.7.6). In contrast to the phenylacetate **73** (R = Me), which reacted rapidly with allyl iodide at -78 °C, negligible reaction was observed at -78 °C after several hours. Therefore, the reaction mixture was allowed to warm to room temperature. Following workup, a trace of the *O*-allylated product **102** (5%) as well as the starting material **74** (54%) and the auxiliary **68** (25%) were isolated from the reaction mixture. The *O*-allylated product was formed as a 58:42 mixture of geometrical isomers.[51*]

Scheme 2.7.6 Attempted Enolate Alkylation Reaction of the Phenylacetate **74** (R = Ph)



Reagents and conditions: (a) LDA, THF, -78 °C, 30 min; allyl iodide, -78 °C to rt, 20 h.

Interestingly, under the same reaction conditions, the two auxiliaries **63** (R = Me) and **68** (R = Ph) behaved quite differently. The alkylation reaction proceeded readily using the smaller auxiliary **63** (R = Me); however, it did not proceed using the larger auxiliary **68** (R = Ph). Greater steric hindrance in the latter auxiliary may have prevented

---

* This does not necessarily imply a non-selective enolization because at elevated temperatures (*e.g.* between 0 °C and rt), decomposition of isomeric enolates can become competitive with *O*-alkylation. As (*E*)-enolates generally decompose faster than (*Z*)-enolates, the initial (*E*)/(*Z*)-enolate ratio was likely higher than that indicated by the ratio of *O*-alkylated products.

efficient deprotonation or, more likely, slowed the subsequent reaction of the enolate with allyl iodide.

Typically, when an ester enolate is unreactive with an alkylating agent, it is reprotonated during the "workup" step to regenerate the starting ester (*e.g.* phenylacetate **74**, Figure 2.7.8). However, ester enolates are also known to react *via* an $E1_{CB}$ (E = elimination, 1 = unimolecular, CB = conjugate base) mechanism whereby the enolate collapses to form the ketene **104** and phenoxide **105** intermediates. This is a possible explanation for the isolation of the auxiliary **68** in this attempted enolate alkylation reaction.

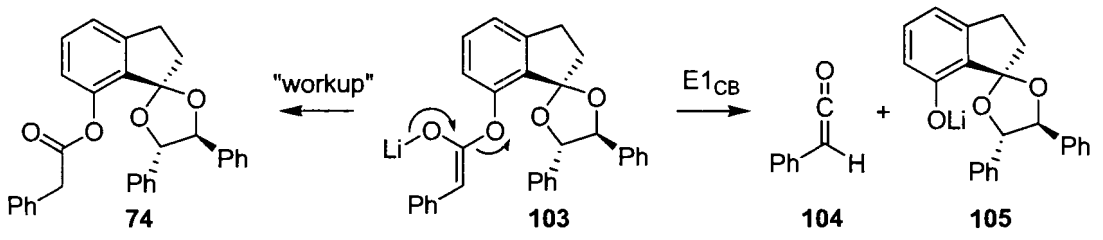


Figure 2.7.8 Proposed $E1_{CB}$ enolate decomposition mechanism.

The $E1_{CB}$ cleavage mechanism of esters has been shown to proceed in systems involving stable phenoxide leaving groups (*i.e.* $pKa_{conjugate\ acid} < 6.7$ in water) or severely hindered phenoxide leaving groups (*e.g.* 2,6-di-*t*-butyl-4-methylphenoxide). In the latter case, the nucleophilic addition to the carbonyl carbon that is required in an ester cleavage reaction *via* a $B_{Ac}2$ (B = base-promoted, Ac = acyl oxygen cleavage, 2 = bimolecular) mechanism is prevented by steric hindrance around the carbonyl carbon.[54,55]

Vaughan and co-workers proposed a ketene intermediate in the self-condensation reaction of the zinc ester enolate of α-bromoisobutyrate.[56] As well, Rathke and co-workers have shown that the enolate generated from *t*-butyl bis(trimethylsilyl)acetate, undergoes an $E1_{CB}$ reaction to form a stable ketene, which was isolated by distillation.[57] Evans also stated that lithium enolates of the substrate-oxazolidinones decompose above

0 °C *via* a ketene pathway (see: Scheme 2.7.2).[48]

A mechanistic alternative for the formation of the phenoxide **105** was that following protonation during the "workup" step, the resultant phenylacetate **74** (R = Ph) underwent a $B_{Ac}2$ reaction whereby a nucleophile attacked the ester carbonyl carbon. The mild "workup" conditions (*i.e.* saturated aqueous ammonium chloride), in which the major nucleophilic species were water and chloride, does not support this mechanism. In addition, other esters of the auxiliary have been found to be stable to both mildly basic and acidic aqueous solutions. Regarding the possible $B_{Ac}2$ cleavage reaction involving diisopropylamine as a nucleophile (formed from lithium *N*,*N*-diisopropylamide upon enolate formation), Cho and co-workers have shown that a variety of substituted *p*-nitrophenyl phenylacetates undergo $E1_{CB}$ cleavage upon exposure to diisopropylamine in acetonitrile.[58] The resultant amide from the $B_{Ac}2$ cleavage by diisopropylamine was not observed in this study.

To facilitate the alkylation reaction of the phenylacetate **74** (R = Ph), the deprotonation of the ester was performed, under conditions developed by Ireland, using lithium *N*,*N*-diisopropylamide in tetrahydrofuran/23% hexamethylphosphoramide (Scheme 2.7.7).[50a*] Allyl iodide was added to the resultant enolate solution and, after 2 h, the desired alkylation products **106** and **107** were isolated as an inseparable mixture in 83% yield. The diastereoselectivity of the reaction was 72:28 (**106**:**107**) as determined from the ^{1}H NMR spectrum of the crude reaction product.

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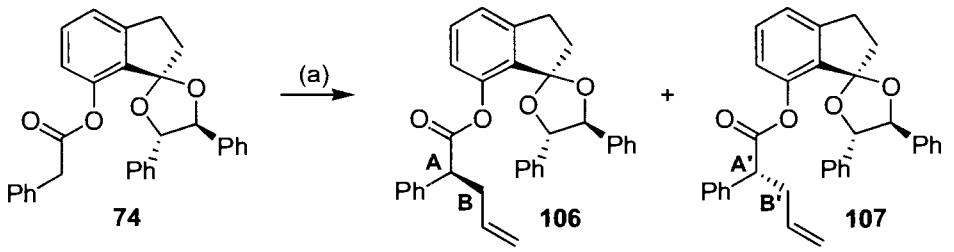
* Ireland and co-workers have shown that the use of lower HMPA concentrations leads to less selective enolate formation. For example, they have found that the use of THF/6% HMPA afforded an (*E*)- to (*Z*)-enolate ratio of 53:47 while THF/11% HMPA led to a 77:23 ratio. As well, they reported that HMPA is not soluble in THF at -78 °C at a concentration greater than 23% (volume:volume). Thus, using higher concentrations of HMPA will likely have a negligible effect on the enolate ratio.

Scheme 2.7.7 Enolate Alkylation Reaction of the Phenylacetate **74** (R = Ph) in the Presence of HMPA

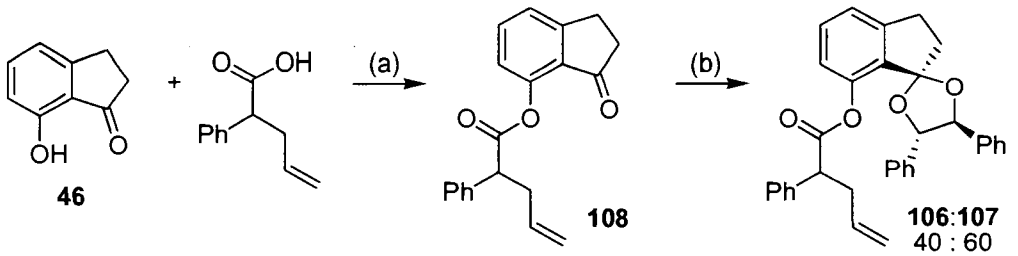


Reagents and conditions: (a) LDA, THF/23% HMPA, -78 °C, 30 min; allyl iodide, 2 h.

Thus, the addition of hexamethylphosphoramide proved to be essential in order for the desired reaction to proceed. The structures of the diastereomeric alkylation products **106** and **107** were determined unambiguously by two-dimensional NMR spectroscopy and independent synthesis. In the COSY spectrum of the purified inseparable mixture, crosspeaks between the α-carbonyl hydrogen (**A** and **A′**, δ 4 ppm) and the allyl methylene hydrogens (**B** and **B′**, δ 2.5 to 3 ppm) were evident for both diastereomers. As well, in the IR spectrum of the diastereomeric mixture of compounds **106** and **107**, a strong sharp absorption at 1758 cm^{-1} and a medium absorption at 1617 cm^{-1} were indicative of an ester and vinyl group, respectively.

A diastereomeric mixture of the alkylation products was prepared by the reaction of 7-hydroxyindan-1-one **46** with racemic 2-phenyl-4-pentenoic acid, 2-chloro-*N*-methylpyridinium iodide and triethylamine (Scheme 2.7.8). The resultant racemic ketoester **108** and the diol **29** (R = Ph) were heated in the presence of catalytic amount of *p*-toluenesulfonic acid to afford a diastereomeric mixture of the acetals **106** and **107**. Interestingly, the condensation reaction partially resolved the racemic ketoester **108**. The diastereomeric condensation products were formed in an unequal amount (**106**:**107** = 40:60).

Scheme 2.7.8 Synthesis of the Diastereomeric Alkylation Products **106** and **107** by an Alternate Route



Reagents and Conditions: (a) 2-chloro-*N*-methylpyridinium iodide, Et_3N, CH_2Cl_2, 43%. (b) diol **29** (R = Ph), PPTS, benzene, reflux, 3 days, 52%.

Comparison of the ^1H NMR spectra for the purified product mixture from the asymmetric alkylation reaction and that for this latter material confirmed that the compounds were identical (see below: Figure 2.7.9). Other spectroscopic data for the asymmetric alkylation and independently synthesized was also in agreement.

Two additional bases were evaluated in the enolate alkylation reaction. The phenylacetate **74** (R = Ph) could be deprotonated with potassium triphenylmethanide, which is known to generate enolates irreversibly, in tetrahydrofuran and was alkylated with allyl iodide.[59,62*] The reaction was complete after 10 min at -78 °C and the desired alkylated products **106** and **107** were isolated in 54% yield. The diastereomeric alkylation products were produced in a 58:42 (**106**:**107**) ratio as determined from the ^1H NMR spectrum of the crude reaction product.

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* Sarakinos and Corey have indirectly shown that potassium triphenylmethanide is able to stereoselectively form (*Z*)-enolates.

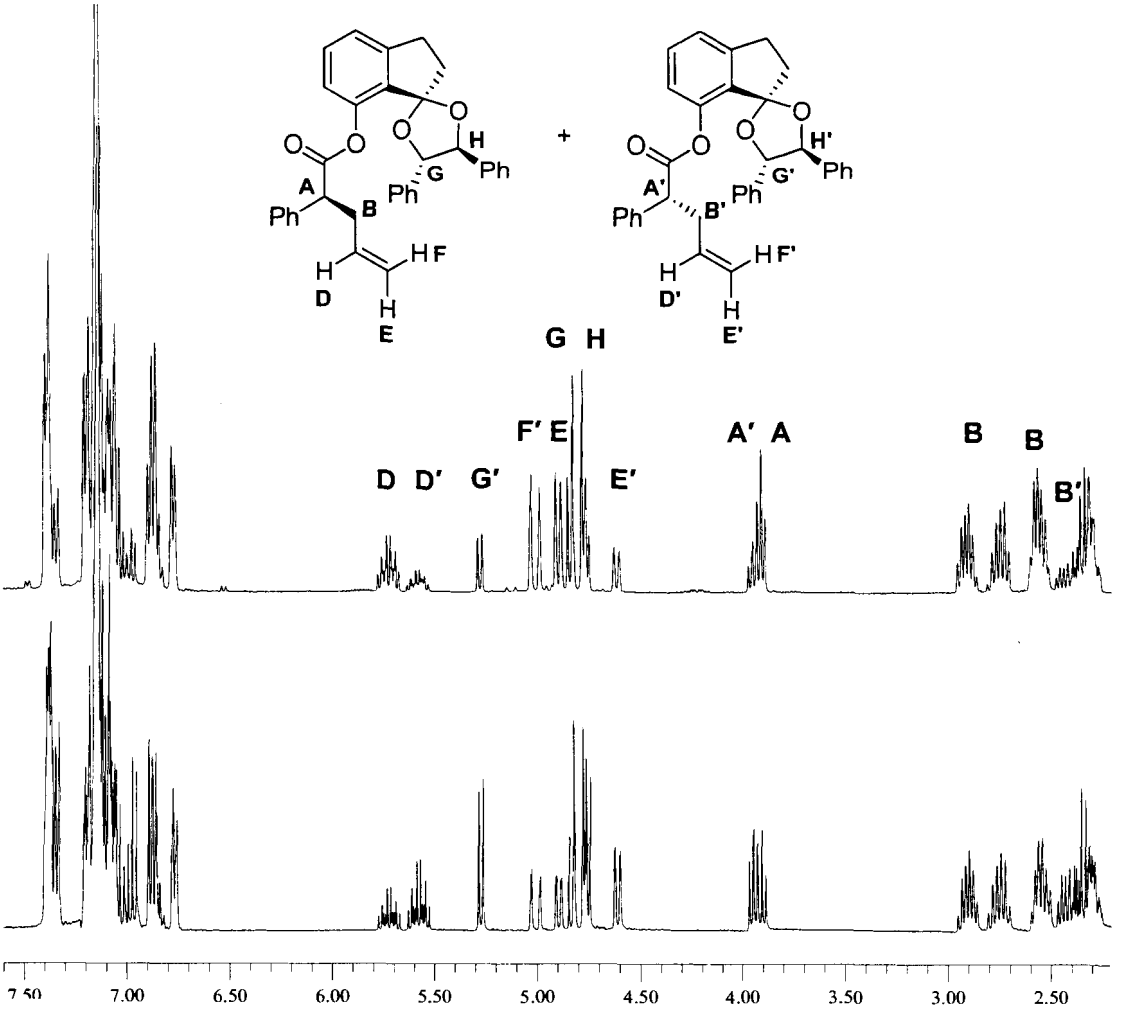


Figure 2.7.9 ^{1}H NMR (400 MHz, C_6D_6) spectra of the purified alkylation products **106** and **107** formed in LDA/THF/23% HMPA alkylation reaction (top) and the diastereomeric alkylation products **106** and **107** prepared by independent synthesis (bottom).

Lithium hexamethyldisilazide, which is known as well to generate kinetic enolates, was also used to deprotonate the phenylacetate **74** (R = Ph) in tetrahydrofuran/23% hexamethylphosphoramide and the enolate was subsequently alkylated with allyl iodide.[60*] In this case, the desired *C*-alkylated products were formed rapidly at -78 °C and isolated in 77% yield. As determined from the ^{1}H NMR spectrum

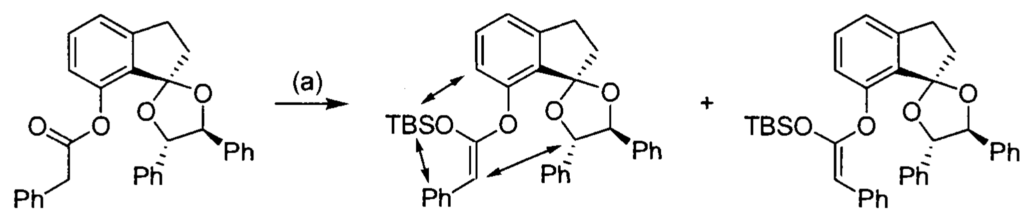
* The deprotonation with LHMDS in THF was not attempted as Ireland and co-workers as well as Heathcock and co-workers have reported that this reaction is inefficient in the absence of polar solvents such as HMPA.

of the crude reaction product, the diastereoselectivity of the reaction was 70:30 (**106**:**107**). Thus, the use of lithium *N,N*-diisopropylamide or lithium hexamethyldisilazane in tetrahydrofuran/23% hexamethylphosphoramide afforded the major alkylation product of the same absolute stereochemistry in similar yield and with good diastereoselectivity.

2.7.6 Determination of the Enolate Ratio and Geometry for the Phenylacetate [74 (R = Ph)]

The phenylacetate **74** (R = Ph) was deprotonated with lithium hexamethyldisilazane in tetrahydrofuran/23% hexamethylphosphoramide at -78 °C and reacted with *t*-butyldimethylsilyl chloride.* After 1 h, the (*Z*)/(*E*)-silylketene acetals **109** and **110** were formed in a 93:7 ratio as determined from the ^{1}H NMR spectrum of the crude reaction product (Scheme 2.7.9). The stereochemistry of the major silylketene acetal (*Z*)-**109** was established by means of a NOESY experiment. Correlations were present between the silyl methyl and *t*-butyl hydrogens and the hydrogen atoms of both the phenyl and indanyl rings but not the olefinic hydrogen.

Scheme 2.7.9 Determination of the Enolate Ratio and Geometry for the Phenylacetate **74** (R = Ph)



74 (*Z*)-**109** 93 : (*E*)-**110** 7

Reagents and conditions: (a) LHMDS, THF/23% HMPA, -78 °C, 45 min; TBSCl, 1 h 15 min, 77%.

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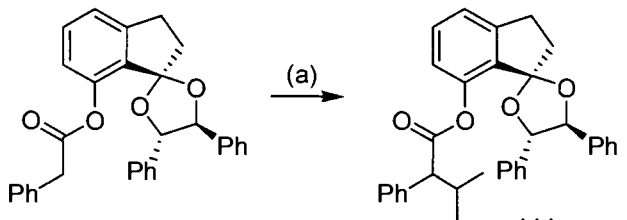
* Ireland and co-workers have shown that LHMDS in THF/23% HMPA consistently produces high (*E*)/(*Z*)-enolate ratios (*i.e.* ≥ 90:10) in the presence of various limiting quantities of ester and in the presence of excess ester. Whereas, using LDA in THF/23% HMPA, they found that high enolate ratios are obtained only when 1:1 and 1.2:1 ester:base ratios were employed (85:15 and 93:7, respectively). In the presence of limiting quantities of ester, the (*Z*)/(*E*)-enolate ratio decreased as the ester:base ratio was lowered.

The olefinic hydrogen showed enhancement from the hydrogen atoms of the phenyl and acetal methine groups only; no transfer of magnetization to the hydrogens of the silyl methyl or *t*-butyl substituents was observed. The formation of the (*Z*)-silylketene acetal **109** upon silylation of the (*Z*)-enolate **103** under these reaction conditions was congruent with the general trend observed in the kinetic formation of ester enolates in the presence of hexamethylphosphoramide. Of note, the silylketene acetal mixture **109** and **110** was stable to flash chromatography on silica gel.

2.7.7 Variation of the Substrate and Electrophile

The phenylacetate **74** was also reacted with a different electrophile, 2-iodopropane (Scheme 2.7.10). The lithium enolate of the phenylacetate **74** (R = Ph) generated using lithium hexamethyldisilazane in tetrahydrofuran/23% hexamethylphosphoramide reacted only to a negligible extent with 2-iodopropane after several hours at -78 °C; however, upon warming to room temperature, the *C*-alkylated product **111** was formed in 75% yield. The diastereomeric ratio was 53:47 as determined from the ^{1}H NMR spectrum of the crude reaction product. The absolute stereochemical configuration of the major diastereomer was not determined.

Scheme 2.7.10 Enolate Alkylation Reaction of the Phenylacetate **74** (R = Ph) with 2-Iodopropane



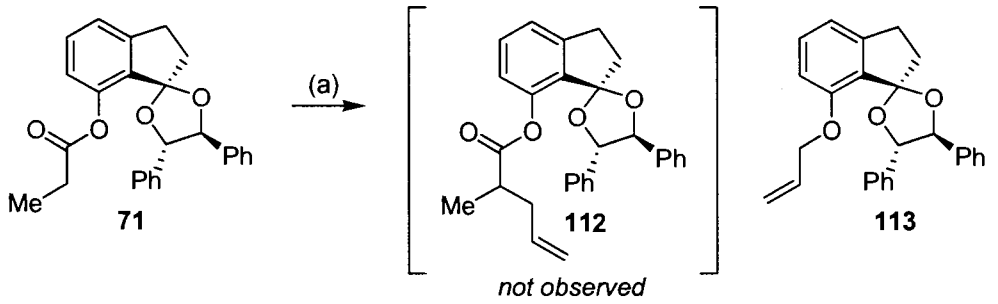
74 **111** ***dr = 53:47***

Reagents and conditions: (a) LHMDS, THF/23% HMPA, -78 °C, 30 min; 2-iodopropane, -78 °C to rt, 16 h, 75%.

The propanoate **71** (R = Ph) was also deprotonated with lithium hexamethyldisilazane in tetrahydrofuran/23% hexamethylphosphoramide and treated

with allyl iodide (Scheme 2.7.11). Intriguingly, no *C*-alkylation product **112** was observed. Instead, the allyl ether **113** was isolated from the reaction mixture in 73% yield. The IR spectrum of the product of this reaction confirmed the absence of a carbonyl group in the ether **113** and its COSY spectrum confirmed that the allyl group was attached to either a quaternary carbon or oxygen atom.

Scheme 2.7.11 Attempted Enolate Alkylation of the Propanoate **71** (R = Ph)



Reagents and conditions: (a) LHMDS, THF/23% HMPA, -78 °C, 30 min; allyl iodide, -78 °C, 1 h, 73%.

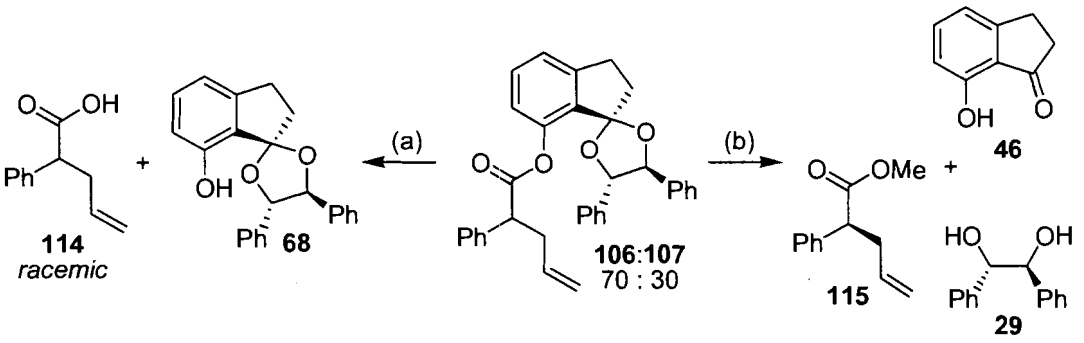
Evidently, the enolate of the propanoate **71** (R = Ph) was unstable and decomposed to its corresponding phenolate **105** which then reacted with allyl iodide to form the observed ether **113**. Thin-layer chromatographic experiments performed on the reaction mixture at -78 °C and on the purified ether **113** suggested that the decomposition and allylation sequence occurred during the reaction. This was in accord with the decomposition of the phenylacetate **74** (R = Ph) to the auxiliary **68** when its alkylation reaction was attempted in the absence of hexamethylphosphoramide.

2.7.8 Determination of the Stereochemical Outcome in the Enolate Alkylation Reaction

To rationalize the stereochemical outcome in the stereoselective alkylation reactions, the alkylated products **106** and **107** (dr = 70:30) formed using lithium hexamethyldisilazane in tetrahydrofuran/23%hexamethylphosphoramide were hydrolyzed using lithium hydroperoxide to liberate the enantiomerically-enriched

alkylated product **114** and the chiral auxiliary **68** (Scheme 2.7.12).[61] However, this transformation resulted in complete racemization of the carboxylic acid product **114**.

Scheme 2.7.12 Acid- and Base-Catalyzed Solvolysis Reactions of the Diastereomeric Alkylation Products **106** and **107**



Reagents and Conditions: (a) LiOH, H_2O_2, THF:H_2O (3:1), rt, 40 h. (b) $MeSO_3H$, MeOH, reflux, 6 h, **115** (73%).

For this reason, the product mixture **106** and **107** was subjected to a methanesulfonic acid-catalyzed solvolysis reaction to liberate the alkylation product as its methyl ester **115** (major enantiomer shown).[62] The acetal moiety of the alkylation products **106** and **107** was found to be unstable to these reaction conditions and so the auxiliary was not recovered. The absolute stereochemical configuration of the major methyl ester **115** was determined by comparison of the sign of its optical rotation to that of the known compound.[62]

The stereochemistry of the major alkylation product **106** can be rationalized if the (*Z*)-enolate **103**: (i) adopted a conformation parallel to the plane of the indanone ring system and (ii) allyl iodide approached from the less hindered *Re*-face (back face as drawn, Figure 2.7.10). Here, the phenyl group of the acetal is oriented away from the enolate. The NOESY spectrum of (*Z*)-silylketene acetal **109** showed crosspeaks between the "interior" acetal hydrogen and the *t*-butylsilyl hydrogens suggesting that it adopted a similar conformation to the conformation of the enolate **103**. As the (*Z*)-enolate was formed in high stereoselectivity (93:7), it follows that the good diastereoselection (dr =

70:30) was a result of efficient differentiation of the two diastereotopic faces of the (*Z*)-enolate by the chiral auxiliary **68** (R = Ph).

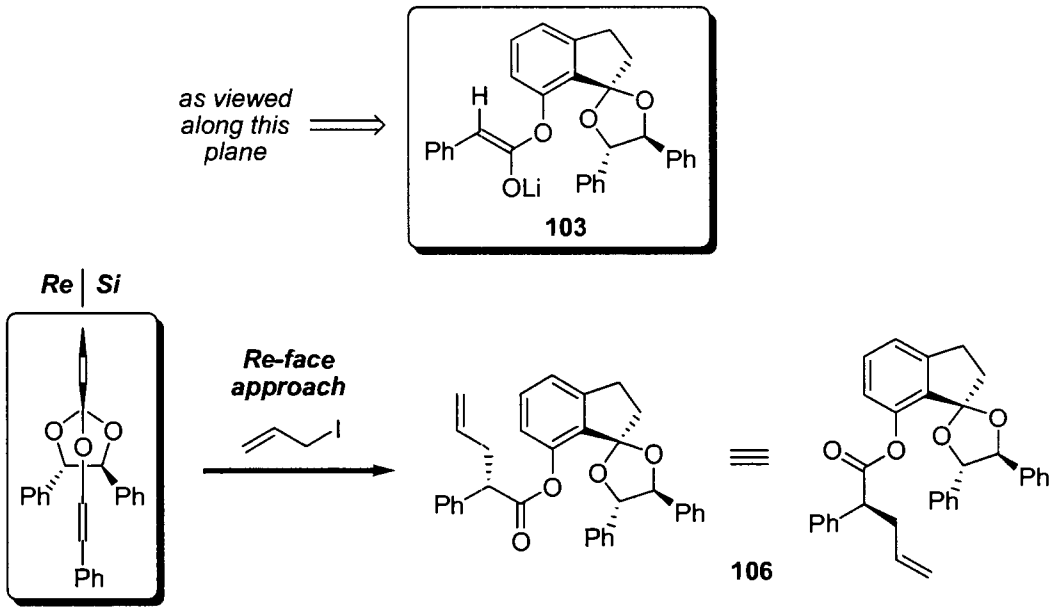


Figure 2.7.10 Rationale of the stereochemical outcome in the asymmetric enolate alkylation reaction of the phenylacetate **74** (R = Ph).

The alkylation of the potassium enolate did not require hexamethylphosphoramide to facilitate the reaction. However, potassium enolates are often more reactive than lithium enolates and react with esters in more "open" transition states. This can result in the predominance of a (*Z*)-enolate.[63,64] Therefore, the formation of the same major diastereomer in the potassium enolate alkylation reaction, albeit in lower diastereoselectivity (dr = 58:42), as that formed using the lithium bases is likely a result of reaction of allyl iodide with the same major geometrical enolate from the same diastereotopic face (*Re*).

2.8 Asymmetric Cyclopropanation Reactions

2.8.1 Introduction

Denmark states that a remaining challenge in cyclopropanation reactions is the stereoselective "delivery of methylene to an unfunctionalized alkene on the basis of steric effects alone".[65] Several chiral auxiliaries have produced high levels of asymmetric induction in the cyclopropanation reaction. However, the use of electron-rich alkenes (*e.g.* enol ethers) or alkenes with directing groups (*e.g.* allylic alcohols) has often been required in order for these reactions to proceed.[66,67] As well, several chiral auxiliaries have been shown to be effective only if they contain heteroatoms to which the incoming cyclopropanation reagent can coordinate.[68,69]

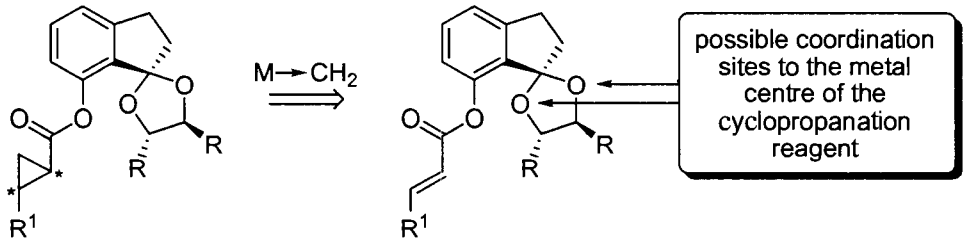


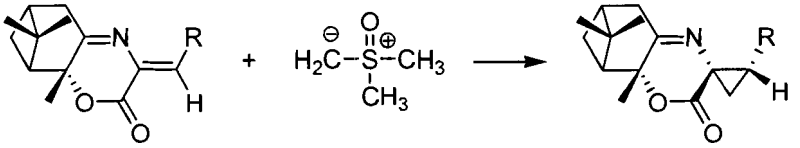
Figure 2.8.1 Diastereoselective cyclopropanation reaction based on steric and/or chelation control.

The asymmetric cyclopropanation reaction could be used to evaluate the ability of the indanone-derived chiral auxiliaries to induce asymmetry in chemical reactions based on steric effects imposed by the cyclic acetal subunit (Figure 2.8.1). As well, the ability of these chiral auxiliaries to provide increased stereocontrol through coordination and direction of reagents by one or both of the oxygen atoms of the acetal moiety could be evaluated in this reaction. Electron-poor (*e.g.* α,β-unsaturated esters) and electron-rich (*e.g.* allylic ethers) substrates derived from the auxiliaries **63** (R = Me) and **68** (R = Ph) were examined. In addition, several different methods of cyclopropanation were selected for study: sulfur ylide, Simmons-Smith and palladium-catalyzed diazomethane reactions.

2.8.2 Background

Recently, a 2-hydroxypinan-3-one chiral auxiliary has been used in the sulfur ylide-type cyclopropanation reaction of α,β-unsaturated amino acid substrates **116**. The methylide **117**, generated by deprotonation of trimethylsulfoxonium iodide with sodium hydride, reacted with the various substrates in high diastereoselectivity (Scheme 2.8.1).[70,71,72]

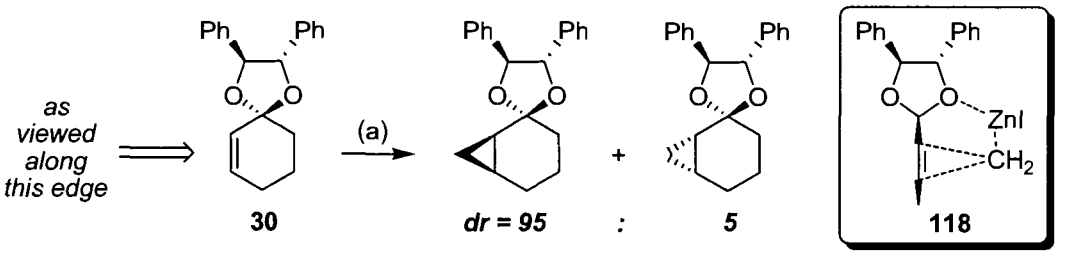
Scheme 2.8.1 Asymmetric Sulfur Ylide Cyclopropanation Reaction Using a 2-Hydroxypinan-3-one Chiral Auxiliary



116 **117** ***dr > 99:1***

In 1985, Mash and co-workers used the Simmons-Smith reaction to cyclopropanate the cycloalkenone acetal **30** derived from a 1,2-diol chiral auxiliary (Scheme 2.8.2).[67,68] The high diastereoselectivities in these reactions were shown to be a result of chelation control by which the zinc carbenoid **118** coordinated to the more-accessible acetal oxygen. This directed the cyclopropanation reaction to occur selectively from the top face (as shown). When a carbocyclic analogue of these acetals was prepared, the reaction rate decreased significantly and the reaction was completely unselective (dr ~ 50:50).[29]

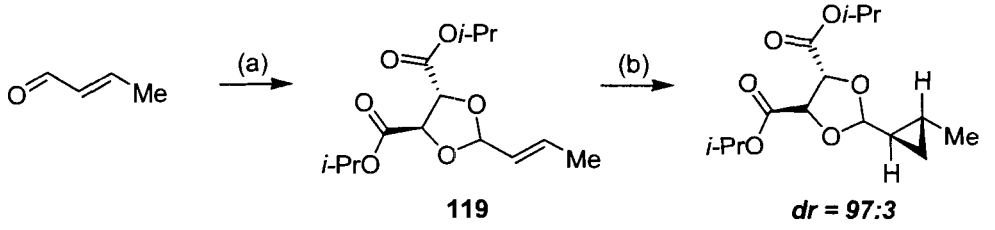
Scheme 2.8.2 Simmons-Smith Cyclopropanation Reaction Using the Diol **29** (R = Ph) as an Auxiliary



Reagents and conditions: (a) CH_2I_2, Zn/Cu couple, ether, rt, 90%.

Yamamoto and co-workers, using Furukawa's modified Simmons-Smith conditions, have shown that the tartrate-derived acetal **119** of an α,β-unsaturated aldehyde could be cyclopropanated in high yield and diastereoselectivity (Scheme 2.8.3).[73]

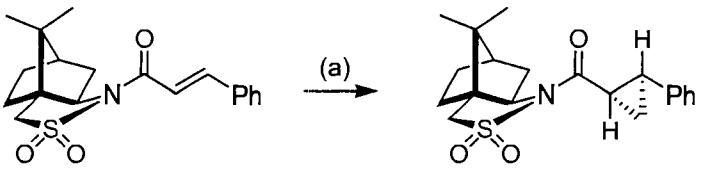
Scheme 2.8.3 Asymmetric Simmons-Smith-type Cyclopropanation Reaction Using a Tartrate as a Chiral Auxiliary



Reagents and conditions: (a) (i) $(EtO)_3CH$ (1.2 equiv), NH_4NO_3 (*cat.*), EtOH, rt, 4 h. (ii) (2*R*,3*R*)-(+)-diisopropyl tartrate (1.1 equiv), PPTS, benzene, reflux, 1.5 h. (b) Et_2Zn, CH_2I_2, -20 to 0 °C, 12 h, 90%.

In 1992, Hacksell and co-workers reported a highly diastereoselective cyclopropanation reaction of an α,β-unsaturated carboxylic acid derivative **120** involving the palladium-catalyzed decomposition of diazomethane.[74] In this report, a variety of β-aryl- and β-alkyl-substituted substrates were derivatized with Oppolzer's sultam and cyclopropanated in excellent diastereoselectivities (*e.g.* dr = 93:7).

Scheme 2.8.4 Oppolzer's Sultam in a Palladium-Catalyzed Cyclopropanation Reaction



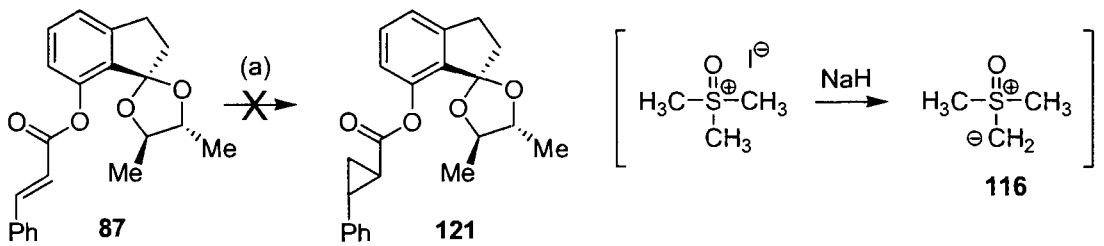
120 ***dr* = 93:7**

Reagents and conditions: (a) CH_2N_2, $Pd(OAc)_2$ (0.5 mol %), CH_2Cl_2, 0 °C, 3 h, 73%.

2.8.3 Sulfur Ylide-Type Cyclopropanation Reactions

A solution of the cinnamate **87** (R = Me) in *N*,*N*-dimethylformamide at room temperature was added to the ylide **116**, prepared from trimethylsulfoxonium iodide and sodium hydride. After 24 h, the auxiliary **63** (R = Me) was isolated in 73% yield. No cyclopropane product **121** was observed. It is likely that the ylide **116** cleaved the ester linkage of the cinnamate **87** (R = Ph) by reaction with the ester moiety in a nucleophilic substitution process. Corey has observed that the methylide **116** can react competitively in a 1,2-fashion with α,β-unsaturated substrates containing acyl chloride or methyl ester functional groups.[71] However, both Hamdouchi and co-workers and Meyers and co-workers have found that chiral auxiliaries containing methyl ester and γ-lactam functionalities, respectively, were stable to these reaction conditions.[75] Further studies using the Corey-Chaykovsky cyclopropanation reaction conditions were not undertaken.

Scheme 2.8.5 Attempted Cyclopropanation Reaction of the Cinnamate **87** (R = Me) Using a Sulfur Ylide



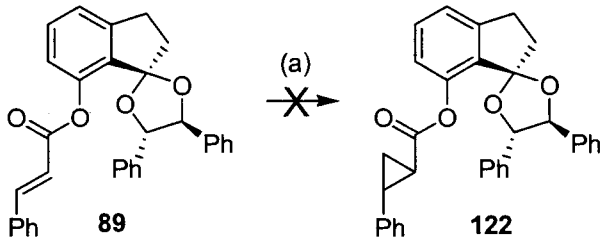
87 **121** **116**

Reagents and conditions: (a) trimethylsulfoxonium iodide, NaH, DMF, rt, 20 min; cinnamate **87**, DMF, 24 h.

2.8.4 Simmons-Smith-Type Cyclopropanation Reactions

A Furukawa-modified Simmons-Smith cyclopropanation reaction of the cinnamate **89** (R = Ph) was attempted (Scheme 2.8.6). The cinnamate **89** was reacted with diethylzinc and diiodomethane in dichloromethane at room temperature. After 24 h, no observable reaction had occurred to form the cyclopropane **122** as determined by thin-layer chromatography.*

Scheme 2.8.6 Attempted Simmons-Smith-type Cyclopropanation of the Cinnamate **89** (R = Ph)



Reagents and conditions: (a) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 24 h.

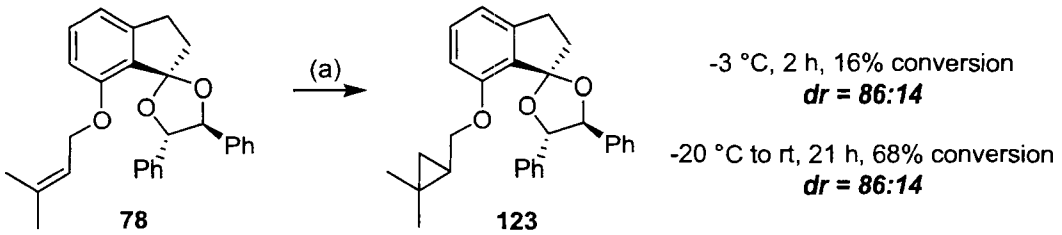
In most cases, electron-poor substrates such as α,β-unsaturated esters are known not to react readily under Simmons-Smith-type conditions.[76] For this reason, the more electron-rich prenyl ether **78** (R = Ph) was evaluated using these cyclopropanation conditions. To a solution of the ether **78** (R = Ph) in 1,2-dichloroethane at -3 °C was added diethylzinc and diiodomethane and within a few minutes, a white precipitate was deposited (Scheme 2.8.7).[77†] After 2 h, it appeared no reaction had occurred by thin-layer chromatography; therefore, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. The ^1H NMR spectrum of the crude reaction product revealed that the reaction had actually proceeded to 16% completion. As well, the cyclopropane **123** was formed in high diastereoselectivity (dr = 86:14).

---

* The cinnamate **89** and cyclopropane **122** were not co-polar by thin-layer chromatography.

† Denmark and co-workers have reported that the use of 1,2-dichloroethane, in many instances, increases the yields, rates and/or diastereoselectivities in diethylzinc-mediated cyclopropanation reactions.

Scheme 2.8.7 Simmons-Smith-type Cyclopropanation Reaction of the Ether **78** (R = Ph)



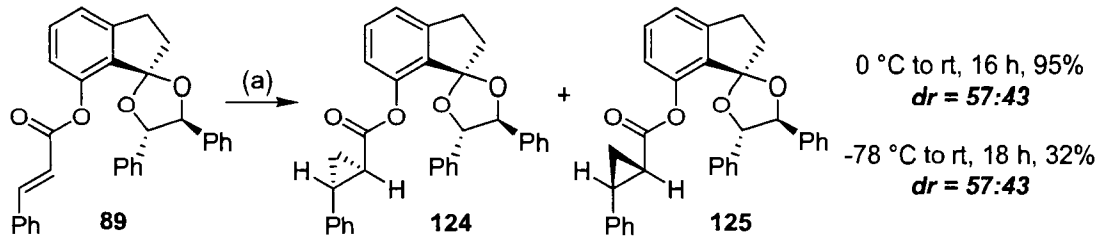
Reagents and conditions: (a) Et_2Zn, CH_2I_2, 1,2-dichloroethane.

The reaction was repeated and allowed to proceed for 21 h from -20 °C to room temperature. Following workup, the crude reaction product was obtained as a yellow oil. As determined by ^1H NMR spectroscopy, the cyclopropanation reaction had proceeded to 68% conversion. The cyclopropanes **123** were again formed in a high diastereomeric ratio (dr = 86:14). The mixture of ether **78** and cyclopropanes **123** were inseparable by thin-layer chromatography in a variety of solvent systems; therefore, the product was not purified. Attempts to liberate the cyclopropane from the auxiliary to determine its absolute stereochemistry were not undertaken.

2.8.5 Palladium-Catalyzed Cyclopropanation Reactions

It was found that the cinnamate **89** (R = Ph) could be cyclopropanated with diazomethane in the presence of catalytic quantities of palladium acetate. An ethereal azeotrope of diazomethane was distilled into a solution of the cinnamate **89** and palladium(II) acetate at 0 °C and the reaction mixture was allowed to warm slowly to room temperature. After 16 h, an inseparable mixture of cyclopropanes **124** and **125** was isolated in 95% yield. The diastereomeric ratio was 57:43 (**124**:**125**) as determined from the ^1H NMR spectrum of the crude reaction product (Scheme 2.8.8).

Scheme 2.8.8 Palladium-Catalyzed Cyclopropanation Reaction of the Cinnamate **89** (R = Ph)



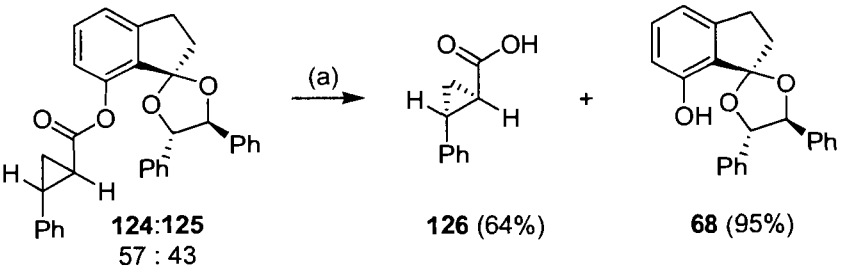
Reagents and conditions: (a) *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, KOH, EtOH, ether, 0 °C, 5 min; cinnamate **89**, $Pd(OAc)_2$ (0.5 mol %), CH_2Cl_2.

The reaction was repeated at -78 °C by distilling an ethereal azeotrope of diazomethane into a solution of the cinnamate **89** and a catalytic amount of palladium(II) acetate. The cyclopropanation reaction proceeded to a negligible extent after 2 h at -78 °C; therefore, it was allowed to warm slowly to room temperature over 16 h. The reaction did not proceed to completion and the cyclopropanes **124** and **125** were only isolated in 32% yield. As determined by ^{1}H NMR spectroscopy, the diastereoselectivity was similarly disappointing (dr = 57:43).

2.8.6 Determination of the Stereochemical Outcome in the Cyclopropanation Reaction

The diastereomeric mixture of cyclopropanes **124** and **125** (R = Ph, dr = 57:43) from the palladium-catalyzed cyclopropanation reaction of the cinnamate **89** was subjected to a lithium hydroxide-promoted hydrolysis reaction to determine the absolute stereochemical configuration of the major cyclopropane **124** (Scheme 2.8.9). The sign of the rotation of the carboxylic acid **126** was then compared to that of the known compound (major enantiomer shown).[78,74b]

Scheme 2.8.9 Lithium Hydroxide-Promoted Hydrolysis Reaction of the Diastereomeric Cyclopropanes **124** and **125**



Reagents and conditions: (a) LiOH, THF:H_2O (3:1), rt, 16 h.

The sense of stereochemical induction for the major cyclopropane **124** can be rationalized if the metal carbenoid **127** approached from the *Re* face (back face as drawn) of the *s-cis* conformer of the cinnamate **89** (Figure 2.8.2). The low diastereoselectivity observed in the cyclopropanation reaction could be a result of a competitive reaction of the *s-trans* conformation of the cinnamate, which would have afforded the diastereomeric product **125**.

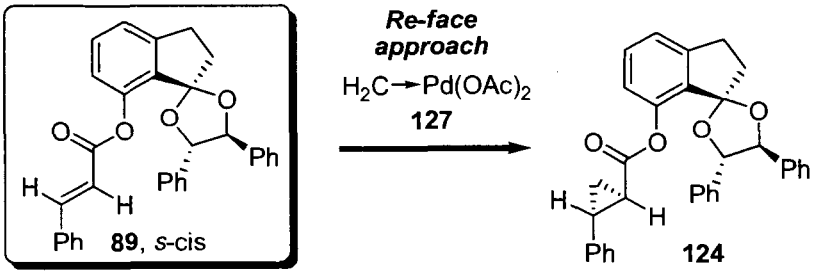


Figure 2.8.2 Rationale of the stereochemical outcome in the asymmetric palladium-catalyzed cyclopropanation reaction.

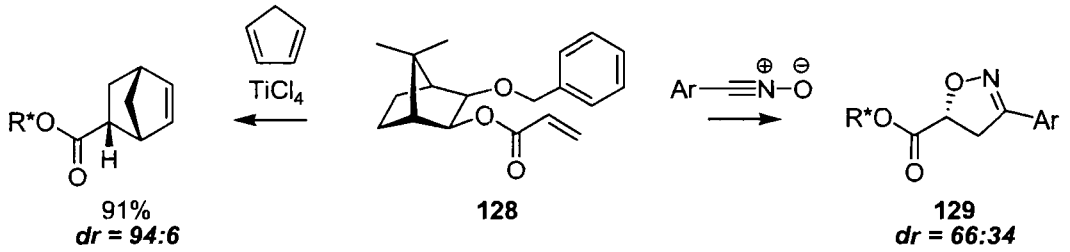
2.9 Asymmetric 1,3-Dipolar Cycloaddition Reactions of a Nitrile Oxide

2.9.1 Introduction and Background

The cycloaddition reactions of nitrile oxides and acrylates, derivatized with many chiral auxiliaries, have historically afforded the heterocyclic products in low diastereoselectivities even when using auxiliaries that have induced high levels of asymmetry in other chemical reactions. For example, in 1987, Curran and co-workers

used a series of known chiral auxiliaries to which they attached dipolarophiles for subsequent cycloaddition reactions with achiral nitrile oxides.[79] In their report, acrylates of L-menthol, Oppolzer's isoborneol and Oppolzer's sulfonamide auxiliaries were reacted with *p*-nitrobenzonitrile oxide (the acrylate **128** of Oppolzer's isoborneol is depicted, Scheme 2.9.1). The resultant 5-substituted isoxazolines **129** were produced regioselectively; however, the diastereoselectivities were low (dr = 52:48, 55:45 and 66:34, respectively). In contrast, Oppolzer's isoborneol had previously produced high diastereoselectivities (dr = 94:6) in the Lewis-acid promoted Diels-Alder reaction.

Scheme 2.9.1 Isoborneol as a Chiral Auxiliary in the Lewis Acid-Promoted Diels-Alder and Nitrile Oxide Addition Reactions of an Acrylate



91%
dr = 94:6

128

129
dr = 66:34

This suggested that the isoborneol auxiliary had the ability to effectively shield one of the diastereotopic faces of the substrate. The low diastereoselectivities observed in the nitrile oxide cycloaddition were attributed to poor conformational control of the acrylate, not to poor π-facial shielding of the acrylate.The 1,3-dipolar cycloaddition reaction of nitrile oxides could be used to evaluate the ability of the indanone-derived auxiliaries to bias the acrylate such that it reacted *via* a preferred conformation (Figure 2.9.1). The auxiliary **172** (R = *i*-Pr) showed good levels of facial selectivity in another cycloaddition reaction, the Diels-Alder reaction (dr = 91:9, see: Chapter 2.10.4).

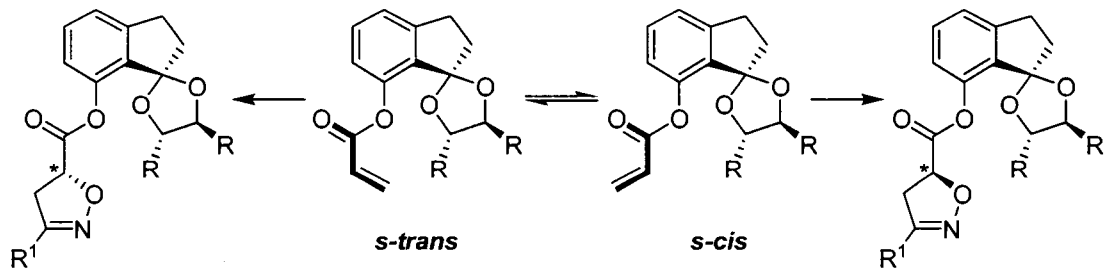


Figure 2.9.1 Nitrile oxide addition to *s-trans* and *s-cis* acrylate conformers forms diastereomeric products.

The 1,3-dipolar cycloaddition reaction is one of the most important synthetic methods to prepare five-membered heterocycles and often proceeds stereospecifically and with high regioselectivity.[80] In the cycloaddition reaction of nitrile oxides **130** to monosubstituted alkenes such as acrylates **131**, chiral 5-substituted isoxazolines **132** are usually formed as essentially single regioisomers (Figure 2.9.2).

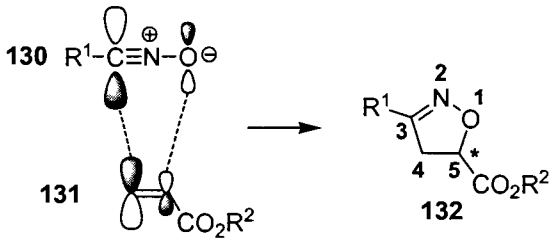
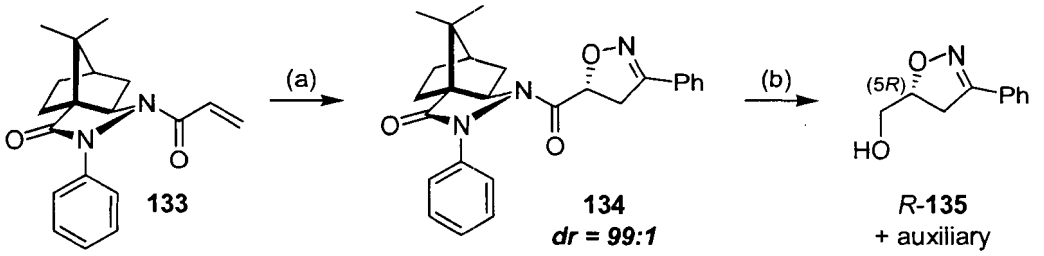


Figure 2.9.2 Frontier molecular orbitals in the reaction of a nitrile oxide **130** and acrylate **131**.

More recently, several chiral auxiliaries have been reported that impart high levels of asymmetric induction in the nitrile oxide addition reaction of α,β-unsaturated substrates. For example, the acrylamide **133** of a hydrazide chiral auxiliary reacted quantitatively with benzonitrile oxide with almost complete diastereoselection to afford the isoxazoline **134** (Scheme 2.9.2).[81] Reductive removal of the auxiliary liberated the alcohol **135**. The authors proposed that the auxiliary provided high conformational control based solely on steric interactions.

Scheme 2.9.2 Asymmetric Cycloaddition Reaction of Benzonitrile Oxide Using a Hydrazide Chiral Auxiliary

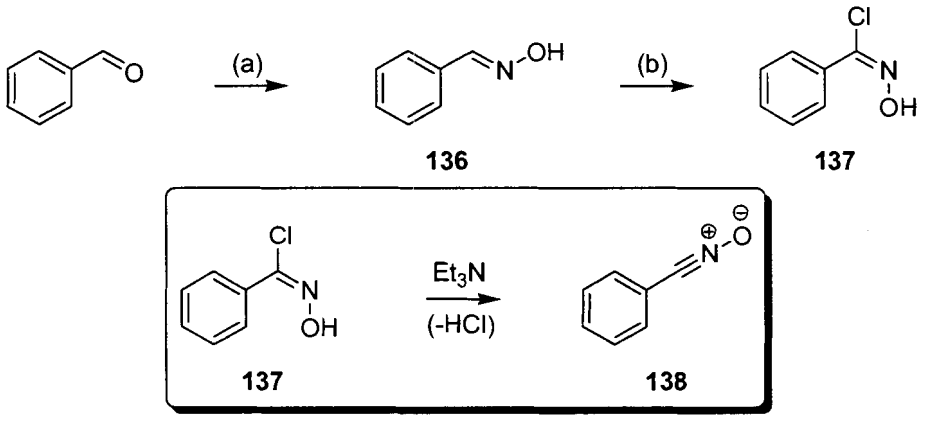


Reagents and conditions: (a) benzohydroximinoyl chloride, Et_3N, CH_2Cl_2, rt., 97% (b) lithium tri-*sec*-butylborohydride, THF, -78 °C, **135** (53%).

2.9.2 Nitrile Oxide Cycloaddition Reactions

The acrylate **76** (R = Ph), crotonate **88** (R = Ph), cinnamate **89** (R = Ph) and methacrylate **77** (R = Ph) were evaluated in 1,3-dipolar cycloaddition reactions with benzonitrile oxide. Benzonitrile oxide was prepared *in situ* by the action of triethylamine on benzohydroximinoyl chloride, as it is known to readily dimerize.[82,83] The chloride **137** was synthesized by a known two-step sequence from benzaldehyde and hydroxylamine hydrochloride (Scheme 2.9.3).[84] The resultant oxime **136** was reacted with *N*-chlorosuccinimide to afford the chloride **137**.

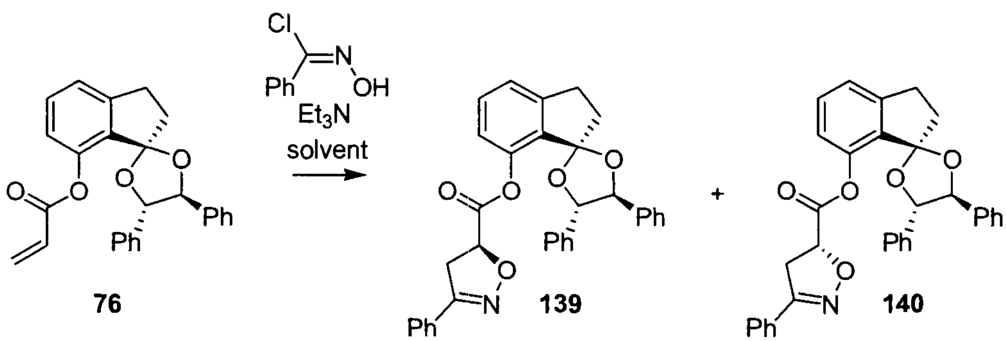
Scheme 2.9.3 Synthesis of Benzohydroximinoyl Chloride: A Benzonitrile Oxide Precursor



Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, NaOH, rt, 16 h, 66%. (b) NCS, DMF, 0 °C to rt, 2 h, 92%.

In the first attempted 1,3-dipolar cycloaddition reaction, triethylamine was added over 5 min to a solution of the acrylate **76** (R = Ph) and benzohydroximinoyl chloride **137** in benzene at 0 °C (entry 1, Table 2.9.1). The acrylate **76** reacted rapidly with the benzonitrile oxide **138** to form the isoxazolines **139** and **140** in 74% yield. As determined from the ^{1}H NMR spectrum of the crude reaction product, the diastereomeric ratio was 61:39 (**139**:**140**, for the major regioisomer) and the regioselectivity of the reaction was 88:12. A solution of the acrylate **76** and the chloride **137** in toluene at -78 °C was also treated with triethylamine. Again, the diastereomeric isoxazolines **139** and **140** were formed rapidly. However, in this case, the diastereoselectivity and regioselectivity remained essentially unchanged (entry 2).

Table 2.9.1 Optimization of the 1,3-Dipolar Cycloaddition Reaction of the Acrylate **76** (R = Ph) and Benzonitrile Oxide **138**



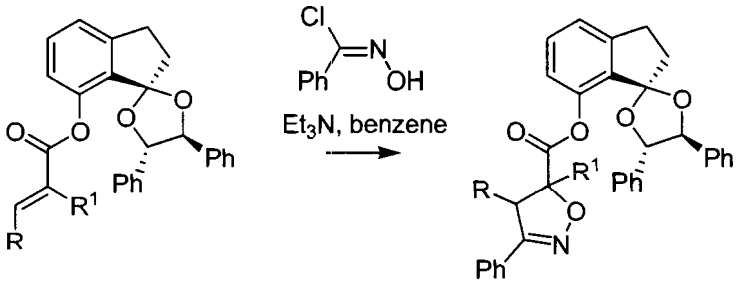
entry	substrate	solvent	conditions	yield[a]	dr (139:140)[b]	regioselectivity[b]
1	acrylate	benzene	0 °C, 10 min	74%	61:39	88:12
2	acrylate	toluene	-78 °C, 10 min	71%	57:43	89:11
3	acrylate	CH_2Cl_2	-78 °C, 4.5 h	72%	53:47	94:6
4	acrylate	THF	-78 °C, 3 h	n/d	52:48	93:7

[a] Isolated yields for the combined mixtures of regio- and diastereomers. [b] Determined from the ^{1}H NMR spectra of the crude reaction products.

Variation of the solvent to dichloromethane or tetrahydrofuran led to lower diastereoselectivities. The process, however, became slightly more regioselective (entries

3 and 4).* The nitrile oxide addition to both the crotonate **88** (R^1= Me) and cinnamate **89** (R^1 = Ph) substrates produced cycloadducts in similar diastereoselectivities but in lower regioselectivities (entries 1 and 2, Table 2.9.2). In the case of the methacrylate **77**, it was converted completely and rapidly to the cycloadducts upon reaction with benzonitrile oxide **138** (entry 3). The diastereoselectivity was, however, low but the regioselectivity remained relatively high.

Table 2.9.2 1,3-Dipolar Cycloaddition Reactions Involving Benzonitrile Oxide **138**: Variation of the α,β-Unsaturated Substrate



entry	substrate	conditions	yield	dr[a]	regioselectivity[a]
1	crotonate **88** (R^1 = H, R = Me)	0 °C to rt 3 days	n/d	57:33	66:34
2	cinnamate **89** (R^1 = H, R = Ph)	0 °C to rt 2 days	67%	60:40	78:22
3	methacrylate **77** (R^1 = Me, R = H)	0 °C to rt 20 min	n/d	56:44	84:16

[a] Determined from the ^{1}H NMR spectra of the crude reaction products.

2.9.3 Determination of the Stereochemical Outcome in the Nitrile Oxide Cycloaddition Reaction

The diastereomeric mixture of isoxazolines **139** and **140** (R = Ph, dr = 61:39) was reductively cleaved from the auxiliary **68** (R = Ph) using lithium tri-*sec*-butylborohydride and the absolute stereochemical configuration of the major adduct *S*-**135** was determined

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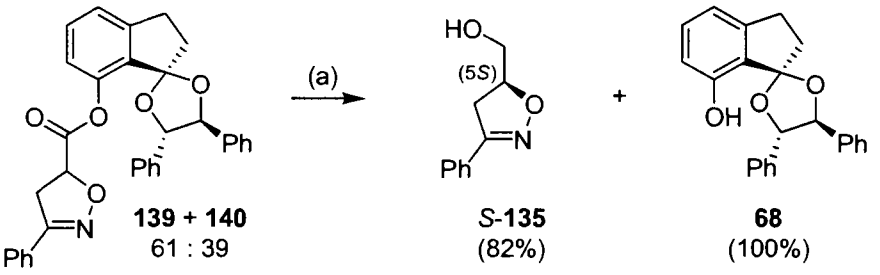
The minor diastereomer was relatively insoluble in ether and benzene. Thus, suspension of the diastereomeric mixture (dr = 61:39) in ether and filtration through a plug of silica gel provided the product in 54% yield. The diastereomeric ratio was found to be significantly enhanced (dr = 93:7).

by comparison of the sign of its optical rotation to that of the known compound.[85]

Scheme 2.9.4 Lithium Tri-*sec*-butylborohydride Reduction Reaction of the Diastereomeric Isoxazolines **139** (R = Ph) and **140** (R = Ph)



Reagents and conditions: (a) lithium tri-*sec*-butylborohydride, THF, 0 °C, 15 min.

The stereochemical configuration of the major isoxazoline **139** can be rationalized if benzonitrile oxide **138** approached from the *Si* face (top face as drawn) of the *s-cis* conformer of the acrylate **76** (Figure 2.9.3).[86*]

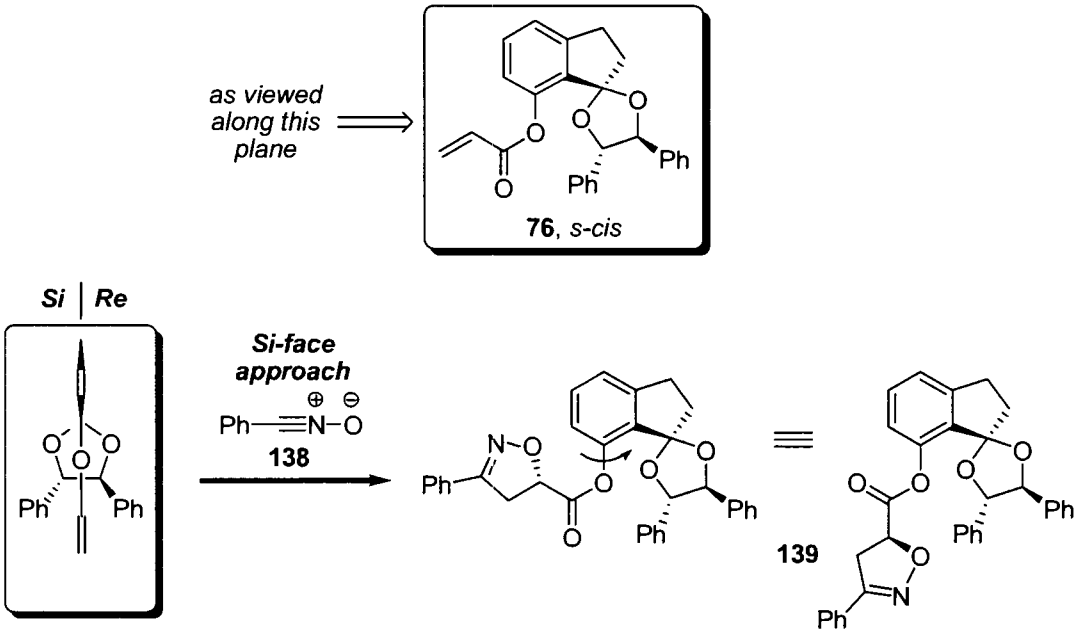


Figure 2.9.3 Rationale of the stereochemical outcome in the asymmetric 1,3-dipolar cycloaddition reaction.

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* Curran and co-workers have calculated that, in the case of the cycloaddition reaction of acrylic acid and the simplest nitrile oxide, fulminic acid, the *s-cis* transition state is favoured by 1.7 kcal/mol.

As the auxiliary **172** (R = *i*-Pr) had induced excellent levels of stereochemical induction in other reaction types (up to dr = 91:9, Chapter 2.10.4), the lack of any significant diastereoselection is likely a result of poor conformational control in this thermal reaction. Specifically, the difference in activation energies ($\Delta\Delta G^{\ddagger}$) for the reaction of the *s-cis* and *s-trans* conformations from a given face (*i.e.* back or front-face) was probably small.

2.10 Asymmetric Diels-Alder Reactions

2.10.1 Introduction

Asymmetric Diels-Alder reactions have been performed using both chiral dienes and dienophiles in the presence and absence of Lewis acids.[87] Uncatalyzed approaches that involve both chiral dienes and dienophiles have generally produced poor to moderate diastereoselectivities. However, Lewis acid-promoted Diels-Alder reactions involving both chiral dienes and dienophiles have proven to be more effective. The reason for enhanced levels of asymmetric induction in Lewis acid-catalyzed Diels-Alder reactions is two-fold. Firstly, Lewis acid coordination to a chiral acrylate significantly increases its reactivity often allowing the subsequent Diels-Alder reaction to be performed at low temperatures. Secondly, Lewis acid coordination to an acrylate usually results in a strong *s-trans* conformational preference and, as stated by Houk and co-workers, "the conformation of the dienophile in the transition state is an important element controlling the stereochemical outcome of the Diels-Alder reactions of chiral dienophiles" (Figure 2.10.1).[88*]

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* Houk and co-workers have calculated, for various acrylates that the *s-trans* conformation is more stable than the *s-cis* conformation primarily based upon minimization of unfavourable steric interactions.

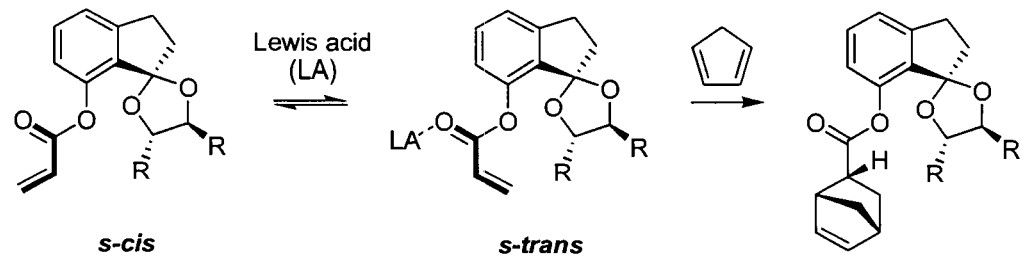


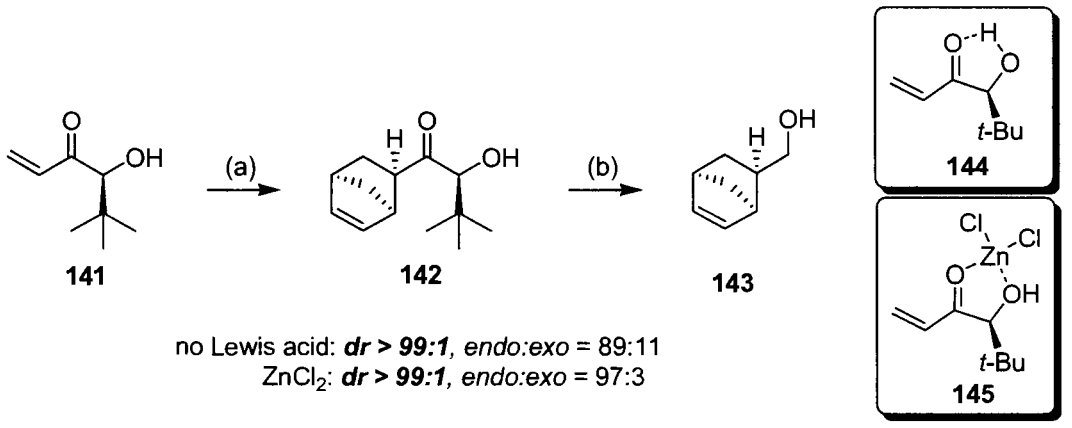
Figure 2.10.1 Ester conformational control upon Lewis acid coordination in the Diels-Alder reaction.

The Lewis acid-catalyzed Diels-Alder reaction could be used to evaluate the ability of the 7-hydroxyindan-1-one-derived chiral auxiliaries to differentiate the π-faces of α,β-unsaturated esters, particularly acrylates, in that this reaction often proceeds with a high degree of conformational control within the substrate.

2.10.2 Background

A diastereoselective Diels-Alder reaction was reported by Masamune and co-workers in 1983 in which a chiral acrylate **141** was reacted with cyclopentadiene to form the Diels-Alder adduct **142** with high diastereoselectivity both in the absence and in the presence of a Lewis acid (Scheme 2.10.1).

Scheme 2.10.1 A Chiral Dienophile in an Asymmetric Diels-Alder Reaction



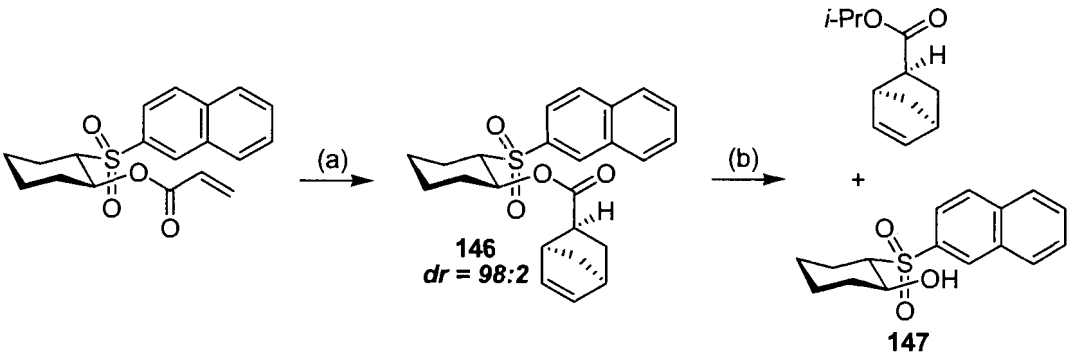
no Lewis acid: ***dr* > 99:1**, *endo:exo* = 89:11
$ZnCl_2$: ***dr* > 99:1**, *endo:exo* = 97:3

Reagents and conditions: (a) cyclopentadiene, toluene, -20 °C, 24 h, 90% *or* cyclopentadiene, $ZnCl_2$ (1 equiv), toluene, -43 °C, 1 h, 95%. (b) (i) DIBAL (3 equiv), -43 °C, toluene. (ii) $NaIO_4$, MeOH:H_2O (4:1), 24 h. (iii) DIBAL (3 equiv), -43 °C, toluene, 58% (over three steps).

In the absence of a Lewis acid, the acrylate was presumably activated by the formation of the intramolecular hydrogen bonded intermediate **144**. When zinc chloride was included, the rate, yield and *endo*:*exo* ratio all increased through the transient formation of a more activated dienophile, the zinc chelate **145**. Formally, this approach did not involve a chiral auxiliary in that following the iterative reduction/oxidation cleavage reactions that were used to liberate the cycloadduct **143**, the chiral director was consumed.

A recent example of a highly effective chiral auxiliary **147**, prepared by a lipase-catalyzed kinetic resolution of an racemic alcohol precursor, is that developed by Sarakinos and Corey (Scheme 2.10.2).[62]

Scheme 2.10.2 A Chiral Sulfone Auxiliary in an Asymmetric Diels-Alder Reaction

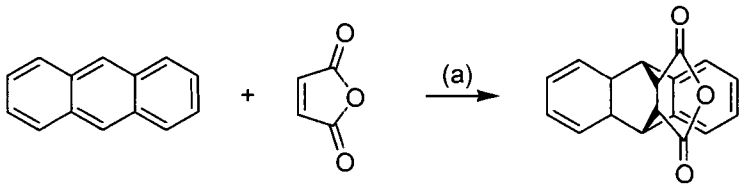


Reagents and conditions: (a) cyclopentadiene, BCl_3 (1 equiv), toluene, -78 °C, 30 min, 99%, *endo*:*exo* > 98:2. (b) $Ti(O\textit{i}\text{-}Pr)_4$ (3.3 equiv), *i*-PrOH, 85 °C, 57 h.

As determined by X-ray crystallography, the β-naphthyl ring of the auxiliary **147** is involved in a π-stacking interaction with the acrylate subunit. The author's argued that the excellent diastereoselectivities observed in the boron trichloride-catalyzed Diels-Alder reaction was a result of this π-stacking interaction. The chiral auxiliary **147** was recovered by cleaving the Diels-Alder adduct **146** in a Lewis acid-promoted transesterification reaction.[89]

In 1960, Yates and co-workers discovered a phenomenal rate enhancement in the Diels-Alder reaction of anthracene and maleic anhydride when the reaction was performed in the presence of the Lewis acid, aluminum trichloride (Scheme 2.10.3). Extrapolation of the rate curve for the uncatalyzed reaction indicated that the reaction would require nearly seven months to reach 95% conversion.

Scheme 2.10.3 The First Lewis-Acid Promoted Diels-Alder Reaction

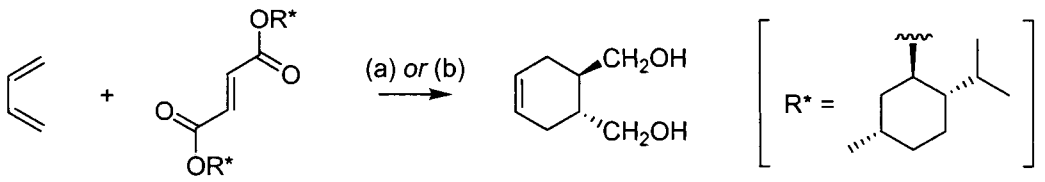


$AlCl_3$: **1.5 min**
none: **~ 4800 h**

Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, rt, quantitative.

In 1961, Walborsky and co-workers showed that the use of aluminum trichloride, here in a stoichiometric quantity, provided a remarkable increase in both the rate (-80 °C, 1 h *vs.* 67 °C, 6 h) and diastereoselectivity obtained in the Diels-Alder reaction of butadiene and a chiral menthol-derived fumarate **148**.[90]

Scheme 2.10.4 The First Lewis Acid-Promoted Stoichiometric Asymmetric Diels-Alder Reaction



148

none: ***dr = 51:49***
$AlCl_3$: ***dr = 78:22***

Reagents and conditions: (a) (i) chiral fumarate **148**, butadiene (7.4 equiv), hydroquinone (*cat.*), benzene, 67 °C, 6 h. (ii) $LiAlH_4$ 72% (over two steps) *or* (b) (i) chiral fumarate **148**, butadiene (7.4 equiv), $AlCl_3$ (1 equiv), benzene, -80 °C, 1 h, 71%. (ii) $LiAlH_4$, 71% (over two steps)

The mechanism of the Diels-Alder reaction has been extensively studied. Frontier molecular orbital theory has been successfully used to rationalize both the

stereochemistry and regiochemistry of the Diels-Alder reaction.[91] One particular stereochemical aspect of the Diels-Alder reaction, the "*Endo* Rule", deserves further explanation.[92*] Woodward and Hoffmann rationalized the "*Endo* rule" invoking the concept of secondary orbital interactions (Figure 2.10.2).[93]

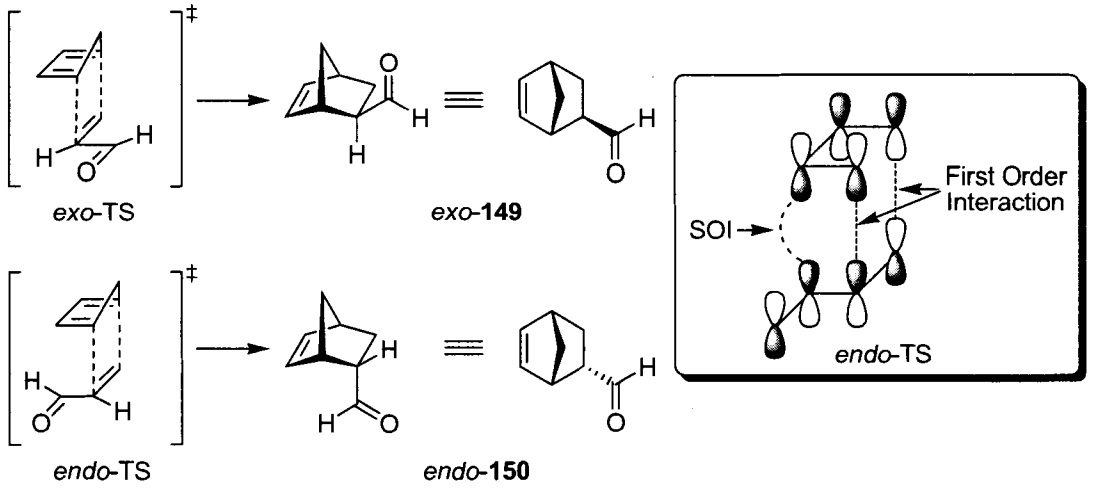


Figure 2.10.2 Frontier molecular orbital rationale for the *endo*-selectivity in kinetic Diels-Alder reactions.

First order interactions (or primary orbital interactions) are those that lead directly to the formation of new chemical bonds; whereas, secondary orbital interactions are those, favourable or unfavourable, that lead to additional attractive or repulsive forces, respectively, between the reacting components. In the *endo*-transition state, favourable (in-phase) secondary orbital interactions are present between the diene and dienophile increasing the net bonding in the transition state, thus, lowering the activation energy for *endo*-approach. The thermodynamic stability of the *exo*-adduct **149** is greater than that of the *endo*-adduct **150** based on steric considerations. Thus, when Diels-Alder reactions are performed under kinetic conditions (*i.e.* low temperature, reactive diene/dienophile), the *endo*-adduct tends to be formed preferentially while under thermal conditions, where

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* *endo*- within, from the Greek word, *endon*. *exo*- without, from the Greek word, *exon*. These terms are used to denote the relative positions of the dienophilic substituent and the diene in the reaction transition state and product.

the reaction pathway is made reversible, the more stable *exo*-isomer accumulates.

2.10.3 Diels-Alder Reactions: Survey of Lewis Acids

The nature of the Lewis acid plays a pivotal role in regio- and stereoselective Diels-Alder reactions and, for this reason, a variety of Lewis acids were screened for the reaction of the acrylate **76** (R = Ph) and cyclopentadiene (Table 2.10.1). Typically, the Lewis acid was added to a solution of the acrylate **76** (R = Ph) at -78 °C before the addition of an excess amount of cyclopentadiene (10 to 50 equivalents). The *endo*:*exo* ratio and diastereoselectivity of the major *endo* isomer were determined by ^{1}H NMR analysis of the product mixtures.* In most cases, the minor *exo* adduct was undetectable by ^{1}H NMR (*i.e.* *endo*:*exo* > 98:2). In certain cases, the diastereomeric Diels-Alder adduct mixture **151** and **152** was not isolated from the reaction mixture. Rather, the percent conversion was determined from its ^{1}H NMR spectrum.

In the first case, the cycloaddition reaction did not occur when the strongly Lewis acidic aluminum trichloride was employed and, as suggested by thin-layer chromatography, significant polymerization of cyclopentadiene occurred (entry 1, Table 2.10.1). The use of boron trifluoride etherate afforded the cycloadducts **151** and **152** in good overall conversion but low diastereoselectivity (entry 2) and boron trichloride led to significant decomposition of the acrylate **76** (entry 3). Zinc chloride was not sufficiently active to catalyze the reaction to an appreciable extent and the cycloadducts **151** and **152** were produced unselectively (entry 4). A series of titanium Lewis acids were also screened. Titanium isopropoxide produced the Diels-Alder adducts in high yield but with no diastereoselectivity (entry 5).

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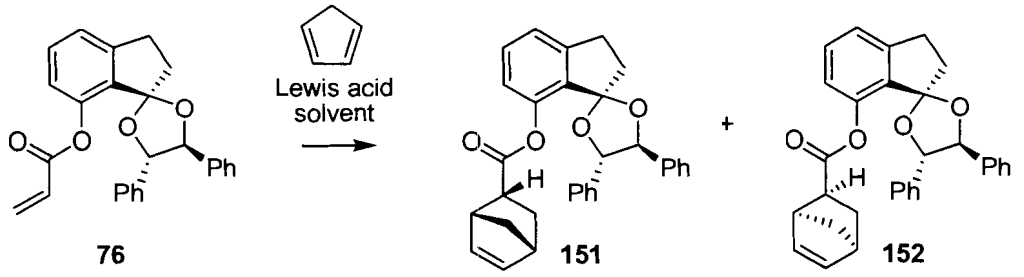
* To unambiguously determine the diastereoselectivities from the ^{1}H NMR spectrum of the Diels-Alder adducts **151 and 152**, a mixture of all 4 possible diastereomers was prepared by reacting the auxiliary **68** (R = Ph) with racemic 5-norbornenecarboxylic acid chloride (*endo*:*exo* ~ 50:50).

Table 2.10.1 Selection of the Lewis Acid for the Diels-Alder Reaction of the Acrylate **76** (R = Ph) and Cyclopentadiene



76 **151** **152**

entry	Lewis acid	conditions[a]	yield	dr (151:152)[b]
1	$AlCl_3$ (0.70 equiv)	-78 °C to rt, 16 h	no rxn.	n/a
2	$BF_3{\cdot}OEt_2$ (1.2 equiv)	-78 °C to rt, 16 h	81%[c]	55:45
3	BCl_3 (2.0 equiv)	-78 °C to rt, 16 h	decomposition	n/a
4	$ZnCl_2$ (1.0 equiv)	-78 °C to rt, 16 h	18%[c]	55:45
5	$Ti(O\textit{i}Pr)_4$ (1.0 equiv)	-78 °C to rt, 48 h	90%	50:50
6	$(Cp)_2TiCl_2$ (0.76 equiv)	-78 °C to rt, 24 h	68%[c]	53:47[d]
7	$TiCl_4$ (0.75 equiv)	-78 °C, 45 min	37%[e]	24:76
8	$SnCl_4$ (2.0 equiv)	-78 °C to rt, 16 h	~ 50%[c]	~ 50:50
9	Et_2AlCl (1.5 equiv)	-78 °C, 10 min	83%	74:26
10	Et_2AlCl (1.5 equiv)	-78 °C, 10 min[f]	89%	83:17

[a] 10 to 50 equivalents of cyclopentadiene were added and the solvent was CH_2Cl_2 unless otherwise specified. [b] Determined from the ^1H NMR spectra of the crude reaction products; *endo*:*exo* ratio > 98:2 unless otherwise specified. [c] % conversion. [d] *endo*:*exo* = 86:14. [e] 52% yield based on recovered starting material. [f] The solvent employed was toluene.

Bis(cyclopentadienyl)titanium dichloride gave a lower conversion and produced a slight stereochemical induction; however, the *endo*:*exo* selectivity was lower (entry 6). The highly active Lewis acid, titanium tetrachloride, produced the cycloadducts within 45 min at -78 °C with moderate diastereoselectivity. However, the recovered yield was low

due to partial decomposition of the acrylate (entry 7).* Interestingly, in this case, a reversal in asymmetric induction occurred. The ^{1}H NMR spectrum of the crude reaction indicated that the diastereomer **152** was the major constituent. The use of tin tetrachloride led to incomplete conversion but with no observable stereochemical induction (entry 8). Lastly, it was found that diethylaluminum chloride could rapidly promote the Diels-Alder reaction in good yield and diastereoselectivity (dr = 74:26, entry 9). For this reason, it was selected as the Lewis acid for subsequent optimization studies.

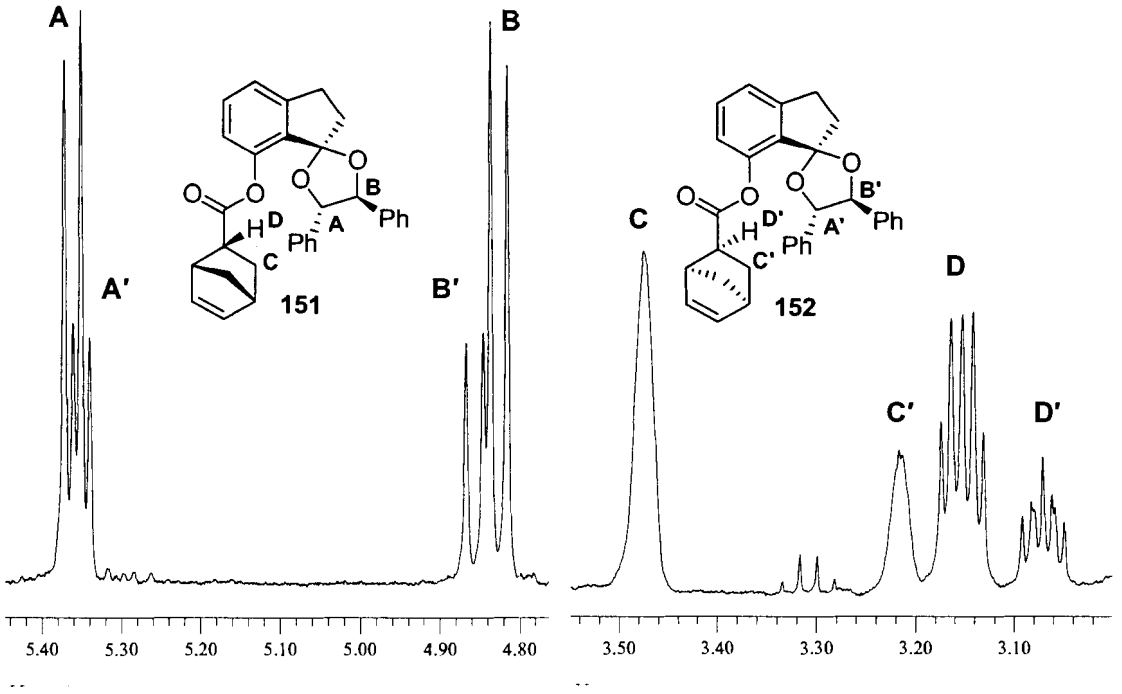


Figure 2.10.3 Regions of the ^{1}H NMR (400 MHz, C_6D_6) spectrum for the crude diastereomeric Diels-Alder adducts **151** and **152** prepared using diethylaluminum chloride in dichloromethane (entry 9, Table 2.10.1).

The reaction solvent was varied to determine its effect on the efficiency of the Diels-Alder reaction. When the Diels-Alder reaction was performed in toluene, the adducts **151** and **152** were formed rapidly and in high yield (89%, entry 10).

* The Diels-Alder adduct was recovered in 76% yield and in similar diastereoselectivity when the reaction was performed in the presence of 4 Å molecular sieves.

Interestingly, the diastereomeric ratio increased significantly (dr = 83:17) when this solvent was employed.

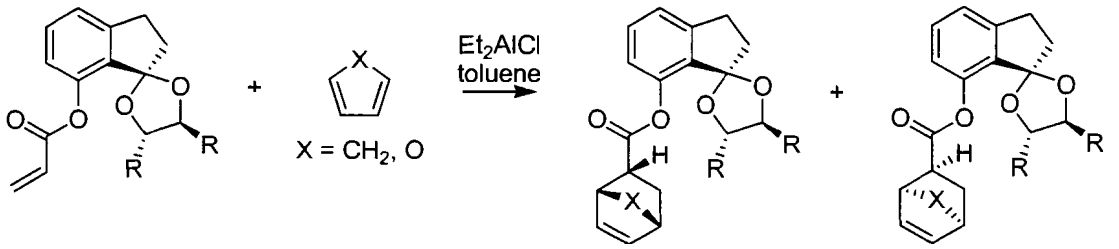
Two regions of the ^{1}H NMR spectrum of the product mixture **151** and **152** (entry 9, Table 2.10.1) were suitable for determination of the diastereoselectivity of the Diels-Alder reaction (Figure 2.10.3). Only signals for the *endo* isomers could be identified. The "interior" acetal hydrogen (**A**) was observed downfield of the "exterior" hydrogen (**B**) by δ 0.6 ppm and was again indicative of the distinct chemical environments of the two faces of the acetal moiety. The partially resolved acetal hydrogen signals (**A′** and **B′**) are those of the minor *endo*-diastereomer **152**. In the upfield region of the spectrum, signals for the bridge hydrogens (**C** and **C′**) and α-hydrogens (**D** and **D′**) of the major and minor *endo*-diastereomers were well resolved. Integration of these resolved signals allowed for the diastereomeric ratio to be determined.

2.10.4 Variation of the Auxiliary, Dienophile and Diene Structure

A series of Diels-Alder reactions involving the acrylates **75** (R = Me), **80** (R = CH_2OMe), **81** (R = CH_2OBn) and **82** [R = CH_2O(1-Np)] using diethylaluminum chloride as the Lewis acid in toluene were performed (Table 2.10.2). The acrylate **75** (R = Me) readily reacted with cyclopentadiene at -78 °C in good yield (entry 1). As determined by ^{1}H NMR spectroscopy, the *endo*:*exo* ratio was > 98:2 and the diastereoselectivity was 64:36 (**153**:**154**). The *endo*:*exo* ratio remained high for most of the remaining reactions. The tartrate-derived acrylate **80** (R = CH_2OMe) reacted more slowly with cyclopentadiene and the diastereomeric Diels-Alder adducts **155** and **156** were isolated, after 3.5 h, as an inseparable mixture in 65% yield (entry 2). The diastereomeric ratio was 55:45 as determined from the ^{1}H NMR spectrum of the crude reaction product. The second tartrate-derived acrylate **81** (R = CH_2OBn) afforded the Diels-Alder adducts **157** and **158** in higher yield; however, in similarly low

diastereoselectivity (entry 3).

Table 2.10.2 Diethylaluminum Chloride-Promoted Diels-Alder Reactions: Variation of the Auxiliary, Solvent, Temperature and Diene



entry	acrylate	Lewis acid	conditions[a]	yield	dr[b] (products)
1	**75** (R = Me)*	Et_2AlCl (1.5 equiv)	-78 °C, 15 min	72%	64:36 **(153:154)**
2	**80** (R = CH_2OMe)	Et_2AlCl (1.5 equiv)	-78 °C, 3.5 h	65%	55:45 **(155:156)**
3	**81** (R = CH_2OBn)	Et_2AlCl (1.5 equiv)	-78 °C, 2 h	86%	54:46 **(157:158)**
4	**82** [R = CH_2O(1-Np)]	Et_2AlCl (1.5 equiv)	-78 °C, 2.5 h	77%	68:32 **(159:160)**
5	**83** (R = *i*-Pr)	Et_2AlCl (1.5 equiv)	-78 °C, 1 h	71%	91:9 **(161:162)**
6	**76** (R = Ph)	Et_2AlCl (1.5 equiv)	-98 °C, 10 min	85%	87:13 **(151:152)**
7	**76** (R = Ph)	Et_2AlCl (1.5 equiv)	-78 °C, 15 min[c]	66%	87:13[d] **(151:152)**
8	**76** (R = Ph)	Et_2AlCl (1.5 equiv)	5 °C, 15 min[e]	58%	66:34[f] **(151:152)**
9	**76** (R = Ph)	Et_2AlCl (1.5 equiv)	-78 °C to rt, 18 h[g]	no rxn.	n/a **(163:164)**

[a] 50 equivalents of cyclopentadiene (X = CH_2) were added and the solvent was toluene unless otherwise stated. [b] Determined from the ^1H NMR spectra of the crude reaction products; *endo*:*exo* ≥ 98:2 unless otherwise stated. [c] The solvent was toluene:fluorobenzene (5:1). [d] *endo*:*exo* = 94:6. [e] The solvent was hexafluorobenzene. [f] *endo*:*exo* = 90:10. [g] 50 equivalents of furan (X = O) were added. *Enantiomers of those indicated in the reaction scheme.

The third tartrate-derived acrylate **82** [R = CH_2O(1-Np)] reacted with cyclopentadiene within 2.5 h at -78 °C to afford the Diels-Alder adducts **159** and **160** in 77% yield. In this case, the diastereoselectivity was found to be 68:32 (**159**:**160**,

entry 4). The last tartrate-derived acrylate, 7-acryloyloxyindan-1-one (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol acetal **83** (R = *i*-Pr), was more reactive than the previous tartrate-derived acrylates affording the Diels-Alder adducts **161** and **162** in 71% after 1 h at -78 °C (entry 5).As determined by ^{1}H NMR spectroscopy, the *endo*:*exo* ratio was > 98:2 and the cycloadducts **161** and **162** were produced in an excellent ratio (91:9). Although the acrylate **83** (R = *i*-Pr) was found to react with the highest diastereoselectivity, the ease of preparation of the acrylate **76** (R = Ph) from the commercially-available diol **29** (R = Ph) and the good selectivities that were obtained using this compound made it a good candidate for further studies.* Thus, three additional reactions were performed using the acrylate **76** (R = Ph).

When the reaction temperature was lowered from -78 °C to -98 °C, the Diels-Alder reaction rate remained essentially the same and the adducts were obtained in similar yield and slightly increased diastereoselectivity (dr = 87:13 *vs.* 83:17 at -78 °C, entry 6). The Diels-Alder reaction was performed at -78 °C in a 5:1 mixture of toluene:fluorobenzene. Although the diastereoselectivity increased slightly, the yields and *endo*:*exo* ratio decreased to 66% and 94:6, respectively (entry 7). When hexafluorobenzene was employed as the reaction solvent, the Diels-Alder reaction rapidly proceeded at 5 °C; however, the yield, diastereoselectivity and *endo*:*exo* ratio were all lower (entry 8).† The Diels-Alder adducts **163** and **164** in the reaction of furan (X = O) and the acrylate **76** (R = Ph) were not produced after an extended reaction time (entry 9).

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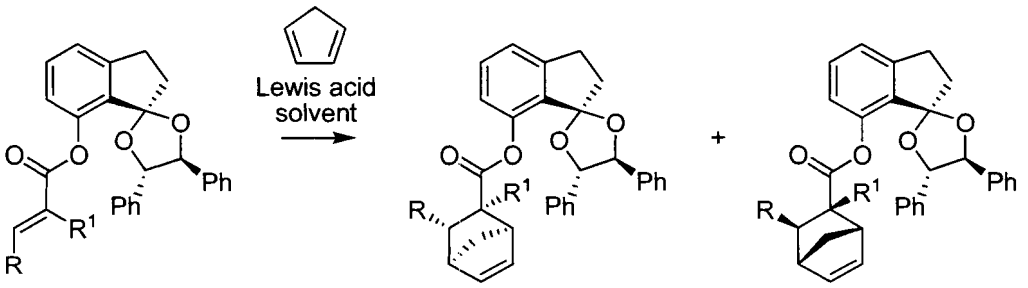
* The diol **56** (R = *i*-Pr) required a six-step synthesis from (2*R*,3*R*)-diethyl tartrate.

† Fluorobenzene and hexafluorobenzene were used as solvents to determine if a π-π interaction between the auxiliary and the solvent could result in an increase in the diastereoselectivity of the reaction. The reaction was significantly more diastereoselective when performed in toluene as compared to dichloromethane. Of note, the melting point of hexafluorobenzene is 4 °C; therefore, the Diels-Alder reaction involving its use as a solvent was performed at 5 °C.

The crotonate **87**, cinnamate **89** and methacrylate **77** were evaluated in the Lewis-acid promoted Diels-Alder reaction with cyclopentadiene (Table 2.10.3). The crotonate **87** reacted completely after 1 h to afford exclusively the *endo* adducts **165** and **166** (> 98:2) in low diastereoselectivity (dr = 53:47, entry 1). The cinnamate **89** (R = Ph) was found to be unreactive with cyclopentadiene and diethylaluminum chloride at -78 °C (entry 2). Even when the reaction mixture was allowed to warm to room temperature, no cycloadducts were formed.

Table 2.10.3 Diethylaluminum Chloride-Promoted Diels-Alder Reactions: Variation of the α,β-Unsaturated Substrate



entry	substrate	Lewis acid	conditions[a]	yield	dr[b] (products)
1	crotonate **87** (R = Me, R^1 = H)	Et_2AlCl (1.5 equiv)	-78 °C, 1 h toluene	90%	53:47 (**165**:**166**)
2	cinnamate **89** (R = Ph, R^1 = H)	Et_2AlCl (1.5 equiv)	-78 °C to rt, 16 h, toluene	no rxn.	n/a (**167**:**168**)
3	cinnamate **89** (R = Ph, R^1 = H)	$TiCl_4$ (0.75 equiv)	-78 °C to rt, 16 h, CH_2Cl_2	decomposition	n/a (**167**:**168**)
3	cinnamate **89** (R = Ph, R^1 = H)	Et_2AlCl (1.5 equiv)	-78 °C to rt, 16 h, CH_2Cl_2	no rxn.	n/a (**167**:**168**)
4	methacrylate **77** (R = Ph, R^1 = Me)	Et_2AlCl (1.5 equiv)	-78 °C to rt, 22 h, toluene	32%[c]	54:46 (**169**:**170**)

[a] 50 equivalents of cyclopentadiene were added [b] Determined from the ^1H NMR spectra of the crude reaction products; *endo*:*exo* > 98:2 unless otherwise stated. [c] *endo*:*exo* = 68:32; the diastereomeric ratio for the *exo*-adducts was 64:36.

The reaction was repeated using the stronger Lewis acid, titanium tetrachloride; however, significant decomposition of the cinnamate **89** occurred (entry 3). The

methacrylate **77** was less-reactive than the acrylate or the crotonate affording the cycloadducts in relatively low yield (34%, entry 4). The *endo*:*exo* and diastereomeric ratios were also found to be low.

2.10.5 Preliminary Studies Using Diethylaluminum Chloride

During the course of preliminary studies involving diethylaluminum chloride in the Diels-Alder reaction of the acrylate **76** (R = Ph) and cyclopentadiene, an interesting discovery was made. It was found that a commercially-available solution of diethylaluminum chloride in hexanes, in which some white precipitate had formed, was able to catalyze the Diels-Alder reaction in higher yield (93%) and diastereoselectivity (dr = 92:8). Freshly-prepared solutions of diethylaluminum chloride were found to catalyze the same reaction in 89% yield and with a diastereomeric ratio of 83:17 (entry 10, Table 2.10.1).* This "old" solution was also observed to catalyze the Diels-Alder reaction of the acrylate **82** [R = CH_2O(1-Np)] and cyclopentadiene with significantly higher diastereoselection (74% yield, dr = 87:13 *vs.* 77% yield, dr = 68:32, entry 4, Table 2.10.2).

An investigation to discover the reason for the enhanced stereoselectivities observed in these Diels-Alder reactions was undertaken. A potential explanation, in this case, was that the concentration of diethylaluminum chloride was somewhat lower because of hydrolysis on storage. The white precipitate in the solution supported this theory if it was an insoluble product of the hydrolysis of diethylaluminum chloride. For this reason, the Diels-Alder reaction was repeated using less than 1 equivalent of a freshly-prepared solution of diethylaluminum chloride.

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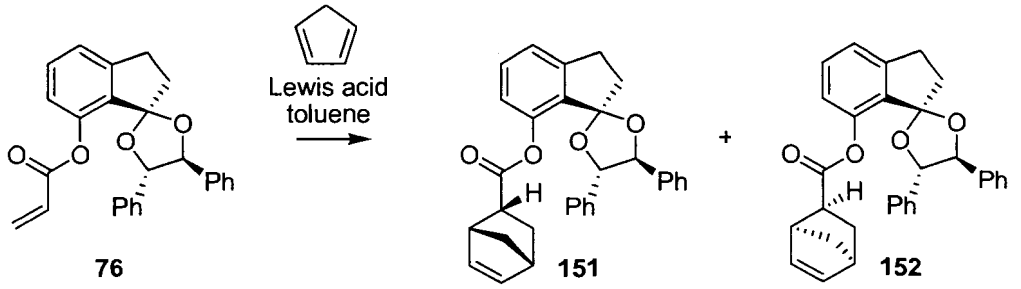
* Freshly-prepared solutions of diethylaluminum chloride were used in all of the previous studies described.

Table 2.10.4 Aluminum Lewis Acid-Catalyzed Diels-Alder Reactions of the Acrylate **76** (R = Ph) and Cyclopentadiene



76 **151** **152**

entry	Lewis acid	conditions[a]	yield	dr[b]
1	Et_2AlCl[c] (1.5 equiv)	-78 °C, 10 min	93%	92:8
2	Et_2AlCl (1.5 equiv)	-78 °C, 10 min[d]	89%	83:17
3	Et_2AlCl (0.78 equiv)	-78 °C, 20 min	84%	83:17
4	$MeAlCl_2$ (1.5 equiv)	-78 °C, 10 min	n/d	82:18
5	Me_3Al (1.5 equiv)	-78 °C to rt, 16 h	64%[e]	58:42[f]
6	MAO (1.5 equiv)	-78 °C, 45 min	90%	68:32

[a] 50 equivalents of cyclopentadiene were added and the solvent was toluene. [b] Determined from the ^1H NMR spectra of the crude reaction products; *endo*:*exo* > 98:2 unless otherwise stated. [c] "Old" solution of Et_2AlCl was used. [d] Freshly-prepared solution of Et_2AlCl was used. [e] % conversion. [f] *endo*:*exo* = 82:18.

However, when the reaction was performed using 0.78 equivalents of diethylaluminum chloride, although the reaction required slightly longer to go to completion (20 min at -78 °C *vs.* 10 min when 1.5 equivalents diethylaluminum chloride was used), the Diels-Alder adducts **151** and **152** were obtained in 84% yield (entry 2 *vs.* entry 3, Table 2.10.4). In this case, the diastereomeric ratio was found to be 83:17 as determined by analysis of the ^1H NMR spectrum of the crude reaction product. Three additional aluminum-containing Lewis acids of varying Lewis acidity were screened to determine if the active component in the "old" solution of diethylaluminum chloride was a more or less acidic species than diethylaluminum chloride. Thus, the more Lewis acidic, methylaluminum dichloride, was used to promote the Diels-Alder reaction which

proceeded rapidly at -78 °C to afford the cycloadducts. The diastereoselectivity remained high (dr = 82:18, entry 4).[94] The crude ^{1}H NMR spectrum from this reaction revealed some decomposition products as well as constituents resulting from the polymerization of cyclopentadiene; however, the desired Diels-Alder adducts were present as the major component. The mild Lewis acid, trimethylaluminum, was found to catalyze the Diels-Alder reaction; however, an extended period of time and a higher reaction temperature was required (entry 5). After 16 h, the reaction had proceeded to 68% conversion and the cycloadducts **151** and **152** were obtained in low diastereoselectivity (dr = 58:42). As well, the typically high *endo*:*exo* ratio observed in other cases decreased to 82:12 when this Lewis acid was employed.[95,96,97*] Lastly, the Lewis acid, methylalumoxane, which has been used almost exclusively as a co-catalyst in olefin polymerizations, was evaluated as a promoter in the Diels-Alder reaction.[98,99†] Although this Lewis acid was an effective catalyst in the Diels-Alder reaction rapidly producing exclusively the *endo*-adducts in high yield, the diastereoselectivity in the reaction was low (entry 6, dr = 68:32).

In addition, a series of experiments were performed using diethylaluminum chloride solutions that were partially hydrolyzed by the addition of varying amounts of water (Table 2.10.5). Experimentally this was achieved by adding an aliquot of water to a stirred solution of diethylaluminum chloride (1.0 M) at -78 °C and allowing the solution to warm to room temperature. Portions of these partially hydrolyzed solutions were then used in the subsequent Diels-Alder reactions. In one instance, the cycloaddition was

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* Trimethylaluminum has been used to catalyze cation-alkene addition reactions; however, few examples of its use to catalyze Diels-Alder reactions have been reported likely due to its ability to act as a nucleophilic source of a methyl group. However, modification of trimethylaluminum by reaction with bulky phenols or chiral nonracemic binaphthols have afforded more reactive achiral and chiral catalysts, the latter being used in asymmetric hetero Diels-Alder reactions.

† Methylalumoxane promotes the asymmetric Diels-Alder reaction of di-L-menthyl fumarates in good diastereoselectivity.

performed using a solution of the Lewis acid that contained 1.5 equivalents of diethylaluminum chloride and 0.75 equivalents of water, both with respect to the acrylate **76** (R = Ph, entry 1). The reaction proceeded rapidly and afforded the Diels-Alder adducts with slightly increased diastereoselection (dr = 86:14). Another reaction was performed using diethylaluminum chloride (1.5 equivalents) and water (0.37 equivalents) which rapidly afforded the products with an increased diastereoselectivity (dr = 90:10, entry 2). In addition, using diethylaluminum chloride (1.5 equivalents) and a trace amount of water (0.15 equivalents), the cycloadducts were produced rapidly in a diastereomeric ratio of 85:15 (entry 3).

Table 2.10.5 Diels-Alder Reactions of the Acrylate **76** (R = Ph) and Cyclopentadiene Using Partially Hydrolyzed Diethylaluminum Chloride

entry	Lewis acid	conditions[a]	yield (%)	dr[b] (*endo*:*exo*)
1	Et_2AlCl (1.5 equiv):H_2O (0.75 equiv)	-78 °C, 10 min	n/d	86:14
2	Et_2AlCl (1.5 equiv):H_2O (0.37 equiv)	-78 °C, 10 min	n/d	90:10
3	Et_2AlCl (1.5 equiv):H_2O (0.15 equiv)	-78 °C, 10 min	n/d	85:15
4	Et_2AlCl (1.0 equiv)	-78 °C, 10 min	n/d	90:10

[a] 50 equivalents of cyclopentadiene were added and the solvent was toluene. [b] Determined from the ^1H NMR spectra of the crude reaction products; *endo*:*exo* > 98:2.

Assuming that water reacted only once with diethylaluminum chloride; in theory, the amount of unreacted diethylaluminum chloride remaining to catalyze the Diels-Alder reaction would have been 0.75 equivalents in entry 1 (dr = 86:14)*, ~ 1.1 equivalents in entry 2 (dr = 90:10) and 1.35 equivalents in entry 3 (dr = 85:15). At a late stage in these

* When 0.78 equiv of diethylaluminum chloride was used under anhydrous conditions, a similar result was obtained: the yield was 84% and the diastereoselectivity was 83:17.

studies, a final experiment was performed using 1 equivalent of diethylaluminum chloride. Again, the reaction proceeded rapidly to completion. Here, the diastereomeric ratio of the cycloadducts **151** and **152** was found to be 90:10.

Therefore, a possible explanation for the slightly increased diastereoselectivities observed in the preliminary Diels-Alder experiments was that, when added, only ~ 1 equivalent of Lewis acid was present to catalyze the reaction. With both sub-stoichiometric and greater than stoichiometric quantities of diethylaluminum chloride, the diastereoselectivities ranged from 83:17 to 86:14. However, the use of 1 equivalent of diethylaluminum chloride resulted in a diastereomeric ratio of 90:10 which was comparable to the preliminary finding (dr = 92:8). This brief investigation indicates that the ratio of Lewis acid to acrylate used in these Diels-Alder reactions appears to be an important factor controlling the levels of diastereoselection. However, it cannot be ruled out that the diethylaluminum chloride solution used in the preliminary studies contained an unidentified hydrolyzed or oxidized aluminum species that was able to catalyze these Diels-Alder reactions in a highly diastereoselective manner.

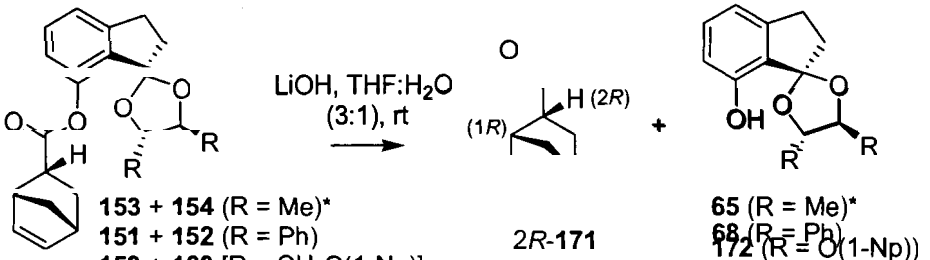
2.10.6 Determination of the Stereochemical Outcome in the Diels-Alder Reactions

The Diels-Alder adducts **153** and **154** (R = Me), **151** and **152** (R = Ph), **159** and **160** [R = CH_2O(1-Np)] as well as **161** and **162** (R = *i*-Pr), which were produced in diastereoselectivities sufficiently high to allow for their absolute stereochemical configurations to be determined by optical rotation measurements, were liberated from their respective chiral auxiliaries. Three methods were used to cleave the auxiliaries: (i) reductive cleavage with lithium aluminum hydride, (ii) solvolysis with sodium methoxide and (iii) hydrolysis with lithium hydroxide. The latter method was experimentally simple and readily afforded the enantiomerically-enriched cycloadducts (2*R*)-**171** (major enantiomer shown) and auxiliaries **65**, **68**, **172** and **173** (Table 2.10.6). There was no

evidence of epimerization of the cycloadduct (*endo*:*exo* > 98:2) as determined by ^{1}H NMR spectroscopy.

The Diels-Alder adducts **153** and **154** (R = Me, dr = 64:36) were hydrolyzed with lithium hydroxide in tetrahydrofuran and water at room temperature for 20 h to afford the (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2*R*-**171** and the (*R*,*R*)-diol-derived auxiliary **65** (R = Me) (entry 1, Table 2.10.6).

Table 2.10.6 Lithium Hydroxide-Promoted Hydrolysis Reactions of the Diastereomeric Diels-Alder Adducts



153 + **154** (R = Me)*
151 + **152** (R = Ph)
159 + **160** [R = CH_2O(1-Np)]
161 + **162** (R = *i*-Pr)

2*R*-**171**

65 (R = Me)*
68 (R = Ph)
172 (R = O(1-Np))
173 (R = *i*-Pr)

	cycloadducts (diol configuration)	time	yield (acid/auxiliary)	$[\alpha]_D^{20}$	configuration
1	**153** + **154*** (R = Me) (*R*,*R*)	20 h	(2*S*)-**171**[b] (72%) **65*** (78%)	- 39	1*S*,2*S*,4*S*
2	**151** + **152** (R = Ph) (*S*,*S*)	40 h	(2*R*)-**171** (76%) **68** (85%)	+ 82	1*R*,2*R*,4*R*
3	**159** + **160** [R = CH_2O(1-Np)] (*S*,*S*)	42 h	(2*R*)-**171** (60%) **172** (63%)	+ 35	1*R*,2*R*,4*R*
4	**161** + **162** (R = *i*-Pr) (*S*,*S*)	48 h	(2*R*)-**171** (67%) **173** (80%)	+ 115	1*R*,2*R*,4*R*

The structures for the major diastereomers **153**, **151**, **159** and **161** are shown in the reaction scheme. *The enantiomer of that indicated in the reaction scheme was prepared. [b] (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (2*S*)-**171** was the major enantiomer produced.

The Diels-Alder adducts **151** and **152** (R = Ph, dr = 83:17), **159** and **160** [R = CH_2O(1-Np), dr = 68:32] as well as **161** and **162** (R = *i*-Pr, dr = 91:9) were hydrolyzed in

a similar manner for 2 days to afford the (1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2*S*-**171** and the respective (*S*,*S*)-diol-derived auxiliaries **68** (R = Ph), **172** [R = CH_2O(1-Np)], **173** (R = *i*-Pr) (entries 2-4). Thus, a correlation existed: the (*R*,*R*)-configured chiral auxiliary produced the optically-enriched (1*S*,2*S*,4*S*)-acid 2*S*-**171** and the (*S*,*S*)-configured chiral auxiliaries all afforded the enantiomeric (1*R*,2*R*,4*R*)-acid 2*R*-**171**.

A rationale for the stereochemical outcome, in these cases, involves coordination of diethylaluminum chloride to the acrylate carbonyl oxygen to form the activated acrylate, which adopts a preferred *s-trans* conformation (Figure 2.10.4).[100] The planes of the coordinated substrate and indanone ring system are proposed to have adopted an approximately coplanar conformation upon Lewis acid coordination.

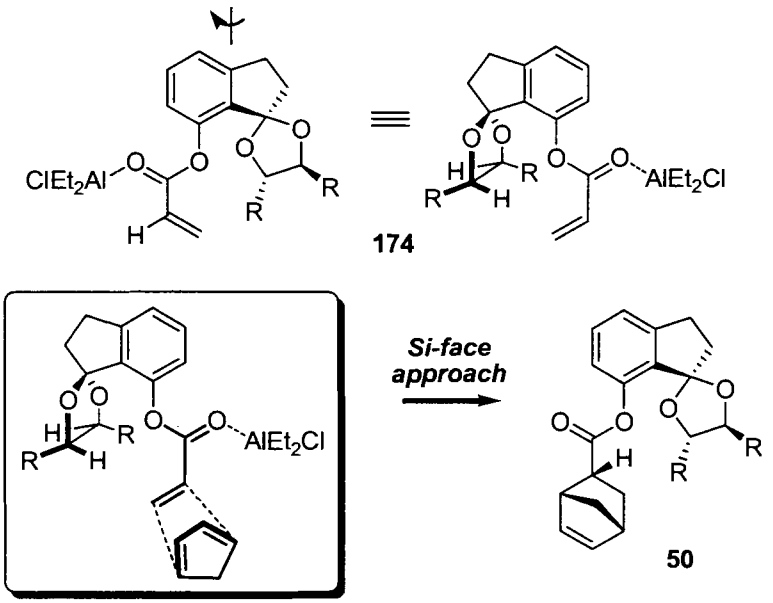


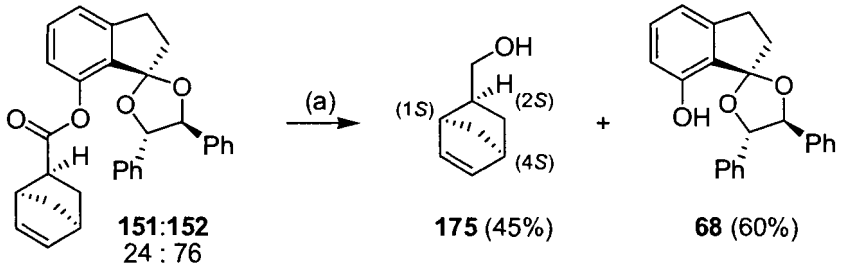
Figure 2.10.4 Proposed transition state for the diethylaluminum chloride-promoted Diels-Alder reactions.

Endo approach of cyclopentadiene from the less-hindered *Si* face of the acrylate would afford the Diels-Alder adduct of the observed configuration. The acrylate **75** (R = Me) derived from the enantiomeric (*R*,*R*)-diol **52** afforded the enantiomeric (1*S*,2*S*,4*S*)-

carboxylic acid 2*S*-**171**. Thus, an enantiomeric transition state to that depicted below would lead to the observed (2*S*)-cycloadducts **153** and **154** (see: Figure 2.10.4).

The cycloadducts **151** and **152** (dr = 24:76) produced under titanium chloride-catalysis were reacted with lithium aluminum hydride to afford the (1*S*,2*S*,4*S*)-alcohol **175** (major diastereomer and enantiomer shown, Scheme 2.10.5). This confirmed that a reversal of diastereoselection had occurred when titanium tetrachloride was used as compared to the reactions performed with diethylaluminum chloride (or any other of the Lewis acids screened).

Scheme 2.10.5 Lithium Aluminum Hydride Reduction Reaction of the Diastereomeric Cycloadducts **151** and **152**



Reagents and conditions: (a) $LiAlH_4$, 0 °C to rt, 16 h; reflux, 6 h. The structure for the major diastereomer **152** is shown in the reaction scheme.

A rationale for the observed stereochemistry of the product involved coordination of titanium tetrachloride to both the carbonyl oxygen of the acrylate **76** (R = Ph), again in an *s-trans* conformation, as well as to the more accessible acetal oxygen (Figure 2.10.5).[101*]

* An X-ray crystal structure of a titanium tetrachloride complex of an acrylamide attached to a bornane-10,2-sultam auxiliary has been determined by Oppolzer and co-workers in which titanium tetrachloride is in a "pseudo-octahedral environment" with the carbonyl and a sultam oxygen occupying equatorial positions around the titanium centre.

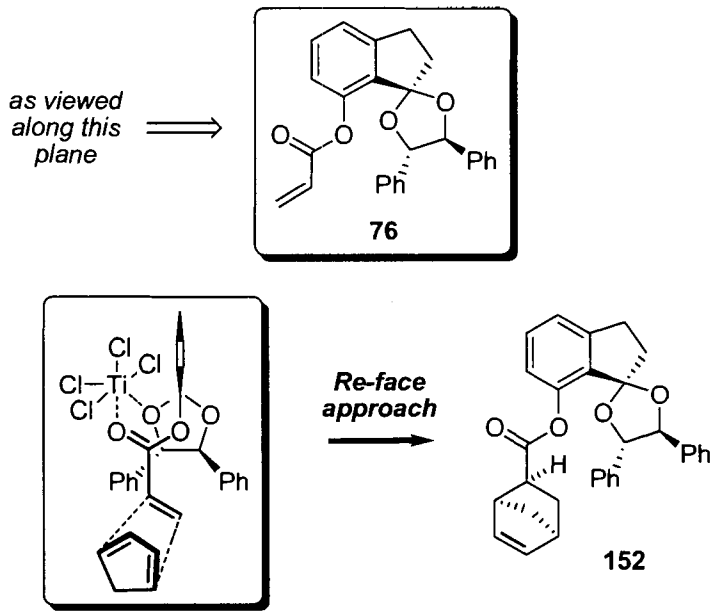


Figure 2.10.5 Proposed transition state for the titanium chloride-promoted Diels-Alder reaction.

The *Re*-face of the resultant 8-membered ring chelate is then more accessible to cyclopentadiene and, the cycloaddition reaction proceeds to afford the observed major (2*S*)-adduct. Of note, the bidentate coordination of the acrylate **76** (R = Ph) to titanium tetrachloride would have caused the acrylate moiety to adopt an approximately orthogonal relationship with the indanone ring system. This is in contrast to the coplanar conformation adopted on coordination to the monobasic Lewis acid, diethylaluminum chloride.

2.11 Conclusions

A variety of 7-hydroxyindan-1-one-derived chiral auxiliaries were synthesized and evaluated in asymmetric enolate alkylation, cyclopropanation, 1,3-dipolar cycloaddition and Diels-Alder reactions. In the best case, the Diels-Alder reaction involving an acrylate and cyclopentadiene, a high level of asymmetric induction was obtained (dr = 91:9, *endo*:*exo* > 98:2, 71% yield). In the asymmetric enolate alkylation reactions, the acetal subunit of the two auxiliaries examined, **73** (R = Me) and **74** (R =

Ph), proved to be the most important variable. When the phenylacetates **73** (R = Me) and **74** (R = Ph) were alkylated, the former reacted readily in non-polar solvents with but no diastereoselection. The latter required the addition of the polar solvent, hexamethylphosphoramide, in order for the alkylation reaction to occur. In this case, good diastereoselectivities were obtained (up to dr = 71:29). The selective formation of the (*E*)- or (*Z*)-enolates and the stability of these enolates were also dependent on the auxiliary employed. The efficiency of the auxiliary **74** (R = Ph) was also affected by the temperature at which the alkylation reactions could be performed. When the less-reactive electrophile, 2-iodopropane, was used, it was necessary to allow the reaction to warm to room temperature which resulted in a significant decrease in the diastereoselectivity of the reaction. The sense of stereochemical induction which led to the major product **106** (R = Ph) in the enolate alkylation reaction of the phenylacetate **74** (R = Ph) was predictable. Here, the acetal substituent blocked one face of the enolate preferentially and the electrophile approached from the opposite and less hindered *Re* face.

Several types of cyclopropanation reactions were evaluated for the asymmetric cyclopropanation of the cinnamate **89** (R = Ph). It was possible to cyclopropanate the cinnamate **89** in high yield (up 95%) using diazomethane and a catalytic amount of palladium acetate. However, the diastereoselectivities obtained were low (up to dr = 59:41). The absolute stereochemical outcome leading to the major cyclopropane **124** (R = Ph) was rationalized in terms of approach of the carbenoid from the more accessible *Re* face of the cinnamate subunit. As well, although the cinnamate **89** (R = Ph) was found to be unreactive with the reagents diethylzinc and diiodomethane, a 3,3-dimethyl-2-propenyl ether **78** (R = Ph) was found to be reactive and was converted in 68% yield to its corresponding cyclopropane **123** (R = Ph). The diastereoselectivity of this reaction was high (dr = 86:14). In the former reaction, the low diastereoselectivity is likely a result of poor *s-cis/s-trans* conformational control by the auxiliary. In the latter reaction,

although multiple reactive conformations are in theory accessible, the diastereoselectivity obtained was high. This can be explained if the zinc carbenoid reagent coordinated to one of the acetal oxygen atoms which directed the subsequent cyclopropanation reaction.

The 1,3-dipolar cycloaddition reaction of benzonitrile oxide **138** and several α,β-unsaturated substrates produced isoxazolines with varying diastereoselectivities and regioselectivities. The acrylate **76** (R = Ph) reacted in slightly higher diastereoselectivity in aromatic solvents (up to dr = 61:39) and in all of the solvents utilized, reacted with good regioselectivity (≥ 88:12). The reaction of the acrylate **76** (R = Ph) proceeded rapidly at -78 or 0 °C, interestingly, with no substantial change in the level of asymmetric induction. With respect to the acrylate **76**, the crotonate **87** (R = Ph) and the cinnamate **89** (R = Ph) both reacted more slowly and with lower regioselectivities. As well, the diastereomeric ratios obtained for these substrates did not exceed 60:40. However, the methacrylate **77** (R = Ph) was found to react as rapidly but both the diastereomeric ratio (dr = 56:44) and regioselectivity (86:14) were found to be lower. Assuming that the acrylate **76** (R = Ph) reacted in an s-*cis* conformation, benzonitrile oxide **138** likely approached from the less-hindered *Si* face. The low diastereoselectivities are attributed to poor conformational control of the substrate by the auxiliary.

Asymmetric Diels-Alder reactions were performed using six different auxiliaries. The acrylate **83** (R = *i*-Pr) was superior and afforded the cycloadducts **161** and **162** (R = Ph) in 71% yield and with excellent diastereoselectivity (dr = 91:9). The acrylate **76** (R = Ph) was also quite efficient affording the diastereomeric Diels-Alder adducts as an 83:17 mixture. A variety of Lewis acids were screened in the Diels-Alder reactions and diethylaluminum chloride was found to be the most general and effective promoter. A solvent effect was also discovered. Here, reactions in toluene were more diastereoselective than those performed in dichloromethane. The scope of the reaction was found to be relatively narrow. In these cases, Diels-Alder reactions with different

α,β-unsaturated substrates and different dienes were either non-selective or did not proceed.

The diethylaluminum-chloride promoted Diels-Alder reactions of the acrylates **81** (R = CH_2OBn) and **82** [R = CH_2O(1-Np)], both prepared from tartrate-derived diols of significant steric bulk, were either poorly or moderately diastereoselective (dr = 54:46 to 68:32). This indicated that, in these reactions, high levels of asymmetric induction occur only when large substituents of the acetal moiety are in close proximity to the indanone ring system and, more importantly, to the substrate. This was the case for the acrylates **76** (R = Ph) and **83** (R = *i*-Pr).

Near the end of the studies, it was found that the highest diastereoselectivities were obtained when 1 equivalent of diethylaluminum chloride was employed. The diastereoselectivity increased in the diethylaluminum-promoted Diels-Alder reaction of the acrylate **76** (R = Ph) from 83:17 to 90:10 when the amount of Lewis acid was decreased from 1.5 to 1 equivalent. Excess diethylaluminum chloride may have coordinated to the oxygen(s) of the acetal moiety and contributed to a decrease in the reaction diastereoselectivity.

It was also found that the Diels-Alder reaction of the acrylate **76** (R = Ph) and cyclopentadiene catalyzed by titanium tetrachloride afforded cycloadducts of opposite stereochemical configuration to those produced by any of the other Lewis acids screened. In all of the diethylaluminum chloride-promoted reactions involving chiral auxiliaries of the same absolute stereochemical configuration, cyclopentadiene preferentially approached from the more accessible *Si* face of the acrylates, which adopted an *s-trans* conformation. It is likely that titanium tetrachloride coordinated in a bidentate manner to the acrylate **76** (R = Ph) thus exposing the diastereomeric *Re* face for reaction with cyclopentadiene.

In summary, this novel class of chiral auxiliaries can be rapidly assembled using

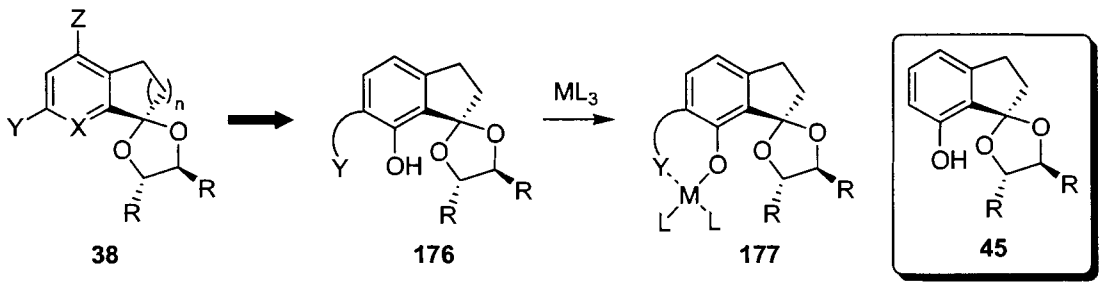
short and divergent syntheses to afford multi-gram quantities of material for use in asymmetric synthesis. The auxiliaries were found to be stable under a variety of reaction conditions and it has been shown that they can be recovered for re-use in subsequent chemical reactions. The 7-hydroxyindan-1-one-derived chiral auxiliaries produce high levels of asymmetric induction in certain chemical reactions. In steric terms, the most efficient auxiliaries were those with large, closely situated substituents. π-π interactions did not appear to be a controlling factor as both the auxiliaries **68** (R = Ph) and **173** (R = *i*-Pr) produced similar diastereoselectivities. In addition, the benzyl and naphthyl-containing tartrate-derived auxiliaries that, in theory, could engage in π-π interactions did not produce high levels of stereochemical induction. The chelating abilities of the acetal oxygen atoms as well as additional heteroatoms in the acetal subunit could, in certain cases, increase the levels of asymmetric induction [*e.g.* in the modified Simmons-Smith cyclopropanation of the ether **78** (R = Ph)]. These studies in auxiliary-directed asymmetric reactions have shown that the general acetal framework is effective as a chiral director. The development and evaluation of chiral ligands and catalysts based on this concept are discussed in the following chapters.

CHAPTER 3: RESULTS AND DISCUSSION

THE SYNTHESIS AND EVALUATION OF 7-HYDROXYINDAN-1-ONE-DERIVED CYCLIC ACETALS FOR USE AS CHIRAL LIGANDS IN CATALYTIC ASYMMETRIC SYNTHESIS

3.1 Introduction

In the previous chapter, a derivative of the general acetal structure **38** was demonstrated to be an effective chiral director. The 7-hydroxyindan-1-one-derived chiral auxiliaries were evaluated in several reactions and, in the Lewis acid-promoted Diels-Alder reaction, high levels of stereochemical induction were achieved. To extend this concept into the catalytic domain, a series of 7-hydroxyindan-1-one-derived chiral ligands **176** based upon the general chiral acetal **38** were synthesized and evaluated in several catalytic asymmetric reactions (Figure 3.1.1).



X = attachment/binding site (*e.g.* COH, N). Y = binding site (*e.g.* N, P, O). Z = attachment site to a solid support or a site to modify the electronics of the system. M = metal. L = counterion/ligand.

Figure 3.1.1 7-Hydroxyindan-1-one-derived chiral ligands and metal complexes.

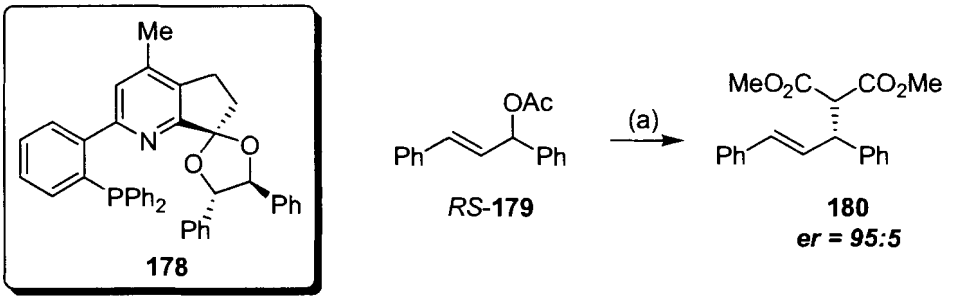
The chiral auxiliary structure **45**, designed and synthesized previously, was selected as a key precursor to a series of ligands. It was envisioned that simple one- or two-step functionalizations at the *ortho*-position could produce the requisite ligand **176**. The ligand **176** could complex with a metal source (ML_3) in a bidentate (or tridentate) fashion to afford the desired chiral metal complex **177** for subsequent use in catalytic

asymmetric synthesis.

In a divergent manner, the chiral auxiliary **68** (R = Ph) could be converted in two synthetic steps *via* a key salicylaldehyde intermediate into tridentate Schiff bases. These ligands could be evaluated in metal-catalyzed asymmetric sulfoxidation and hetero Diels-Alder reactions. In addition, bidentate 1,3-amino alcohol ligands could be prepared in one synthetic step from the auxiliary *via* the Mannich reaction and evaluated in, for example, the metal-catalyzed Diels-Alder reaction. It was decided to use the diphenyl-substituted auxiliary **68** (R = Ph) because it had previously generated high levels of stereochemical induction in earlier studies. In addition, the diol **29** (R = Ph), from which this acetal was derived, was commercially-available or could be prepared in multi-gram quantities.

Concurrent studies in our research group have shown that highly effective chiral ligands based on the general structure **38** can be prepared. For example, the chiral bidentate *P,N*-chiral acetal ligand **178** has been used effectively in a palladium-catalyzed allylic substitution reaction (Scheme 3.3.1).[102]

Scheme 3.1.1 *P,N*-Chiral Acetal Ligand **178** for Palladium-Catalyzed Allylic Alkylation Reactions



Reagents and conditions: (a) *P,N*-ligand **178** (6.25 mol %), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.5 mol %), dimethylmalonate (3 equiv), Cs_2CO_3 (3 equiv), 0 °C, 4 h, 91%.

In this reaction, a chiral palladium π-allyl complex, formed in a reaction involving the ligand **178** and allylic acetate *RS*-**179**, reacted with the nucleophilic conjugate base of dimethylmalonate. The optically-active alkylation product **180** was formed in high

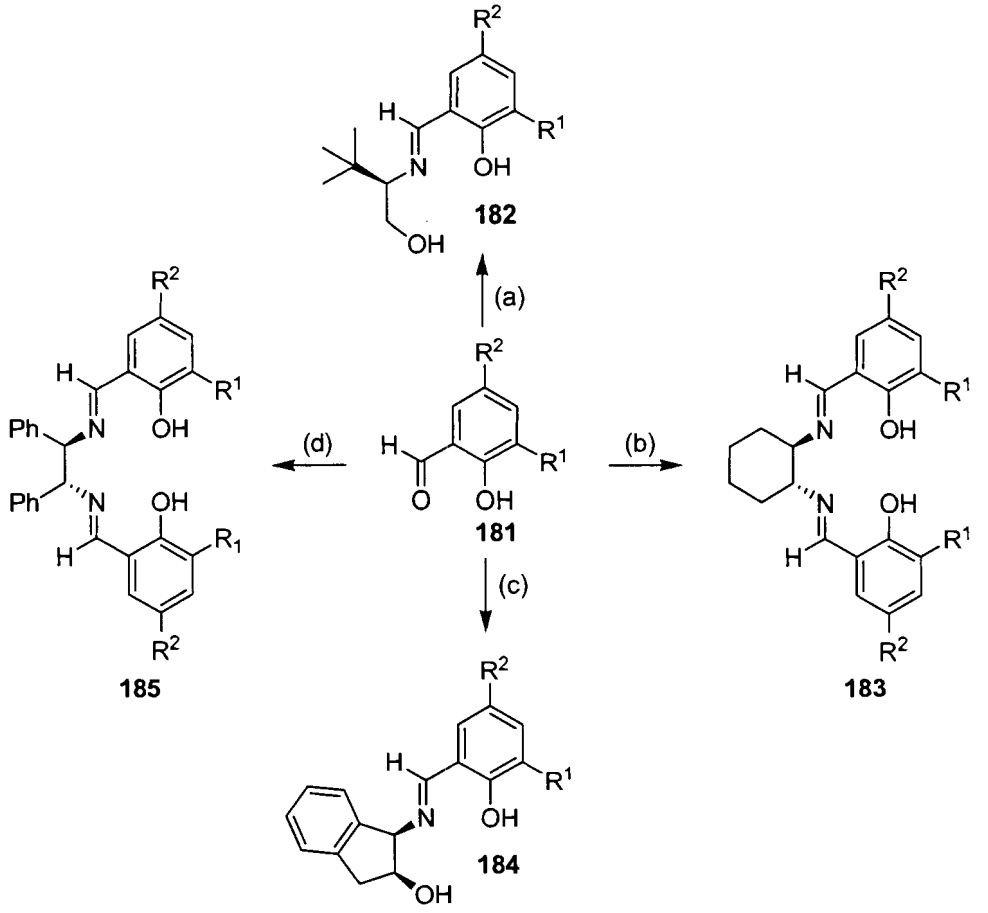
enantioselectivity (er = 95:5).

3.2 Chiral Tridentate Schiff Base Ligands Derived from the 7-Hydroxyindan-1-one Auxiliary [68 (R = Ph)]

3.2.1 Background

Salicylaldehydes **181** have served as important synthetic scaffolds around which many chiral ligands have been constructed (Scheme 3.2.1).

Scheme 3.2.1 Selected Salicylaldehyde-Derived Chiral Schiff Base Ligands



Chiral 1,2-amino alcohol precursors: (a) (2*S*)-2-amino-2-*t*-butylethanol, **182** (R^1 = *t*-Bu, R^2 = NO_2). (b) (1*R*,2*R*)-1,2-diaminocyclohexane, **183** (R^1 = R^2 = *t*-Bu). (c) (1*R*,2*S*)-2-aminoindan-1-ol, **184** (R^1 = R^2 = *t*-Bu). (d) (*R*,*R*)-1,2-diphenyl-1,2-ethanediamine, **185** [R^1 = CH(Et)Ph, R^2 = H].

In 1990, Jacobsen and Katsuki independently reported the preparation of the tetradentate Schiff bases (salen) **183** ($R^1 = R^2 = t$-Bu) and **185** [R^1 = CH(Et)Ph, R^2 = H], respectively, and demonstrated their use as chiral ligands in metal-catalyzed asymmetric epoxidation reactions. Yoon and Jacobsen have grouped the salen ligands **183** and **185** with binaphthol, the bis(oxazolines) and the cinchona alkaloids referring to them as, "privileged chiral catalysts...creating effective asymmetric environments for mechanistically unrelated reactions".[103] In 1995, Bolm and co-workers condensed (2*S*)-2-amino-2-*t*-butylethanol with the salicylaldehyde **181** to form the chiral tridentate Schiff base **182** (R^1 = *t*-Bu, R^2 = NO_2) and used it in the metal-catalyzed oxidation of sulfides.[104] More recently, Jacobsen and co-workers have prepared a chiral tridentate Schiff base **184** derived from the (1*R*,2*S*)-2-aminoindan-1-ol and demonstrated its suitability for chromium-catalyzed asymmetric hetero Diels-Alder and hetero ene reactions.[105]

3.2.2 Synthesis of the Chiral Tridentate Schiff Bases (190 and 191)

Several synthetic procedures exist for the *ortho*-formylation of phenols to produce salicylaldehydes. However, some of these procedures are not regioselective and afford *para*-formylated products as well.[106] Other methods require the use of strongly Lewis acid reagents (*e.g.* tin tetrachloride).[107]

In this study, the auxiliary **68** (R = Ph) was converted to the salicylaldehyde **186** in 77% yield by heating the auxiliary **68**, magnesium chloride, triethylamine and paraformaldehyde in acetonitrile at 60 °C for 20 h (Scheme 3.2.2).[108,109*] Notably, the *ortho*-formyl phenol **186** was the only regioisomer observed under these reaction conditions.

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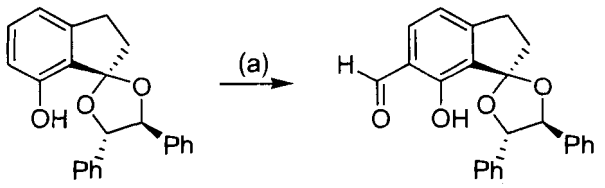
* The literature procedure involved heating various phenols at reflux in acetonitrile (bp 81-82 °C) for 2 to 4 h. Although the formylation of the auxiliary **68** (R = Ph) could be performed at these temperatures, it was found that higher yields could be obtained at lower reaction temperatures. A 63% yield was obtained when the reaction was performed at reflux.

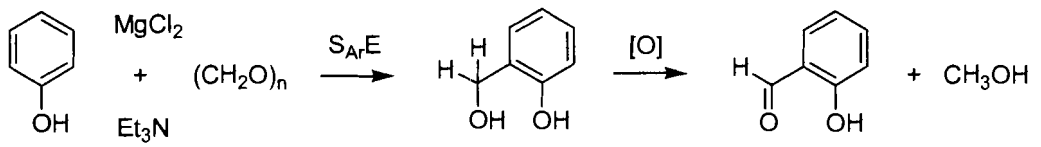
Scheme 3.2.2 Synthesis of the 7-Hydroxyindan-1-one-Derived Chiral Salicylaldehyde **186** (R = Ph)



68 **186**

Reagents and conditions: (a) $MgCl_2$ (1.5 equiv), Et_3N (4.0 equiv), paraformaldehyde (7.1 equiv), CH_3CN, 60 °C, 20 h, 77%.

The mechanism of this mild *ortho*-formylation reaction entails a tandem magnesium chloride-promoted electrophilic aromatic substitution and oxidation reaction (Figure 3.2.1). The $S_{Ar}E$ reaction involves activation of the electrophile, formaldehyde, by magnesium chloride. Formaldehyde is generated *in situ* by the dissociation of its polymeric precursor, paraformaldehyde. Simultaneously, through coordination to both the phenolic and aldehydic oxygen atoms, magnesium chloride directs the addition of formaldehyde to the *ortho*-position. The excess formaldehyde present then oxidizes the intermediate alcohol **187** to the salicylaldehyde **188**. Formaldehyde is simultaneously reduced to methanol.



187 **188**

Figure 3.2.1 Tandem magnesium chloride-promoted electrophilic aromatic substitution and oxidation reaction to form salicylaldehyde.

The salicylaldehyde **186** was then condensed with 2-aminophenol and 2-amino-1,1-diphenylethanol **189**[110*] to afford the Schiff bases **190** and **191**. Upon addition of the

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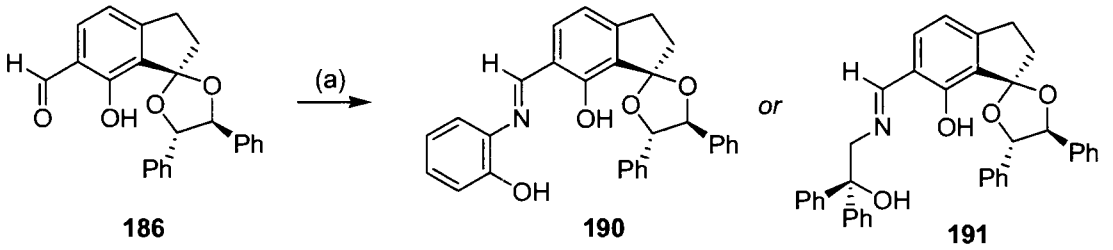
* 2-Amino-1,1-diphenylethanol **189** was prepared in a Grignard reaction between the ethyl ester of glycine hydrochloride and phenylmagnesium bromide (see: Chapter 7: Experimental Section).

amines to the salicylaldehyde, the solutions immediately adopted a bright yellow colour, which persisted throughout the reaction. The resultant tridentate Schiff bases were purified by flash chromatography on silica gel to afford analytically pure material.*

Scheme 3.2.3 Synthesis of the Chiral Tridentate Schiff Bases **190** and **191**



186 **190** **191**

Reagents and conditions: (a) 2-aminophenol, EtOH, rt, 18 h, 97% *or* 1,1-diphenyl-2-aminoethanol, EtOH, rt, 18 h, 96%.

In addition to the diagnostic coupling pattern for the aromatic indanyl hydrogens in ^{1}H NMR spectrum of the salicylaldehyde **186**, two other prominent features supported the *ortho*-relationship of the phenol and formyl groups (Figure 3.2.2). Specifically, the downfield shift of the phenolic hydrogen (**C**) from δ 6.6 ppm in the auxiliary **68** to δ 12.2 ppm (**C′**) in the salicylaldehyde **186** was indicative of an intramolecular hydrogen bond. As well, this intramolecular hydrogen bonding likely changed the chemical environment of the proximal acetal hydrogen (**B′**) which resonated downfield from that in the auxiliary **68** (**B**). The IR spectrum of the salicylaldehyde **186** displayed a strong, sharp stretch at 1650 cm^{-1}, which is characteristic to salicylaldehydes.[111]

The ^{1}H NMR spectrum for the tridentate Schiff base **190** showed a characteristic signal (**D″**) at δ 8 ppm for the aryl imine hydrogen which was upfield by over 1 ppm from the signal (**D′**) for its aldehydic precursor. The phenolic hydrogen (**C″**) was shifted downfield by δ 1 ppm in the Schiff base **190** with respect to that of the salicylaldehyde

* Preliminary studies involving the synthesis of salen-type ligands derived from the salicylaldehyde **186** and 1,2-diaminobenzene were encouraging. Reaction of the 1,2-diaminobenzene with 2 equiv of the aldehyde produced approximately a 1:1:1 mixture of the mono-imine, bis-imine and unreacted aldehyde **186** as determined by ^{1}H NMR spectroscopy.

(C′), which was likely due to intramolecular hydrogen bonding to the more Lewis basic imine nitrogen. The NMR data for the ethanolamine-derived Schiff base **191** displayed similar characteristics. Elemental analysis of this Schiff base revealed that a molecule of water was incorporated into the crystal lattice possibly stabilized by hydrogen bonding to the phenol and/or imine groups.

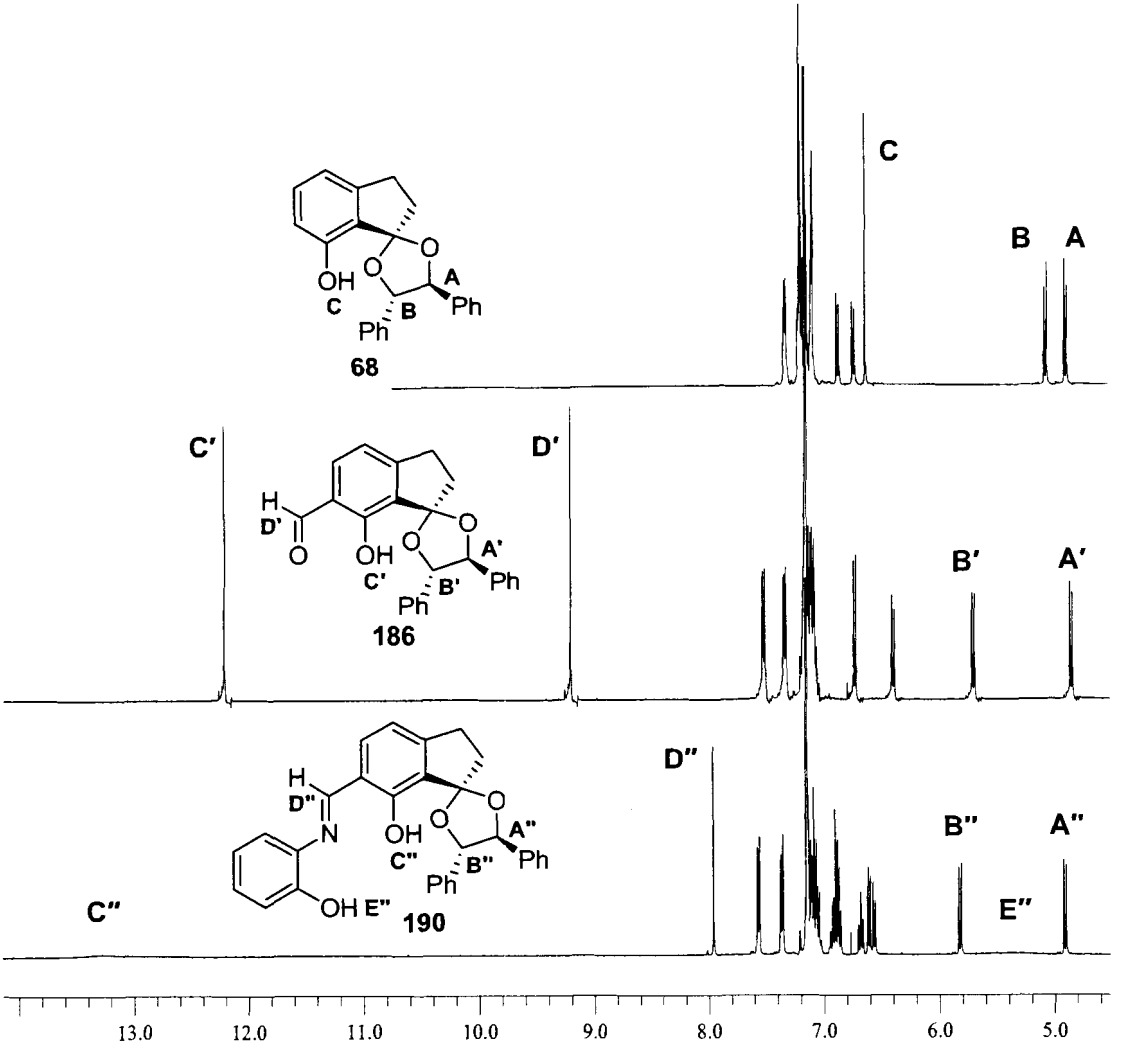


Figure 3.2.2 ^{1}H NMR (400 MHz, C_6D_6) spectra of the auxiliary **68** (R = Ph), salicylaldehyde **186** (R = Ph) and tridenate Schiff Base **190** (R = Ph).

3.3 Vanadium-Catalyzed Asymmetric Sulfoxidation Reactions

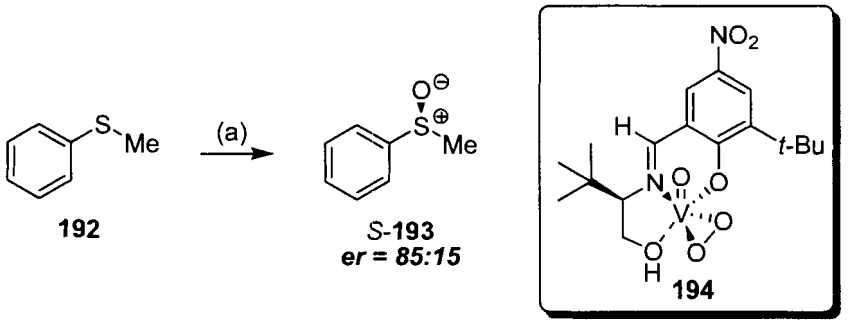
3.3.1 Introduction

The tridentate Schiff bases **190** and **191** were evaluated as ligands in the metal-catalyzed asymmetric sulfoxidation of phenylmethyl sulfide. As well, two additional ligands incorporating an additional stereogenic element were tested in this sulfoxidation reaction. This reaction was of particular interest because no examples of asymmetric sulfoxidation reactions using chiral Schiff base that incorporate chirality *only* in the salicylaldehyde component have been reported. Most ligands are based on the directing ability of a chiral amino alcohol or, in a few cases, on a amino alcohol in combination with another element of chirality.[112,113]

3.3.2 Background

Bolm and co-workers showed that metal complexes generated from vanadyl acetoacetate and the Schiff base **182** (Scheme 3.2.1) could induce good levels of asymmetry in sulfoxidation reactions (Scheme 3.3.1). Based upon ^{51}V NMR studies, the active catalytic oxidant was proposed to be the vanadium(V)-complex **194**.[112a,114]

Scheme 3.3.1 An Asymmetric Sulfoxidation Reaction Using a Vanadium(V)-Tridentate Schiff Base Complex



192 S-**193** ***er = 85:15*** **194**

Reagents and conditions: (a) $VO(acac)_2$ (1 mol %), Schiff base **182** (1 mol %), H_2O_2, rt, CH_2Cl_2, 94%.

The mechanism of sulfide oxidation by peroxo complexes, chiral or achiral, is believed to proceed by a nucleophilic mechanism whereby the sulfide reacts with one of

the peroxo oxygen atoms to generate the sulfoxide and a bisoxo species which is re-oxidized by, for example, hydrogen peroxide for re-entry into the catalytic cycle (Figure 3.3.1).[115]

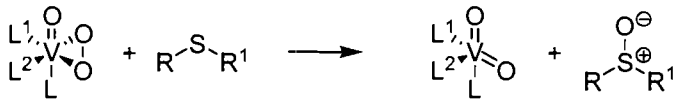
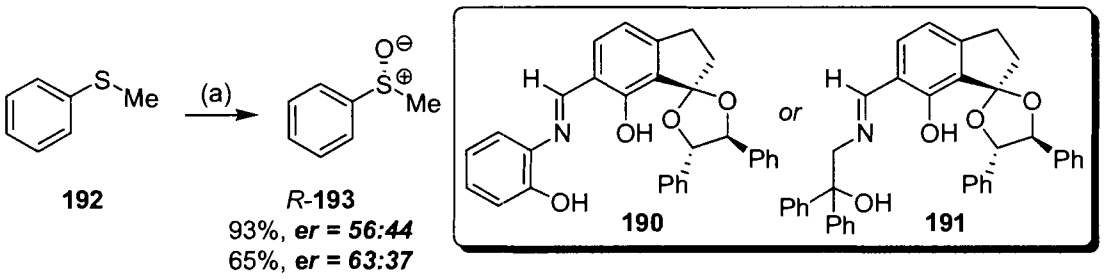


Figure 3.3.1 Proposed mechanism of the sulfide oxidation by a peroxovanadium(V) complex.

3.3.3 Chiral Tridentate Schiff Base Ligands in the Catalytic Sulfoxidation Reaction

The sulfoxidation reaction of phenylmethyl sulfide **192** was performed using catalytic quantities of vanadyl acetoacetate and the tridentate Schiff bases **190** and **191**. Typically, a solution of vanadyl acetoacetate (1 mol %) and the Schiff base **190** or **191** (1.5 mol %) in dichloromethane at 0 °C was treated with the sulfide **192** and an aqueous solution of hydrogen peroxide and the bi-phasic mixture was allowed to warm to room temperature over 16 to 20 h (Scheme 3.3.2).

Scheme 3.3.2 Vanadium-Catalyzed Sulfoxidation Reaction of Phenylmethylsulfide Using the Tridentate Schiff Bases **190** and **191**



192 *R*-**193**
93%, ***er* = 56:44**
65%, ***er* = 63:37**

190 **191**

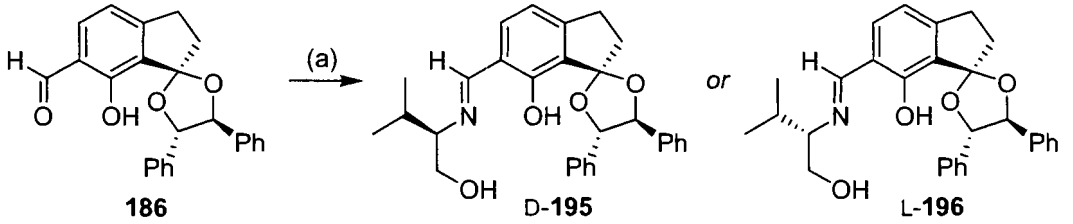
Reagents and conditions: (a) $VO(acac)_2$ (1.0 mol %), Schiff base **190** *or* **191** (1.5 mol %), H_2O_2 (*aq.*, 30 wt. %), CH_2Cl_2, 0 °C to rt, 16 to 20 h.

Using the aminophenol-derived Schiff base **190**, the sulfoxide *R*-**193** was isolated as a colourless oil in 93% yield after 16 h. The enantiomeric ratio, as determined by chiral HPLC analysis of the purified product mixture, was 56:44. The absolute stereochemical configuration of the sulfoxide *R*-**193** was determined by comparison of

the sign of its optical rotation to that of the known compound.[116] Using the larger aminoethanol-derived Schiff base **191**, the sulfoxidation reaction proceeded less rapidly and afforded the sulfoxide *R*-**193** in 65% yield after 20 h. In this case, as determined by chiral HPLC analysis, the enantiomeric ratio had increased to 63:37. When the same reaction was performed using *t*-butylhydroperoxide (1.1 equivalents) as the oxidant and the aminoethanol-derived ligand **191**, the sulfoxide was recovered in similar yield (63%) after 16 h at room temperature.[112b] However, the enantioselectivity decreased dramatically (er = 51:49).

Two additional tridentate Schiff bases that incorporated an additional element of chirality were prepared for examination in the sulfoxidation reaction. Double stereochemical induction can sometimes provide remarkable enhancements in stereoselectivity above that produced when either element of chirality is used singularly.[64,113*] To explore this facet of asymmetric synthesis, the salicylaldehyde **186** was condensed with both D- and L-valinol to afford the diastereomeric Schiff bases D-**195** and L-**196** (Scheme 3.3.3). Of note, chiral tridentate Schiff bases incorporating valinol have been used in the asymmetric sulfoxidation reaction.[117]

Scheme 3.3.3 Synthesis of D- and L-Valinol-Containing Chiral Tridentate Schiff Bases D-**195** and L-**196**



186 D-**195** L-**196**

Reagents and conditions: (a) D- *or* L-valinol, EtOH, rt, 1.5 to 20 h, ~ quantitative.

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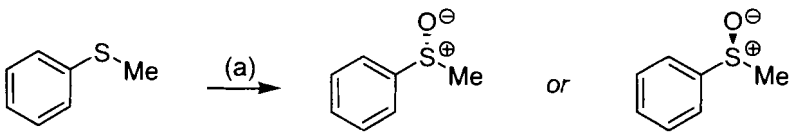
* In the case of a chiral ligand, double asymmetric induction can occur if it contains more than one chiral subunit. A chiral ligand with "matched" subunits will produce higher enantioselectivities than ligands constructed from only one of the chiral subunits. A ligand with "mismatched" subunits will afford levels of stereochemical induction lower than that produced by a ligand containing only one of these subunits.

Interestingly, the diastereomeric Schiff bases D-**195** and L-**196** each catalyzed the sulfoxidation reaction with an opposite sense of asymmetric induction (Scheme 3.3.4). The ligand D-**195** afforded the (*R*)-sulfoxide *R*-**193** in a moderate enantioselectivity (er = 73:27). The ligand L-**196** produced the enantiomeric (*S*)-sulfoxide *S*-**193** in the *same* moderate enantioselectivity (er = 73:7). Therefore, it appeared that the chirality introduced by the amino alcohol subunit completely overrode the directing abilities of the chiral acetal subunit.

Scheme 3.3.4 Vanadium-Catalyzed Sulfoxidation of Phenylmethylsulfide Using the Diastereomeric Schiff Bases D-**195** and L-**196**



192

R-**193**
55%, ***er* = 73:27**
(using D-**195**)

S-**193**
67%, ***er* = 73:27**
(using L-**196**)

Reagents and conditions: (a) $VO(acac)_2$ (1.0 mol %), Schiff base D-**195** *or* L-**196** (1.5 mol %), CH_2Cl_2, 0 °C to rt, 20 to 24 h.

The Schiff base ligand of the peroxovanadium(V) complexes can occupy axial or equatorial positions around the metal centre (Scheme 3.3.1 and Figure 3.3.1) and phenylmethyl sulfide can approach in several orientations. This makes rationalization of the stereochemical outcome in these reactions difficult. The attempts at "matched" double asymmetric induction were unsuccessful. However, these studies helped to reveal the stereochemical course of these reactions. Particularly, the D-valinol-derived Schiff base D-**195** as well as both the aminophenol- and aminoethanol-derived Schiff bases **190** and **191** afforded the (*R*)-sulfoxide *R*-**193** as the major enantiomer. In all three of these structures, the top faces (as depicted, Scheme 3.3.2 and Scheme 3.3.3) were more sterically-hindered. Therefore, it is postulated that phenylmethyl sulfide approached from the less hindered bottom face of the Schiff base ligands **190**, **191** and D-**195** such to

avoid unfavourable steric interactions with the "interior" acetal substituent, and, in the case of the ligand D-**195**, to avoid interaction with the isopropyl substituent as well.

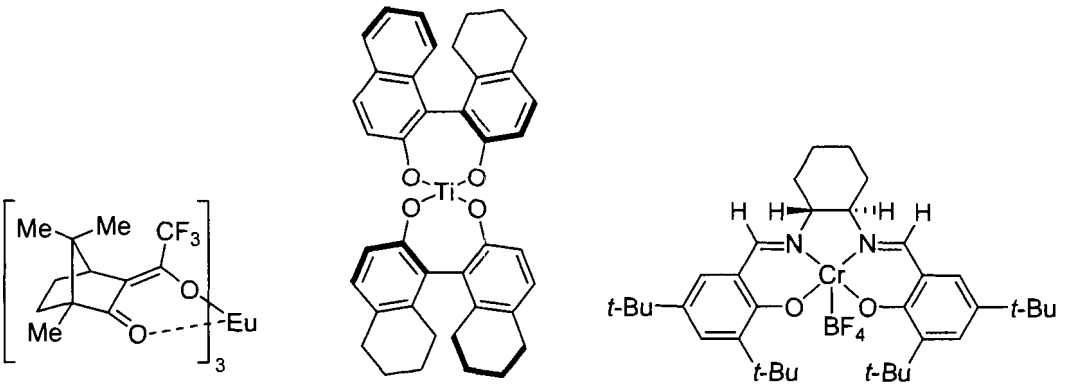
3.4 Chromium-Catalyzed Asymmetric Hetero Diels-Alder Reactions

3.4.1 Introduction

Chromium(III)-complexes of the tridentate Schiff bases **190** and **191** were prepared and examined as catalysts in the asymmetric hetero Diels-Alder reaction of Danishefsky's diene and benzaldehyde. In part, this reaction was of interest because there are no examples of chiral tridentate Schiff bases for use in the metal-catalyzed hetero Diels-Alder reaction, chromium or otherwise, that incorporate chirality into the salicylaldehyde backbone.

3.4.2 Background

The asymmetric hetero Diels-Alder reaction of dienes and aldehydes has been catalyzed by a variety of metal complexes. Typically, aldehydes are not active dienophiles even following Lewis acid-activation; therefore, reactive dienes have often been employed.[118] The electron-rich diene, 4-methoxy-2-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) is particularly reactive and chiral europium **197**, titanium **198** and chromium **199** complexes have been used to catalyze its reaction with a variety of aldehydes (Figure 3.4.1).[119,120] The titanium complex **198**, selected from a library of related complexes of BINOL-derived ligands, was particularly effective and afforded the corresponding Diels-Alder adducts (from benzaldehyde) in quantitative yield as a single enantiomer.[120b]



197 (82%)
er = 59:41

198 (> 99%)
er > 99:1

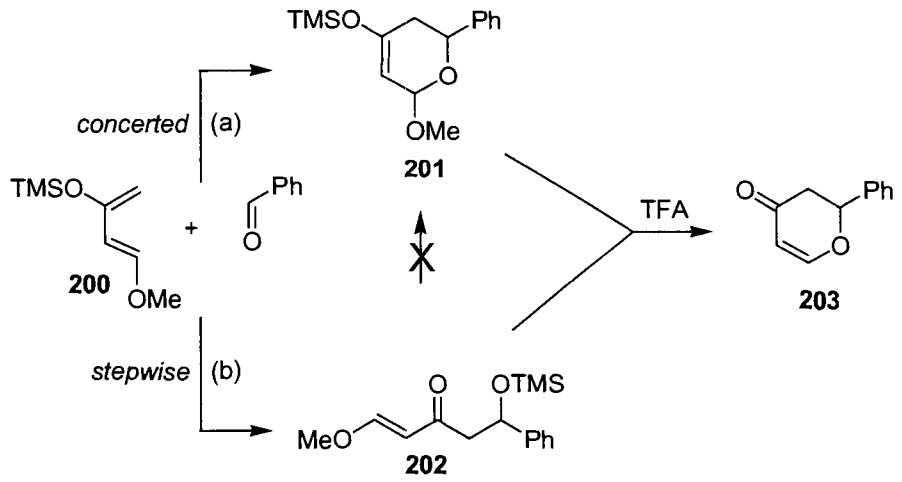
199 (85%)
er = 94:6

Figure 3.4.1 Chiral Lewis acids used in the hetero Diels-Alder reaction of Danishefsky's diene and benzaldehyde.

The mechanism of the Lewis acid-catalyzed hetero Diels-Alder reaction has been studied and two pathways are found to occur (Scheme 3.4.1). A concerted mechanism has been shown to take place in the presence of zinc chloride and the chiral europium and chromium complexes **197** and **199**.[119] Jacobsen and co-workers observed the cycloadduct **201** by ^{1}H NMR spectroscopy in the hetero Diels-Alder reaction catalyzed by the chromium complex **199** and, following independent synthesis, they were *unable* to convert the aldol product **202** into the cycloadduct **201** upon exposure to the chromium complex.[120c] Using boron trifluoride etherate as a Lewis acid catalyst, the cycloaddition reaction has been found to proceed *via* a two-step aldol/Michael addition pathway.[121] In this case, the aldol intermediate **202** has been isolated.

In the former case, trifluoroacetic acid catalyzes the elimination reaction of the unstable cycloadduct **201** to form the dihydropyranone **203**. In the latter case, trifluoroacetic acid catalyzes an intramolecular Michael addition reaction of the aldol intermediate **202** to form the same dihydropyranone **203**.

Scheme 3.4.1 Mechanism of the Hetero Diels-Alder Reactions of Danishefsky's Diene **200** and Benzaldehyde

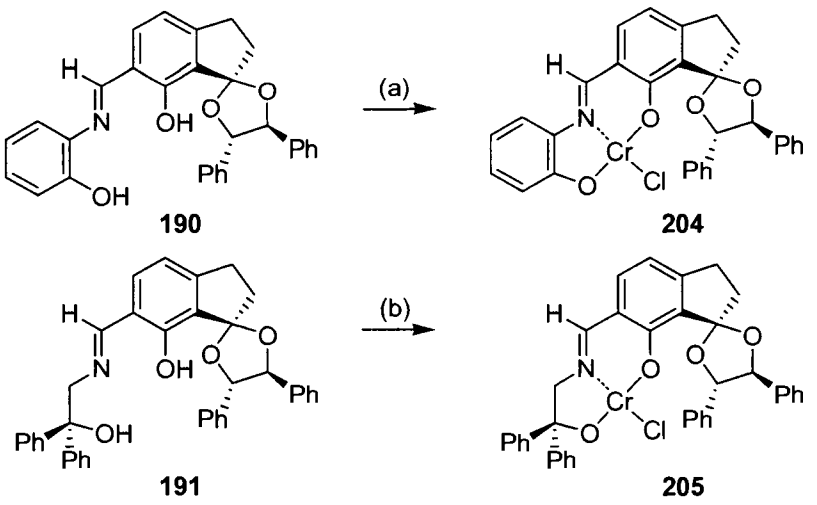


Reagents and conditions: (a) $ZnCl_2$, chiral europium **197** and chromium **199** complexes (b) $BF_3{\cdot}OEt_2$.

3.4.3 Preparation of the Chromium(III)-Complexes 204 and 205

According to the method of Jacobsen and co-workers, the chromium(III)-complexes **204** and **205** were prepared in a glove box by the addition of solutions of the Schiff bases **190** and **191** to chromium(II) chloride (Scheme 3.4.2).[105a] The bright orange or yellow Schiff base solutions immediately adopted a dark brown colour and, over the course of a few hours, the suspended grey chromium(II) chloride dissolved completely. It was determined by thin-layer chromatography that the Schiff bases had reacted completely. The presumed intermediate chromium(II) species were then stirred, exposed to the atmosphere, for 14 to 16 h during which time they were oxidized to the chromium(III)-complexes **204** and **205**. During this stage, the dark brown solutions became slightly green in colour. 2,6-dimethylpyridine was then added, presumably to react with any hydrogen chloride that had formed over the course of the reaction.

Scheme 3.4.2 Preparation of the Chromium(III)-Complexes **204** and **205** from the Chiral Tridentate Schiff Bases **190** and **191**



Reagents and conditions: (a) $CrCl_2$, THF, 4 h, rt; open to atmosphere, 14 h; 2,6-dimethylpyridine, 4 h, 95%. (b) $CrCl_2$, THF, 4 h, rt; open to atmosphere, 16 h; 2,6-dimethylpyridine, 4 h, 97%.

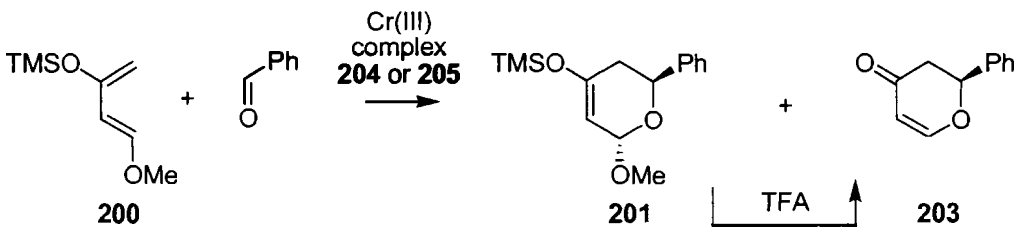
The reaction mixtures were then subjected to an aqueous workup in which the neutral chromium(III)-complexes were extracted with *t*-butylmethyl ether. The solvent was then evaporated to afford the chromium(III)-complexes as dark brown solids which were used without further purification. Chromium(III) complexes are paramagnetic, therefore, the complexes **204** and **205** were not characterized by NMR spectroscopy. Attempts to determine the molecular weights of the complexes by MALDI-TOF mass spectrometry were unsuccessful.

3.4.4 Chiral Tridentate Schiff Base Complexes in the Catalytic Hetero Diels-Alder Reaction

A solution containing equimolar quantities of Danishefsky's diene **200** and benzaldehyde as well as the chromium(III)-complex **204** (10 mol %) and 4 Å molecular sieves in *t*-butylmethyl ether was prepared at -20 °C and allowed to warm slowly to room

temperature (entry 1, Table 3.4.1).[105b*]

Table 3.4.1 Chromium(III)-Complex **204** and **205**-Catalyzed Hetero Diels-Alder Reaction of Danishefsky's Diene **200** and Benzaldehyde



entry	catalyst	yield	er[a]	configuration[b]
1	**204** (10 mol %)	56%	64:36	*S*
2	**204** (6.5 mol %)	88%	74:26	*S*
3	**205** (6.5 mol %)	84%	67:33	*S*

[a] Determined by chiral HPLC analysis of the purified pyranone **203**. [b] Determined by comparison of the sign of its optical rotation to that of the known compound.[120c]

After 19 h, as determined by thin-layer chromatography and ^{1}H NMR spectroscopy, the crude reaction product was composed of a mixture of the Diels-Alder adduct **201** as well as the dihydropyranone **203**. A trifluoroacetic acid-catalyzed elimination reaction was then performed on this crude mixture to convert the Diels-Alder adduct **201** completely to the dihydropyranone **203** which was then isolated in 56% yield. The dihydropyranone **203** was produced in moderate enantioselectivity (er = 64:36) as determined by chiral HPLC analysis of the purified product. Using the chiral titanium complex **198** (see: Figure 3.4.1), Ding and co-workers found the hetero Diels-Alder reaction of Danishefsky's diene and benzaldehyde to proceed in higher yield and enantioselectivity when the reaction was performed in the absence of solvent.[119b]

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* Jacobsen and co-workers solved a crystal structure for the chromium(III) complex of the tridentate Schiff base **184** (Scheme 3.2.1) and found that the chromium centre bore a water ligand. They postulated that molecular sieves served to abstract a water molecule from this complex thus freeing a coordination site for the aldehyde. In the absence of desiccants, they found that the cycloaddition reactions did not proceed.

Therefore, the diene **200** (1 equivalent), benzaldehyde (1.04 equivalents), chromium(III)-complex **204** (6.5 mol %) and 4 Å molecular sieves were stirred at room temperature in the absence of solvent. After 22 h, the dihydropyranone **203** was obtained, following hydrolysis with trifluoroacetic acid, in excellent yield (88%, entry 2). As well, the dihydropyranone **203** was produced in good enantioselectivity (er = 74:26) as determined by chiral HPLC analysis. This was a significant increase in both the yield and enantiomeric ratio as compared to the same reaction performed in *t*-butylmethyl ether.

The larger aminoethanol-derived chromium(III)-complex **205** was then evaluated in the hetero Diels-Alder reaction. Under identical solvent-free conditions, the Diels-Alder reaction proceeded more slowly but afforded the dihydropyranone **203** in a good yield (84%, entry 3). However, in this case, the dihydropyranone was produced in lower enantioselectivity (er = 67:33). In the three cases, the dihydropyranone **203** was determined to be of an (*S*)-configuration, by comparison of the sign of its optical rotation to that of the known compound.[119c]

A possible rational for the stereochemical outcome in the hetero Diels-Alder reactions involves coordination of the aldehyde carbonyl oxygen to the chromium centre from the bottom face (as drawn) so as to avoid unfavourable steric interactions with the acetal moiety (Figure 3.4.2). Approach of the diene **200** to the *Re*-face of the benzaldehyde (front face as drawn) would lead to the Diels-Alder adduct **201** and pyranone **203** with the observed (*S*)-absolute stereochemical configuration. The hetero Diels-Alder reaction catalyzed by the aminoethanol-derived chromium(III)-complex **205** proceeded less rapidly. Therefore, the slightly lower enantiomeric ratio obtained may be explained if the non-catalyzed (background) reaction became more significant. This does not preclude the possibility that the aldehyde adopted an alternate reactive conformation in which its diastereotopic *Si*-face became partially exposed.

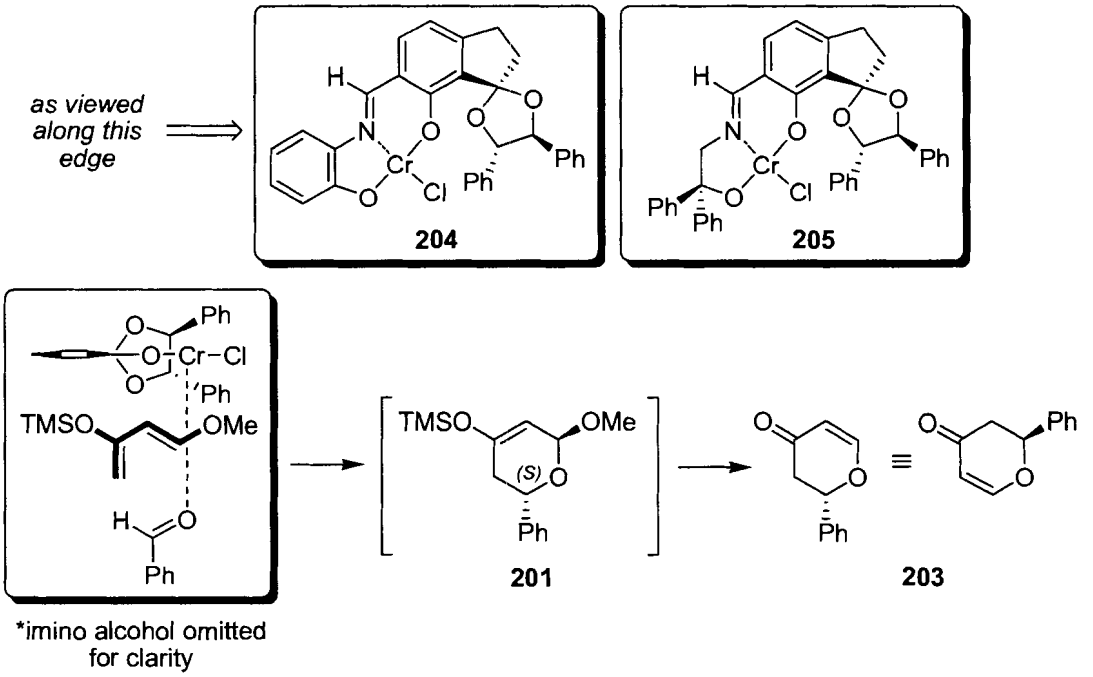


Figure 3.4.2 Rationale of the stereochemical outcome in the chromium(III)-complex **204** and **205**-catalyzed hetero Diels-Alder reactions.

3.5 Chiral 1,3-Amino Alcohol Ligands Derived from the 7-Hydroxy-indan-1-one Auxiliary [68 (R = Ph)]

3.5.1 Introduction

Chiral 1,3-amino alcohols **206** were prepared using the Mannich reaction and evaluated as ligands in the catalytic asymmetric: (i) addition of diethylzinc to aldehydes and (ii) Diels-Alder reaction of α,β-unsaturated aldehydes. The Mannich reaction of the auxiliary **68** (R = Ph) provides a simple one-step synthesis that would allow for the preparation of a variety of chiral 1,3-amino alcohols by variation of the secondary amine component **207** (Figure 3.5.1).

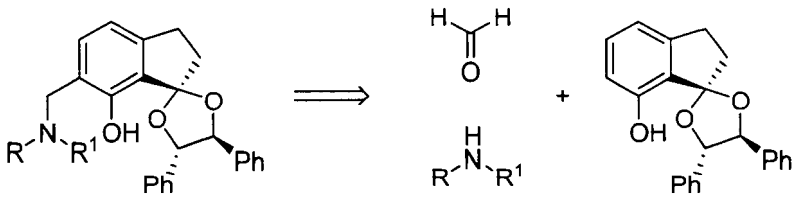
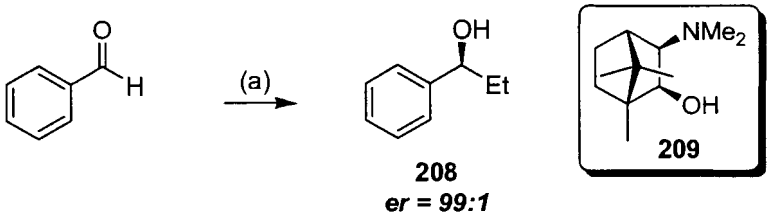


Figure 3.5.1 Preparation of the 1,3-amino alcohols **206** using the Mannich reaction.

3.5.2 Background

Chiral 1,2- and 1,3-amino alcohols have been used extensively as chiral auxiliaries and ligands in metal-catalyzed asymmetric synthesis as well as in the preparation of heterocyclic chiral auxiliaries and ligands.[122,23] In 1986, Noyori and co-workers reported the use of an isoborneol-derived 1,2-amino alcohol **209** as a ligand in the catalytic asymmetric addition of diethylzinc to aldehydes (Scheme 3.5.1).[123] This ligand **209** showed high catalytic activity and produced remarkable levels of stereochemical induction in this reaction.

Scheme 3.5.1 *N,N*-Dimethylaminoisoborneol-Catalyzed Asymmetric Addition Reaction of Diethylzinc and Benzaldehyde



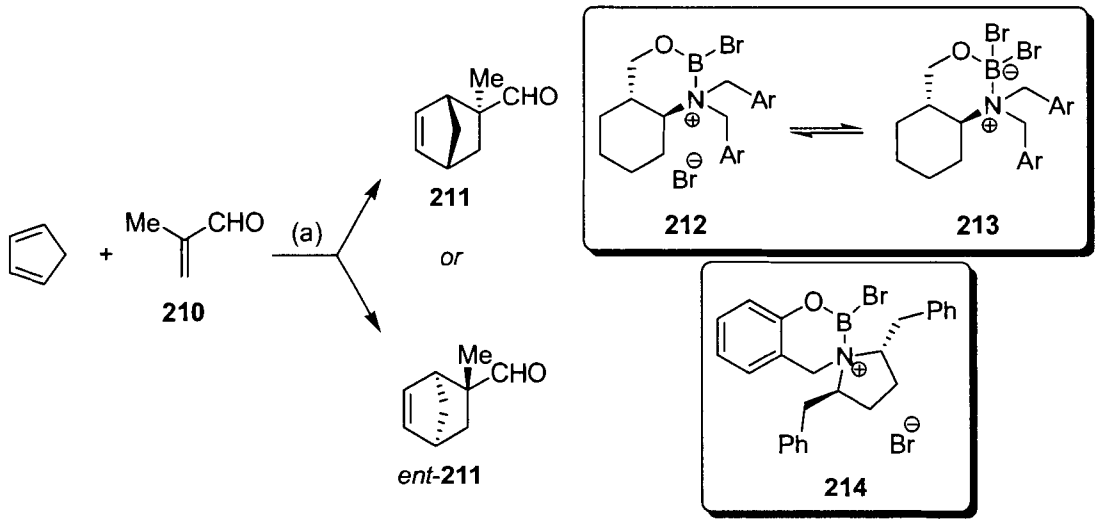
Reagents and conditions: (a) isoborneol **209** (2 mol %), Et_2Zn (1 equiv), 0 °C, toluene, 6 h, 97%.

Non-linear effects were later shown to be operative. Using the isoborneol **209** (8 mol %) of low enantiomeric purity (er = 58:42), 1-phenyl-1-propanol **208** could be recovered in 92% yield and in excellent enantioselectivity (er = 98:2) after 7 h at 0 °C.[124] These results have been explained by the formation of a stable, non-catalytic (achiral) *meso*-zinc complex derived from enantiomeric isoborneol molecules. The corresponding chiral zinc-complex derived from isoborneol molecules of the same stereochemical

configuration was less stable and able to dissociate into the monomeric and catalytically-active species.

In 1996 and 2003, Corey and co-workers reported the use of the boron complexes **212/213** and **214** of 1,3-amino alcohols as catalysts in the asymmetric Diels-Alder reaction of a variety of dienes and α-substituted unsaturated aldehydes (Scheme 3.5.2).[125] For example, the boron-catalyzed reaction of methacrolein **210** and cyclopentadiene afforded the cycloadduct **211** in high enantioselectivity (up to er = 98:2).

Scheme 3.5.2 Cationic Chiral Boron Catalysts for Asymmetric Diels-Alder Reactions



Reagents and conditions: (a) oxazaborinane **212/213**, CH_2Cl_2, -94 °C, 2 h, 99%, *exo*:*endo* = 88:12, er = 95:5 *or* oxazaborinane **214**, CH_2Cl_2, -94 °C, 1 h, 96%, *exo*:*endo* > 99:1, er = 98:2.

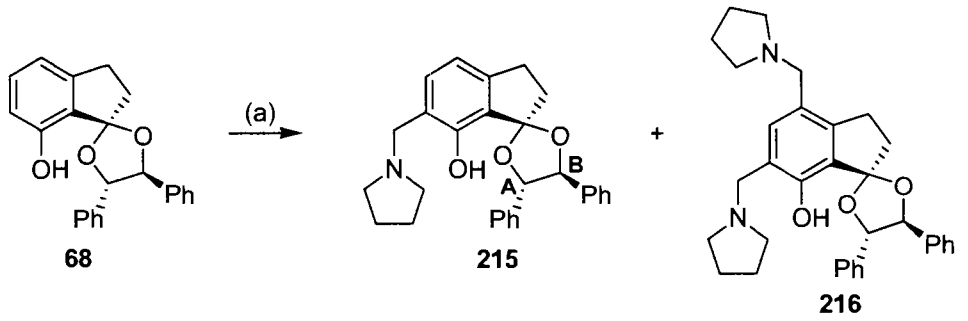
Using ^1H and ^{13}B NMR spectroscopy, the oxazaborinane **212/213** was found to consist of an equilibrium mixture of the cationic form **212**, believed to be the active catalyst, and the zwitterionic form **213**. The more recent pyrrolidine-derived complex **214** was shown to be more stable, more active and, in most cases, more selective than the cyclohexane-derived complex **212/213**. It could be prepared at 10 °C as compared to the cyclohexane-derived structure **212/213**, which was found to decompose at temperatures above -60 °C. The authors attributed the increased stability of the pyrrolidine-derived

complex **214** to the reduced propensity of its aryl carbon-oxygen bond to undergo a cleavage reaction.

3.5.3 Synthesis of the Chiral 1,3-Amino Alcohol [215 (R = Ph)]

A solution of the auxiliary **68**, pyrrolidine (1 equivalent) and excess formaldehyde was heated at reflux for 1.5 h after which time the desired *ortho*-pyrrolidinomethyl-substituted acetal **215** was isolated in 54% yield (Scheme 3.5.3). The regioselectivity of the reaction was determined unambiguously by ^{1}H NMR spectroscopy. The moderate yield was a result of competitive dialkylation of the auxiliary to form the *o*,*p*-substituted acetal **216**. This compound could be formed as the major product if the reaction was performed in the presence of excess pyrrolidine. The ^{1}H NMR spectrum of the amino alcohol **215** was again indicative of the distinct chemical environments of the two faces of the acetal subunit. The "interior" acetal methine hydrogen (**A**) resonated over 1 ppm downfield from the "exterior" acetal methine hydrogen (**B**) (Scheme 3.5.3).

Scheme 3.5.3 Synthesis of the Indan-1-one-Derived Chiral 1,3-Amino Alcohol **215**



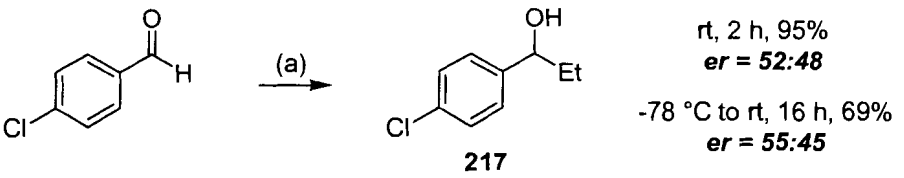
Reagents and conditions: (a) pyrrolidine, paraformaldehyde, EtOH, reflux, 1.5 h, **215** (54%).

3.6 Catalytic Asymmetric Addition Reactions of Diethylzinc and *p*-Chlorobenzaldehyde

The 1,3-amino alcohol **215** was examined as a chiral ligand in the addition reaction of diethylzinc and *p*-chlorobenzaldehyde (Scheme 3.6.1). To a solution of *p*-chlorobenzaldehyde and the amino alcohol **215** (5 mol %) in toluene at room temperature

was added a solution of diethylzinc in hexanes (3 equivalents). The reaction proceeded rapidly and the 1-aryl-1-propanol **217** was isolated in essentially quantitative yield after 2 h. No purification was required. Of note, in the absence of the ligand, the reaction did not proceed over the course of many hours at room temperature. The enantioselectivity of the product **217** was, however, low (er = 52:48) as determined by chiral HPLC analysis. The absolute stereochemical configuration of the major enantiomer of the product, therefore, was not determined.

Scheme 3.6.1 Chiral Amino Alcohol **215** in the Catalytic Addition Reaction of Diethylzinc and *p*-Chlorobenzaldehyde



Reagents and conditions: (a) amino alcohol **215** (5 mol %), Et_2Zn (3 equiv), toluene.

The reaction was also performed at -78 °C using 5 mol % of the ligand **215**. After several hours at -78 °C, no reaction was observed by thin-layer chromatography. Therefore, the reaction was allowed to warm slowly to room temperature over 16 h. The addition product was isolated in 69% yield. In this case, the enantiomeric ratio of the product **217** remained essentially unchanged (er = 55:45) as determined by chiral HPLC analysis.

3.7 Boron-Catalyzed Asymmetric Diels-Alder Reactions

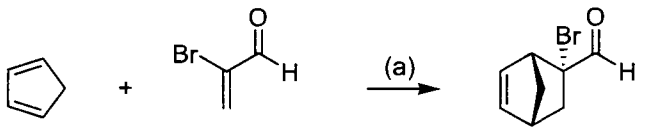
The 1,3-amino alcohol **215** was also used as a ligand in the boron tribromide-catalyzed Diels-Alder reaction of α-bromoacrolein **218** and cyclopentadiene (Scheme 3.7.1).[87a*] α-Bromoacrolein was prepared following a literature procedure in which

* Lewis acid-catalyzed enantioselective Diels-Alder reactions between α,β-unsaturated aldehydes and dienes have typically proceeded with lower enantioselectivities when the aldehyde does not contain an α-substituent.

acrolein was reacted with molecular bromine and triethylamine.[126]

To a solution of the amino alcohol **215** (8 mol %) in dichloromethane at 0 °C was added 2,6-di-*t*-butylpyridine (8 mol %) followed by boron tribromide (8 mol %). After 20 min, the orange solution was cooled to -78 °C and freshly-distilled α-bromoacrolein (1 equivalent) and cyclopentadiene (5 equivalents) were added. After 2 h, the reaction was allowed to slowly warm to -50 °C over 2 h after which time the reaction was quenched by the addition of triethylamine.

Scheme 3.7.1 Chiral Amino Alcohol **215** in the Cationic Boron-Catalyzed Diels-Alder Reaction of α-Bromoacrolein **218** and Cyclopentadiene

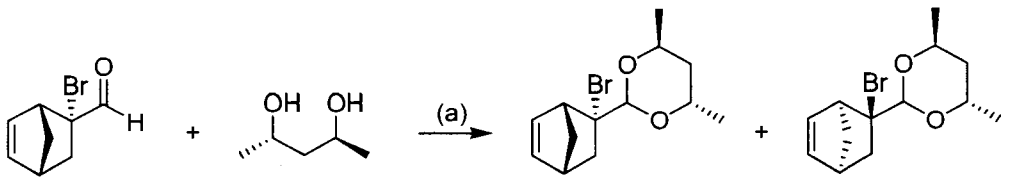


218 *rel*-**219**
***er* = 50:50**

Reagents and conditions: (a) 1,3-amino alcohol **215** (8 mol %), 2,6-di-*t*-butylpyridine (8 mol %), BBr_3 (8 mol %), cyclopentadiene (5 equiv), CH_2Cl_2, -78 to -50 °C, 4 h, 42%.

The *exo*-cycloadduct *rel*-**219** was isolated in 42% yield (*exo*:*endo* > 95:5). The product *rel*-**219** was assigned as the *exo*-isomer by comparison of its ^{1}H NMR spectral data to that of the known compound. In turn, the enantiomeric purity of the purified Diels-Alder adduct *rel*-**219** was determined by derivatization with a chiral nonracemic diol. Thus, a solution of the cycloadduct *rel*-**219**, (2*S*,4*S*)-2,4-pentanediol **220** and a catalytic amount of pyridinium *p*-toluenesulfonate in acetonitrile was stirred at room temperature for 16 h to afford the corresponding diastereomeric acetals **221** and **222** (Scheme 3.7.2).[127] The ^{1}H NMR spectrum indicated that the crude reaction product was a 50:50 mixture of diastereomers. Thus, the boron-catalyzed Diels-Alder reaction was not enantioselective.

Scheme 3.7.2 Determination of the Enantiomeric Ratio of the Diels-Alder Adduct *rel*-**219**



rel-**219** **220** **221** : **222**

50 50

Reagents and conditions: (a) (2*S*,4*S*)-2,4-pentanediol, PPTS, CH_3CN, rt, 16 h.

3.8 Conclusions

In a divergent manner, the chiral auxiliary **68** (R = Ph) was used as a synthetic intermediate for the preparation of several novel chiral ligands. All of the ligands were prepared in simple, one or two synthetic steps. The auxiliary was converted in two steps *via* the chiral salicylaldehyde intermediate **185** into four tridentate Schiff bases. Two of these salicylaldehyde-derived ligands are unique in that they represent the first chiral Schiff base ligands that incorporate chirality only in the salicylaldehyde subunit.

In the asymmetric sulfoxidation reaction, increasing the size of the achiral amino alcohol moiety resulted in an increase in enantioselectivity (from 56:14 to 63:37). These modest enantioselectivities showed, at least, that these ligands were able to form catalytically-active metal complexes. When the enantiomers of valinol were attached to the chiral salicylaldehyde, the resultant diastereomeric Schiff bases catalyzed the sulfoxidation reaction with equal but opposite enantioselectivities. This suggested that the chirality introduced through the amino alcohol subunit had a greater influence on the levels of asymmetric induction that these tridentate Schiff bases could impart, at least in the asymmetric sulfoxidation reaction. The diastereomeric Schiff bases provided further support for the proposal that the substrate approached from the side of the tridentate Schiff bases such to avoid unfavourable steric interactions with the acetal's "interior" phenyl substituent.

Chromium complexes **204** and **205** of the tridentate Schiff bases **190** and **191** were used in the hetero Diels-Alder reaction of Danishefsky's diene and benzaldehyde affording, following a trifluoroacetic acid-catalyzed elimination reaction, the heterocyclic dihydropyranone **203** in good yield and in enantioselectivities up to 74:26. Here, the less-hindered Schiff base complex **204** catalyzed the reaction at a faster rate and produced higher levels of stereochemical induction (er = 74:26 *vs.* 67:33). The observed (*S*)-cycloadducts could be accounted for if benzaldehyde coordinated to the chromium(III)-complex so as to minimize unfavourable steric interaction with the acetal's "interior" phenyl substituent.

The chiral 1,3-amino alcohol **215** was prepared in one step from the auxiliary **68** (R = Ph) using the Mannich reaction. This ligand catalyzed the addition of diethylzinc to *p*-chlorobenzaldehyde in high yield at room temperature; however, the levels of asymmetric induction were low (er = 52:48). When the same reaction was performed at lower temperatures (*i.e.* -78 °C), the isolated yield of the addition product decreased and the reaction became only slightly more enantioselective (er = 55:45). In the catalytic asymmetric Diels-Alder reaction of α-bromoacrolein and cyclopentadiene, the cycloadduct *rel*-**219** was isolated in low yield (42%) with no stereochemical induction being observed. These results suggest that the 1,3-amino alcohol **215** does, in certain cases, form catalytically-active complexes. It cannot be precluded that the latter reaction was catalyzed by unbound boron tribromide to form the observed racemic cycloadduct *rel*-**219**. However, the diethylzinc addition reaction did *not* proceed in the absence of the ligand. In both cases the reactions ranged from unselective to poorly enantioselective suggesting that the 1,3-amino alcohol **215** did not provide a good chiral environment for efficient asymmetric induction to occur.

The studies reported here have shown that 7-hydroxyindan-1-one-derived ligands can induce good levels of stereochemical induction in catalytic asymmetric processes.

The use of the readily-available indanone-derived auxiliaries as precursors and the simplicity of the chemistry utilized to construct the chiral ligands presented here make these targets deserving of further study. The wide range of chiral 1,2-diols, 1,2-amino alcohols and amines that are commercially-available or readily-prepared will allow for a large number of structurally-diverse ligands to be prepared.

The evaluation of tridentate Schiff base ligands derived from various chiral 1,2-diols in the catalytic asymmetric hetero Diels-Alder reaction should be a future research goal. As well, although the initial results using the 1,3-amino alcohol ligand **215** (R = Ph) were not encouraging, the preparation of several more structures derived from the same auxiliary **68** (R = Ph) and other symmetrical and unsymmetrical secondary amines is worthy of future investigation. Finally, the preparation of salen-type ligands from the salicylaldehyde **186** (R = Ph) for evaluation as chiral tetradentate ligands for asymmetric synthesis could be a further research goal.

CHAPTER 4: RESULTS AND DISCUSSION

THE SYNTHESIS AND EVALUATION OF PYRIDINE-AND PYRROLIDINOPYRIDINE-DERIVED CHIRAL ACETALS FOR USE IN CATALYTIC ASYMMETRIC SYNTHESIS

4.1 Introduction

In this chapter, the synthesis and evaluation of chiral catalysts based upon the general chiral acetal framework **38** is described. The chiral 4-pyrrolidinopyridine structure **223** was a specific synthetic target for evaluation in several catalytic asymmetric processes including the kinetic resolution of secondary alcohols (Figure 4.1.1). The proposed synthesis of the pyrrolidinopyridines **223** involved the acid-catalyzed condensation reaction of the heterocyclic ketone **224** and diols **36** as a key synthetic step.

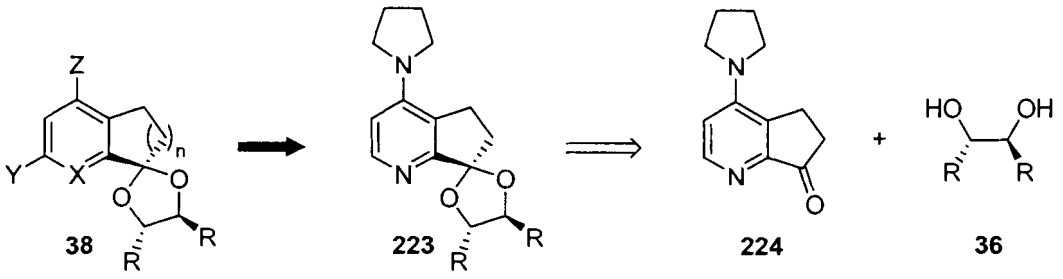
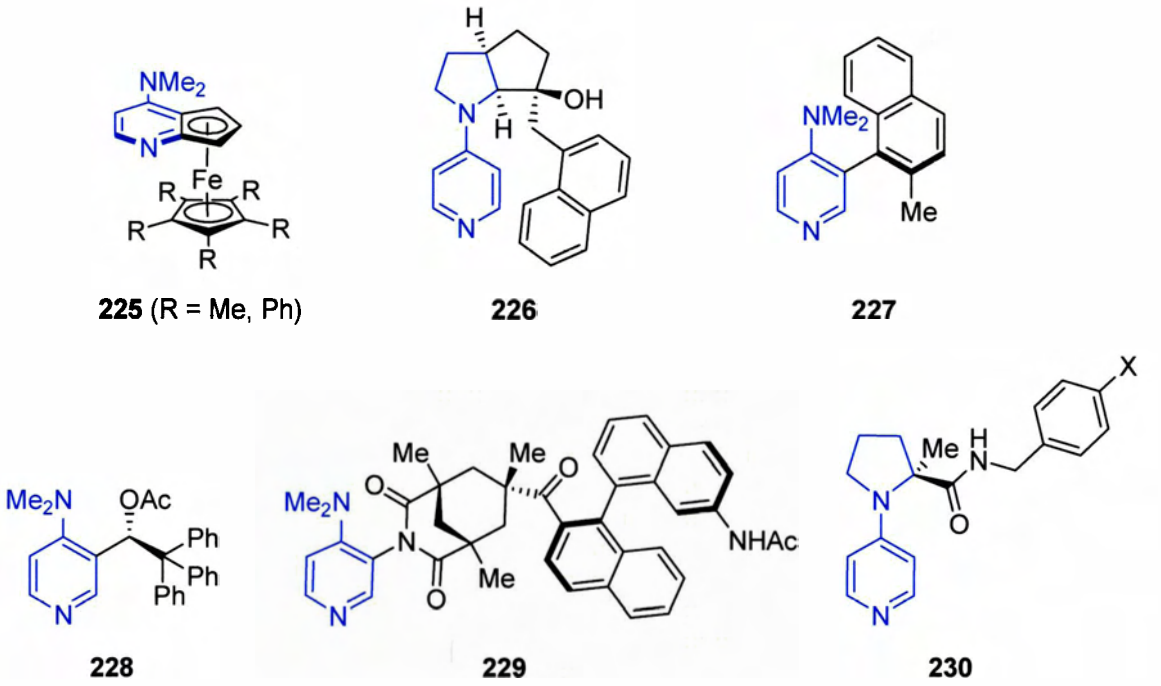


Figure 4.1.1 Proposed chiral pyrrolidinopyridine derivatives **223**.

4.2 Background

Chiral *N,N*-dimethyl-4-aminopyridine and 4-pyrrolidinopyridine derivatives have been the focus of much recent study. A structurally-diverse array of chiral *N,N*-dimethyl-4-aminopyridine and pyrrolidinopyridine derivatives have been prepared over the last decade for use in both stoichiometric and catalytic asymmetric reactions such as the kinetic resolution of secondary alcohols,[128] the addition of alcohols or pyrroles to ketenes[129] and the rearrangement of *O*-acylated azlactones (Figure 4.2.1).[130] Of these structures, the chiral ferrocene derivatives **225** have afforded the highest levels of

asymmetric induction in a range of *N*,*N*-dimethyl-4-aminopyridine-catalyzed reactions. The majority of other chiral *N*,*N*-dimethyl-4-aminopyridine and pyrrolidinopyridine derivatives have been used in the kinetic resolution of racemic alcohols.[131] The stereochemical elements of these structures include planar (**225**)[132] and axial chirality (**227**[131a] and **229**[131b]). The remaining compounds **226**[128b], **228**[131d] and **230**[128d] have one or more stereogenic centres integrated into their structures. Of note, the chiral pyrrolidinopyridine derivative **230** was attached to a solid support so that it could be recycled for further reactions.



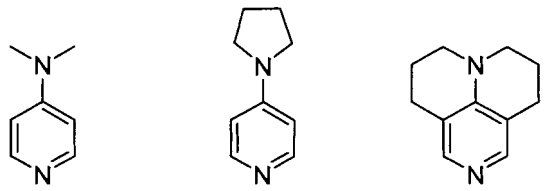
225 (R = Me, Ph) **226** **227**

228 **229** **230**

Figure 4.2.1 Chiral *N*,*N*-dimethyl-4-aminopyridine and 4-pyrrolidinopyridine derivatives (X = solid support).

More than three decades ago, *N*,*N*-dimethyl-4-aminopyridine was introduced as a nucleophilic acylation catalyst (Figure 4.2.2).[133] In the initial report, the rate of benzoylation of *m*-chloroaniline occurred ~ 10^4 times faster in the presence of catalytic quantities of *N*,*N*-dimethyl-4-aminopyridine ($pKa_{conjugate\ acid}$ = 9.7 in water) as compared to pyridine.[134] 4-Pyrrolidinopyridine ($pKa_{conjugate\ acid}$ = 9.9 in water) has been shown to be

a slightly more active catalyst.[134] Recently, the known pyridonaphthyridine derivative **231** ($pKa_{conjugate\ acid}$ = unknown) has been shown to be ~ 6 times more active than *N*,*N*-dimethyl-4-aminopyridine and ~ 2.5 times more active than 4-pyrrolidinopyridine in the acylation reaction of a tertiary alcohol.[135] The differences in basicities of these derivatives is likely a good measure of their relative nucleophilicities as each has a similar steric environment around its pyridyl nitrogen.

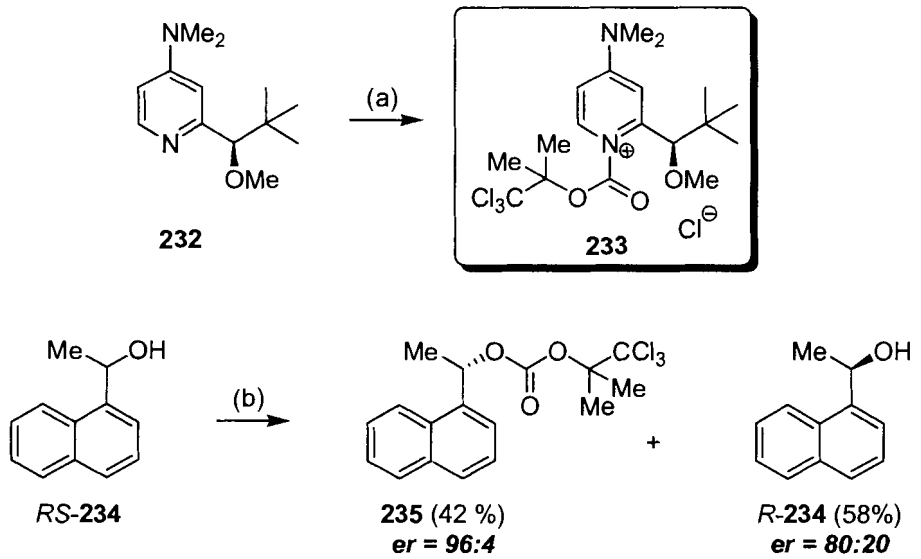


231

Figure 4.2.2 *N*,*N*-dimethyl-4-aminopyridine, 4-pyrrolidinopyridine and a pyridonaphthyridine derivative **231**.

In 1996, Vedejs and co-workers reported the first chiral *N*,*N*-dimethyl-4-aminopyridine derivative for asymmetric synthesis, here used for the kinetic resolution of secondary alcohols (Figure 4.2.1).[128a] Due to significant steric hindrance around the catalytic site of the chiral pyridine **232**, the kinetic resolution involved pre-formation of the chiral acyl donor **233** and its use as a stoichiometric reagent to in its reaction with the secondary alcohol *RS*-**234**. As well, Lewis acid-catalysis was required to facilitate the acylation reaction. However, the carbonate product **235** was formed in high enantioselectivity (er = 96:4) and the unreacted alcohol *R*-**234** was recovered in a good enantiomeric ratio (er = 80:20).

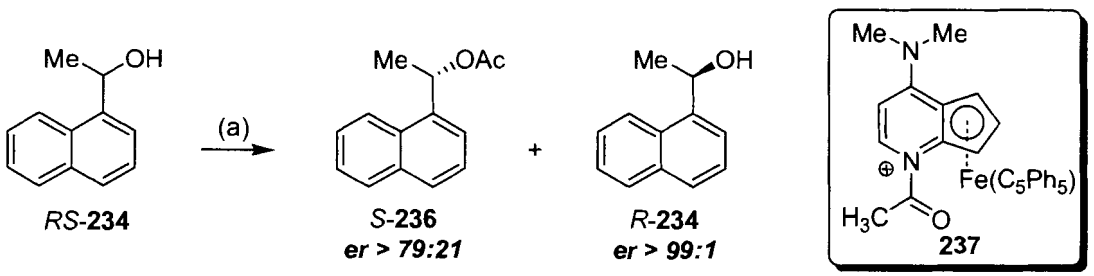
Scheme 4.2.1 Chiral *N,N*-Dimethyl-4-Aminopyridine-Derivative **232** in the Stoichiometric Kinetic Resolution of 1-(1-Naphthyl)ethanol



Reagents and conditions: (a) 1,1-dimethyl-2,2,2-trichloroethylchloroformate, CH_2Cl_2, 0 °C to rt, 2 h. (b) chiral acyl DMAP **233** (50 mol %), $MgBr_2$ (1 equiv), Et_3N (1.5 equiv), ether, rt, 14 h.

In 1997, Fu and co-workers used the chiral *N,N*-dimethyl-4-aminopyridine **225** (R = Ph) in the kinetic resolution of a variety of secondary alcohols (Scheme 4.4.2). At 63% conversion, the alcohol *R*-**234** was recovered in essentially enantiomerically-pure form (er > 99:1). Of note, the chiral pyridine **225** was prepared in a racemic 12-step synthesis and required preparative chiral HPLC separation.

Scheme 4.2.2 Planar Chiral *N,N*-Dimethyl-4-Aminopyridine **225** in the Kinetic Resolution of 1-(1-Naphthyl)ethanol



Reagents and conditions: (a) chiral DMAP **225** (R = Ph, 2 mol %), Ac_2O (0.75 equiv), Et_3N (0.75 equiv), ether, rt, 27 h.

The proposed mechanism of this kinetic resolution, which is similar to others that have been reported, involves initial reaction of the highly-nucleophilic chiral *N,N*-dimethyl-4-aminopyridine with acetic anhydride to form the activated acyl intermediate **237** (with an acetate counterion).[134*] The acyl pyridinium salt **237** is a more reactive acylating agent than acetic anhydride; therefore, it preferentially reacts with the alcohol.

The chiral environment in this system causes one of the enantiomers of the racemic alcohol *RS*-**234** to react at a faster rate, thus, kinetically resolving the mixture into the chiral nonracemic acetate product *S*-**236** and the unreacted chiral nonracemic alcohol *R*-**234**. Fu and co-workers have solved the molecular structure of the acyl pyridine **237** (with a hexafluoroantimonate counterion) by X-ray crystallography. In the X-ray structure, the *N,N*-dimethyl-4-aminopyridine and acetyl groups were coplanar which is consistent with extended conjugation. As well, the amino-aryl bond in the acylated planar chiral catalyst **237** was found to be shorter than that in the neutral catalyst **225**. This was suggested to be a result of the electron-releasing and stabilizing interaction that the *N,N*-dimethyl-4-amino group conferred to the cationic species **237**. From ^{1}H NMR studies, the rotational barrier for the *N,N*-dimethyl-4-amino-aryl bond of the acyl pyridine **237** was found to be significantly higher than that for the parent pyridine **225** ($\Delta G^{\ddagger} > 21$ kcal/mol *vs.* ~ 10 kcal/mol).

In the same year, Fuji and co-workers prepared the pyrrolidinopyridine derivative **226** for the kinetic resolution of secondary alcohols (Figure 4.2.1).[128b] High selectivities using this catalyst were achieved through an intriguing "induced fit" process. A π-π interaction between the electron-rich naphthyl and electron-poor acetyl pyridinium ring systems provided selective shielding of one of the diastereotopic faces of the pyrrolidinopyridine. NOE contacts as well as diagnostic upfield and downfield ^{1}H NMR

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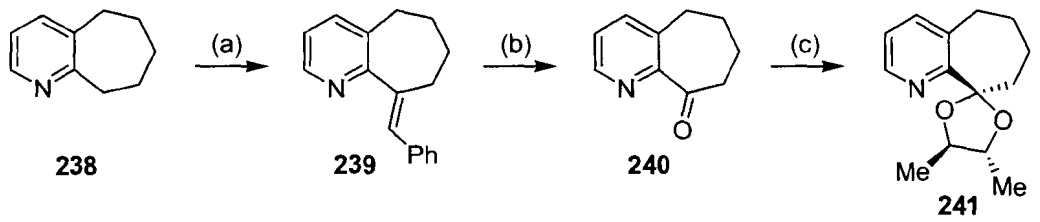
* Höfle and co-workers found that a mixture of 4-pyrrolinopyridine and acetic anhydride (1.5 equiv) at -115 °C was converted completely into the corresponding acyl pyridinium salt.

chemical shifts were suggestive of the proposed π-stacked reaction intermediate. Aromatic alcoholic substrates that allowed for the possibility of additional π-π stacking were resolved with the highest enantioselectivities (er > 99:1).

4.3 Model Studies: Synthesis of Chiral Acetal Derivatives of Cyclohepta[b]pyridine

The last step of the proposed synthesis of the chiral pyrrolidinopyridine derivatives **223** was the acid-catalyzed condensation reaction of the pyridyl ketone **224** and the chiral 1,2-diols **36**. To determine if this key step could be achieved, a model study involving a short synthesis of a chiral pyridine derivative was performed. In addition, as pyridine itself is known to catalyze a variety of reactions, the chiral pyridine derivative was also synthesized for examination as a chiral catalyst. Thus, the known pyridin-9-one **240** was prepared in two synthetic steps from the commercially-available cyclohepta[b]pyridine **238** (Scheme 4.3.1).[136*]

Scheme 4.3.1 Synthesis of 5,6,7,8-Tetrahydrocyclohepta[b]pyridin-9-one (2*R*,3*R*)-butanediol acetal **241** (R = Me)



238 **239** **240** **241**

Reagents and Conditions: (a) Ac_2O, benzaldehyde, reflux, 5 days, 73%. (b) ozone, MeOH, -78 °C, 45 min; Me_2S, -78 °C to rt, 24 h, 68%. (c) (2*R*,3*R*)-butanediol **52**, *p*-TsOH, benzene, reflux, 2 days, 62%.

The pyridine **238**, benzaldehyde and acetic anhydride were heated for 5 days in a condensation reaction to afford the alkene **239** in 73% yield. The known alkene **239** was subsequently subjected to an ozonolysis reaction to produce, following a reductive

* During the course of these studies, the 5- and 6-membered pyridine-derivatives, cyclopenta- and cyclohexa[b]pyridine, were not commercially available and their syntheses are not trivial. Therefore, the 7-membered pyridine-derivative **238** was selected for the model studies.

workup, the pyridin-9-one **240** in 68% yield. A solution of the pyridine-9-one **241** and (2*R*,3*R*)-butanediol **52** was then heated in the presence of a catalytic amount of *p*-toluenesulfonic acid. After 1 day, the reaction had proceeded to a negligible extent. However, when a stoichiometric quantity of *p*-toluenesulfonic acid was added to the reaction mixture, the condensation reaction was found to proceed and the acetal **241** (R = Me) was isolated in 62% yield after an additional 2 days at reflux. The ^{1}H NMR spectrum of the acetal **241** is indicative of the distinctive chemical environments the two faces of the acetal moiety. Here, the "interior" methyl (**C**) and methine (**B**) hydrogens resonate downfield from their "exterior" counterparts (Figure 4.3.1).

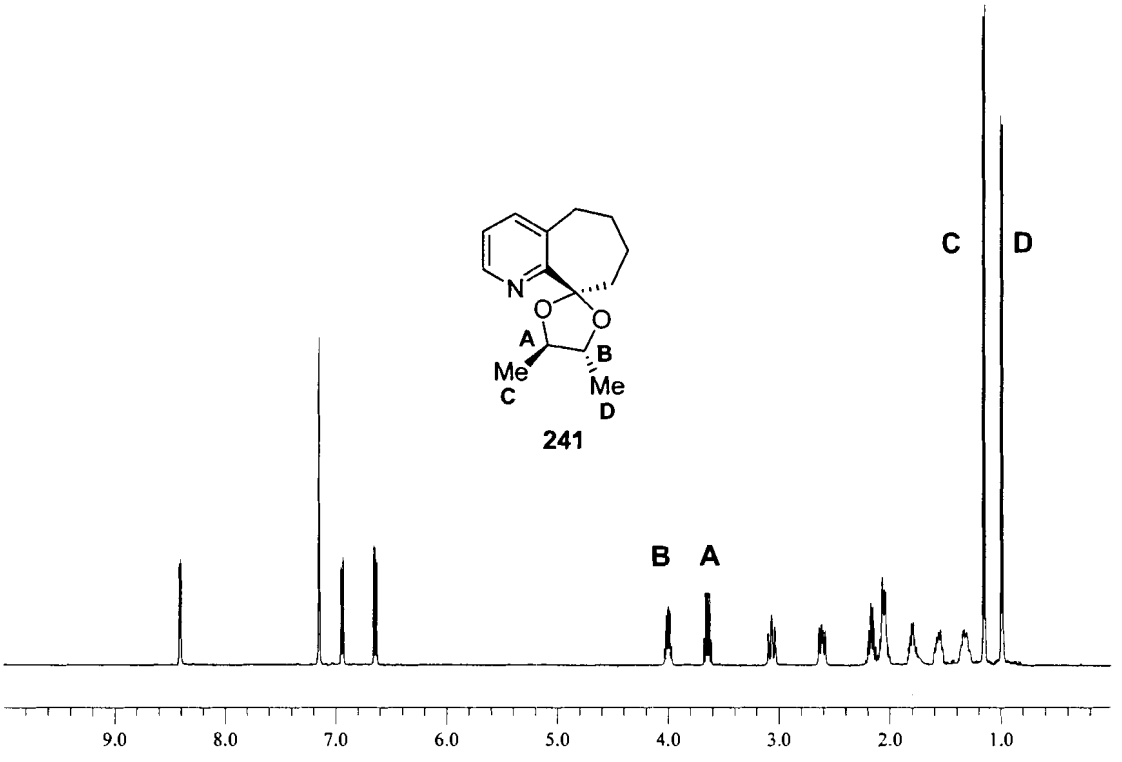


Figure 4.3.1 ^{1}H NMR (400 MHz, C_6D_6) spectra of 5,6,7,8-tetrahydrocyclohepta[b]pyridin-9-one (2*R*,3*R*)-butanediol acetal **241**.

4.4 Synthesis of Chiral Acetal Derivatives of Pyrrolidinopyridine

Retrosynthetic analysis of the chiral pyrrolidinopyridines **223** indicated that they could be prepared from the known 4-chloropyridine *N*-oxide **242** *via* a nucleophilic

aromatic displacement, sigmatropic rearrangement, hydrolysis, oxidation and acetal condensation reaction sequence (Figure 4.4.1). The *N*-oxide **242** had previously been prepared in three synthetic steps from the commercially-available cyclopenta[b]pyridine **243**.[137]

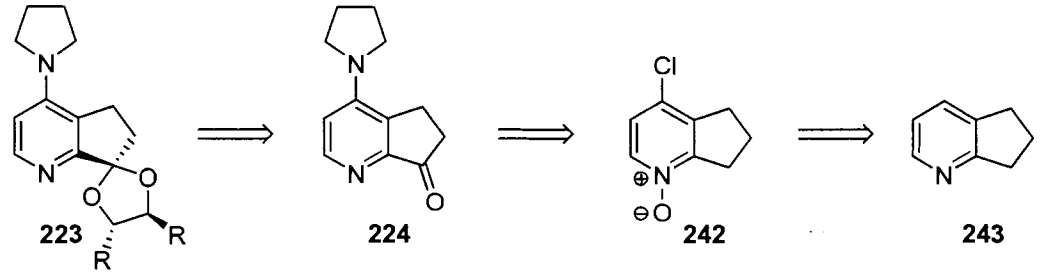
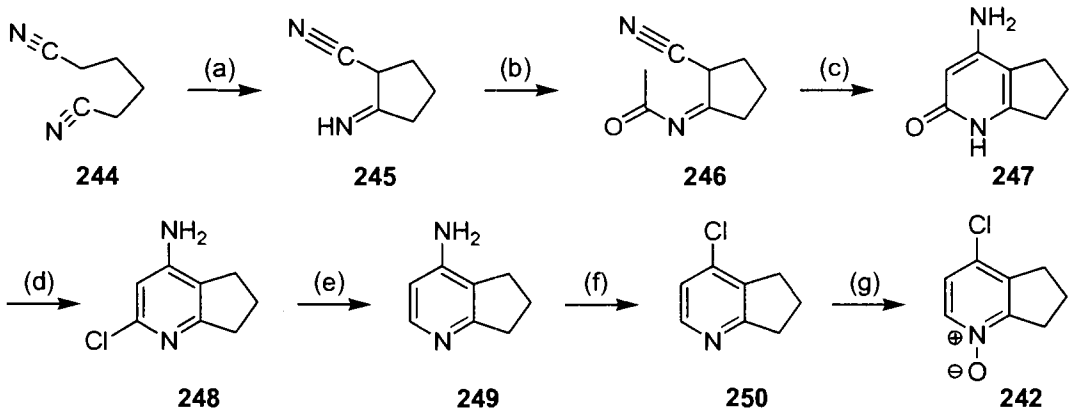


Figure 4.4.1 Retrosynthetic analysis of the chiral pyrrolidinopyridines **223**.

However, at the commencement of the synthesis, it was found that the pyridine **243** was no longer commercially-available. For this reason, an alternate route to the target chiral pyrrolidinopyridines **223** was devised that preserved the 4-chloropyridine *N*-oxide **242** as a synthetic intermediate.[129] Following a known synthetic sequence, adiponitrile **244** was reacted with molten sodium in toluene to form the imine **245** (Scheme 4.4.1).[138]

Scheme 4.4.1 Synthesis of the 4-Chloropyridine *N*-Oxide Derivative **242**



Reagents and Conditions: (a) Na, toluene, 100 °C, 16 h, 53%. (b) Ac_2O, rt, 16 h, 82%. (c) $NaNH_2$, NH_3, 4 h, 52%. (d) $PhP(O)Cl_2$, 160 °C, 16 h, 84%. (e) H_2, Pd/C, NaOH, EtOH, 95%. (f) $NaNO_2$, conc. HCl, 0 °C, 2 h, 86%. (g) H_2O_2, glacial AcOH, 80 °C, ~24 h, 89%.

The imine **245** was reacted with acetic anhydride to produce the acetamide **246**, which was treated with sodium amide in liquid ammonia to afford the pyridinone **247**. In the latter reaction, presumably the enolate of the acetate added to the nitrile group to form the second ring of the bicyclic system **247**.* The pyridinone **247** was de-oxygenated in a two-step sequence by chlorination with phosphorus oxychloride and reduction with hydrogen and a catalytic amount of palladium on activated carbon, which afforded the novel 4-aminopyridine **249**. The 4-aminopyridine **249** was then converted to the 4-chloropyridine **250** by reaction with sodium nitrite and concentrated hydrochloric acid. Subsequently, the 4-chloropyridine **250** was oxidized with hydrogen peroxide to form the known pyridine *N*-oxide **242**.

To complete the synthesis, an aqueous solution of the 4-chloro-*N*-oxide **242** and pyrrolidine was heated in a sealed tube at 140 °C for 1 day (Scheme 4.4.2).[129] The pyrrolidino-*N*-oxide **251** was treated with neat acetic anhydride at room temperature for 1.5 h and then heated at 100 °C for 4.5 h. Under these conditions, the *N*-oxide **251** was *O*-acetylated and, at elevated temperatures, the *O*-acetate underwent a [3,3]-sigmatropic rearrangement to form the acetate **252**.[129,139] The acetate **252** was readily hydrolyzed with lithium hydroxide to form the alcohol **253**. A Swern oxidation of the alcohol **253** produced the ketone **224**.[140] The final synthetic step involved a condensation reaction of the ketone and chiral 1,2-diols **36** to afford the desired chiral pyrrolidinopyridines **223**. In the presence of stoichiometric quantities of *p*-toluenesulfonic acid, the ketone **224** was condensed with (2*R*,3*R*)-2,3-butanediol **52** and (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29** to install the chiral acetal groups of the respective chiral pyrrolidinopyridine **254** (R = Me) and **255** (R = Ph).

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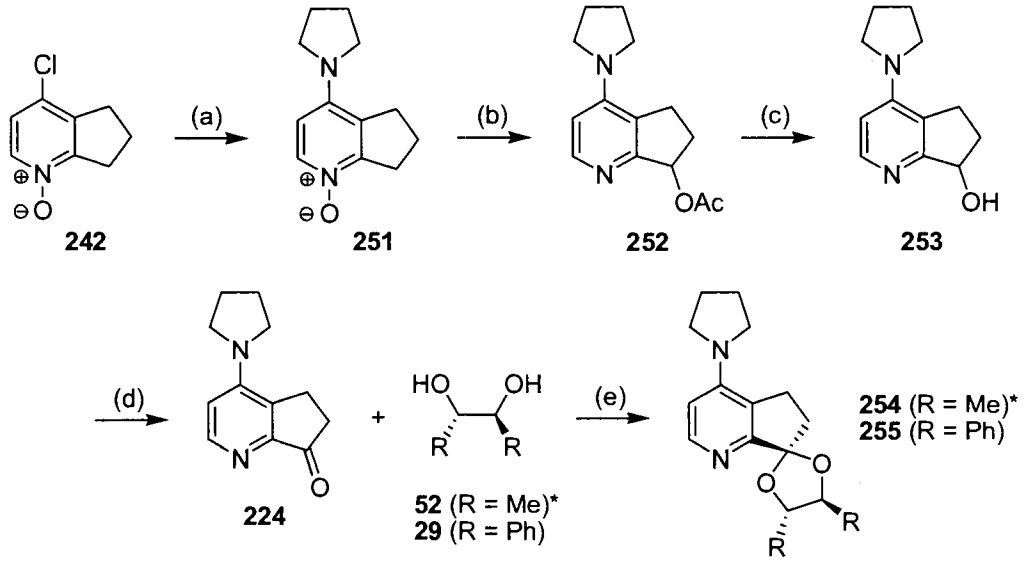
* The IR and ^{13}C NMR data support the pyridinone as the major tautomer. In the IR spectrum, a strong sharp peak at 1640 cm^{-1} is indicative of an amide/lactam carbonyl group. In the ^{13}C NMR spectrum, a signal at δ 167.50 is also suggestive of an amide/lactam carbonyl carbon.

Scheme 4.4.2 Synthesis of the Pyrrolidinopyridine-Derived Chiral Acetals **254** (R = Me) and **255** (R = Ph)



Reagents and conditions: (a) pyrrolidine, H_2O, 140 °C, 24 h, ~ 100%. (b) Ac_2O, rt, 1.5 h; 100 °C, 3 h, 90%. (c) LiOH, THF:H_2O (3:1), rt, 6 h, 95%. (d) oxalyl chloride, DMSO, CH_2Cl_2; Et_3N, -78 °C to -25 °C, 2 h, 67%. (e) diols **52** (R = Me)* and **29** (R = Ph), *p*-TsOH, benzene, reflux, 20 h, **254** (77%, R = Me)*, **255** (69%, R = Ph). *The enantiomer of that indicated in the reaction scheme was prepared.

The ketone **224** was sparingly soluble in boiling benzene and toluene. Thus, it was necessary to perform the acetal condensation reactions under dilute conditions (30 mM or less in ketone) in order to achieve efficient conversion to the desired products. The condensation reaction required extended reaction times (~ 2 to 5 days) when performed using higher concentrations of the ketone **224**. In addition, these reactions did not proceed to completion and, partial degradation of the ketone **224** occurred.

Even under dilute conditions (~ 30 mM), the condensation reaction of the ketone **224** and diol **29** (R = Ph) did not proceed to a significant extent in the presence of catalytic quantities of *p*-toluenesulfonic acid. The reaction mixture remained heterogeneous throughout the course of these reactions. In contrast, the reaction mixtures became homogeneous over their course when stoichiometric quantities of *p*-toluenesulfonic acid were used. The conjugate acid of the ketone **224**, the pyridinium

sulfonate, may have been more soluble in benzene than the neutral ketone **225**, thus increasing the rate at which the condensation reaction proceeded.

The ^{1}H NMR spectra for the alcohol **253** displayed signals at δ 5.1 and 5.7 ppm for the hydrogens of the secondary alcohol group (**E** and **F**, Figure 4.4.2). The aromatic hydrogens of the ketone **224** resonated downfield with respect to those of the alcohol **253**. The signals for the acetal subunit of the chiral pyrrolidinopyridine are evident (**G**, **H**, **I** and **J**).

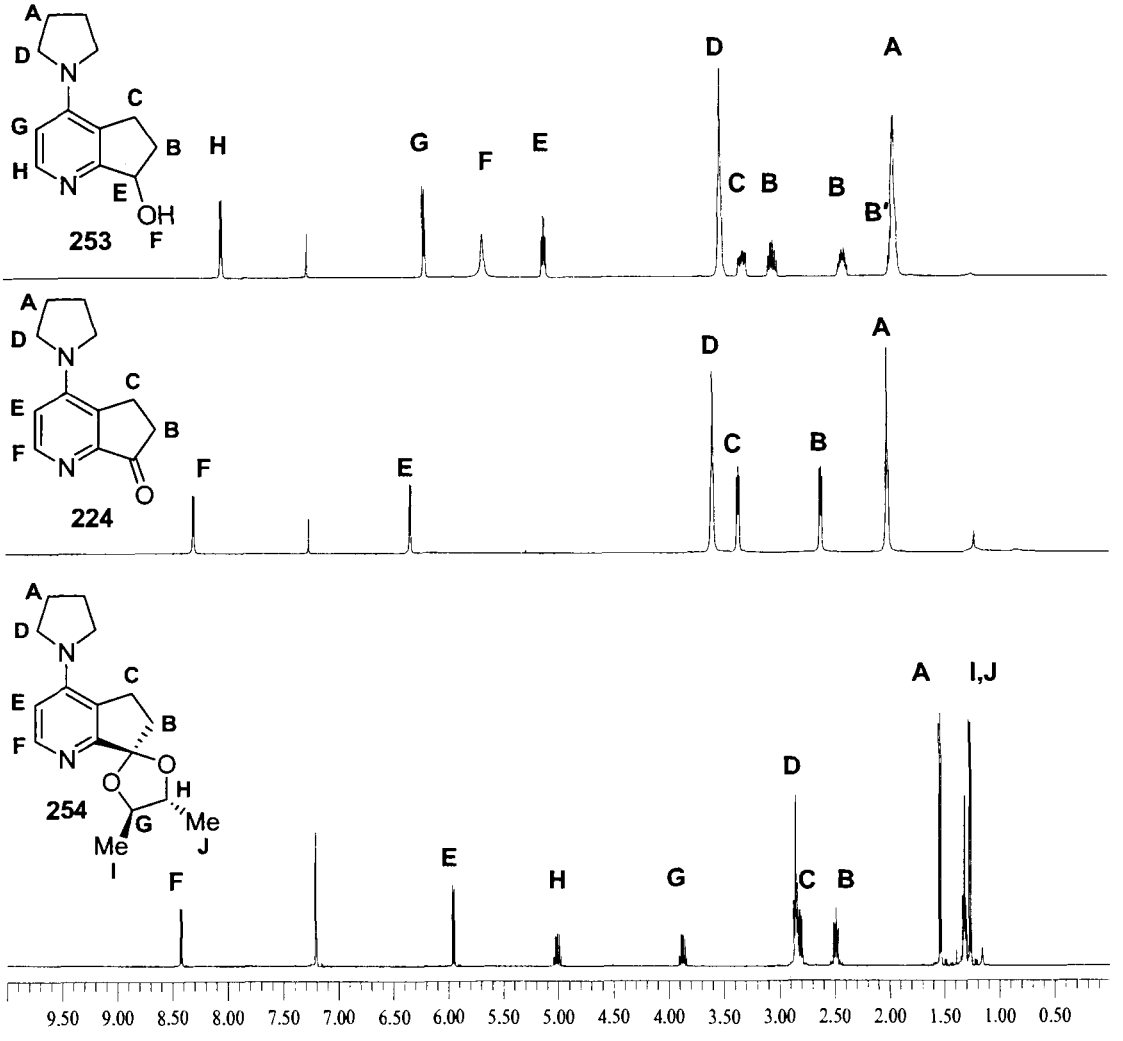


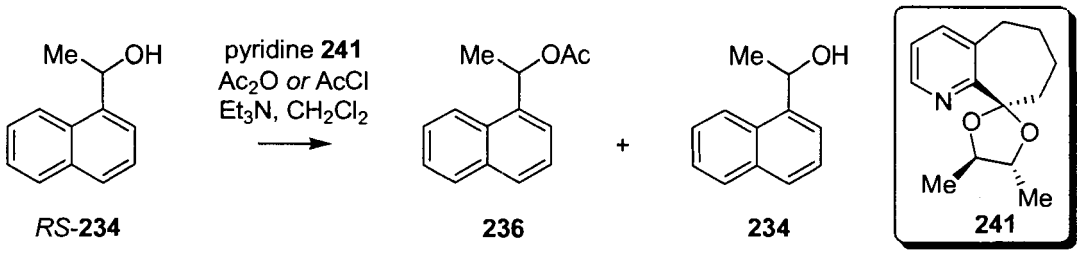
Figure 4.4.2 ^{1}H NMR (400 MHz) spectra of the pyrrolidinopyridine alcohol **253** ($CDCl_3$), ketone **224** ($CDCl_3$) and acetal **254** (R = Me, C_6D_6)

4.5 Kinetic Resolutions of Secondary Alcohols

The chiral pyridine **241** (R = Me) and pyrrolidinopyridine **254** (R = Me) and **255** (R = Ph) were evaluated as catalysts in the kinetic resolution of the chiral secondary alcohol, 1-(1-naphthyl)ethanol *RS*-**234** which was prepared from 1-naphthaldehyde by a known procedure.[141] A sample of the corresponding racemic acetate *RS*-**236** was also prepared from the alcohol for use as a reference for subsequent chiral HPLC analysis of the kinetic resolution reactions.

In the first experiment, a solution of the chiral pyridine **241** (R = Me, 0.10 equivalents), the alcohol *RS*-**236**, acetic anhydride (0.78 equivalents) and triethylamine (0.75 equivalents) in dichloromethane was stirred at 0 °C to room temperature for 20 h (entry 1, Table 4.5.1). The reaction proceeded to a negligible extent as determined by thin-layer chromatography. The enantiomeric ratios of the acetate product **236** and unreacted alcohol **234** were, therefore, not determined. Because no product was formed in the first instance, the reaction was next performed using an increased amount of both the chiral pyridine and reagents. The reaction was performed using stoichiometric quantities of the chiral pyridine **241**, acetic anhydride and triethylamine (entry 2). After 20 h, the reaction had only proceeded to a negligible extent; therefore, excess acetic anhydride and triethylamine were added. After an additional 16 h, ethanol was added to quench the excess acetic anhydride, converting it to ethyl acetate. The reaction mixture was then concentrated and the crude reaction product was purified by flash chromatography to afford the naphthyl acetate **236** (49%) and unreacted alcohol **234** (43%). The alcohol **234** and acetate **236** were each found to be racemic as determined by comparison of the magnitudes of their respective optical rotations to those of the known compounds.[142] The reaction proceeded to 16% completion using acetyl chloride (0.75 equivalents) as the acylating agent with no optical enrichment in either the alcohol **234** or acetate **236** as determined by chiral HPLC analysis (entry 3).

Table 4.5.1 Attempted Kinetic Resolution of 1-(1-Naphthyl)ethanol Using the Chiral Pyridine **241** (R = Me)



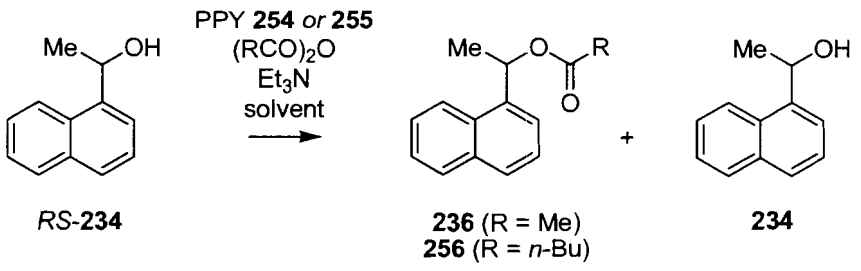
RS-**234** **236** **234** **241**

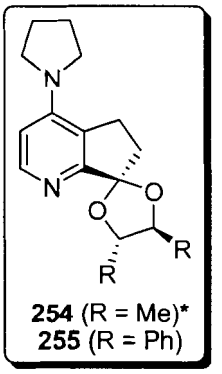
entry	catalyst	reagents and conditions	yield (acetate)	er (acetate)	yield (alcohol)	er (alcohol)
1	**241** (R = Me) (0.10 equiv)	Et_3N (0.75 equiv) Ac_2O (0.78 equiv) CH_2Cl_2, 0 °C to rt, 20 h	trace	n/a	n/d	n/a
2	**241** (R = Me) (1.0 equiv)	Et_3N (24 equiv) Ac_2O (30 equiv) CH_2Cl_2, 0 °C to rt, 36 h	49%	50:50[a]	43%	50:50[a]
3	**241** (R = Me) (0.5 equiv)	AcCl (0.75 equiv) CH_2Cl_2 0 °C to rt, 15 h	16%[b]	50:50[c]	84%[b]	50:50[c]

[a] Determined by comparison of the magnitude of its optical rotation to that of the known compound; for the enantiomerically-pure (*R*)-alcohol *R*-**234**, $[\alpha]_D^{28}$ + 75.5 (*c* 1, $CHCl_3$).[142] [b] % conversion. [c] Determined by chiral HPLC analysis of the crude reaction product.

A solution of the dimethyl-substituted chiral pyrrolidinopyridine **254** (R = Me, 0.19 equivalents), the alcohol *RS*-**234**, acetic anhydride (2 equivalents) and triethylamine (0.75 equivalents) in dichloromethane was then allowed to warm slowly from 0 °C to room temperature (entry 1, Table 4.5.2). After 22 h, the naphthyl acetate **236** (49%) and unreacted alcohol **234** (48%) were isolated by flash chromatography. However, both were found to be racemic as determined by comparison of the magnitude of their optical rotations to those of the known compounds. The use of the larger acylating agent, butyric anhydride, resulted in a slower conversion of the alcohol to the acetate **256** (R = *n*-Bu). No kinetic resolution resulted (entry 2).

Table 4.5.2 Attempted Kinetic Resolution of 1-(1-Naphthyl)ethanol Using the Chiral Pyrrolidinopyridines **254** (R = Me) and **255** (R = Ph)





254 (R = Me)*
255 (R = Ph)

entry	catalyst	reagents and conditions[a]	yield (ester)	er (ester)	yield (alcohol)	er (alcohol)
1	**254** (R = Me) (0.19 equiv)	Ac_2O (2 equiv) CH_2Cl_2, 0 °C to rt, 22 h	49%	50:50[c]	48%	50:50[c]
2	**254** (R = Me) (0.20 equiv)	$(n\text{-ButCO})_2O$ (1.5 equiv) CH_2Cl_2, 0 °C to rt, 30 h	12%[b]	50:50[b,c]	80%	50:50[c]
3	**255** (R = Ph) (0.10 equiv)	Ac_2O (0.75 equiv) CH_2Cl_2, rt, 69 h	38%	51:49	62%	49:51
4	**255** (R = Ph) (0.10 equiv)	Ac_2O (0.75 equiv) toluene, rt, 17 h	3%[d]	50:50[e]	97%[d]	50:50[e]
5	**255** (R = Ph) (0.10 equiv)	Ac_2O (0.75 equiv) *t*-amyl alcohol, rt, 5 h	trace	n/d	trace	n/d
6	**255** (R = Ph) (0.11 equiv)	Ac_2O (5 equiv) CH_2Cl_2, rt, 20 h[f]	72%[d]	50:50[e]	28%[d]	50:50[e]
7	**255** (R = Ph) (0.11 equiv)	Ac_2O (5 equiv) toluene, 22 h[f]	51%	50:50[e]	44%	50:50[e]

[a] All reactions were performed using Et_3N (0.75 equivalents) and the ester used was the acetate **236** (R = Me) unless otherwise stated. [b] The product was the butanoate **256** (R = *n*-Bu). [c] Determined by comparison of the magnitude of its optical rotation to that of the known compound. [d] % conversion. [e] Determined by chiral HPLC analysis of the purified product. [f] 1 equivalent of Et_3N was added. *The enantiomer of that indicated in the reaction scheme was used.

The kinetic resolution was then attempted using the diphenyl-substituted chiral pyrrolidinopyridine **255** (R = Ph, 0.11 equivalents), acetic anhydride (0.75 equivalents) and triethylamine (0.75 equivalents) in dichloromethane (entry 3). After 69 h, the acetate **236** was isolated in 38% yield and the alcohol **234** recovered in 62% yield. Within experimental error, the two compounds were found to be racemic (entry 3).The kinetic resolution was then attempted in two other solvents.[128c*] When the reaction was performed in toluene, the reaction proceeded to only 3% conversion after 17 h at room temperature in the presence of the chiral pyrrolidinopyridine **255** (R = Ph, 0.10 equivalents) and the acetate and alcohol were determined to be racemic (entry 4). In *t*-amyl alcohol, the reaction did not proceed (entry 5). Two final reactions were performed using excess acetic anhydride (5 equivalents) in toluene and dichloromethane (entries 6, 7). The reaction proceeded to 72% conversion in dichloromethane. However, the alcohol **234** or acetate **236** were racemic (entry 6). In toluene, the acetate **236** was isolated in 51% yield but no kinetic resolution had occurred (entry 7).

4.6 Chiral Pyrrolidinopyridine Derivatives: Potential General Acid/General Base Catalysts and Chiral Ligands

The chiral pyridine **254** (R = Me) and pyrrolidinopyridine derivatives **255** (R = Me) and **255** (R = Ph) were not effective nucleophilic catalysts in the kinetic resolution of a secondary alcohol. However, chiral *N,N*-dimethyl-4-aminopyridine and pyrrolidinopyridine derivatives have been employed in catalytic asymmetric processes in which the reaction mechanism does not involve nucleophilic catalysis. Therefore, the use of the chiral pyrrolidinopyridine **254** and **255** in several mechanistically different reactions was explored. Specifically, the two chiral pyrrolidinopyridines were tested as potential chiral general acid catalysts in the addition of pyrrole to a ketene and as chiral

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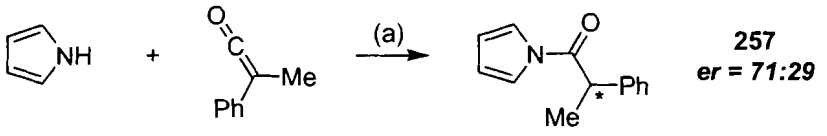
* Fu and co-workers have observed significant solvent effects in the kinetic resolution of secondary alcohols using the chiral *N,N*-dimethyl-4-aminopyridine **225**.

general base catalysts in the desymmetrization of a *meso*-anhydride. As well, they were examined as chiral ligands in a copper-catalyzed cyclopropanation reaction and an osmium-catalyzed dihydroxylation reaction.

4.6.1 Catalytic Addition Reaction of Pyrrole and Phenylmethylketene

The planar chiral ferrocene-derived pyridine **225** (see: Figure 4.2.1) has been used to catalyze the reaction of various pyrroles and ketenes in enantioselectivities up to 99:1 (Scheme 4.6.1).[129] For example, the pyridine **225** (2 mol %) catalyzed the reaction of pyrrole and phenylmethyl ketene at room temperature to form the chiral *N*-acylpyrrole **257** in moderate enantioselectivity (er = 71:29).

Scheme 4.6.1 Asymmetric Addition Reaction of Pyrrole and Phenylmethylketene



Reagents and conditions: (a) planar chiral DMAP **225** (2 mol %), toluene, rt, 25 h.

Hodous and Fu provided evidence that the stereochemical and rate-determining step was the protonation of the achiral enolate **259** by the conjugate acid of the chiral dimethylaminopyridine **225** (Figure 4.6.1).

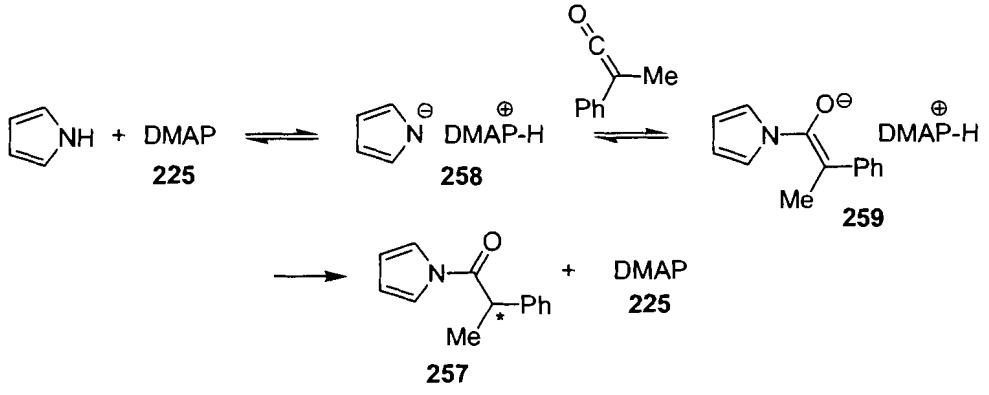


Figure 4.6.1 Proposed mechanism of the *N,N*-dimethyl-4-aminopyridine **225**-catalyzed pyrrole acylation reaction.

Thus, the protonated *N,N*-dimethyl-4-aminopyridine was acting as a chiral Brønsted acid. They proposed that the pyridine **225** initially deprotonated the pyrrole to form the ion pair **258** which in turn reacted with phenylmethyl ketene to form the enolate **259**.

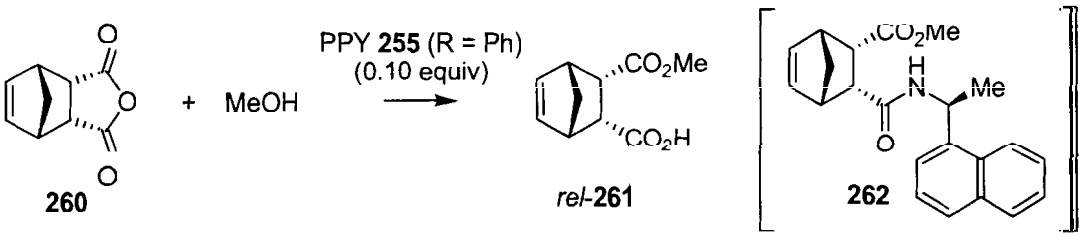
In theory, the basicity of pyrrolidinopyridine derivatives **254** and **255** should be similar to that of *N,N*-dimethyl-4-aminopyridine and, for example, the planar chiral pyridine **225**. Therefore, the chiral pyrrolidinopyridine **254** (R = Me) was examined as a catalyst in this reaction. A solution of phenylmethyl ketene (1 equivalent) in toluene was added over 30 min to a solution of the chiral pyrrolidinopyridine **254** (8 mol %) and pyrrole (2.2 equivalents) in toluene at room temperature. After 20 h, the reaction mixture was concentrated and the crude reaction product was analyzed by ^{1}H NMR spectroscopy. However, none of the product was observed.

4.6.2 Catalytic Desymmetrization of *cis*-5-Norbornene-*endo*-2,3-Dicarboxylic Acid Anhydride

The cinchona alkaloids have been used stoichiometrically and catalytically in the ring-opening reaction of *meso*-anhydrides with methanol to form chiral nonracemic compounds in excellent enantioselectivities (up to er = 99:1).[143] Oda and co-workers have shown that for cinchonine, the mechanism of the reaction involves general-base catalysis whereby stereochemical induction occurs as the chiral alkaloid abstracts the proton of the incoming methanol nucleophile.[144]

Therefore, the chiral pyrrolidinopyridine **255** (R = Ph) was examined in this reaction to determine if it could act as a chiral general-base catalyst. A suspension of the anhydride **260** (1 equivalent), pyrrolidinopyridine **255** (0.10 equivalents) and methanol (3 equivalents) was allowed to react for 24 h over which time the suspended anhydride completely dissolved (entry 1, Table 4.6.1).

Table 4.6.1 Attempted Chiral Pyrrolidinopyridine **255** (R = Ph)-Catalyzed Ring Opening of a *meso*-Anhydride



260 *rel*-261 262

entry	conditions	conversion	er[a]
1	toluene 0 °C to rt 24 h	20%	50:50
2	Hünig's base, ether 0 °C to rt	< 5%	n/d

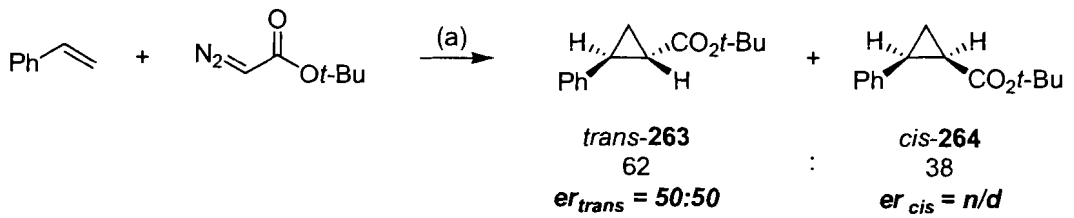
[a] Determined by ^{1}H NMR spectroscopy after derivatization with (*S*)-1-(1-naphthyl)ethylamine.

As determined by ^{1}H NMR spectroscopy, the reaction had proceeded to 20% completion. To determine the enantiomeric ratio of the ring-opened product *rel*-**261**, the crude ester-acid was reacted with thionyl chloride and (*S*)-1-(1-naphthyl)ethylamine. The resultant mixture of chiral amides **262** (diastereomer not shown) was analyzed by ^{1}H NMR and was found to be a 50:50 mixture of diastereomers. A solution of the anhydride (1 equivalent), pyrrolidinopyridine **255** (0.10 equivalents), Hünig's base (1 equivalent) and methanol (3 equivalents) in ether was then allowed to react for 20 h. However, as determined by ^{1}H NMR spectroscopy of the crude reaction product, the reaction had proceeded to less than 5% conversion. Therefore, the enantiomeric ratio of the product was not determined. The carboxylic acid product *rel*-**261** of the ring-opening reaction could, in theory, protonate the catalyst **255**. This would reduce the concentration of active neutral catalyst. Therefore, Hünig's base was added to maintain an alkaline pH during the course of the reaction.

4.6.3 Copper-Catalyzed Cyclopropanation Reaction of Styrene

Copper complexes of chiral bipyridines and bis(oxazolines) have been used extensively to catalyze the asymmetric cyclopropanation reaction of styrene and diazoacetates.[145] Recently, monodentate ligands; namely, chiral oxazolines, have been used in the asymmetric cyclopropanation reaction of styrene and ethyl diazoacetate affording cyclopropane products with enantiomeric ratios up to 69:31.[146,147*] However, chiral pyridine and pyrrolidinopyridine derivatives have not been used as ligands in metal-catalyzed cyclopropanation reactions. Therefore, the chiral pyrrolidinopyridine **255** (R = Ph) was tested as a ligand in the copper(I) catalyzed cyclopropanation reaction of styrene and *t*-butyl diazoacetate (Scheme 4.6.2).[148]

Scheme 4.6.2 Copper(I)-Catalyzed Cyclopropanation Reaction of Styrene and *t*-Butyl Diazoacetate Using the Pyrrolidinopyridine **255** (R = Ph)



trans-**263** : *cis*-**264**
62 : 38
er_{trans} = **50:50** er_{cis} = **n/d**

Reagents and conditions: (a) $Cu(OTf)_2$ (1 mol %), PPY **255** (R = Ph, 2.5 mol %), $PhNHNH_2$, CH_2Cl_2, rt, 16 h, 47% (combined yield).

A suspension of the chiral pyrrolidinopyridine **255** (2.5 mol %) and copper(II) triflate (1 mol %) in dichloromethane was stirred at room temperature for 30 min over which time the copper(II) triflate completely dissolved. Phenylhydrazine (1 mol %) was added, to reduce the initial copper(II) complex to the active copper(I) complex, followed by styrene (1.6 equivalents). To this solution was added a solution of *t*-butyl diazoacetate in dichloromethane over 4 h. After an additional 12 h, the reaction mixture was

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* A chiral monodentate oxazoline has been used in a nickel-catalyzed coupling reaction between enones and alkynes affording formal Michael addition products in higher enantioselectivities than bis(oxazoline) and BINAP ligands.

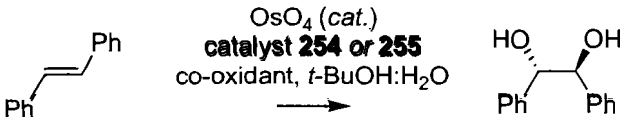
concentrated and the *trans*- and *cis*-cyclopropane products **263** and **265** were isolated by flash chromatography in a 47% combined yield. The *trans*:*cis* ratio was determined to be 62:38 by ^{1}H NMR analysis of the crude reaction product. The enantiomeric ratio of the *trans*-isomer **263** was 50:50 as determined by chiral HPLC analysis of the purified product.

4.6.4 Catalytic Dihydroxylation Reaction of (*E*)-Stilbene

The Sharpless asymmetric dihydroxylation of alkenes is one of the most general and efficient catalytic asymmetric reactions in organic synthesis.[149] The ability of amines to form complexes with osmium tetroxide and to catalyze its reaction with alkenes is well established.[150] *N*,*N*-Dimethyl-4-aminopyridine is also known to accelerate the rate of osmylation/dihydroxylation reactions of alkenes.[151,152] Although several other chiral amines have been used in catalytic[153] and stoichiometric[154] quantities in the asymmetric dihydroxylation reaction, the use of a chiral *N*,*N*-dimethyl-4-aminopyridine derivative has not been reported. For this reason, the chiral pyrrolidinopyridine **254** (R = Me) and **255** (R = Ph) were evaluated as potential chiral ligands in the asymmetric dihydroxylation reaction of (*E*)-stilbene (Table 4.6.2). To a solution of the chiral pyrrolidinopyridine **254** (R = Me, 16 mol %) in *t*-butanol:water (1:1) at room temperature was added osmium tetroxide (13 mol %), excess potassium carbonate, the co-oxidant potassium ferricyanide and (*E*)-stilbene (entry 1). After 42 h, the diol **29** was recovered in 39% yield. As determined by the magnitude of its optical rotation, the diol **29** was racemic.

The chiral pyrrolidinopyridine **255** (R = Ph) was then evaluated to determine if the larger phenyl substituents of this acetal would lead to measurable levels of asymmetric induction in the dihydroxylation reaction. Using similar reaction conditions [osmium tetroxide (9 mol %), pyrrolidinopyridine **255** (14 mol %)], the diol **29** was isolated in 72% yield after 68 h (entry 2).

Table 4.6.2 Chiral Pyrrolidinopyridine **254** (R = Me) and **255** (R = Ph)-Catalyzed Asymmetric Dihydroxylation Reaction of (*E*)-Stilbene



29

entry	catalyst	conditions	yield	optical rotation[a]	er[b]
1	**254** (R = Me) (16 mol %)	K_3FeCN_6 (3 equiv) K_2CO_3 (3 equiv), rt 42 h	39%	0	50:50
2	**255** (R = Ph) (14 mol %)	K_3FeCN_6 (3 equiv) K_2CO_3 (3 equiv), rt 68 h	72%	-5.9	53:47
3	**255** (R = Ph) (13 mol %)	NMO (1.2 equiv), rt 18 h	79%	-7.7	54:46

[a] For enantiomerically-pure (1*S*,2*S*)-diol **29**, $[\alpha]_D^{25}$ - 94 (*c* 1, EtOH).[155] [b] Determined by comparison of the magnitude of its optical rotation to that of the known compound.

In this case, the enantiomeric ratio was found to be 53:47 (entry 2). The dihydroxylation reaction was repeated using the co-oxidant, *N*-methylmorpholine *N*-oxide, which has also been used in asymmetric dihydroxylation reactions (entry 3).[149] A solution of (*E*)-stilbene, the pyrrolidinopyridine **255** (R = Ph, 13 mol %), osmium tetroxide (10 mol %) and *N*-methylmorpholine *N*-oxide (1.2 equivalents) was stirred at room temperature for 18 h. The diol **29** was isolated in 79% yield and in a similar enantioselectivity (er = 54:46). In the latter two cases, the (1*S*,2*S*)-enantiomer of the diol **29** was formed as the major isomer as determined by comparison of the sign of its optical rotation to that of the known compound.

4.7 Conclusions

A chiral pyridine **241** (R = Me) and pyrrolidinopyridine derivatives **254** (R = Me) and **255** (R = Ph) based upon the general chiral acetal framework **38** have been prepared. The chiral pyridine **241** (R = Me) was synthesized in three steps from the commercially-

available pyridine **238**. The chiral pyrrolidinopyridine derivatives **254** (R = Me) and **255** (R = Ph) were prepared in a twelve-step synthesis starting from adiponitrile **244**. The use of inexpensive substrates and reagents and the simplicity of all of the synthetic steps allows for the preparation of multi-gram quantities of the pyrrolidinopyridines. This synthesis also represents a novel preparation of the 4-chloropyridine *N*-oxide **242**, a precursor of planar chiral pyridine derivatives.

Both the chiral pyridine and pyrrolidinopyridine derivatives were evaluated in the kinetic resolution of a secondary alcohol. However, asymmetric induction was not observed in any of these reactions. The chiral pyridine and pyrrolidinopyridine structures appeared to be catalytically-inactive due to steric hindrance around the catalytic site imposed by the adjacent acetal group. This finding is supported by other reports. For example, the chiral pyridine **232** prepared by Vedejs and co-workers, which contained a bulky substituent at the *ortho*-position was not catalytically-active.[128a] Also, Fu and co-workers observed that installation of a methyl group into the 7-position of their heterocycle **225**, the same position at which the chiral acetal is present in the pyrrolidinopyridine-structures studied here, completely destroyed catalytic activity. This was presumably due to steric hindrance around the catalytic site.[156] Moreover, the previous studies involving the 7-hydroxyindan-1-one-derived auxiliary and ligands have shown that high levels of stereochemical induction can be achieved. At least some asymmetric induction would be expected if the chiral pyrrolidinopyridine was catalytically-active.

In regard to the other reaction types that were screened using the chiral pyrrolidinopyridine **254** and **255**, the addition of pyrrole to phenylmethyl ketene did not proceed and the ring-opening of *cis-endo*-norbornenecarboxylic acid anhydride proceeded only to a negligible extent with no stereochemical induction being observed. In these reactions, the chiral pyrrolidinopyridine was required to act as a chiral general

acid or base catalyst, respectively. However, the chiral pyrrolidinopyridine was likely catalytically-inactive in these reactions, which again could be due to steric hindrance around the aryl nitrogen centre. Although proton transfer reactions can be less susceptible to steric effects, steric hindrance around the acidic/basic site can slow the rate of these processes.[157]

The use of the pyrrolidinopyridines **254** and **255** as chiral ligands in metal-catalyzed reactions produced mixed results. In the copper-catalyzed cyclopropanation reaction, the reaction proceeded, however, no asymmetric induction was observed. Unbound copper is known to catalyze this reaction which may have been operative here.[158] As well, even if the reaction was catalyzed by a copper-pyrrolidinopyridine complex, chiral monodentate ligands often produce poor enantioselectivities in catalytic asymmetric reactions.[159] The use of the chiral pyrrolidinopyridine **254** (R = Me) and **255** (R = Ph) in the osmium-catalyzed dihydroxylation reaction produced some encouraging preliminary results. The smaller dimethyl-substituted pyrrolidinopyridine **254** (R = Me) catalyzed the dihydroxylation of (*E*)-stilbene in low yield but with no enantioselectivity. However, the larger diphenyl-substituted pyrrolidinopyridine **254** (R = Ph) appeared to be more active and produced the diol product in good yield (72 or 79%) using two co-oxidants. As well, irrespective of the co-oxidant, the diol was produced in a similar enantiomeric ratio (er = 53:47 or 54:46). Although the enantioselectivities are modest, these results show that there is stereochemical communication between the chiral pyrrolidinopyridine (R = Ph) and substrate. This represents the first example of a chiral *N*,*N*-dimethyl-4-aminopyridine- or pyrrolidinopyridine-catalyzed asymmetric dihydroxylation reaction.

CHAPTER 5: RESULTS AND DISCUSSION

CHIRAL TETRAHYDROQUINOLINES IN THE CATALYTIC ASYMMETRIC IMINIUM ION-PROMOTED DIELS-ALDER REACTION

5.1 Introduction

The goal of this project was to prepare a series of structurally diverse tetrahydroquinolines using an experimentally simple three-component coupling reaction. The chiral nonracemic tetrahydroquinolines **43** were then to be evaluated as secondary amine catalysts in the enantioselective iminium ion-promoted Diels-Alder reaction of, for example, cinnamaldehyde and cyclopentadiene. Here the imino Diels-Alder reaction could be used to prepare a variety of racemic tetrahydroquinolines **43** from a series of readily-available alkenes **40**, aldehydes **41** and anilines **42** in one synthetic step (Figure 5.1.1). The racemic tetrahydroquinolines would then be resolved and their absolute stereochemical configurations determined.

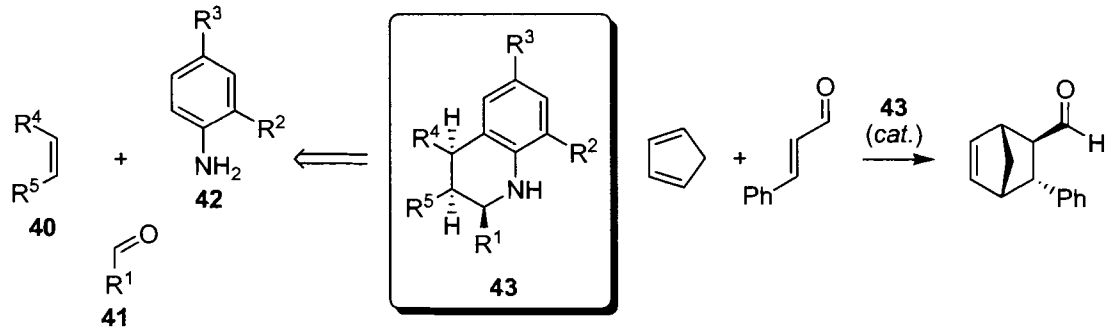


Figure 5.1.1 Imino Diels-Alder synthesis of chiral tetrahydroquinolines for use in the iminium ion-promoted enantioselective Diels-Alder reaction.

Aniline and aldehyde precursors of the chiral tetrahydroquinolines were selected so that both the steric and electronic environment around the secondary amine site could be modified. Cyclopentadiene was chosen as the alkene component because it has been shown to react with *N*-arylimines, to form stable molecules, in high regio- and

stereoselectivities.[160] As well, the resultant fused tricyclic ring system of the corresponding tetrahydroquinolines would rigidify these structures. It is known that conformationally-constrained structures can reduce the number of competing reactive conformations in catalytic asymmetric processes.[35]

5.2 Background

Chiral secondary amines have recently been used as "organocatalysts" in a variety of asymmetric reactions.[17,18] Recently, Northrop and MacMillan have used the phenylalanine-derived heterocycle **265** as a chiral secondary amine catalyst in the asymmetric iminium ion-promoted Diels-Alder reaction of α,β-unsaturated aldehydes and cyclopentadiene (Figure 5.2.1).[161]

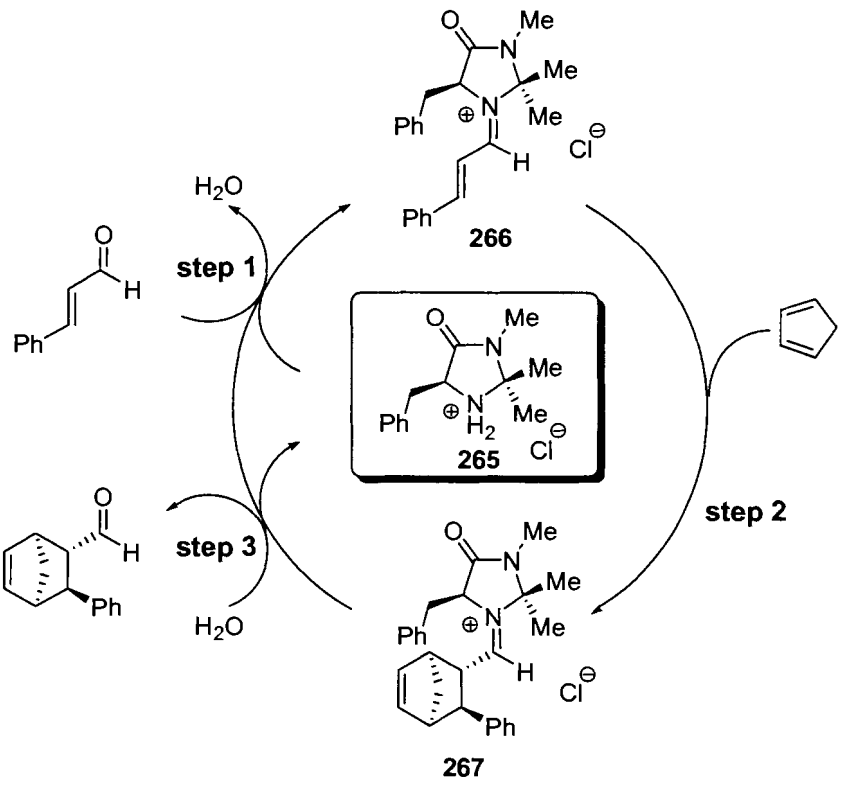
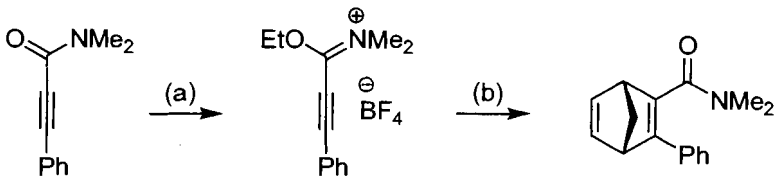


Figure 5.2.1 Mechanism of the iminium ion-promoted Diels Alder reaction of cinnamaldehyde and cyclopentadiene.

Their proposed mechanism involves the iminium ion **266** as a key intermediate, formed in the acid-catalyzed condensation reaction of the heterocycle **265** and the aldehyde (*e.g.* cinnamaldehyde) (**step 1**). The positively-charged α,β-unsaturated iminium ion **266** behaves as a more reactive dienophile than its precursor, the α,β-unsaturated aldehyde, and reacts more readily with cyclopentadiene (**step 2**). This is analogous to the ability of Lewis acids to increase the reactivity of dienophiles in the normal electron-demand Diels-Alder reaction.[87] Hydrolysis of the chiral nonracemic iminium ion adduct **267** liberates the Diels-Alder adduct and allows the amine **265** to re-enter the catalytic cycle (**step 3**).

Baum and Viehe reported the first iminium ion-promoted Diels-Alder reaction.[162] They observed that the acetylenic iminium salt **269** was an active dienophile in the cycloaddition reaction with cyclopentadiene (Scheme 5.2.1). The iminium ion salt **269** was prepared by reaction of the amide **268** with the powerful alkylating agent, triethyloxonium tetrafluoroborate.

Scheme 5.2.1 Acetylenic Iminium Ions as Dienophiles

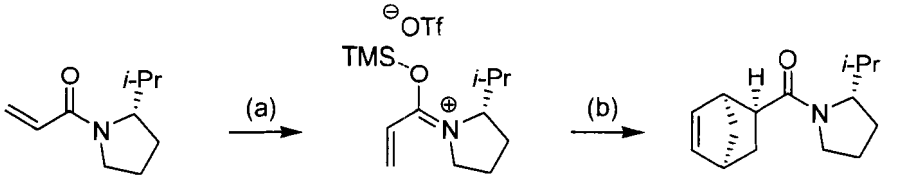


268 **269**

Reagents and conditions: (a) Et_3OBF_4, CH_2Cl_2, rt, 16 h, 85%. (b) (i) cyclopentadiene, CH_2Cl_2, rt, 70 h, 85%. (ii) K_2CO_3, water, rt, 72%.

Jung and co-workers subsequently reported the first stoichiometric asymmetric iminium ion-promoted Diels-Alder reaction of a dienophilic chiral alkoxy iminium salt **271** and cyclopentadiene (Scheme 5.2.2).[163] Here, the iminium ion **271** was synthesized by treatment of the chiral amide **270** with trimethylsilyl triflate.

Scheme 5.2.2 Stoichiometric Asymmetric Diels-Alder Reaction Using a Chiral Iminium Ion **271** as a Dienophile



270 **271** ***dr = 96:4***

Reagents and conditions: (a) TMSOTf (1.1 equiv), CH_2Cl_2, 0 °C, 1 h; cyclopentadiene (2 equiv), CH_2Cl_2, -40 °C, 10 h, 90%.

Recently, Cavill and co-workers have shown that simple achiral secondary amines, hydroxylamines and substituted hydrazines can catalyze the Diels-Alder reaction of cinnamaldehyde and cyclopentadiene.[164] The reactions also proceeded only when an acid co-catalyst was present. Catalytic quantities of acid are presumably required to promote the formation of the iminium ion intermediate.

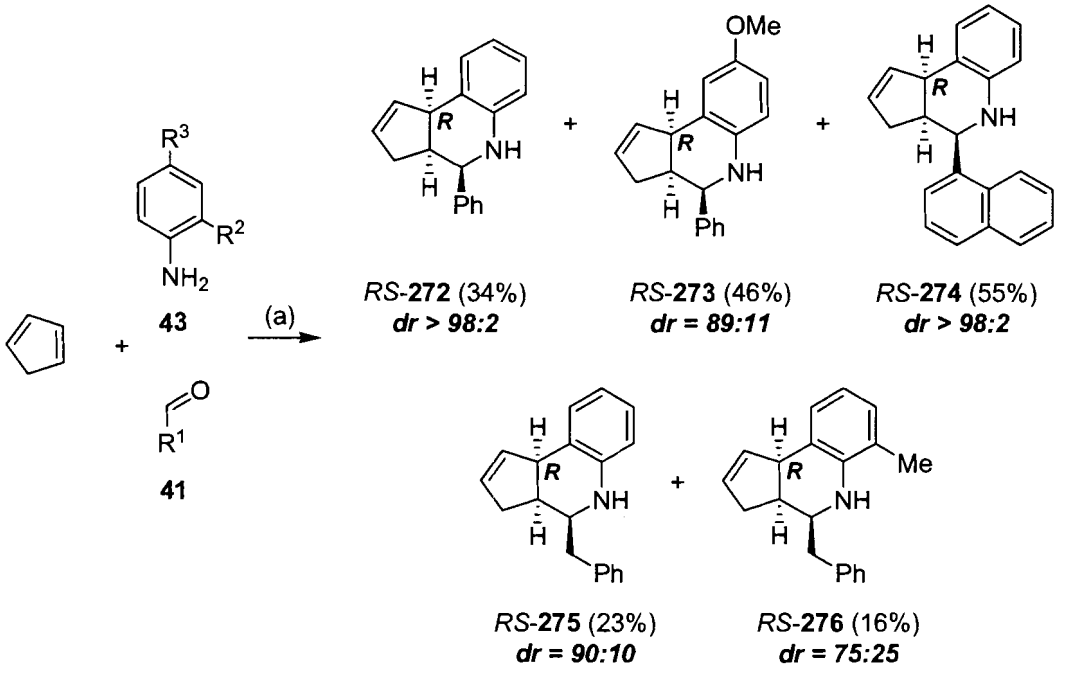
5.3 Synthesis of the Racemic Tetrahydroquinolines

Tetrahydroquinolines have been synthesized in Brønsted and Lewis acid-catalyzed imino Diels-Alder reactions.[165,166] As well, chiral nonracemic tetrahydroquinolines have been prepared using both chiral auxiliaries[167] and chiral Lewis acid catalysts.[168] However, these stoichiometric or catalytic asymmetric syntheses were either not amenable to the preparation of the desired tetrahydroquinoline structures **43** or did not produce the requisite structures in high stereoselectivities. Therefore, the experimentally simple Brønsted acid-promoted racemic synthesis of the tetrahydroquinolines **43** was performed. The racemic compounds were then resolved.

A series of tetrahydroquinoline structures *RS*-**272**-**276** were synthesized by reaction of the substituted anilines **42** and substituted aldehydes **41** with cyclopentadiene and trifluoroacetic acid in acetonitrile at 0 °C to room temperature for 1 to 2.5 h

(Scheme 5.3.1).[165,166*†] The aryl aldehyde-derived tetrahydroquinolines *RS*-**272** (R^1 = Ph), *RS*-**273** (R^3 = OMe) and *RS*-**274** (R^1 = 1-Np) were formed in higher yields than the aliphatic aldehyde derivatives. As well, the aryl aldehyde-derived tetrahydroquinolines were formed in higher diastereoselectivities as determined by comparison of their respective crude ^{1}H NMR spectra. The tetrahydroquinolines *RS*-**272** (R^1 = Ph) and *RS*-**274** (R^1 = 1-Np) were formed as single diastereomers (dr > 98:2) and the tetrahydroquinoline *RS*-**273** (R^3 = OMe) was formed in as an 89:11 ratio of diastereomers.

Scheme 5.3.1 Trifluoroacetic Acid-Promoted Imino Diels-Alder Synthesis of the Tetrahydroquinolines *RS*-**272-276***



Reagents and conditions: (a) TFA, CH_3CN, 0 °C to rt, 1 to 2.5 h. *The yields are those for the diastereomerically pure compounds. The diastereomeric ratios were determined from the ^{1}H NMR spectra of the crude tetrahydroquinoline reaction products.

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* *RS* or *R* or *S* refers to the stereochemistry at carbon 9b (Scheme 5.3.1); *RS* indicating that the compound is racemic.

† The preformed imine of aniline and benzaldehyde could be reacted with cyclopentadiene in an indium trichloride-promoted Diels-Alder reaction to form the tetrahydroquinoline *RS*-**272** in 60% yield.

The latter compound was isolated as a single diastereomer by recrystallization. The aliphatic aldehyde-derived structures *RS*-**275** (R^1 = Bn) and *RS*-**276** (R^1 = Bn, R^2 = Me) were obtained as single diastereomers by chromatographic separation from their respective minor diastereomers. The flexible benzyl substituent of the tetrahydroquinolines **275** and **276** was introduced to determine if π-π interactions with the electron-poor α,β-unsaturated substrate could be exploited. This non-covalent interaction could then provide increased shielding of one of the diastereotopic faces of the substrate and lead to enhanced levels of stereochemical induction. Of note, *N*-alkylimines can homocouple in an inverse-electron demand Diels-Alder process whereby the tautomeric enamine acts as a formal dienophile.[169] This competing reaction is a likely explanation for the lower yields of aliphatic aldehyde-derived adducts *RS*-**275** and *RS*-**276**.[170*]

The ^{1}H NMR spectrum for the tetrahydroquinoline *R*-**276** (R^1 = Bn, R^2 = Me) is representative of those for all of the tetrahydroquinoline compounds. Here, essentially every non-equivalent hydrogen atom is in a distinct chemical environment as indicated by the well-resolved spectra (Figure 5.3.1).[†] Of note, at the 3-position, the hydrogen on the concave face ($\mathbf{3_1}$) of the tetrahydroquinoline resonated downfield (Δδ 0.4 ppm) from that on the convex face ($\mathbf{3_2}$) which was suggestive of the inherently different chemical environment of the two faces of this structure.

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* A more efficient synthesis of aliphatic aldehyde-derived tetrahydroquinolines has recently been reported by Powell and Batey which employed lanthanide(III) salts as catalysts in an analogous three-component coupling reaction.

† COSY and difference NOE experiments were used to assign the signals in the ^{1}H NMR spectrum of the tetrahydroquinoline *RS*-**276**.

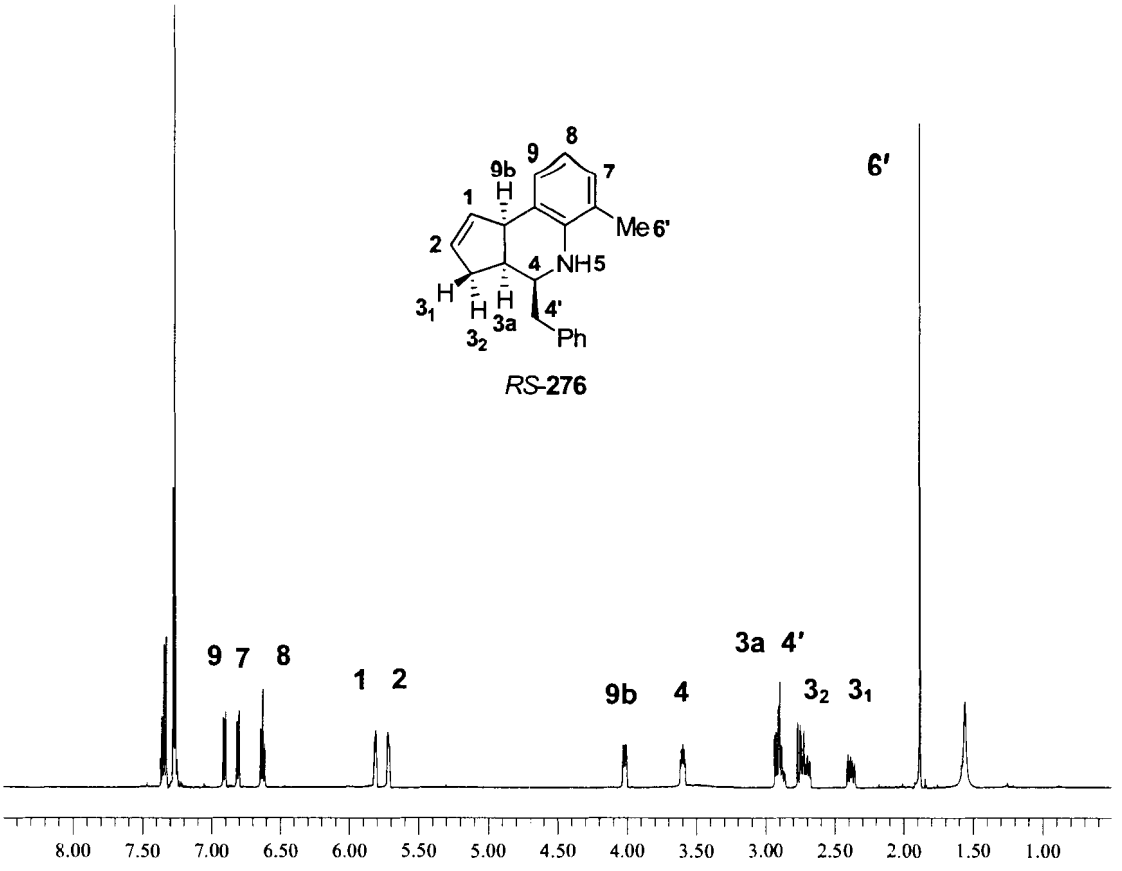


Figure 5.3.1 ^{1}H NMR spectrum ($CDCl_3$) of tetrahydroquinoline *RS*-**276**.

The mechanism of the acid-catalyzed three-component imino Diels-Alder reaction involves initial acid-promoted condensation of the aldehyde **41** and aniline **42** to form the iminium ion intermediate **277** (Figure 5.3.2).

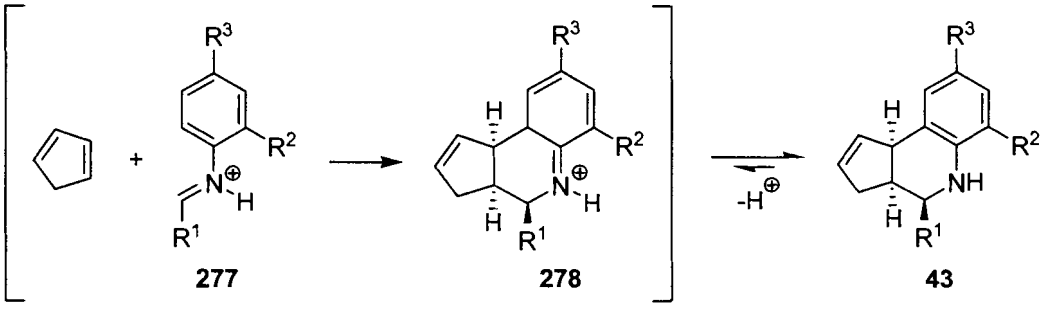


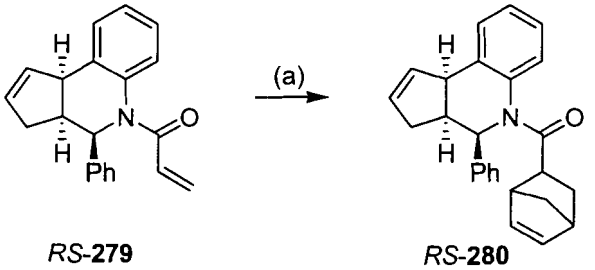
Figure 5.3.2 Mechanism of the Brønsted acid-catalyzed imino Diels-Alder reaction.

The iminium ion **277** then acts as an electron-poor diene in an inverse-electron demand hetero Diels-Alder reaction with the alkene (*e.g.* cyclopentadiene). The resultant adduct **278** then tautomerizes to regenerate aromaticity and afford the tetrahydroquinoline **43**.

5.4 Use of the Tetrahydroquinoline (*RS*-272) as a Chiral Auxiliary in a Lewis Acid-Promoted Diels-Alder Reaction

The ability of the tetrahydroquinoline *RS*-**272** to act as an asymmetric director was demonstrated by employing it as a chiral auxiliary. The tetrahydroquinoline *RS*-**272** was reacted with acryloyl chloride to form the acrylamide *RS*-**279** (Scheme 5.4.1). The acrylamide *RS*-**279** reacted with cyclopentadiene in a diethylaluminum chloride-promoted Diels-Alder reaction to form the cycloadduct *RS*-**280** in 86% yield and with excellent diastereoselectivity (dr = 94:6, *endo*:*exo* > 98:2). Attempts to cleave the cycloadduct from the tetrahydroquinoline under a variety of acidic and basic conditions were unsuccessful; therefore, further studies were not undertaken. As well, the relative stereochemistry of the bicyclo[2.2.1]hept-5-ene portion of the cycloadduct *RS*-**280** was not determined.

Scheme 5.4.1 Diethylaluminum Chloride-Promoted Diels-Alder Reaction of the Acrylamide *RS*-**279**



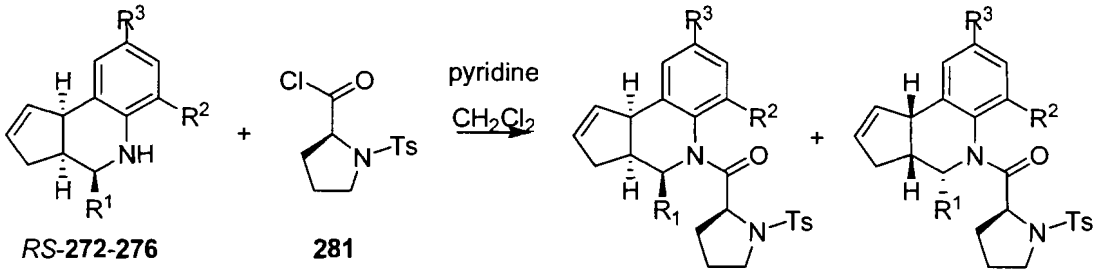
RS-**279** *RS*-**280**

Reagents and conditions: (a) Et_2AlCl (1.5 equiv), cyclopentadiene (50 equiv), CH_2Cl_2, rt, 3 h, 86%.

5.5 Synthesis of the Diastereomeric L-Proline Tetrahydroquinoline Derivatives

The racemic tetrahydroquinolines *RS*-**272-276** were reacted with *N*-tosyl-L-prolyl chloride **281** in the presence of pyridine to form the corresponding diastereomeric amides *R*-**282-285** and *S*-**286-289**.[171,172] Each pair of diastereomeric amides was then separated readily by chromatography (Table 5.5.1). ^{1}H NMR analysis of the separated amides revealed that each was a single diastereomer.

Table 5.5.1 Synthesis of the Diastereomeric Tetrahydroquinoline-Proline Derivatives *R*-**282-285** and *S*-**286-289**



RS-**272-276** **281** *R*-**282-285** *S*-**286-289**

entry[a]	L-Proline-THQ	R^1	R^2	R^3	yield (*R*)	yield (*S*)
1	*R*-**282**/*S*-**286**	Ph	H	H	35%	32%
2	*R*-**283**/*S*-**287**	Ph	H	OMe	39%	35%
3	*R*-**284**/*S*-**288**	Bn	H	H	28%	26%
4[b]	*R*-**285**/*S*-**289**	Bn	Me	H	26%	19%

[a] All reactions were performed at rt for 17 to 20 h unless otherwise stated. [b] DMAP was subsequently added to the reaction mixture and the reaction mixture was heated at reflux for 3 h.

The rate of the acylation reaction of the tetrahydroquinoline *RS*-**276** (R^1 = Ph, R^2 = Me) was particularly slow and required *N*,*N*-dimethyl-4-aminopyridine catalysis as well as elevated reaction temperatures. Unreacted starting material *RS*-**276** was nevertheless recovered from the reaction mixture. In addition, the sterically-encumbered tetrahydroquinoline *RS*-**274** (R^1 = 1-Np) did not react with the resolving agent to any

appreciable extent. Further studies with this structure *RS*-**274** were, therefore, not undertaken.

In all cases, the amides *R*-**282-285** eluted more rapidly from the column than their diastereomeric amides *S*-**286-289** during chromatographic purification. In addition, all of the *R*-diastereomers had positive optical rotations, whereas, the *S*-diastereomers displayed negative optical rotations. The tetrahydroquinolines *R*-**272**, **273**, **275** and **276** were found to react more rapidly with the resolving agent than the enantiomeric tetrahydroquinolines *S*-**272**, **273**, **275** and **276**. The kinetics of this reaction were further revealed in the resolution of the tetrahydroquinoline *RS*-**272** (R^1 = Ph). At 90% conversion, the enantiomeric purity of the unreacted starting material *S*-**272** was found to be > 99:1. This suggested a potential application of *N*-tosyl-L-prolyl chloride **281** in the kinetic resolution of these tetrahydroquinolines.[173*] However, *N*-tosyl-L-prolyl chloride was found to partially racemize upon extended exposure to pyridine or triethylamine. This was ascertained by trapping the prolyl chloride **281** with chiral nonracemic (S)-α-methylbenzylamine following exposure of the prolyl chloride to base for varying amounts of time. The resultant amide was then analyzed by ^{1}H NMR spectroscopy to determine its diastereomeric purity.

5.6 X-Ray Crystallographic Analysis of the L-Prolyl Tetrahydroquinoline Derivatives

The absolute stereochemical configurations of the tetrahydroquinolines were determined by X-ray diffraction analysis of the crystalline L-proline tetrahydroquinoline derivatives. The amides *R*-**282**, *S*-**288** and *S*-**289** were all highly crystalline, whereas, in the latter two cases, the diastereomeric amides *R*-**284** and *R*-**285** were amorphous solids.

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* Recently, an α-methyl-substituted tetrahydroquinoline has been kinetically resolved using the prolyl chloride **281.** The resolution was performed in the *absence of any base.*

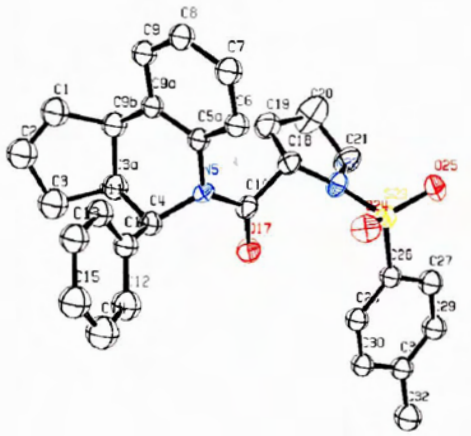


Figure 5.6.1 Crystal structure of L-proline tetrahydroquinoline derivative *R*-**282** (R^1 = Ph) (with thermal ellipsoids drawn at a 25% probability level).

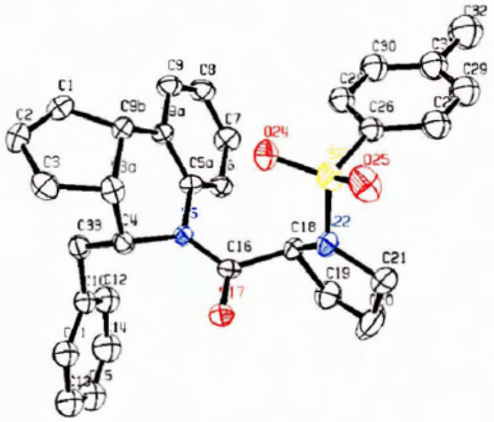


Figure 5.6.2 Crystal structure of the L-proline tetrahydroquinoline derivative *S*-**288** (R^1 = Bn) (with thermal ellipsoids drawn at a 25% probability level).

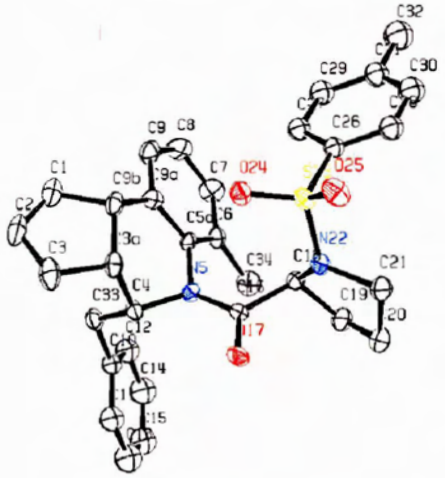


Figure 5.6.3 Crystal structure of the L-proline tetrahydroquinoline derivative *S*-**289** (R^1 = Bn, R^2 = Me) (with thermal ellipsoids drawn at a 25% probability level).

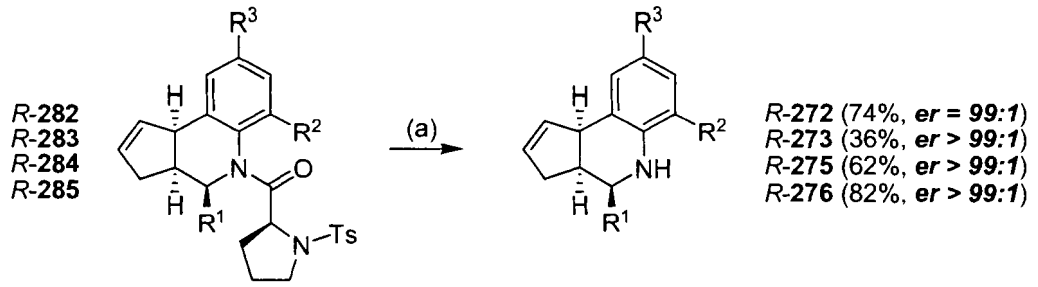
In the case of the tetrahydroquinoline *R*-**273** (R^2 = Ph, R^3 = OMe), the assignment of the absolute stereochemical configuration was based on observations that the amide *R*-**283** from which it was derived displayed physical and chemical properties that were consistent with the amides *R*-**282**, *R*-**284** and *R*-**285**.

For the tetrahydroquinoline derivative *R*-**282** (R^1 = Ph), the phenyl substituent and cyclopentadienyl fragment both occupy the top face (as depicted, Figure 5.6.1). In the structures *S*-**288** (R^1 = Bn) and *S*-**289** (R^1 = Bn, R^2 = Me), the benzyl substituent and cyclopentadienyl fragment both occupy the bottom face (as depicted, Figure 5.6.2 and Figure 5.6.3). In addition, the benzyl groups in these structures are oriented in the direction of the tetrahydroquinoline nitrogen and effectively block one face of the tetrahydroquinoline. The benzyl substituents in these structures possibly adopt this conformation to avoid unfavourable steric interactions with the cyclopentadienyl fragment. In all three structures, the torsion angle (C5a-N5-C16-O17) was between 0 and 3° indicating that there was no significant strain in the amide bond. As well, for all three structures the bond angle (N5-C16-O17) was 122-123° suggesting that steric interactions between the tetrahydroquinoline moiety and the large L-prolyl substituent was not causing any significant angle strain in the amide. The torsion angle (C6-C5a-N5-C16) for the structures *S*-**288** (R^1 = Bn) and *S*-**289** (R^1 = Bn, R^2 = Me) were 59° and 68°, respectively. The larger torsion angle in the structure *S*-**289** can be explained by the presence of an unfavourable steric interaction between the methyl substituent and the L-prolyl group.

5.7 Solvolysis of the *R*-Tetrahydroquinoline Proline Derivatives

The amides *R*-**282**-**285** were solvolyzed using sodium ethoxide to afford the tetrahydroquinolines *R*-**272**, **273**, **275** and **276** (Scheme 5.7.1). All of these structures were enantiomerically pure as determined by chiral HPLC analysis (er $\geq$ 99:1).

Scheme 5.7.1 Solvolysis of the Diastereomerically-Pure Amides *R*-**282-285**



Reagents and conditions: (a) NaOEt, EtOH, reflux, 30 min to 3 h.

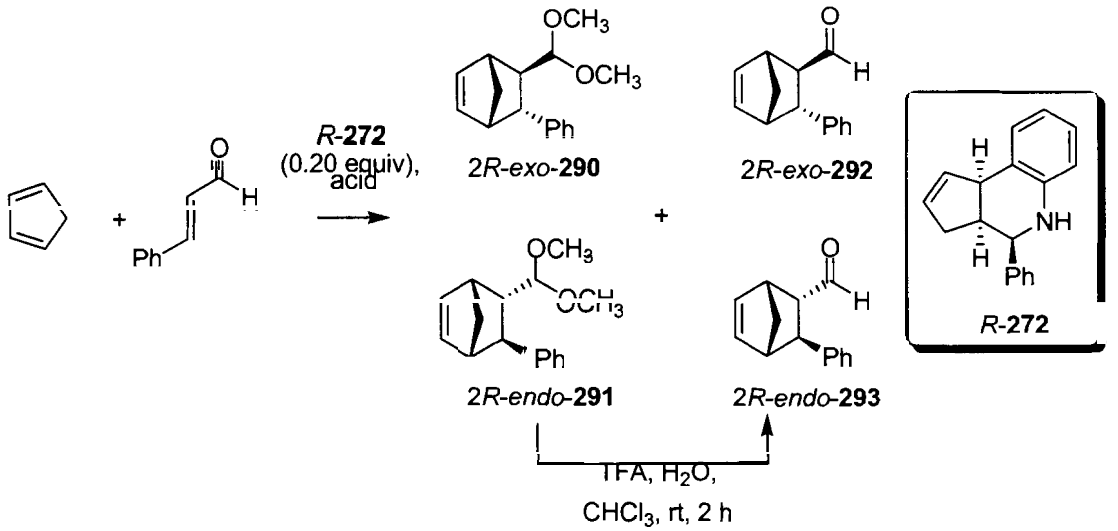
The racemic tetrahydroquinoline structures were used as standards to determine the retention times for each enantiomer. In all cases, the *R*-enantiomers eluted less rapidly than the *S*-enantiomers from the HPLC column (Chiralcel OD). Of note, attempts to resolve the tetrahydroquinoline *RS*-**272** by diastereomeric salt formation with several chiral nonracemic acids [(2*R*,3*R*)-tartaric acid dibenzoate, (1*R*)-10-camphorsulfonic acid, (*R*)-mandelic acid] in a variety of solvents (methanol, ethanol, water) were unsuccessful. As well, it is interesting that the solvolysis of the amide linkage of all the proline-derivatized tetrahydroquinolines **282-285** proceeded readily while the amide linkage of the Diels-Alder adduct *RS*-**280** was completely resistant to solvolysis.

5.8 Tetrahydroquinoline-Catalyzed Asymmetric Diels-Alder Reactions

A series of tetrahydroquinoline-catalyzed asymmetric Diels-Alder reactions of cinnamaldehyde and cyclopentadiene were performed. In the first instance, the reaction conditions developed by MacMillan were utilized.[161] Thus, a solution of cinnamaldehyde (1 equivalent), cyclopentadiene (3 equivalents) and the tetrahydroquinoline *R*-**272** as its hydrochloride salt in methanol:water (95:5) was stirred for 21 h (entry 1, Table 5.8.1). The crude reaction product of aldehydic *exo* and *endo* Diels-Alder adducts **292** and **293** and their corresponding dimethyl acetals **290** and **291** was reacted with trifluoroacetic acid in chloroform:water (3:1) for 2 h at room temperature to hydrolyze the dimethyl acetal adducts to the aldehydes **292** and **293**. This simplified the subsequent analysis and

characterization of the product mixture.*

Table 5.8.1 Acid Co-catalyst Screen in the Diels-Alder Reaction of Cinnamaldehyde and Cyclopentadiene



entry	acid	solvent	time	yield	exo: endo[a]	er_{exo} (%)[b]	er_{endo} (%)[b]
1	HCl	MeOH:H_2O	21 h	60%	70:30	75:25	73:27
2	none	MeOH	72 h	< 10%	n/d	n/d	n/d
3	HCl	MeOH	18 h	38%	70:30	76:24	76:24
4	HBr[c]	MeOH:H_2O	40 h	58%	48:32	63:37	54:46
5	*p*-TsOH	MeOH:H_2O	40 h	65%	69:31	75:25	72:28

[a] *Exo*:*endo* ratio and enantioselectivity determined by chiral GC. [b] Absolute configuration determined through comparison to known compounds. [c] The tetrahydroquinoline *R*-**272** was added as its HBr salt. [d] 0.20 equivalents of *p*-TsOH were added.

The crude mixture was then purified by flash chromatography to afford an inseparable mixture of *exo* and *endo* Diels-Alder adducts **292** and **293** in 60% yield. The ^{1}H NMR spectrum for this mixture was compared to spectroscopic data for the known

* The use of methanol as the reaction solvent resulted in the Diels-Alder adducts **292** and **293** being partially converted into their corresponding dimethyl acetals. The dimethyl acetals **290** and **291** could be isolated from the reaction mixture prior to the trifluoroacetic acid-catalyzed hydrolysis reaction in 55% yield.

exo and *endo* compounds, which established that the *exo* isomer **292** was the major component (~ 71:29 ratio).[174] The mixture was then analyzed by chiral gas chromatography to accurately determine the *exo*:*endo* ratio as well as the enantiomeric ratios for each of these isomers.

A racemic sample of the Diels-Alder adducts **292** and **293** was prepared using the racemic tetrahydroquinoline *RS*-**272**. Using MacMillan's commercially-available non-racemic catalyst **265**, a sample of the chiral nonracemic adducts of known absolute stereochemistry was also synthesized (er > 95:5 for each of the *exo* and *endo* isomers).[161] Using these samples, chiral analytical GC conditions were developed so that each of the four products (*i.e.* the enantiomers of both the *exo* and *endo* isomers) could be separated with baseline resolution. As well, the GC retention times for each of the four stereoisomeric products were assigned. GC analysis of the purified mixture of Diels-Alder adducts **292** and **293** revealed an *exo*:*endo* ratio of 70:30 (entry 1). As well, the *exo* and *endo* adducts **292** and **293** were both produced with good enantioselectivity (er = 75:25 and 73:27, respectively). From the GC analysis, the major enantiomers for the *exo* and *endo* isomers were found to be the (2*R*)-adducts 2*R*-*exo*-**292** and 2*R*-*endo*-**293**.

The reaction was then performed under anhydrous conditions and in the absence of the acid co-catalyst. In the absence of acid, the Diels-Alder reaction did not proceed to an appreciable extent after 72 h as determined by thin-layer chromatography (entry 2). In the absence of water, the Diels-Alder reaction afforded the cycloadducts in similar *exo*:*endo* ratio and enantioselectivities; however, the recovered yield was significantly lower (entry 3).

Following this, several acid co-catalysts were screened to determine the role of the acid strength and the counterion in these reactions. Hydrogen bromide co-catalysis produced the adducts **292** and **293** in comparable yield (*c.f.* entry 1). However, both the enantioselectivities and *exo*:*endo* ratio were reduced (entry 4). Interestingly, the *endo*

isomer was formed in a slight excess over the *exo* isomer in this case. The Diels-Alder reaction using *p*-toluenesulfonic acid as a co-catalyst proceeded more slowly (*c.f.* entry 3) but similar diastereo- and enantioselectivities were obtained (entry 5).

Using the *R*-tetrahydroquinoline catalyst **272** (R^1 = Ph) and hydrogen chloride, the solvent was then varied. The reaction rates, yields and selectivities were all lower when dimethylsulfoxide:water was employed (entry 2, Table 5.8.2) and the reaction proceeded to a negligible extent when 1,1,1,3,3,3-hexafluoroisopropanol:water was used (entry 3). Of note, 1,1,1,3,3,3-hexafluoroisopropanol was screened as a solvent because of its known ability to stabilize charged transition states. For example, it has a higher ionizing power (and a lower nucleophilicity) than 1,1,1-trifluoroethanol.[175] The retarded reaction rate observed in this case may be explained if significant stabilization of the ground-state of the tetrahydroquinoline salt **272**·HCl reduced its catalytic activity.*

The tetrahydroquinoline *R*-**273** (R^1 = Ph, R^3 = OMe) was found to catalyze the Diels-Alder reaction of cinnamaldehyde and cyclopentadiene. However, its activity was lower than that of the parent tetrahydroquinoline *R*-**272** (R^1 = Ph) and it led to adducts **292** and **293** with slightly lower enantioselectivities (entry 4).† The 4-benzyl-substituted tetrahydroquinoline *R*-**275** was found to be more active and produced the adducts **292** and **293** in slightly higher yield (entry 5). However, the enantioselectivities of each adduct were found to be lower. Intriguingly, a reversal in asymmetric induction occurred when the catalyst *R*-**275** (R^1 = Bn) was employed affording the (2*S*)-cycloadducts 2*S*-*exo*-**292** and 2*S*-*endo*-**293** (enantiomeric to the stereochemical configuration shown). Lastly, the catalyst *R*-**276** (R^1 = Bn, R^2 = Me) was found to retain the activity of the 4-benzyl

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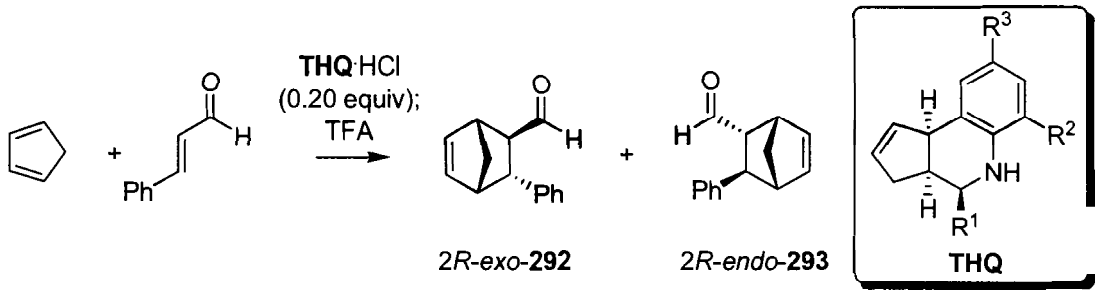
* When the reaction was performed in hexafluoroisopropanol using the tetrahydroquinoline *R*-**272** *with no acid co-catalyst present*, a negligible amount of adducts **292** and **293** were formed after 5 days.

† The fact that the tetrahydroquinoline *R*-**273** (R^3 = OMe) catalyzed the Diels-Alder reaction with the same sense of stereochemical induction is further support that the absolute stereochemistry of this catalyst has been assigned correctly.

structure *R*-**275** and afforded the (2*R*)-adducts **292** and **293** in similar yield (62%). The highest enantioselectivities were produced by this catalyst for all of the tetrahydroquinolines screened (er_{exo} = 79:21).

Table 5.8.2 Solvent and Catalyst Screen in the Diels-Alder Reaction of Cinnamaldehyde Cyclopentadiene

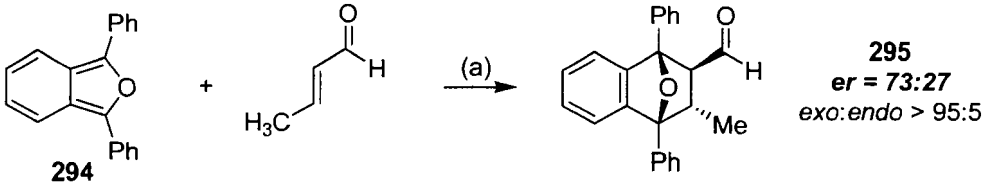


entry[a]	THQ	solvent	time	yield	exo: endo[b]	er_{exo} (%)[b,c]	er_{endo} (%)[b,c]
1	*R*-**272** (R^1 = Ph)	MeOH:H_2O	21 h	60%	70:30	75:25	73:27
2	*R*-**272** (R^1 = Ph)	DMSO:H_2O	68 h	17%	66:34	59:41	56:44
3	*R*-**272** (R^1 = Ph)	HFIA[d]:H_2O	72 h	<10%	n/d	n/d	n/d
4	*R*-**273** (R^3 = OMe)	MeOH:H_2O	40 h	30%	70:30	70:30	66:34
5	*R*-**275** (R^1 = Bn)	MeOH:H_2O	11 h	64%	69:31	35:65	46:54
6	*R*-**276** (R^2 = Me)	MeOH:H_2O	14 h	62%	66:34	79:21	70:30

[a] All reactions were performed using HCl as the co-catalyst. [b] The *exo*:*endo* ratio and enantioselectivity were determined by chiral GC analysis. [c] Absolute configuration determined by comparison with the known compounds. [d] HFIA = 1,1,1,3,3,3-hexafluoroisopropanol. *The enantiomers to those indicated in the reaction scheme were prepared.

The diene and dienophile components in this reaction were then varied. The parent tetrahydroquinoline *R*-**272**·HCl (R^1 = Ph) was found to catalyze the Diels-Alder reaction of 1,3-diphenylisobenzofuran **294** and (*E*)-crotonaldehyde to afford the known cycloadduct **295** in good yield (86%).[161a] The enantiomeric ratio, as determined by comparison of the magnitude of the optical rotation to that of the known compound, was also found to be good (er = 73:27, Scheme 5.8.1). In this case, the *exo*:*endo* ratio increased significantly as determined by ^{1}H NMR spectroscopy (> 95:5).

Scheme 5.8.1 Tetrahydroquinoline *R*-**272** (R^1 = Ph)-Catalyzed Diels-Alder Reaction of 1,3-Diphenylisobenzofuran **294** and Crotonaldehyde

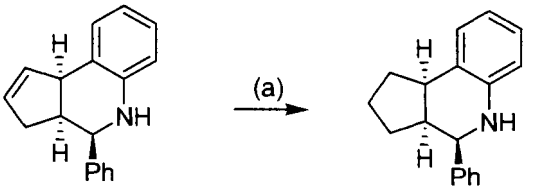


Reagents and conditions: (a) THQ *R*-**272**·HCl (0.20 equiv), DMF:H_2O (95:5), rt, 20 h, 86%.

5.9 Synthesis and Resolution of the Hydrogenated Tetrahydroquinolines

Analysis of the recovered tetrahydroquinoline *R*-**272** (R^1 = Ph) by ^1H NMR spectroscopy and chiral HPLC following the Diels-Alder reaction of cinnamaldehyde and cyclopentadiene showed that no epimerization or racemization had occurred (er > 99:1). However, partial degradation and racemization of the catalyst occurred during the subsequent trifluoroacetic acid-catalyzed hydrolysis reaction (er = 65:35). The decomposition and racemization of the tetrahydroquinoline *R*-**272** could be prevented by a minor modification to its structure (Scheme 5.9.1). Specifically, the chiral nonracemic tetrahydroquinoline *R*-**272** was hydrogenated quantitatively to afford the saturated structure *R*-**296**.* No sign of racemization of this material occurred in this reaction as determined by chiral HPLC analysis.

Scheme 5.9.1 Hydrogenation of the Tetrahydroquinoline *R*-**272**



R-**272** *R*-**296**

Reagents and conditions: (a) H_2, Pd/C, MeOH, rt, 2 h, 100%.

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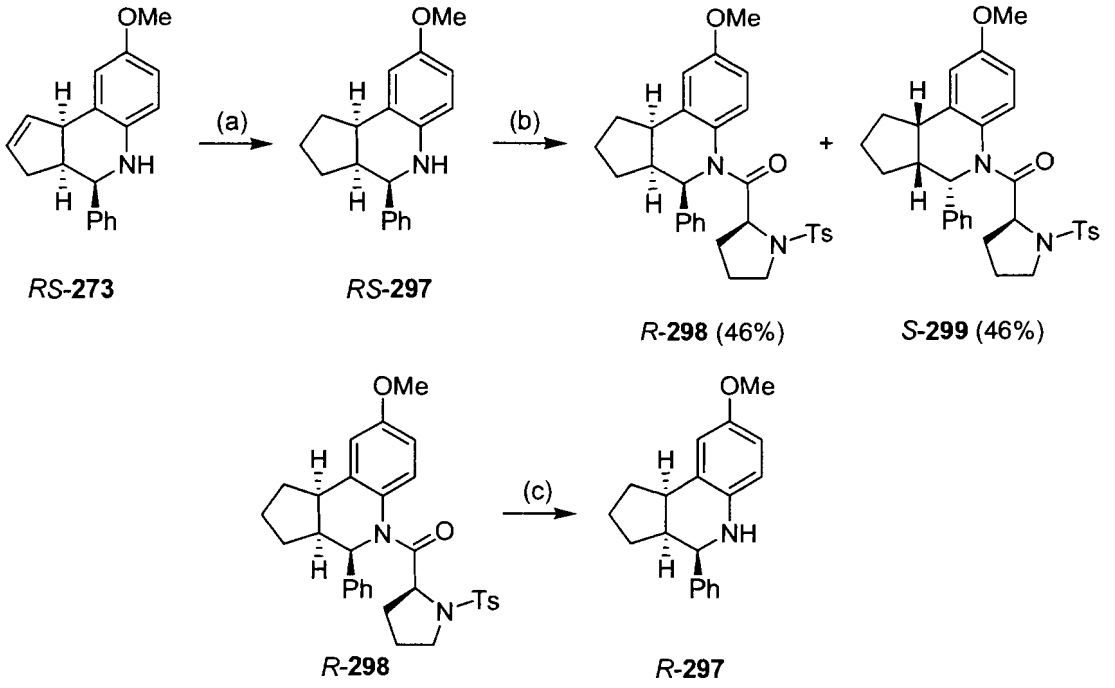
* A racemic sample of the hydrogenated tetrahydroquinoline *RS*-**296** was prepared to determine the chiral HPLC retention times of both enantiomers.

The racemic tetrahydroquinoline *RS*-**273** (R^3 = OMe) was also reacted with hydrogen and palladium on activated carbon in high yield to form the hydrogenated tetrahydroquinoline *RS*-**297** (Scheme 5.9.2).*

Scheme 5.9.2 Hydrogenation of the Tetrahydroquinoline *RS*-**273** and Subsequent Resolution



Reagents and conditions: (a) H_2, Pd/C, EtOH, rt, 1.5 h, 96%. (b) *N*-tosyl-L-prolyl chloride, pyridine, CH_2Cl_2. (c) NaOEt, EtOH, reflux, 30 min, 100%.

This structure could be resolved more efficiently than its unsaturated precursor *RS*-**273**. The hydrogenated tetrahydroquinoline *RS*-**297** (R^3 = OMe) was reacted *N*-tosyl-L-prolyl chloride and the resultant diastereomeric amides *RS*-**298** and *RS*-**299** were each isolated in 46% yield. Most impressively, the amide *R*-**298** reacted with sodium ethoxide in ethanol to form the hydrogenated tetrahydroquinoline *R*-**298** in quantitative yield. The enantiomeric purity was determined to be > 99:1 by chiral HPLC analysis. The corresponding unsaturated structure *R*-**273** was isolated in only 36% yield following the same solvolysis reaction, which suggested that it (or its amide precursor *R*-**283**) was

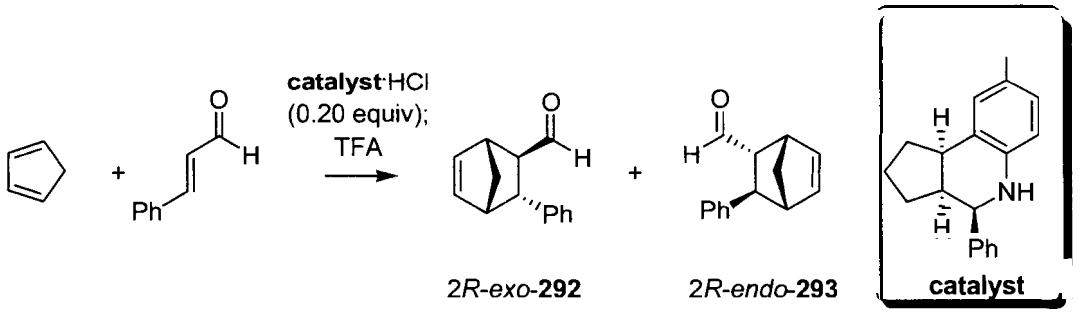
* The tetrahydroquinoline *RS*-**275** (R^1 = Bn) could also be hydrogenated in good yield.

relatively unstable to this reaction.

The absolute stereochemical configuration of the hydrogenated tetrahydroquinoline *R*-**297** was not assigned by X-ray crystallography. The stereochemistry of this structure was assigned on the basis that the hydrogenated amide *R*-**298**, from which it was derived, displayed physical and chemical properties that were consistent with the unsaturated amides *R*-**282-285**.

The two hydrogenated tetrahydroquinolines *R*-**296** (R^1 = Ph) and *R*-**297** (R^3 = OMe) were then evaluated as catalysts in the iminium ion-promoted Diels-Alder reaction of cinnamaldehyde and cyclopentadiene. The hydrogenated tetrahydroquinoline *R*-**296** (R^1 = Ph) was found to catalyze the Diels-Alder reaction and the *exo*:*endo* ratios increased (Table 5.9.1). However, both the yield and enantioselectivity of each the *exo* and *endo* adducts decreased (entry 1 *vs.* entry 2). For the hydrogenated tetrahydroquinoline *R*-**297** (R^3 = OMe), the yield, *exo*:*endo* ratio and enantioselectivities all increased (entry 3 *vs.* entry 4). Following the trifluoroacetic acid-catalyzed hydrolysis reaction, both of the hydrogenated tetrahydroquinoline structures *R*-**296** and *R*-**297** (R^3 = OMe) were isolated and analyzed by ^{1}H NMR spectroscopy and chiral HPLC. *No epimerization or racemization of these structures was observed.*

Table 5.9.1 Hydrogenated Tetrahydroquinolines in the Iminium Ion-Promoted Diels-Alder Reaction



2*R*-*exo*-**292** 2*R*-*endo*-**293**

entry	catalyst	time	yield	*exo*: *endo*[a]	er_{exo} (%)[a]	er_{endo} (%)[a]
1	*R*-**272**	21 h	60%	70:30	75:25	73:27
2	*R*-**296**	18 h	30%	74:26	68:32	65:35
3	*R*-**273** (R^3 = OMe)	40 h	30%	70:30	70:30	66:34
4	*R*-**297** (R^3 = OMe)	68 h	65%	74:26	73:27	69:31

[a] The *exo*:*endo* ratio and enantioselectivity were determined by chiral GC analysis.

5.10 Proposed Mechanism of the Racemization of the Tetrahydroquinoline [*R*-272 (R^1 = Ph)]

The tetrahydroquinoline *R*-**272** (R^1 = Ph), which contains three contiguous stereogenic centres, was observed to racemize during the trifluoroacetic acid-catalyzed hydrolysis reaction which followed the catalytic asymmetric Diels-Alder reaction.

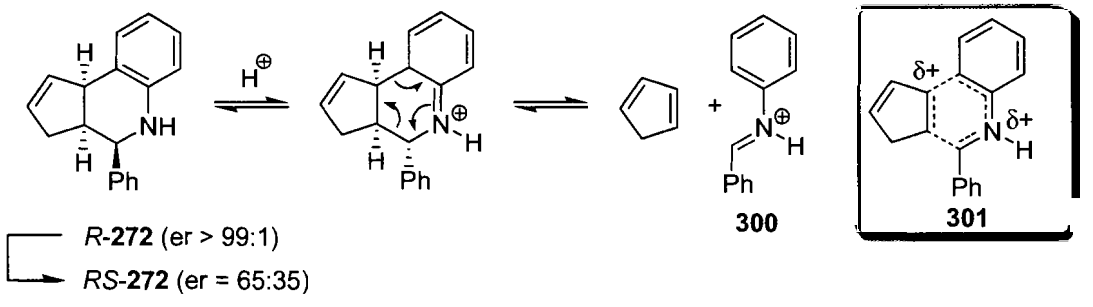


Figure 5.10.1 Proposed mechanism of the trifluoroacetic acid-catalyzed racemization of the tetrahydroquinoline *R*-**272**.

A possible mechanism to account for this involves an initial acid-catalyzed retro Diels-Alder reaction (Figure 5.10.1). The achiral anilinium ion **300** and cyclopentadiene could then recombine in a Diels-Alder reaction to form the racemic tetrahydroquinoline. The tetrahydroquinoline *RS*-**272** was isolated in a decreased enantiomeric ratio (er = 65:35) indicating that the compound did not completely racemize during the trifluoroacetic acid-catalyzed hydrolysis reaction. As well, the tetrahydroquinoline was recovered in only ~ 25% yield which suggested that decomposition was competitive with racemization.

The instability of the *R*-**272** can be attributed to the ability of the allylic π-bond to stabilize the development of positive charge in the transition state **301** during the retro Diels-Alder reaction. The hydrogenated tetrahydroquinoline structures *R*-**296** (R^1 = Ph) and *R*-**297** (R^3 = OMe) were, therefore, likely stable to the acidic conditions because no such transition state stabilization was possible.

5.11 Stereochemical Aspects of the Tetrahydroquinoline-Catalyzed Diels-Alder Reactions

5.11.1 Evidence for the Formation of an Iminium Ion Intermediate

The *in situ* formation of the proposed iminium ion intermediates were supported by two observations. Firstly, upon mixing cinnamaldehyde (3 equivalents) and *R*-**275**·HCl (R^1 = Bn, 1 equivalent) in methanol-d_4, the ^{1}H NMR spectrum showed the formation of one new species in ~ 30% yield (Figure 5.11.1).* Under the acidic conditions, cinnamaldehyde was converted into the dimethyl acetal **303**. Its olefinic hydrogen signals (**B″** and **C″**) that are present in the region of the spectrum are depicted. The characteristic peaks that have been tentatively assigned as those of the iminium ion

* Whether this was one geometrical isomer [the (*Z*)-iminium isomer is shown in *R*-**300**·HCl] or a rapidly converting mixture of the (*E*)- and (*Z*)-iminium ions could not be determined by ^{1}H NMR spectroscopic methods.

R-**302**·HCl are: the imine hydrogen (**A′**) and the olefinic hydrogen (**C′**), shifted downfield by δ 0.3 ppm with respect to that in cinnamaldehyde (**C**). As well, the olefinic hydrogens of the tetrahydroquinoline ring system of *R*-**302**·HCl are believed to be the signals, **D′** and **E′**, which occur downfield from those of *R*-**275**·HCl (**D** and **E**).

Secondly, solutions of each tetrahydroquinoline hydrochloride rapidly became yellow or orange in colour upon the addition of cinnamaldehyde suggesting that a structure of extended conjugation was formed.

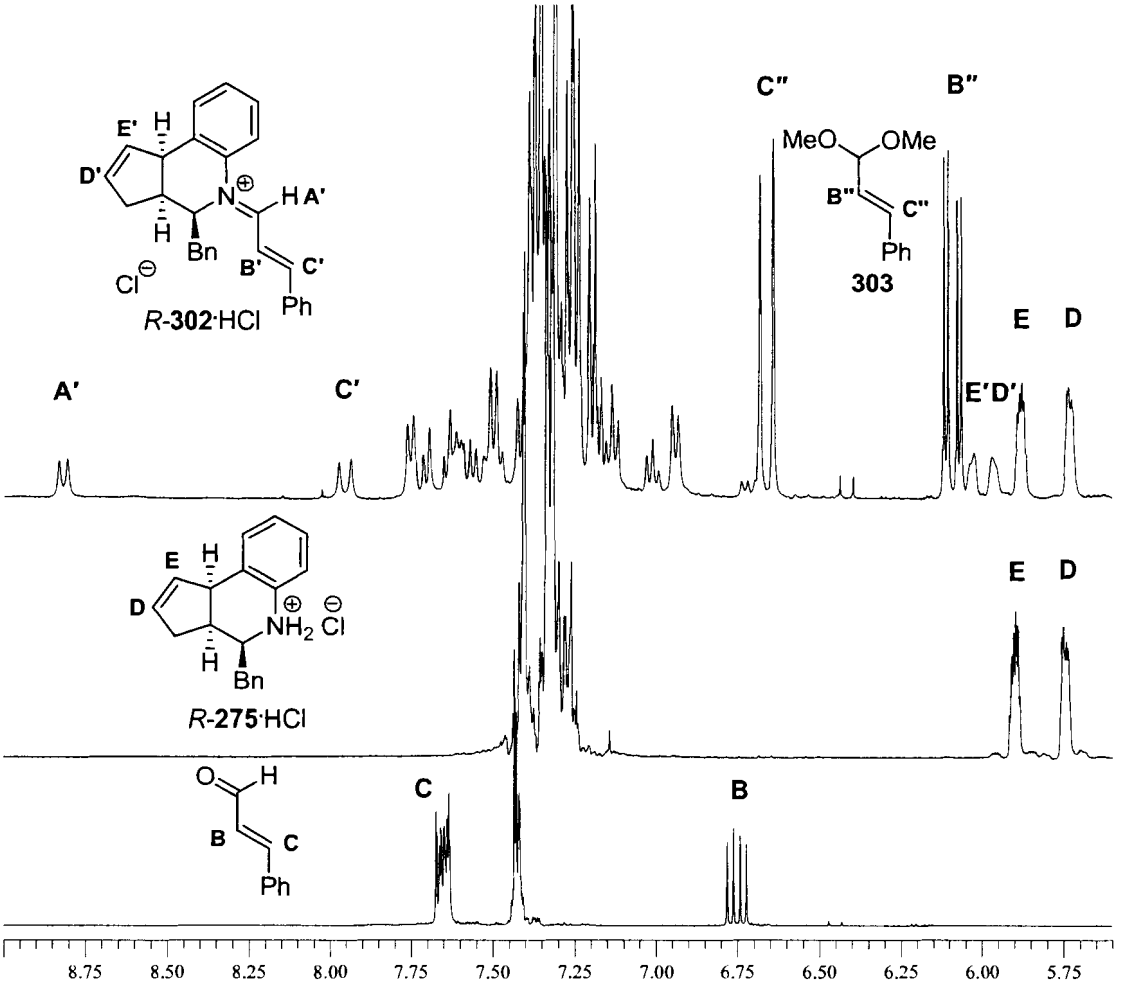


Figure 5.11.1 ^{1}H NMR (400 MHz, methanol-d_4) spectra of (*E*)-cinnamaldehyde (bottom), tetrahydroquinoline *R*-**285**·HCl (R^1 = Bn, middle) and tetrahydroquinoline *R*-**285**·HCl (R^1 = Bn) + (*E*)-cinnamaldehyde (3 equivalents, top).

5.11.2 Rationale of the Absolute Stereochemical Outcome

The crystal structure of *R*-**282** was of assistance in rationalizing the stereochemical outcomes of the Diels-Alder reactions (Figure 5.6.1). The phenyl substituent and cyclopentadienyl fragment sterically hinder the top face (as depicted). In all cases, cyclopentadiene was proposed to have approached from the face opposite to these substituents. The formation of the major adducts 2*R*-*exo*-**292** and 2*R*-*endo*-**293** in the tetrahydroquinoline *R*-**272** (R^1 = Ph)-catalyzed Diels-Alder reaction can then be accounted for if cyclopentadiene approached from the *Re* (bottom) face of the (*Z*)-iminium ion **304** in an *exo* or *endo* trajectory, respectively (Cl^- omitted for clarity, Figure 5.11.2). The reaction is believed to proceed *via* the (*Z*)-iminium ion **304** with the substrate adopting an *s-trans* conformation such to minimize unfavourable steric interactions between the phenyl substituent of the catalyst and the substrate.

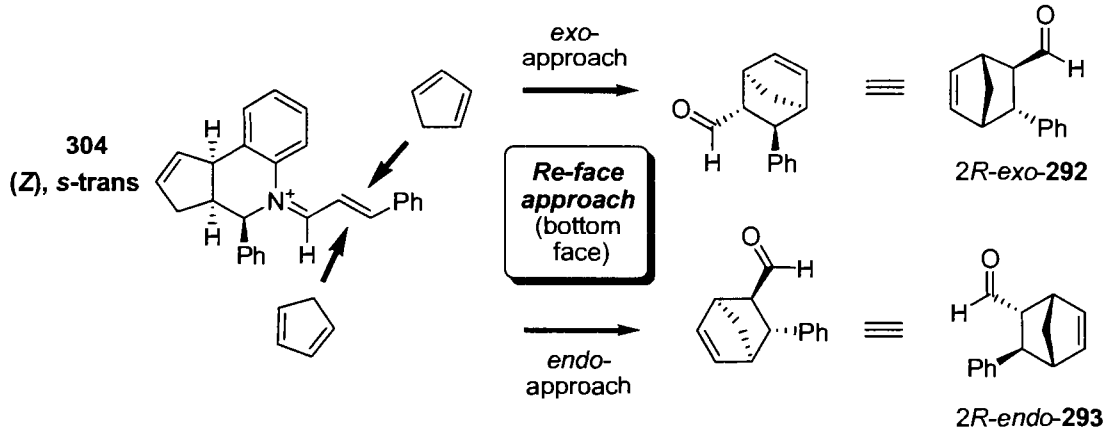
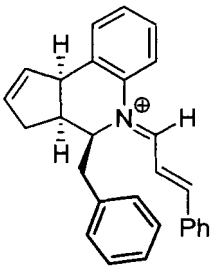


Figure 5.11.2 Rationale of the stereochemical outcome in the tetrahydroquinoline *R*-**272**-catalyzed asymmetric Diels-Alder reaction (counterion omitted from clarity).

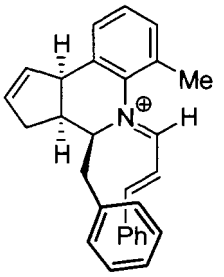
In order to account for the stereochemical outcome in the case of the tetrahydroquinoline *R*-**275** (R^1 = Bn), the approach of cyclopentadiene to the isomeric (*E*)-iminium ion from the diastereotopic *Si* (bottom) face in both *exo* and *endo* trajectories would afford the observed enantiomeric (2*S*)-adducts 2*S*-*exo*-**292** and 2*S*-*endo*-**293** (Figure 5.11.3). Here, repulsive steric interactions between the aromatic ring of

the tetrahydroquinoline and substrate are proposed to override those between the conformationally-mobile α-benzyl substituent and substrate thus disfavouring the reaction of the (*Z*)-isomer. In addition, the proximity of the substrate and α-benzyl substituent allowed for a possible and favourable π-π interaction between the electron-poor olefin and the benzyl group.



305
(*E*), *s*-trans

Figure 5.11.3 Proposed reactive intermediate **305** in the tetrahydroquinoline *R*-**275** (R^1 = Bn)-catalyzed asymmetric Diels-Alder reaction.



306
(*E*), *s*-cis

Figure 5.11.4 Proposed reactive intermediate **306** in the tetrahydroquinoline *R*-**276** (R^1 = Bn, R^2 = Me)-catalyzed asymmetric Diels-Alder reaction.

The results for the *ortho*-methyl structure **276** are complicated to rationalize. The formation of the major 2*R*-*exo*-**292** and 2*R*-*endo*-**293** adducts in the *R*-**276** (R^1 = Bn, R^2 = Me)-catalyzed Diels-Alder reaction can be accounted for if cyclopentadiene again approached the *Re* (bottom) face of the (*E*)-iminium ion **306** here reacting *via* an *s*-*cis* conformation (Figure 5.11.4). The (*Z*)-iminium ion should be further destabilized [as compared to one hypothetically formed in the case of the tetrahydroquinoline *R*-**275**

(R^1 = Bn)] by steric interactions with the *ortho*-methyl group. The *o*-methyl substituent may have further influenced the system such that a favourable π-π interaction between the tetrahydroquinoline benzyl and substrate phenyl groups existed only when the substrate adopted an *s-cis* conformation. The fact that the tetrahydroquinoline *R*-**276** (R^1 = Bn, R^2 = Me) afforded significantly higher enantioselectivities than the tetrahydroquinoline *R*-**275** (R^1 = Bn) is likely due to better conformational control imparted by this former structure.

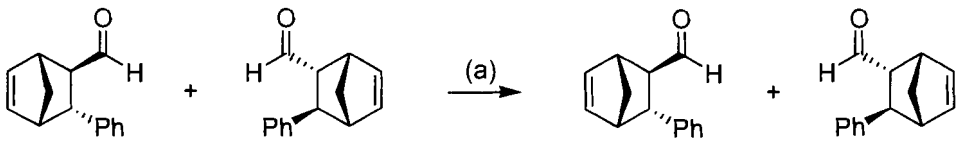
5.11.3 Rationale of the Relative Stereochemical Outcome: The *Exo* Adduct Predominance

MacMillan and co-workers have found that in asymmetric iminium ion-promoted Diels-Alder reactions of several α,β-unsaturated aldehydes (including cinnamaldehyde) and cyclopentadiene, the *exo*:*endo* ratios ranged from 50:50 to 56:44.[161a] As well, Cavill and co-workers reported an *exo*:*endo* ratio of 62:38 in the *N*,*N*-dimethylamine-catalyzed Diels-Alder reaction of cinnamaldehyde and cyclopentadiene.[164] In the tetrahydroquinoline-catalyzed Diels-Alder reactions, the *exo*:*endo* ratios were typically 70:30 or higher. A possible explanation for the *exo*-predominance in the systems studied here is that the Diels-Alder reactions were reversible and allowed the more thermodynamically stable *exo*-adducts to accumulate.

To determine whether these iminium ion-promoted Diels-Alder reactions were under kinetic or thermodynamic control, a racemic sample of the Diels-Alder adduct *RS*-**292** and **293** was exposed to the chiral nonracemic tetrahydroquinoline *R*-**272**·HCl (0.10 equivalents) and cyclopentadiene (2 equivalents) for 1 day in methanol:water (95:5, Scheme 5.11.1).

No change in the *exo*:*endo* ratio or in the enantiomeric ratio of the cycloadducts was observed by chiral GC analysis suggesting that under these conditions, the Diels-Alder reaction was indeed irreversible.

Scheme 5.11.1 Attempted Equilibration of Racemic Diels-Alder Adducts *rac*-**292** and *rac*-**293**



2*RS*-*exo*-**292** (racemic) 2.09	:	2*RS*-*endo*-**293** (racemic) 1	2*RS*-*exo*-**292** ***er* = 50:50** 2.05	:	2*RS*-*endo*-**293** ***er* = 50:50** 1

Reaction conditions: THQ *R*-**272**·HCl (0.10 equiv), cyclopentadiene (2 equiv), MeOH:H_2O (95:5), rt, 1 day.

In many Diels-Alder reactions under kinetic control in which the *exo*-adduct predominates, favourable secondary orbital interactions are argued to become subordinate to unfavourable steric interactions, in the *endo*-transition state.[176,177] In close relation to the studies here, a theoretical study (AM1 level) of the Diels-Alder reaction of an α,β-unsaturated iminium ion and cyclopentadiene found an *exo*-preference. This was attributed to minimization of steric interactions in the transition state.[178] Others have argued that favourable secondary orbital interactions can be minimized in the *endo*-transition state due to cross-conjugation within the dienophile.[179] In the systems studied here, the diastereomeric preference is likely dictated by a subtle competition between steric effects and secondary orbital interactions.

5.12 Conclusions

These studies represent the first instance that chiral tetrahydroquinolines have been used in catalytic asymmetric synthesis. The series of tetrahydroquinolines studied were prepared in a simple acid-catalyzed three-component coupling reaction. The known *N*-tosyl-L-prolyl resolving agent was generally applicable to the resolution of all the tetrahydroquinoline structures studied here. The iminium ion-promoted Diels-Alder reaction has shown that the family of chiral nonracemic tetrahydroquinolines could act as effective secondary amine catalysts affording cycloadducts with good enantioselectivities

(up to er = 79:21). The two hydrogenated tetrahydroquinoline structures prepared were more robust than their unsaturated precursors and were stable to strongly acidic conditions. As well, the racemic hydrogenated tetrahydroquinoline *RS*-**272** (R^3 = OMe) could be resolved more efficiently and showed higher activity and enantiocontrol in the Diels-Alder reaction than its unsaturated precursor.

These iminium ion-promoted Diels-Alder reactions have also provided insight into the structural features of the tetrahydroquinolines required to achieve high levels of stereochemical induction while, at the same time, maintaining catalytic activity. Subsequent studies will involve screening these chiral tetrahydroquinolines in a variety of other secondary amine-catalyzed processes. As well, the experimental ease with which these structures are prepared, the modular three-component coupling reaction utilized and the large number of aldehydes, anilines and alkenes that are commercially-available suggest that combinatorial chemistry would readily allow for a library of chiral tetrahydroquinolines to be prepared. Future work could also include the preparation of chiral nonracemic tetrahydroquinolines using catalytic asymmetric synthesis. Finally, adapting these structures into chiral bidentate ligands for use in catalytic asymmetric synthesis is another potential research goal.

CHAPTER 6: GENERAL CONCLUSIONS

A series of chiral auxiliaries, ligands and catalysts were prepared in experimentally simple and modular two- or three-component coupling reactions. The common structural motif of the first class of reagents and ligands, that were described, was a chiral cyclic acetal. These compounds were prepared efficiently by the acid-catalyzed condensation reaction of derivatives of indan-1-one and corresponding heterocyclic analogues with a variety of chiral C_2-symmetric 1,2-diols. The acetal subunits of these novel chiral directors were found to be stable to strong Lewis acids, Brønsted bases, nucleophilic and electrophilic reagents as well as to oxidizing and reducing agents. Importantly, the chiral acetals were shown to afford moderate to high levels of stereochemical induction in several stoichiometric and catalytic asymmetric reactions. The results obtained using these novel acetals will provide further impetus for the design, synthesis and evaluation of related chiral acetals for use in asymmetric synthesis.

In addition, a series of chiral tetrahydroquinoline catalysts were synthesized in an acid-promoted imino Diels-Alder reaction of cyclopentadiene with a variety of aldehydes and anilines. The chiral tetrahydroquinolines were efficiently resolved and employed as metal-free catalysts in the iminium ion-promoted Diels-Alder reaction. Several of the chiral nonracemic tetrahydroquinolines were found to catalyze the Diels-Alder reaction of cinnamaldehyde and cyclopentadiene to form cycloadducts in good yields and enantioselectivities. This second class of novel chiral directors offer addition potential for further development and application in other catalytic asymmetric processes.

CHAPTER 7: EXPERIMENTAL SECTION

7.1 General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen, unless stated otherwise, at temperatures that were those of the external bath. Diethyl ether (ether) and tetrahydrofuran were dried over sodium/benzophenone and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, dichloromethane, pyridine, toluene and triethylamine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. Cyclopentadiene was distilled from its dimer through a 30-cm Vigreux column collecting the distillate at -78 °C and was used immediately. All other solvents and reagents were purified by standard techniques or used as supplied.[180] Brine refers to a saturated aqueous solution of sodium chloride. Silica gel chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh).[181]

Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected.

Optical rotations were measured using a Perkin-Elmer 341 digital polarimeter at room temperature.

All proton and carbon nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR, respectively) spectra were recorded using a Bruker AMX 400 FT spectrometer (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at ambient temperature unless otherwise noted. Otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian Unity Inova 500 spectrometer (operating frequencies: ^{1}H, 499.79; ^{13}C, 125.67 MHz). Chemical shifts for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform were 7.26 and 77.16 ppm for ^{1}H and ^{13}C NMR spectra, respectively. Those

used for deuterated benzene were 7.15 and 128.02 ppm, respectively. Those used for deuterated dichloromethane were 5.26 and 54.00 ppm, respectively. The precision of the ^{1}H coupling constants (J) is approximately ± 0.5 Hz for all spectra that were acquired.

Infrared spectra were recorded as films (neat) or as evaporated films using a Perkin Elmer 599B IR spectrophotometer.

Mass spectra were recorded on a Hewlett Packard 5985 GC-mass spectrometer. The modes of ionization used were electron impact or chemical ionization using isobutane. Matrix-assisted laser desorption/ionization time-of-flight mass spectra were recorded on a PerSeptive Biosystems Voyager-DE spectrometer using 2,5-dihydroxybenzoic acid as the matrix. Fast-atom-bombardment high-resolution mass spectra were recorded by Dr. David MacGillvray at the University of Victoria on a Kratos Concept IH mass spectrometer.

Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer.

HPLC analyses were performed on a Hewlett-Packard Series 1050 instrument monitoring by UV detection at a wavelength of 254 nm. All HPLC separations were performed on a Chiralcel OD column using hexanes:isopropanol (9:1) as eluant at a flow rate of 0.5 mL/min.

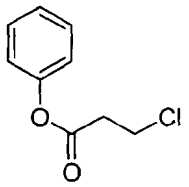
GC analyses were performed on a Varian 3400 instrument monitoring by flame ionization detection. All GC runs were performed on a Cyclosil-B column with helium as a carrier gas at 18 p.s.i. at an oven temperature of 150 °C. An optically enriched mixture of (1*S*,2*S*,3*S*,4*R*)- and (1*R*,2*S*,3*S*,4*S*)-3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde 2*S*-*exo*-**192** and 2*S*-*endo*-**193** was prepared according to the procedure described by MacMillan and co-workers using (5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride **265** (obtained from Aldrich).[161]

X-ray crystallographic analysis of the phenylacetates **73** (R = Me) and **74** (R = Ph) was performed by Drs. Ray Batchelor and Fred Einstein at Simon Fraser University. X-ray crystallographic analysis of the amides *R*-**282**, *S*-**288** and *S*-**289** was performed by Neil Draper and Dr. Daniel Leznoff at Simon Fraser University. Either a Rigaku RAXIS-RAPID curved image plate area detector with graphite monochromated Cu Kα radiation or a Enraf Nonius CAD4F with graphite monochromated Mo Kα radiation diffractometers were used for these compounds.

7.2 Experimental Procedures and Characterization Data Concerning Chapter 2

7.2.1 Synthesis of 7-Hydroxyindan-1-one (46)

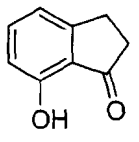
***Phenyl 3-chloropropanoate* (51).**[182]



51

To 3-chloropropanoic acid (100 g, 922 mmol) in a 1 L round-bottom flask equipped with a pressure-equalized addition funnel, phosphorus trichloride (29 mL, 0.33 mol) was added over 30 min with stirring. A condenser was attached and the contents were heated at 110-120 °C for 3 h. The reaction mixture was then allowed to cool to room temperature and a solution of phenol (86.6 g, 920 mmol) in toluene (125 mL) was added slowly through the top of the condenser. The flask contents were stirred at room temperature overnight and then heated at reflux for 3 h. After allowing the reaction mixture to cool to room temperature, the resultant colourless gum was diluted with ether (75 mL) and washed with an aqueous solution of sodium hydroxide (5 wt. %, 5 × 40 mL), a saturated aqueous solution of ammonium chloride (25 mL) and brine (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow liquid. The crude liquid was purified by distillation to afford the *title compound* **51** (92.5 g, 54%) as a colourless liquid. **Bp** 95-125 °C, 2 mm Hg, (lit.[37] 120-125 °C, 7 mm Hg); **^{1}H NMR** ($CDCl_3$) δ 3.01 (2H, m, C*H*$_2$CO), 3.83 (2H, apparent t, J = 6.7 Hz, C*H*$_2$Cl), 7.07 (2H, apparent dd, J = 7.6, 0.9 Hz, Ar*H*), 7.21 (1H, m, Ar*H*), 7.41 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 37.84, 38.99, 121.57, 126.20, 129.61, 150.59, 169.00; **IR** (neat) 1764, 1593, 1494, 1365, 1191, 1136, 931, 752, 692 cm^{-1}; **MS** (EI) *m/z* 184 (M), 94.

***7-Hydroxyindan-1-one* (46).**[182]



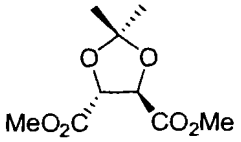
46

To a 3-neck, 1 L round-bottom flask equipped with an air condenser and mechanical stirrer were added aluminum chloride (270 g, 2.02 mol) and phenyl 3-chloropropanoate **51** (92.0 g, 0.509 mol). The reaction mixture

was stirred and heated to 90 °C over 2 h, then maintained between 90 and 100 °C for 1 h. The reaction temperature was then increased over the course of 4 h to 180 °C and maintained at this temperature for 1 h. After allowing the reaction mixture to cool to room temperature, the mixture was further cooled in an ice-bath. Ice was then added slowly until the evolution of hydrogen chloride had ceased. Hydrochloric acid (37 wt. %, 100 mL) was added and the mixture was stirred at room temperature overnight. The resultant black gummy residue was steam distilled in two portions until a pale red solution containing only traces of an organic residue remained. The distillates were dissolved in toluene (150 mL), washed with brine (2 × 50 mL), dried over anhydrous magnesium sulfate and concentrated to afford the *title compound* **46** (30.5 g, 40%) as a white solid. An analytical sample of the product, as white needles, was prepared by recrystallization from benzene. **Mp** 108-109 °C, benzene, (lit.[37] 111 °C, benzene); **^{1}H NMR** ($CDCl_3$) δ 2.72 (2H, m, ArC*H*$_2$), 3.11 (2H, t, *J* = 5.9 Hz, C*H*$_2$CO), 6.76 (1H, dd, *J* = 8.1, 0.7 Hz, Ar*H*), 6.94 (1H, dd, *J* = 7.4, 0.7 Hz, Ar*H*), 7.47 (1H, t, *J* = 7.7 Hz, Ar*H*), 9.07 (1H, br s, O*H*); **^{13}C NMR** ($CDCl_3$) δ 26.01, 36.14, 113.66, 117.52, 122.89, 137.71, 155.35, 157.79, 210.04; **IR** (ef) 3364, 1676, 1617, 1599, 1466, 1327, 1200, 830, 639 cm^{-1}; **MS** (CI) *m/z* 149 (M+H).

7.2.2 Synthesis of Chiral 1,2-Diols Derived from L-Tartaric Acid

***(4R,5R)-Dimethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate* (307).**[40]

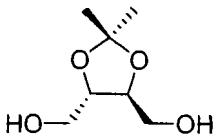


307

A stirred mixture of (2*R*,3*R*)-tartaric acid **26** (101 g, 0.675 mol), 2,2-dimethoxypropane (291 mL, 2.37 mol), *p*-toluenesulfonic acid monohydrate (0.40 g, 2.1 mmol) and methanol (40 mL) was heated at 100 °C for 1.5 h. Cyclohexane (450 mL) and additional 2,2-dimethoxypropane (95 mL, 0.77 mol) were then added. An azeotrope of cyclohexane, methanol and excess 2,2-dimethoxypropane (~ 600 mL) was removed by distillation (30 cm Vigreux column) over 36 h by heating the reaction mixture at 40-50 °C for 30 h and at 70 °C for the remaining 6

h. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (1.01 g, 7.31 mmol) was added. After 1.5 h, the reaction mixture was concentrated to afford a red-brown liquid. The crude liquid was purified by distillation to afford the *title compound* **307** (115 g, 78%) as a yellow liquid. **Bp** 105-110 °C, 2 mm Hg, (lit.[40] 94-101 °C, 0.5 mm Hg); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.43 (6H, s, 2 × CH_3C), 3.75 (6H, s, 2 × CH_3O), 4.69 (2H, s, 2 × $CHCO_2$Me); **^{13}C NMR** ($CDCl_3$, 500 MHz) δ 26.37, 52.74, 77.19, 113.72, 169.66; **IR** (neat) 1761, 1439, 1385, 1376, 1255, 1212, 1112, 1013, 859 cm^{-1}; **MS** (CI) *m/z* 219 (M+H), 203.

***(3S,4S)-3,4-Isopropylidene-1,3,4,6-hexanetetrol* (57).**[40]

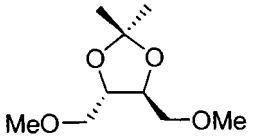


57

In a 3-neck, 2 L round-bottom flask equipped with a condenser, pressure-equalized dropping funnel and solid addition funnel, lithium aluminum hydride (33.6 g, 0.884 mol) was added slowly to ether (550 mL) with stirring. The solid addition funnel was then replaced with a thermometer and the resultant grey suspension was heated at a gentle reflux for 30 min. The reaction mixture was then allowed to cool to room temperature and a solution of the diester **307** (115 g, 0.526 mol) in ether (280 mL) was added to the reaction mixture over the course of 3 h. During this time, the exothermicity of the reaction caused the reaction mixture to reflux gently (CAUTION: *hydrogen gas evolved*). The reaction mixture was heated at reflux for an additional 2 h at which time a violent explosion occurred destroying the thermometer, dropping funnel and condenser. After extinguishing the fire, the reaction mixture was cooled to 0 °C and, under a stream of nitrogen gas, ethyl acetate (100 mL) was added slowly with swirling and stirring. After 16 h, water (15 mL), an aqueous solution of sodium hydroxide (4 M, 15 mL) and additional water (45 mL) were slowly added in succession. The reaction mixture was then filtered with ether (200 mL) and the filtrate was concentrated to afford a yellow liquid (30.2 g). The crude reaction product was purified by distillation to afford the *title compound* **57** (20.5 g, 24%) as a colourless

liquid. **Bp** ~ 120 °C, 2 mm Hg, (lit.[40] 94-106 °C, 0.4 mm Hg); **^{1}H NMR** ($CDCl_3$) δ 1.41 (6H, s, 2 × CH_3CO), 2.70-2.84 (2H, broad s, 2 × O*H*), 3.72 (4H, ddd, *J* = 11.7, 2.8, 1.3 Hz, 2 × CH_2OH), 3.93-3.99 (2H, m, 2 × $CHCH_2OH$); **^{13}C NMR** ($CDCl_3$) δ 27.10, 62.18, 78.30, 109.39; **IR** (neat) 3375, 1651, 1456, 1374, 1255, 1216, 1164, 1054, 988, 846 cm^{-1}; **MS** (CI) *m/z* 203 (M+H), 163.

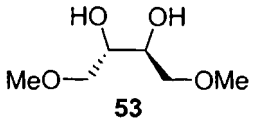
***(3S,4S)-3,4-Isopropylidene-1,6-dimethoxyhexane-3,4-diol* (58).**[40]



58

A solution of the diol **57** (1.70 g, 10.5 mmol) in tetrahydrofuran (5 mL) was added over 5 min to a stirred suspension of sodium hydride [1.31 g, 32.8 mmol, 60 wt. % dispersion in mineral oil, washed with hexanes (2 × 5 mL)] in tetrahydrofuran (5 mL) over which time a grey gel formed and the reaction mixture ceased to stir. After 15 min, methyl iodide (1.6 mL, 26 mmol) and additional tetrahydrofuran (5 mL) was added. After 16 h, over which time the reaction began to stir again, the resultant mixture was heated at reflux for 3 h. After allowing the light brown solution to cool to room temperature, water was added (10 mL). The reaction mixture was then concentrated to a volume of ~ 10 mL, diluted with water (50 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **58** (1.95 g, ~ 100%) as a light brown liquid which was used without further purification.

***(3S,4S)-1,6-Bis(methoxy)hexane-3,4-diol* (53).**[40]

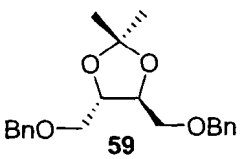


53

A stirred solution of the crude acetal **58** (1.95 g) and hydrochloric acid (1 M, 1 mL) in methanol (20 mL) was distilled at atmospheric pressure (10 cm Vigreux column). An azeotrope of methanol and acetone (~ 10 mL) was collected over 2 h. The reaction mixture was then allowed to cool to room temperature and then was diluted with a saturated aqueous solution of sodium bicarbonate (50 mL) and extracted with chloroform (4 × 20 mL). The aqueous layer was concentrated to near dryness and extracted with chloroform (3 × 20 mL). The combined

organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a white gummy solid (874 mg). Purification by flash chromatography using ethyl acetate as the eluant afforded the *title compound* **53** (135 mg, 9% over two steps) as a white flocculent solid. **^{1}H NMR** ($CDCl_3$) δ 2.18-3.15 (2H, broad s, 2 × O*H*), 3.40 (6H, s, 2 × C*H*$_3$), 3.51-3.55 (4H, m, 2 × C*H*$_2$O), 3.80-3.84 (2H, m, 2 × C*H*CH$_2$OMe); **^{13}C NMR** ($CDCl_3$) δ 59.42, 70.59, 74.67; **IR** (ef) 3404, 1648, 1455, 1196, 1123, 1071, 961, 917 cm^{-1}; **MS** (CI) *m/z* 151 (M+H-H$_2$O), 119.

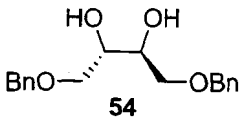
***(3S,4S)-3,4-Isopropylidene-1,6-bis(benzyloxy)hexane-3,4-diol* (59).**[40]



59

A solution of the diol **57** (1.14 g, 7.06 mmol) in tetrahydrofuran (5 mL) was added over 5 min to a stirred suspension of sodium hydride [1.33 g, 33.2 mmol, 60 wt. % dispersion in mineral oil, washed with hexanes (2 × 5 mL)] in tetrahydrofuran (5 mL) over which time a grey gel formed and the reaction mixture ceased to stir. The reaction mixture was then diluted with an additional portion of tetrahydrofuran (5 mL) and after, 15 min, benzyl bromide (2.5 mL, 21 mmol) was added. After 15 h, over which time the reaction mixture began to stir again, the resultant mixture was heated at reflux for 3 h. After allowing the light brown solution to cool to room temperature, water (10 mL) was added. The reaction mixture was then concentrated to a volume of ~ 10 mL, diluted with water (50 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **59** (2.51 g, ~ 100%) as a yellow liquid which was used without further purification.

***(3S,4S)-3,4-1,6-Bis(benzyloxy)hexane-3,4-diol* (54).**[40]

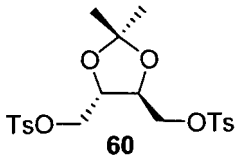


54

A stirred solution of the crude acetal **59** (2.51 g) and hydrochloric acid (1 M, 1 mL) in methanol (20 mL) was distilled at atmospheric pressure (10 cm Vigreux column). An azeotrope of methanol and acetone (~ 10 mL) was collected over 2 h. The reaction mixture was then allowed to cool

to room temperature and was diluted with a saturated aqueous solution of sodium bicarbonate (50 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow liquid, which solidified on standing (2.13 g). Purification by flash chromatography using hexanes:ethyl acetate (2:1 to 1:1) as the eluant afforded the *title compound* **54** (1.37 g, 64% over two steps) as a pale yellow solid. **^{1}H NMR** ($CDCl_3$) δ 2.43-3.02 (2H, broad s, 2 × O*H*), 3.61 (4H, ddd, *J* = 15.9, 9.6, 4.3 Hz, 2 × CH_2OBn), 3.85-3.90 (2H, m, 2 × C*H*CH_2OBn), 4.53 (2H, d, *J* = 11.9 Hz, 2 × C*H*HPh), 4.57 (2H, d, *J* = 11.9 Hz, 2 × CH*H*Ph), 7.27-7.38 (10H, m Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 70.71, 72.13, 73.75, 127.92, 127.99, 128.62, 137.87; **IR** (ef) 3299, 1454, 1091, 1062, 1029, 735, 696 cm^{-1}; MS (CI) *m/z* 303, 181.

***(3S,4S)-3,4-1,6-Bis(p-toluenesulfonyloxy)hexane-3,4-diol* (60).**[183]

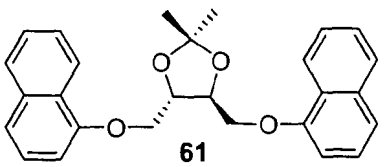


60

To a stirred solution of the diol **57** (3.00 g, 18.5 mmol), pyridine (4.0 mL, 50 mmol) and *N*,*N*-dimethyl-4-aminopyridine (75 mg, 0.61 mmol) in dichloromethane (20 mL) at 0 °C was added *p*-toluenesulfonyl chloride (7.56 g, 39.6 mmol) in portions over 30 min and the reaction mixture was allowed to warm slowly to room temperature. After 16 h, the reaction mixture was cooled to 0 °C and ice-water (40 mL) was added over 2 h. The reaction mixture was then extracted with dichloromethane (2 × 50 mL) and the combined organic extracts were washed with hydrochloric acid (0.5 M, 4 × 50 mL), water (50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a colourless oil which solidified on standing. Recrystallization from ethanol (20 mL) afforded the *title compound* **60** (2.99 g, 42%) as a pale yellow needles. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.31 (6H, s, 2 × CH_3C), 2.48 (6H, s, 2 × CH_3Ar), 3.98-4.02 (2H, m, 2 × C*H*CH_2OTs), 4.04-4.12 (4H, m, 2 × CH_2O), 7.36 (4H, d, *J* = 7.9 Hz, Ar*H*), 7.78 (4H, d, *J* = 8.4 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$, 500 MHz) δ 21.80, 26.85, 68.42, 68.53, 75.14,

110.94, 128.11, 130.11, 132.51, 145.36; **IR** (ef) 1598, 1453, 1362, 1191, 1177, 1096, 986, 815, 666 cm^{-1}.

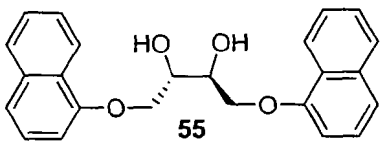
***(3S,4S)-3,4-Isopropylidene-1,6-bis(1-naphthyloxy)hexane-3,4-diol* (61).**[183]



61

To a stirred solution of 1-naphthol (1.44 g, 9.49 mmol) in *N,N*-dimethylformamide (20 mL) at 0 °C was added sodium hydride (0.75 g, 19 mmol, 60 wt. % dispersion in mineral oil) in portions over 5 min. After 1 h, the reaction mixture was allowed to warm to room temperature over 30 min. A solution of the ditosylate **60** (1.46 g, 3.11 mmol) in *N,N*-dimethylformamide (10 mL) was then added over 5 min. After 40 h, the dark brown reaction mixture was poured into an aqueous solution of sodium hydroxide (15 wt. %, 150 mL) and extracted with ether (3 × 75 mL). The combined organic extracts were washed with a saturated aqueous solution of ammonium chloride (15 mL), brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **61** (2.42 g, > 100%) as a brown oil which was used without further purification.

***(3S,4S)-1,6-Bis(1-naphthyloxy)hexane-3,4-diol* (55).**[183]



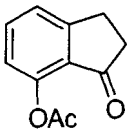
55

A solution of the crude acetal **61** (2.42 g) and hydrochloric acid (37 wt. %, 10 drops) in ethanol (12 mL) and water (12 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and was diluted with a saturated aqueous solution of sodium bicarbonate (100 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **55** (673 mg, 58% over two steps) as a pale purple solid which was used without further purification. An analytical sample of the product, as a white solid, was prepared by flash chromatography using hexanes:ether (1:1) as the eluant **^{1}H NMR** (CD_2Cl_2, 500 MHz) δ

2.85 (1H, broad s, O*H*), 4.35-4.42 (4H, m, 2 × CH_2O), 4.40-4.49 [2H, m, 2 × C*H*CH_2O(1-Np)], 6.90 (2H, dd, J = 7.6, 0.7 Hz, Ar*H*), 7.39 (2H, apparent dd, J = 8.2, 7.6 Hz, Ar*H*), 7.43-7.52 (6H, m, Ar*H*), 7.82 (2H, apparent d, J = 8.1 Hz, Ar*H*) 8.23 (2H, apparent d, J = 8.4 Hz, Ar*H*); **^{13}C NMR** (CD_2Cl_2, 500 MHz) δ 69.90, 70.66, 70.77, 105.58, 121.24, 122.14, 125.86, 125.92, 126.41, 127.01, 128.05, 135.04, 154.60; **IR** (ef) 3285, 1569, 1580, 1509, 1459, 1403, 1272, 1242, 1104, 788, 767 cm^{-1}; **MS** (CI) *m/z* 375 (M+H-H_2O), 276, 267, 249, 145.

7.2.3 Synthesis of 7-Hydroxyindan-1-one-Derived Chiral Auxiliaries

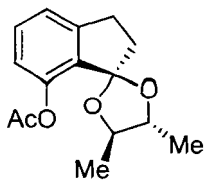
***7-Acetoxyindan-1-one* (65).**[184]



65

To a stirred solution of 7-hydroxyindan-1-one **46** (101 mg, 0.681 mmol) in dichloromethane (3 mL) at 0 °C were added pyridine (164 μL, 2.03 mmol) and acetyl chloride (96 μL, 1.4 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 18 h. The resultant mixture was then poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow oil. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **65** (115 mg, 89%) as a white crystalline solid. **Mp** 75-77 °C, hexanes:ether, (lit.[184] 78-79 °C, ether); **^{1}H NMR** ($CDCl_3$) δ 2.40 (3H, s, CH_3), 2.67 (2H, m, ArCH_2), 3.14 (2H, m, CH_2CO), 6.97 (1H, ddd, J = 7.9, 1.5, 0.9 Hz, Ar*H*), 7.34 (1H, ddd, J = 7.6, 1.5, 0.9 Hz, Ar*H*), 7.58 (1H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 20.85, 25.62, 36.73, 120.62, 124.45, 128.73, 135.92, 147.72, 157.02, 169.33, 203.80; **IR** (ef) 1770, 1710, 1610, 1472, 1368, 1245, 1187, 1013 cm^{-1}; **MS** (CI) *m/z* 191 (M+H), 149; **Anal.** Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.30; H, 5.35.

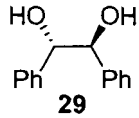
7-Acetoxyindan-1-one (2R,3R)-2,3-butanediol acetal **(66).**



66

A stirred solution of the acetate **65** (192 mg, 1.01 mmol), (2*R*,3*R*)-2,3-butanediol **52** (115 μL, 1.26 mmol) and *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol) in benzene (4 mL) was heated at reflux for 16 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.2 g) was added. After 15 min, direct purification of the reaction mixture by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **66** (238 mg, 90%) as a colourless oil. $[\alpha]_D^{20}$ + 17.6 (*c* 1.14, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 1.06 (3H, d, *J* = 6.1 Hz, C*H*$_3$CH), 1.08 (3H, d, *J* = 5.8 Hz, C*H*$_3$CH), 1.90 (3H, s, C*H*$_3$CO), 2.10-2.25 (2H, m, ArCH$_2$C*H*$_2$), 2.56 (1H, ddd, *J* = 15.9, 8.5, 4.0 Hz, ArC*H*H), 2.63-2.72 (1H, m, ArCH*H*), 3.46 (1H, dq, *J* = 8.5, 6.1 Hz, C*H*CH$_3$), 3.81 (1H, dq, *J* = 8.2, 6.1 Hz, C*H*CH$_3$), 6.74 (1H, apparent dd, *J* = 7.3, 0.9 Hz, Ar*H*), 6.96 (1H, dd, *J* = 7.9, 0.9 Hz, Ar*H*), 7.02 (1H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 16.05, 17.24, 20.78, 28.53, 39.49, 78.83, 79.29, 116.67, 121.71, 122.68, 130.49, 133.89, 146.61, 148.05, 167.89; **MS** (MALDI) *m/z* 285 (M+Na), 263 (M+H); **IR** (neat) 1762, 1615, 1590, 1473, 1368, 1307, 1204, 1172, 1113, 1085 cm^{-1}; **Anal.** Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.55; H, 7.13.

(1S,2S)-1,2-Diphenyl-1,2-ethanediol **(29).**[185]

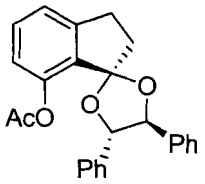


29

A suspension of AD-mix-α (51.2 g) in *t*-butanol (240 mL) and water (240 mL) was cooled to 0 °C. (*E*)-stilbene (8.75 g, 48.5 mmol) was added and the mixture was stirred at 0-5 °C for 24 h. Sodium sulfite (74.2 g, 0.589 mol) was then added and the mixture was stirred for 30 min. The reaction mixture was then diluted with ethyl acetate (250 mL) and the aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated to afford a white solid. Purification by flash chromatography using hexanes:ethyl acetate (5:2) as the eluant afforded unreacted

stilbene and the $(DHQ)_2PHAL$ ligand. Continued elution using ethyl acetate as the eluant afforded the *title compound* **29** (10.1 g, 94%) as a white crystalline solid which was recrystallized from ether by slow evaporation (8.78 g, 82%). $[\alpha]_D^{20}$ - 94 (*c* 2.50, ethanol), lit.[155] - 94.1 (*c* 1, ethanol); **^{1}H NMR** ($CDCl_3$) δ 2.85 (2H, broad s, 2 × CHO*H*), 4.71 (2H, s, 2 × ArC*H*), 7.10-7.30 (10H, m, 10 × Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 79.21, 127.06, 128.05, 128.25, 139.97; **IR** (ef) 3499, 3390, 1451, 1045, 777, 705, 695 cm^{-1}; **MS** (CI) *m/z* 197 ($M+H-H_2O$).

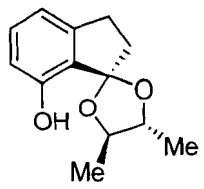
***7-Acetoxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (67).**



67

A stirred solution of the acetate **65** (196 mg, 1.03 mmol), (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29** (258 mg, 1.20 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.10 mmol) in benzene (2 mL) was heated at reflux for 40 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.1 g) was added. After 10 min, direct purification of the reaction mixture by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **67** (332 mg, 83%) as a colourless gum. $[\alpha]_D^{20}$ - 158 (*c* 1.70, chloroform); **^{1}H NMR** (C_6D_6) δ 1.82 (3H, s, CH_3), 2.28-2.44 (2H, m, $ArCH_2CH_2$), 2.63 (1H, ddd, *J* = 15.9, 8.5, 2.1 Hz, ArC*H*H), 2.72-2.83 (1H, m, ArCH*H*), 4.80 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.17 (1H, d, *J* = 8.5 Hz, C*H*Ph), 6.82 (1H, apparent dd, *J* = 5.5, 2.7 Hz, Ar*H*), 7.09-7.12 (3H, m, Ar*H*), 7.13-7.19 (5H, m, Ar*H*), 7.34 (2H, m, Ar*H*), 7.40 (2H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 20.87, 28.60, 39.17, 85.87, 86.98, 118.40, 121.92, 122.79, 127.03, 127.18, 128.55, 128.66, 128.79, 130.92, 133.31, 136.84, 137.86, 146.98, 148.14, 168.10; **MS** (MALDI) *m/z* 409 (M+Na); **IR** (ef) 1746, 1616, 1590, 1473, 1403, 1307, 1225, 1153, 1114, 1084 cm^{-1}; **Anal.** Calcd for $C_{25}H_{22}O_4$: C, 70.06; H, 6.61. Found: C, 70.30; H, 6.52.

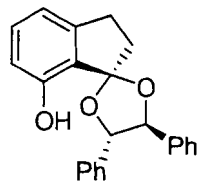
7-Hydroxyindan-1-one (2R,3R)-2,3-butanediol acetal **(63).**



64

To a solution of the acetal **66** (132 mg, 0.502 mmol) in tetrahydrofuran (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (106 mg, 2.53 mmol). The resultant opaque solution was stirred at room temperature for 16 h and then diluted with a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a colourless oil. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **63** (93 mg, 84%) as a colourless oil which solidified on standing. **Mp** 46-49 °C, hexanes:ether; $[\alpha]_D^{20}$ - 19.0 (*c* 1.02, chloroform); **^{1}H NMR** (C_6D_6) δ 0.89 (3H, d, *J* = 6.4 Hz, C*H*$_3$), 0.91 (3H, d, *J* = 6.4 Hz, C*H*$_3$), 2.07 (2H, m, ArCH$_2$C*H*$_2$), 2.59-2.75 (2H, m, ArC*H*$_2$), 3.37-3.48 (2H, m, 2 × C*H*CH$_3$), 6.62 (1H, dd, *J* = 7.3, 0.9 Hz, Ar*H*), 6.90 (1H, apparent dd, *J* = 7.9, 0.6 Hz, Ar*H*), 6.94 (1H, s, O*H*), 7.06 (1H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 16.50, 18.11, 28.89, 39.14, 79.11, 79.34, 114.46, 117.02, 117.84, 125.93, 131.89, 145.32, 154.85; **IR** (ef) 3448, 3379, 1678, 1620, 1600, 1469, 1314, 1199, 1114, 1078, 932, 778, 745 cm^{-1}; **MS** (CI) *m/z* 221 (M+H); **Anal.** Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; Found: C, 70.52; H, 7.51.

7-Hydroxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal **(68).**

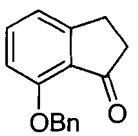


68

To a solution of the acetal **67** (91 mg, 0.24 mmol) in tetrahydrofuran (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (50 mg, 1.2 mmol). The resultant opaque solution was stirred at room temperature for 40 h and then diluted with a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale orange oil. Purification by flash chromatography using

hexanes:ether (4:1) as the eluant afforded the *title compound* **68** (74 mg, 91%) as a white solid. **Mp** 50-52 °C, hexanes:ether; $[\alpha]_D^{20}$ - 100 (*c* 3.16, chloroform); **^{1}H NMR** (C_6D_6) δ 2.25 (1H, ddd, *J* = 12.8, 7.6, 3.7 Hz, $ArCH_2CHH$), 2.30-2.39 (1H, m, $ArCH_2CHH$), 2.67 (1H, ddd, *J* = 15.9, 8.2, 4.0 Hz, $ArCHH$), 2.71-2.80 (1H, m, $ArCHH$), 4.85 (1H, d, *J* = 8.2 Hz, $CHPh$), 5.02 (1H, d, *J* = 8.5 Hz, CHPh), 6.58 (1H, s, O*H*), 6.68 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.82 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.01-7.19 (9H, m, Ar*H*), 7.26-7.30 (2H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 28.88, 38.93, 85.94, 86.08, 114.69, 117.34, 119.58, 125.91, 126.69, 127.24, 128.34, 128.68, 128.76, 128.85, 132.13, 136.53, 138.33, 146.00, 154.66; **IR** (ef) 3446, 1619, 1598, 1469, 1317, 1166, 1123, 1047, 936, 745 cm^{-1}; **MS** (CI) *m/z* 345 (M+H), 238; **Anal.** Calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.02; H, 5.97.

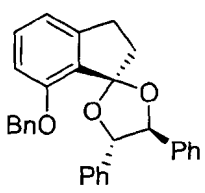
***7-Benzyloxyindan-1-one* (308).**[186]



306

To a stirred suspension of 7-hydroxyindan-1-one **46** (1.00 g, 6.78 mmol) and potassium carbonate (9.40 g, 68.0 mmol) in *N*,*N*-dimethylformamide (20 mL) was added benzyl bromide (1.50 mL, 12.6 mmol) over 5 min. After 4 h, the reaction mixture was diluted with ether (200 mL) and washed with water (6 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow oil. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **308** (1.49 g, 92%) as a pale yellow solid. **Mp** 62-63 °C, hexanes:ether; **^{1}H NMR** ($CDCl_3$) δ 2.68 (2H, m, $ArCH_2$), 3.08 (2H, apparent t, *J* = 6.1 Hz, $ArCH_2CH_2$), 5.28 (2H, s, CH_2O), 6.76 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.99 (1H, d, *J* = 7.3 Hz, Ar*H*), 7.29 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.37 (2H, m, 2 × Ar*H*), 7.43 (1H, m, Ar*H*), 7.50 (2H, d, *J* = 7.6 Hz, 2 × Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 25.65, 36.93, 70.28, 111.06, 118.86, 126.02, 126.79, 127.82, 128.67, 136.16, 136.80, 157.24, 157.90, 204.18; **IR** (ef) 1704, 1590, 1476, 1452, 1299, 1277, 1232, 1062, 1020, 738 cm^{-1}; **MS** (CI) *m/z* 239 (M+H), 149, 91; **Anal.** Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.40; H, 5.96.

***7-Benzyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (69).**

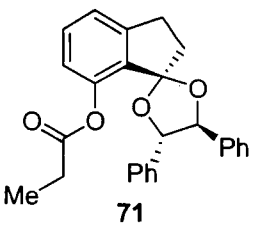


69

A stirred solution of the benzyl ether **308** (958 mg, 4.02 mmol), (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol (1.13 g, 5.29 mmol) and *p*-toluenesulfonic acid monohydrate (90 mg, 0.47 mmol) in benzene (10 mL) was heated at reflux for 2 days with azeotropic removal of water. An additional portion of *p*-toluenesulfonic acid monohydrate (91 mg, 0.48 mmol) was added and heating was continued for 2 days. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.5 g) was added. After 10 min, the reaction mixture was filtered and concentrated to afford a yellow solid. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **69** [1.39 g, 80% (91% based on recovered starting material)] as a white solid and the unreacted benzyl ether **305** (111 mg). **Mp** 145-146 °C, hexanes:ether; $[\alpha]_D^{20}$ - 245 (*c* 1.55, chloroform); **^{1}H NMR** (C_6D_6) δ 2.48 (1H, ddd, *J* = 13.1, 7.9, 2.1 Hz, $ArCH_2CH\mathit{H}$), 2.56-2.67 (1H, m, $ArCH_2CH\mathit{H}$), 2.74 (1H, ddd, *J* = 15.6, 8.8, 1.8 Hz, $ArC\mathit{H}H$), 2.85-2.95 (1H, m, $ArC\mathit{H}H$), 4.69 (1H, d, 19.8 Hz, $C\mathit{H}HO$), 4.74 (1H, d, *J* = 19.8 Hz, $CH\mathit{H}O$), 4.77 (1H, d, *J* = 8.5 Hz, $C\mathit{H}Ph$), 5.27 (1H, d, *J* = 8.5 Hz, $C\mathit{H}Ph$), 6.60 (1H, d, *J* = 8.2 Hz, $Ar\mathit{H}$), 6.79 (1H, d, *J* = 7.6 Hz, $Ar\mathit{H}$), 6.96-7.31 (16H, m, $Ar\mathit{H}$); **^{13}C NMR** (C_6D_6) δ 28.83, 39.56, 70.40, 86.10, 86.65, 110.21, 117.95, 119.07, 127.24, 127.44, 128.59, 128.90, 130.37, 131.29, 137.03, 137.11, 138.38, 147.03, 156.48; **IR** (ef) 3062, 3032, 2940, 2873, 1593, 1494, 1479, 1463, 1454, 1316, 1266, 1124, 1058, 1037, 1027, 745 cm^{-1}; **MS** (CI) *m/z* 435 (M+H), 328, 239; **Anal.** Calcd for $C_{30}H_{26}O_3$: C, 82.92; H, 6.03. Found: C, 83.23; H, 5.99.

7.2.4 Synthesis of Saturated Substrates for Enolate Alkylation Reactions

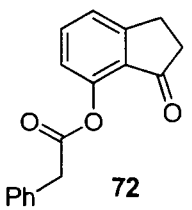
***7-Propanoyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (71).**



71

A solution of the phenol **68** (150 mg, 0.436 mmol), *N,N*-dimethyl-4-aminopyridine (5 mg, 0.04 mmol), triethylamine (0.20 mL, 1.4 mmol) and propanoic anhydride (110 μL, 0.858 mmol) was stirred at 0 °C for 1.5 h. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (3 × 15 mL), filtered and concentrated to afford an opaque gum. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **71** (152 mg, 87%) as a colourless gum which solidified on standing. **Mp** 88-90 °C, hexanes:ether; $[\alpha]_D^{20}$ - 186 (*c* 0.75, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 0.93 (3H, t, *J* = 7.5 Hz, C*H*$_3$), 2.28 (2H, q, *J* = 7.5 Hz, C*H*$_2$), 2.30-2.44 (2H, m, ArCH$_2$C*H*$_2$), (1H, ddd, *J* = 15.9, 8.6, 2.0 Hz, ArC*H*H), 2.74-2.83 (1H, m, ArCH*H*), 4.81 (1H, d, *J* = 8.4 Hz, C*H*Ph) 5.20 (1H, d, *J* = 8.4 Hz, C*H*Ph), 6.82 (1H, dd, *J* = 6.9, 0.8 Hz, Ar*H*), 7.02-7.18 (8H, m, Ar*H*), 7.30 (2H, dd, *J* = 6.7, 1.6 Hz, Ar*H*), 7.36 (2H, dd, *J* = 7.0, 1.5 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 9.03, 27.95, 28.61, 39.18, 85.86, 86.98, 118.39, 121.92, 122.74, 127.02, 127.15, 128.56, 128.65, 128.78, 130.93, 133.29, 136.79, 137.81, 146.98, 148.21, 171.89; **IR** (ef) 1764, 1617, 1590, 1473, 1455, 1316, 1142, 1046, 750 cm^{-1}; **MS** (CI) *m/z* 401 (M+H), 294, 253, 243; **Anal.** Calcd for C, 77.98; H, 6.04. Found: C, 78.05; H, 6.15.

***7-Phenylacetyloxyindan-1-one* (72).**

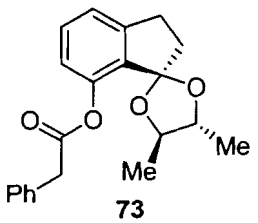


72

A stirred solution of 7-hydroxyindan-1-one **46** (3.16 g, 21.3 mmol), *N,N*-dimethyl-4-aminopyridine (228 mg, 1.86 mmol), pyridine (3.5 mL, 43 mmol) and phenylacetyl chloride (4.2 ml, 32 mmol) in dichloromethane (50 mL) at 0 °C was allowed to warm slowly to room

temperature. After 3 days, additional pyridine (2.6 mL, 32 mmol) and phenylacetyl chloride (2.8 mL, 21 mmol) were added and the reaction mixture was heated at reflux for 2 days. The reaction mixture was then allowed to cool to room temperature and was diluted with ether (150 mL) and washed with saturated aqueous solutions of ammonium chloride (4 × 20 mL) and sodium bicarbonate (4 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated to afford a yellow solid. Purification by flash chromatography using hexanes:ethyl acetate (5:1 to 1:1) as the eluant afforded the *title compound* **72** (5.35 g, 94%) as pale yellow solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from hexanes:ethyl acetate by slow evaporation. **Mp** 100-102 °C, hexanes:ethyl acetate; **^{1}H NMR** ($CDCl_3$) δ 1.98-2.03 (2H, m, $ArCH_2CH_2$), 2.13-2.19 (2H, m, $ArCH_2$), 3.97 (2H, broad s, $CH_2C{=}O$), 6.63 (2H, d, J = 7.9 Hz, Ar*H*), 6.92-6.97 (1H, m, Ar*H*), 7.02-7.08 (1H, m, Ar*H*), 7.12-7.18 (2*H*, m, Ar*H*), 7.41 (2H, d, J = 7.1 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 25.25, 36.48, 41.14, 110.57, 120.50, 123.95, 127.26, 128.70, 130.20, 134.29, 135.15, 148.45, 156.78, 169.53, 202.47; **IR** (ef) 1758, 1698, 1610, 1126, 1092 cm^{-1}; **MS** (CI) *m/z* 267 (M+H), 149, 118; **Anal.** Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.88, H, 5.13.

***7-Phenylacetyloxyindan-1-one (2R,3R)-2,3-butanediol acetal* (73).**

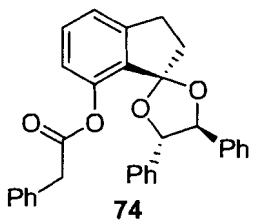


73

A stirred solution of the ketoester **72** (1.85 g, 6.93 mmol), (2*R*,3*R*)-2,3-butanediol **52** (0.95 mL, 10 mmol) and *p*-toluenesulfonic acid monohydrate (208 mg, 1.09 mmol) in benzene (50 mL) was heated at reflux with azeotropic removal of water for 3 days. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (2.5 g) was added. After 30 min, the reaction mixture was filtered and concentrated to afford a yellow solid. Purification by flash chromatography using hexanes:ethyl acetate (8:1 to 4:1) as the eluant afforded the *title compound* **73** (1.85 g, 79%) as pale yellow solid. An

analytical sample of the product, as colourless crystals, was prepared by recrystallization from hexanes:ether by slow evaporation. **Mp** 90-91 °C, hexanes:ether; $[\alpha]_D^{20}$ + 7.2 (*c* 0.58, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.04 (3H, d, *J* = 6.0 Hz, CH_3), 1.08 (3H, d, *J* = 6.0 Hz, CH_3), 2.09-2.26 (2H, m, $ArCH_2CH_2$), 2.49-2.59 (1H, m, ArCHH), 2.62-2.73 (1H, m, ArCHH), 3.42-3.50 (1H, m, $CHCH_3$), 3.66 (2H, broad s, CH_2Ph), 3.68-3.77 (1H, m, $CHCH_3$), 6.73 (1H, d, *J* = 7.4 Hz, ArH), 6.86 (1H, d, *J* = 7.9 Hz, ArH), 6.96 (1H, t, *J* = 7.5 Hz, ArH), 7.01-7.07 (1H, m, ArH), 7.10 (2H, d, *J* = 7.7 Hz), 7.28 (2H, d, *J* = 7.2 Hz); **^{13}C NMR** (C_6D_6) δ 16.15, 17.36, 28.57, 39.51, 41.50, 78.84, 79.29, 110.58, 116.72, 121.59, 122.75, 127.39, 128.83, 129.75, 130.52, 133.91, 134.12, 146.66, 148.08, 168.94; **IR** (ef) 1762, 1473, 1306, 1225, 1122, 1085, 939 cm^{-1}; **MS** (CI) *m/z* 339 (M+H), 267, 191, 149; **Anal.** Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.46; H, 6.52.

***7-Phenylacetyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (74).**



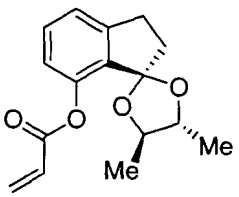
74

A stirred solution of the ketoester **72** (936 mg, 3.50 mmol), (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29** (1.08 g, 5.02 mmol) and pyridinium *p*-toluenesulfonate (155 mg, 0.618 mmol) in benzene (20 mL) was heated at reflux with azeotropic removal of water for 4 days. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (1.23 g) was added. After 30 min, the reaction mixture was filtered and concentrated to afford a pale yellow solid. Purification by flash chromatography using hexanes:ethyl acetate (5:1) as the eluant afforded the *title compound* **74** (1.42 g, 88%) as a white solid. **Mp** 97-98 °C, hexanes:ethyl acetate; $[\alpha]_D^{20}$ - 127 (*c* 0.50, chloroform); **^{1}H NMR** (C_6D_6) δ 2.29-2.45 (2H, m, $ArCH_2CH_2$), 2.57 (1H, ddd, *J* = 15.8, 8.4, 2.0 Hz, ArCHH), 2.72-2.82 (1H, m, ArCHH), 3.61 (1H, d, *J* = 15.5 Hz, CHHC=O), 3.67 (1H, d, *J* = 15.5 Hz, CHHC=O), 4.82 (1H, d, *J* = 8.4 Hz, CHPh), 5.20 (1H, d, *J* = 8.4 Hz, CHPh), 6.79 (1H, d, *J* = 7.1 Hz, ArH), 6.97-7.20 (13H, m, ArH), 7.29 (2H, apparent d, *J* = 8.0, ArH), 7.37 (2H, apparent d, *J* = 8.2 Hz, ArH); **^{13}C NMR** (C_6D_6) δ 28.64,

39.22, 41.54, 85.86, 86.94, 118.41, 121.80, 122.85, 127.13, 127.19, 127.35, 128.50, 128.55, 128.70, 128.75, 128.79, 129.70, 130.95, 133.31, 133.83, 136.87, 137.96, 146.98, 148.22, 169.21; **IR** (ef) 1763, 1590, 1496, 1473, 1454, 1315, 1224, 1177, 1122, 1100, 1046, 940, 747 cm^{-1}; **MS** (MALDI) *m/z* 485 (M+Na); **Anal.** Calcd for $C_{31}H_{26}O_4$: C, 80.50; H, 5.67. Found: C, 80.33; H, 5.84.

7.2.5 Synthesis of α,β-Unsaturated Substrates for Cycloaddition Reactions

***7-Acryloyloxyindan-1-one (2R,3R)-2,3-butanediol acetal* (75).**

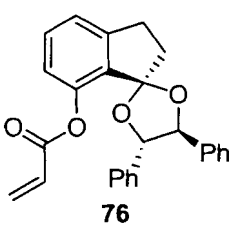


75

A solution of the phenol **63** (124 mg, 0.562 mmol), triethylamine (94 μL, 0.67 mmol) and acryloyl chloride (55 μL, 0.68 mmol) in benzene (4 mL) at 0 °C was stirred for 1.5 h. The reaction mixture, in which a white precipitate had been deposited, was allowed to warm to room temperature over 30 min. During this time, the reaction mixture became a pale yellow solution. The reaction mixture was then diluted with a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a colourless gum. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **75** (136 mg, 88%) as a white solid. **Mp** 35-37 °C, hexanes:ether; $[\alpha]_D^{20}$ -4.1 (*c* 1.14, chloroform); **^{1}H NMR** (C_6D_6) δ 1.07 (3H, d, *J* = 6.1 Hz, C*H*$_3$), 1.11 (3H, d, *J* = 6.1 Hz, C*H*$_3$), 2.12-2.28 (2H, m, ArCH$_2$C*H*$_2$), 2.57 (1H, ddd, *J* = 15.9, 8.5, 4.3 Hz, ArC*H*H), 2.62-2.71 (1H, m, ArCH*H*), 3.47 (1H, dq, *J* = 8.5, 6.1 Hz, C*H*CH$_3$), 3.83 (1H, dq, *J* = 8.5, 6.1 Hz, C*H*CH$_3$), 5.33 (1H, apparent dd, *J* = 10.4, 1.5 Hz, CH=C*H*H), 6.15 (1H, dd, *J* = 17.4, 10.4 Hz, C*H*=CH$_2$), 6.42 (1H, dd, *J* = 17.4, 1.5 Hz, CH=CH*H*), 6.74 (1H, apparent dd, *J* = 7.3, 0.9 Hz, Ar*H*), 6.92 (1H, dd, *J* = 7.9, 0.9 Hz, Ar*H*), 7.00 (1H, dd, *J* = 7.9, 7.3 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 16.03, 17.21, 28.56, 39.52, 78.96, 79.20, 116.66, 121.71, 122.86, 128.58, 130.57, 131.72, 134.16, 146.79, 147.78, 163.75; **IR** (ef)

1746, 1616, 1590, 1473, 1403, 1307, 1225, 1153, 1114, 1084 cm^{-1}; **MS** (CI) *m/z* 275 (M+H), 203, 127; **Anal.** Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.30; H, 6.52.

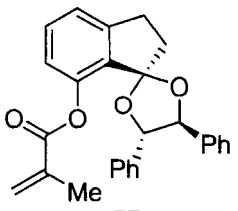
***7-Acryloyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (76).**



76

A solution of the phenol **68** (80 mg, 0.23 mmol), triethylamine (39 μL, 0.28 mmol) and acryloyl chloride (23 μL, 0.28 mmol) in benzene (3 mL) at 0 °C was stirred for 2 h. The reaction mixture, in which a white precipitate had been deposited, was allowed to warm to room temperature over 30 min. During this time, the reaction mixture became a pale yellow solution. The reaction mixture was then diluted with a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a colourless gum. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **76** (79 mg, 85%) as a white solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from hexanes:ether by slow evaporation. **Mp** 82-83 °C, hexanes:ether; $[\alpha]_D^{20}$ - 197 (*c* 1.98, chloroform); **^{1}H NMR** (C_6D_6) δ 2.29-2.45 (2H, m, $ArCH_2CH_2$), 2.57 (1H, ddd, *J* = 15.6, 8.2, 1.8 Hz, ArCHH), 2.78 (1H, m, ArCHH), 4.80 (1H, d, *J* = 8.5 Hz, CHPh), 5.14 (1H, d, *J* = 8.5 Hz, CHPh), 5.18 (1H, dd, *J* = 10.4, 0.9 Hz, CH=CHH), 6.11 (1H, dd, *J* = 17.4, 10.4 Hz, $CH=CH_2$), 6.34 (1H, dd, *J* = 17.4, 1.1 Hz, CH=CHH), 6.82 (1H, d, *J* = 7.0 Hz, ArH), 7.01-7.20 (10H, m, ArH), 7.28 (2H, d, *J* = 6.4 Hz, ArH), 7.35 (2H, d, *J* = 6.4 Hz, ArH); **^{13}C NMR** (C_6D_6) δ 28.63, 39.18, 85.99, 86.82, 118.33, 121.94, 122.98, 127.13, 127.23, 128.48, 128.58, 128.69, 132.20, 133.65, 136.73, 137.86, 147.06, 147.94, 163.91; **IR** (ef) 1746, 1473, 1403, 1316, 1224, 1146, 1048, 751 cm^{-1}; **MS** (CI) *m/z* 399 (M+H), 292, 203; **Anal.** Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.51; H, 5.55.

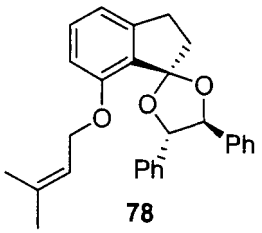
***7-Methacryloyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (77).**



77

A solution of the phenol **68** (49 mg, 0.14 mmol), triethylamine (40 μL, 0.29 mmol) and methacryloyl chloride (22 μL, 0.22 mmol) in benzene (3 mL) was stirred at room temperature for 12 h and heated at reflux for 1 h. The reaction mixture was then allowed to cool to room temperature and was concentrated to afford a pale yellow solid. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **77** (44 mg, 75%) as a colourless gum. $[\alpha]_D^{20}$ - 201 (*c* 1.95, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 1.82-1.83 (3H, m, C*H*$_3$), 2.33 (1H, ddd, *J* = 13.2, 8.0, 2.1 Hz, ArCH$_2$C*H*H), 2.36-2.45 (1H, m, ArCH$_2$CH*H*), 2.57 (1H, ddd, *J* = 15.8, 8.5, 2.0 Hz, ArC*H*H), 2.74-2.85 (1H, m, ArCH*H*), 4.80 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.16 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.21 (1H, apparent t, *J* = 1.5 Hz, C*H*H=C), 6.29-6.31 (1H, m, CH*H*=C), 6.82 (1H, dd, *J* = 7.5, 0.8 Hz, Ar*H*), 6.99 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.01-7.19 (7H, m, Ar*H*), 7.27-7.33 (4H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 18.51, 28.63, 39.24, 85.85, 86.59, 118.24, 122.07, 122.91, 126.70, 127.02, 127.24, 128.44, 128.50, 128.69, 130.98, 133.74, 136.59, 136.90, 137.87, 147.11, 148.39, 165.34; **IR** (film) 1739, 1637, 1617, 1590, 1497, 1474, 1454, 1316, 1235, 1177, 1128, 1045, 944, 749 cm^{-1}, **MS** (CI) *m/z* 413 (M+H), 395, 306; **Anal.** Calcd for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C, 78.41; H, 5.77.

***7-(3-Methylbut-2-enyloxy)indan-1-one(1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (78).**

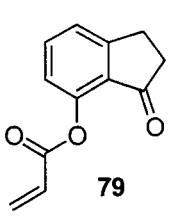


78

A stirred suspension of the phenol **68** (461 mg, 1.34 mmol), 4-bromo-2-methyl-2-butene (0.46 mL, 4.0 mmol) and potassium carbonate (1.88 g, 13.6 mmol) in *N*,*N*-dimethylformamide (5 mL) was heated at 55 °C for 3 h. The reaction mixture was then allowed to cool to room temperature and was diluted with ether (50 mL) and washed with water (5 × 5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow gum (512 mg). Purification by flash

chromatography using hexanes:ether (10:1) as the eluant afforded the *title compound* **78** (429 mg, 78%) as a white solid. **Mp** 93-95 °C, hexanes:ether; **^{1}H NMR** (C_6D_6) δ 1.40 (3H, s, C*H*$_3$), 1.48 (3H, s, C*H*$_3$), 2.51 (1H, ddd, *J* = 13.2, 8.2, 2.4 Hz, ArCH$_2$C*H*H), 2.64 (1H, ddd, *J* = 16.7, 13.3, 7.9 Hz, ArCH$_2$CH*H*), 2.75 (1H, ddd, *J* = 15.7, 8.8, 2.6 Hz, ArC*H*H), 2.85-2.95 (1H, m, ArCH*H*), 4.29 (1H, dd, *J* = 10.9, 6.7 Hz, C*H*HO), 4.42 (1H, dd, *J* = 10.9, 6.7 Hz, C*H*HO), 4.84 (1H, d, *J* = 8.6 Hz, C*H*Ph), 5.45-5.52 (1H, m, C*H*=C), 5.64 (1H, d, *J* = 8.6 Hz, C*H*Ph), 6.68 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.85 (1H, d, *J* = 7.2 Hz, Ar*H*), 7.12-7.30 (7H, m, Ar*H*), 7.46 (2H, dd, *J* = 8.4, 1.4 Hz, Ar*H*), 7.54 (2H, dd, *J* = 8.0, 1.6 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 17.89, 25.60, 28.80, 39.57, 64.71, 86.58, 86.85, 110.19, 117.63, 119.21, 120.49, 127.13, 128.57, 130.54, 131.24, 137.51, 137.83, 138.58, 146.89, 156.59; **IR** (ef) 1594, 1496, 1479, 1454, 1315, 1282, 1264, 1126, 1057, 1025, 746 cm^{-1}, **MS** (MALDI) *m/z* 435 (M+Na); **Anal.** Calcd for $C_{28}H_{28}O_3$: C, 81.52; H, 6.84. Found: C, 81.81; H, 6.97.

***7-Acryloyloxyindan-1-one* (79).**

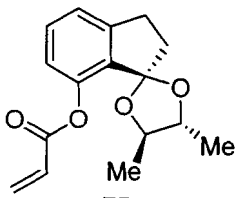


79

A stirred solution of 7-hydroxyindan-1-one **46** (1.00 g, 6.75 mmol), triethylamine (1.0 mL, 7.2 mmol) and acryloyl chloride (0.60 mL, 7.4 mmol) in dichloromethane (15 mL) at 0 °C was allowed to warm slowly to room temperature over 12 h. The reaction mixture was then diluted with ether (50 mL) and washed with saturated aqueous solutions of ammonium chloride (2 × 10 mL) and sodium bicarbonate (2 × 10 mL), brine (10 mL) and water (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a white solid. Purification by flash chromatography using hexanes:ether (3:2) as the eluant afforded the *title compound* **79** (1.27 g, 93%) as a white crystalline solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from hexanes:ether by slow evaporation. **Mp** 83-84 °C, hexanes:ether; **^{1}H NMR** ($CDCl_3$) δ 2.67 (2H, m, ArC*H*$_2$), 3.14 (2H, m, C*H*$_2$C=O), 6.06 (1H, dd, *J* =

10.4, 1.2 Hz, CH=C*H*H), 6.40 (1H, dd, J = 17.4, 10.4 Hz, C*H*=CH_2), 6.65 (1H, dd, J = 17.1, 1.2 Hz, CH=CH*H*), 7.03 (1H, d, J = 7.9 Hz, Ar*H*), 7.35 (1H, d, J = 7.6, Ar*H*), 7.59 (1H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 25.66, 36.77, 120.72, 124.54, 127.62, 128.75, 133.05, 135.88, 147.55, 157.02, 164.16, 203.59; **IR** (ef) 1737, 1699, 1607, 1150 cm^{-1}; **MS** (CI) *m/z* 203 (M+H), 149; **Anal.** Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.26; H, 4.95.

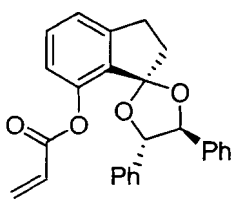
***7-Acryloyloxyindan-1-one (2R,3R)-2,3-butanediol acetal* (75).**



75

A stirred solution of the ketoester **79** (104 mg, 0.513 mmol), diol **52** (R = Me, 56 μL, 0.60 mmol) and *p*-toluenesulfonic acid monohydrate (8.6 mg, 0.045 mmol) in benzene (2 mL) was heated at reflux for 4 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.1 g) was added. After 10 min, direct purification of the reaction mixture by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **75** (131 mg, 93%) as a colourless oil which solidified on standing. The ^{1}H NMR spectral data were consistent with that reported above.

***7-Acryloyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (76).**

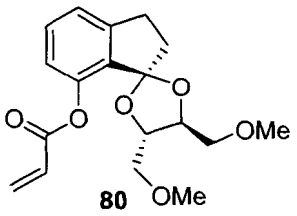


76

A stirred solution of the ketoester **79** (1.03 g, 5.10 mmol), diol **29** (R = Ph, 1.33 g, 6.22 mmol) and pyridinium *p*-toluenesulfonate (130 mg, 0.52 mmol) in benzene (15 mL) was heated at reflux for 2 days with azeotropic removal of water. *p*-Toluenesulfonic acid monohydrate (46 mg, 0.24 mmol) was then added and the mixture was heated at reflux with azeotropic removal of water for an additional 2 days. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.2 g) was added. After 15 min, the reaction mixture was filtered and concentrated to afford a yellow gum. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the

title compound **76** (1.88 g, 92%) as a colourless gum which solidified on standing. The ^{1}H NMR spectral data were consistent with that reported above.

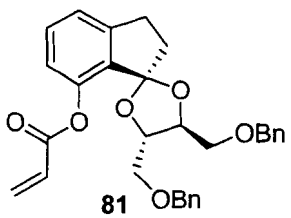
***7-Acryloyloxyindan-1-one (2S,3S)-1,4-dimethoxy-2,3-butanediol acetal* (80).**



80

A stirred solution of the ketoester **79** (101 mg, 0.500 mmol), diol **53** (R = CH_2OMe, 91 mg, 0.60 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol) in benzene (2 mL) was heated at reflux for 12 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.1 g) was added. After 10 min, the reaction mixture was filtered and concentrated to afford a light brown oil (187 mg). Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **80** (137 mg, 82%) as a white solid. **Mp** 77-78 °C, hexanes:ether; $[\alpha]_D^{20}$ - 15.8 (*c* 1.11, chloroform); **^{1}H NMR** (C_6D_6) δ 2.13-2.29 (2H, m, $ArCH_2CH_2$), 2.53 (1H, ddd, *J* = 15.8, 8.1, 3.3 Hz, ArC*H*H), 2.61-2.71 (1H, m, ArCH*H*), 3.11 (3H, s, CH_3), 3.13 (3H, s, CH_3), 3.43 (2H, ddd, *J* = 18.0, 10.3, 4.0 Hz, CH_2OCH_3), 3.63 (2H, ddd, *J* = 14.7, 10.7, 4.4 Hz, CH_2OCH_3), 4.13-4.19 (1H, m, C*H*CH_2OMe), 4.20-4.26 (1H, m, C*H*CH_2OMe), 5.37 (1H, dd, *J* = 10.3, 1.5 Hz, CH=C*H*H), 6.22 (1H, dd, *J* = 17.3, 10.3 Hz, C*H*=CH_2), 6.52 (1H, dd, *J* = 17.3, 1.5 Hz, CH=CH*H*), 6.78 (1H, dd, *J* = 7.4, 1.1 Hz, Ar*H*), 7.00 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.06 (1H, dd, *J* = 8.1, 7.4 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 28.61, 39.13, 59.18; 72.90, 73.34, 78.31, 78.90, 118.25, 121.77, 122.83, 128.71, 130.83, 131.78, 133.36, 146.84, 148.06, 163.80; **IR** (ef) 1746, 1617, 1403, 1226, 1153, 1105 cm^{-1}; **MS** (CI) *m/z* 335 (M+H); **Anal.** Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.40; H, 6.53.

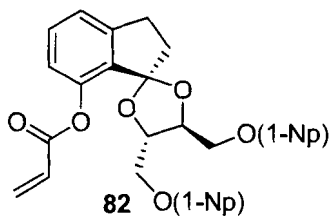
7-Acryloyloxyindan-1-one (2S,3S)-1,4-dibenzyloxy-2,3-butanediol acetal **(81).**



81

A stirred solution of the ketoester **79** (105 mg, 0.517 mmol), diol **54** (R = CH_2OBn, 188 mg, 0.620 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.052 mmol) in benzene (2 mL) was heated at reflux for 12 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.1 g) was added. After 10 min, the reaction mixture was filtered and concentrated to afford an orange gum. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **81** (201 mg, 80%) as a yellow oil. $[\alpha]_D^{20}$ - 9.3 (*c* 1.22, chloroform); **^{1}H NMR** (C_6D_6) δ 2.13-2.30 (2H, m, $ArCH_2CH_2$), 2.52 (1H, ddd, *J* = 15.8, 8.5, 3.3 Hz, ArC*H*H), 2.61-2.70 (1H, m, ArCH*H*), 3.58 (2H, ddd, *J* = 19.8, 10.3, 3.7 Hz, $CHCH_2O$), 3.71 (2H, d, *J* = 4.0 Hz, $CHCH_2O$), 4.24-4.33 (2H, m, C*H*CH_2OBn), 4.34-4.41 (4H, m, 2 × $PhCH_2$), 5.28 (1H, dd, *J* = 10.7, 1.5 Hz, CH=C*H*H), 6.12 (1H, dd, *J* = 17.3, 10.7 Hz, C*H*=CH_2), 6.39 (1H, dd, *J* = 17.3, 1.5 Hz, CH=CH*H*), 6.72 (1H, d, *J* = 7.3 Hz, Ar*H*), 6.92-7.09 (3H, m, Ar*H*), 7.09-7.19 (4H, m, Ar*H*), 7.20-7.29 (5H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 28.61, 39.09, 70.50, 70.79, 73.54, 73.58, 78.19, 79.16, 118.29, 121.77, 122.83, 128.51, 128.54, 128.59, 130.86, 131.87, 133.29, 138.87, 146.85, 148.05, 163.81; **IR** (ef) 1746, 1617, 1590, 1473, 1403, 1314, 1152, 739 cm^{-1}; **MS** (CI) *m/z* 487 (M+H), 433; **Anal.** Calcd for $C_{30}H_{30}O_6$: C, 74.06; H, 6.21. Found: C, 73.81; H, 6.19.

7-Acryloyloxyindan-1-one (2S,3S)-1,4-bis(1-naphthyloxy)-2,3-butanediol acetal **(82).**

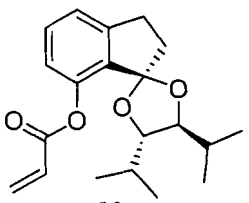


82

A stirred solution of the ketoester **79** (186 mg, 0.919 mmol), diol **55** [R = CH_2O(1-Np), 398 mg, 1.06 mmol) and *p*-toluenesulfonic acid monohydrate (15 mg, 0.080 mmol) in benzene (7 mL) was heated at reflux for 40 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room

temperature and potassium carbonate (0.1 g) was added. After 15 min, the reaction mixture was filtered and concentrated to afford an orange-red gum. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **82** (281 mg, 55%) as a pale pink foam/solid. **Mp** 50-70 °C, hexanes:ether; $[\alpha]_D^{20}$ - 13 (*c* 0.50, chloroform); **^{1}H NMR** (C_6D_6) δ 2.28-2.42 (2H, m, $ArCH_2CH_2$), 2.55 (1H, ddd, *J* = 16.2, 7.9, 4.3 Hz, ArC*H*H), 2.67-2.77 (1H, m, ArCH*H*), 4.17-4.38 (4H, m, 2 × CH_2O), 4.65-4.77 (2H, m, 2 × $CHCH_2O$), 5.19 (1H, dd, *J* = 10.4, 1.2 Hz, CH=C*H*H), 6.22 (1H, dd, *J* = 10.4, 7.4 Hz, $CH=CH_2$), 6.47 (1H, dd, *J* = 17.4, 1.5 Hz, CH=CH*H*), 6.68 (2H, m, Ar*H*), 6.81 (1H, dd, *J* = 7.3, 0.9 Hz, Ar*H*), 7.01 (1H, dd, *J* = 7.9, 0.9 Hz, Ar*H*), 7.08 (1H, m, Ar*H*), 7.22-7.44 (8H, m, Ar*H*), 7.68 (2H, m, Ar*H*), 8.50-8.64 (2H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 28.60, 39.31, 68.38, 68.69, 76.78, 79.02, 105.52, 105.57, 118.92, 121.26, 121.33, 121.87, 122.39, 122.46, 123.02, 125.66, 125.71, 126.02, 126.22, 126.32, 126.81, 131.10, 132.32, 133.04, 135.11, 135.18, 146.89, 147.90, 154.71, 154.81, 163.88; **IR** (ef) 1598, 1579, 1509, 1472, 1396, 1318, 1267, 1240, 1178, 1157, 1121, 1103, 790, 771 cm^{-1}; **MS** (MALDI) *m/z* 596 (M+K), 581 (M+Na), 558 (M); **Anal.** Calcd for $C_{36}H_{30}O_6$: C, 77.40; H, 5.41. Found: C, 77.26; H, 5.46.

***7-Acryloyloxyindan-1-one (1S,2S)-1,2-disopropyl-1,2-ethanediol acetal* (83).**



83

A stirred solution of the ketoester **79** (132 mg, 0.653 mmol), diol **56** (R = *i*-Pr)[42*] (109.4 mg, 0.748 mmol) and *p*-toluenesulfonic acid monohydrate (6.9 mg, 0.036 mmol) in benzene (6 mL) was heated at reflux for 20 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.2 g) was added. After 30 min, the reaction mixture was filtered and concentrated to afford a light brown oil (231 mg). Purification by flash chromatography using hexanes:ether (8:1)

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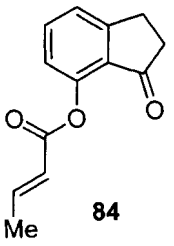
* (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol **56** was prepared in our laboratory by Mr. Michael P. A. Lyle.

as the eluant afforded the *title compound* **83** (173 mg, 80%) as a white crystalline solid. **Mp** 83-84 °C, hexanes:ether; $[\alpha]_D^{20}$ - 76 (*c* 0.78, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 0.94 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 0.95 (3H, d, *J* = 6.7 Hz, C*H*$_3$CH), 1.01 (3H, d, *J* = 6.7 Hz, C*H*$_3$CH), 1.04 (3H, d, *J* = 6.7 Hz, C*H*$_3$CH), 1.60-1.69 (1H, m, C*H*CH$_3$), 1.76-1.86 (1H, m, C*H*CH$_3$), 2.08 (2H, dd, *J* = 5.5, 5.2 Hz, ArCH$_2$C*H*$_2$), 2.47 (1H, dt, *J* = 15.9, 5.5 Hz, ArC*H*H), 2.66-2.76 (1H, m, ArCH*H*), 3.56 (1H, dd, *J* = 8.2, 4.9 Hz, C*H*O), 3.79 (1H, dd, *J* = 8.2, 4.6 Hz, C*H*O), 5.36 (1H, dd, *J* = 10.4, 1.5 Hz, CH=C*H*H), 6.21 (1H, dd, *J* = 17.4, 10.1 Hz, C*H*=CHH), 6.46 (1H, dd, *J* = 17.4, 1.5 Hz, CH=CH*H*), 6.74 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.91 (1H, d, *J* = 8.2 Hz, Ar*H*), 6.97-7.02 (1H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 17.35, 17.70, 20.11, 20.38, 28.62, 30.53, 31.04, 39.31, 83.46, 84.36, 116.67, 121.77, 122.80, 128.75, 130.55, 131.52, 134.07, 146.76, 147.95, 163.80; **IR** (ef) 1750, 1617, 1591, 1471, 1403, 1316, 1254, 1232, 1225, 1153, 1048, 985, 799, 755 cm^{-1}; **MS** (C.I) *m/z* 331 (M+H), 203, 183; **Anal.** Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.41; H, 7.99.

***7-(E)-Crotonyloxyindan-1-one* (84).**

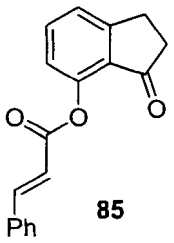


84

A solution of 7-hydroxyindan-1-one **46** (254 mg, 1.72 mmol), triethylamine (0.35 mL, 2.5 mmol) and (*E*)-crotonoyl chloride (195 μL, 2.03 mmol) in dichloromethane (3 mL) at 0 °C was stirred for 45 min. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride (20 mL) and extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow solid. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **84** (335 mg, 90%) as a white crystalline solid. **Mp** 100-102 °C, hexanes:ether; **^{1}H NMR** ($CDCl_3$) δ 1.88 (3H, dd, *J* = 7.0, 1.8 Hz, C*H*$_3$), 2.55 (2H, m, ArC*H*$_2$), 3.02 (2H, m, ArCH$_2$C*H*$_2$), 6.02 (1H, dq, *J* = 15.6, 1.8 Hz, C*H*=CHCH$_3$), 6.90 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.08-7.18 (1H, m, CH=C*H*CH$_3$), 7.22 (1H, apparent d, *J* = 7.6 Hz, Ar*H*), 7.15 (1H, m,

Ar*H*); ^{13}**C NMR** ($CDCl_3$) δ 18.40, 25.63, 36.76, 120.83, 121.80, 124.32, 128.88, 135.81, 147.51, 147.80, 156.96, 164.40, 203.68; **IR** (ef) 2922, 1740, 1711, 1609, 1095 cm^{-1}; **MS** (CI) *m/z* 217 (M+H); **Anal.** Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.23; H, 5.51.

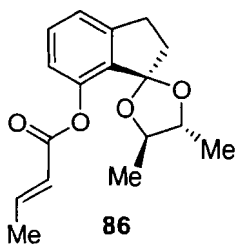
***7-(E)-Cinnamoyloxyindan-1-one* (85).**



85

A stirred solution of 7-hydroxyindan-1-one **46** (100 mg, 0.678 mmol), triethylamine (0.20 mL, 1.4 mmol) and (*E*)-cinnamoyl chloride (159 mg, 0.956 mmol) in benzene (4 mL) was heated at reflux for 2 h. The reaction mixture was then allowed to cool to room temperature and was poured into a saturated aqueous solution of ammonium chloride and extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow oil which solidified on standing. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **85** (164 mg, 87%) as a white crystalline solid. **Mp** 100-102 °C, hexanes:ether; ^{1}**H NMR** (C_6D_6) δ 2.15 (2H, m, ArCH_2), 2.33 (2H, m, CH_2C=O), 6.82 (1H, dd, *J* = 7.6, 0.9 Hz, Ar*H*), 6.91 (1H, d, *J* = 16.2 Hz, C*H*=CHC=O), 6.98-7.10 (4H, m, Ar*H*), 7.14-7.21 (3H, m, Ar*H*), 8.16 (1H, d, *J* = 15.9 Hz, CH=C*H*C=O); ^{13}**C NMR** ($CDCl_3$) δ 25.54, 36.66, 116.93, 120.70, 124.28, 128.39, 128.75, 128.87, 130.57, 134.30, 135.71, 146.95, 147.68, 156.85, 164.82, 203.51; **IR** (ef) 1773, 1712, 1633, 1611, 1449, 1133, 1072 cm^{-1}; **MS** (CI) *m/z* 279 (M+H), 131; **Anal.** Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.44; H, 5.07.

***7-(E)-Crotonoyloxyindan-1-one (2R,3R)-2,3-butanediol acetal* (86).**

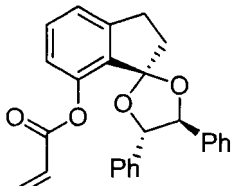


86

A stirred solution of the ketoester **84** (100 mg, 0.465 mmol), (2*R*,3*R*)-2,3-butanediol **52** (64 μL, 0.69 mmol) and *p*-toluenesulfonic acid monohydrate (15 mg, 0.076 mmol) in benzene (2 mL) was heated at reflux for 8 h with azeotropic removal of

water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.1 g) was added. After 10 min, direct purification of the reaction mixture by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **86** (131 mg, 90%) as a colourless oil which solidified on standing. **Mp** 67-68 °C, hexanes:ether; $[\alpha]_D^{20}$ - 7.8 (*c* 1.28, chloroform); **^{1}H NMR** (C_6D_6) δ 1.09 (3H, d, *J* = 6.2 Hz, C*H*$_3$CH) 1.15 (3H, d, *J* = 5.9 Hz, C*H*$_3$CH), 1.35 (3H, dd, *J* = 7.0, 1.8 Hz, C*H*$_3$CH=CH), 2.15-2.31 (2H, m, ArCH$_2$C*H*$_2$), 2.60 (1H, ddd, *J* = 15.8, 8.1, 4.0 Hz, ArC*H*H), 2.64-2.73 (1H, m, ArCH*H*), 3.50 (1H, dq, *J* = 8.4, 5.9 Hz, C*H*CH$_3$), 3.93 (1H, dq, *J* = 8.4, 5.9 Hz, C*H*CH$_3$), 6.00 (1H, dq, *J* = 15.4, 1.8 Hz, C*H*=CHCH$_3$), 6.76 (1H, apparent d, *J* = 6.6 Hz, CH=C*H*CH$_3$), 6.99-7.09 (3H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 16.01, 17.22, 17.61, 28.58, 39.58, 78.98, 79.24, 116.76, 121.92, 122.64, 122.75, 130.50, 134.31, 146.12, 146.59, 148.06, 163.96; **IR** (ef) 1742, 1656, 1615, 1590, 1473, 1443, 1307, 1225, 1154, 1101, 1085, 998, 971 cm^{-1}; **MS** (CI) *m/z* 288 (M+H), 285, 217; **Anal.** Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.66, H 7.10.

***7-(E)-Crotonoyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (87).**

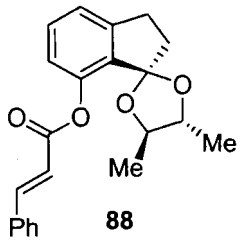


87

A stirred solution of the ketoester **84** (176 mg, 0.816 mmol), (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29** (312 mg, 1.45 mmol) and pyridinium *p*-toluenesulfonate (44 mg, 0.17 mmol) in benzene (5 mL) was heated at reflux with azeotropic removal of water for 5 days. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.4 g) was added. After 30 min, the reaction mixture was filtered and concentrated to afford a yellow solid. Purification by flash chromatography using hexanes:ethyl acetate (6:1) as the eluant afforded the *title compound* **87** (302 mg, 90%) as a white crystalline solid. **Mp** 63-65 °C, hexanes:ethyl acetate; $[\alpha]_D^{20}$ - 169 (*c* 1.11, chloroform); **^{1}H NMR** (C_6D_6) δ 1.19 (3H, dd, *J* = 6.7, 0.9 Hz, C*H*$_3$), 2.29-2.48 (2H, m, ArCH$_2$C*H*$_2$), 2.60 (1H, ddd, *J* = 15.6, 8.2, 1.8 Hz, ArC*H*H), 2.74-2.86 (1H, m, ArCH*H*),

4.81 (1H, d, J = 8.5 Hz, C*H*Ph), 5.21 (1H, d, J = 8.5 Hz, C*H*Ph), 5.93 (1H, apparent dd, J = 15.6, 1.5 Hz, C*H*=CHCH$_3$), 6.84 (1H, apparent d, J = 6.4 Hz, Ar*H*), 6.95 (1H, dd, J = 15.6, 7.0 Hz, CH=C*H*CH$_3$), 6.99-7.18 (8H, m, Ar*H*), 7.29 (2H, d, J = 7.0 Hz, Ar*H*), 7.37 (2H, d, J = 7.0 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 17.53, 28.65, 39.29, 85.97, 86.83, 118.39, 122.13, 122.46, 122.79, 127.19, 127.28, 128.46, 128.54, 128.68, 130.93, 133.77, 136.79, 137.93, 146.82, 147.00, 148.18, 164.12; **IR** (ef) 1742, 1655, 1473, 1314, 1222, 1151, 1099, 1112, 1047, 750 cm^{-1}; **MS** (MALDI) *m/z* 436 (M+Na); **Anal.** Calcd. for $C_{32}H_{26}O_4$: C, 78.62; H, 5.86. Found: C, 78.50; H, 6.02.

***7-(E)-Cinnamoyloxyindan-1-one (2R,3R)-2,3-butanediol acetal* (88).**

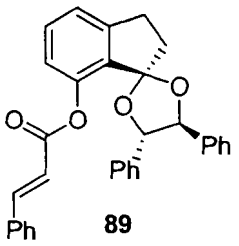


88

A stirred solution of the ketoester **85** (611 mg, 2.20 mmol), (2*R*,3*R*)-2,3-butanediol **52** (294 μL, 3.22 mmol) and *p*-toluenesulfonic acid monohydrate (88 mg, 0.076 mmol) in benzene (15 mL) was heated at reflux for 8 h with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (1.0 g) was added. After 40 min, the reaction mixture was filtered and concentrated to a afford a brown solid. Purification by flash chromatography using hexanes:ethyl acetate (7:1 to 5:1) as the eluant afforded the *title compound* **88** (736 mg, 96%) as a pale yellow crystalline solid. **Mp** 132-133 °C, hexanes:ethyl acetate; $[\alpha]_D^{20}$ - 15 (0.58, chloroform); **^{1}H NMR** (C_6D_6) δ 1.03 (3H, d, J = 6.1 Hz, C*H*$_3$CH), 1.12 (3H, d, J = 5.8 Hz, C*H*$_3$CH), 2.19 (1H, ddd, J = 13.1, 8.2, 4.3 Hz, ArCH$_2$C*H*H), 2.27 (1H, ddd, J = 15.2, 8.2, 7.0 Hz, ArCH$_2$CH*H*), 2.62 (1H, ddd, J = 15.9, 8.2, 4.3 Hz, ArC*H*H), 2.70 (1H, m, ArCH*H*), 3.48 (1H, dq, J = 8.5, 6.1 Hz, C*H*CH$_3$), 3.97 (1H, dq, J = 8.5, 6.1 Hz, C*H*CH$_3$), 6.69 (1H, d, J = 15.9 Hz, C*H*=CHPh), 6.77-6.81 (1H, m, Ar*H*), 6.94-6.99 (3H, m, Ar*H*), 7.04-7.10 (2H, m, Ar*H*), 7.13-7.17 (2H, m, Ar*H*), 7.96 (1H, d, J = 16.2 Hz, CH=C*H*Ph); **^{13}C NMR** (C_6D_6) δ 16.09, 17.27, 28.65, 39.61, 79.08, 79.38, 116.83, 118.30, 121.95, 122.79, 128.34, 129.08, 130.46, 130.60, 134.36, 134.71, 146.22, 146.72, 148.20, 164.55; **IR** (ef)

1738, 1637, 1614, 1588, 1471, 1449, 1309, 1234, 1142, 995, 763 cm^{-1}; **MS** (CI) *m/z* 351 (M+H), 203, 149, 131; **Anal.** Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.21; H, 6.28.

***7-(E)-Cinnamoyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (89).**

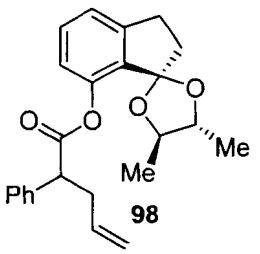


89

A stirred solution of the ketoester **85** (460 mg, 1.65 mmol), (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29** (533 mg, 2.49 mmol) and pyridinium *p*-toluenesulfonate (85 mg, 0.34 mmol) in benzene (5 mL) was heated at reflux for 4 days with azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (0.6 g) was added. After 30 min, the reaction mixture was filtered and concentrated to afford a yellow solid. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **89** (772 mg, 99%) as a white crystalline solid. **Mp** 95-97 °C, hexanes:ether; $[\alpha]_D^{20}$ - 125 (*c* 0.82, chloroform); **^{1}H NMR** (C_6D_6) δ 2.33-2.51 (2H, m, $ArCH_2CH_2$), 2.62 (1H, ddd, *J* = 15.9, 8.5, 2.1 Hz, ArC*H*H), 2.83 (1H, m, ArCH*H*), 4.83 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.30 (1H, d, *J* = 8.5 Hz, C*H*Ph), 6.61 (1H, d, *J* = 15.9 Hz, C*H*=CHPh), 6.85-7.10 (12H, m, Ar*H*), 7.13-7.24 (4H, m, Ar*H*), 7.28 (2H, d, *J* = 7.3 Hz, Ar*H*), 7.87 (1H, d, *J* = 16.2 Hz, CH=C*H*Ph); **^{13}C NMR** (C_6D_6) δ 28.68, 39.33, 85.99, 86.98, 118.08, 122.15, 122.89, 127.09, 127.38, 128.56, 128.62, 128.91, 130.40, 131.01, 133.84, 134.50, 136.83, 137.72, 146.57, 147.08, 148.27, 164.62; **IR** (ef) 2924, 2853, 1735, 1635, 1469, 1309, 1222, 1135, 1095; **MS** (MALDI) *m/z* 497 (M+Na); **Anal.** Calcd for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 80.92; H, 5.54.

7.2.6 Asymmetric Enolate Alkylation Reactions

***7-(2-Phenyl-3-butenoyloxy)indan-1-one (2R,3R)-2,3-butanediol acetal* (98).**

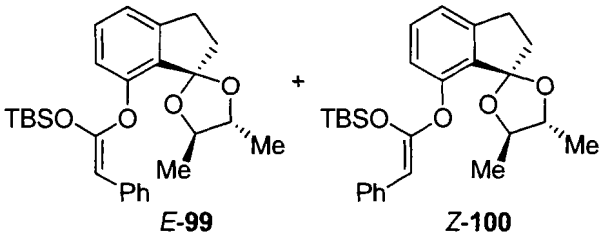


98

A solution of lithium *N,N*-diisopropylamide was prepared by adding *n*-butyllithium (2.5 M in hexanes, 0.30 mL, 0.75 mmol) to *N,N*-diisopropylamine (0.13 mL, 0.93 mmol) in tetrahydrofuran (5 mL) at 0 °C and stirring the resultant mixture for 30 min. To the stirred solution of lithium *N,N*-diisopropylamide at -78 °C was added a solution of the phenylacetate **73** (201 mg, 0.594 mmol) in tetrahydrofuran (6 mL) over 5 min. After 30 min, allyl iodide (0.27 mL, 3.0 mmol) was added. After 1 h 45 min, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (2 × 25 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford pale yellow oil (220 mg). Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **98** (170 mg, 76%) as a colourless oil. The diastereomeric ratio of the products was 53:47 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. $[\alpha]_D^{20}$ + 31 (*c* 1.44, tetrahydrofuran); **^{1}H NMR** (C_6D_6, mixture of diastereomers) δ 0.83 (3H, d, *J* = 5.6 Hz, C*H*$_3$), 0.95 (3H, d, *J* = 6.0 Hz, C*H*$_3$), 1.12 (3H, d, *J* = 6.0 Hz, C*H*$_3$), 1.13 (3H, d, *J* = 6.0 Hz, C*H*$_3$), 2.08-2.26 (4H, m, ArCH$_2$C*H*$_2$), 2.44-2.59 (2H, m, 2 × ArC*H*H and 2 × C*H*HCH=CH), 2.61-2.76 (2H, m, 2 × ArCH*H*), 2.90-3.07 (2H, m, 2 × CH*H*CH=CH), 3.36-3.47 (3H, m, 3 × C*H*CH$_3$), 3.75 (1H, dq, *J* = 8.3, 6.0 Hz, C*H*CH$_3$), 3.84-3.91 (2H, m, 2 × C*H*C=O), 4.97 (2H, apparent d, *J* = 10.2 Hz, 2 × C*H*H=CH), 5.08 (2H, apparent d, *J* = 17.1 Hz, 2 × CH*H*=CH), 5.72-5.88 (2H, m, 2 × C*H*=CH$_2$), 6.71 (2H, apparent t, *J* = 6.4 Hz, Ar*H*), 6.85 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.91-7.13 (9H, m, Ar*H*), 7.32-7.36 (4H, m, Ar*H*); **^{13}C NMR** (C_6D_6, mixture of diastereomers) δ 15.81, 16.29, 17.27, 28.54, 38.92, 39.42, 39.48, 39.62, 51.97, 52.15, 78.59, 78.82, 79.06, 79.12, 116.57, 116.61, 117.32,

117.43, 121.40, 121.53, 122.66, 127.59, 127.70, 128.46, 129.00, 129.04, 130.38, 133.93, 135.51, 135.67, 138.69, 138.82, 146.62, 147.98, 148.17, 146.66, 171.48; **IR** (neat) 1758, 1617, 1589, 1495, 1473, 1454, 1315, 1131, 1046, 749 cm^{-1}; **MS** (MALDI) *m/z* 525 (M+Na); **Anal.** Calcd for $C_{34}H_{30}O_4$: C, 81.25; H, 6.02. Found: C, 81.60; H, 6.14.

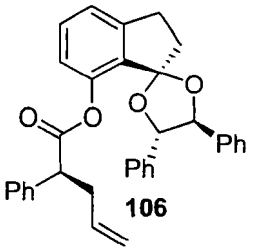
(E)- and ***(Z)-t-Butyldimethylsilylketene acetals of 7-(2-Phenyl-3-butenoyloxy)indan-1-one (2R,3R)-2,3-butanediol acetal* (*E*-99** and ***Z*-100).**



E-**99** *Z*-**100**

To a stirred solution of lithium *N,N*-diisopropylamide [prepared from *n*-butyllithium (2.5 M in hexanes, 0.23 mL, 0.58 mmol) and *N,N*-diisopropylamine (94 μL, 0.67 mmol)] in tetrahydrofuran (3 mL) at -78 °C was added a solution of the phenylacetate **73** (149 mg, 0.440 mmol) in tetrahydrofuran (3 mL) over 5 min. After 30 min, a solution of *t*-butyldimethylsilyl chloride (98 mg, 0.65 mmol) in tetrahydrofuran (1 mL) was added over 3 min. After 2.5 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (5 mL) and allowed to warm to room temperature. The reaction mixture was then diluted with pentane (40 mL) and the organic layer was washed with a saturated aqueous solution of sodium bicarbonate (3 × 5 mL) and water (2 × 5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford the *title compounds E*-**99** and *Z*-**100** (213 mg, ~ 100%) as a yellow oil. The diastereomeric ratio of the products was 68:32 (*E*-**99**:*Z*-**100**) as determined by analysis of the ^1H NMR spectrum of the crude reaction product. The stereochemistry of the geometrical isomers was determined by a NOESY experiment of the crude ketene acetal mixture. Attempted purification by flash chromatography on silica gel or on alumina (neutral, Brockman activity I, 60-325 mesh) using hexanes:ether (10:1) as the eluant in both cases resulted in decomposition of the crude reaction product.

7-((2S)-2-Phenyl-3-butenoyloxy)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal (**106** and **107**) - *deprotonation with lithium N,N-diisopropylamide.*

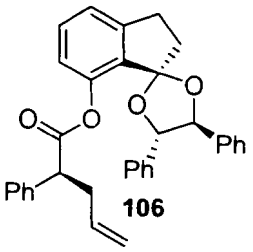


106

To a stirred solution of lithium *N,N*-diisopropylamide [prepared from *n*-butyllithium (2.5 M in hexanes, 65 μL, 0.16 mmol) and *N,N*-diisopropylamine (26 μL, 0.19 mmol)] in tetrahydrofuran (2 mL) at -78 °C was added a solution of the phenylacetate **74** (51 mg, 0.11 mmol) in tetrahydrofuran (3 mL) and hexamethylphosphoramide (0.19 mL) over 5 min. After 1 h, allyl iodide (100 μL, 1.09 mmol) was added and the reaction mixture was allowed to warm slowly to 0 °C over 16 h. The reaction mixture was then quenched by the addition of a saturated aqueous solution of ammonium chloride (4 mL) and extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine (3 × 2 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow-brown oil (153 mg). Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded an inseparable mixture of the *title compounds* **106** and **107** (46 mg, 83%) as a colourless oil (major diastereomer **106** shown). The diastereomeric ratio of the products was 71:29 (**106**:**107**) as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. $[\alpha]_D^{20}$ - 159 (*c* 1.16, tetrahydrofuran); **^{1}H NMR** (C_6D_6, mixture of diastereomers) δ 2.22-2.42 (4H, m, 2 × $ArCH_2CH_2$), 2.42-2.62 (4H, m, 2 × ArC*H*H and 2 × C*H*HCH=CH), 2.68-2.81 (2H, m, 2 × ArCH*H*), 2.84-2.98 (2H, m, 2 × CH*H*CH=CH_2), 3.87-3.98 (2H, m, 2 × C*H*C=O), 4.61 (1H, d, *J* = 10.1 Hz, C*H*H=CH), 4.73-4.80 (2H, m, 2 × C*H*Ph), 4.80-4.86 (2H, m, C*H*Ph and CH*H*=CH), 4.89 (1H, apparent d, *J* = 10.1 Hz, C*H*H=CH), 5.01 (1H, apparent d, *J* = 17.1 Hz, CH*H*=CH), 5.27 (1H, d, *J* = 8.2 Hz, C*H*Ph), 5.52-5.64 (1H, m, C*H*=CH_2), 5.66-5.78 (1H, m, C*H*=CH_2), 6.77 (2H, apparent d, *J* = 6.7 Hz, 2 × Ar*H*), 6.81-6.91 (4H, m, Ar*H*), 6.95-7.22 (24H, m, Ar*H*), 7.32-7.41 (6H, m, Ar*H*); **^{13}C NMR** (C_6D_6, mixture of diastereomers) δ 28.17, 37.79, 38.63, 38.71, 38.98, 51.65, 51.97, 85.23, 85.57, 85.85, 86.53, 116.98,

117.83, 117.97, 121.07, 121.17, 122.25, 122.33, 126.43, 126.61, 126.74, 127.03, 127.09, 128.20, 128.47, 128.70, 130.41, 132.73, 132.89, 134.62, 134.99, 136.44, 136.58, 137.67, 137.86, 138.35, 146.39, 146.53, 147.66, 148.06, 171.08, 171.30; **IR** (neat) 1758, 1617, 1589, 1495, 1473, 1454, 1315, 1131, 1046, 749 cm^{-1}; **MS** (MALDI) *m/z* 525 (M+Na); **Anal.** Calcd for $C_{34}H_{30}O_4$: C, 81.25; H, 6.02. Found: C, 81.60; H, 6.14.

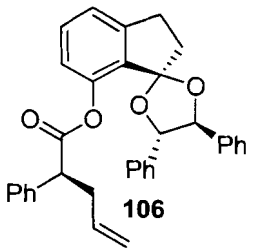
7-((2S)-2-Phenyl-3-butenoyloxy)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal (**106** and **107**) - *deprotonation with lithium hexamethyldisilazide.*



106

A solution of lithium hexamethyldisilazide was prepared by adding *n*-butyllithium (2.5 M in hexanes, 112 μL, 0.28 mmol) to hexamethyldisilazane (68 μL, 0.32 mmol) in tetrahydrofuran (1 mL) at 0 °C and stirring the resultant solution for 30 min. To the stirred solution of lithium hexamethyldisilazide and hexamethylphosphoramide (0.7 mL) at -78 °C was added a solution of the phenylacetate **74** (100 mg, 0.216 mmol) in tetrahydrofuran (2 mL) over 3 min. After 30 min, allyl iodide (100 μL, 1.09 mmol) was added. After an additional 30 min, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (3 × 5 mL) and brine (5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow oil (102 mg). Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded an inseparable mixture of the *title compounds* **106** and **107** (84 mg, 77%) as a colourless oil (major diastereomer **106** shown). The diastereomeric ratio of the products was 70:30 (**106**:**107**) as determined by analysis of the ^1H NMR spectrum of the purified product mixture. The ^1H NMR spectral data were consistent with that reported above.

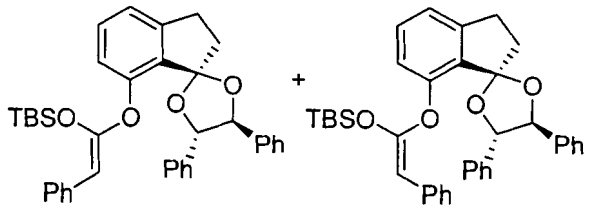
7-((2S)-2-Phenyl-3-butenoyloxy)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal (**106** and **107**) - *deprotonation with potassium triphenylmethanide.*



106

A solution of triphenylmethane (250 mg, 1.02 mmol) and dimethylsulfoxide (20 μL) in 1,2-dimethoxyethane (2 mL) was added to potassium hydride [(169 mg, 1.01 mmol, 24 wt. % dispersion in mineral oil, washed with hexanes (4 mL)] and the resultant mixture was stirred and heated at 40 °C for 15 min. To a stirred solution of the phenylacetate **74** (105 mg, 0.226 mmol) in 1,2-dimethoxyethane (1 mL) at -78 °C was added a portion of the blood red solution of potassium triphenylmethanide was added dropwise until a red colour persisted. After 15 min, allyl iodide (100 μL, 1.09 mmol) was added. After a further 10 min, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (3 mL), diluted with water (15 mL) and extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow solid (205 mg). Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded an inseparable mixture of the *title compounds* **106** and **107** (61 mg, 54%) as a colourless oil (major diastereomer **106** shown). The diastereomeric ratio of the products was 58:42 (**106**:**107**) as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. The ^{1}H NMR spectral data were consistent with that reported above.

(Z)- and ***(E)-t-Butyldimethylsilylketene acetals of 7-(2-Phenyl-3-butenoyloxy)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal*** (*Z*-**109** and *E*-**110**).

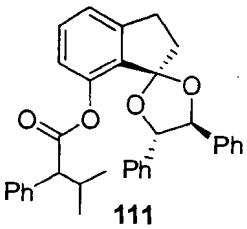


Z-**109** *E*-**110**

To a stirred solution of lithium hexamethyldisilazide [prepared from n-butyllithium (2.5 M in hexanes, 112 μL, 0.280 mmol) and

hexamethyldisilazane (68 μL)] in tetrahydrofuran (1 mL) and hexamethylphosphoramide (0.7 mL) at -78 °C was added a solution of the phenylacetate **74** (98 mg, 0.21 mmol) in tetrahydrofuran (2 mL) over 5 min. After 45 min, a solution of *t*-butyldimethylsilyl chloride (150 mg, 0.994 mmol) in hexane (1 mL) was added over 1 min. After 1.5 h, the reaction mixture was quenched by the addition of a saturated solution of sodium bicarbonate (5 mL) and allowed to warm to room temperature. The reaction mixture was then diluted with pentane (40 mL) and the organic layer was washed with water (5 × 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford an opaque gum (152 mg). Purification of a sample of the crude gum (52 mg) by flash chromatography using hexanes:ether (10:1) as the eluant afforded an inseparable mixture of the *title compounds* *Z*-**109** and *E*-**110** (34 mg, 77%) as a white foam. The diastereomeric ratio of the products was 93:7 (*Z*-**109**:*E*-**110**) as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. The major isomer was determined to be the (*Z*)-isomer by a NOESY experiment on the crude ketene acetal product. **^{1}H NMR** (C_6D_6, major isomer) δ 0.18 (3H, s, C*H*$_3$Si), 0.19 (3H, s, C*H*$_3$Si), 0.92 (9H, s, (C*H*$_3$)$_3$CSi), 2.40-2.48 (1H, ddd, *J* = 13.3, 8.1, 2.2 Hz, ArCH$_2$C*H*H), 2.49-2.58 (1H, m, ArCH$_2$CH*H*), 2.63-2.73 (1H, ddd, *J* = 15.9, 8.7, 2.0 Hz, ArC*H*H), 2.81-2.92 (1H, m, ArCH*H*), 4.83 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.43 (1H, s, C*H*=C), 5.47 (1H, d, *J* = 8.5 Hz, C*H*Ph), 6.78-6.83 (1H, m, Ar*H*), 6.99-7.26 (29H, m, Ar*H*), 7.38 (2H, apparent d, *J* = 8.5 Hz, Ar*H*), 7.50 (2H, apparent d, *J* = 8.4 Hz, Ar*H*), 7.61 (2H, apparent d, *J* = 8.5 Hz, Ar*H*); **^{13}C NMR** (C_6D_6, major isomer) δ -3.92, -3.84, 18.25, 25.43, 25.88, 26.42, 28.74, 39.46, 86.59, 86.70, 91.55, 110.55, 116.63, 118.39, 120.56, 125.36, 127.14, 127.77, 128.02, 128.26, 128.45, 128.62, 128.82, 131.49, 136.25, 136.45, 138.01, 147.38, 153.32, 154.76; **IR** (ef) 1657, 1590, 1472, 1365, 1315, 1256, 1152, 1050, 1024, 746 cm^{-1}; **MS** (MALDI) *m/z* 476. Satisfactory elemental analysis could not be obtained for this reaction product.

***7-(3-Methyl-2-phenylbutanoyloxy)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (111)** - *deprotonation with lithium hexamethyldisilazide.*

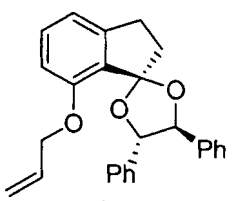


111

To a stirred solution of lithium hexamethyldisilazane solution [prepared from n-butyllithium (2.5 M in hexanes, 112 μL, 0.28 mmol) and hexamethyldisilazane (68 μL, 0.32 mmol)] in tetrahydrofuran (1 mL) and hexamethylphosphoramide (0.7 mL) at -78 °C was added a solution of the phenylacetate **74** (98 mg, 0.21 mmol) in tetrahydrofuran (2 mL) over 5 min. After 30 min, 2-iodopropane (108 μL, 1.08 mmol) was added and, after a further 6 h, the reaction mixture was allowed to warm slowly to room temperature over 10 h. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (5 × 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow oil (114 mg). Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound* **111** (80 mg, 75%) as a colourless oil. The diastereomeric ratio of the products was 53:47 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product (using line fitting analysis). $[\alpha]_D^{20}$ - 152 (*c* 1.39, tetrahydrofuran); **^{1}H NMR** (C_6D_6, 500 MHz, mixture of diastereomers) δ 0.56 (3H, d, *J* = 6.7 Hz, C*H*$_3$), 0.68 (3H, d, *J* = 6.7 Hz, C*H*$_3$), 0.96 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 1.15 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 2.22-2.47 (6H, m), 2.50-2.58 (2H, m, ArC*H*H), 2.68-2.81 (2H, m, ArCH*H*), 3.53 (1H, d, *J* = 10.1 Hz, C*H*C=O), 3.55 (1H, d, *J* = 10.7 Hz, C*H*C=O), 4.70 (1H, d, *J* = 8.4 Hz, C*H*Ph), 4.73 (1H, d, *J* = 8.5 Hz, C*H*Ph), 4.74 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.34 (1H, d, *J* = 8.4 Hz, C*H*Ph), 6.73-6.86 (5H, m, Ar*H*), 6.93-7.00 (2H, m, Ar*H*), 7.05-7.21 (21H, m, Ar*H*), 7.34-7.39 (4H, m, Ar*H*), 7.42-7.46 (4H, m, Ar*H*); **^{13}C NMR** (C_6D_6, 500 MHz, mixture of diastereomers) δ 20.03, 20.34, 21.66, 21.84, 28.57, 28.64, 32.27, 33.98, 39.10, 59.84, 60.44, 85.72, 86.05, 86.12, 87.00, 118.35, 118.40, 121.54, 121.58, 122.65, 122.68,

126.79, 126.84, 127.45, 127.49, 127.54, 127.73, 127.82, 128.21, 128.31, 128.34, 128.38, 128.52, 128.56, 128.59, 128.66, 128.68, 128.70, 128.86, 128.88, 129.06, 130.76, 130.90, 133.22, 133.29, 136.82, 137.26, 137.67, 138.08, 138.56, 146.79, 147.04, 148.06, 148.68, 171.95, 172.21; **IR** (neat) 1756, 1615, 1584, 1472, 1454, 1310, 1225, 1106, 1046, 750 cm^{-1}; **MS** (MALDI) *m/z* 516; **Anal.** Calcd for $C_{34}H_{32}O_4$: C, 80.93; H, 6.39. Found: C, 80.64; H, 6.47.

***7-Allyloxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (113).**

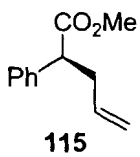


113

To a stirred solution of lithium hexamethyldisilazide [prepared from n-butyllithium (2.5 M in hexanes, 0.18 mL, 0.45 mmol) and hexamethyldisilazane (110 μL, 0.52 mmol)] in tetrahydrofuran (1.5 mL) and hexamethylphosphoramide (1.1 mL) at -78 °C was added a solution of the propanoate **71** (139 mg, 0.346 mmol) in tetrahydrofuran (3 mL) over 5 min. After 30 min, allyl iodide (0.32 mL, 3.5 mmol) was added. After a further 1 h, the reaction mixture poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (5 × 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a colourless oil. Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded the *title compound* **113** (97 mg, 73%) as a colourless oil which solidified on standing. **Mp** 91-92 °C, hexanes:ether; $[\alpha]_D^{20}$ - 191 (*c* 1.38, tetrahydrofuran); **^{1}H NMR** (C_6D_6, 500 MHz) δ 2.50 (1H, ddd, *J* = 13.3, 8.3, 2.6 Hz, $ArCH_2CHH$), 2.59-2.66 (1H, m, $ArCH_2CHH$), 2.75 (1H, ddd, *J* = 15.7, 8.9, 2.5 Hz, ArC*H*H), 2.84-2.92 (1H, m, ArCH*H*), 4.19 (1H, dd, *J* = 12.2, 5.8 Hz, C*H*HO), 4.26 (1H, dd, *J* = 12.2, 5.5 Hz, CH*H*O), 4.86 (1H, d, *J* = 8.5 Hz, C*H*Ph), 4.94 (1H, dd, *J* = 10.4, 1.4 Hz, C*H*H=CH), 5.12 (1H, dd, *J* = 17.2, 1.4 Hz, CH*H*=CH), 5.57 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.86 (1H, ddd, *J* = 22.8, 11.0, 5.7 Hz, C*H*=CH_2), 6.53 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.78 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.07-7.21 (7H, m, Ar*H*), 7.39 (2H, apparent d, *J* = 7.2 Hz,

Ar*H*), 7.48 (2H, apparent d, J = 6.7 Hz, Ar*H*); **^{13}C NMR** (C_6D_6, 500 MHz) δ 28.77, 39.52, 69.13, 86.68, 86.79, 110.40, 117.90, 118.13, 119.18, 127.17, 127.90, 128.31, 128.37, 128.41, 128.60, 130.33, 131.25, 133.67, 137.43, 138.42, 146.96, 156.17; **IR** (ef) 1606, 1594, 1479, 1455, 1316, 1265, 1124, 1059, 933, 747 cm^{-1}; **MS** (CI) *m/z* 385 (M+H), 307, 278. Satisfactory elemental analysis could not be obtained for this reaction product.

***(2S)-Methyl 2-phenyl-4-pentenoate* (115).**

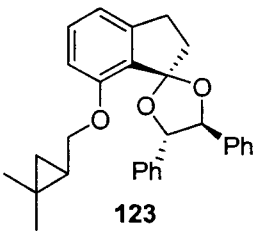


115

A solution of the diastereomeric alkylation products **106** and **107** (74 mg, 0.15 mmol, dr = 70:30) and methanesulfonic acid (0.50 mL, 7.7 mmol) in methanol (5 mL) was stirred at 0 °C for 1.5 h and then heated at reflux for 6 h. The reaction mixture was then allowed to cool to room temperature and was poured into a saturated aqueous solution of sodium bicarbonate (30 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with water (2 × 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a brown wax. Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded the *title compound* **115** (20 mg, 73%) as a light brown oil (major enantiomer shown). $[\alpha]_D^{20}$ + 13.8 (*c* 2.05, chloroform), lit.[62] - 89 (*c* 1.49, chloroform) for the (2*R*)-enantiomer; **^{1}H NMR** ($CDCl_3$) δ 2.42-2.50 (1H, m, C*H*HCH=CH), 2.74-2.82 (1H, m, C*H*HCH=CH_2), 3.59 (1H, d, J = 8.5, 7.1 Hz, C*H*Ph), 3.60 (3H, s, CH_3), 4.95 (1H, d, J = 10.1 Hz, C*H*H=CH), 5.02 (1H, d, J = 17.1, 1.4 Hz, CH*H*=CH), 5.62-5.72 (1H, m, C*H*=CH_2), 7.16-7.32 (5H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 37.73, 51.52, 52.15, 117.13, 127.48, 128.04, 128.78, 135.37, 138.65, 174.02; **IR** (film) 1739, 1455, 1436, 1270, 1230, 1198, 1164, 917 cm^{-1}; **MS** (CI) *m/z* 192 (M+H).

7.2.7 Asymmetric Cyclopropanation Reactions

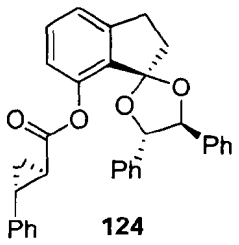
***7-((2,2-Dimethylcyclopropyl)methyloxy)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (123).**



123

To a stirred solution of the ether **78** (60 mg, 0.15 mmol) in 1,2-dichloroethane (4 mL) at -20 °C (dry ice/brine bath) was added diethylzinc (0.77 M in hexanes, 0.95 mL, 0.73 mmol) over 3 min. Diiodomethane (116 μL, 1.44 mmol) was then added over 5 min. After 2 h, the reaction mixture was allowed to warm slowly to room temperature over 3 h. After a further 16 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford a yellow oil (88 mg). Purification by flash chromatography using hexanes:ether (20:1) as the eluant afforded the *title compound* **123** (58 mg) as a colourless oil. The reaction had proceeded to 68% conversion and the diastereomeric ratio of the reaction products was 86:14 as determined by analysis of the ^{1}H NMR spectrum of the purified product. **^{1}H NMR** (C_6D_6, major diastereomer) δ -0.05-0.00 (1H, m, C*H*H), 0.28 (1H, dd, *J* = 8.7, 4.6 Hz, CH*H*), 0.85 (3H, s, CH_3), 0.97 (3H, s, CH_3), 2.46-2.56 (1H, m, ArCH$_2$C*H*H), 2.57-2.68 (1H, m, ArCH$_2$CH*H*), 2.69-2.79 (1H, m, ArC*H*H), 2.85-2.96 (1H, m, ArCH*H*), 3.73 (1H, dd, *J* = 10.0, 6.5 Hz, C*H*HO), 3.83 (1H, dd, *J* = 10.0, 8.3 Hz, CH*H*O), 4.86 (1H, d, *J* = 8.7 Hz, C*H*Ph), 5.69 (1H, d, *J* = 8.7 Hz, C*H*Ph), 6.59 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.77-6.82 (1H, m, Ar*H*), 6.93-7.24 (6H, m, Ar*H*), 7.33-7.36 (1H, m, Ar*H*), 7.44-7.51 (3H, m, Ar*H*), 7.68-7.72 (1H, m, Ar*H*).

7-((1S,2S)-2-Phenylcyclopropanecarboxyl)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal **(124** and **125).**

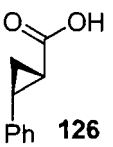


124

To a stirred solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (2.35 g, 11.0 mmol) in ether (15 mL) at 0 °C was added a solution of potassium hydroxide (0.39 g, 7.0 mmol) in ethanol (8 mL). After 5 min, the resultant yellow ethereal solution of diazomethane was distilled over 20 min into a stirred solution of the cinnamate **89** (211 mg, 0.446 mmol) and palladium(II) acetate (1 mg, 0.004 mmol) in dichloromethane (5 mL) at 0 °C (CAUTION: *explosion hazard; use blast shield*). The reaction mixture was then allowed to warm slowly to room temperature. After 16 h, the reaction mixture was purged with nitrogen gas for 5 min, filtered through alumina washing with ether (50 mL) and concentrated to afford an inseparable mixture of the *title compounds* **124** and **125** (208 mg, 95%) as a white solid (major diastereomer **124** shown). The diastereomeric ratio of the products was 57:43 (**124**:**125**) as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. An analytical sample of the product, as colourless crystals that was enriched in the minor diastereomer **125** (dr = 20:80), was prepared by recrystallization from hexanes:ether by slow evaporation. **Mp** 164-165 °C, hexanes:ether; $[\alpha]_D^{20}$ - 82.3 (*c* 0.830, tetrahydrofuran); **^{1}H NMR** (C_6D_6, 500 MHz, minor diastereomer **125**) δ 1.60-1.67 (1H, m, C*H*HCHC=O), 2.17-2.23 (1H, m, CH*H*CHC=O), 2.31-2.50 (2H, m, $ArCH_2CH_2$), 2.51-2.65 (2H, m, ArC*H*H and PhC*H*CH_2), 2.71-2.82 (1H, m, ArCH*H*), 4.89 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.18 (1H, d, *J* = 8.5 Hz, C*H*Ph), 6.51 (2H, dd, *J* = 8.4, 1.5 Hz, Ar*H*), 6.78-7.00 (4H, m, Ar*H*), 7.00-7.22 (10H, m, Ar*H*), 7.39 (2H, dd, *J* = 7.9, 1.4 Hz, Ar*H*); **^{13}C NMR** (C_6D_6, 500 MHz, minor diastereomer **125**) δ 18.80, 23.75, 27.08, 28.68, 39.22, 86.27, 86.91, 118.67, 121.82, 122.76, 126.25, 126.43, 127.12, 127.45, 127.90, 128.14, 128.54, 128.60, 130.96, 133.47, 136.97, 138.12, 139.84, 146.99, 148.39, 171.21; **IR** (ef) 1748, 1473, 1455, 1401, 1316, 1237, 1142, 1048, 748

cm^{-1}; **MS** (MALDI) *m/z* 527 (M+K), 511 (M+Na); **Anal.** Calcd for $C_{33}H_{28}O_4$: C, 81.12; H, 5.78. Found: C, 81.14; H, 5.80.

***(1S,2S)-2-Phenylcyclopropanecarboxylic acid* (126).**

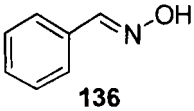


126

A solution of the diastereomeric cyclopropanes **124** and **125** (170 mg, 0.348 mmol, dr = 57:43) and lithium hydroxide monohydrate (148 mg, 3.53 mmol) in tetrahydrofuran (3 mL) and water (1 ml) was stirred at room temperature for 16 h. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with ether (2 × 25 mL). The aqueous layer was then acidified to pH ~ 2 with hydrochloric acid (1 M) and extracted with ether (3 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow oil (191 mg). Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *auxiliary* **68** (114 mg, 95%) as a colourless gum. The ^{1}H NMR spectral data for the *auxiliary* **68** were consistent with that reported above. Continued elution using ether as the eluant afforded the *title compound* **126** (36 mg, 64%) as a white solid (major enantiomer shown). $[\alpha]_D^{20}$ - 11.0 (*c* 1.82, chloroform), lit.[187] + 368 (*c* 1.3, chloroform) for the enantiomer; **^{1}H NMR** (C_6D_6, 500 MHz) δ 1.42 (1H, ddd, *J* = 11.3, 6.8, 4.7 Hz, C*H*HCH), 1.64-1.69 (1H, m, CH*H*CH), 1.91 (1H, ddd, *J* = 9.1, 5.2, 4.3 Hz, C*H*C=O), 2.61 (1H, ddd, *J* = 10.6, 6.7, 4.1 Hz, C*H*Ph); **^{13}C NMR** (C_6D_6, 500 MHz) δ 17.67, 24.17, 27.26, 126.38, 126.82, 128.65, 139.59, 180.25; **IR** (ef) 1688, 1461, 1446, 1432, 1338, 1326, 1236, 1220, 937, 752 cm^{-1}; **MS** (CI) *m/z* 163 (M+H).

7.2.8 Asymmetric 1,3-Dipolar Cycloaddition Reactions

***(E)-Benzaldehyde oxime* (136).**[188]

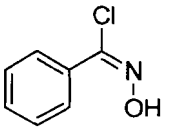


136

To a stirred suspension of sodium hydroxide (14.1 g, 353 mmol) and benzaldehyde (21 mL, 0.21 mol) in water (40 mL) was added hydroxylamine hydrochloride (15.0 g, 216 mmol) in portions. The resultant yellow

solution was stirred overnight over which time a white solid was deposited. The reaction mixture was then diluted with water (400 mL) and carbon dioxide was bubbled through the resultant solution until the pH ~ 7. The solution, in which a white oil was suspended, was extracted with ether (3 × 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow oil. The resultant yellow oil was purified by distillation to afford the *title compound* **136** (16.4 g, 66%) as an opaque liquid. **Bp** 118-120 °C, 15 mm Hg, (lit.[189] 122-124 °C, 12 mm Hg); **^{1}H NMR** ($CDCl_3$) δ 7.35-7.45 (3H, m, Ar*H*), 7.56-7.62 (2H, m, Ar*H*), 8.17 (1H, s, C*H*=N); **^{13}C NMR** ($CDCl_3$) δ 127.19, 128.92, 130.20, 150.54; **IR** (neat) 3307, 1632, 1578, 1494, 1445, 1302, 1210, 1100, 950, 870, 755 cm^{-1}; **MS** (CI) *m/z* 122 (M+H).

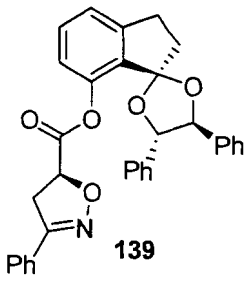
***(E)-Benzohydroximinoyl chloride* (137).**[190]



137

To a stirred solution of the oxime **136** (5.06 g, 41.8 mmol) in *N*,*N*-dimethylformamide (35 mL) at 0 °C was added *N*-chlorosuccinimide (1.12 g, 8.39 mmol). The resultant pale yellow solution was stirred at 0 °C for 10 min and then at room temperature for 20 min (CAUTION: *exothermic*). After re-cooling the reaction mixture to 0 °C, additional *N*-chlorosuccinimide (4.44 g, 33.2 mmol) was added in portions. The resultant green-blue solution was stirred at 0 to 5 °C for 30 min and then at room temperature for 1 h. After re-cooling the mixture to 0 °C, ice-water (150 mL) was added and the reaction mixture was extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (8 × 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **137** (6.00 g, 92%) as an orange-yellow solid. **^{1}H NMR** ($CDCl_3$) δ 7.38-7.49 (3H, m, Ar*H*), 7.82-7.86 (2H, m, Ar*H*), 8.30-8.60 (1H, broad s, O*H*); **^{13}C NMR** ($CDCl_3$) δ 127.36, 128.67, 130.90, 132.56, 140.43; **IR** (ef) 3378, 1604, 1578, 1494, 1447, 1235, 993, 936, 762, 689, 668 cm^{-1}; **MS** (CI) *m/z* 158 (^{37}Cl, M+H), 156 (^{35}Cl, M+H), 120.

7-((5S)-4,5-Dihydro-3-phenylisoxazole-5-carboxyl)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal **(139** and **140).**

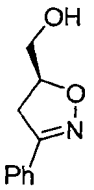


139

To a stirred solution of the cinnamate **89** (135 mg, 0.339 mmol) and benzohydroximinoyl chloride **137** (181 mg, 1.16 mmol) in benzene (7 mL) at 0 °C was added triethylamine (164 μL, 1.18 mmol) over 2 min. After 10 min, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride (25 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow liquid. Purification by flash chromatography using hexanes:dichloromethane (1:1) to elute the dipole dimer and then with dichloromethane as the eluant afforded a mixture of the *title compounds* **139** and **140** (130 mg, 74%) as a white solid (major diastereomer **139** shown). The diastereomeric ratio of the products was 61:39 (**139**:**140**) and the regioselectivity for the major diastereomer **139** was 88:12 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. **Mp** 86-88 °C, hexanes:dichloromethane; $[\alpha]_D^{20}$ - 104 (*c* 1.51, tetrahydrofuran); **^{1}H NMR** (C_6D_6, 500 MHz, mixture of diastereomers) δ 2.29-2.43 (4H, m, 2 × $ArCH_2CH_2$), 2.51-2.70 (4H, 2 × ArC*H*H and 2 × C*H*HC=N), 2.71-2.83 (2H, m, 2 × ArCH*H*), 3.34 (1H, dd, *J* = 16.9, 6.7 Hz, CH*H*C=N), 3.39 (1H, dd, *J* = 16.9, 7.6 Hz, CH*H*C=N), 4.78 (1H, d, *J* = 8.5 Hz, C*H*Ph), 4.84 (1H, d, *J* = 8.6 Hz, C*H*Ph), 4.92 (1H, dd, *J* = 11.9, 7.6 Hz, C*H*C=O), 5.00 (1H, dd, *J* = 11.9, 6.7 Hz, C*H*C=O), 5.52 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.59 (1H, d, *J* = 8.6 Hz, C*H*Ph), 6.78-6.83 (2H, d, *J* = 7.3 Hz, Ar*H*), 6.88-6.94 (2H, m, Ar*H*), 6.94-7.09 (10H, m, Ar*H*), 7.10-7.25 (12H, m, Ar*H*), 7.32 (2H, m, Ar*H*), 7.34-7.38 (2H, m, Ar*H*), 7.41 (2H, d, *J* = 7.0 Hz, Ar*H*), 7.45 (2H, d, *J* = 7.2 Hz, Ar*H*), 7.53 (2H, d, *J* = 7.2 Hz, Ar*H*); **^{13}C NMR** (C_6D_6:CD_2Cl_2, 500 MHz, mixture of diastereomers) δ 28.69, 38.60, 39.14, 39.16, 39.21, 52.93, 53.14, 53.36, 78.35, 78.68, 85.85, 86.00, 86.35, 118.00, 118.11,

121.30, 121.48, 123.52, 126.66, 127.07, 127.11, 127.13, 127.20, 127.30, 127.51, 127.57, 128.26, 128.30, 128.53, 128.57, 128.68, 128.71, 128.74, 128.81, 128.87, 128.92, 130.30, 130.37, 131.10, 131.17, 133.01, 133.14, 136.03, 136.49, 137.70, 138.02, 147.31, 147.34, 147.43, 147.67, 155.90, 156.17, 168.97, 169.17; **IR** (ef) 1759, 1619, 1589, 1497, 1473, 1449, 1355, 1316, 1224, 1177, 1153, 1119, 1046 cm^{-1}; **MS** (MALDI) *m/z* 556 (M+K), 540 (M+Na); **Anal.** Calcd for $C_{33}H_{27}NO_5$: C, 76.58; H, 5.26; N, 2.71. Found: C, 76.64; H, 5.39; N, 2.87.

***(5S)-5-Hydroxymethyl-3-phenyl-4,5-dihydroisoxazole* (*S*-135).**

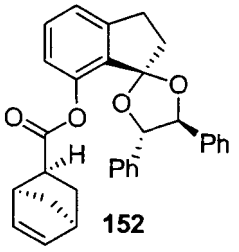


S-**135**

To a stirred solution of the diastereomeric isoxazolines **139** and **140** (115 mg, 0.222 mmol, dr = 61:39) at 0 °C was added lithium tri-*sec*-butylborohydride (1.0 M in tetrahydrofuran, 0.90 mL, 0.90 mmol) over 2 min. After 15 min, the reaction mixture was quenched by the addition of water (150 μL), an aqueous solution of sodium hydroxide (10 wt. %, 150 μL) and an aqueous solution of hydrogen peroxide (30 wt. %, 150 μL). The reaction mixture was then diluted with ethyl acetate (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow liquid. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *auxiliary* **68** (79 mg, ~ 100%). The ^{1}H NMR spectral data for the *auxiliary* were consistent with that reported above. Continued elution using ether as the eluant afforded the *title compound* *S*-**135** (32 mg, 82%) as a white solid (major enantiomer shown). $[\alpha]_D^{20}$ + 32.4 (*c* 1.62, chloroform); **^{1}H NMR** ($CDCl_3$) δ 2.07-2.28 (1H, broad s, O*H*), 3.28 (1H, dd, *J* = 16.6, 7.8 Hz, C*H*HC=N), 3.38 (1H, dd, *J* = 16.6, 10.8 Hz, CH*H*C=N), 3.69 (1H, dd, *J* = 12.2, 4.7 Hz, C*H*HOH), 3.87 (1H, dd, *J* = 12.2, 3.3 Hz, CH*H*OH), 4.84-4.90 (1H, m, C*H*), 7.38-7.42 (3H, m, Ar*H*), 7.66 (2H, apparent dd, *J* = 7.7, 1.8 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 36.43, 63.79, 81.35, 126.82, 128.83, 129.39, 130.32, 157.21; **IR** (ef) 3328, 1447, 1362, 1054, 1042, 917, 897, 811, 755 cm^{-1}; **MS** (CI) *m/z* 178 (M+H).

7.2.9 Asymmetric Diels-Alder Reactions

7-((1S,2S,4S)-Bicyclo[2.2.1]hept-5-ene-2-carboxyl)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal **(151** and **152)** - *using titanium tetrachloride as the Lewis acid and dichloromethane as the solvent, Table 2.10.1, entry 7.*

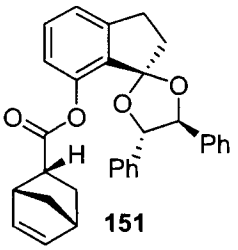


152

To a stirred suspension of the acrylate **76** (100 mg, 0.251 mmol) and flame-dried molecular sieves (4 Å, 0.1 g) in dichloromethane (5 mL) at -78 °C was added titanium tetrachloride (1.0 M in dichloromethane, 0.19 mL, 0.19 mmol) over 1 min. The resultant light brown suspension was stirred for 10 min at -78 °C and then cyclopentadiene (0.5 mL, 6 mmol) was added. The reaction mixture was stirred for 6 h at -78 °C and then for 16 h while the reaction warmed slowly to room temperature. The reaction mixture was then diluted with ether (40 mL) and washed with a saturated aqueous solution of ammonium chloride (2 × 10 mL), a saturated aqueous solution of sodium bicarbonate (2 × 10 mL) and brine (2 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to afford a yellow gum (110 mg). Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded an inseparable mixture of the *title compounds* **151** and **152** (89 mg, 76%) as a white foam (major diastereomer **152** shown). The diastereomeric ratio of the products was 26:74 (**151**:**152**) and the *endo*:*exo* ratio of the major product **152** was > 98:2 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. An analytical sample of the product, as colourless crystals, was prepared by recrystallization from hexanes:ether by slow evaporation. **Mp** 134-135 °C, hexanes:ether; $[\alpha]_D^{20}$ - 154 (*c* 1.46, chloroform); **^{1}H NMR** (C_6D_6, major diastereomer) δ 0.81 (1H, d, *J* = 8.3 Hz, C*H*H-bridge), 1.22 (1H, apparent dd, *J* = 8.3, 2.0 Hz, CH*H*-bridge), 1.70-1.80 (2H, m, CH_2CHC=O), 2.30-2.49 (2H, m, ArCH$_2$CH_2), 2.54-2.65 (3H, m, C*H*-bridgehead and ArC*H*H), 2.74-2.85 (1H, m, ArCH*H*), 3.01 (1H, m, C*H*C=O), 3.16 (1H, broad s, C*H*-bridgehead), 4.86 (1H, d, *J* = 8.3

Hz, C*H*Ph), 5.35 (1H, d, *J* = 8.3 Hz, C*H*Ph), 6.08 (1H, dd, *J* = 5.6, 3.2 Hz, C*H*=CH), 6.23 (1H, dd, *J* = 5.6, 2.9 Hz, CH=C*H*), 6.81 (1H, m, Ar*H*), 7.01-7.20 (8H, m, Ar*H*), 7.35-7.40 (4H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 28.62, 30.00, 39.27, 43.01, 44.38, 46.18, 49.71, 85.82, 86.91, 118.42, 121.97, 122.51, 127.00, 127.25, 128.48, 128.63, 128.82, 130.81, 132.44, 132.84, 133.21, 136.85, 137.93, 138.27, 146.94, 148.50, 172.43; **IR** (ef) 1758, 1616, 1590, 1496, 1473, 1454, 1316, 1227, 1145, 1106, 1047, 1019, 746 cm^{-1}; **MS** (CI) *m/z* 465 (M+H), 358, 317.

7-((1R,2R,4R)-Bicyclo[2.2.1]hept-5-ene-2-carboxyl)indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal **(151** and **152)** – *using diethylaluminum chloride as the Lewis acid and toluene as the solvent, Table 2.10.1, entry 10.*

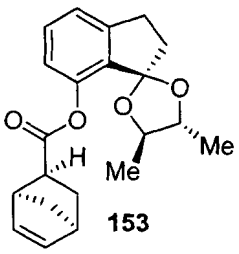


151

To a stirred solution of the acrylate **76** (102 mg, 0.255 mmol) in toluene (7 mL) at -78 °C was added diethylaluminum chloride (1.0 M in hexanes, 0.38 mL, 0.38 mmol) over 1 min. Cyclopentadiene (1.0 mL, 12 mmol) was then added to the resultant bright yellow solution was added. After 10 min, the slightly opaque yellow solution was poured into a saturated aqueous solution of sodium bicarbonate (25 mL) at which time the colour faded completely. The resultant mixture was extracted with dichloromethane (2 × 25 mL) and the combined organic extracts were washed with brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow semi-solid (131 mg). Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded an inseparable mixture of the *title compounds* **151** and **152** (106 mg, 89%) as a white solid (major diastereomer **151** shown). The diastereomeric ratio of the products was 83:17 (**151**:**152**) and the *endo*:*exo* ratio of the major product **151** was > 98:2 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. An analytical sample of the product, as colourless crystals enriched in the major diastereomer (dr > 98:2), was prepared by recrystallization from hexanes:ether by slow evaporation. **Mp** 138-139 °C,

hexanes:ether; $[\alpha]_D^{20}$ - 117 (*c* 1.67, chloroform); **^{1}H NMR** (C_6D_6, major diastereomer) δ 0.88 (1H, d, *J* = 8.2 Hz, C*H*H-bridge), 1.31 (1H, apparent dd, *J* = 8.2, 1.8 Hz, CH*H*-bridge), 1.49-1.62 (2H, m, CH_2CHC=O), 2.30-2.45 (2H, m, $ArCH_2CH_2$), 2.49 (1H, broad s, C*H*-bridgehead), 2.58 (1H, ddd, *J* = 10.2, 8.5, 8.2 Hz, ArC*H*H), 2.75-2.86 (1H, m, ArCH*H*), 3.10 (1H, m, C*H*C=O), 3.42 (1H, broad s, C*H*-bridgehead), 4.82 (1H, d, *J* = 8.2 Hz, C*H*Ph), 5.36 (1H, d, *J* = 8.2 Hz, C*H*Ph), 6.08 (1H, dd, *J* = 5.5, 3.0 Hz, C*H*=CH), 6.23 (1H, dd, *J* = 5.5, 2.8 Hz, CH=C*H*), 6.82 (1H, d, *J* = 7.3 Hz, Ar*H*), 7.01-7.20 (8H, m, Ar*H*), 7.36 (2H, d, *J* = 6.7 Hz, Ar*H*), 7.45 (2H, d, *J* = 7.0 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 28.62, 29.80, 39.22, 42.97, 44.18, 46.26, 49.81, 85.92, 87.08, 118.51, 122.09, 122.60, 127.06, 127.26, 128.55, 128.64, 128.82, 130.79, 132.45, 133.40, 137.03, 137.98, 138.29, 146.90, 148.34, 172.24; **IR** (ef) 1760, 1616, 1590, 1473, 1316, 1146, 1105 cm^{-1}; **MS** (CI) *m/z* 465 (M+H), 358, 317, 269, 121; **Anal.** Calcd for $C_{31}H_{28}O_4$: C, 80.15; H, 6.08. Found: C, 80.30; H, 6.01.

***7-((1S,2S,4S)-Bicyclo[2.2.1]hept-5-ene-2-carboxyl)indan-1-one (2R,3R)-2,3-butanediol acetal* (153** and **154)** – *using diethylaluminum chloride as the Lewis acid and dichloromethane as the solvent, Table 2.10.2, entry 1.*

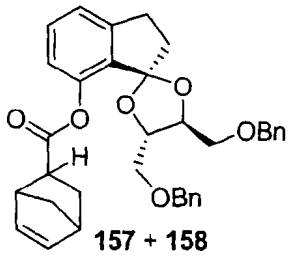


153

To a stirred solution of the acrylate **75** (102 mg, 0.370 mmol) in dichloromethane (7 mL) at -78 °C was added diethylaluminum chloride (1.0 M in hexanes, 0.55 mL, 0.55 mmol). After allowing the bright yellow solution to stir for 5 min at -78 °C, cyclopentadiene (1.5 mL, 18 mmol) was added. After 15 min, the slightly opaque yellow solution was poured into a saturated aqueous solution of sodium bicarbonate (25 mL) at which time the colour faded completely. The resultant mixture was extracted with dichloromethane (2 × 25 mL) and the combined organic extracts were washed with brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow semi-solid (128 mg). Purification by flash chromatography using

hexanes:ether (5:1) as the eluant afforded an inseparable mixture of the *title compounds* **153** and **154** (91 mg, 72%) as a white solid (major diastereomer **151** shown). The diastereomeric ratio of the products was 63:37 (**153**:**154**) and the *endo*:*exo* ratio of the major product **153** was > 98:2 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. **Mp** 44-46 °C, hexanes:ether; $[\alpha]_D^{20}$ + 5.3 (1.44, chloroform); **^{1}H NMR** (C_6D_6) δ 1.03 (1H, apparent dd, *J* = 8.5, 1.5 Hz, C*H*H-bridge), 1.12-1.21 (6H, m, 2 × CH_3CH), 1.38 (1H, apparent dd, *J* = 8.5, 1.5 Hz, CH*H*-bridge), 1.71-1.82 (2H, m, CH_2CHC=O), 2.13-2.30 (2H, m, ArCH$_2$CH_2), 2.51-2.78 (3H, m, ArCH_2 and C*H*-bridgehead), 3.13-3.18 (1H, m, C*H*C=O), 3.35 (1H, m, C*H*-bridgehead), 3.48-3.56 (1H, m, C*H*CH$_3$), 3.94-4.05 (1H, m, C*H*CH$_3$), 6.13 (1H, dd, *J* = 5.8, 3.0 Hz, C*H*=CH), 6.16-6.20 (1H, m, CH=C*H*), 6.75 (1H, m, Ar*H*) 6.95 (1H, dd, *J* = 7.9, 0.9 Hz, Ar*H*), 7.03 (1H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 16.26, 16.29, 17.38, 17.44, 28.59, 29.85, 29.92, 39.52, 39.57, 43.07, 43.12, 44.09, 44.15, 46.32, 46.44, 49.91, 78.76, 78.97, 79.36, 79.41, 116.83, 116.87, 121.77, 121.80, 122.47, 130.40, 130.43, 132.63, 132.74, 133.78, 133.83, 138.06, 146.61, 148.23, 148.39, 172.06; **IR** (ef) 1759, 1716, 1615, 1590, 1473, 1336, 1307, 1229, 1170, 1147, 1130, 1107, 1085, 1015, 712 cm^{-1}; **MS** (CI) *m/z* 341 (M+H), 193; **Anal.** Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.24; H, 7.19.

7-(Bicyclo[2.2.1]hept-5-ene-2-carboxyl)indan-1-one (2S,3S)-1,4-dibenzyloxy-2,3-butanediol acetal **(157** and **158)** - *using diethylaluminum chloride as the Lewis acid and toluene as the solvent, Table 2.10.2, entry 3.*

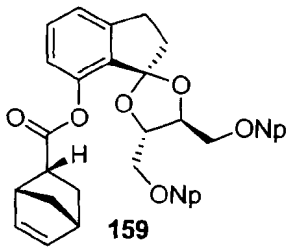


157 + 158

To a stirred solution of the acrylate **81** (137 mg, 0.282 mmol) in toluene (8 mL) at -78 °C was added diethylaluminum chloride (1.0 M in hexanes, 0.42 mL, 0.42 mmol). After allowing the bright yellow solution to stir for 1 min at -78 °C, cyclopentadiene (1.2 mL, 14 mmol) was added. After 2 h, the yellow solution was poured into a saturated aqueous solution of sodium bicarbonate (25 mL) at which time

the colour faded completely. The resultant mixture was extracted with dichloromethane (2 × 25 mL) and the combined organic extracts were washed with brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a colourless oil. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the an inseparable mixture of the *title compounds* **157** and **158** (134 mg, 86%) as a colourless opaque oil. The diastereomeric ratio of the products was 54:46 and the *endo*:*exo* ratio of the major product was > 98:2 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. $[\alpha]_D^{20}$ - 30.1 (1.43, tetrahydrofuran); **^{1}H NMR** (C_6D_6, mixture of diastereomers) δ 0.98 (2H, t, *J* = 8.2 Hz, C*H*H-bridge), 1.34 (2H, dd, *J* = 8.3, 1.8 Hz, CH*H*-bridge), 1.67-1.76 (4H, m, C*H*$_2$CHC=O), 2.13-2.30 (4H, m, ArCH$_2$C*H*$_2$), 2.45-2.58 (2H, m, ArC*H*H), 2.63 (2H, broad s, C*H*-bridgehead), 2.66-2.77 (2H, m, ArCH*H*), 3.18-3.28 (2H, m, C*H*C=O), 3.31 (1H, broad s, C*H*-bridgehead), 3.37 (1H, broad s, C*H*-bridgehead), 3.56-3.80 (8H, m, 2 × C*H*$_2$OBn), 4.16-4.23 (2H, m, C*H*CH$_2$OBn), 4.36-4.45 (8H, m, 2 × C*H*$_2$Ph), 4.49-4.58 (2H, m, C*H*CH$_2$OBn), 6.12 (2H, dd, *J* = 5.6, 3.0 Hz, C*H*=CH), 6.15-6.22 (2H, m, CH=C*H*), 6.71-6.76 (2H, m, Ar*H*), 6.91-7.20 (16H, m, Ar*H*), 7.21-7.30 (8H, m, Ar*H*); **^{13}C NMR** (C_6D_6, mixture of diastereomers) δ 28.60, 29.77, 29.81, 39.15, 39.19, 43.04, 43.08, 43.91, 44.02, 46.22, 46.36, 49.82, 49.88, 70.31, 70.38, 71.02, 71.07, 73.58, 73.71, 77.98, 78.10, 79.18, 79.38, 118.30, 121.82, 121.94, 122.35, 122.47, 128.59, 130.67, 132.69, 132.88, 137.94, 138.11, 138.82, 146.67, 146.72, 148.36, 148.55, 172.23; **IR** (film) 1759, 1615, 1590, 1473, 1454, 1336, 1316, 1234, 1146, 1106, 738 cm^{-1}; **MS** (CI) *m/z* 553 (M+H), 487, 405; **Anal.** Calcd for $C_{35}H_{36}O_6$: C, 76.06; H, 6.57. Found: C, 76.30; H, 6.62.

7-((1R,2R,4R)-Bicyclo[2.2.1]hept-5-ene-2-carboxyl)indan-1-one (2S,3S)-1,4-bis(1-naphthyloxy-2,3-butanediol acetal **(159** and **160)** - *using diethylaluminum chloride as the Lewis acid and toluene as the solvent, Table 2.10.2, entry 4.*

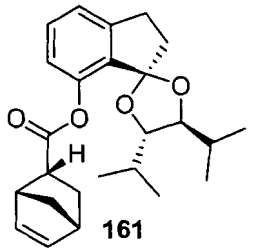


159

To a stirred solution of the acrylate **82** (97 mg, 0.17 mmol) in toluene (5 mL) at -78 °C was added diethylaluminum chloride (1.0 M in hexanes, 0.26 mL, 0.26 mmol) over 1 min. Cyclopentadiene (0.75 mL, 9.1 mmol) was then added to the resultant bright orange solution was added. After 2 h 30 min, the solution was poured into a saturated aqueous solution of sodium bicarbonate (25 mL) at which time the colour faded completely. The resultant mixture was extracted with dichloromethane (2 × 20 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale pink gum (127 mg). Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded an inseparable mixture of the *title compounds* **159** and **160** (84 mg, 77%) as a pale pink foam (major diastereomer **159** shown). The diastereomeric ratio of the products was 68:32 (**159**:**160**) and the *endo*:*exo* ratio of the major product **159** was > 98:2 as determined by analysis of the ^{1}H NMR spectrum of the crude reaction product. **Mp** 74-76 °C, hexanes:ether; $[\alpha]_D^{20}$ - 12.2 (*c* 1.30, tetrahydrofuran); **^{1}H NMR** (C_6D_6, major diastereomer) δ 0.64-0.72 (1H, m, C*H*H-bridge), 1.13-1.21 (1H, m, CH*H*-bridge), 1.51-1.75 (2H, m, CH_2CHC=O), 2.26-2.40 (2H, m, ArCH$_2$CH_2), 2.44-2.62 (2H, m, C*H*-bridgehead and ArC*H*H), 2.69-2.84 (1H, m, ArCH*H*), 3.12-3.36 (2H, m, C*H*-bridgehead and C*H*C=O), 4.19-4.48 (4H, m, 2 × CH_2O), 4.53-4.62 [1H, m, C*H*CH$_2$O(1-Np)], 4.93-5.01 [1H, m, C*H*CH$_2$O(1-Np)], 6.05-6.11 (1H, m, C*H*=CH), 6.13-6.20 (1H, m, CH=C*H*), 6.63-6.70 (2H, m, Ar*H*), 6.74-6.80 (1H, m, Ar*H*), 6.93-7.10 (2H, m, Ar*H*), 7.12-7.40 (8H, m, Ar*H*) 7.57-7.68 (2H, m, Ar*H*), 8.44-8.63 (2H, m, Ar*H*); **^{13}C NMR** (C_6D_6, major diastereomer) δ 28.59, 29.70, 39.58, 42.97, 43.94, 46.36, 49.72, 68.67, 68.78, 76.91,

78.88, 105.56, 105.71, 119.16, 121.32, 121.39, 122.04, 122.38, 122.41, 122.66, 125.71, 125.80, 126.03, 126.06, 126.20, 126.29, 126.82, 126.88, 127.89, 130.93, 132.35, 132.62, 132.96, 135.13, 135.19, 138.27, 146.73, 148.22, 154.74, 172.25; **IR** (ef) 1759, 1580, 1397, 1270, 1104, 771 cm^{-1}; **MS** (MALDI) *m/z* 648 (M+Na), 625 (M+H); **Anal.** Calcd for $C_{41}H_{36}O_6$: C, 78.83; H, 5.81. Found: C, 78.74; H, 6.08.

***7-((1R,2R,4R)-Bicyclo[2.2.1]hept-5-ene-2-carboxyl)indan-1-one (1S,2S)-1,2-diisopropyl-1,2-ethanediol acetal* (161** and **162)** - *using diethylaluminum chloride as the Lewis acid and toluene as the solvent, Table 2.10.2, entry 5.*

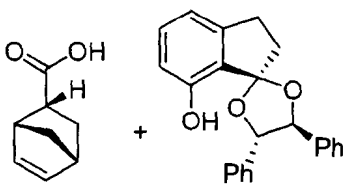


161

To a stirred solution of the acrylate **83** (85 mg, 0.26 mmol) in toluene (7 mL) at -78 °C, diethylaluminum chloride (1.0 M in hexanes, 0.39 mL, 0.39 mmol) was added over 1 min. Cyclopentadiene (1.0 mL, 12 mmol) was then added to the resultant yellow solution. After 1 h, the slightly opaque yellow solution was poured into a saturated aqueous solution of sodium bicarbonate (25 mL) at which time the colour faded completely. The reaction mixture was then extracted with dichloromethane (2 × 25 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow gum (112 mg). Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded an inseparable mixture of the *title compounds* **161** and **162** (73 mg, 71%) as a colourless oil which solidified on standing (major diastereomer **161** shown). The diastereomeric ratio of the products was 91:9 (**161**:**162**) and the *endo*:*exo* ratio of the major product **161** was > 98:2 as determined by analysis of the ^1H NMR (600 MHz) spectrum of the crude reaction product. **Mp** 81-82 °C, hexanes:ether; $[\alpha]_D^{20}$ - 39 (0.86, tetrahydrofuran); **^1H NMR** (C_6D_6, major diastereomer) δ 0.97 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.00 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.03 (3H, d, *J* = 6.7 Hz, C*H*$_3$CH), 1.08 (1H, m, C*H*H-bridge), 1.12 (3H, d, *J* = 6.7 Hz, C*H*$_3$CH), 1.40 (1H, dq, *J* = 8.2, 1.8 Hz, CH*H*-

bridge), 1.62-1.72 (1H, m, C*H*CH_3), 1.73-1.83 (2H, m, CH_2C*H*C=O), 1.83-1.95 (1H, m, C*H*CH_3), 1.99-2.12 (2H, m, ArCH_2C*H*$_2$), 2.46 (1H, ddd, *J* = 15.9, 7.9, 2.4 Hz, ArC*H*H), 2.67 (1H, broad s, C*H*-bridgehead), 2.69-2.79 (1H, m, ArCH*H*), 3.23-3.29 (1H, m, C*H*C=O), 3.41 (1H, broad s, C*H*-bridgehead), 3.60 (1H, dd, *J* = 7.9, 4.6 Hz, C*H*O) 3.90 (1H, dd, *J* = 7.9, 5.2 Hz, C*H*O), 6.13 (1H, dd, *J* = 5.6, 2.9 Hz, C*H*=CH), 6.17 (1H, dd, *J* = 5.7, 2.7 Hz, C*H*=CH), 6.75 (1H, dd, *J* = 7.5, 0.7 Hz, Ar*H*), 6.88 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.02 (1H, m, Ar*H*); **^{13}C NMR** (C_6D_6 , major diastereomer) δ 17.53, 17.67, 20.19, 20.37, 28.62, 29.59, 30.68, 31.32, 39.33, 43.15, 43.94, 46.45, 50.05, 83.44, 84.61, 116.92, 122.01, 122.48, 130.40, 132.30, 133.83, 138.18, 146.66, 148.43, 172.05; **IR** (ef) 1763, 1616, 1591, 1472, 1316, 1234, 1176, 1164, 1147, 1130, 1106, 1041, 755, 711 cm^{-1}; **MS** (CI) *m/z* 397 (M+H), 269, 249, 183, 121; **Anal.** Calcd for $C_{26}H_{22}O_4$: C, 75.73; H, 8.13. Found: C, 75.42; H, 8.23.

(1R,2R,4R)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **(2*R*-171)** *- from the diethylaluminum chloride-promoted Diels-Alder reaction of acrylate* **76** *(R = Ph).*

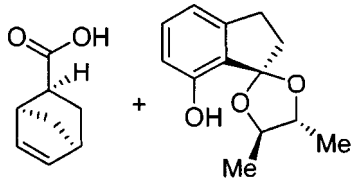


2R-**171** **68**

To a stirred solution of the diastereomeric cycloadducts **151** and **152** (90 mg, 0.19 mmol, dr = 83:17) in tetrahydrofuran (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (165 mg, 3.93 mmol) and the resultant opaque white solution was stirred at room temperature for 40 h. The reaction mixture was then diluted with a saturated aqueous solution of ammonium chloride (50 mL) and extracted with dichloromethane (2 × 15 mL). The aqueous layer was then acidified to pH ~ 2 with hydrochloric acid (1 M) and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow gum. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *auxiliary* **68** (57 mg, 85%) as a white gum. The ^{1}H NMR spectral data for the *auxiliary* **68** (R = Ph)

were consistent with that reported above. Continued elution afforded the *title compound* 2*R*-**171** (20.2 mg, 76%) as a colourless oil (major enantiomer shown). $[\alpha]_D^{20}$ + 82 (*c* 1.17, 95% *aq.* ethanol), lit.[191] - 144 (*c* 1.00, 95% *aq.* ethanol) for the enantiomer; **^{1}H NMR** ($CDCl_3$) δ 1.24-1.31 (1H, m, C*H*HCHCO$_2$H), 1.37-1.48 (2H, m, C*H*H(bridge) and CH*H*CHCO$_2$H)), 1.92 (1H, ddd, *J* = 13.0, 9.5, 3.7 Hz, CH*H*(bridge)), 2.92 (1H, broad s, C*H*(bridgehead)), 2.99 (1H, dt, *J* = 9.3, 4.0 Hz, C*H*CO$_2$H), 3.23 (1H, broad s, C*H*(bridgehead)), 5.99 (1H, dd, *J* = 5.6, 2.9 Hz, C*H*=CH), 6.21 (1H, dd, *J* = 5.6, 2.9 Hz, CH=C*H*); **^{13}C NMR** (C_6D_6) δ 29.27, 42.68, 43.33, 45.83, 49.87, 132.57, 138.04, 180.82; **IR** (film) 3034, 2977, 2947, 2870, 1704, 1420, 1338, 1276, 1235, 709 cm^{-1}; **MS** (CI) *m/z* 139 (M+H).[192]

(1R,2R,4R)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (2*S*-**171**) – *from the diethylaluminum chloride-promoted Diels-Alder reaction of acrylate* **75** *(R = Me).*

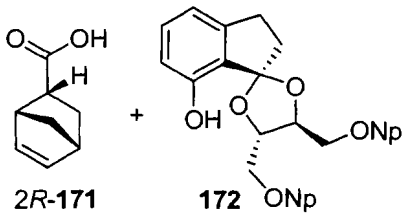


2*S*-**171** **64**

To a stirred solution of the diastereomeric cycloadducts **153** and **154** (64 mg, 0.19 mmol, dr = 64:36) in tetrahydrofuran (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (158 mg, 3.77 mmol) and the opaque white solution was stirred at room temperature for 20 h. The reaction mixture was then diluted with a saturated solution of ammonium chloride (50 mL) and extracted with dichloromethane (2 × 15 mL). The aqueous layer was then acidified to pH ~ 2 with hydrochloric acid (10 wt. %) and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow oil. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *auxiliary* **63** (32 mg, 78%) as a colourless oil followed by the *title compound* 2*S*-**171** (19 mg, 72%) as a colourless gummy solid (major enantiomer shown). $[\alpha]_D^{20}$ - 39 (*c* 1.06, 95% *aq.* ethanol), lit.[191] - 144 (*c* 1.00, 95% *aq.* ethanol). The ^{1}H NMR spectral data for the *title compound* and *auxiliary* **75** (R =

Me) were consistent with that reported above.

(1R,2R,4R)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (*2R*-**171**) - *from the diethylaluminum chloride-promoted Diels-Alder reaction of acrylate* **82** *[R = CH_2O(1-Np)].*

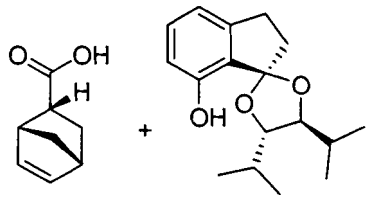


2R-**171** **172**

To a stirred solution of the diastereomeric cycloadducts **159** and **160** (79 mg, 0.13 mmol, dr = 68:32) in tetrahydrofuran (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (110 mg, 2.64 mmol) and the resultant opaque white solution was stirred at room temperature for 42 h. The reaction mixture was then diluted with a saturated solution of ammonium chloride (50 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic extracts was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale pink gum. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *auxiliary* **172** (10 mg, 60%) as a white solid. **Mp** 77-80 °C, hexanes:ether; $[\alpha]_D^{20}$ + 23.4 (1.28, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 2.28 (1H, ddd, *J* = 15.2, 8.4, 6.8 Hz, ArC*H*H), 2.43 (1H, ddd, *J* = 12.7, 7.9, 3.9 Hz, ArCH*H*), 2.66 (1H, ddd, *J* = 15.8, 8.4, 3.9 Hz, $ArCH_2CHH$), 2.74-2.83 (1H, m, $ArCH_2CHH$), 3.83-3.90 (2H, m, 2 × C*H*HO), 3.98 (1H, dd, *J* = 10.2, 5.2 Hz, CH*H*O), 4.19 (1H, dd, *J* = 10.6, 3.2 Hz, CH*H*O), 4.41 [1H, apparent dt, *J* = 7.7, 3.0 Hz, $CHCH_2O$(1-Np)], 4.74 [1H, ddd, *J* = 9.3, 5.0, 4.5 Hz, $CHCH_2O$(1-Np)], 6.54 (2H, dd, *J* = 7.7, 0.7 Hz, Ar*H*), 6.62 (1H, dd, *J* = 7.4, 0.7 Hz, Ar*H*), 6.93 (1H, dd, *J* = 8.1, 0.7 Hz, Ar*H*), 7.08 (1H, m, Ar*H*), 7.17-7.24 (2H, m, Ar*H*), 7.24-7.30 (3H, m, Ar*H*), 7.34-7.42 (3H, m, Ar*H*), 7.43 (1H, sharp s, O*H*), 7.61-7.67 (2H, m, Ar*H*), 8.37-8.43 (1H, m, Ar*H*), 8.69 (1H, apparent d, *J* = 8.4 Hz, Ar*H*), **^{13}C NMR** (C_6D_6) δ 28.94, 39.16, 67.08, 68.26, 76.15, 77.66, 105.47, 106.25, 114.94, 116.98, 120.08, 121.42, 121.92, 122.16, 122.47, 125.06, 125.78, 125.99, 126.11, 126.16, 126.24, 126.86, 126.99, 127.90, 132.42, 135.15, 135.18, 145.58, 154.53, 154.60, 155.11; **IR** (ef)

3469, 3052, 2932, 1598, 1579, 1509, 1472, 1396, 1318, 1267, 1240, 1178, 1157, 1121, 1103, 790, 771 cm^{-1}; **MS** (MALDI) *m/z* 506; **HRMS** (FAB) *m/z* Calcd for $C_{33}H_{28}O_5$: 505.1970, 504.1937. Found: 505.1993, 505.1978. The aqueous layer was then acidified to pH ~ 2 with hydrochloric acid (10 wt. %) and extracted with dichloromethane (2 × 15 mL). These combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a colourless oil. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* 2*R*-**171** (4.1 mg, 63%) as a colourless oil (major enantiomer shown). $[\alpha]_D^{20}$ + 35 (*c* 1.04, 95% *aq.* ethanol), lit.[191] - 144 (*c* 1, 95% *aq.* ethanol) for the enantiomer. The ^{1}H NMR spectral data were consistent with that reported above.

(1R,2R,4R)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **(2*R*-171)** – *from the diethylaluminum chloride-promoted Diels-Alder reaction of acrylate* **83** *(R = i-Pr).*

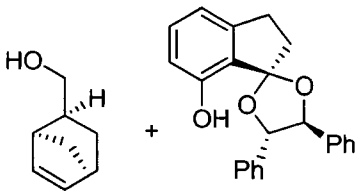


2*R*-**171** **173**

To a stirred solution of the diastereomeric cycloadducts **161** and **162** (166 mg, 0.419 mmol, dr = 91:9) in tetrahydrofuran (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (178 mg, 4.24 mmol) and the resultant opaque white solution was stirred at room temperature for 2 days. An additional portion of lithium hydroxide monohydrate was added (210 mg, 5.01 mmol) and stirring was continued for 2 days. The mixture was then diluted with a saturated solution of ammonium chloride (50 mL) and extracted with dichloromethane (2 × 15 mL). The aqueous layer was then acidified to pH ~ 2 with hydrochloric acid (1 M) and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow gum. Purification by flash chromatography using hexanes:ether (15:1) as the eluant afforded the *auxiliary* **173** (92 mg, 80%) as a white solid. **Mp** 50-52 °C, hexanes:ether; $[\alpha]_D^{20}$ - 58 (*c* 1.15, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 0.65 (3H, d, *J* = 6.9 Hz, CH_3CH), 0.85 (3H,

d, J = 6.9 Hz, C*H*$_3$CH), 0.92 (3H, d, J = 6.7 Hz, C*H*$_3$CH), 0.95 (3H, d, J = 6.7 Hz, C*H*$_3$CH), 1.46-1.62 (2H, m, ArCH$_2$C*H*$_2$), 1.91-2.05 (2H, m, C*H*CH$_3$ and C*H*CH$_3$), 2.56 (1H, ddd, J = 15.7, 7.6, 2.9 Hz, ArC*H*H), 2.68-2.78 (1H, m, ArCH*H*), 3.36 (1H, apparent t, J = 7.2 Hz, C*Hi*-Pr), 3.56 (1H, dd, J = 6.6, 4.3 Hz, C*Hi*-Pr), 6.61 (1H, d, J = 6.6 Hz, Ar*H*), 6.91 (1H, d, J = 8.0 Hz, Ar*H*), 7.06 (1H, s, O*H*), 7.07 (1H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 16.69, 19.04, 19.10, 20.12, 29.05, 31.37, 32.97, 38.85, 84.58, 85.03, 114.39, 116.79, 118.23, 125.34, 132.02, 145.35, 155.21; **IR** (ef) 3474, 1602, 1473, 1319, 1106, 1043, 1035, 995, 748 cm^{-1}; **MS** (CI) *m/z* 276 (M+H); **Anal.** Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.59; H, 8.82. Continued elution using hexanes:ether (3:1) as the eluant afforded the *title compound* 2*R*-**171** (39 mg, 67%) as a colourless oil (major enantiomer shown). $[\alpha]_D^{20}$ + 115 (*c* 1.18, 95% *aq.* ethanol), lit.[191] - 144 (*c* 1, 95% *aq.* ethanol) for the enantiomer. The ^{1}H NMR spectral data were consistent with that reported above.

***(1S,2S,4S)-Bicyclo[2.2.1]hept-5-ene-2-methanol* (175)** - *from the titanium chloride-promoted Diels-Alder reaction of acrylate* **76** *(R = Ph).*



175 **68**

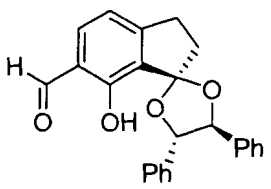
Lithium aluminum hydride (6 mg, 0.2 mmol) was suspended in tetrahydrofuran (2 mL) at 0 °C. After 10 min, a solution of the diastereomeric cycloadducts **151** and **152** (34 mg, 0.074 mmol, dr = 24:76) in tetrahydrofuran (5 mL) at 0 °C was added and the reaction mixture was allowed to warm slowly to room temperature. After 16 h, the reaction mixture was heated at reflux for 4 h. An additional portion of lithium aluminum hydride (5 mg, 0.1 mmol) was then added and heating was continued for 2 h. The reaction mixture was then cooled to 0 °C and water (11 μL), an aqueous solution of sodium hydroxide (15 wt. %, 33 μL) and water (33 μL) were added successively. After 15 min, the white precipatate was removed by filtration through Celite® with ether (10 mL). The filtrate was then concentrated to afford a

colourless oil. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *auxiliary* **68** (15 mg, 60%) as a white foam. The ^{1}H NMR spectral data for the auxiliary **68** (R = Ph) were consistent with that reported above. Continued elution afforded the *title compound* **175** (4.1 mg, 45%) as a colourless oil (major enantiomer shown). $[\alpha]_D^{20}$ - 15.3 (*c* 0.30, 95% *aq.* ethanol), lit.[193] - 93 (*c* 0.5, 95% *aq.* ethanol); **^{1}H NMR** ($CDCl_3$) δ 0.52 (1H, ddd, *J* = 11.6, 4.4, 2.6 Hz, C*H*HCH), 1.26 (1H, apparent d, *J* = 8.3 Hz, C*H*H-bridge), 1.42-1.49 (2H, m, CH*H*-bridge and OH), 1.82 (1H, ddd, *J* = 13.0, 9.2, 3.8 Hz, CH*H*CH), 2.24-2.34 (1H, m, CH_2CH), 2.81 (1H, broad s, C*H*-bridgehead), 2.93 (1H, broad s, C*H*-bridgehead), 3.26 (1H, dd, *J* = 10.4, 8.9 Hz, C*H*HOH), 3.40 (1H, dd, *J* =10.4, 6.5 Hz, CH*H*OH), 5.96 (1H, dd, *J* = 5.7, 2.9 Hz, C*H*=CH), 6.14 (1H, dd, *J* = 5.7, 3.1 Hz, CH=C*H*); **IR** (neat) 3345, 1455, 1381, 1090, 1050, 881 cm^{-1}; **MS** (CI) *m/z* 139 (M-H), 93.

7.3 Experimental Procedures and Characterization Data Concerning Chapter 3

7.3.1 Synthesis of 7-Hydroxyindan-1-one-Derived Chiral Tridentate Schiff Bases

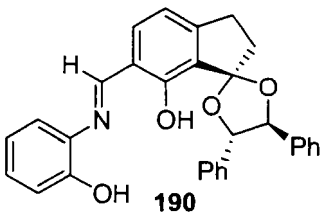
***6-Formyl-7-hydroxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (186).**



186

A stirred suspension of the phenol **68** (951 mg, 2.76 mmol), triethylamine (1.54 mL, 11.0 mmol), anhydrous magnesium chloride (400 mg, 4.20 mmol) and paraformaldehyde (591 mg, 19.7 mmol) in acetonitrile (25 mL) was heated at 60 °C for 20 h.[108] The resultant yellow reaction mixture was allowed to cool to room temperature and was poured into a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to afford a yellow gum. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **186** (790 mg, 77%) as a white foam/solid. **Mp** 107-108 °C, hexanes:ether; $[\alpha]_D^{20}$ - 260 (*c* 1.02, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 2.37-2.72 (4H, m, ArC*H*$_2$C*H*$_2$), 4.85 (1H, d, *J* = 8.6 Hz, C*H*Ph), 5.68 (1H, d, *J* = 8.6 Hz, C*H*Ph), 6.40 (1H, d, *J* = 7.8 Hz, Ar*H*), 6.73 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.33 (2H, d, apparent d, *J* = 6.6 Hz), 7.51 (2H, apparent d, *J* = 8.0 Hz, Ar*H*), 9.21 (1H, s, C*H*O), 12.20 (1H, s, O*H*); **^{13}C NMR** (C_6D_6) δ 29.39, 39.23, 86.69, 87.14, 116.67, 117.98, 120.38, 127.14, 127.77, 128.60, 128.85, 130.05, 135.74, 136.80, 137.86, 155.29, 159.62, 196.12; **IR** (ef) 1650, 1633, 1582, 1495, 1454, 1434, 1327, 1219, 1126, 1089, 1036, 944, 759 cm^{-1}; **MS** (MALDI) *m/z* 395 (M+Na); **Anal.** Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.27; H, 5.49.

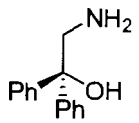
***6-Formyl-7-hydroxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal 2-aminophenol imine* (190).**



190

A solution of the salicylaldehyde **186** (201 mg, 0.540 mmol) and 2-aminophenol (71 mg, 0.65 mmol) in ethanol (5 mL) was stirred at room temperature for 18 h. The reaction mixture was then concentrated to afford a bright yellow gum. The gum was dissolved in dichloromethane (5 mL) and the solution was concentrated to afford a bright yellow solid. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **190** (244 mg, 97%) as a bright yellow solid. **Mp** 78-80 °C, hexanes:ether; $[\alpha]_D^{20}$ - 138 (*c* 1.31, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 2.48-2.58 (1H, m, $ArCH_2CHH$), 2.60-2.76 (2H, m, $ArCH_2CHH$ and $ArCHH$), 2.78-2.89 (1H, m, $ArCHH$), 4.91 (1H, d, *J* = 8.8 Hz, CHPh) 5.82 (1H, d, *J* = 8.8 Hz, CHPh), 6.56 (1H, dd, *J* = 8.0, 1.1 Hz, Ar*H*), 6.61 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.68 (1H, apparent t, *J* = 7.3 Hz, Ar*H*), 6.83-6.96 (3H, m, Ar*H*), 7.01-7.15 (6H, m, Ar*H*), 7.37 (2H, d, *J* = 6.9 Hz, Ar*H*), 7.57 (2H, d, *J* = 6.9 Hz, Ar*H*), 7.96 (1H, s, CH=N), 12.92-13.69 (1H, broad s, O*H*); **^{13}C NMR** (C_6D_6) δ 29.27, 39.52, 86.64, 87.08, 116.26, 118.55, 118.90, 119.38, 120.87, 126.88, 127.22, 127.92, 128.41, 128.57, 129.82, 134.94, 136.48, 136.99, 138.10, 150.34, 151.90, 158.94, 164.28; **IR** (ef) 3238, 1617, 1596, 1455, 1325, 1126, 1091, 1038, 751 cm^{-1}; **MS** (MALDI) *m/z* 486 (M+Na), 463 (M); **Anal.** Calcd for $C_{30}H_{25}NO_4$: C, 77.74; H, 5.44; N, 3.02. Found: C, 77.59; H, 5.57; N, 2.98.

***2-Amino-1,1-diphenylethanol* (189).**[110]

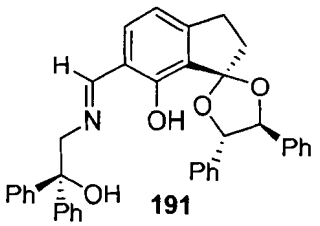


189

To a stirred solution of phenylmagnesium bromide [prepared from magnesium metal (1.11 g, 45.7 mmol), bromobenzene (4.5 mL, 43 mmol) and iodine (1 crystal)] in tetrahydrofuran (45 mL) at 0 °C was added a suspension of glycine ethyl ester hydrochloride (1.00 g, 7.16 mmol) in tetrahydrofuran (70 mL) over 20 min and the reaction mixture was allowed to warm slowly to room

temperature. After 18 h, the reaction mixture was quenched by the addition of water (20 mL) and diluted with ether (100 mL). The organic layer was washed with brine (2 × 75 mL) and the combined aqueous extracts were back-extracted with ether:tetrahydrofuran (3:2, 2 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to afford the *title compound* **189** (1.12 g, 73%) as an orange solid which was used without further purification. **^{1}H NMR** (C_6D_6) δ 1.76-2.66 (3H, broad s, O*H* and NH_2), 3.38-3.46 (2H, broad s, CH_2), 7.19-7.35 (6H, m, Ar*H*), 7.44 (4H, apparent d, *J* = 7.3 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 126.00, 126.59, 126.82, 127.40, 128.10, 128.71, 145.35; **IR** (ef) 3359, 3299, 1666, 1598, 1492, 1448, 1061, 756 cm^{-1}; **MS** (CI) *m/z* 214 (M+H), 196, 183.

***6-Formyl-7-hydroxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal 1,1-diphenyl-2-aminoethanol imine* (191).**



191

A solution of the salicylaldehyde **186** (207 mg, 0.555 mmol) and 1,1-diphenyl-2-aminoethanol[110] (146 mg, 0.683 mmol) in ethanol (10 mL) was stirred at room temperature for 18 h. The reaction mixture was then concentrated to afford a bright yellow gum. The gum was dissolved in dichloromethane (5 mL) and the solution was concentrated to afford a bright yellow solid. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **191** (302 mg, 96%) as a bright yellow solid. **Mp** 162-163 °C, hexanes:ether; $[\alpha]_D^{20}$ - 168 (*c* 1.25, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 1.88-2.32 (1H, broad s, O*H*), 2.50 (1H, ddd, *J* = 12.9, 9.0, 3.5 Hz, ArCH$_2$C*H*H), 2.58-2.85 (3H, m, ArCH_2 and ArCH$_2$CH*H*), 3.78 (1H, d, *J* = 12.6 Hz, C*H*HN), 3.99 (1H, d, *J* = 12.6 Hz, CH*H*N), 4.86 (1H, d, *J* = 8.6 Hz, C*H*Ph), 5.77 (1H, d, *J* = 8.6 Hz, C*H*Ph), 6.56 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.86 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.98-7.26 (12H, m, Ar*H*), 7.36 (2H, d, *J* = 7.0 Hz, Ar*H*), 7.41-7.48 (4H, m, Ar*H*), 7.55 (2H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 7.78 (1H, s, C*H*=N), 13.59-14.02 (1H, broad s,

ArO*H*); **^{13}C NMR** (C_6D_6:$CDCl_3$, 3:1) δ 29.13, 39.38, 68.99, 78.31, 86.45, 87.19, 115.40, 118.15, 118.70, 126.74, 126.91, 126.94, 127.39, 128.15, 128.46, 128.43, 128.52, 128.55, 129.29, 133.88, 137.05, 138.04, 145.45, 145.57, 150.64, 159.28, 167.72; **IR** (ef) 3360, 1631, 1466, 1448, 1324, 1125, 1091, 1056, 1037, 761 cm^{-1}; **MS** (MALDI) *m/z* 590 (M+Na), 568 (M+H); **Anal.** Calcd for $C_{38}H_{33}NO_4 \cdot H_2O$: C 77.93; H 6.02; N, 2.39. Found: C, 77.91; H, 5.95; N, 2.15.

7.3.2 Vanadium-Catalyzed Asymmetric Sulfoxidation Reactions

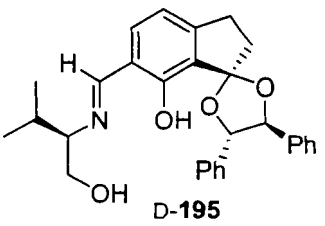
Typical procedure for asymmetric sulfoxidation reactions of thioanisole catalyzed by chiral tridentate Schiff bases **190**, **191**, D-**195** *and* L-**196**:

***(R)-Phenylmethylsulfoxide* (*R*-193).**

R-**193**

To a stirred solution of the Schiff base **190** (21 mg, 0.037 mmol) in dichloromethane (6 mL) was added vanadyl acetoacetate (7 mg, 0.02 mmol). After 5 min, thioanisole (0.29 mL, 2.5 mmol) was added and the solution was cooled to 0 °C. An aqueous solution of hydrogen peroxide (30 wt. %, 0.17 mL) was then added over 5 min and the reaction mixture was allowed to warm slowly to room temperature. After 20 h, the reaction mixture was concentrated to afford a brown liquid. Purification by flash chromatography using ether as the eluant afforded the *title compound R*-**193** (228 mg, 65%) as a brown liquid. The enantiomeric ratio of the purified product was 63:37 as determined by chiral HPLC analysis (80:20 hexanes:isopropanol, 0.5 mL/min, $t_{R(major)}$ = 16.2 min, $t_{R(minor)}$ = 18.4 min). $[\alpha]_D^{20}$ + 35 (*c* 1.58, acetone), lit.[116] + 136 (*c* 1, acetone); **^{1}H NMR** ($CDCl_3$) δ 2.73 (3H, s, C*H*$_3$), 7.48-7.57 (3H, m, Ar*H*), 7.65 (2H, apparent dd, *J* = 8.2, 1.8 Hz); **^{13}C NMR** ($CDCl_3$) δ 43.92, 123.49, 129.36, 131.05, 145.62; **IR** (film) 3473, 1659, 1478, 1444, 1417, 1163, 1091, 1073, 1046, 957, 751 cm^{-1}.

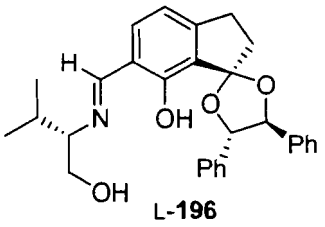
***6-Formyl-7-hydroxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal D-valinol imine* (D-195).**



D-**195**

A solution of the salicylaldehyde **186** (33 mg, 0.090 mmol) and D-valinol (11 mg, 0.11 mmol) in ethanol (1.5 mL) was stirred at room temperature for 20 h. The reaction mixture was then concentrated to afford a bright yellow gum. The gum was dissolved in dichloromethane (5 mL) and the solution was concentrated to afford the *title compound* D-**195** (42 mg, ~ 100%) as a bright yellow foam. **^{1}H NMR** (C_6D_6) δ 0.67 (3H, d, J = 6.8 Hz, CH_3), 0.76 (3H, d, J = 6.8 Hz, CH_3), 1.51-1.61 (1H, m, C*H*CH_3), 2.54 (1H, ddd, J = 13.3, 9.0, 2.9 Hz, $ArCH_2CHH$) 2.61-2.78 (2H, m, $ArCH_2CHH$ and ArC*H*H), 2.81-2.91 (1H, m, ArCH*H*), 3.34 (1H, dd, J = 11.1, 8.5 Hz, C*H*HOH), 3.46 (1H, dd, J = 11.1, 3.6 Hz, CH*H*OH), 4.90 (1H, d, J = 8.6 Hz, C*H*Ph), 5.90 (1H, d, J = 8.6 Hz, C*H*Ph), 6.58 (1H, d, J = 7.7 Hz, Ar*H*), 6.95 (1H, d, J = 7.7 Hz, Ar*H*), 7.03-7.14 (6H, m, Ar*H*), 7.32 (2H, apparent dd, J = 7.9, 1.6 Hz, Ar*H*), 7.61 (2H, apparent dd, J = 8.4, 1.4 Hz, Ar*H*), 7.96 (1H, s, CH=N); **IR** (ef) 3402, 1628, 1498, 1454, 1324, 1126, 1090, 1038, 761 cm^{-1}; **MS** (MALDI) *m/z* 479 (M+Na), 458 (M+H).

***6-Formyl-7-hydroxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal L-valinol imine* (L-196).**



L-**196**

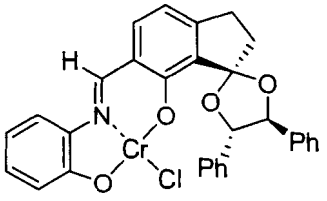
A solution of the salicylaldehyde **186** (35 mg, 0.094 mmol) and L-valinol (10 mg, 0.093 mmol) in ethanol (1.5 mL) was stirred at room temperature for 1.5 h. The reaction mixture was then concentrated to afford a bright yellow gum. The gum was dissolved in dichloromethane (5 mL) and the solution was concentrated to afford the *title compound* L-**196** (44 mg, ~ 100%) as a bright yellow foam. **^{1}H NMR** (C_6D_6) δ 0.64 (3H, d, J = 6.8 Hz, CH_3), 0.69 (3H, d, J = 6.8 Hz, CH_3), 1.47-1.58 (1H, m, C*H*CH_3), 2.52 (1H, ddd, J = 13.2, 8.9, 2.6 Hz, $ArCH_2CHH$), 2.60-2.77 (2H, m,

$ArCH_2CH\mathit{H}$ and $ArC\mathit{H}H$), 2.82-2.93 (1H, m, $ArCH\mathit{H}$), 3.28 (1H, dd, J = 11.1, 3.6 Hz, $C\mathit{H}HOH$), 3.43 (1H, dd, J = 11.1, 8.7 Hz, $CH\mathit{H}OH$), 4.89 (1H, d, J= 8.6 Hz, $C\mathit{H}Ph$), 5.88 (1H, d, J= 8.6 Hz, $C\mathit{H}Ph$), 6.62 (1H, d, J = 7.6 Hz, $Ar\mathit{H}$), 6.98 (1H, d, J = 7.6 Hz, $Ar\mathit{H}$), 7.02-7.16 (6H, m, $Ar\mathit{H}$), 7.32 (2H, dd, J = 7.9, 1.7 Hz, $Ar\mathit{H}$), 7.59 (2H, apparent dd, J = 8.1, 1.4 Hz, $Ar\mathit{H}$), 8.01 (1H, s, $C\mathit{H}$=N), 13.81-15.03 (1H, broad s, $ArO\mathit{H}$); **^{13}C NMR** (C_6D_6) δ 18.70, 19.72, 29.18, 30.01, 39.61, 64.28, 77.73, 86.53, 87.00, 115.46, 118.25, 118.69, 127.21, 128.43, 128.49, 128.59, 129.64, 133.92, 137.12, 138.24, 150.63, 159.89, 166.06; **IR** (ef) 3415, 1629, 1498, 1454, 1325, 1125, 1091, 1037, 946, 761 cm^{-1}; **MS** (MALDI) *m/z* 479 (M+Na), 458 (M+H).

7.3.3 Chromium-Catalyzed Asymmetric Hetero Diels-Alder Reactions

Typical procedure for the preparation of chromium(III)-complexes of the chiral tridenate Schiff bases **204** *and* **205**:

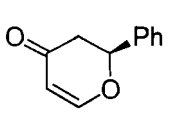
***Chromium(III)-complex of 6-Formyl-7-hydroxyindan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal 2-aminophenol imine* (204).**



204

In a glove box, a yellow solution of the Schiff base **190** (111 mg, 0.240 mmol) in tetrahydrofuran (4.5 mL) was added to a stirred suspension of chromium(II) chloride (35 mg, 0.28 mmol) in tetrahydrofuran (1.5 mL) at room temperature at which time the reaction mixture immediately became dark brown. After 5 h, the resultant dark brown solution was removed from the glove box and was stirred open to the atmosphere at room temperature for 16 h. 2,6-lutidine (66 μL, 0.57 mmol) was then added. After 4 h, the reaction mixture was diluted with *t*-butylmethyl ether (30 mL) and washed with a saturated solution of ammonium chloride (3 × 10 mL) and brine (2 × 10 mL). The brown organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford *the title compound* **204** (125 mg, 95%) as a dark brown solid which was used without further purification.

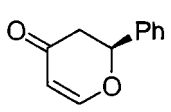
***(2S)-2-Phenyl 2,3-dihydropyran-4-one* (203)** - *using chromium(III)-complex* **204** *and t-butylmethyl ether as the solvent.*



203

To a stirred suspension of the chromium(III)-complex **204** (25 mg) and flame-dried powdered molecular sieves (4 Å, 197 mg) in *t*-butylmethyl ether (1 mL) was added benzaldehyde (48 μL, 0.47 mmol). After 5 min, the reaction mixture was cooled to -20 °C (dry ice/brine bath) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (90%, 92 μL, 0.42 mmol) was added. After 1 h, the reaction mixture was allowed to warm to room temperature over 1 h. After 17 h, the reaction mixture was diluted with dichloromethane (2 mL) and trifluoroacetic acid (1 drop) was added. After 15 min, the reaction mixture was filtered and concentrated to afford a brown liquid (90 mg). Purification by flash chromatography using hexanes:ether (4:1 to 3:1) as the eluant afforded the *title compound* **203** (42 mg, 56%) as a pale brown oil. The enantiomeric ratio of the purified product was 64:36 as determined by chiral HPLC analysis (90:10 hexanes:isopropanol, 1 mL/min, $t_{R(major)}$ = 15.4 min, $t_{R(minor)}$ = 19.1 min). $[\alpha]_D^{20}$ + 31 (*c* 0.88, chloroform), lit.[120c] - 87.1 (*c* 1.03, chloroform) for the (*R*)-enantiomer, er > 99:1; **^{1}H NMR** ($CDCl_3$) δ 2.67 (1H, dd, *J* = 16.9, 3.5 Hz, C*H*HC=O) 2.92 (1H, dd, *J* = 16.8, 14.4 Hz, C*H*HC=O), 5.43 (1H, dd, *J* = 14.4, 3.4 Hz, C*H*Ph), 5.53 (1H, d, *J* = 6.0 Hz, CH=C*H*C=O), 7.35-7.46 (5H, m, Ar*H*), 7.49 (1H, d, *J* = 6.0 Hz, C*H*=CHC=O); **^{13}C NMR** ($CDCl_3$) δ 43.52, 81.23, 107.51, 126.23, 128.98, 129.07, 137.97, 163.29, 192.24; **IR** (neat) 1681, 1596, 1404, 1272, 1228, 1209, 1039, 990, 934, 759 cm^{-1}; **MS** (CI) *m/z* 175.

***(2S)-2-Phenyl 2,3-dihydropyran-4-one* (203)** - *using chromium(III)-complex* **204** *with no solvent.*

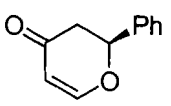


203

A suspension of benzaldehyde (220 μL, 2.16 mmol), flame-dried powdered molecular sieves (4 Å, 450 mg), the chromium(III)-complex **204** (74 mg, 0.13 mmol) and 1-methoxy-3-trimethylsilyloxy-1,3-

butadiene (90%, 0.45 mL, 2.1 mmol) was stirred at room temperature for 22 h. The resultant dark brown reaction mixture was diluted with dichloromethane (3 mL) and trifluoroacetic acid (4 drops) was added. After 30 min, the reaction mixture was filtered and the filtrate was concentrated to afford brown liquid (665 mg). Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **203** (318 mg, 88%) as a pale yellow liquid. The enantiomeric ratio of the purified product was 74:26 as determined by chiral HPLC analysis. $[\alpha]_D^{20}$ + 49.9 (*c* 1.51, chloroform). The ^{1}H NMR spectral data were consistent with that reported above.

***(2S)-2-Phenyl 2,3-dihydropyran-4-one* (203)** - *using chromium(III)-complex* **205** *with no solvent.*

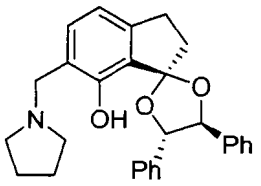


203

A suspension of benzaldehyde (220 μL, 2.16 mmol), flame-dried powdered molecular sieves (4 Å, 450 mg), the chromium (III)-complex **205** (86 mg, 0.132 mmol) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (90%, 0.45 mL, 2.1 mmol) was stirred at room temperature for 44 h. The dark brown reaction mixture was then diluted with dichloromethane (3 mL) and trifluoroacetic acid (4 drops) was added. After 30 min, the reaction mixture was filtered and the filtrate was concentrated to afford brown liquid. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **203** (305 mg, 84%) as a pale yellow liquid. The enantiomeric ratio was 67:33 as determined by chiral HPLC of the purified product. $[\alpha]_D^{20}$ + 32.9 (*c* 1.26, chloroform). The ^{1}H NMR spectral data were consistent with that reported above.

7.3.4 Synthesis of the 7-Hydroxyindan-1-one-Derived Chiral 1,3-Amino Alcohol (215)

***7-Hydroxy-6-((1-pyrrolidinyl)methyl) indan-1-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (215).**

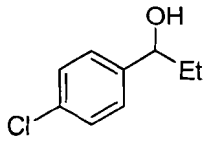


215

A stirred solution of the phenol **68** (189 mg, 0.548 mmol), pyrrolidine (22 μL, 0.26 mmol) and an aqueous solution of formaldehyde (37 wt. %, 0.46 g, 5.3 mmol) in ethanol was heated at reflux for 45 h. Additional pyrrolidine (22 μL, 0.26 mmol) was then added and the reaction was heated at reflux for 45 min. The reaction mixture was then allowed to cool to room temperature and was concentrated to afford a yellow oil. Purification by flash chromatography using hexanes:ether (4:1 to 2:1) as the eluant afforded the *title compound* **215** (122 mg, 54%) as a white gum. $[\alpha]_D^{20}$ - 216 (*c* 0.835, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 1.22-1.32 (4H, m, 2 × C*H*$_2$CH$_2$N), 2.07-2.17 (4H, m, 2 × C*H*$_2$N), 2.59 (1H, ddd, *J* = 10.4, 7.8, 2.0 Hz, ArCH$_2$C*H*H), 2.70-2.86 (2H, m, ArC*H*H and ArCH$_2$CH*H*), 2.92-3.02 (1H, m, ArCH*H*), 3.31 (1H, d, *J* = 13.7 Hz, C*H*HN), 3.58 (1H, d, *J* = 13.7 Hz, CH*H*N), 4.92 (1H, d, *J* = 8.5 Hz, C*H*Ph), 5.97 (1H, d, *J* = 8.5 Hz, C*H*Ph), 6.72 (1H, d, *J* = 7.5 Hz, Ar*H*), 6.89 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.03-7.19 (6H, m, Ar*H*), 7.36-7.40 (2H, m, Ar*H*), 7.73-7.68 (2H, m, Ar*H*); **^{13}C NMR** (C_6D_6) δ 23.63, 28.66, 39.90, 53.31, 59.03, 86.69, 87.07, 115.43, 119.28, 121.29, 127.20, 128.10, 128.41, 128.49, 129.16, 129.85, 137.90, 138.60, 145.96, 155.96; **IR** (film) 1625, 1591, 1497, 1458, 1319, 1126, 1087, 1077, 1026, 943, 758 cm^{-1}; **MS** (MALDI) *m/z* 428 (M+H), 379; **Anal.** Calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.81; H, 7.02, N, 3.39.

7.3.5 Catalytic Asymmetric Addition Reaction of Diethylzinc and *p*-Chlorobenzaldehyde

***1-(4-Chlorophenyl)propan-1-ol* (217).**

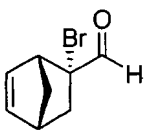


217

To a stirred solution of the amino alcohol **215** (25 mg, 0.59 mmol) in toluene (2.5 mL) at room temperature was added diethylzinc (0.77 M in hexanes, 4.6 mL, 3.6 mmol). After 20 min, *p*-chlorobenzaldehyde (173 mg, 1.19 mmol) was then added. After 2 h, the reaction mixture was quenched by the addition of hydrochloric acid (1 M, 10 mL), diluted with water (10 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated to afford a pale yellow oil. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **217** (201 mg, 96%) as a colourless oil. The enantiomeric ratio of the purified product was 52:48 as determined by chiral HPLC analysis (95:5 hexanes:isopropanol, 0.5 mL/min, $t_{R(major)}$ = 17.4 min, $t_{R(minor)}$ = 18.8 min). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.81 (3H, t, J = 7.5 Hz, CH_3), 1.57-1.74 (2H, m, CH_2), 1.75-1.83 (1H, broad s, O*H*), 4.47-4.51 (1H, m, C*H*OH), 7.16-7.19 (2H, m, Ar*H*), 7.20-7.23 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$, 500 MHz) δ 10.12, 32.08, 75.41, 127.47, 128.63, 133.20, 143.11, 172.49; **IR** (neat) 3362, 1598, 1492, 1463, 1409, 1091, 1013, 824 cm^{-1}.

7.3.6 Boron-Catalyzed Diels-Alder Reaction

***exo-2-Bromobicyclo[2.2.1]hept-5-ene-2-carbaldehyde* (*rel*-219).**[125a]



rel-**219**

The amino alcohol **215** (17 mg, 0.040 mmol) was azeotropically-dried by evaporation from a stirred toluene solution under high-vacuum overnight. To a stirred solution of the dried amino alcohol **215** in dichloromethane (1 mL) and 2,6-di-*t*-butylpyridine (9 μL, 0.04 mmol) at 0 °C was added boron tribromide (0.5 M in dichloromethane, 80 μL, 0.040 mmol) over 5 min. After 15 min, the reaction mixture was cooled to -78 °C and α-bromoacrolein **218**[126] (41 μL, 0.51 mmol) was added

followed by cyclopentadiene (200 μL, 2.42 mmol). After 2 h, the reaction mixture was allowed to warm slowly to -50 °C over 2 h at which time triethylamine (100 μL, 7.2 mmol) was added. The reaction mixture was then allowed to warm to room temperature and was concentrated to afford a yellow gummy solid. Purification by flash chromatography using hexanes:ether (15:1) as the eluant afforded the *title compound rel-***219** (43 mg, 42%) as a pale yellow oil. The enantiomeric ratio was of the purified product was 50:50 as determined by ^{1}H NMR spectroscopy of a chiral acetal derivative.*

^{1}H NMR ($CDCl_3$) δ 1.32 (1H, apparent d, *J* = 9.3 Hz, C*H*HCBr), 1.49 (1H, dd, *J* = 13.4, 3.7 Hz, CH*H*-bridge), 1.53-1.58 (1H, m, C*H*HCBr), 2.65 (1H, dd, *J* = 13.5, 3.6 Hz, C*H*H-bridge), 2.98 (1H, broad s, C*H*-bridgehead), 3.24-3.27 (1H, m, C*H*-bridgehead), 6.14 (1H, dd, *J* = 5.6, 3.0 Hz, C*H*=CH), 6.45 (1H, dd, *J* = 5.6, 3.1 Hz, CH=C*H*), 9.54 (1H, s, C*H*O).

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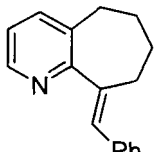
* A solution of a sample of the purified aldehyde *rel*-**219** (1 equiv), (2*S*,4*S*)-2,4-pentanediol **220** (1.5 equiv) and pyridinium *p*-toluenesulfonate (0.1 equiv) in acetonitrile was stirred at room temperature for 16 h. The diastereomeric ratio of the acetals **221** and **222** was determined as 50:50 by analysis of the ^{1}H NMR spectrum of the crude reaction product.

7.4 Experimental Procedures and Characterization Data Concerning Chapter 4

7.4.1 Synthesis of the Model Chiral Pyridine [241 (R = Me)]

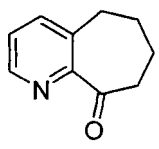
***(E)-9-Benzylidene-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine* (239).**



239

A stirred solution of 6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine **238** (2.6 mL, 17 mmol), acetic anhydride (3.1 mL, 33 mmol) and benzaldehyde (2.6 mL, 25 mmol) was heated at reflux for 5 days. The reaction mixture was then allowed to cool to room temperature and was concentrated under high vacuum (with stirring). The residue was dissolved in water (20 mL), basified to pH ~ 10 with an aqueous solution of sodium hydroxide (2 M) and extracted with dichloromethane (4 × 25 mL). The combined organic extracts were washed with water (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a brown oil. Purification by flash chromatography using hexanes:ethyl acetate (4:1 to 3:1) as the eluant afforded the *title compound* **239** (2.91 g, 73%) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$) δ 1.79-1.94 (4H, m, $ArCH_2CH_2CH_2$), 2.66-2.72 (2H, m, $ArCH_2CH_2CH_2CH_2$), 2.81 (2H, dd, J = 6.4, 5.0 Hz, $ArCH_2$), 7.03 (1H, broad s, C*H*Ph), 7.11 (1H, dd, J = 7.5, 4.8 Hz, Ar*H*), 7.23-7.29 (1H, m, Ar*H*), 7.34-7.40 (2H, m, Ar*H*), 7.43 (1H, dd, J = 7.6, 1.4 Hz, Ar*H*), 7.48 (2H, d, J = 7.4 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 26.86, 28.17, 29.55, 33.69, 122.08, 126.94, 128.29, 129.25, 131.52, 135.29, 137.11, 137.75, 143.19, 146.91, 161.30; **IR** (neat) 1581, 1562, 1493, 1445, 1426, 919, 779 cm^{-1}; **MS** (CI) *m/z* 234 (M+H), 206.

***5,6,7,8-Tetrahydrocyclohepta[b]pyridin-9-one* (240).**

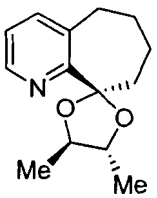


240

A stirred suspension of the alkene **239** (2.68 g, 11.4 mmol) in methanol (85 mL) was purged with oxygen for 30 min at room temperature. The suspension was then cooled to -78 °C and a stream of ozone and oxygen was bubbled through the reaction mixture for 45 min. Dimethyl sulfide (1.4 mL, 19 mmol) was then added and the reaction mixture was allowed to warm slowly to room

temperature. After 24 h, the reaction mixture was concentrated to afford a brown liquid. Purification by flash chromatography using hexanes:ethyl acetate (3:2) as the eluant afforded the *title compound* **240** (1.24 g, 68%) as a yellow oil. **^{1}H NMR** ($CDCl_3$) δ 1.66-1.80 (4H, m, $ArCH_2CH_2CH_2$), 2.61-2.66 (2H, m, $ArCH_2$), 2.76 (2H, dd, *J* = 6.7, 5.5 Hz, $CH_2C{=}O$), 7.19 (1H, dd, *J* = 7.7, 4.6 Hz, Ar*H*), 7.45 (1H, apparent dd, *J* = 7.7, 1.4 Hz, Ar*H*), 8.46 (1H, dd, *J* = 4.7, 1.4 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 21.06, 24.81, 30.78, 40.20, 125.50, 136.19, 137.87, 147.98, 154.64, 204.28; **IR** (neat) 1698, 1567, 1456, 1287, 1099, 1089, 806 cm^{-1}; **MS** (EI) *m/z* 161 (M), 132, 118, 105, 92.

***5,6,7,8-Tetrahydrocyclohepta[b]pyridin-9-one (2R,3R)-butanediol acetal* (241).**



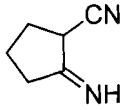
241

A stirred solution of the ketone **240** (511 mg, 3.17 mmol), (2*R*,3*R*)-butanediol **52** (507 mg, 5.63 mmol) and *p*-toluenesulfonic acid monohydrate (734 mg, 3.86 mmol) in benzene (10 mL) was heated at reflux with azeotropic removal of water for 2 days. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (2.0 g) was added. After 30 min, the reaction mixture was filtered and concentrated to afford a brown oil. Purification by flash chromatography using hexanes:ethyl acetate (1:1) then ethyl acetate:methanol (20:1) as the eluant afforded the *title compound* **241** (456 mg, 62%) as a yellow oil that solidified on standing. **Mp** 84-85 °C, hexanes:ethyl acetate:methanol; $[\alpha]_D^{20}$ - 29 (*c* 1.04, chloroform); **^{1}H NMR** (C_6D_6) δ 0.99 (3H, d, *J* = 6.1 Hz, CH_3), 1.15 (3H, d, *J* = 6.1 Hz, CH_3), 1.26-1.39 (1H, m, $ArCH_2CHH$), 1.51-1.62 (1H, m, $ArCH_2CHH$), 1.72-1.86 (1H, $ArCH_2CH_2CHH$), 1.99-2.11 (2H, m, $ArCH_2CH_2CHH$ and $ArCH_2CH_2CH_2CHH$), 2.12-2.21 (1H, m, $ArCH_2CH_2CH_2CHH$), 2.61 (1H, dd, *J* = 13.2, 8.0 Hz, $ArCHH$), 3.07 (1H, dd, *J* = 13.2, 11.8 Hz, $ArCHH$), 3.64 (1H, dq, *J* = 8.1, 6.1 Hz, $CHCH_3$), 4.00 (1H, dq, *J* = 8.0, 6.1 Hz, $CHCH_3$), 6.64 (1H, dd, *J* = 7.4, 4.7 Hz, Ar*H*), 6.94 (1H, dd, *J* = 7.4, 1.4 Hz, Ar*H*), 8.41 (1H, dd, *J* = 4.7, 1.6 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 17.10, 17.61, 25.97, 27.89, 34.58, 38.51, 79.09, 79.41, 109.81, 122.61, 136.67,

137.73, 145.78, 161.52; **IR** (ef) 1452, 1296, 1196, 1100, 1089, 1082, 984, 958 cm^{-1}; **MS** (CI) *m/z* 234 (M+H), 162; **Anal.** Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.15; H, 8.32; N, 6.16.

7.4.2 Synthesis of the Chiral Pyrrolidinopyridines 254 (R = Me) and 255 (R = Ph)

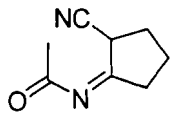
***2-Imino-cyclopentanecarbonitrile* (245).**[194]



245

In a 2-neck, 1 L round-bottom flask equipped with a pressure-equalized dropping funnel and condenser, a molten suspension of sodium metal (23.4 g, 1.02 mol) in toluene (350 mL) was prepared on heating at reflux for 1 h. To this mixture, adiponitrile **244** (105 mL, 0.92 mol) was added over 6 h. After 10 h, over which time a white solid was deposited, the reaction mixture was allowed to cool to room temperature and the solid was isolated by filtration and washed with benzene (100 mL). The solid was then suspended in benzene (200 mL), cooled to 0 °C and ice (~ 200 g) was added slowly. The resultant mixture was allowed to slowly warm to room temperature overnight and then was re-cooled to 0 °C and the white solid product was isolated by filtration. The crude reaction product was extracted with hot benzene (3 × 175 mL) and the combined organic extracts were concentrated to afford the *title compound* **245** (52.7 g, 53%) as an off-white solid. **^{1}H NMR** ($CDCl_3$) δ 1.86-1.96 (2H, m, $CH_2CH_2CH_2$), 2.44 (2H, apparent t, *J* = 7.6 Hz, CH_2CCN=H), 2.52 (2H, apparent tt, *J* = 7.0, 1.2 Hz, CH_2CHCN), 4.21-4.73 (2H, broad s, *CH*CN and N*H*); **^{13}C NMR** ($CDCl_3$) δ 22.09, 31.34, 34.37, 74.66, 119.07, 162.43; **IR** (ef) 3429, 3351, 3235, 2181, 1644, 1608, 1412, 1197 cm^{-1}; **MS** (CI) *m/z* 109 (M+H).

***N-(2-Cyanocyclopentylidene)acetamide* (246).**[194]

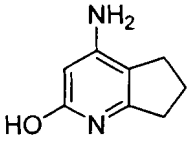


246

The carbonitrile **245** (48.6 g, 0.449 mol) was dissolved in acetic anhydride (315 mL, 3.34 mol) on gentle heating using a water bath. The resultant orange-brown solution was allowed to cool slowly to room

temperature overnight and then was cooled to -10 °C. The precipitate was isolated by filtration, air-dried overnight and then dried further under high vacuum at 50 °C to afford the *title compound* **246** (55.3 g, 82%) as a pale yellow solid. **^{1}H NMR** ($CDCl_3$) δ 1.93-2.04 (2H, m, $CH_2CH_2CH_2$), 2.12 (3H, s, CH_3), 2.47-2.53 (2H, m, CH_2CCN=H), 3.11 (2H, apparent tt, J = 7.6, 2.1 Hz, CH_2CHCN), 8.12-8.24 (1H, broad s, $CHCN$); **^{13}C NMR** ($CDCl_3$) δ 22.26, 24.19, 30.04, 33.73, 87.55, 116.62, 157.00, 168.27; **IR** (ef) 3341, 3280, 3214, 3122, 2204, 1719, 1637, 1513, 1467, 1422, 1379, 1239, 1043, 998 cm^{-1}; **MS** (CI) *m/z* 151 (M+H); **Anal.** Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.85; H, 6.73; N, 18.83.

***4-Amino-2-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine* (247).**[194]

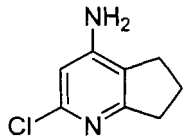


247

In a 2-neck, 1 L round-bottom flask at -78 °C equipped with a cold-finger (-78 °C) was condensed ammonia (~ 550 mL). Sodium metal (0.50 g, 22 mmol) was added and the resultant stirred solution turned an intense blue colour (CAUTION: *H_2 evolved*). Iron(III) nitrate nonahydrate (0.57 g, 1.4 mmol) was then added and the solution became light brown. Additional sodium metal (14.5 g, 652 mmol) was then added in portions over 30 min during which time a grey suspension was formed. The acetamide **246** (20.0 g, 133 mmol) was then added in portions over 45 min and stirring was continued for 2 h. Additional acetamide **246** (20.0 g, 233 mmol) was then added in portions over 45 min and stirring was continued for an additional 4 h. Ammonium chloride (42.7 g) was then added slowly to the reaction mixture and the ammonia was allowed to evaporate overnight. Water (135 mL) was added slowly to the resultant brown-grey solid and the mixture was heated at 90 °C for 30 min. The mixture was then cooled to 0 °C and the resultant grey solid was removed by filtration. The grey solid was dissolved in hot water (900 mL), decolourized with charcoal and filtered. The filtrate was cooled to 0 °C and a light brown solid precipitated. The solid was isolated by filtration, washed with cold water. The filtrates were

combined, concentrated to a volume of ~ 100 mL, cooled to 0 °C and the additional portion of a light brown solid that precipitated was isolated by filtration and washed with cold water. The combined precipitates were dried under high-vacuum at 110 °C for 3 days to afford *title compound* **247** (20.6 g, 52%). An analytical sample of the product, as white needles, was prepared by recrystallization from water. **^{1}H NMR** (CD_3OD) δ 2.06-2.16 (2H, m, $ArCH_2CH_2$), 2.57-2.64 (2H, m, $ArCH_2$), 2.73-2.80 (2H, m, $ArCH_2$), 5.40 (1H, broad s, Ar*H*); **^{13}C NMR** (CD_3OD) δ 23.06, 27.90, 31.96, 91.87, 112.28, 150.26, 158.36, 167.50; **IR** (ef) 3299, 3090, 1641, 1603, 1550, 1481, 1457, 1273, 1254, 1193, 1116, 1046, 918, 821, 802 cm^{-1}; **MS** (CI) *m/z* 151 (M+H); **Anal.** Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.92; H, 6.74; N, 18.34.

***4-Amino-2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine* (248).**

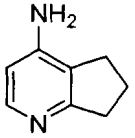


248

A stirred suspension of the 2-hydroxypyridine **247** (12.2 g, 80.9 mmol) in phenylphosphonic dichloride (90%, 60 mL, 0.38 mol) was heated at 160 °C. Within 1 h, the 2-hydroxypyridine **247** had dissolved completely to form an opaque black solution. After 2 h, a grey precipitate began to be deposited and continued to form over the remaining course of the reaction. After 16 h, the reaction mixture was cooled to 0 °C and a few small pieces of ice were added. After 30 min, the reaction mixture began to bubble and ice-water was added until the foaming had ceased. The reaction mixture was then diluted with water (300 mL), basified to pH ~ 10 by the addition of potassium carbonate and extracted with dichloromethane (5 × 175 mL). The combined orange organic extracts were dried over anhydrous magnesium sulfate and concentrated of afford the *title compound* **248** (11.5 g, 84%) as a light brown solid. An analytical sample of the product, as pale brown rosettes, was prepared by recrystallization from benzene. **Mp** 156-157 °C, benzene; **^{1}H NMR** (CD_3OD) δ 1.99-2.09 (2H, m, $ArCH_2CH_2$), 2.56-2.21 (2H, m, $ArCH_2$), 2.77-2.83 (2H, m, $ArCH_2$), 6.28 (1H, s, Ar*H*); **^{13}C NMR** (CD_3OD) δ 21.85, 26.52, 33.70, 105.52, 119.27, 128.10, 149.37,

151.54, 165.00; **IR** (ef) 3364, 3303, 3126, 1650, 1590, 1463, 1405, 1318, 1262, 1206, 1128, 1034, 900, 846 cm^{-1}; **MS** (CI) *m/z* 171 (^{37}Cl, M+H), 169 (^{35}Cl, M+H); **Anal.** Calcd for $C_8H_9ClN_2$: C, 56.98; H, 5.38; N, 16.61. Found: C, 57.33; H, 5.49, N, 16.34.

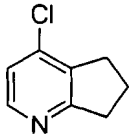
***4-Amino-6,7-dihydro-5H-cyclopenta[b]pyridine* (249).**



249

To a solution of the 2-chloropyridine **248** (11.5 g, 68.3 mmol) in ethanol (150 mL) were added sodium hydroxide (5.42 g, 136 mmol) and palladium on activated carbon (10 wt. %, 0.93 g). The reaction mixture was shaken (Parr apparatus) under an atmosphere of hydrogen (50 p.s.i.) for 2 days and then filtered through Celite® with methanol (75 mL). The yellow filtrate was concentrated to afford a pale yellow gummy solid. The solid was then dissolved in dichloromethane (225 mL) and washed with brine (3 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **249** (8.68 g, 95%) as a pale yellow solid which was used without further purification. **^{1}H NMR** ($CDCl_3$) δ 2.04-2.12 (2H, m, $ArCH_2CH_2$), 2.68 (2H, apparent t, J = 7.4 Hz, $ArCH_2$), 2.86-2.91 (2H, m, $ArCH_2$), 2.92-3.05 (2H, broad s, NH_2), 6.31 (1H, d, J = 5.7 Hz, Ar*H*), 7.85 (1H, d, J = 5.7 Hz, Ar*H*); **IR** (ef) 3460, 3438, 3337, 3192, 1646, 1601, 1573, 1490, 1449, 1352, 1071, 824 cm^{-1}; **MS** (CI) *m/z* 135 (M+H).

***4-Chloro-6,7-dihydro-5H-cyclopenta[b]pyridine* (250).**[195]

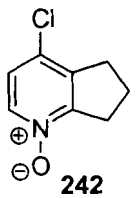


250

To the 4-aminopyridine **249** (8.68 g, 64.7 mmol) was added hydrochloric acid (37 wt. %, 280 mL) and the reaction mixture was stirred at 0 °C until a yellow solution had formed. Sodium nitrite (13.4 g, 194 mmol) was then added in portions over 1 h and the resultant bright orange reaction mixture was stirred for an additional 2 h at 0 to 5 °C. The reaction mixture was then transferred to a 1 L Erlenmeyer flask with water (100 mL), cooled to 0 °C and an aqueous solution of sodium hydroxide (15 wt. %, 500 mL) was added slowly such that the internal temperature did not exceed 50 °C (CAUTION: *foaming; brown gas evolved*). The reaction mixture was

then basified to pH ~ 10 by the slow addition of sodium hydroxide pellets with swirling (CAUTION: *latency of reaction*). The mixture was then extracted with dichloromethane (4 × 150 mL) and washed with water (2 × 50 mL). The combined orange organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to afford the *title compound* **250** (8.53 g, 86%) as a red-brown liquid which was used without further purification. **^{1}H NMR** ($CDCl_3$) δ 2.08-2.19 (2H, m, $ArCH_2CH_2$), 2.98 (2H, t, J = 7.6 Hz, $ArCH_2$), 3.03-3.10 (2H, m), 7.03 (1H, d, J = 5.5 Hz), 8.21 (1H, d, J = 5.5 Hz); **^{13}C NMR** ($CDCl_3$) δ 22.09, 30.01, 35.10, 121.49, 135.90, 140.79, 148.59, 167.35; **IR** (neat) 1583, 1557, 1458, 1390, 1316, 1141, 903, 817 cm^{-1}; **MS** (CI) *m/z* 156 (^{37}Cl, M+H), 154 (^{35}Cl, M+H).

***4-Chloro-6,7-dihydro-5H-cyclopenta[b]pyridine N-oxide* (242).**

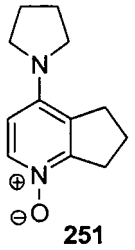


242

To a stirred solution of the 4-chloropyridine **250** (8.53 g, 55.5 mmol) in glacial acetic acid (40 mL) was added an aqueous solution of hydrogen peroxide (30 wt. %, 6 mL) and the resultant mixture was heated at 80 °C for 3 h. Additional hydrogen peroxide (30 wt. %, 4 mL) was then added and the mixture was heated at 80 °C overnight. Additional hydrogen peroxide (30 wt. %, 2 mL) was then added and the reaction mixture was heated at 80 °C for a further 4 h. The reaction mixture was then cooled to 0 °C, basified to pH ~ 10 with an aqueous solution of sodium hydroxide (40 wt. %) and extracted with dichloromethane (3 × 75 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **242** (8.36 g, 89%) as an off-white solid which was used without further purification. An analytical sample of the product, as a white solid, was prepared by precipitation from ethyl acetate on the addition of hexanes. **^{1}H NMR** ($CDCl_3$) δ 2.17-2.26 (2H, m, $ArCH_2CH_2$), 3.02-3.09 (2H, m, $ArCH_2$), 3.19-3.25 (2H, m, $ArCH_2$), 7.08 (1H, d, J = 6.7 Hz, Ar*H*), 7.98 (1H, d, J = 6.7 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 21.38, 30.72, 31.37, 124.27, 129.08, 138.56, 140.37, 154.10; **IR** (ef) 3388,

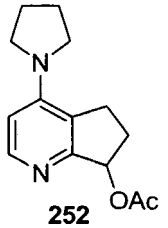
1639, 1561, 1432, 1326, 1311, 1254, 1234, 1182, 1015, 821, 729 cm^{-1}; **MS** (CI) *m/z* 172 (^{37}Cl, M+H), 170 (^{35}Cl, M+H), 154, 156.

***4-(Pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridine N-oxide* (251).**[130]


251

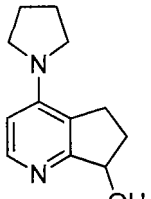
A glass tube was charged with the 4-chloropyridine *N*-oxide **242** (3.36 g, 19.8 mmol), pyrrolidine (14 mL, 0.17 mol) and water (21 ml). The tube was then sealed and heated in a sand bath at 140 °C for 24 h (CAUTION: *use blast shield*). The reaction mixture was then allowed to cool to room temperature and was cooled further to -78 °C before being opened. The reaction mixture was concentrated onto potassium carbonate (2.5 g). The resultant brown gummy solid was extracted with acetone (5 × 50 mL) and the combined extracts were filtered though a plug of anhydrous magnesium sulfate and concentrated to afford the *title compound* **251** (4.06 g, ~ 100%) as a brown solid which was used without further purification. **^{1}H NMR** ($CDCl_3$) δ 1.93-1.99 (4H, m, 2 × CH_2CH_2N), 2.03-2.12 (2H, m, $ArCH_2CH_2$), 3.09-3.15 (2H, apparent t, *J* = 7.6 Hz, $ArCH_2$), 3.21-3.28 (2H, m, $ArCH_2$), 3.42-3.49 (4H, m, 2 × CH_2N), 6.18 (1H, d, *J* = 7.3 Hz, Ar*H*), 7.82 (1H, d, *J* = 7.3 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 22.26, 25.54, 29.89, 33.07, 49.40, 107.69, 122.82, 137.38, 144.97, 153.66; **IR** (ef) 3385, 1623, 1498, 1458, 1233, 980 cm^{-1}; **MS** (CI) *m/z* 205 (M+H), 189.

***4-(Pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate* (252).**[130,139]


252

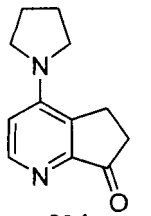
A solution of the 4-pyrrolidinopyridine *N*-oxide **251** (3.68 g, 18.0 mmol) in acetic anhydride (37 mL, 0.39 mol) was stirred at room temperature for 90 min and then at heated at 100 °C for 3 h over which time the reaction mixture became dark brown. The reaction mixture was then allowed to cool to room temperature and was concentrated to afford a brown oil. Purification by flash chromatography using ether:methanol (15:1) then ether:methanol:triethylamine (10:1:1) as the eluant afforded the *title compound* **252** (4.01 g, 90%) as an orange-red gum. The product was used in the next synthetic step without characterization.

***4-(Pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol* (253).**


253

A solution of the acetate **252** (4.01 g, 16.3 mmol) and lithium hydroxide monohydrate (2.15 g, 51.2 mmol) in tetrahydrofuran:water (3:1, 60 mL) was stirred at room temperature for 6 h. The resultant orange reaction mixture was then diluted with water (175 mL), extracted with dichloromethane (3 × 75 mL) and washed with brine (25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound* **253** (3.15 g, 95%) as an orange solid. An analytical sample of the product, as pale yellow needles, was prepared by recrystallization from ether:dichloromethane by slow evaporation. **Mp** 164-165 °C, ether:dichloromethane; **^{1}H NMR** ($CDCl_3$) δ 1.88-2.02 (4H, m, 2 × CH_2CH_2N and ArC*H*H), 2.36-2.47 (1H, m, ArCH*H*), 2.99-3.09 (1H, m, $ArCH_2CHH$), 3.31 (1H, ddd, J = 15.2, 8.8, 4.0 Hz, $ArCH_2CHH$), 3.48-3.55 (4H, m, 2 × CH_2CH_2N), 5.07-5.14 (1H, m, CHO*H*), 5.67 (1H, broad s, O*H*), 6.20 (1H, d, J = 5.8 Hz, Ar*H*), 8.03 (1H, d, J = 5.8 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 25.54, 29.00, 32.35, 49.10, 74.19, 106.68, 118.66, 147.83, 151.66, 164.90; **IR** (ef) 3083, 1586, 1500, 1486, 1389, 1322, 1085, 1057, 831 cm^{-1}; **MS** (CI) *m/z* 205 (M+H); **Anal.** Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.35; H, 7.85; N, 13.55.

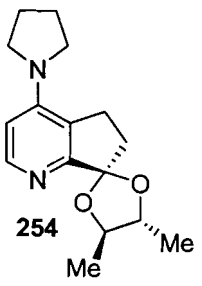
***4-(Pyrrolidin-1-yl)-5,6-dihydrocyclopenta[b]pyridin-7-one* (224).**


224

To solution of oxalyl chloride (0.75 mL, 8.6 mmol) in dichloromethane (50 mL) at -78 °C, dimethylsulfoxide (2.0 mL, 28 mmol) was added (CAUTION: *gas evolved*). After 10 min, a solution of the pyridin-7-ol **253** (1.43 g, 7.01 mmol) in dichloromethane (30 mL) was added over 10 min. After 10 min, triethylamine (4.9 mL, 35 mmol) was added and after an additional 1 h, the reaction mixture was allowed to warm slowly to -25 °C over 1 h. The reaction mixture was then washed with water (4 × 15 mL), brine (15 mL), dried over anhydrous

magnesium sulfate, filtered and concentrated to afford a dark brown solid. Purification by flash chromatography using chloroform then chloroform:methanol (95:5) as the eluant afforded the *title compound* **224** (953 mg, 67%) as a pale brown solid. An analytical sample of the product, as a white solid, was prepared by repeated flash chromatography using ether:methanol (4:1) as the eluant. **Mp** 185-190 °C (decomposition), ether:methanol; **^{1}H NMR** (C_6D_6) δ 2.00-2.06 (4H, m, 2 × C*H*$_2$CH$_2$N), 2.63 (2H, apparent t, *J* = 5.4 Hz, ArC*H*$_2$), 3.37 (2H, apparent t, *J* = 5.4 Hz, ArCH$_2$C*H*$_2$), 3.57-3.63 (4H, 2 × C*H*$_2$N), 6.34 (1H, d, *J* = 5.5 Hz, Ar*H*), 8.30 (1H, d, *J* = 5.5 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 24.92, 25.53, 34.40, 49.33, 109.25, 135.08, 151.15, 152.30, 154.39, 206.30; **IR** (ef) 3415, 1721, 1584, 1508, 1400, 1289, 1080 cm^{-1}; **MS** (CI) *m/z* 203 (M+H). Satisfactory elemental analysis could not be obtained for this reaction product.

***4-(Pyrrolidin-1-yl)-5,6-dihydrocyclopenta[b]pyridin-7-one (2R,3R)-2,3-butanediol acetal* (254).**

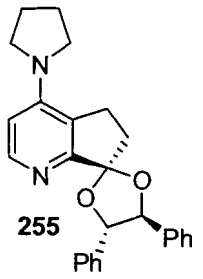


254

A brown suspension of the ketone **224** (74 mg, 0.36 mmol), (2*R*,3*R*)-2,3-butanediol **52** (68 μL, 0.74 mmol) and *p*-toluenesulfonic acid monohydrate (106 mg, 0.556 mmol) in benzene (12 mL) was purged with nitrogen gas for 15 min. The suspension was then heated at reflux with azeotropic removal of water for 20 h over which time the reaction mixture became a dark brown solution. The reaction mixture was then allowed to cool to room temperature and was poured into a saturated aqueous solution of sodium carbonate (25 mL) and extracted with chloroform (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil (135 mg). Purification by flash chromatography using acetone as the eluant afforded the *title compound* **254** (78 mg, 77%) as a white solid. **Mp** 86-87 °C, acetone; $[\alpha]_D^{20}$ - 10.9 (*c* 1.23, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 1.21 (3H, d, *J* = 6.1 Hz, C*H*$_3$), 1.24-1.29 (4H, m, 2 × C*H*$_2$CH$_2$N), 1.49

(3H, d, J = 6.0 Hz, CH_3), 2.43 (2H, apparent ddd, J = 10.1, 6.0, 3.0 Hz, ArCH$_2$CH_2), 2.73-2.84 (6H, m, 2 × CH_2N and ArCH_2), 3.82 (1H, dq, J = 8.1, 6.0 Hz, CHCH$_3$), 4.96 (1H, dq, J = 8.1, 6.1 Hz, CHCH$_3$), 5.90 (1H, d, J = 5.6 Hz, ArH), 8.37 (1H, d, J = 5.6 Hz, ArH); **^{13}C NMR** (C_6D_6) δ 16.84, 17.69, 25.26, 27.04, 36.14, 48.58, 79.13, 79.86, 107.21, 114.79, 119.32, 149.74, 151.09, 163.72; **IR** (ef) 1587, 1546, 1536, 1501, 1485, 1390, 1297, 1200, 1089, 1005, 808 cm^{-1}; **MS** (CI) *m/z* 275 (M+H), 203, 189; **Anal.** Calcd for $C_{12}H_{14}N_2O$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.99; H, 7.89; N, 10.05.

***4-(Pyrrolidin-1-yl)-5,6-dihydrocyclopenta[b]pyridin-7-one (1S,2S)-1,2-diphenyl-1,2-ethanediol acetal* (255).**



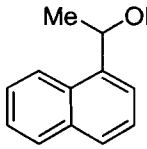
255

A brown suspension of the ketone **224** (75 mg, 0.37 mmol), (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **29** (162 mg, 0.757 mmol) and *p*-toluenesulfonic acid monohydrate (105 mg, 0.551 mmol) in benzene (12 mL) was purged with nitrogen gas for 15 min. The suspension was then heated at reflux with azeotropic removal of water for 20 h over which time the reaction mixture became a dark brown solution. The reaction mixture was then allowed to cool to room temperature and was poured into a saturated aqueous solution of sodium carbonate (25 mL) and extracted with chloroform (3 × 20 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil. Purification by flash chromatography using ether as the eluant afforded the *title compound* **255** (102 mg, 69%) as a white foam. **Mp** 83-84 °C, ether; $[\alpha]_D^{20}$ - 104 (*c* 1.09, tetrahydrofuran); **^{1}H NMR** (C_6D_6) δ 1.25-1.34 (4H, m, 2 × CH_2CH$_2$N), 2.54-2.67 (2H, m, ArCH$_2$CH_2), 2.78-2.88 (6H, m, 2 × CH$_2$CH_2N and ArCH_2), 5.04 (1H, d, J = 8.5 Hz, CHPh), 5.94 (1H, d, J = 5.6 Hz, ArH), 6.27 (1H, d, J = 8.5 Hz, CHPh), 7.03-7.12 (4H, m, ArH), 7.13-7.20 (2H, m, ArH), 7.38 (2H, d, J = 7.2 Hz, ArH), 7.83 (2H, d, J = 7.6 Hz, ArH), 8.48 (1H, d, J = 5.6 Hz, ArH); **^{13}C NMR** (C_6D_6) δ 25.28, 27.08, 36.28, 48.63,

86.63, 87.24, 107.48, 115.88, 119.89, 127.31, 128.47, 137.73, 138.35, 150.15, 151.24, 163.28; **IR** (ef) 1588, 1500, 1484, 1455, 1390, 1299, 1198, 1159, 1092, 1052, 1024, 937, 814, 759 cm^{-1}; **MS** (CI) *m/z* 399 (M+H), 203, 135, 117; **Anal.** Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.03; H, 6.79; N, 6.80.

7.4.3 Synthesis of the Racemic Alcohol (*RS*-234) and Acetate (*RS*-236) for Kinetic Resolutions

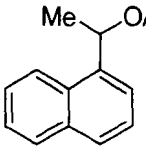
***1-(1-Naphthyl)ethanol* (*RS*-234).**



RS-**234**

To a stirred solution of methyllithium (1.4 M in ether, 48 mL, 68 mmol) at -78 °C was added a solution of 1-naphthaldehyde (9.0 mL, 64 mmol) in ether (15 mL) over 45 min. After 1 h, the yellow reaction mixture was allowed to warm to room temperature over 1 h. After 1 h, the dark brown reaction mixture was cooled to 0 °C and a saturated aqueous solution of potassium carbonate (40 mL) was added dropwise (CAUTION: *methane gas evolved*). The organic layer was separated and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford the *title compound RS*-**234** (12.1 g, 96%) as yellow oil that solidified on standing. Purification by recrystallization from hexanes:ether (5:1) by slow evaporation afforded the product as fine white needles. **^{1}H NMR** ($CDCl_3$) 1.68 (3H, d, J = 6.5 Hz, C*H*$_3$), 1.96 (1H, broad s, O*H*), 5.68 (1H, q, J = 6.5 Hz, C*H*CH$_3$), 7.47-7.56 (3H, m, Ar*H*), 7.68 (1H, apparent d, J = 7.1 Hz, Ar*H*), 7.79 (1H, d, J = 8.2 Hz, Ar*H*), 7.88 (1H, dd, J = 9.4, 7.8 Hz, Ar*H*), 8.12 (1H, apparent d, J = 8.4 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 24.49, 67.28, 122.13, 123.31, 125.67, 126.16, 128.08, 129.03, 130.44, 133.97, 141.50; **IR** (ef) 3359, 1596, 1509, 1110, 1066, 1011, 897, 800, 777 cm^{-1}; **MS** (CI) *m/z* 172 (M), 155.

***1-(1-Naphthyl)ethyl acetate* (*RS*-236).**



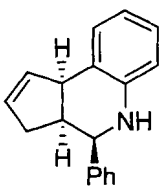
RS-**236**

To a stirred solution of the alcohol *RS*-**234** (323 mg, 1.87 mmol) and *N*,*N*-dimethyl-4-aminopyridine (31 mg, 0.25 mmol) in triethylamine (5.0 mL, 19 mmol) at 0 °C was added acetic anhydride (250 μL, 2.65 mmol) over 3 min and the reaction mixture was allowed to warm slowly to room temperature. After 24 h, additional acetic anhydride (250 μL, 2.65 mmol) was added. After 4 h, the reaction mixture was diluted with ether (25 mL) and washed with hydrochloric acid (1 M, 2 × 5 mL) and a saturated solution of sodium carbonate (2 × 5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow oil. Purification by flash chromatography using hexanes:ether (5:1) as the eluant afforded the *title compound RS*-**236** (393 mg, 98%) as a colourless oil. **^{1}H NMR** ($CDCl_3$) δ 1.71 (3H, d, J = 6.6 Hz, CH_3CH), 2.13 (3H, s, CH_3C=O), 6.66 (1H, q, J = 6.6 Hz, $CHCH_3$), 7.45-7.57 (3H, m, Ar*H*), 7.61 (1H, d, J = 7.0 Hz, Ar*H*), 7.81 (1H, d, J = 8.2 Hz, Ar*H*), 7.88 (1H, apparent dd, J = 9.4, 7.9 Hz), 8.09 (1H, d, J = 7.9 Hz, Ar*H*); **^{13}C NMR** (C_6D_6) δ 21.50, 21.85, 69.60, 123.34, 125.49, 125.80, 126.44, 128.58, 129.05, 130.42, 133.99, 137.58, 170.47; **IR** (film) 1738, 1598, 1512, 1446, 1370, 1235, 1172, 1235, 1172, 1089, 1070, 1022, 942, 800, 778 cm^{-1} **MS** (CI) *m/z* 214, 155.

7.5 Experimental Procedures and Characterization Data Concerning Chapter 5

7.5.1 Synthesis of the Racemic Tetrahydroquinolines

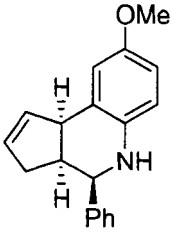
(3aRS,4SR,9bSR)-4-Phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (*RS*-272).[196]



RS-272

To a stirred solution of aniline (2.4 mL, 26 mmol) and cyclopentadiene (6.0 mL, 73 mmol) in acetonitrile (10 mL) was added trifluoroacetic acid (2.1 mL, 27 mmol , CAUTION: *exothermic*). After allowing the resultant brown-orange solution to cool to room temperature, benzaldehyde (2.7 mL, 27 mmol) was added over 1 min and the solution was stirred for 1 h. The brown-red solution was then diluted with a saturated aqueous solution of sodium bicarbonate (30 mL) and extracted with ether (100 mL). The deep red organic layer was washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and concentrated to afford a red solid. Purification by recrystallization from ether:hexanes (1:1) by slow evaporation afforded the *title compound RS*-**272** (2.20 g, 34%) as large colourless crystals. **^{1}H NMR** ($CDCl_3$) δ 1.82 (1H, apparent dd, *J* = 16.5, 8.8 Hz, C*H*HCH=CH), 2.59-2.74 (1H, m, CH*H*CH=CH), 3.03 (1H, ddd, *J* = 18.0, 9.1, 3.4 Hz, C*H*CH_2), 3.54-3.95 (1H, broad s, N*H*), 4.13 (1H, d, *J* = 8.5 Hz, C*H*CH=CH), 4.65 (1H, d, *J* = 3.0 Hz, C*H*NH), 5.63-5.70 (1H, m, C*H*=CH), 5.82-5.89 (1H, m, CH=C*H*), 6.64 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.77 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.00 (1H, apparent t, *J* = 7.3 Hz, Ar*H*), 7.07 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.27-7.33 (1H, m, Ar*H*), 7.35-7.41 (2H, m, Ar*H*), 7.45 (2H, d, *J* = 7.3 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 31.61, 46.14, 46.52, 58.22, 116.06, 119.32, 126.25, 126.47, 126.63, 127.36, 128.63, 129.12, 130.51, 134.12, 142.96, 145.74, **IR** (film) 3357, 3050, 2913, 2846, 1607, 1586, 1497, 1474, 1452, 1360, 1311, 1289, 1260, 1228, 111, 1034, 1008, 750, 702 cm^{-1}; **MS** (CI) *m/z* 248 (M+H), 247 (M).

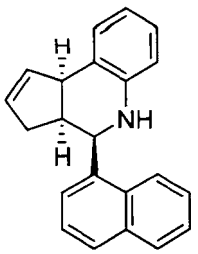
(3aRS,4SR,9bSR)-8-Methoxy-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline **(*RS*-273).**[197]



RS-**273**

To a stirred solution of 4-methoxyaniline (661 mg, 5.37 mmol) in acetonitrile (10 mL) at 0 °C was added trifluoroacetic acid (0.41 mL, 5.4 mmol), cyclopentadiene (0.89 mL, 11 mmol) and benzaldehyde (0.55 mL, 5.4 mmol). The resultant suspension was stirred at 0 °C for 30 min and then at room temperature for 1.5 h over which time the reaction mixture became a dark brown solution. The reaction mixture was then diluted with a saturated aqueous solution of sodium carbonate (75 mL) and extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (25 mL) and concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded the *title compound RS*-**273** (682 mg, 46%) as a colourless gum which solidified on standing. An analytical sample of the product was prepared by recrystallization from ethanol. **Mp** 102-104 °C, ethanol; **^{1}H NMR** ($CDCl_3$) δ 1.83 (1H, apparent dd, *J* = 16.3, 8.7 Hz, C*H*HCH=CH), 2.60-2.71 (2H, m, CH*H*CH=CH), 3.01 (1H, ddd, *J* = 18.0, 9.0, 3.4 Hz, ArCHC*H*), 3.76 (3H, s, CH_3), 4.10 (1H, apparent d, *J* = 9.0 Hz, ArC*H*), 4.58 (1H, d, *J* = 3.0 Hz, C*H*NH), 5.65-5.70 (1H, m, C*H*=CH), 5.81-5.86 (1H, m, CH=C*H*), 6.61 (2H, apparent d, *J* = 2.6 Hz, Ar*H*) 6.67 (1H, apparent d, *J* = 2.3 Hz, Ar*H*), 7.27-7.32 (1H, m, Ar*H*), 7.34-7.40 (2H, m, Ar*H*), 7.45 (2H, apparent d, *J* = 7.3 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 31.56, 45.90, 47.00, 55.85, 58.67, 112.51, 114.24, 116.87, 126.63, 127.30, 127.38, 128.57, 130.79, 133.82, 139.59, 143.07, 153.13; **IR** (film) 3349, 1504, 1466, 1250, 1233, 1041, 702 cm^{-1}, **MS** (CI) *m/z* 278 (M+H); **Anal.** Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.42; H, 6.84; N, 4.81.

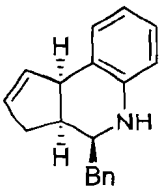
***(3aRS,4SR,9bSR)-4-(1-Naphthyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline* (*RS*-274).**



RS-**274**

A solution of aniline (0.49 mL, 5.4 mmol), 1-naphthaldehyde (0.73 mL, 5.4 mmol), cyclopentadiene (0.89 mL, 11 mmol) and trifluoroacetic acid (0.41 mL, 5.4 mmol) in acetonitrile (5 mL) was stirred at 0 °C for 2 h. The reaction mixture was then poured into a saturated aqueous solution of sodium carbonate (75 mL) and extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a brown-red oil. Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded the *title compound RS*-**274** (0.88 g, 55%) as a white solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from ether by slow evaporation. **Mp** 121-122 °C, ether; **^{1}H NMR** ($CDCl_3$) δ 1.65 (1H, dd, *J* = 16.0, 8.8 Hz, C*H*HCH=CH), 2.60-2.75 (1H, m, CH*H*CH=CH), 3.33 (1H, ddd, *J* = 18.0, 9.0, 3.2 Hz, C*H*CH_2), 3.74 (1H, broad s, N*H*), 4.26 (1H, d, *J* = 9.0 Hz, C*H*CH=CH), 5.45 (1H, d, *J* = 2.9 Hz, C*H*NH), 5.61-5.66 (1H, m, C*H*=CH), 5.84-5.88 (1H, m, CH=C*H*), 6.71 (1H, d, *J* = 7.5 Hz, Ar*H*), 6.78-6.85 (1H, m, Ar*H*), 7.00-7.07 (1H, m, Ar*H*), 7.14 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.49-7.58 (3H, m, Ar*H*), 7.82 (2H, d, *J* = 7.9 Hz, Ar*H*), 7.90-7.93 (1H, m, Ar*H*), 8.14 (1H, d, *J* = 7.9 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 32.04, 43.92, 46.60, 53.93, 116.27, 119.41, 122.58, 122.98, 125.60, 125.69, 126.24, 126.47, 126.59, 127.77, 129.14, 129.17, 130.44, 130.62, 133.87, 134.10, 138.37, 146.23; **IR** (ef) 3354, 3049, 2930, 2849, 1605, 1586, 1498, 1474, 1285, 908, 786 cm^{-1}; **MS** (CI) *m/z* 354 (M+isobutane), 298 (M+H); **Anal.** Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 89.06; H, 6.31; H, 4.75.

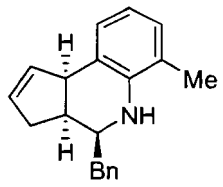
***(3aSR,4SR,9bRS)-4-Benzyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline* (*RS*-275).**



RS-**275**

To a stirred solution of aniline (1.4 mL, 16 mmol) in acetonitrile (10 mL) at 0 °C was added trifluoroacetic acid (1.5 mL, 20 mmol) and cyclopentadiene (13 mL, 0.16 mol). A solution of phenylacetaldehyde (90%, 2.0 mL, 15 mmol) in acetonitrile (10 mL) was then added over 1 h. After 30 min, the reaction mixture was allowed to warm to room temperature over the course of 1 h and then was diluted with ether (100 mL). The resultant orange solution was washed with a saturated aqueous solution of sodium bicarbonate (5 × 75 mL), brine (75 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford a yellow gum. Purification by flash column chromatography using hexanes:ether (10:1) as the eluant afforded the *title compound RS*-**275** (0.91 g, 23%) as a yellow gum. **^{1}H NMR** ($CDCl_3$) δ 2.39 (1H, dddd, *J* = 16.0, 8.8, 2.4, 1.7 Hz, C*H*HCH=CH), 2.66-2.77 (2H, m, PhC*H*H and CH*H*CH=CH), 2.82-2.94 (2H, m, PhCH*H* and C*H*CH_2), 3.44 (1H, broad s, N*H*), 3.64-3.70 (1H, m, C*H*CH=CH), 4.00 (1H, d, *J* = 8.8 Hz, C*H*NH), 5.73-5.78 (1H, m, C*H*=CH), 5.84-5.88 (1H, m, CH=C*H*), 6.45 (1H, dd, *J* = 7.9, 1.1 Hz, Ar*H*), 6.68-6.74 (1H, m, Ar*H*), 6.93 (1H, apparent t, *J* = 8.0 Hz, Ar*H*), 7.02 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.25-7.32 (3H, m, Ar*H*), 7.34-7.40 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 31.60, 40.66, 42.92, 46.49, 55.02, 115.76, 119.02, 126.27, 126.47, 126.77, 128.86, 129.08, 129.26, 130.21, 134.61, 138.60, 145.49; **IR** (ef) 3371, 1604, 1589, 1496, 1476, 1454, 751, 701 cm^{-1}; **MS** (CI) *m/z* 262 (M+H); **Anal.** Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.20; H, 7.48; N 5.55.

(3aSR,4SR,9bRS)-4-Benzyl-6-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (*RS*-276).

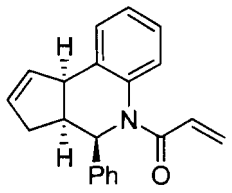


RS-**276**

A solution of 2-methylaniline (1.0 mL, 9.4 mmol), phenylacetaldehyde (90%, 1.2 mL, 9.2 mmol), cyclopentadiene (2.8 mL, 34 mmol) and trifluoroacetic acid (0.72 mL, 9.3 mmol) in acetonitrile (8 mL) was stirred at 0 °C for 30 min and then at room temperature for 30 min. The reaction mixture was then poured into a saturated aqueous solution of sodium bicarbonate (100 mL) and extracted with ether (2 × 75 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a bright orange liquid. Purification by flash chromatography on neutral alumina (Brockman-activity I, 60-325 mesh) using hexanes:ether (10:1) as the eluant afforded the *title compound RS*-**276** (0.42 g, 16%) as a white solid. **Mp** 106-108 °C, hexanes:ether; **^{1}H NMR** ($CDCl_3$) δ 1.89 (3H, s, ArC*H*$_3$), 2.38 (1H, dddd, *J* = 15.9, 8.7, 2.4, 1.7 Hz, C*H*HCH=CH), 2.66-2.79 (2H, m, PhC*H*H and CH*H*CH=CH), 2.84-2.96 (2H, m, PhC*H*H and C*H*CH$_2$), 3.41 (1H, broad s, N*H*), 3.58-3.64 (1H, m, C*H*NH), 4.03 (1H, d, *J* = 9.0 Hz, C*H*CH=CH), 5.71-5.75 (1H, m, C*H*=CH), 5.80-5.85 (1H, m, CH=C*H*), 6.63 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.81 (1H, d, *J* = 7.3 Hz, Ar*H*), 6.91 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.27-7.30 (3H, m, Ar*H*), 7.33-7.38 (2H, m, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 16.89, 31.68, 40.53, 42.85, 46.84, 55.15, 118.20, 122.51, 125.77, 126.74, 126.82, 127.44, 128.83, 129.15, 130.05, 134.90, 138.78, 143.74; **IR** (ef) 3390, 1597, 1489, 1474, 1454, 753, 702 cm^{-1}; **MS** (CI) *m/z* 276 (M+H); **Anal.** Calcd for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found: C, 87.45; H, 7.84; N, 4.95.

7.5.2 Lewis Acid-Promoted Asymmetric Diels-Alder Reaction Using the Tetrahydroquinoline (*RS*-272) as a Chiral Auxiliary

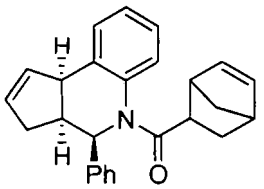
***(3aRS,4SR,9bSR)-5-Acryloyl-4-phenyl-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline* (*RS*-279).**



RS-**279**

Triethylamine (1.2 mL, 9.0 mmol) and acryloyl chloride (0.54 mL, 6.6 mmol) were added to a stirred solution of the tetrahydroquinoline *RS*-**272** (1.49 g, 6.00 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature over the course of 2 h and then was diluted with hydrochloric acid (1 M, 50 mL). The resultant mixture was extracted with dichloromethane (3 × 25 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a brown solid. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound RS*-**279** (1.73 g, 96%) as an orange solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from hexanes:ether:dichloromethane by slow evaporation. **Mp** 125-127 °C, hexanes:ether:dichloromethane; **^{1}H NMR** ($CDCl_3$) δ 2.08 (1H, d, *J* = 17.4 Hz, C*H*HCH=CH), 2.57 (1H, ddd, *J* = 17.4, 9.8, 2.1 Hz, CH*H*CH=CH), 3.54 (1H, ddd, *J* = 18.9, 9.8, 4.6 Hz, C*H*CH_2), 4.10 (1H, d, *J* = 10.4 Hz, C*H*CH=CH), 5.64-5.72 (2H, m, C*H*=CHH and C*H*NH), 6.12 (1H, dd, *J* = 5.5, 2.4 Hz, C*H*=CH), 6.23 (1H, d, *J* = 8.5 Hz, CH=C*H*), 6.44 (1H, dd, *J* = 16.8, 2.7 Hz, CH=C*H*H), 6.53 (1H, dd, *J* = 16.8, 9.8 Hz, CH=CH*H*), 6.82 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.91 (2H, d, *J* = 7.3 Hz, Ar*H*), 7.00-7.07 (2H, m, Ar*H*), 7.07-7.14 (2H, m, Ar*H*), 7.20-7.25 (1H, m, Ar*H*), 7.42 (1H, d, *J* = 7.6 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 36.03, 40.50, 45.46, 56.08, 126.13, 126.27, 126.59, 127.45, 127.79, 128.17, 129.21, 129.74, 131.46, 132.06, 135.25, 136.40, 138.27, 164.40; **IR** (ef) 3059, 3032, 2923, 2852, 1652, 1615, 1577, 1490, 1407, 1319, 1249, 701 cm^{-1}; **MS** (CI) *m/z* 302 (M+H); **Anal.** Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.49; H, 6.31; H, 4.80.

***(3aRS,4SR,9bSR)-5-(Bicyclo[2.2.1]hept-5-ene-2-carboxyl)-4-phenyl-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline* (*RS*-280).**

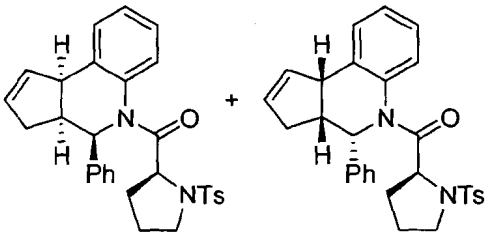


RS-**280**

Diethylaluminum chloride (1.0 M in hexanes, 0.50 mL, 0.50 mmol) was added to a stirred solution of the acrylamide *RS*-**279** (100 mg, 0.332 mmol) in dichloromethane (6.5 mL) at 0 °C. The resultant orange solution was stirred for 1 min and then cyclopentadiene (1.4 mL, 17 mmol) was added. After 3 h 15 min, the light brown reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (25 mL) and extracted with dichloromethane (2 × 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford an off-white solid. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound RS*-**279** (89 mg, 72%) as a white solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from ether:dichloromethane (5:1) by slow evaporation. **Mp** 160-162 °C, ether:dichloromethane; **^{1}H NMR** ($CDCl_3$) δ 1.08 (1H, d, *J* = 7.9 Hz, C*H*H-bridge), 1.23 (1H, d, *J* = 7.9 Hz, CH*H*-bridge), 1.68-1.88 (2H, m, CH_2CHC=O), 2.06 (1H, d, *J* = 17.4 Hz, C*H*HCH=CH), 2.49 (1H, broad s, C*H*-bridgehead), 2.49-2.62 (1H, m, CH*H*CH=CH), 2.88 (1H, broad s, C*H*-bridgehead), 3.43-3.49 (1H, m, C*H*C=O), 3.50-3.58 (1H, m, C*H*CH_2), 4.13 (1H, d, *J* = 10.7 Hz, C*H*CH=CH), 5.73-5.81 (1H, m, C*H*=CH), 5.85-5.93 (1H, m, CH=C*H*), 6.17-6.29 (2H, m, C*H*=C*H*), 6.83 (2H, d, *J* = 7.9 Hz, Ar*H*), 6.94 (1H, d, *J* = 7.0 Hz, Ar*H*), 6.98-7.03 (2H, m, Ar*H*), 7.05-7.13 (2H, m, Ar*H*), 7.21-7.25 (1H, m, Ar*H*), 7.44 (1H, d, *J* = 7.6 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 30.10, 35.95, 40.73, 42.16, 43.13, 45.71, 45.77, 50.20, 56.49, 126.24, 126.48, 126.71, 127.10, 127.27, 127.73, 129.29, 130.99, 131.35, 132.49, 137.58, 137.83, 138.25, 172.89; **IR** (ef) 1651, 1489, 1240, 702 cm^{-1}; **MS** (CI) *m/z* 368 (M+H); **Anal.** Calcd for $C_{26}H_{25}NO$: C, 84.98; H, 6.86; N, 3.81. Found: C, 84.69; H, 6.90; N, 4.04.

7.5.3 Resolution of the Tetrahydroquinolines

(3aS,4R,9bR)-4-Phenyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline (*R*-**282**) and ***(3aR,4S,9bS)-4-Phenyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline*** (*S*-**286**).

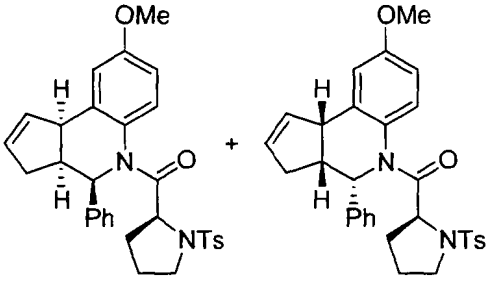


R-**282** *S*-**286**

Oxalyl chloride (0.87 mL, 9.1 mmol) was added to a stirred solution of *N*-tosyl-L-proline hemibenzenate[198] (1.89 g, 6.12 mmol) and *N*,*N*-dimethylformamide (1 drop) in dichloromethane (10 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature over the course of 1 h (CAUTION: *gas evolved*). The solvent was then removed under reduced pressure to afford the corresponding acid chloride. A solution of the crude acid chloride in dichloromethane (10 mL) was then added over 5 min to a stirred solution of the tetrahydroquinoline *RS*-**272** (1.00 g, 4.06 mmol) and pyridine (0.65 mL, 8.0 mmol) in dichloromethane (10 mL) at 0 °C and the reaction mixture was allowed to warm slowly to room temperature. After 20 h, the reaction mixture was diluted with ether (75 mL) and washed with hydrochloric acid (1 M, 3 × 20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow foam. Purification by flash chromatography using dichloromethane:ethyl acetate (20:1) as the eluant afforded the *title compound R*-**282** (714 mg, 35%) as white foam. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from hexanes:ether (1:1) by slow evaporation. **Mp** 140-142 °C, hexanes:ether; $[\alpha]_D^{20}$ + 110 (*c* 1.25, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2) δ 1.92-2.09 (2H, m), 2.41 (3H, s), 2.50-2.60 (1H, m), 3.28-3.38 (1H, m), 3.45-3.57 (2H, m), 4.03 (1H, d, J = 10.4 Hz), 5.02-5.08 (1H,

m), 5.31 (1H, t, J = 1.1 Hz), 5.76 (1H, broad s), 6.09-6.24 (2H, m), 6.86 (1H, m), 7.02-7.08 (2H, m), 7.09-7.14 (1H, m), 7.17-7.31 (5H, m), 7.42 (1H, d, J = 7.6 Hz), 7.68 (2H, d, J = 8.2 Hz); **^{13}C NMR** (CD_2Cl_2) δ 21.80, 25.06, 31.89, 36.32, 41.13, 45.96, 49.35, 56.99, 59.63, 127.16, 127.39, 127.77, 127.85, 127.89, 128.23, 129.65, 130.08, 131.40, 132.87, 136.55, 136.99, 138.45, 144.04, 171.15; **IR** (ef) 1665, 1492, 1345, 1156, 730 cm^{-1}; **MS** (CI) *m/z* 499 (M+H); **Anal.** Calcd for $C_{30}H_{30}N_2O_3S$: C, 72.26; H, 6.06; N, 5.62. Found: C, 71.95; H, 5.98; N, 5.88. Continued elution using dichloromethane:ethyl acetate (10:1) as the eluant afforded the diastereomeric *title compound S*-**286** (650 mg, 32%) as a white foam. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from ethanol by slow evaporation. **Mp** 161-162 °C, ethanol; $[\alpha]_D^{20}$ - 309 (*c* 0.81, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2) δ 1.39-1.52 (1H, m), 1.79-1.93 (1H, m), 1.96-2.18 (3H, m), 2.34 (3H, s), 2.59 (1H, dddd, J = 14.7, 10.0, 4.7, 2.4 Hz), 3.12-3.22 (1H, m), 3.51-3.59 (1H, m), 3.63-3.76 (1H, m), 4.39-4.49 (1H, m), 5.69-5.75 (1H, m), 6.18-6.23 (1H, m), 6.25 (1H, d, J = 8.6 Hz), 6.61 (1H, d, J = 7.8 Hz), 6.89-6.94 (2H, m), 7.00-7.06 (3H, m), 7.06-7.14 (3H, m), 7.35-7.40 (1H, m), 7.59 (1H, d, J = 7.6 Hz); **^{13}C NMR** (CD_2Cl_2) δ 21.71, 25.69, 32.36, 36.26, 40.12, 46.01, 50.41, 56.63, 57.40, 126.47, 126.63, 127.13, 127.70, 127.79, 128.17, 128.26, 129.80, 130.08, 131.97, 132.43, 134.14, 137.33, 137.87, 138.90, 144.03, 171.19; **IR** (ef) 1662, 1492, 1349, 1247, 1160, 727 cm^{-1}; **MS** (CI) *m/z* 499 (M+H).

(3aS,4R,9bR)-8-Methoxy-4-phenyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline (*R*-**283**) and ***(3aR,4S,9bS)-8-Methoxy-4-phenyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline*** (*S*-**287**).

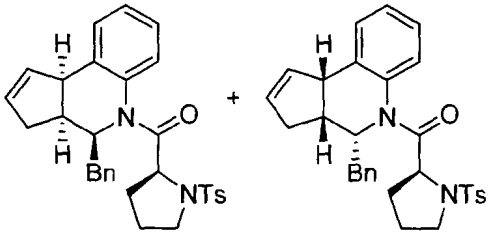


R-**283** *S*-**287**

A solution of *N*-tosyl-L-prolyl chloride [prepared from *N*-tosyl-L-proline hemibenzenate (341 mg, 1.11 mmol), oxalyl chloride (154 μL, 1.62 mmol) and *N*,*N*-dimethylformamide (1 drop) in dichloromethane (5 mL)] in dichloromethane (5 mL) was added to a stirred solution of the tetrahydroquinoline *RS*-**273** (200 mg, 0.719 mmol) and pyridine (150 μL, 1.85 mmol) in dichloromethane (5 mL) at 0 °C and the reaction mixture was allowed to warm slowly to room temperature. After 19 h, the reaction mixture was diluted with ether (40 mL) and washed with hydrochloric acid (1 M, 3 × 10 mL), a saturated aqueous solution of sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow gum. Purification by flash chromatography using dichloromethane:ethyl acetate (20:1) as the eluant afforded the *title compound R*-**283** (150 mg, 39%) as a white solid. **Mp** 149-150 °C, dichloromethane:ethyl acetate; $[\alpha]_D^{20}$ + 37 (*c* 1.70, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2) δ 1.52-1.64 (4H, m), 1.91-2.06 (2H, m), 2.40 (3H, s), 2.47-2.58 (1H, m), 3.27-3.36 (1H, m), 3.42-3.54 (2H, m), 3.82 (3H, s), 3.98 (1H, d, *J* = 10.4 Hz), 4.97-5.03 (1H, m), 5.74-5.80 (1H, m), 6.15 (2H, d, *J* = 8.2 Hz), 6.74 (1H, ddd, *J* = 8.7, 2.9, 0.8 Hz), 6.86 (2H, d, *J* = 7.0 Hz), 6.92-6.95 (1H, dd, *J* = 3.0, 1.2 Hz), 7.04-7.16 (3H, m), 7.19 (1H, d, *J* = 8.8 Hz), 7.27 (2H, d, *J* = 8.2 Hz); **^{13}C NMR** (CD_2Cl_2) δ 21.79, 25.06, 31.74, 36.27, 40.84, 46.28, 49.33, 55.97, 57.04, 59.52, 112.29, 113.11, 127.80, 127.89, 128.23, 128.38, 129.73, 130.05, 131.12, 133.02, 136.58, 138.43, 138.48, 143.98, 158.80, 171.03; **IR** (ef)

1665, 1497, 1341, 1158, 665 cm^{-1}; **MS** (MALDI) *m/z* 567 (M+K), 551 (M+Na), 529 (M+H); **Anal.** Calcd for $C_{31}H_{32}N_2O_4S$: C, 70.43; H, 6.10; N, 5.30. Found: C, 70.69; H, 6.21; N, 5.19. Continued elution using dichloromethane:ethyl acetate (10:1) as the eluant afforded the diastereomeric *title compound S*-**287** (134 mg, 35%) as a pale yellow solid. **Mp** 153-155 °C, dichloromethane:ethyl acetate; $[\alpha]_D^{20}$ - 204 (*c* 1.22, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2) δ 1.40-1.52 (1H, m), 1.79-1.90 (1H, m), 1.96-2.04 (1H, m), 2.05-2.14 (2H, m), 2.35 (3H, s), 2.53-2.62 (1H, m), 2.58 (1H, dddd, *J* = 14.6, 9.9, 4.7, 2.3 Hz), 3.14-3.22 (1H, m), 3.50-3.57 (1H, m), 3.61-3.73 (1H, m), 3.89 (3H, s), 4.28-4.35 (2H, m), 5.69-5.75 (1H, m), 6.16-6.20 (1H, m), 6.23 (1H, d, *J* = 8.7 Hz), 6.52 (1H, d, *J* = 8.5 Hz), 6.65 (1H, ddd, *J* = 8.5, 2.7, 0.8 Hz), 6.91 (2H, d, *J* = 8.5 Hz), 7.01-7.14 (8H, m); **^{13}C NMR** (CD_2Cl_2) δ 21.77, 25.73, 32.42, 36.27, 39.96, 46.39, 50.39, 56.11, 56.79, 57.35, 111.95, 113.36, 127.38, 127.80, 128.18, 129.91, 130.05, 130.32, 131.74, 132.59, 138.92, 139.31, 144.04, 158.95, 171.16; **IR** (ef) 1660, 1498, 1347, 1160, 664 cm^{-1}; **MS** (MALDI) *m/z* 551 (M+Na), 529 (M+H).

(3aS,4S,9bR)-4-Benzyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline (*R*-**284**) and ***(3aR,4R,9bS)-4-Benzyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline*** (*S*-**288**).



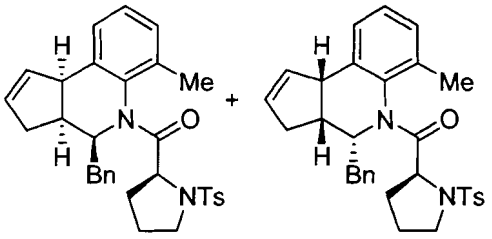
R-**284** *S*-**288**

A solution of *N*-tosyl-L-prolyl chloride [prepared from *N*-tosyl-L-proline·½benzene (416 mg, 1.35 mmol), oxalyl chloride (0.19 mL, 2.0 mmol) and *N*,*N*-dimethylformamide (1 drop) in dichloromethane (5 mL)] in dichloromethane (5 mL) was added to a stirred solution of the tetrahydroquinoline *RS*-**275** (233 mg, 0.891 mmol) and pyridine (144 μL, 1.78 mmol) in dichloromethane (5 mL) at 0 °C and the reaction mixture was allowed to warm slowly to room temperature. After

18 h, the reaction mixture was diluted with ether (50 mL) and was washed with hydrochloric acid (1 M, 3 × 10 mL), a saturated aqueous solution of sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow foam. Purification by flash chromatography using dichloromethane:ether (20:1) as the eluant afforded the *title compound R*-**284** (127 mg, 28%) as a white foam/solid. **Mp** 204-206 °C, dichloromethane:ether; $[\alpha]_D^{20}$ + 25.0 (*c* 1.13, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2, mixture of two rotamers) δ 0.81-1.01 (1H, m), 1.39-1.50 (1H, m), 1.51-1.64 (2H, m), 1.75-1.93 (1H, m), 2.10 (1H, dd, *J* = 14.6, 12.2 Hz), 2.20-2.29 (½ × 1H, m), 2.40 (½ × 3H, s), 2.41 (½ × 3H, s), 2.44-2.47 (½ × 1H, broad s), 2.52-2.66 (1H and ½ × 1H, m), 2.68-2.80 (½ × 1H, m), 2.89-3.01 (1H, m), 3.18-3.37 (3H, m), 4.00 (½ × 1H, d, *J* = 5.5 Hz), 4.10 (½ × 1H, broad s), 4.34 (½ × 1H, dd, *J* = 8.2, 4.3 Hz), 4.38-4.47 (½ × 1H, m), 5.06-5.13 (1H and ½ × 1H, m), 5.84-5.90 (1H, m), 5.96-6.01 (1H, m), 6.96 (½ × 2H, d, *J* = 7.0 Hz), 7.01 (½ × 2H, d, *J* = 7.3 Hz), 7.15-7.50 (10H, m), 7.65 (1H, d, *J* = 8.2 Hz); **^{13}C NMR** (CD_2Cl_2, mixture of two rotamers) δ 17.88, 21.71, 25.43, 32.30, 32.66, 35.83, 39.37, 46.80, 50.67, 56.72, 126.48, 126.53, 126.75, 127.73, 128.64, 128.67, 129.08, 130.03, 130.83, 133.53, 134.22, 134.54, 135.70, 138.19, 139.46, 143.94, 173.28; **IR** (ef) 1666, 1493, 1339, 1156, 664 cm^{-1}; **MS** (MALDI) *m/z* 512 (M); **Anal.** Calcd for $C_{31}H_{32}N_2O_3S$: C, 72.63; H, 6.29; N, 5.46. Found: C, 72.35; H, 6.33; N, 5.69. Continued elution afforded the diastereomeric *title compound S*-**288** (117 mg, 26%) as a white foam/solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from ethanol by slow evaporation. **Mp** 219-220 °C, ethanol; $[\alpha]_D^{20}$ - 195 (*c* 1.38, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2) δ 1.37-1.47 (1H, m), 1.67-1.79 (2H, m), 1.94-2.04 (1H, m), 2.12 (1H, dd, *J* = 14.7, 12.5 Hz), 2.34 (3H, s), 2.45 (1H, d, *J* = 17.3 Hz), 2.68 (1H, dd, *J* = 14.9, 3.5 Hz), 2.74-2.84 (1H, m), 3.03-3.11 (1H, m), 3.29-3.36 (1H, m), 3.45-3.52 (1H, m), 4.16-4.22 (1H, m), 4.25-4.30 (1H, m), 5.27

(1H, ddd, J = 12.3, 6.2, 3.7 Hz), 5.84-5.90 (1H, m), 6.00-6.05 (1H, m), 6.52 (1H, d, J = 7.9 Hz), 6.92 (2H, d, J = 7.2 Hz), 6.95 (2H, d, J = 8.4 Hz), 7.05-7.21 (5H, m), 7.40 (1H, dt, J = 7.5, 1.1 Hz), 7.61 (1H, d, J = 7.7 Hz); **^{13}C NMR** (CD_2Cl_2) δ 21.70, 25.54, 32.21, 32.74, 36.06, 39.64, 46.07, 50.26, 57.04, 126.25, 126.41, 126.69, 126.75, 127.70, 128.38, 129.20, 129.27, 130.02, 131.20, 133.55, 134.08, 135.79, 136.45, 139.59, 143.92, 171.59; **IR** (ef) 1664, 1492, 1347, 1159, 662 cm^{-1}; **MS** (MALDI) *m/z* 512 (M).

(3aS,4S,9bR)-4-Benzyl-6-methyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl] 3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline (*R*-**285**) and ***(3aR,4R,9bS)-4-Benzyl-6-methyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-3,3a,4,9b-tetrahydro-3H-cyclopenta[c]quinoline*** (*S*-**289**).



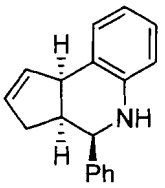
R-**285** *S*-**289**

A solution of *N*-tosyl-L-prolyl chloride [prepared from *N*-tosyl-L-proline·½benzene (674 mg, 2.18 mmol), oxalyl chloride (0.32 mL, 3.4 mmol) and *N*,*N*-dimethylformamide (1 drop) in dichloromethane (7 mL)] in dichloromethane (5 mL) was added to a stirred solution of the tetrahydroquinoline *RS*-**276** (300 mg, 1.09 mmol) and pyridine (144 μL, 1.78 mmol) in dichloromethane (5 mL) at 0 °C. After 2 h, *N*,*N*-dimethyl-4-aminopyridine (5 mg, 0.04 mmol) was added and the reaction mixture was allowed to warm slowly to room temperature. After 14 h, the reaction mixture was heated at reflux for 3 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ether (50 mL) and washed with hydrochloric acid (1 M, 2 × 10 mL), a saturated aqueous solution of sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale orange foam/solid. Purification by flash chromatography using dichloromethane:ether (20:1) as the eluant afforded the *title compound* *R*-**285** (149 mg, 26%) as a solid white foam. **Mp** 138-140 °C,

dichloromethane:ether; $[\alpha]_D^{20}$ + 73 (*c* 0.85, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2, mixture of two rotamers) δ 1.13-1.22 (½ × 1H, m), 1.25-1.40 (2H, m), 1.50-1.63 (½ × 1H, m), 1.71 (½ × 3H, s), 1.73 (½ × 3H, s), 1.74-1.82 (½ × 1H, m), 2.01 (½ × 1H, d, *J* = 15.6, 12.5 Hz), 2.13 (½ × 1H, d, *J* = 14.3, 11.9 Hz), 2.33-2.41 (½ × 1H, m), 2.41 (½ × 3H, s), 2.42 (½ × 3H, s), 2.55 (½ × 1H, d, *J* = 17.1 Hz), 2.63-2.74 (1H and ½ × 1H, m), 2.85-2.95 (½ × 1H, m), 3.00-3.07 (½ × 1H, m), 3.18-3.25 (½ × 1H, m), 3.29-3.42 (2H, m), 3.96 (½ × 1H, d, *J* = 9.2 Hz), 4.13 (½ × 1H, d, *J* = 8.2 Hz), 4.37-4.42 (½ × 1H, m), 4.56 (½ × 1H, ddd, *J* = 11.6, 5.5, 2.7 Hz), 4.75 (½ × 1H, dd, *J* = 8.2, 4.3 Hz), 5.28-5.35 (½ × 1H, m), 5.94-6.02 (1H, m), 5.81-5.88 (1H, m), 6.87 (1H, d, *J* = 7.0 Hz), 6.95 (1H, d, *J* = 7.3 Hz), 7.09 (1H, d, *J* = 7.6 Hz), 7.14-7.35 (7H, m), 7.61 (1H, d, *J* = 8.2 Hz), 7.73 (1H, d, *J* = 8.2 Hz); **^{13}C NMR** (CD_2Cl_2, mixture of two rotamers) δ 17.73, 19.30, 21.81, 24.34, 25.62, 30.23, 31.85, 31.94, 33.87, 35.86, 36.86, 39.84, 41.80, 45.92, 46.27, 48.73, 48.91, 54.37, 59.31, 61.43, 61.78, 126.14, 126.35, 126.67, 126.93, 127.11, 127.79, 128.01, 128.69, 128.91, 128.98, 129.04, 129.60, 129.73, 129.82, 130.08, 130.31, 131.29, 133.54, 134.17, 134.61, 134.82, 134.91, 135.29, 135.67, 135.79, 136.95, 137.42, 139.15, 139.96, 143.66, 144.17, 171.78, 172.22; **IR** (ef) 1669, 1341, 1156, 662 cm^{-1}; **MS** (MALDI) *m/z* 526 (M); **Anal.** Calcd for $C_{32}H_{34}N_2O_3S$: C, 72.97; H, 6.51; N, 5.32. Found: C, 73.14; H, 6.43; N, 5.41. Continued elution afforded the diastereomeric *title compound S*-**289** (107 mg, 19%) as a white foam/solid. An analytical sample of the product, as large colourless crystals, was prepared by recrystallization from ethanol by slow evaporation. **Mp** 230-231 °C, ethanol; $[\alpha]_D^{20}$ - 206 (*c* 1.52, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2) δ 1.36 (3H, s), 1.45-1.64 (2H, m), 1.83-1.94 (1H, m), 2.07 (1H, dd, *J* = 15.4, 12.6 Hz), 2.14-2.25 (1H, m), 2.33 (3H, s), 2.14 (1H, d, *J* = 16.0 Hz), 2.72-2.82 (2H, m), 2.90-2.98 (1H, m), 3.35-3.44 (1H, m), 3.53-3.61 (1H, m), 3.71 (1H, dd, *J* = 8.6, 3.4 Hz), 4.30 (1H, d, *J* = 8.0 Hz), 5.49 (1H, ddd, *J* = 12.6, 6.2, 4.3 Hz), 5.80-5.86 (1H, m), 6.00-6.05 (1H, m), 6.74 (2H, d, *J* = 8.3 Hz), 6.92 (2H, d, *J* = 7.4 Hz) 6.96-7.31 (6H, m), 7.32-7.38 (1H, m), 7.45 (1H, d,

J = 7.7 Hz); **^{13}C NMR** (CD_2Cl_2) δ 17.88, 21.71, 25.43, 32.30, 32.66, 35.83, 39.37, 46.80, 50.67, 54.03, 56.72, 126.48, 126.53, 126.75, 127.73, 128.64, 128.67, 129.08, 130.03, 130.83, 133.53, 134.22, 134.54, 135.70, 138.19, 139.46, 143.94, 173.28; **IR** (ef) 1657, 1348, 1160, 661 cm^{-1}; **MS** (MALDI) *m/z* 549 (M+Na), 526 (M).

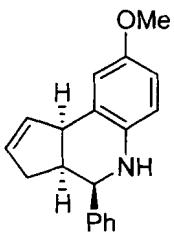
***(3aS,4R,9bR)-4-Phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline* (*R*-272).**



R-**272**

The amide *R*-**282** (262 mg, 0.524 mmol) was added in one portion to a stirred solution of sodium ethoxide [prepared by the addition of sodium metal (0.29 g, 13 mmol) to ethanol (5 mL) and allowing the mixture to stir for 15 min] at room temperature. The resultant mixture was heated at reflux for 30 min. The reaction mixture was then allowed to cool to room temperature, poured into water (15 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford a brown solid. Purification by flash chromatography using hexanes:ether (8:1) as the eluant afforded the *title compound* *R*-**272** (96 mg, 74%) as a white solid. The enantiomeric ratio of the purified product was > 99:1 as determined by chiral HPLC analysis (90:10 hexanes:isopropanol, 0.5 mL/min, $t_{R(minor)}$ = 15.8 min, $t_{R(major)}$ = 18.4 min). $[\alpha]_D^{20}$ + 8.2 (*c* 1.11, tetrahydrofuran). The ^{1}H NMR spectral data were consistent with that reported above for compound *RS*-**272**.

***(3aS,4R,9bR)-8-Methoxy-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline* (*R*-273).**

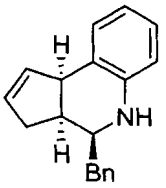


R-**273**

A solution of amide *R*-**283** (200 mg, 0.378 mmol) in ethanol (3 mL) was added in one portion to a stirred solution of sodium ethoxide (9.8 mmol) in ethanol (9 mL) at room temperature. The resultant mixture was heated at reflux for 30 min. The reaction mixture was then allowed to cool to room temperature and was concentrated to near dryness, diluted with water (40 mL) and extracted with ether (3 × 25 mL). The combined organic extracts

were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a brown solid. Purification by flash chromatography using hexanes:ether (15:1) as the eluant afforded the tetrahydroquinoline *R*-**273** (38 mg, 36%) as a pale green solid. The enantiomeric ratio of the purified product was > 99:1 as determined by chiral HPLC analysis (90:10 hexanes:isopropanol, 0.5 mL/min, $t_{R(minor)}$ = 17.1 min, $t_{R(major)}$ = 20.0 min). $[\alpha]_D^{20}$ - 32 (*c* 0.42, tetrahydrofuran). The ^{1}H NMR spectral data were consistent with that reported for compound *RS*-**273**.

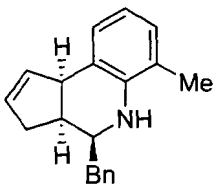
(3aS,4S,9bR)-4-Benzyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline **(*R*-275).**



R-**275**

To the amide *R*-**284** (122 mg, 0.238 mmol) was added a solution of sodium ethoxide (5.5 mmol) in ethanol (6 mL) at room temperature and the stirred reaction mixture was heated at reflux for 3 h. The resultant mixture was concentrated to near dryness, diluted with water (50 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a yellow gum. Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded the tetrahydroquinoline *R*-**275** (39 mg, 62%) as a colourless gum. The enantiomeric ratio of the purified product was > 99:1 as determined by chiral HPLC analysis (90:10 hexanes:isopropanol, 0.5 mL/min, $t_{R(minor)}$ = 14.2 min, $t_{R(major)}$ = 17.7 min). $[\alpha]_D^{20}$ - 59 (*c* 2.21, tetrahydrofuran). The ^{1}H NMR spectral data were consistent with that reported for compound *RS*-**275**.

***(3aS,4S,9bR)-4-Benzyl-6-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline* (*R*-276).**

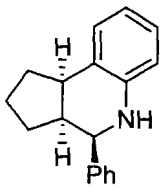


R-**276**

To the amide *R*-**285** (143 mg, 0.272 mmol) was added a solution of sodium ethoxide (10.9 mmol) in ethanol (5 mL) at room temperature. The reaction mixture was then stirred and heated at reflux for 1 h. The resultant mixture was concentrated to near dryness, diluted with water (30 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to afford a white gum. Purification by flash chromatography using hexanes:ether (20:1) as the eluant afforded the tetrahydroquinoline *R*-**276** (61 mg, 82%) as a white solid. The enantiomeric ratio of the purified product was > 99:1 as determined by chiral HPLC analysis (90:10 hexanes:isopropanol, 0.5 mL/min, $t_{R(minor)}$ = 10.9 min, $t_{R(major)}$ = 12.8 min). $[\alpha]_D^{20}$ - 4.2 (*c* 0.51, tetrahydrofuran). The ^{1}H NMR spectral data were consistent with that reported for compound *RS*-**276**.

7.5.4 Hydrogenated Tetrahydroquinolines: Synthesis and Resolution

***(3aS,4R,9bR)-4-Phenyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline* (*R*-296).**

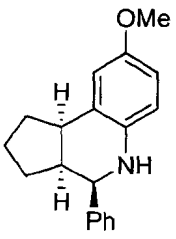


R-**296**

A suspension of the tetrahydroquinoline *R*-**272** (23 mg, 0.090 mmol) and palladium on activated carbon (10 wt. %, 5 mg) in ethanol (3 mL) was stirred under an atmosphere of hydrogen gas (balloon pressure) at room temperature for 1 h. The reaction mixture was then filtered through a pad of Celite® with ether (10 mL) and concentrated to afford a pale yellow solid. Purification by passing a solution of the crude reaction product in hexanes:ether (1:1) through a pad of silica gel afforded the *title compound* *R*-**296** (22 mg, 97%) as white solid. The enantiomeric ratio of the purified product was > 99:1 as determined by chiral HPLC analysis (90:10 hexanes:isopropanol, 0.5 mL/min, $t_{R(minor)}$ = 15.9 min, $t_{R(major)}$ = 17.7 min). **Mp** 98-99 °C, hexanes:ether; $[\alpha]_D^{20}$ + 76 (*c* 1.01, tetrahydrofuran). The ^{1}H NMR spectral

data of this product were consistent with that for the racemic compound.* **^{1}H NMR** ($CDCl_3$, *RS*-**296**) δ 1.18-1.30 (1H, m), 1.36-1.49 (1H, m), 1.50-1.62 (1H, m), 1.68-1.86 (2H, m), 2.16 (1H, ddd, *J* = 20.1, 13.4, 7.9 Hz), 2.49 (1H, ddd, *J* = 13.4, 7.9, 3.0 Hz, CH_2CH), 3.44-3.52 (1H, m, ArC*H*), 3.68-3.96 (1H, broad s, N*H*), 4.58 (1H, d, *J* = 3.0 Hz, C*H*NH), 6.60 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.72-6.80 (1H, m, Ar*H*), 7.01 (1H, apparent dd, *J* = 7.9, 7.3 Hz, Ar*H*), 7.13 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.28 (1H, apparent dd, *J* = 7.3, 7.0 Hz, Ar*H*), 7.33-7.39 (2H, m, Ar*H*), 7.44 (2H, d, *J* = 7.6 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$, *RS*-**296**) δ 23.81, 24.37, 35.17, 40.76, 47.07, 57.92, 115.06, 118.85, 126.31, 126.68, 126.98, 127.21, 128.47, 129.29, 143.57, 145.45; **IR** (ef) 3354, 1504, 1467, 1362, 1253, 1229, 1163, 1043, 703 cm^{-1}; **MS** (CI) *m/z* 250 (M+H); **Anal**. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68, N, 5.62. Found: C, 86.91; H, 7.57; N, 5.40.

***(3aRS,4SR,9bSR)-8-Methoxy-4-phenyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline* (*RS*-297).**



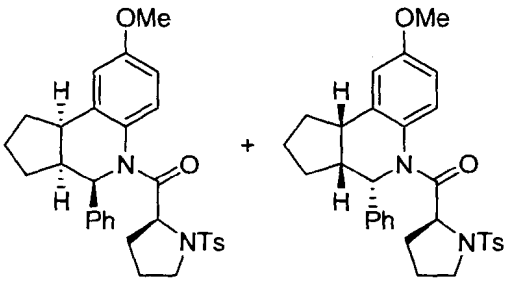
RS-**297**

A suspension of the tetrahydroquinoline *RS*-**273** (64 mg, 0.225 mmol) and palladium on activated carbon (10 wt. %, 6 mg) in ethanol (4 mL) was stirred under an atmosphere of hydrogen gas (balloon pressure) at room temperature for 1.5 h. The reaction mixture was then filtered through a pad of Celite® with ether (10 mL) and concentrated to afford a colourless oil. Purification by passing a solution of the crude reaction product in hexanes through a pad of silica gel afforded the *title compound RS*-**297** (60 mg, 96%) as a colourless oil. **^{1}H NMR** ($CDCl_3$) δ 1.18-1.28 (1H, m), 1.36-1.48 (1H, m), 1.50-1.62 (2H, m), 1.68-1.81 (1H, m), 2.20-2.21 (1H, m), 2.49 (1H, ddd, *J* = 13.4, 7.9, 3.0 Hz), 3.45 (1H, apparent dt, *J* = 7.9, 3.4 Hz), 3.60 (1H, broad s, N*H*), 3.77 (3H, s, OCH_3), 4.49 (1H, d, *J* = 3.0 Hz, C*H*NH), 6.55 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.63 (1H, dd, *J* = 8.5, 2.7 Hz, Ar*H*),

* A sample of the racemic hexahydroquinoline *RS*-**296** was prepared from the racemic tetrahydroquinoline *RS*-**272** in an analogous palladium-catalyzed hydrogenation reaction.

6.71 (1H, d, J = 2.4 Hz, Ar*H*), 7.28 (1H, d, J = 7.3 Hz, Ar*H*), 7.33-7.38 (2H, m, Ar*H*), 7.44 (2H, d, J = 7.0 Hz, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 24.11, 24.50, 35.53, 41.17, 47.06, 55.88, 58.51, 112.47, 114.50, 115.93, 126.74, 127.16, 128.47, 128.56, 139.65, 143.73, 153.01; **IR** (ef) 3354, 1504, 1467, 1362, 1253, 1229, 1163, 1043, 703 cm^{-1}; **MS** (CI) *m/z* 280 (M+H); **Anal.** Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.48; H, 7.72; N, 5.26.

(3aS,4R,9bR)-8-Methoxy-4-phenyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline **(*R*-298)** and ***(3aR,4S,9bS)-8-Methoxy-4-phenyl-5-[(S)-1-(p-tolylsulfonyl)pyrrolidine-2-carboxyl]-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline*** **(*S*-299).**

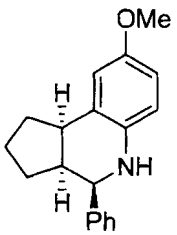


R-298 *S*-299

A solution of *N*-tosyl-L-prolyl chloride [prepared from *N*-tosyl-L-proline (251 mg, 0.814 mmol), oxalyl chloride (115 μL, 1.21 mmol) and *N*,*N*-dimethylformamide (1 drop) in dichloromethane (5 mL)] in dichloromethane (5 mL) was added to a stirred solution of the tetrahydroquinoline *RS*-**297** (128 mg, 0.458 mmol), pyridine (115 μL, 1.42 mmol) and *N*,*N*-dimethyl-4-aminopyridine (3 mg, 0.02 mmol) in dichloromethane (3 mL) at 0 °C and the reaction mixture was allowed to warm slowly to room temperature. After 18 h, the reaction mixture was diluted with dichloromethane (40 mL) and was washed with hydrochloric acid (1 M, 2 × 15 mL), a saturated aqueous solution of sodium bicarbonate (15 mL) and brine (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford a pale yellow gum. Purification by flash chromatography using dichloromethane:ethyl acetate (20:1) as the eluant afforded the amide *R*-**298** (112 mg, 46%) as a white solid. **Mp** 121-122 °C, dichloromethane:ethyl acetate; $[\alpha]_D^{20}$ + 39 (*c* 1.07, tetrahydrofuran); **^{1}H NMR** ($CDCl_3$) δ 0.79-0.94 (1H, m), 1.34-1.45 (1H, m), 1.44-

1.64 (4H, m), 1.65-1.78 (2H, m), 1.87-2.04 (2H, m), 2.10-2.22 (1H, m), 2.36 (3H, s), 2.94-3.13 (2H, m), 3.38-3.49 (2H, m), 3.86 (3H, s), 5.21-5.28 (1H, m), 6.02 (1H, d, J = 8.9 Hz), 6.80-6.96 (4H, m), 7.09-7.24 (5H, m), 7.57 (1H, d, J = 8.5 Hz), 7.68 (2H, d, J = 7.9 Hz); **^{13}C NMR** ($CDCl_3$) δ 21.64, 23.79, 24.63, 28.16, 30.66, 31.42, 39.61, 44.87, 48.45, 55.59, 56.72, 58.90, 111.65, 113.01, 126.97, 127.73, 127.95, 128.12, 128.39, 129.42, 130.11, 136.26, 139.07, 139.75, 143.13, 158.26, 170.99; **IR** (ef) 1665, 1498, 1341, 1158, 912, 732 cm^{-1}; **MS** (MALDI) *m/z* 552 (M+Na), 530 (M); **Anal.** Calcd for $C_{31}H_{34}N_2O_4S$: C, 70.16; H, 6.46; N, 5.28. Found: C, 69.92; H, 6.65; N, 5.16. Continued elution using dichloromethane:ethyl acetate (10:1) as the eluant afforded the diastereomeric amide *S*-**299** (112 mg, 46%) as a white solid. **Mp** 208-209 °C, dichloromethane:ethyl acetate; $[\alpha]_D^{20}$ - 205 (*c* 1.06, tetrahydrofuran); **^{1}H NMR** (CD_2Cl_2) δ 0.82-0.96 (1H, m), 1.40-1.62 (4H, m), 1.81-1.97 (2H, m), 2.02-2.16 (2H, m), 2.19-2.32 (1H, m), 2.37 (3H, s), 3.12-3.24 (2H, m), 3.41-3.58 (2H, m), 3.92 (3H, s), 4.34 (1H, dd, J = 8.5, 4.2 Hz), 6.15 (1H, d, J = 8.9 Hz), 6.76 (2H, s), 6.89-6.95 (2H, m), 7.05-7.19 (8H, m); **^{13}C NMR** (CD_2Cl_2) δ 21.77, 24.40, 25.66, 28.78, 31.51, 32.48, 39.91, 44.40, 50.39, 56.10, 56.84, 57.28, 111.74, 113.50, 127.16, 127.33, 127.79, 128.53, 128.91, 130.02, 131.00, 134.34, 140.90, 144.01, 158.97, 171.59; **IR** (ef) 1661, 1497, 1347, 1160, 735 cm^{-1}; **MS** (MALDI) *m/z* 569 (M+K), 554 (M+Na), 530 (M).

***(3aS,4R,9bR)-8-Methoxy-4-phenyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline* (*R*-297).**



R-**297**

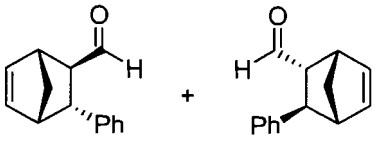
To the amide *R*-**298** (99 mg, 0.19 mmol) was added a solution of sodium ethoxide (12.4 mmol) in ethanol (8 mL) at room temperature. The reaction mixture was then stirred and heated at reflux for 30 min. The resultant mixture was concentrated to near dryness, diluted with water (25 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated

to afford a yellow solid. Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded the tetrahydroquinoline *R*-**297** (52 mg, 100%) as a colourless oil. The enantiomeric ratio of the purified product was > 99:1 as determined by chiral HPLC analysis (90:10 hexanes:isopropanol, 0.5 mL/min,$t_{R(minor)}$ = 16.5 min, $t_{R(major)}$ = 17.8 min). $[\alpha]_D^{20}$ + 50 (*c* 1.16, tetrahydrofuran). The ^{1}H NMR spectral data were consistent with that reported for the compound *RS*-**297**.

7.5.5 Tetrahydroquinoline-Catalyzed Asymmetric Diels-Alder Reactions

Typical procedure for asymmetric Diels-Alder reactions catalyzed by chiral tetrahydroquinolines and hydrogenated tetrahydroquinolines:

***Exo*-and *Endo*-3-Phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (292 and 293).**[199]

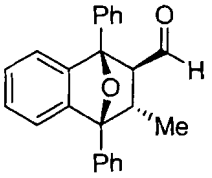


2*R*-*exo*-**292** 2*R*-*endo*-**293**

To a stirred solution of the tetrahydroquinoline *R*-**272** (20 mg, 0.081 mmol) in ether (5 mL) was added a saturated solution of hydrogen chloride in ether (1 mL) to precipitate the tetrahydroquinoline *R*-**272** as its corresponding hydrochloride salt. The solvent was then removed under reduced pressure to afford a white solid. Cinnamaldehyde (52 μL, 0.41 mmol) was then added to a stirred solution of the hydrochloride salt of the tetrahydroquinoline *R*-**272** in methanol:water (95:5, 0.5 mL) at room temperature. After 2 min, cyclopentadiene (100 μL, 1.21 mmol) was added to the resultant pale yellow solution and the reaction mixture was stirred at room temperature for 21 h. The reaction mixture was then diluted with ether (40 mL) and the organic layer was washed with water (2 × 10 mL) and brine (10 mL). The combined organic extracts were then dried over anhydrous sodium sulfate, filtered and concentrated to afford a red oil. A solution of the crude reaction product and trifluoroacetic acid (2 mL) in water:chloroform (1:2, 3 mL) was then stirred at room temperature for 2 h. The resultant mixture was diluted with ether (50 mL) and was washed with a saturated aqueous solution of sodium bicarbonate (3 × 40 mL). The

organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil. Purification by flash chromatography using hexanes:ether (10:1) as the eluant afforded an inseparable mixture of the *title compounds* 2*R*-*exo*-**292** and 2*R*-*endo*-**293** (49 mg, 60%) as a colourless oil. The diastereomeric and enantiomeric ratios were determined by chiral GC analysis of the purified products (He carrier gas at 18 p.s.i., oven temperature = 150 °C); *exo*:*endo* = 70:30, er_{exo} = 75:25 ($t_{R(major)}$ = 37.8 min, $t_{R(minor)}$ = 41.6 min), er_{endo} = 73:27 ($t_{R(major)}$ = 40.2 min, $t_{R(minor)}$ = 43.6 min). **^{1}H NMR** ($CDCl_3$, *exo* and *endo* mixture) δ 1.53-1.64 (3H, m, C*HH*-bridge-*exo* and C*H*H-bridge-*endo*), 1.79-1.83 (1H-*endo*, m, CH*H*-bridge), 2.60 (1H-*exo*, dt, *J* = 5.3, 1.8 Hz, 2.98 (1H-*endo*, ddd, *J* = 5.6, 3.5, 2.3 Hz, C*H*CHO), 3.09 (1H-*endo*, dd, *J* = 4.9, 1.1 Hz, C*H*Ph), 3.20-3.24 (2H-*exo*, m, broad s, 2 × C*H*-bridgehead), 3.33 (1H-*endo*, broad s, C*H*-bridgehead), 3.73 (1H-*exo*, dd, *J* = 5.0, 3.5 Hz, C*H*CHO), 6.07 (1H-*exo*, dd, *J* = 5.6, 3.2 Hz, C*H*=CH), 6.17 (1H-*endo*, dd, *J* = 5.7, 2.8 Hz, C*H*=CH), 6.34 (1H-*exo*, dd, *J* = 5.6, 3.5 Hz, CH=C*H*), 6.42 (1H-*endo*, dd, *J* = 5.7, 3.2 Hz, CH=C*H*), 7.12-7.34 (10H, m, Ar*H*), 9.60 ($1H_{endo}$, *J* = 2.1 Hz, C*H*O), 9.92 ($1H_{exo}$, d, *J* = 2.1 Hz, C*H*O), **^{13}C NMR** ($CDCl_3$, *exo* and *endo* mixture) δ 45.29, 45.60, 45.64, 45.83, 47.27, 47.73, 48.52, 48.58, 59.59, 60.98, 126.33, 126.45, 127.49, 128.01, 128.28, 128.73, 133.92, 136.42, 136.68, 139.35, 142.71, 143.69, 202.88, 203.60; **IR** (neat) 1716, 1601, 1497, 1452, 1334, 1065, 1032, 907, 720 cm^{-1}, **MS** (CI) *m/z* 189 (M+H), 133.

***(1S,8R,9S,10S)-1,8-Diphenyl-10-methyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7)-3,5-triene-9-carboxaldehyde* (295).**[161a]



295

A solution of the tetrahydroquinoline *R*-**272**·HCl [prepared by the addition of a saturated solution of hydrogen chloride in ether (3 mL) to a solution of the tetrahydroquinoline *R*-**272** in ether (3 mL)] was added to a stirred solution of 1,8-diphenylisobenzofuran **294** (224 mg, 0.828 mmol) and methanol (17 μL) in *N*,*N*-dimethylformamide:water (95:5, 0.5 mL) at

room temperature. After 20 h, the reaction mixture was then diluted with ether (20 mL) and washed with water (10 mL). The aqueous layer was then back-extracted with ether (2 × 10 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to afford a bright yellow solid. Purification by flash chromatography using hexanes:ethyl acetate (20:1 to 10:1) as the eluant afforded the *title compound* **295** (120 mg, 86%) as a yellow solid. The enantiomeric ratio was determined as 73:27 by comparison of the magnitude of its optical rotation to that of the known compound.[161a] The *exo*:*endo* ratio was determined to be > 95:5 by analysis of the ^{1}H NMR spectrum of the crude reaction product. $[\alpha]_D^{20}$ + 36.9 (*c* 1.01, chloroform), lit.[161a] - 82.4 (*c* 1.0, chloroform) for the enantiomer; **^{1}H NMR** ($CDCl_3$) δ 0.96 (3H, d, *J* = 6.91 Hz, C*H*$_3$), 2.57 (1H, dd, *J* = 5.8, 4.2 Hz, C*H*CHO), 3.09 (1H, dq, *J* = 6.9, 4.2 Hz, C*H*CH$_3$), 7.04-7.08 (1H, m, Ar*H*), 7.16-7.21 (1H, m, Ar*H*), 7.21-7.25 (2H, m, Ar*H*), 7.35-7.40 (1H, m, Ar*H*), 7.43-7.58 (7H, m, Ar*H*), 7.74-7.78 (2H, m, Ar*H*), 9.36 (1H, d, *J* = 5.8 Hz, C*H*O); **^{13}C NMR** ($CDCl_3$) δ 16.64, 43.20, 66.15, 118.71, 121.90, 126.21, 127.14, 127.44, 127.57, 128.20, 128.76, 128.95, 135.71, 136.84, 145.18, 147.63, 201.99; **IR** (film) 1720, 1498, 1458, 1449, 1380, 1354, 1309, 1059, 1012, 984, 760, 701 cm^{-1}.

APPENDICES

A.1 X-Ray Crystallographic Analysis of the Phenylacetates [73 (R = Me) and 74 (R = Ph)] and Amides [*R*-282 (R^1 = Ph), *S*-288 (R^1 = Bn) and *S*-289 (R^1 = Bn, R^2 = Me)].

A.1.1 General Experimental Concerning X-Ray Crystallography for the Amides [*R*-282 (R^1 = Ph), *S*-288 (R^1 = Bn) and *S*-289 (R^1 = Bn, R^2 = Me)]

Crystallographic data for the amides *R*-**282**, *S*-**288** and *S*-**289** are collected in Table A.1.4. All crystals were mounted on glass fibers using epoxy adhesive. Crystal descriptions for each compound are as follows: amide *R*-**282** was a colourless block having dimensions 0.10 × 0.10 × 0.15 mm^3; amide *S*-**288** was a colourless block having dimensions 0.46 × 0.57 × 0.81 mm^3; amide *S*-**289** was a colourless block having dimensions 0.26 × 0.31 × 0.37 mm^3.

The data for amide *R*-**282** and amide *S*-**288** (R^1 = Bn) were acquired at a temperature of 293 K on a Rigaku RAXIS-RAPID curved image plate area detector with graphite monochromated Cu Kα radiation, at room temperature. Indexing for the amide *R*-**282** was performed using three, 5° oscillations that were exposed for 90 seconds. Indexing for the amide *S*-**288** was performed using three, 5° oscillations that were exposed for 250 seconds. The following data ranges were recorded: *R*-**282** = $7.8° \leq 2\theta \leq 144.3°$; *S*-**288** = $6.5° \leq 2\theta \leq 136.5°$. A total of 27 images were collected for the amide *R*-**282** and 36 images for the amide *S*-**288**. A sweep of data for amide *R*-**282** was done using ω scans from 50.0° to 230.0° in 20° steps, at χ = 50.0° and ϕ = 0.0°. A second sweep was performed using ω scans from 50.0° to 230.0° in 30° steps, at χ = 50.0° and ϕ = 90.0°. A final sweep was performed using ω scans from 50.0° to 230.0° in 30° steps, at χ = 50.0° and ϕ = 180.0°. A sweep of data for the amide *S*-**288** was done using ω scans

from 0.0° to 180.0° in 15° steps, at χ = 0.0° and ϕ = 0.0°. A second sweep was performed using ω scans from 0.0 to 180.0 in 15° steps, at χ = 45.0° and ϕ = 0.0°. A final sweep was performed using ω scans from 0.0° to 180.0° in 15° steps, at χ = 45.0° and ϕ = 90.0°. The exposure rates for the amide *R*-**282** and amide *S*-**288** were 90 sec/°. In each case, the crystal-to-detector distance was 127.40 mm. An empirical absorption correction was applied to the amide *R*-**282** which resulted in the following transmission range: amide *R*-**282** = 0.6401 – 1.[1] A numerical absorption correction was applied to the amide *S*-**288** which resulted in the following transmission range: amide *S*-**288** = 0.9087 – 0.9247.[200]

The data for the amide *S*-**289** (R^1 = Bn, R^2 = Me) were collected at room temperature, using the diffractometer control program DIFRAC[201] and an Enraf Nonius CAD4F diffractometer employing graphite monochromated Mo Kα radiation. The following data range was recorded: amide *S*-**289** = 4° ≤ 2θ ≤ 55°. The data were corrected by integration, for the effects of absorption, using a semi-empirical psi-scan method with the following transmission range: amide *S*-**289** = 0.9694 – 0.9813. Data reduction for the amide *S*-**289** included corrections for Lorentz and polarization effects. Final unit-cell dimensions were determined based on the following well-centred reflections: amide *S*-**289** = 52 reflections with range 30° ≤ 2θ ≤ 36°.

For the amides *R*-**282**, *S*-**288** and *S*-**289** coordinates and anisotropic displacement parameters for the non-hydrogen atoms were refined with the exception of the two phenyl rings [C(11) until C(15)) and C(26) until C(31)] in each structure. For all compounds, hydrogen atoms were placed in calculated positions (C-H bond length = 0.95 Å) and their coordinate shifts were linked with those of the respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon

atoms. Subsequently, the isotropic thermal parameters for the hydrogen atoms were constrained to have identical shifts during refinement. An extinction parameter[202] was included in the final cycles of full-matrix least-squares refinement of the amide *S*-**288** (R^1 = Bn). Selected bond lengths and angles for the *R*-**282**, *S*-**288** and *S*-**289** are found in Table A.1.5, Table A.1.6 and Table A.1.6.

The programs used for all absorption corrections, data reduction and processing of the amide *S*-**289** (R^1 = Bn, R^2 = Me) were from the *NRCVAX* Crystal Structure System.[203] All structures were refined using *CRYSTALS*.[204] Complex scattering factors for neutral atoms were used in the calculation of structure factors.[205]

Table A.1.1 Summary of Crystallographic Data for the Phenylacetates **73** (R = Me)[a] and **74** (R = Ph)[a]

parameter	**73** (R ≡ Me)	**74** (R ≡ Ph)
Empirical formula	$C_{21}H_{22}O_4$	$C_{31}H_{26}O_4$
FW (g mol^{-1})	338.40	462.55
Temperature (K)	293	293
Crystal system	orthorhombic	orthorhombic
Space group	$P\,2_1\,2_1\,2_1$	$P\,2_1\,2_1\,2_1$
a (Å)	5.845(2)	9.1082(8)
b (Å)	14.301(4)	14.5054(13)
c (Å)	21.797(6)	18.1693(19)
α (°)	90	90
β (°)	90	90
γ (°)	90	90
Z	4	4
V (Å^3)	1822.2(10)	2400.5(4)
D_{calc} (g cm^{-3})	1.233	1.280
2θ limits (°)	3.4 – 50.0	4 – 55
R_1, R_w [$I = 2.5\sigma(I)$][b]	0.050, 0.046	0.034, 0.029

[a] Rigaku RAXIS-Rapid curved image plate area detector, Cu *K*α radiation (λ = 1.54180 Å), graphite monochromator. Function minimized $\Sigma w(|F_o|-|F_c|)^2$ where $w^{-1} = \sigma^2(F_o) + 0.0002\,F_o^2$, $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $R_w = (\Sigma w(|F_o|-|F_c|^2)/\Sigma w|F_o|^2)^{1/2}$.

Table A.1.2 Selected Bond Lengths and Angles for the Phenylacetate **73** (R = Me).

Selected Atoms	Bond Lengths / Å	Selected Atoms	Bond Lengths / Å
C1-O1	1.412(8)	C19-C20	1.48(1)
C1-O2	1.427(8)	C20-C21	1.510(9)
O1-C19	1.435(8)	C7-O3	1.400(8)
O2-C20	1.418(8)	O3-C17	1.365(7)
C18-C19	1.515(9)	C17-O4	1.172(8)
Selected Atoms	**Bond Angles / °**	**Selected Atoms**	**Bond Angles / °**
C1-O1-C19	106.3(5)	C18-C19-C20	117.0(8)
C1-O2-C20	108.6(5)	C19-C20-C21	115.8(7)
O1-C1-O2	106.0(6)	C7-O3-C17	118.8(6)
O1-C19-C18	109.6(6)	O3-C17-C10	109.2(6)
O2-C20-C21	109.0(6)	O4-C17-O3	121.8(7)
O1-C19-C20	102.4(6)	O4-C17-C10	129.0(6)
O2-C20-C19	103.6(6)	C11-C10-C17	113.0(6)

Table A.1.3 Selected Bond Lengths and Angles for the Phenylacetate **74** (R = Ph).

Selected Atoms	Bond Lengths / Å	Selected Atoms	Bond Lengths / Å
C1-O1	1.429(4)	C20-C21	1.511(4)
C1-O2	1.416(3)	C30-C31	1.501(4)
O1-C20	1.422(3)	C7-O3	1.402(3)
O2-C30	1.421(3)	O3-C17	1.347(4)
C20-C30	1.517(4)	C17-O4	1.192(4)
Selected Atoms	**Bond Angles / °**	**Selected Atoms**	**Bond Angles / °**
C1-O1-C20	109.2(2)	C20-C30-C31	116.4(3)
C1-O2-C30	106.1(2)	C30-C20-C21	116.1(3)
O1-C1-O2	105.4(2)	C7-O3-C17	118.1(3)
O1-C20-C30	103.0(2)	O3-C17-C10	111.1(3)
O2-C30-C31	110.1(2)	O4-C17-O3	122.8(4)
O1-C20-C21	109.8(2)	O4-C17-C10	126.1(4)
O2-C30-C20	101.8(2)	C11-C10-C17	115.5(3)

Table A.1.4 Summary of Crystallographic Data for the Amides *R*-**282**[a], *S*-**288**[a] and *S*-**289**[b]

parameter	amide *R*-282	amide *S*-288	amide *S*-289
Empirical formula	$C_{30}H_{30}N_2O_3S$	$C_{31}H_{32}N_2O_3S$	$C_{32}H_{34}N_2O_3S$
FW (g mol^{-1})	498.65	512.67	526.69
Temperature (K)	293	293	293
Crystal system	orthorhombic	orthorhombic	orthorhombic
Space group	$P\,2_1\,2_1\,2_1$	$P\,2_1\,2_1\,2_1$	$P\,2_1\,2_1\,2_1$
a (Å)	7.5764(1)	10.4931(6)	10.4099(10)
b (Å)	13.7511(1)	15.8623(7)	16.1371(15)
c (Å)	25.7986(4)	16.3279(8)	16.6872(17)
α (°)	90	90	90
β (°)	90	90	90
γ (°)	90	90	90
Z	4	4	4
U (Å^3)	2687.80(6)	2717.7(2)	2803.2(5)
D_{calc} (g cm^{-3})	1.232	1.259	1.248
2θ limits (°)	6-137	8-145	4-55
Reflections collected	17455	17935	3796
Independent reflections	2691	4761	3630
Reflections observed [$I = 2.5\sigma(I)$]	1364	2202	1710
Goodness-of-fit on *F*	1.160	0.856	1.728
R_1, R_w [$I = 2.5\sigma(I)$][c]	0.055, 0.054	0.048, 0.051	0.056, 0.055

[a] Rigaku RAXIS-Rapid curved image plate area detector, Cu *K*α radiation (λ = 1.54180 Å), graphite monochromator. [b] Enraf-Nonius CAD-4 diffractometer, Mo *K*α radiation (λ = 0.71069 Å), graphite monochromator. [c] Function minimized $\Sigma w(|F_o|-|F_c|)^2$ where $w^{-1} = \sigma^2(F_o) + 0.0002 F_o^2$, $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $R_w = (\Sigma w(|F_o|-|F_c|^2)/\Sigma w|F_o|^2)^{1/2}$. For *R*-**282**, [$I = 2.0\sigma(I)$] for reflections observed and R_1, R_w.

Table A.1.5 Selected Bond Lengths and Angles for the Amide *R*-**282** (R^1 = Ph).

Selected Atoms	Bond Lengths / Å	Selected Atoms	Bond Lengths / Å
C1-C2	1.330(12)	C4-C10	1.515(11)
C1-C9b	1.502(12)	N5-C5a	1.468(9)
C2-C3	1.504(12)	N5-C16	1.408(8)
C3-C3a	1.605(13)	C9a-C9b	1.529(12)
C3a-C4	1.543(11)	C16-O17	1.225(8)
C3a-C9b	1.573(12)	C16-C18	1.550(11)
C4-N5	1.500(9)	C18-N22	1.476(9)
Selected Atoms	**Bond Angles / °**	**Selected Atoms**	**Bond Angles / °**
C1-C2-C3	112.0(10)	C4-C3a-C9b	115.9(8)
C1-C9b-C9a	113.5(8)	C4-N5-C16	118.5(6)
C1-C9b-C3a	104.2(8)	N5-C4-C10	113.9(7)
C2-C3-C3a	104.5(9)	N5-C16-C18	115.4(7)
C3-C3a-C4	114.8(8)	N5-C5a-C6	121.2(7)
C3-C3a-C9b	104.5(8)	N5-C16-O17	122.4(8)
C3a-C4-N5	105.0(6)	C5a-N5-C16	125.5(6)
C3a-C9b-C9a	114.4(8)	O17-C16-C18	122.1(7)
C4-N5-C5a	114.3(5)	C9-C9a-C9b	122.2(8)

Table A.1.6 Selected Bond Lengths and Angles for the Amide *S*-**288** (R^1 = Bn).

Selected Atoms	Bond Lengths / Å	Selected Atoms	Bond Lengths / Å
C1-C2	1.315(7)	C4-C33	1.516(6)
C1-C9b	1.499(7)	N5-C5a	1.423(6)
C2-C3	1.505(7)	N5-C16	1.362(6)
C3-C3a	1.543(8)	C9a-C9b	1.508(7)
C3a-C4	1.540(7)	C16-O17	1.215(6)
C3a-C9b	1.556(7)	C16-C18	1.534(7)
C4-N5	1.463(6)	C18-N22	1.469(6)

Selected Atoms	Bond Angles / °	Selected Atoms	Bond Angles / °
C1-C2-C3	112.0(6)	C4-C3a-C9b	110.8(5)
C1-C9b-C9a	115.2(5)	C4-N5-C16	119.0(4)
C1-C9b-C3a	103.0(5)	N5-C4-C33	111.1(5)
C2-C3-C3a	103.2(5)	N5-C16-C18	116.8(5)
C3-C3a-C4	113.9(5)	N5-C5a-C6	121.5(5)
C3-C3a-C9b	104.4(5)	N5-C16-O17	122.3(5)
C3a-C4-N5	107.0(4)	C5a-N5-C16	123.9(5)
C3a-C9b-C9a	115.0(5)	O17-C16-C18	117.9(5)
C4-N5-C5a	114.7(4)	C9-C9a-C9b	120.1(5)

Table A.1.7 Selected Bond Lengths and Angles for the Amide *S*-**289** (R^1 = Bn, R^2 = Me).

Selected Atoms	Bond Lengths / Å	Selected Atoms	Bond Lengths / Å
C1-C2	1.323(13)	C33-C10	1.501(10)
C1-C9b	1.505(11)	N5-C5a	1.435(8)
C2-C3	1.490(13)	N5-C16	1.360(8)
C3-C3a	1.537(10)	C9a-C9b	1.520(11)
C3a-C4	1.532(10)	C16-O17	1.214(8)
C3a-C9b	1.536(11)	C16-C18	1.523(9)
C4-N5	1.481(8)	C18-N22	1.486(8)
C4-C33	1.529(9)	C8-C34	1.497(11)
Selected Atoms	**Bond Angles / °**	**Selected Atoms**	**Bond Angles / °**
C1-C2-C3	112.6(9)	C4-C3a-C9b	110.7(6)
C1-C9b-C9a	114.6(7)	C4-N5-C16	118.0(6)
C1-C9b-C3a	102.9(7)	N5-C4-C33	111.4(6)
C2-C3-C3a	102.9(8)	N5-C16-C18	119.8(6)
C3-C3a-C4	114.4(7)	N5-C5a-C6	121.2(6)
C3-C3a-C9b	105.6(7)	N5-C16-O17	121.6(7)
C3a-C4-N5	106.8(6)	C5a-N5-C16	125.0(6)
C3a-C9b-C9a	115.7(6)	O17-C16-C18	118.5(6)
C4-N5-C5a	112.6(6)	C9-C9a-C9b	119.5(8)

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