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At last, special thanks are given to all faculty and staff in the Chemistry Department for their assistance.

To my family.....

Abstract

The development of new methodology for the asymmetric synthesis of chiral organic compounds is a major focus in modern organic chemistry.

The use of chiral catalysts is replacing chiral auxiliaries as a new tool for synthetic chemists. An efficient chiral catalyst allows for large quantities of optically active product to be obtained on use of relatively small amount of enantiopure material, without the need for the removal and recovery of a chiral auxiliary. Furthermore, the most practical catalytic methods utilize an inexpensive and readily available chiral ligand that can provide high and predictable enantioselectivity across a wide range of substrates.

In our project, two type of versatile, upgraded chiral ligands have been designed and synthesized. Their application in Simmons-Smith type cyclopropanation is investigated, and the pleasing results suggest that they are the potential catalytic enantioselective candidates to build C-C bonds.

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List of Abbreviations

e.e.	enantiometric excess
Bu	butyl
TADDOL	(4R,5R)-2,2-dimethyl-α,α,α,'α'-tetraphenyl-1,3-dioxolane-5-dimethanol
LDA	lithium diisopropylamide
TMEDA	N,N,N',N'-tetramethylenediamine
TEAA	triethylammonium acetate
HPLC	high performance liquid chromatography
DMAP	4-(N,N-dimethylamino) pyridine
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
THF	tetrahydrofuran
GC	gas chromatography
TLC	thin layer chromatography
IR	infrared spectroscopy
HRMS	high resolution mass spectrometry
MS (FAB)	fast atom bombardment mass spectrometry
Ac	acetyl
Et	ethyl
DIBAL	Diisobutylaluminium chloride
PCC	Pyridinium chlorochromate
MS	molecular sieves

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Chapter I. Introduction

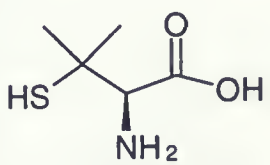
1.1 Molecular chirality and its importance

Chirality is a fundamental symmetry property of three-dimensional objects. A molecule is said to be chiral if it cannot be superimposed upon its mirror image. Many compounds can be obtained in two different forms in which the molecular structures are constitutionally identical but differ in the three-dimensional configuration of atoms such that they are related as mirror images. In such cases the two possible forms are called enantiomers[1]. Despite having many identical chemical activities and physical properties such as melting point, NMR spectra, density etc., a pair of enantiomers do have some different physical properties and can have markedly different biological properties. For example, one enantiomer will rotate the plane of polarized light in the opposite direction to the other. This property was originally discovered in 1815 by a physicist named Jean-Maptiste Biot (1774-1862) who showed that certain natural products such as camphor and turpentine interact differently with a polarized light source. He concluded that certain organic compounds were "optically active" having the ability to rotate polarized light clockwise (+) or counter-clockwise (-), although he did not understand the relationship to the three dimensional configuration of the molecule. Many years later, two chemists named Jacobus Henricus Van't Hoff (1852-1911) and Joseph Achille Le Bel (1870-1930), using the additional valuable experimental results of Pasteur, confirmed that the ability to rotate a source of polarized light was due to the difference in three dimensional arrangement of atoms existing in the molecule. Furthermore, they also confirmed another

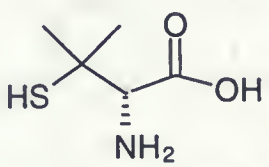
of Pasteur's discoveries, that an equal amount of both enantiomers contained in a solution did not rotate the plane of polarized light at all. Such a mixture is called a racemic mixture, or referred to simply as a racemate.

In terms of biological properties, the three dimensional configurational stability of organic molecules is of great fundamental importance. Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will elicit different responses[2]. A variety of functions responsible for metabolism and numerous biological responses occur because enzymes receptors, and other natural binding sites recognize substrates with a specific chirality. The relationship of stereochemistry and biological activity through the so called "lock and key" description is now considered fundamental in the chemical-biological sciences. Developing chiral molecules to interact with a biological receptor has become a very important issue in pharmaceutical industry.

Different enantiomers could possess different levels of biological activity: one may act as a very effective therapeutic drug whereas the other may be highly toxic. For example, the cases of penicilliamine[3] and thalidomide[4] are well known (see Figure 1. and Figure 2.).

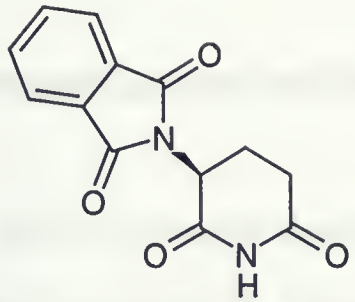


D-penicilliamine
chelating agent used to remove heavy metals from the body, e.g. Cu, Au, Pb, Hg

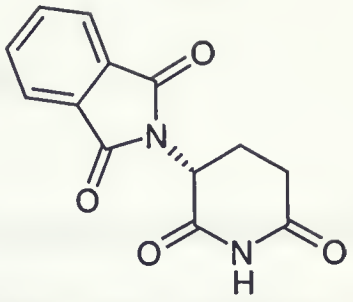


L-penicilliamine
causes optic atrophy and, ultimately, blindness

Figure 1. Two enantiomers of penicilliamine



(S)-thalidomide
sedative and hypnotic



(R)-thalidomide
Teratogenic: fetal death,
congenital malformation

Figure 2. Two enantiomers of thalidomide

In 1997, troglitazon[5] was approved for marketing by Parke-Davis. It is a 5-substituted glitazone (1,3-thiazolidine-2,4-diones). As we can see (Figure 3), the drug is actually a mixture of four isomers: one asymmetric center is C-5 of the thiazolidine ring while the second one is at the 2-position of the chromane ring system. Research shows that only two diastereoisomers have drug activity against diabetes, the other two had been plagued by potentially fatal liver damage. Similar glitazones drugs such as the pioglitazone marketed by Eli Lilly and Takeda Pharmaceuticals America, New York City, and the rosiglitazone marketed by SmithKline Beecham, Philadelphia have encountered similar problems.

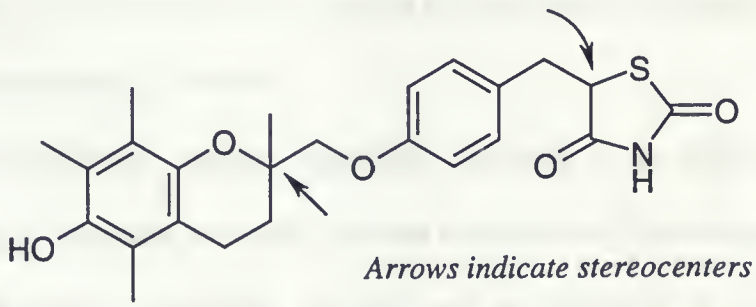


Figure 3. Troglitazone (Parke-Davis), one type of 'Glitazones'

1.2 Asymmetric syntheses used to achieve chirality

The above examples show the dramatic biological or pharmacological difference that may be exhibited by chiral compounds during drug development. It is the responsibility of organic synthetic chemists to provide highly efficient and reliable methods to synthesize desired compounds in an enantiometrically pure state, i.e., with 99.5% enantiometric excess (% ee). Recent rulings of the Food and Drug Administration (FDA) in the United States require pharmaceutical industries to provide rigorous justification to obtain the FDA's approval of racemates[6].

Basically, there are two ways to obtain enantiometrically pure materials:

(1) Prepare the molecule in racemic form, then do a resolution. This method suffers from the problem that two extra chemical steps may be necessary to install the resolving agent and remove it. Additionally, only half of a racemic mixture is the desired isomer. The maximum yield, therefore, is 50%, at best; the rest is wasted.

(2) Prepare the molecule *via* an asymmetric synthesis. Methods can include the chiral pool approach, chiral auxiliaries (also known as stoichiometric asymmetric synthesis) and catalytic asymmetric synthesis.

Among these fields, catalytic asymmetric synthesis is the most desirable and challenging strategy in organic synthesis. A chiral catalyst molecule or catalyst can create millions of chiral product molecules. This approach is regarded as an ideal method to synthesize optically active compounds in large quantities. The efficiency of chirality multiplication, defined as [(major enantiomer-minor enantiomer) / chiral sources][6] can

be, in theory, infinite for asymmetric catalysis. It avoids narrow compound selection, which is a disadvantage of the chiral pool method. It also prevents the extra steps required by the chiral auxiliary method.

Most catalytic asymmetric syntheses are actually enantioselective version of classic organic reactions. A general chemistry process[7] is presented in Figure 4.

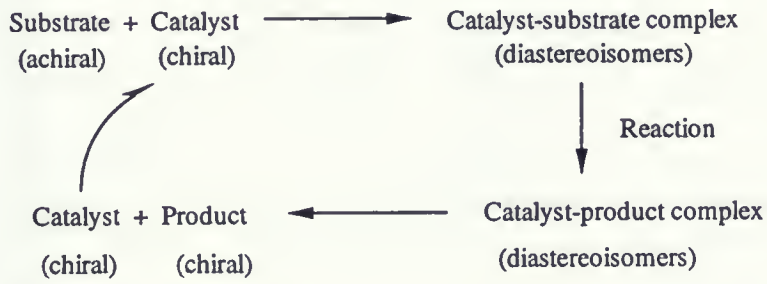


Figure 4. Schematic representation of enantioselective catalysis

The catalytic system must first permit precise discrimination among enantiotopic atoms, groups or faces of achiral molecules. Here, the catalyst center (usually a Lewis acid) acts as a template which regulates the organic reaction in its coordination sphere. More importantly, the chiral ligand modifies the catalyst and creates an asymmetric environment. With this influence, the reaction may proceed via two diasteromeric states that may be different in energy by10 KJ/mol or less[8] (see Figure 5). Energetically, one diasteromeric transition state is favored and this diasteromeric transition state dissociates to products (dominated by one enantiomer) and catalyst (which may be recovered and then may enter the next catalytic cycle).

During the last decade, catalytic asymmetric synthesis has become an important and practical tool to obtain enantiometrically pure or enriched compounds and the field

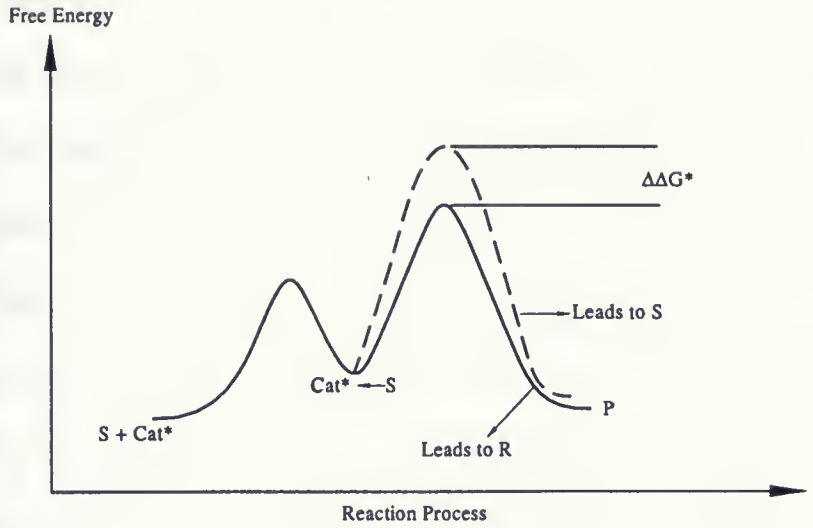


Figure 5. The dialogue of the free energy change during the reaction process

has occupied the attention of chemists in synthetic chemistry, medicinal chemistry, agricultural chemistry, natural products chemistry, the pharmaceutical industries, and the agricultural industries. Many examples of asymmetric synthesis using chiral catalysts can now be found in the literature. The earliest examples studied were the asymmetric transfer of atoms such as hydrogen, oxygen and nitrogen to organic substrates. This work was done by chemists like Noyori, Sharpless and Evans, respectively, in such reactions as hydrogenation, epoxidation and dihydroxylation. Many of these processes are now used routinely by synthetic organic chemists and reach high levels of efficiency. In most cases,

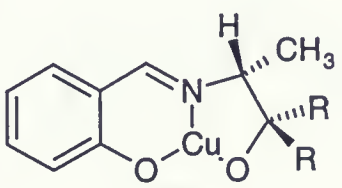
a very low amount of catalyst (<5%) can turnover a high yield of substrate, almost quantitatively, with extremely high levels of asymmetric induction (ee>99%).

More recent work concerns the ability to perform carbon-carbon bond forming reactions using asymmetric catalysis. Asymmetric catalytic variants of Diels-Alder, aldol, cyclopropanation and conjugate addition reactions have been developed. Specific examples of these reactions are numerous. For examples, the reader is refered to the following: the asymmetric Diels-Alder reactions using bisoxazolines[9]; aldol condensations using Cu(II) with silly ketone acetals[10] or using tin (II) with stannous enolates[11]; dialkylzincs to aldehydes; cyclopropanation of allylic alcohols[12]; allylic alkylation[13]; and Michael reactions promoted by BINOL complex[14].

The benefit at an industrial level for asymmertic catalysis is great: a number of catalytic asymmetric reactions, such as the "Sumitomo process[15,16] (see Scheme 1) and the "Takasago process[17] (see Scheme 2) were commercialized in 1980's.

Scheme 1. Sumitomo Process

1 92%e.e.



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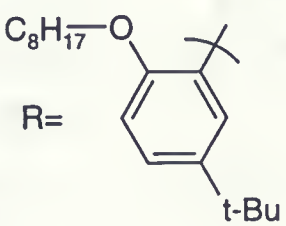
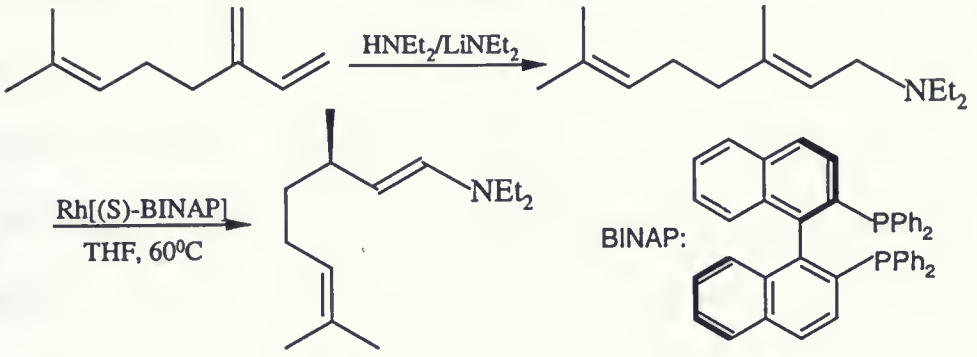


Scheme 2. Asymmetric Isomerization of Allylamines
--------- Takasago process

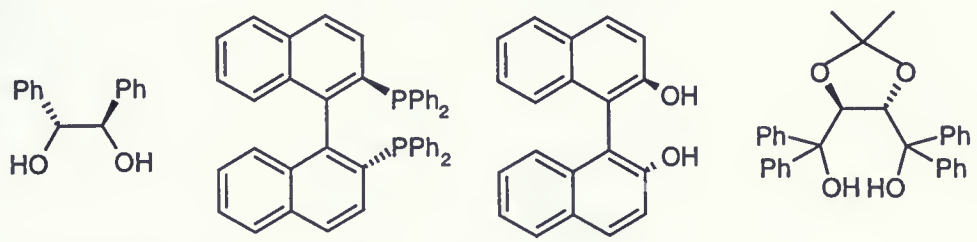


3 **4**

100% conversion, 98%e.e.

1.3 C_2-Symmetrical Ligands

In catalytic asymmetric synthesis, the most widely applied chiral ligands are C_2-symmetrical ligands. The term C_2-symmetrical ligand applies to a number of chiral compounds containing a C_2 axis of chirality, which upon rotation of 180^0 allows the compound to map onto itself. All C_2-symmetrical ligands exhibit a form of configurational isomerism due to the presence of restricted bond rotation along the central axis[18]. Some well known C_2-symmetrical ligands are shown in Figure 6.



(R)-Hydrobenzoin **(R)-BINAP** **(R)-BINOL** **(S)-TADDOL**

5 **4** **6** **7**

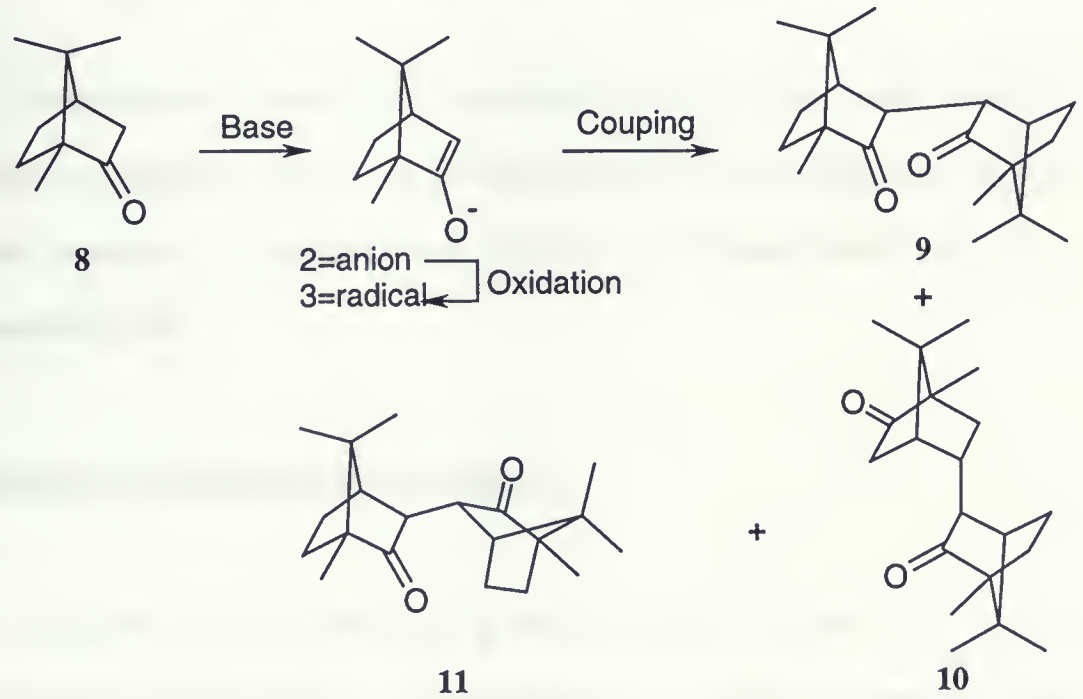
Figure 6. Representative examples of commerically available C_2-symmetrical ligands

Among those C_2-symmetrical ligands, 1,4 diols have proven to be an important class of chiral ligand due to their versatile applications. However, the available choice is limited.

The monoterpenoid camphor derivatives, such as Oppolzer camphor sultams, have been widely used as chiral auxiliaries to achieve high diastereoselectivity. The unique structural features of the camphor skeletons inspired McNulty and Millar to select the chiral pool ketone camphor as a precursor for making a new class of ligand.

A short synthetic route was envisioned for the production of a C_2-symmetrcal 1,4-diol from camphor whose key step was the initial coupling reaction. Previous efforts involving the oxidative dimerization of camphor enolates resulted in three diasteromers (see Scheme 3).

Scheme 3. Oxidative dimerization of camphor enolates

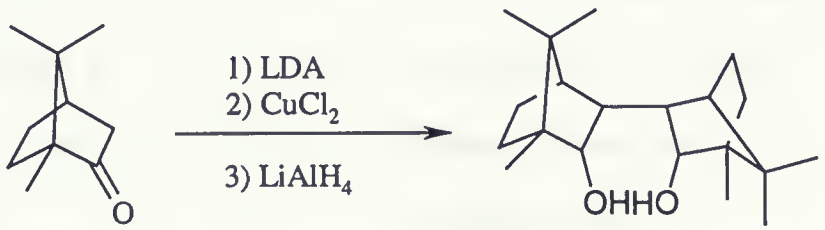


8 9 10 11

In 1999, McNulty and Millar reported a stereoselective oxidative dimerization and the subsequent reduction[19]. They described a method which can give exclusively the *exo, exo'*-3,3'-bicamphor (9) and the C_2-symmetric 1,4 diol *exo, exo'*-3,3'-bisoboroneol (12) after reduction (Scheme 4).

The main advantage of this method is that various kinetic control factors can be adjusted. These include the use of a less polar solvent (toluene) and low temperature (-78 ^{0}C), both of which ensure slow coupling to get the kinetically control product.

Scheme 4. Preparation of BIBOL



8 **12a**

The unambiguous stereochemical assignment for both diols was made possible by two x-ray crystallographic analyses. Modeling studies indicated that compound **12a** is a potentially valuable C_2-symmetric 1,4-diol, and worthy of exploring potential in catalytic asymmetric reactions.

1.4 Catalytic Enantioselective Cyclopropanation

Among the valuable chiral building blocks produced by asymmetric catalysis, those containing optically active cyclopropanes are probably among the most synthetically useful. Cyclopropanes are found as basic structural elements in a wide range

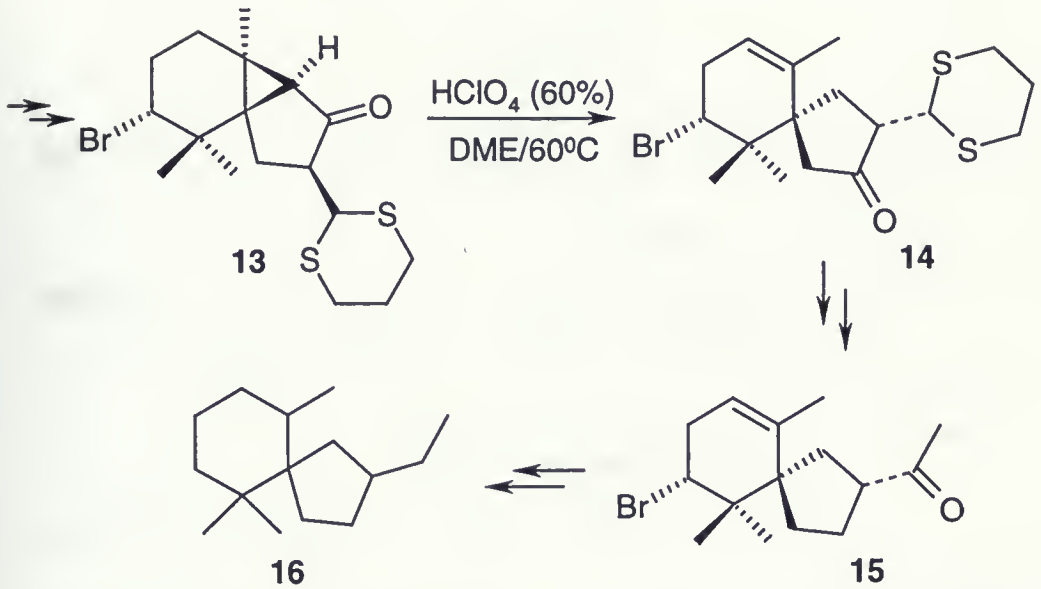
of naturally occurring compounds found in plants and in microorganisms, both fungal and bacterial[20]. They are also generated transiently in primary and secondary metabolic processes. Cyclopropanes are also contained in "unnatural" compounds which are of biological and medicinal importance.

Cyclopropanes are valuable synthetic units because of their versatile chemistry[21]. The cyclopropane chemical reactivity closely resembles that of an olefin double bond due to the "p" character of the C-C bonds, and is highly strained. For example, treatment with various electrophiles results in addition with concomitant fission of the ring.[22,23] The electrophile adds to the carbon with the greater number of hydrogens, generating a cation at the most substituted carbon which is subsequently trapped by a nucleophile.

Scheme 5. Electrophilic Addition of Cyclopropane

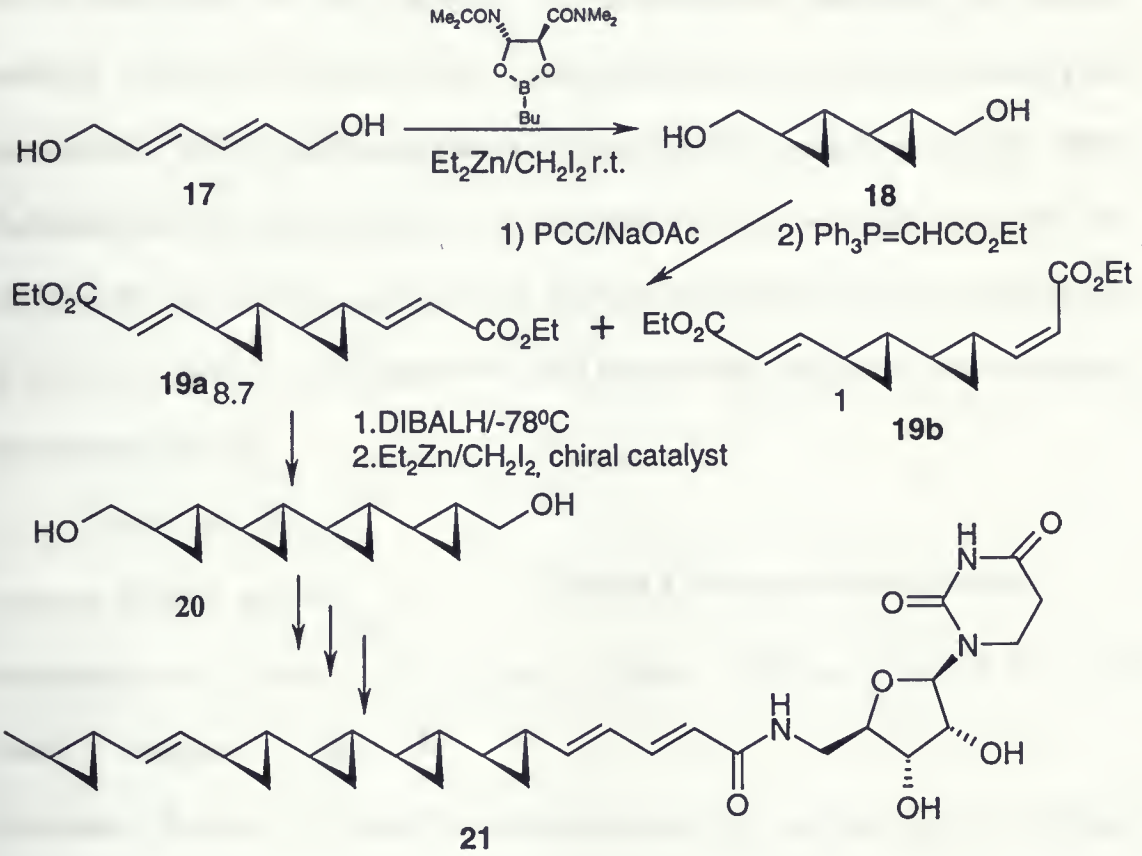
In additon, cyclopropane reactions involving rearrangements are also of synthetic importance: e.g., ring-opening reactions, ring enlargements, and ring contractions. For example, the total synthesis of (±)-*Spirolaurenone*, an antifungal sesquiterpene isolated from the red algae *Laurencia glandulifera*, was prepared by a sequence in which the key step was the cyclopropane opening of a tricyclic ketone (**13**). In presence of 60% $HClO_4$ in DME, compound **13** could be opened to a mixture of *exo* and *endo* olefins[24].

Scheme 6. The total synthesis of Spirolaurenone



Enantioselective cyclopropanation has become a very powerful C-C bond formation methodology to fix the stereocentres in the cyclopropane ring. Subsquent chemistry can allow us to perform a regiostereoselective ring opening, and use the products for synthesis of other more complex compounds. FR-900848, for example, is a nucleoside derivative isolated from the fermentation broth of *Streptovertillium fervens*. It shows potentially selective activity against filamentous fungi such as *Aspergillus niger*. However, it is essentially inactive against non-filamentous fungi such as *Candida albicans* and Gram-positive and -negative bacteria. Structurally, this natural product is quite remarkable since it is graced with five cyclopropane unites, four of which are contiguous. A recent paper on total synthesis of FR-900848, an antifungal agent, provides a nice example of the use of asymmetric cyclopropanation to control ten stereocentres in a natural product synthesis[25](Scheme 7).

Scheme 7. Total synthesis of FR-900848 using asymmetric cyclopropanation



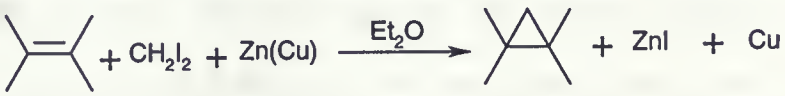
1.5 Review of enantioselective cyclopropanations

By and large, cyclopropanes are generated by the addition of carbenes or carbenoids to alkenes[26]. Carbenes (neutral molecules containing a divalent carbon covalently bonded to two other groups) can be generated from a number of reactions; the most common being the α-elimination of halogenated compounds (which don't contain ß-hydrogens) and decomposition of compounds containing certain types of double bonds such as ketenes, diazo compounds, diazirines, salts of sulfonylhydrazones, epoxides, and

α-halomercury compounds. The latter method generally involves homolytic cleavage of double bonds under various conditions such as photolysis, thermolysis, or metal-ion catalysis. The term carbenoid is used to refer to molecules that behave chemically like free carbenes with the carbenoid carbon atom generally bonded to a transition metal. Carbenoids are of greater synthetic utility than their free carbene counterparts since they are generally less reactive, require simpler reaction procedures for their preparation, can be used in reactions at room temperature, and provide high degrees of chemoselectivity and stereoselectivity.

One of the classic protocols used to generate carbenoids is the Simmon-Smith reaction. As illustrated in Scheme 8, diiodomethane and diethylzinc are used to generate a carbenoid which adds to an alkene (**22**) to give a cyclopropane product (**23**) in high yield.

Scheme 8 Simmon-Smith reaction



22 23

Alternatively, decomposition of diazocarbonyl compounds to form metal-carbenoid intermediates can also be added to alkenes to produce cyclopropanes. The popularity of these α-diazocarbonyl compounds is based on their ease of preparation, facile purification (can be chromatographed on silica gel) and stability (can be stored for a prolonged periods of time without significant decomposition). The use of diazo compounds dominates the carbenoid field and there have been a number of excellent reviews published. Use of a chiral ligand allows for the reaction to proceed asymmetrically. The catalytic cycle for cyclopropanation is shown below:

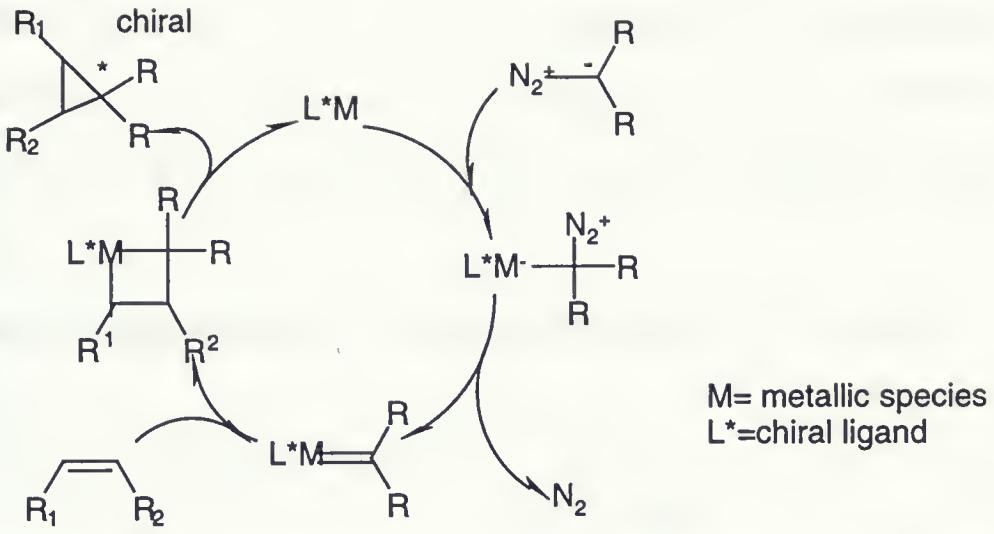
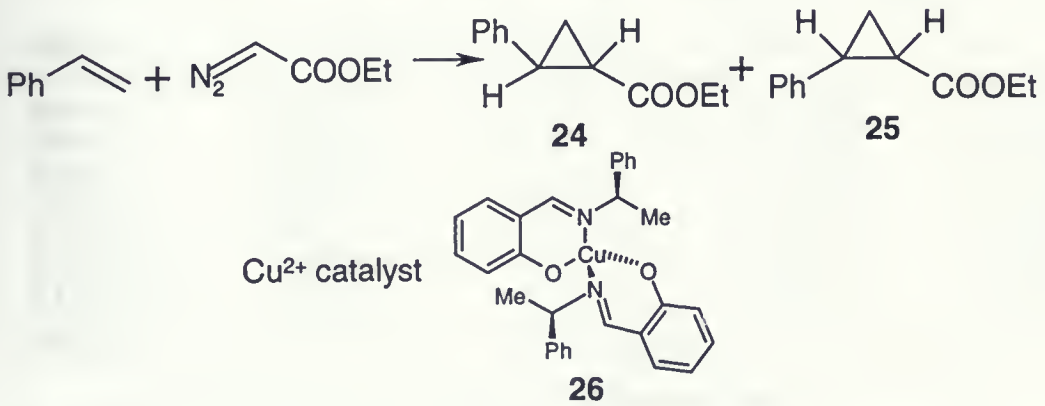


Figure 7. The catalytic cycle of diazocarbonyl decomposition onto to alkene

One of the first reported enantioselective cyclopropanations was achieved using the chiral copper catalyst (**26**) in 1966[27]. The work marks the first reported catalytic asymmetric reaction of a prochiral compound using a soluble chiral metal complex (see Scheme 9 below).

Scheme 9. Enantioselective Cyclopropanation with Schiff base-copper(II) catalyst



Nozaki and his coworkers employed a Schiff base-copper (II) complex, whose chiral ligand was derived from α-phenethylamine, to catalyze the cyclopropanation of styrene with ethyl diazoacetate (around 60% ee)

Pfaltz[28] used semicorrin copper (II) complexes for enantioselective cyclopropanation to obtain good effect. This work was later extended by Pfaltz[29,30] and Masamune[31] and permitted the cyclopropanation of a number of olefins (Scheme 10 and Table 1).

Scheme 10. Cyclopropanation of diazoester with Semicorrin Copper(II)

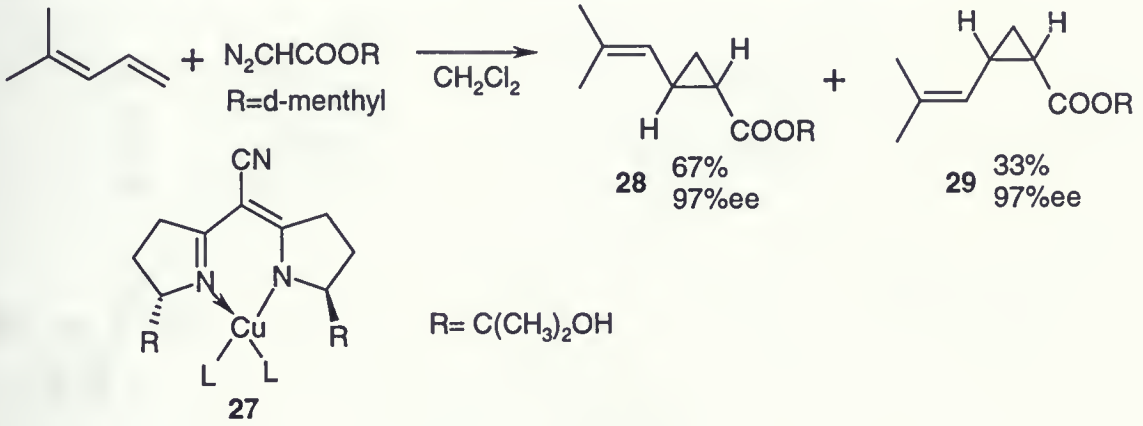


Table 1. Enantioselective Cyclopropanation of Alkenes with Diazo Compounds catalyzed by the Pfaltz Semicorrin Catalyst

			% e.e.[b]	
Alkene	$N_2CHOOCR^a$:R	trans:cis	trans	cis
Styrene	*l*-Menthyl	85:15	91 (1S,2S)	90 (1S,2R)
Styrene	*d*-Menthyl	82:18	97 (1S,2S)	95 (1S,2R)
Styrene	*Tert*-Butyl	81:19	93 (1S,2S)	93 (1S,2R)
Styrene	Ethyl	73:27	92 (1S,2S)	79 (1S,2R)
1-Heptane	*d*-Menthyl	82:18	92 (1S,2S)	92 (1S,2R)
1,3-Butadiene	*d*-Menthyl	63:37	97 (1S,2S)	97 (1S,2R)
4-Mthyl-1,3-Butadiene	*d*-Menthyl	63:37	97 (1S,2S)	97 (1S,2R)

a *d*-Menthyl= (1S,2R,5s)-2-isopropyl-5-methylcyclohexyl.
b Absolute configuration of cyclopropane product in parentheses.

As may be observed, the semicorrin copper catalysts are exceptionally effective with monosubstituted alkenes and.1,3 conjugated diene, such as styrene, 1-heptene and

1,3 butadiene. Overall enantioselectivities are significantly higher than the first generation of copper-Schiff base ligands.

Pfaltz described the active catalyst as a copper derivative with only one semicorrin, and he has provided a mechanistic description which portrays possible transition state geometries (Figure 8).

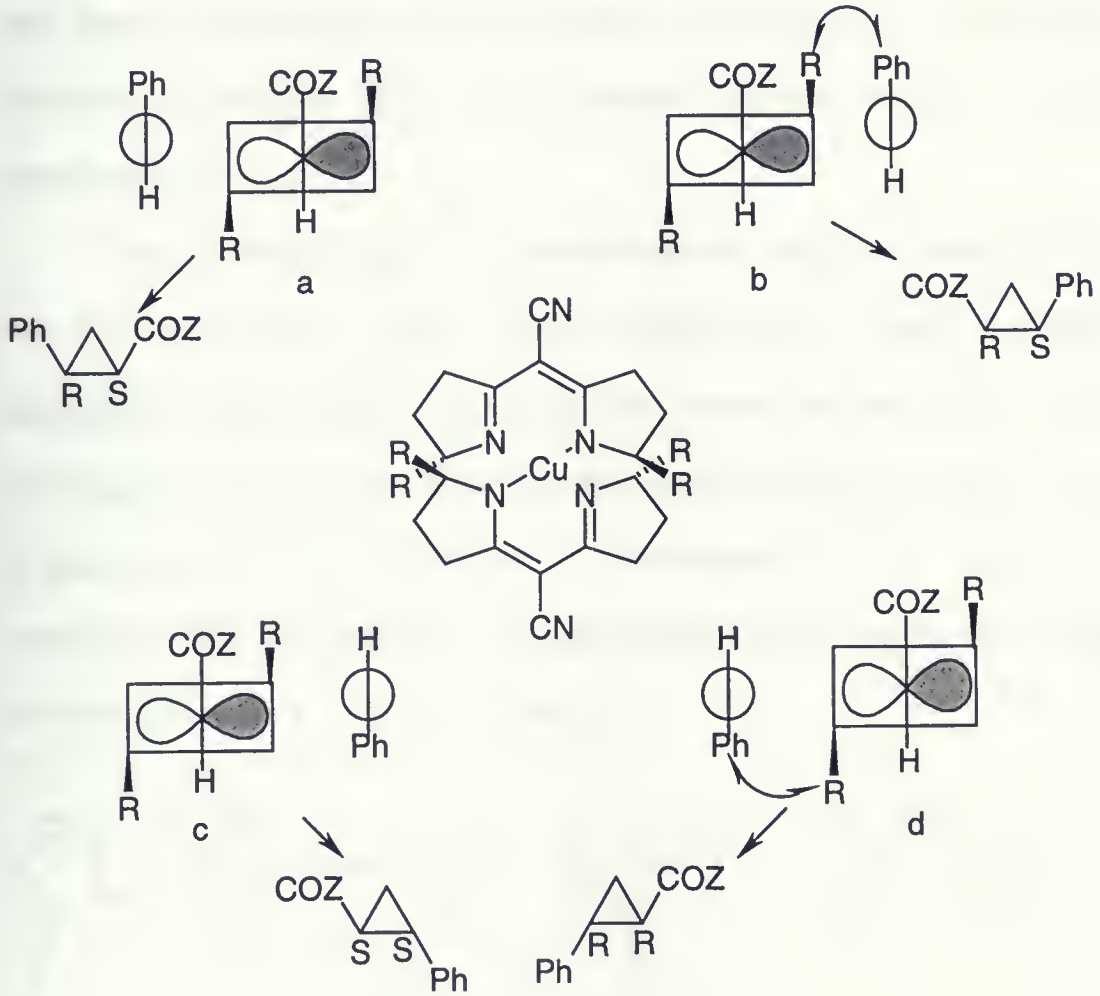
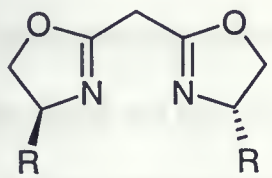


Figure 8. The depiction of Pfaltz catalyst

The preferred conformation for the metal carbene is that in which carbene substituents are oriented to minimize steric interaction with the approaching alkene. Four limiting conformations can be envisioned in this front view of the reaction system (a-d),

of which b and d, the two that have the olefin substituent Ph on the same side as the ligand's R-group, are less stable. Because of the C_2 symmetry of the semicorrin ring, the same enantiomers are formed from these models whether the COZ substituent is positioned up or down. These models suggest that the observed high enantioselectivities arise from interactions of R with olefin substrates. Furthermore, increasing the size of the ester group (COZ) probably changes the orientation of the carbene's carbonyl substituent relative to the semicorrin ring and magnifies the influence of the semicorrin R-group on enantioselection.

Closely related ligands are the bisoxazoline series which have the advantage that their chiral center can be obtained from an α-amino alcohol. Evans[32], for example, employed bisoxazoline copper complexes (**32**) for a series asymmetric cyclopropanations. These ligands (**30-32**) are suitable alternatives to semicorrin ligands for copper in creating a highly enantioselective environment for cyclopropanation. For the first time, diazoacetates with ester substituents as small as ethyl could be used to achieve greater than 90% ee in reactions with styrene (Table 2).



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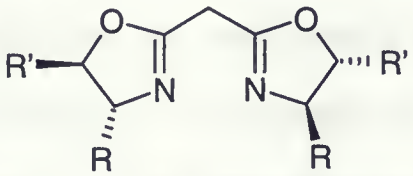

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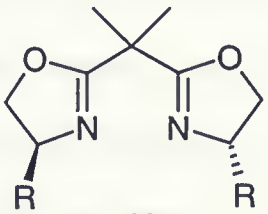

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Just as expected, increasing the size of the R group increases enantioselection, and the buttressing effect on the bisoxazoline ring caused by the geminal dimethyl group in Evan's ligand provides further enhancement of enantiocontrol.

Table 2 Enantioselective Cyclopropanation of Styrene with Diazo Esters using Bisoxazoline Copper Catalysts

	$N_2CHOOCR'$			% e.e.		
Ligand	*R*	R'	trans:cis	trans[a]	cis[b]	Ref.
30	*Ph*	Et	70:30	60	52	33
30	*PhCH*$_2$	Et	71:29	36	15	33
30	*i*-Pr	Et	71:29	46	31	33
30	*i*-Pr	Et	64:36	64	48	34
30	*t*-Bu	Et	75:25	90	77	33
30	*t*-Bu	Et	77:33	98	93	34
30	*t*-Bu	*d*-Menthyl	84:16	98	80	33
30	*t*-Bu	*l*-Menthyl	84:16	98	96	33
30	*t*-Bu	*l*-Menthyl	87:13	96	97	30
30	$Me_2C(OH)$ [c]	*d*-Menthyl	83:17	90[d]	90 [e]	30
31	Me	Et	71:29	28[d]	30 [e]	33
32	*t*-Bu	Et	73:27	99	97	34
32	*t*-Bu	*t*-Bu	81:19	96	93	34
32	*t*-Bu	BHT[f]	94:6	99		38

a Product from styrene has the (1R,2R)-cofiguration.
b Product from styrene has the (1R,2R)-cofiguration.
c Catalyst has opposite configuration to, *8 (R=t-Bu).*
d *(1S,2S)-configuration.*
e *(1S,2R)-configuration*
f *2,6-Di-tert-butyl-4-methylphenyl.*

However, as it can be seen from results in Table 2, the ligand's R substituent has only a minor influence on the trans/cis ratio of cyclopropane products. To increase product diastereoselectivity, Evans increased the size of the ester substituent from ethyl to tert-butyl and then to the bulky BHT esters to provide exceptionally high diastereocontrol in catalytic cyclopropanation reactions. The disadvantage of these BHT esters is their low reactivity to chemical reduction and unreactivity toward hydrolysis.

The use of these catalysts for the asymmetric intermolecular cyclopropanation of alkenes other than styrene have demonstrated the generality applicability (Table 3).

Table 3. Enantioselective Cyclopropanation of Alkenes with Diazo esters Using bisoxazoline Copper catalysts

Alkene	Ligand	$N_2CHCOOR'$:R	Yield(%)	trans:ci	e.e. trans	e.e. cis	ref
1-Octene	30	*l*-Menthyl	76	94:6	99	30	33
		d-Menthyl	72	90:10	75	45	33
α-Methylstyrene	30	*l*-Menthyl	78	89:11	92	79	33
		d-Menthyl	72	85:15	83		33
trans-4-Octene	30	*l*-Menthyl	52	____	88	88	33
2,3,3-Trimethyl-1-1-	30	*l*-Menthyl	60	95:5	80	91	33
		d-Menthyl	55	98:2	77	n.d.[c]	33
Isobutylene	32	Et	91	____	>	99	34
1,1-Diphenylethene	32	Et	75	____	99	99	34

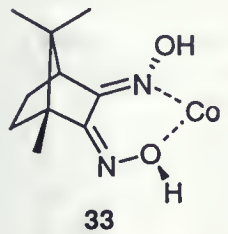
A *R=t-Bu.*
B % de values for reactions with menthyl diazoacetate.
C Not Determined.

The trans/cis (or E/Z) ratios of cyclopropane products are higher than those obtained with styrene, and diastereoselectivities or enantioselectivities for the trans (E) isomer are generally greater than 80%. Although these reactions are generally performed with 1.0 mol% of catalyst, Evans optimized the cyclopropanation of isobutylene to a 0.25 mol scale, using only 0.1 mol% of catalyst, and obtained a 91% yield of (S)-2,2-dimethylcyclopropanecarboxylate, which is employed for the construction of cilastatin, an *in vivo* stabilizer of the antibiotic imipenem, with greater than 99% e.e. — significantly greater than that of the same reaction performed with the Schiff base catalyst.

Scheme 11. Cyclopropanation of isobutylene with catalyst 32

1 99% e.e.

Other efforts to achieve good enantioselectivity in diazoester type cyclopropanation reactions include the use of chiral cobalt (II) catalysts[33] (**33**), chiral dirhodium (II) catalyst (**34,35**)[34,35,36] .



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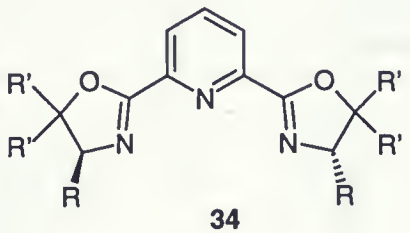

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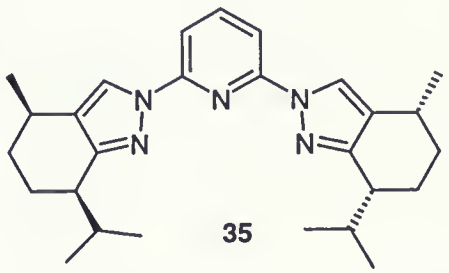

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Only a few examples give better results than those reported above, although most reward good yield with modest ee or modest yield with good ee.

In the late 90s, asymmetric variants of the Simmons-Smith cyclopropanation began to emerge, specifically the reaction of carbeniod intermediates prepared from diethylzinc and diiodomethane and their addition to allylic alcohols.[37,38,39]

Dr. H. Kobayashi[40a,40b] reported an asymmetric Simmons-Smith reaction mediated by a C_2-symmetrical chiral disulfonamide catalyst and using zinc or aluminium as the Lewis acid. A summary of the results of this work are shown below.

Scheme 12. Simmons-Smith cyclopropanation mediated by disulfonamide catalyst

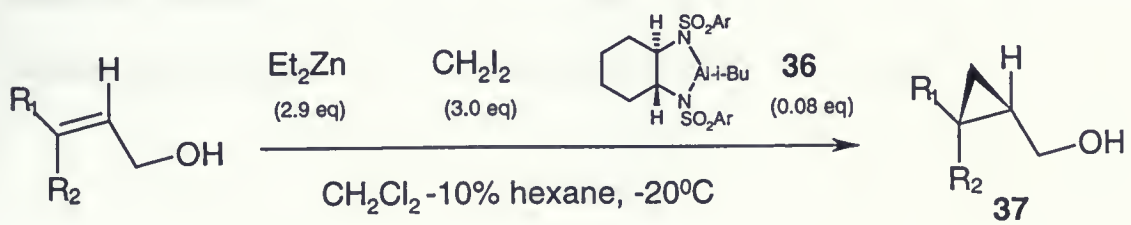

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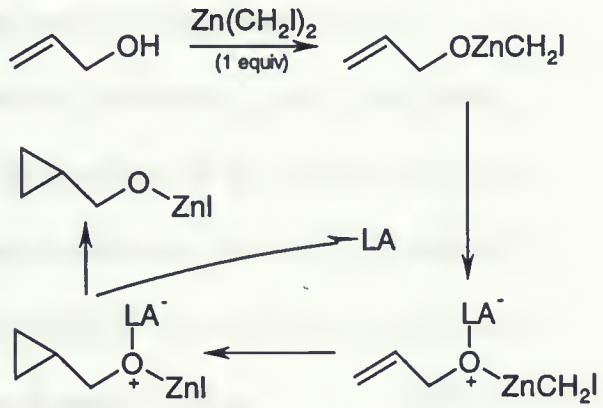
Table 4. Cyclopropanation of allylic alcohols catalyzed by chiral disulfonamide catalyst

	Allylic		Concentratio		Cyclopropane	
Entry	R^1	R^2	mmol/ml	Time/h	Yield/%	e.e.
1	Ph	H	0.04	14	Quant.	76
2	H	Ph	0.04	6	Quant.	73
3	$PhCH_2\ CH_2$	H	0.04	6	Quant.	78
4[c)]	$PhCH_2\ CH_2$	H	0.04	6	95	79
0.04	$TrOCH_2$	H	0.04	12	83	80
6	H	$TrOCH_2$	0.04	12	92	56
7	H	$BnOCH_2$	0.04	26	91	26

a) All reactions except for entry 4 were carried out with an allylic alcohol (0.5 mmol), Et_2Zn(1.0 mmol), and CH_2I_2 (1.5 mmol) in CH_2Cl_2 at -20 ^{0}C.
b) The catalyst was prepared from 1b (0.1 equiv.) and i-Bu_2AlH(0.08 equiv.).
c) Cyclopropanation was carried out in 5 mmol scale.

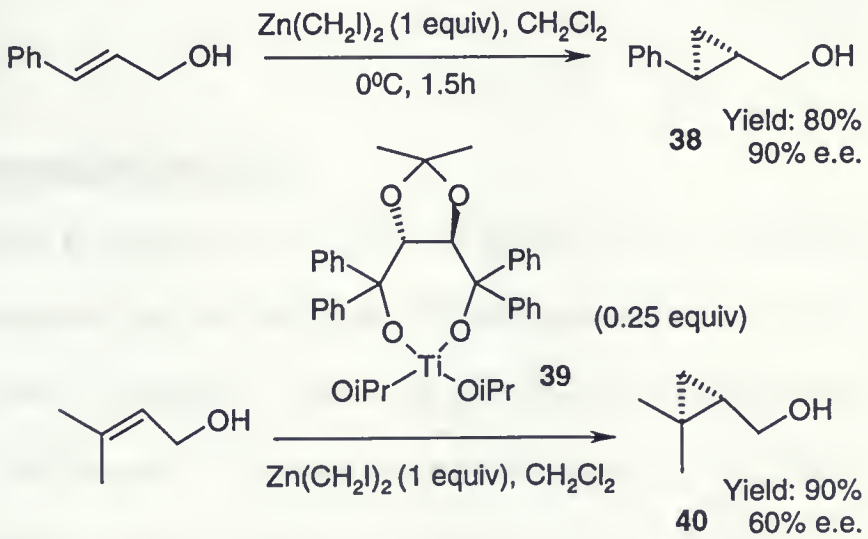
In 1995, Canadian professor A. B. Charette unveiled a new strategy for the Lewis acid-cyclopropanation of allylic alcohols[41]. The basis of the method lies in the fact that treatment of an allylic alcohol with 1 equivalent of $Zn(CH_2I)_2$ should produce the (iodomethyl)zinc alkoxide and CH_3I (Scheme 13). From observations made during his studies directed toward the development of a chiral auxiliary for the cyclopropanation reaction, he found that these alkoxides do not undergo rapid cyclopropanation at low temperature unless a Lewis acid is introduced. Subsequent formation of the halozinc alkoxide and regeneration of the Lewis acid completes the catalytic cycle.

Scheme 13. Lewis acid catalized cyclopropanation circle



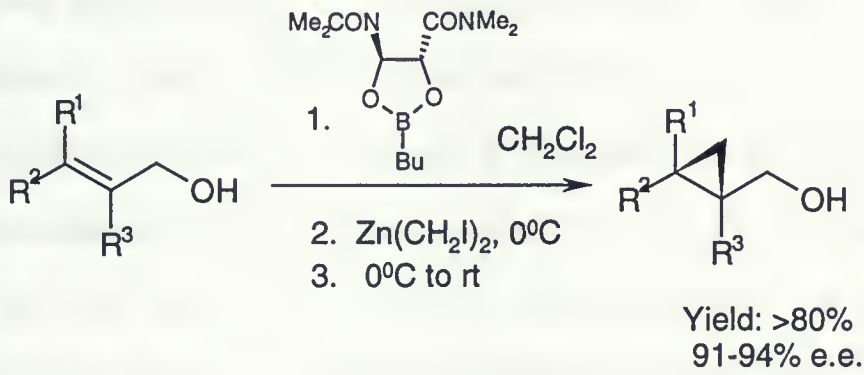
Results using a chiral titanium-TADDOL catalyst confirmed that the Lewis acid is involved in the transition state, and the enantiomeric excess of cyclopropane is found in the products. Two examples were reported and are shown in Scheme 14. Charette pointed out that this system showed some limitations as it is very capricious and highly substrate dependent[42].

Scheme 14. Enantioselective cyclopropanation using TADDOL



Charette has also explored another strategy using a 1,2-diol (derived from tartaric acid) to generate a dioxaborolane ligand[43,44,45]. The unique advantage for this type of chiral ligand is its amphoteric, bifunctional structure. The design of the dioxaborolane relied on the presence of an acidic (boron) and a basic (amide) site that allow simultaneous complexation of acidic halomethylzinc reagent and basic allylic metal alkoxide (see Scheme 15) This ligand was shown to be as efficient and much more reproducible. It could repeatedly convert allylic alcohols enantioselectively to substituted cyclopropylmethanols in both high yield and enantiometric excess.

Scheme 15. Simmons-Smith cyclopropanation using Dioxaborolane



1.6 Proposed project outline

(1) Chiral C_2-symmetric 1,4-diols are an important class of chiral ligand employed in asymmetric catalysis. Examples of ligands which have been shown to impact high degree of asymmetry bearing this functionality include the tartaric acid derived TADDOLs and 2-napthol derived BINOLs. Application was widely used from aldol reactions, Michael additions, Diels-Aldel reactions, alkylations, to various heteroatom transfer reactions including hydrogenation, epoxidation, dihydroxylation, metalesis

and aziridination. Cyclopropanation using a 1,4 diol ligand was repeated for the first time by Charette, it is worthwhile to optimize the catalytic cyclopropanation route in order to develope a reliable methodology through the investigation of a variety of factors including temperature, solvents, different 1,4-diol ligands and different reaction conditions. The more important thing is for the present research work, the development of new members of upgraded 1,4-diol series of ligands is needed due to structural limitations imposed by the synthetic routes to them and allow us to do screening with other potential ligands to deliver high enantioselectivity.

(2) C_2-symmetrical dioxaborolane diamide is a new, promising, amphoteric, bifunctional type chiral ligand. Only a few examples have been reported. The advantage of dioxaborolane is that it is air-stable, reliable, easy modified, etc. The disadvantage is its low efficiency of chirality multiplication. It is necessary to develop different series of dioxaborolane, to enrich this family which will also allow for screening to deliver high e.e., and find better methods in wider applications on asymmetric cyclopropanation such as unconjugated and conjugated polyene, allylic amines and allylic carbamates. Furthermore, we wish to apply dioxaborolane series in other types of carbon-carbon bond forming reactions .

Overall, our project goals are to design, synthesize, modify a new series of upgraded chiral ligands, and develop new methodologies for making various chiral building blocks, with a particular focus on the synthesis of chiral cyclopropanes.

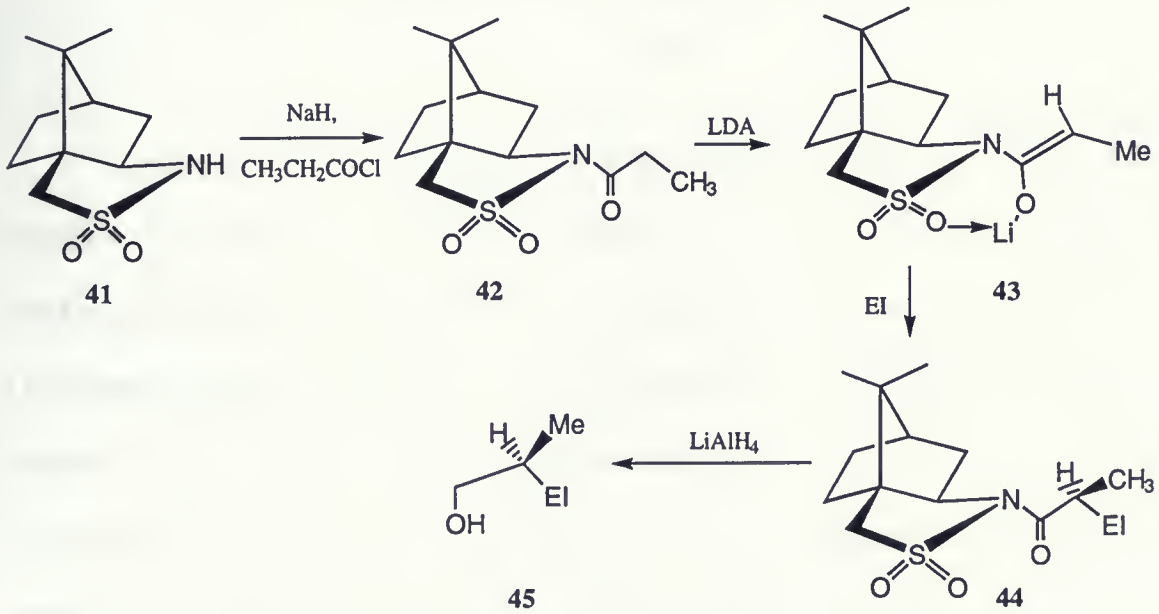
Chapter II Results and Discussion

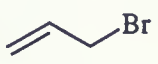
2.1 Asymmetric Cyclopropanations Catalyzed by Titanium-1,4-Diol Complexes

2.1.1 The Preparation of exo, exo'-3,3'-Bisoboroneol (BIBOL) and endo, endo'-3,3'-diphenyl BIBOL

The monoterpenoid camphor derivatives, such as camphor sultams, have been widely used as chiral auxiliaries to achieve high diastereoselectivity. Below is an example using Oppolzer's sultam (**41**) to generate the α-substituted enolate (**43**). Subsequent alkylation takes place from the lower face as the upper face is hindered by the bridged gem dimethyl groups. Reductive cleavage of the sultam results in high production of the alcohol (**44**) with stereochemistry shown[7].

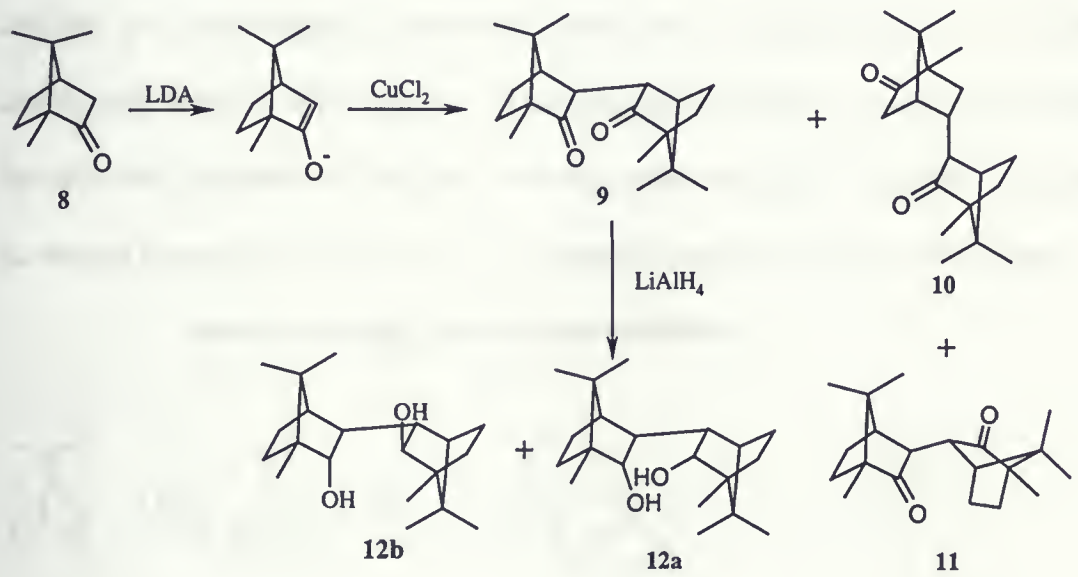
Scheme 16. Stereoselective alkylation using camphor sultam



EI: electrophile, for example 

The unique structure features of the camphor skeleton inspired McNulty and Millar to select it as the backbone for a new class of ligand which would incorporate the C_2-symmetrcal 1,4-diol functionality already known to be successful in asymmetric transformations. The synthesis of the BIBOL ligand is shown in Scheme 17.

Scheme 17. Preparation of BIBOL

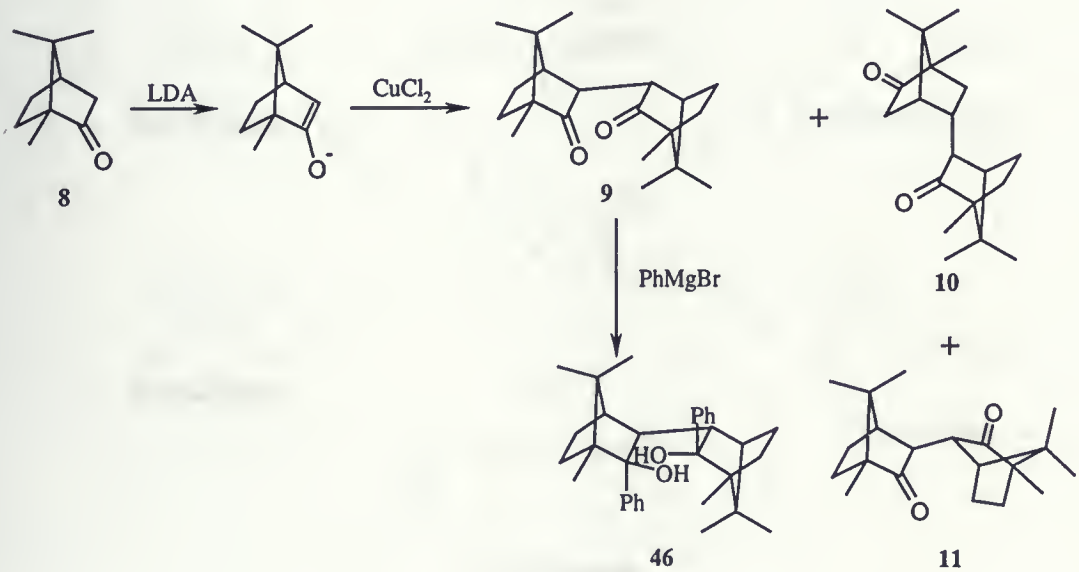


The key step in the synthesis is the kinetic-controlled coupling of the enolate of camphor. Unlike efforts by previous researchers, careful control of the reaction conditions allowed for the production of one major isomer. As shown in Scheme 17, the (1R)-camphor enolate is generatred smoothly by LDA at 0^0 C in dry toluene. Copper(II) chloride in a 5:1 mixture of TMEDA and pyridine is then introduced at -78^0 C and stirring for 24 hours ensures the completion of the coupling process. The subsequent reduction is performed *in situ*, wherein $LiAlH_4$ performs the kinetically controlled reduction of the 1,4 diketone to give the major *exo-exo* diol (**12a**) and the minor *endo-endo* diol (**12b**) in a 5:1 ratio separable by chromatography. The unambiguous

stereochemical assignment for both diols was made possible by two x-ray crystallographic analysis. New stocks of BIBOL needed for the present thesis were prepared by this synthetic route.

Slight modification of Scheme 17 allows for the production of another related 1,4-diol. Rather than reduce the 1,4-diketone generated by the oxidative coupling, addition of phenylmagnesium bromide allows for the synthesis of the aryl tertiary alcohol (**46**) depicted in Scheme 18. While nucleophilic attack of the Grignard reagent should occur predominantly from the endo face under kinetically controlled conditions, the second minor tertiary diol: the *exo-exo* coupled, *endo-exo* diol was unavoidable.

Scheme 18. Preparation of diphenyl-BIBOL



This new diphenyl BIBOL ligand (**46**) has a number of attractive features. The tertiary alcohol is more sterically demanding than the secondary alcohol functionality in BIBOL and, as such, may be better able to stereodirect the course of catalysis.

Additionally, the hydroxyl groups in diphenyl BIBOL are now in a benzylic position. The different electronic character of the O-H group may have some effect on catalysis.

It should be pointed out that while the focus of the present thesis is use of these camphor-based, 1,4 diols in asymmetric cyclopropanations, there are a number of other possible applications that should be explored. Virtually any reaction wherein TADDOL or BINOL have been employed, could be modified to use BIBOL as the ligand. A variety of transformations, such as carbon-carbon bond formations as well as heteroatom transfers, are illustrated in Figure 9.

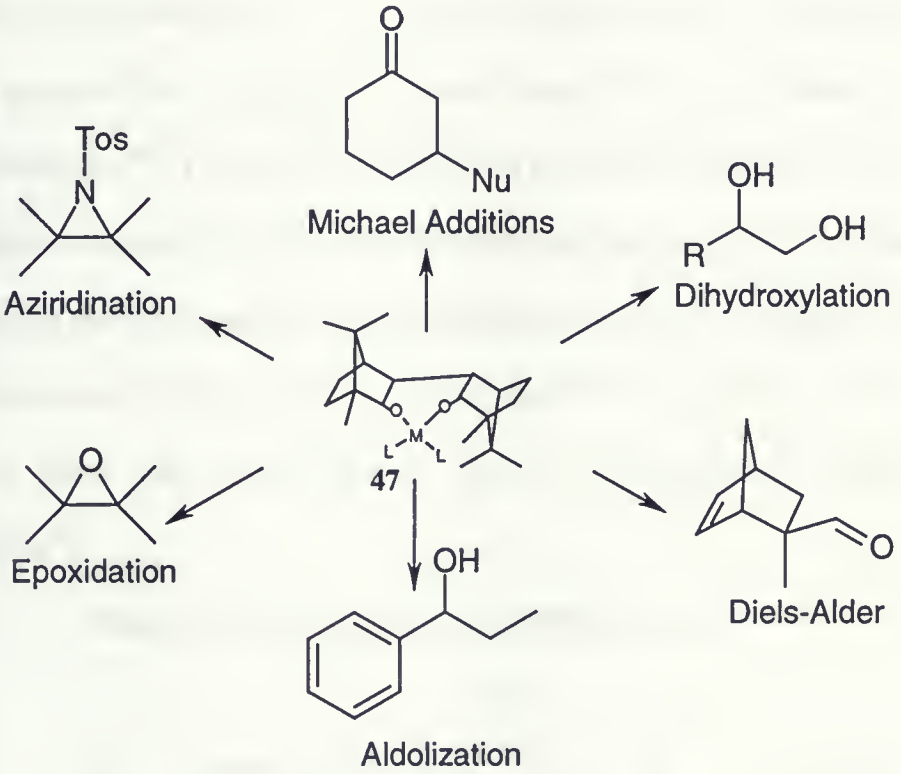


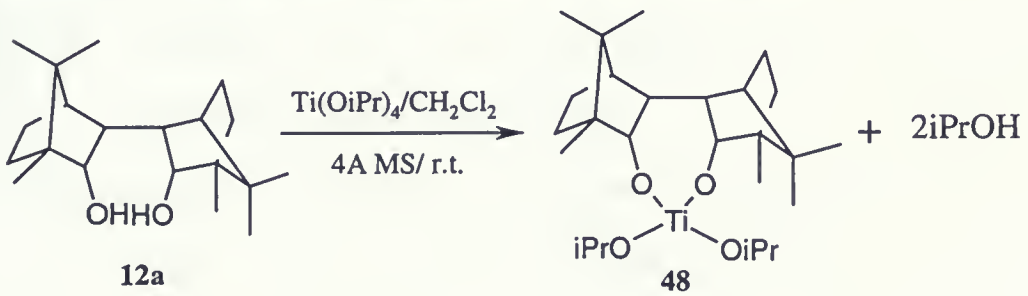
Figure 9. Exploring asymmetric processes

The asymmetric cyclopropanations represent the "tip of the iceberg" with respect to potential application of BIBOL as a ligand.

2.1.2. Preparation of Ti-BIBOL catalyst

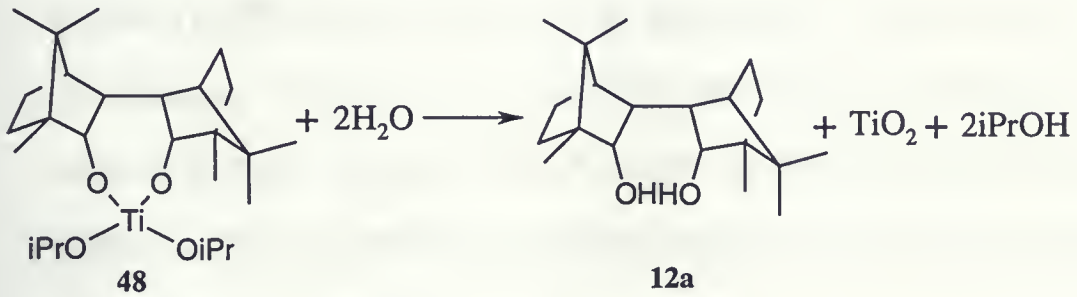
With the BIBOL and diphenyl BIBOL ligands in hand, the next synthetic challenge was the production of the catalyst from the chiral ligands and metal salt precursors. Titanium(IV)-based reagents have demonstated themselves to be excellent catalysts in large part due to the metal's high Lewis acidity, oxyphilic character, the possibility of adjusting reactivity and selectivity by ligand modification. Titanium complex synthesis is achieved by substituting two of the ligands on a commercially available titanium species (in our case, two of isopropoxides in $Ti(iOPr)_4$) with the hydroxy groups of the chiral ligand: a process often refered to as "transesterification" with a free alcohol[46]. The displacement reaction is under equilibrium and can be driven by distillative removal of the more volatile compounds (isopropanol in the present case). Care must be taken to insure that the displacemnt goes to as near completion as possible since mixtures will lead to variable catalytic results[47,48]. According to some reports, molecular sieves can be employed to affect the displacement equilibrium quite substantially[49].

Scheme 19. Preparation of Ti(IV)-BIBOL catalyst



12a **48**

In our preparation of the BIBOL-titanium catalyst, slightly more than one equivalent of chiral ligand (in the presence of 4A molecular sieves) was used followed by exposure to high vacuum to remove any residual isopropanol. It is worthwhile to mention that Ti(IV)-catalysts are very air sensitive: any moisture will result in the formation of titanium oxide. Reactions must be conducted under strictly anydrous conditions: the use of dry argon and preparation of "fresh" catalyst are critical preconditions for enantioselective synthesis.



48 **12a**

2.1.3. Catalytic enantioselective cyclopropanation using chiral Ti-BIBOL catalyst

Charette has spent some time looking at the mechanistic details of the Simmons – Smith cyclopropanation of allylic alcohols catalyzed by titanium complexes (see Scheme 14). In his studies, Charette showed that:

(a) Diethylzinc and diiodomethane combine to form the Simmons-Smith reaction $Zn(CH_2I)_2$ and ethyl iodide.

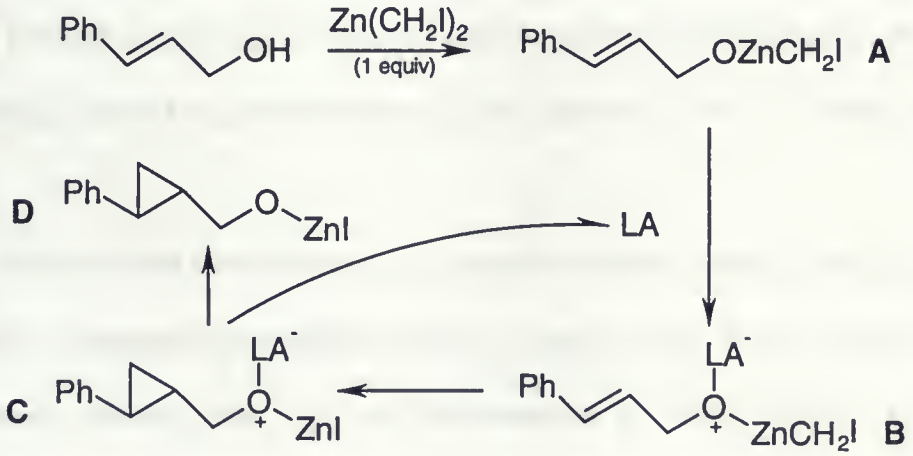
(b) Addition of the allylic alcohol produces the (iodomethyl)zinc alkoxide. This species was characterized by NMR and was shown not to undergo cyclopropanation at low temperartures.

(c) Addition of a Lewis acid triggers the cyclopropanation reaction by increasing the electrophilicity of the methylene group alpha to the zinc.

(d) Upon completion of the cyclopropanation reaction, the iodozinc alkoxide remains and the Lewis acid is regenerated to continue the catalytic cycle.

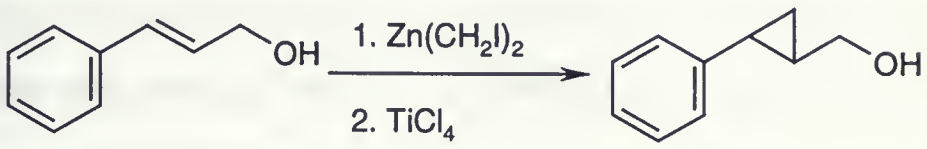
A few additional points are worth considering. Charette makes no comments as to the nature of the tranformation of the conversion from **B** to **C**. Clearly, the Lewis acid added must be intimately involved in the reaction since the use of a chiral titanium-TADDOL catalyst results in an enantiomeric excess of one of the cyclopropanes. Secondly, there is a small but appreciable background reaction at higher temperatures. Finally, according to Charette, the titanium-based catalysts give a better e.e. (the cyclopropane from cinnamyl alcohol formed in 80% yield and 90% e.e.) but the boron-based catalysts give better results.

Scheme 20. Lewis acid catalyzed cyclopropanation cycle



Before carrying out the enantioselective cyclopropanation reaction, a standard sample of the racemic cyclopropane was prepared and an analytical method for e.e.

determination was developed. The cyclopropane of cinnamyl alcohol was prepared according to the following reaction:



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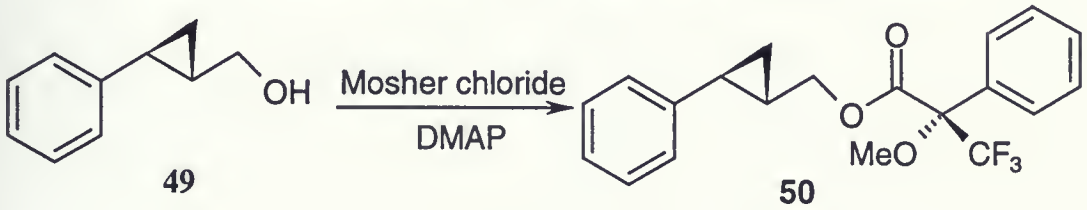
At first, HPLC was used to analyse the ratio of two enantiomers. There are many different chiral columns now available for HPLC. In this experiment, cyclodextrin β-OH and β-PM (Keyston Scientific, Inc.)[50] HPLC columns were used to separate the racemic mixture of cyclopropanes. The mobile phase used was a mixture of methanol and triethylammonium acetate (TEAA) buffer. After numerous tests, the optimum conditions was found for the best resolution: 60% methanol, 40% TEAA at a flow rate of 0.5 mL/min at wavelength of 254 nm and concentration of 2 mg/mL. Although peaks were not baseline resolved, it was the best HPLC separation obtained. Further analysis showed cinnamy alcohol had a retention time comparable to the cyclopropanes. Worries that starting material might be overlapping with products made us abondon the HPLC assay.

Attention was then turned to anaylsis of the Mosher esters of the cyclopropanes via NMR. Commercailly available Mosher chloride allows for a conversion of the enantiometric mixture into a pair of diastereomers for NMR analysis. The Mosher reagent, α-methoxy-α-trifluoromethyl-phenyl-acetic acid (MTPA), is one of the most widely used chiral derivatizing agents since it is stable to racemisation. Induced ^{1}H chemical shift non-equivalence is typically 0.15 ppm. A ^{19}F NMR study is also possible and this has the advantage that ^{19}F spectrum contains only two peaks; one for each

diasteromer. We used the Mosher reagent to derivatize our product by dissolving the cyclopropane in dichloromethane with a small amount of DMAP. The Mosher reagent was added slowly and the reaction went to completion after 2 hours at 0^0C. Workup was done with weak acid to get rid of excess DMAP and then washed with weak base to remove excess Mosher reagent.

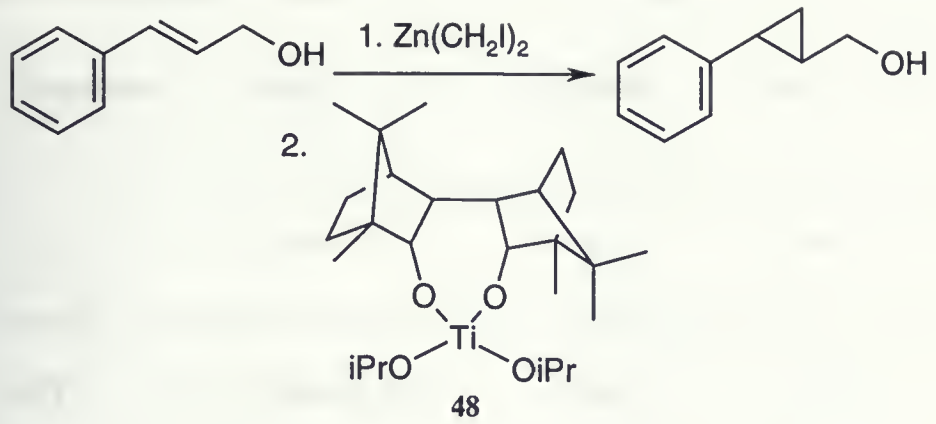
Scheme 21. Preparation of the Mosher derivative of cyclopropane



49 **50**

A ^{1}H-NMR spectrum was obtained for the racemic cyclopropane Mosher ester derivatives. But the two diastereomers were equal on the chemical shift and the e.e. could not be determined. Same result was obtained in the ^{13}C NMR. An ^{19}F NMR spectrum was obtained and this was easily used to determine the e.e. The racemic cyclopropane gave two peaks of equal intensity at -71.38 and -71.46 ppm.

With the analytical method in hand, we carried out asymmetric cyclopropanation of cinnamyl alcohol using Charette's protocol but replaced Ti-TADDOL with Ti-BIBOL.



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The e.e. value obtained was nearly 56%. At this point we questioned whether the low e.e. was a result of BIBOL's inabilty to stereodirect the reaction or experimetal technique. In an effort to answer this question, we carried out a series of reactions wherein TADDOL, BINOL and BIBOL were used as the chiral ligands and the effect of various reaction conditions (temperature, solvent, stoichiometry and catalyst loading) on the enantioselectivity of the cyclopropanation was studied. This should not only help optimize the reaction condition but should also be useful in helping us to better understand the mechanism.

In temperature screening, we used CH_2Cl_2 as the solvent and maintained a substrate / catalyst ratio of 4:1. The reaction was carried out at -78^{0}C, -20^{0}C, 0^{0}C. The results are shown below in Table 5. Note that the % conversion is reported for BIBOL only.

Table 5. The effect of temperature in cyclopropanation

Temperature	BIBOL	TADDOL	BINOL
	e.e.	e.e.	e.e.
-78^{0}C	56%(50%)*	70%	3.7%
-20^{0}C	42%(64%)*	57%	0.6%
0^{0}C	34%(80%)*	41%	1%

* Conversion

From this table, we can see that:

(1) Chiral Lewis acids are involved in the reaction transition state, even at very low temperature since an e.e. was observed.

(2) Using methylene chloride as the solvent and the catalyst loading specified, TADDOL appears better than either the BIBOL or BINOL ligands at inducing enantioselectivity.

(3) BINOL seems to be very poor ligand for this reaction. One can rationalize this if one considers the nature of the alkoxide groups. TADDOL and BIBOL contain aliphatic hydroxy groups in constrast to BINOL's phenols. The increased electron density about a phenolic oxygen makes for a greater

availabilty of electron density for the titanium thereby decreasing its Lewis acidity character and its ability as an effective catalyst.

(4) Enantioselectivity decreases as the reaction temperature increases. This, of course, is not surprising. The two diastereomeric transition states, which leads to either enantiomer, are probably only different by a few kilocalories. At lower temperature, fewer molecular collisions take place with sufficient energy to overcome the higher energy transition state. As a result, the lower energy transition state will more easily access and, thereby, leads to one enantiomer preferentially. In other words, the difference in energy between the two TS ($\Delta\Delta G$) determines the degree of selectivity and the lower energy pathway will provide the major antipode (see Introduction, Figure 5).

(5) The % conversion increases as the temperature increases. Every chemical change relies on molecular collision. At lower temeperatures, there are fewer collisions and, therefore, fewer successful reactions. Conversely, increasing the temperature increases the number of molecular collisions and therefore increase the chances of a greater number of successful transformations.

(6) The Lewis acidity of Ti(IV)-chiral 1,4 diol is greater than the precursor $Ti(OiPr)_4$ since Charette has shown that at –40°C $Ti(OiPr)_4$ only allows for a 4% conversion (*c.f.* 50% conversion with Ti-BIBOL at –78°C) This is convenient since we can use these Ti(IV)-chiral 1,4 diol catalysts at lower temperatures thereby increasing the e.e. but maintaining a reasonable turnover. Additionally, any residual $Ti(OiPr)_4$ which may have been left over

from the formation of the Ti(IV)-chiral 1,4 diol is likely not going to add appreciably to the racemic background reaction.

Examining the effect of solvent on the reaction involved carrying out the cyclopropanation at -20^{0}C with a fixed ratio of substrate and catalyst (25% catalyst loading). The solvent was then changed from CH_2Cl_2, to toluene, to THF. The results are listed below:

Table 6. The effect of solvent in enantioselectivity of cyclopropanation

Solvent	BIBOL	TADDOL	BINOL
	e.e.%	e.e.%	e.e.%
CH_2Cl_2	42(64)*	57	3.7
Toluene	38(65)*	44	2.7
THF	12(71)*	18	1

* conversion

Clearly CH_2Cl_2 is the solvent of choice (with respect to maximal e.e.) which is somewhat better than toluene but markedly better than THF. How does the solvent effect enantioselectivity? In more non-polar solvents (like methylene chloride or toluene), the ligand and metal will associate more closely in order to minimize the interactions between the polar metal complex and the non-polar solvent. The closer the ligand is to the metal, the greater the steric demand of ligands[51] and hence the greater the enantioselectivity. Conversely, a more polar solvent like THF is likely better able to

solvate the metal ligand complex generating a weaker association. The greater the distance of the ligand from the metal, the greater the distance the asymmetric environment is from the reaction center. The net result is lowering the enantioselectivity.

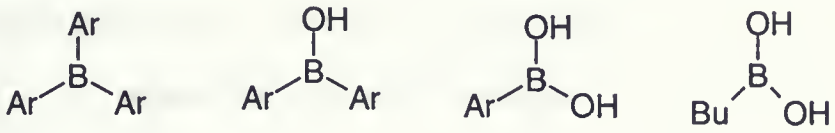
Overall, our studies aimed at optimizing the cyclopropanation enantioselectivity revealed little that we did not expect. Optimal temperature and solvent were applied to the cyclopropanantion reaction using the BIBOL-Ti catalyst with very similar results as previously acquired. The reaction was repeated several times with slightly varying results. Stability of the metal complex seems to be the critical factor. Any adventitious moisture in the reaction results in destruction of the catalytic species. Despite our best efforts we were unable to surpass an e.e. of 70%. It is worth pointing out that we were unable to get the turnover or e.e. described by Charette despite using the identical materials and conditions. Our attention was then focussed on a more reliable Lewis acid catalyst system.

2.2. Asymmetric cyclopropanation catalyzed by chiral boron catalysts

2.2.1. Preparation of Butyl Boron-BIBOL catalyst.

Boron Lewis acids have become popular tools in organic synthesis. Traditional boron Lewis acids of the general formula BX_3 (X=F, Cl, Br, OEt) are very water sensitive, and the presence of a small amount of water causes rapid decomposition or deactivation. To obviate some of theses inherent problems, following compounds

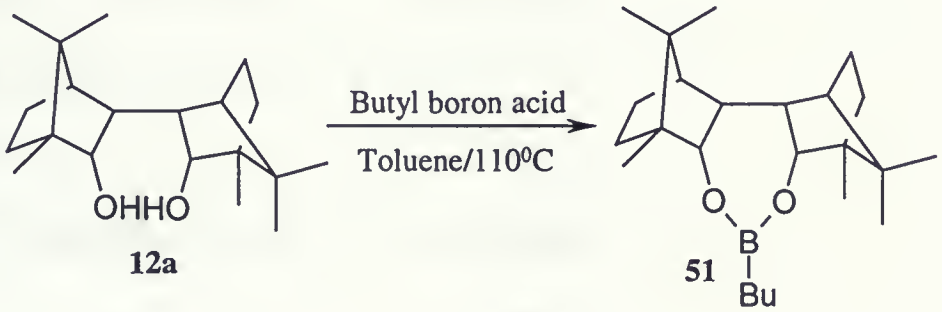
(tris(pentafluorophenyl)boron, and substituent boron acids) have become new classes of boron catalysts[51].



They are generally air stable and water-tolerant Lewis acid. Replacing the OH groups with a suitable chiral ligand has resulted in the production of several chiral catalysts used in Dies-Alder reactions, Mukaiyama aldol reactions[51], allylation reactins[51], etc.

A procedure has been developed for the synthesis of a boron-BIBOL catalyst and is shown in Scheme 22. Treatment of BIBOL with n-butyl boronic acid in toluene allows for the formation of the desired dioxaborolane catalyst.

Scheme 22. Preparation of boron-BIBOL catalyst

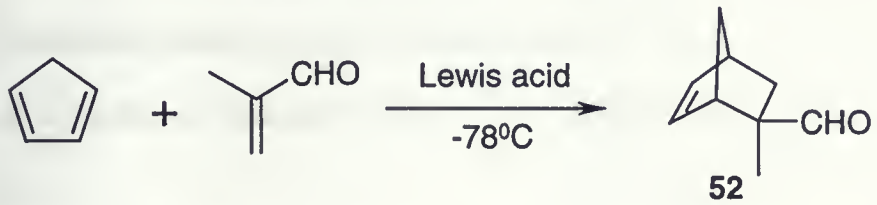


2.2.2 Application of the BIBOL ligand to other reactions.

Other catalytic enantioselective carbon-carbon bonds forming procedures were screened using BIBOL as the ligand on the Lewis acid. Reactions included the Diels-

Alder reaction (Scheme 23), Mukaiyama-type aldol reaction (Scheme 24), alkylation (Scheme 25), metathesis, etc. Unfortunately, these reactions failed to produce satisfactory preliminary results and have been postponed.

Scheme 23. Diels-Alder reaction



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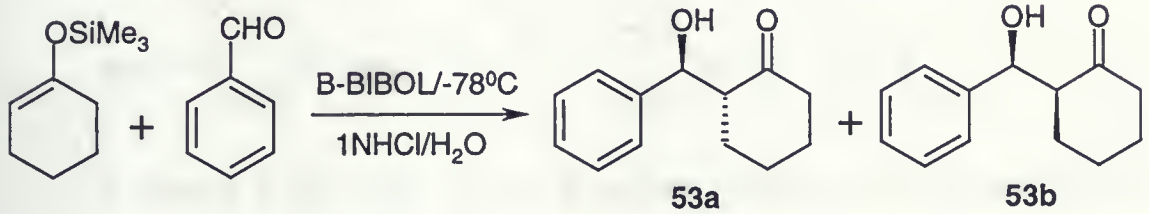
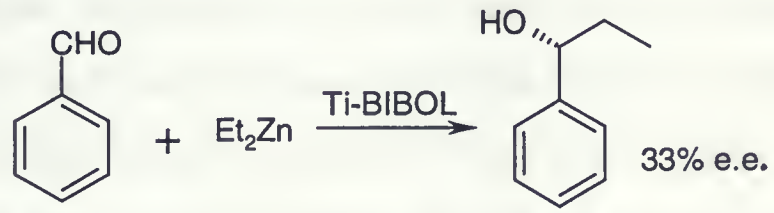
Scheme 24. Mukaiyama type aldol reaction



53a 53b

However, we obtained a good sign on asymmetric aldolization with titanium(IV)-BIBOL catalyst, the best e.e. was up to 33%.

Scheme 25. Asymmetric aldolization using Ti-BIBOL



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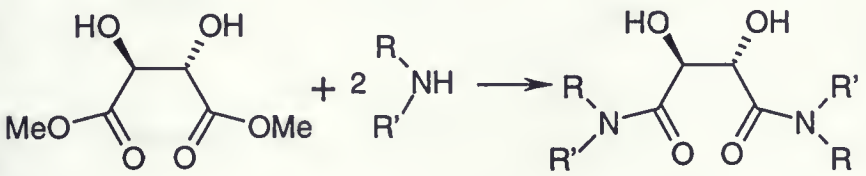
2.2.3 Design and synthesis of the tartaric acid diamide series

Charette has demonstrated the effectiveness of the chiral boron catalyst in his asymmetric cyclopropantion of allylic alcohols[45]. The chiral induction is a result of the dimethyldiamide tartrate backbone of the catalyst whose synthesis is shown in scheme 26.

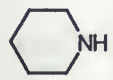
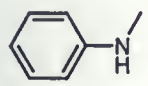
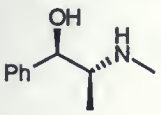
Scheme 26. Preparation of tartaric acid diamide



In looking at this chiral ligand, we became intrigued with the possibility of altering the nature of the diamide moeity in an effort of improving the effectiveness of the catalyst. Specifically, we wished to determine what effect the diamide functionality has on catalysis. As a result, we chose a series of amines (diethyl amine, pyrrolidine, piperidine, morphorine, N-methyl aniline, ephedrine) of different sizes and characteristic of R, R' group (from aliphatic to aromatic) and used them to prepare a series of tartaric acid diamide. The reactivity of the seven amines were quite different and different synthetic routes for the diamide tartrate had to be developed for their preparation.

At first, Seebach's procedure[52,53,54] was used to prepare our desired target molecules. This involved refluxing an excess of the amine and the commercially availble dimethyl tartarate ester to yield the desired amide. The results are listed in the following Table.

Table 7. The results from Scheme 26

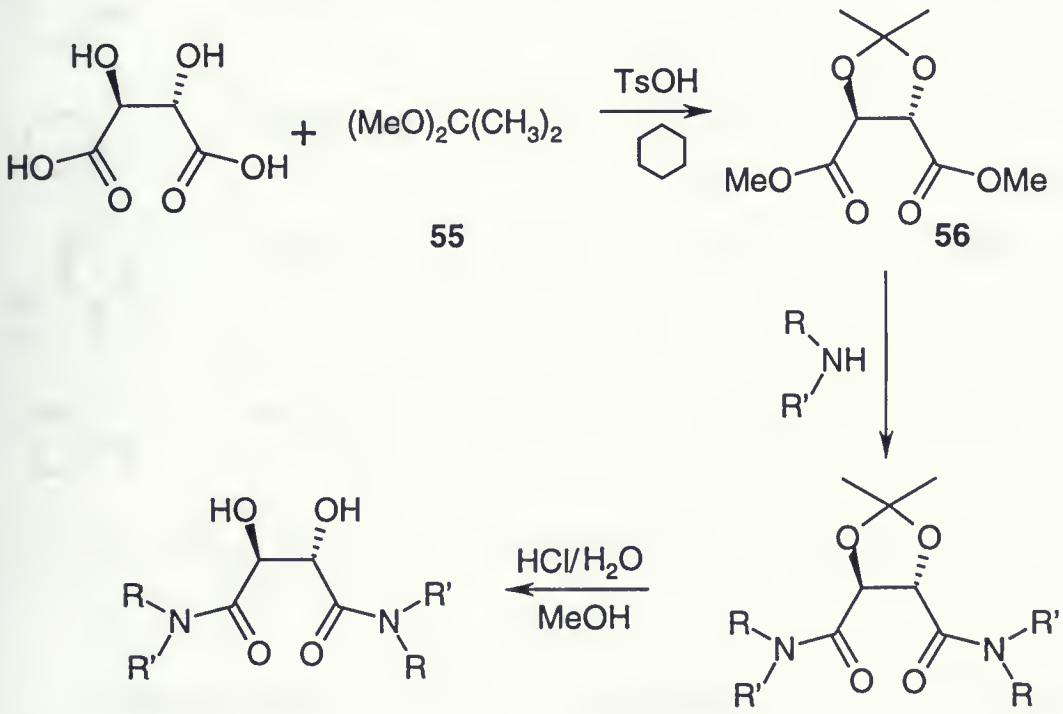
Amine	Solvent	Temperature	Reaction Time	Yield
	Methanol	rt.	3 days	93%
	Toluene	110^{0}C	24hr	no reaction
	Toluene	110^{0}C	24hr	91%
	Toluene	110^{0}C	24hr	Complex product
	Toluene	110^{0}C	24hr	48%
	No Solvent	200^{0}C	24hr	no reaction
	Toluene	110^{0}C	6hr	76%

All above reactions were carried over with the ratio of 3.5:1 for amine to tartrate.

Not surprisingly, the aliphatic amines are more reactive than the aromatic ones. In addition, as the steric bulk of the amines increases, the reaction becomes less effective. Cyclic amines tended to work better than the aliphatic ones. Why the reaction worked in some instances but failed to proceed in others? One explanation may be that the free 1,2 dihydroxy groups of the tartaric ester form hydrogen bonds with the secondary amine thereby decreasing its nucleophilic ability.

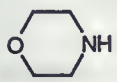
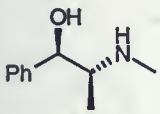
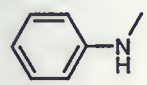
To overcome this problem, we designed an alternative route as a general procedure of preparing tartaric acid diamides (shown in Scheme 27.) This new approach starts from tartaric acid and forms the acetonide and methyl ester in one step. The use of acetonides is a commonly used protection method for 1,2- and 1,3 diols. It has been used extensively in carbohydrate chemistry to mask the hydroxy groups of many different sugars[55-59].

Scheme 27. Alternative approach for making general tartric acid diamide



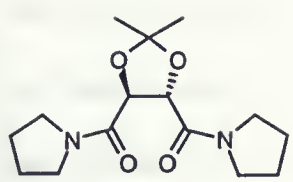
The amide formation with protected tartrate ester was carried out in the same manner as above (excess amine refluxed in the presence of the diester) and the results are shown in Table 8:

Table 8. The results from scheme 27

Amine	Solvent	Reaction temperature	Reaction time	Yield
	Toluene	111^{0}C	12hr	90%
	Toluene	111^{0}C	24hr	No reaction
	Toluene	111^{0}C	24hr	88%
	Toluene	111^{0}C	24hr	85%
	Toluene	111^{0}C	12hr	95%
	No Solvent	195^{0}C	24hr	61%

Although we still couldn't make the diethylamine react, this method significantly improved the reaction for morpholine and N-methyl aniline. For N-methyl aniline, the more important aspect lied on the fact that it is the only aromatic amine in our experiments.

The acetonides of diamides we obtained from above are listed below:



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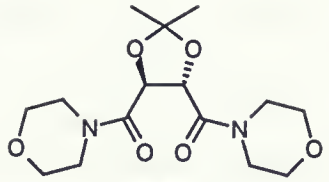

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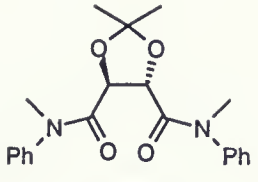

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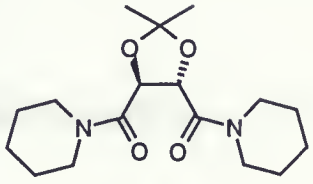

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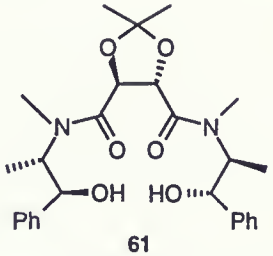

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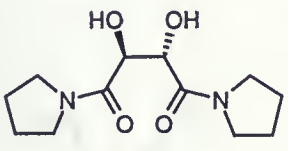
Hydrolysis of the acetonide is achieved under acidic conditions (optimized reaction conditions: the time was 6 hours and 4N HCl was used). Through the above efforts, a series of new, chiral tartaric acid diamides were developed. They are listed



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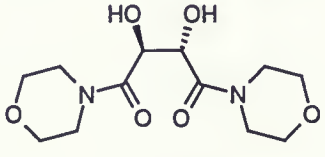

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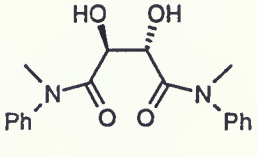

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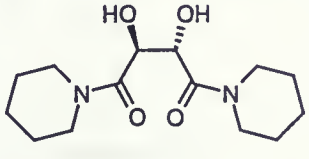

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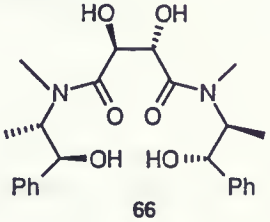

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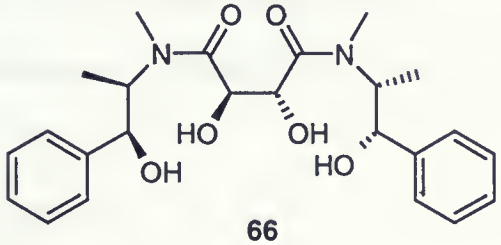
below.

In addition to the systems prepared above, we synthesized a new tetradentate ligand **66** which can potentially coordinate with a suitable metal to form an octahedral complex for general use in



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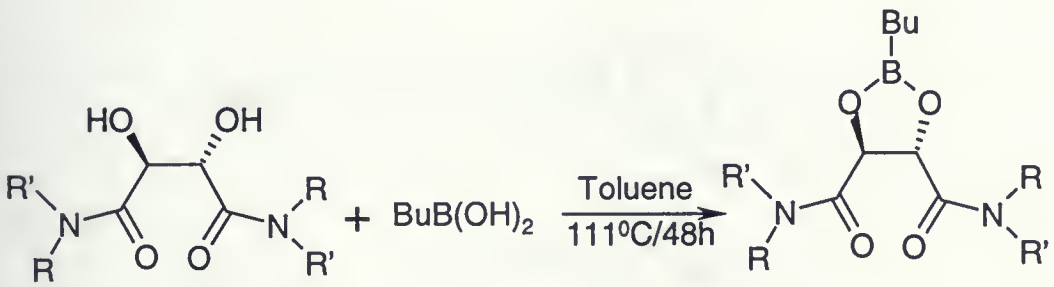
catalytic asymmetric synthesis. Based on ephedrine, the synthesis of the ligand follows the same procedure as that listed above. Octahedral complexes of tetradentate ligands are promising for use in stereoselective catalysis because two coordination sites are available for substitution reactions.

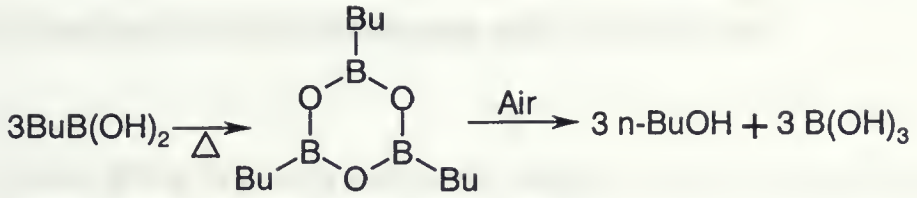
2.2.4 Chiral dioxaborolane synthesis

The chiral dioxaborolane was prepared either from butylboronic acid with chiral tartaric acid diamide under dehydration conditions (Scheme 28) or from diethanolamine derivatives (Scheme 29).

Scheme 28. The preparation of dioxaborolane from butylboronic acid

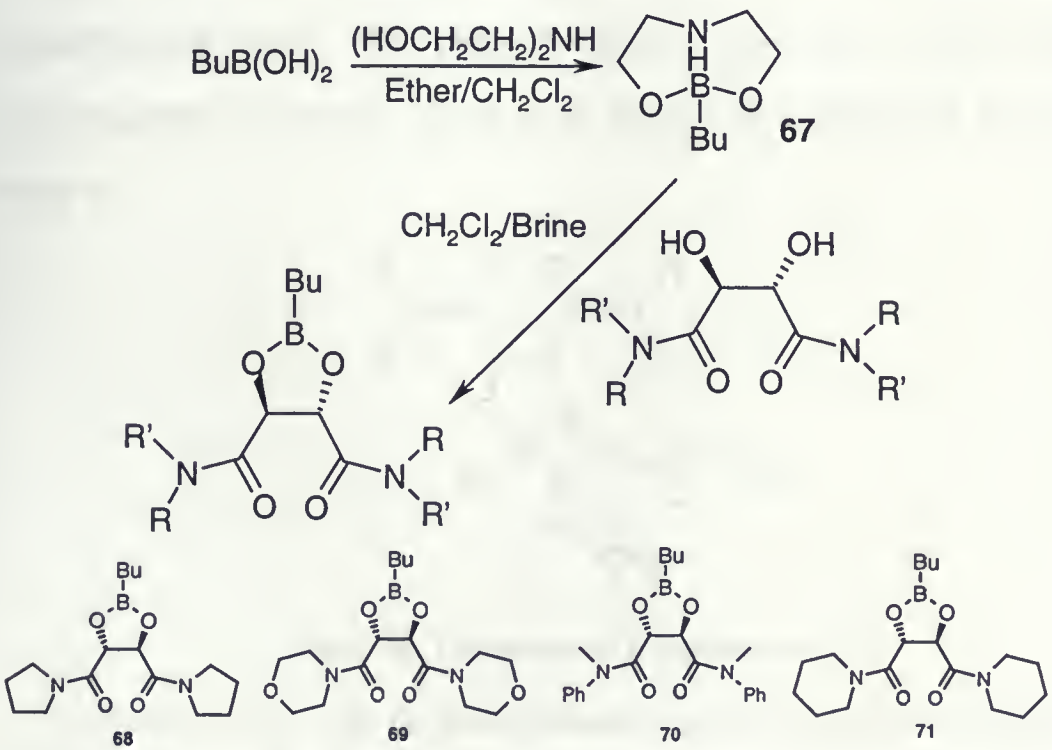


The first procedure (See Scheme 28) is relatively straightforward but does have one drawback. Care must be taken as alkylboronic acids are unstable[45]. Thus, when dehydrated, butyl boronic acid could be transformed into tributylboroxine (a colorless oil) which is readily oxidized by air to n-butanol and boric acid. Alternatively, direct oxidation of butylboronic acid could lead eventually to the same products.



The second procedure (Scheme 29) avoids these complications. It is a quick transformation of the unstable butylboronic acid into its air-stable and more robust diethanolamine derivative. This diethanolamine complex, when treated with an excess of diamide in a biphasic medium for a short period, provids the desired chiral dioxaboralane ligands in 93% isolated yield. This sequence significantly simplified the synthesis of dioxaborolane complexes that could now be prepared on a multigram scale with high purity in a relatively short time.

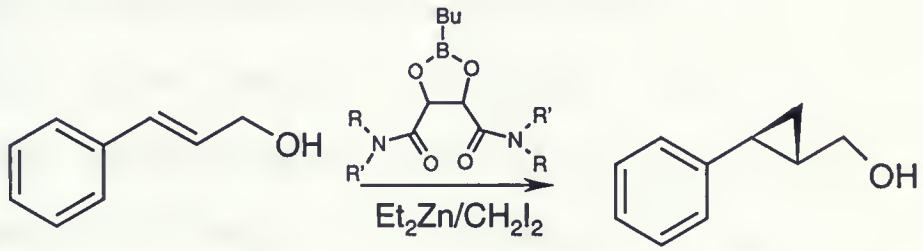
Scheme 29. The preparation of dioxaborolane with diethanolamine



2.2.5. Enantioselective cyclopropanation using Dioxaborolane

Recent efforts have been focused on applying the new prepared dioxaborolane catalysts in the enantioselective Simmons-Smith reaction.

Scheme 30. Enantioselective cyclopropanation using dioxaborolane



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Recall that the mechanism requires the addition of a Lewis acid to "trigger" the cyclopropanation event. The proposed transition state for the enantioselective cyclopropanation of cinnamyl alcohol in the presence of dioxaborolane is shown in Figure 10.

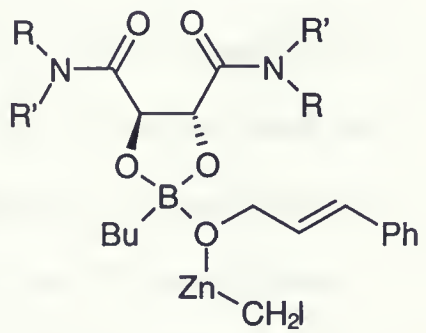


Figure 10. The proposed transition state

Charette's work with the dimethylamide dioxaborolane revealed a number of interesting insights. He assumes that the bulkier butyl substituent on dioxaborolane

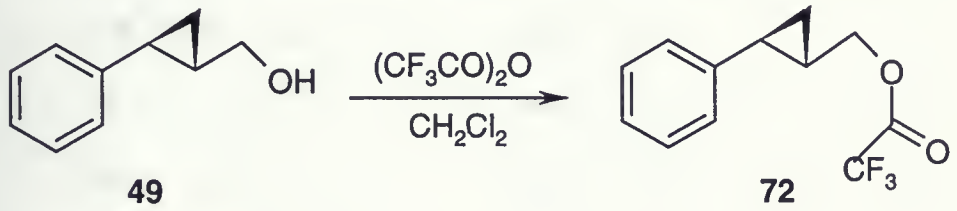
adopts the less congested pseudoaxial position, allowing the complex to act as a bidentate ligand. The zinc reagent should then be complexed simultaneously by both the highly basic carbonyl amide of the dioxaborolane ligand and the oxygen atom of the allylic alkoxide. The most suitable conformation for the methylene delivery is that in which the allylic chain is in its most stable position. This model correctly predicts the absolute configuration for the cyclopropanation of all allylic alcohols.

From the above mechanistic considerations, we believe that the presence of Lewis basic groups on the ligand is critical for obtaining high enantioselectivity. Using dimethyl-amide dioxaborolane, a 93% ee was observed. Can this be improved? Are there any steric or electronic effects involved in the transition state? The new designed amphoteric, bifunctional chiral dioxaborolane with versatile structure enabled us to investigate the influence of basic amide groups.

For enantiometric excess determination, we used gas chromatography (GC) on chiral columns for analysis instead of MTPA. Chiral GC is an attractive method for the analysis of mixtures of enantiomers. The results from this sensitive method are not affected by trace impurities in our cyclopropane derivatives, and it is quick and simple to carry out. The method uses a chiral stationary phase that contains an auxiliary resolving agent of high enantiometric purity. The enantiomers to be analyzed undergo rapid and reversible diastereometric interactions with the stationary phase and hence may be eluted at different rates. There are certain limitations of this method. The sample should be sufficiently volatile and thermally stable; the sample should also be able to be quantitatively resolved on the chiral GC phase. Occasionally, this means that enantiometric mixtures have to be derivatized prior to GC analysis. In the present case,

we determined that the trifluoroacetic acid ester derivative of the cyclopropane gave excellent separations on a Chiraldex G-TA column(gamma cyclodextrin deivatized with trifluoroacetates).

Scheme 31. Preparation of the trifluoroester derivative of cyclopropane



49 **72**

With an analytical method in hand, we carried out a series of reaction designed to examine the effects of various factors on the catalytic, asymmetric cyclopropanation reaction. First, we studied the effect of temperature on the reaction. The reaction was carried with on a 0.22 mmol cinnamyl alcohol scale, with 1 equivalent of catalyst and 2 equivalents of the Simmons-Smith reagent in CH_2Cl_2 solution. Reaction time was limited in 2 hours. The dimethylamide ligand was used as the chiral source.

The results are listed in the following Table 9. This Table shows that both yield and enantioselectivity increase when the reaction temperature rises. This might suggest that this bifunctional catalyst is quite efficient under mild conditions and at room temperatures.

Table 9. Temperature effect in cycloprpanation catalysized by chiral dioxaborolane

Temerature	Yield	e.e.
-78 ^{0}C	30%	68%
0^0 C	60%	70%
RT	98%	93%

During the optimization of the cyclopropanation reaction, we also found that the optimal conditions varied for each individual ligand. The following Table shows the results from the investigation of dipyrrolidine diamide ligand in cyclopropanation carried out with different ratio of Simmons-Smith reagent.

Table 10. Optimization of the cyclopropanation with various amount of Simmons-Smith reagent and various reaction time

IznCH$_2$I: cinnamyl alcohol	Reaction time	Yield%	e.e.
0.8:1	3 hours	70	80
	12 hours	79	78
1.5:1	3 hours	98	90
	12 hours	98.5	87
2:1	3 hours	60	70
	12 hours	70	66

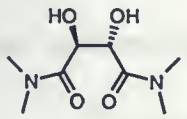
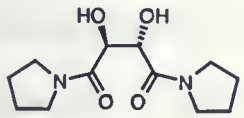
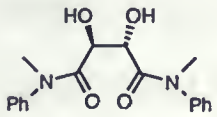
All reactions listed in Table 10 are carried in 0.22 mmol cinnamyl alcohol scale, 1 equivalent butyl boron dipyrrolidinediamide catalyst loading.

The result revealed that 1.5 equivalents of Simmons-Smith reagent in dichloromethane constituted the optimal condition for obtaining the highest conversion and e.e. (compare this to the dimethyldiamide ligand, whose best conditions involved 2 equivalents Simmons-Smith reagent in dichloromethane).

Reaction time was also examined and indicated that the longer reaction time is, the larger the background reaction will be.

Employing the optimal reaction conditions, we tested the efficiency of N-methylanaline diamide ligand. The result is listed below and compared with other diamide ligands.

Table 11. The comparison of different ligands' efficiency

Ligands	Yield %	e.e.%
	96	93
	98	90
	94	20

As we can see, the pyrrolidine-based amide ligand behaved quite similar to the dimethylamide, which suggests that there is really very little difference sterically between it and the dimethylamide catalyst. However, the aromatic substituted amide drops the enantioselectivity dramatically. The lone pair electrons on the nitrogen atom are delocalized into the conjugated aromatic ring. This result in a decreased polarity of the amide bond, therefore, the low efficient enantioselectivity in the reaction was observed.

Though there is more work that has to be done with this family of ligands, at our present stage, we successfully finished the synthesis of a series of new chiral tartaric acid diamides, which should be potential candidate ligands for enantiomeric transformations allowing for the preparation of chiral organic compounds.

2.3 Conclusion

In our research project, two series of upgraded chiral ligands have been designed and synthesized.

One type is C_2-symmetrical 1,4 diol derivatives from the monoterpene camphor, whose synthesis is based on kinetically controlled oxidative dimerization followed by kinetically controlled hydride reaction (BIBOL) or kinetic aldolization (diphenyl BIBOL). This kind of ligand has obvious structural features in common with well known chiral 1,4-diol ligand TADDOL and BINOL. The titanium(IV) catalyst and the boron type catalyst with 1,4 diol ligands have been synthesized and their application in

some catalytic enantioselective transformations have been attempted. A medium e.e. (56% and 33%) were found in cyclopropanation of cinnamyl alcohol and in aldolization of benzoaldhyde respectively. Further optimization in cyclopropanation was investigated. The results suggest that the catalytic asymmetric cyclopropanation with Ti(IV)-chiral 1,4 diol undergoes kinetic demanding control. Enantioselectivity excess highly depends on properly defined condition. Low temperature, anhydrous condition, electronphilic solvents are prerequisites to achieve high enantioselectivity.

Another type of versatile chiral ligand ---tartaric acid diamides and their butyl boron catalyst derivatives---dioxaborolanes have also been designed and synthesized successfully. Various preparation routes were described and discussed. This type of amphoteric, bifunctional chiral catalysts allow us to screen and exam the catalytic effect in different enantioselective transformations. Early independent investigation of these new chiral ligands in Simmons-Smith cyclopropanation disclosed their value. Some optimization procedures have been investigated with a couple of individual catalysts, the impressive recent advances (90%-93% e.e.) was achieved under mild condition. Continuous exploratory research on catalytic enantioselective cyclopropanation with various dioxaborolanes will eventually provide a new range of chiral molecules.

Chapter III. Experimental

3.1 General Procedures

Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. All non-aqueous reactions were conducted in flame dried or oven dried (120 ^{0}C) apparatus under an argon atmosphere. All reactions were magnetically stirred unless otherwise noted. Air-sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced under a positive pressure of argon. Reactions requiring heating were immersed in a Cat M26-controlled silicon oil bath or sea sand bath. The low-temperature baths employed were: acetone / liquid N_2 or dry ice (-78 ^{0}C); acetonitrile / liquid N_2 or dry ice (-41 ^{0}C); CCl_4 / liquid N_2 or dry ice (-20 ^{0}C); and water / ice (0 ^{0}C). All reaction temperatures refer to bath temperatures. Removal of solvents was normally accomplished using a Buchi rotary evaporator connected to an aspirator vacuum.

"Dried azeotropically with benzene" refers to the following procedure wherein benzene was added to the compound to be dried. The solvent was then removed under vacuum (<5 mmHg) and the vessel was filled with argon.

"Concentrated *in vacuo* or evaporated *in vacuo*" refers to the removal of volatile solvents *via* a Buchi rotary evaporator attached to a water aspirator (15-30 mm Hg) followed by evaporation in vacuum (<5 mm Hg) to constant weight.

3.2. Chromatography

Column chromatogrphy was performed using forced flow (flash chromatography) of the indicated solvent system on Aldrich reagent silica gel (70-230 mesh).

Analytical thin layer chromatography (TLC) was performed by using MACHEREY-NAGEL POLYGRAM SIL G/ UV_{254} pre-coated plastic plates (0.2 mm). Visualization was affected either by short-wavelength UV illumination; exposure of the TLC to iodine vapor; or treatment of the TLC with a visualization solution (either anisaldehyde in ethanol, valine in ethanol; concentrated sulfuric acid in ethanol; 2,4-DNP (2,4-dinitrophenolhydrazine) in methanol; or 0.5% ninhydrin in water) followed by heating.

3.3 Reagents and Solvents

Reagent-grade solvents were used for all extractions and work up procedures without any purification. Distilled water was used for all aqueous extractions and for obtaining all aqueous solutions. Reaction solvents and reagents were dried and purified according to published procedures by distillation under argon or vacuum from the appropriate drying agent: sodium-benzophenone (benzene, ether and tetrahydrofuran) magnesium (methanol and ethanol) or calcium hydride (methylene chloride, pyridine, toluene, triethylamine, hexamethylphosphoramide).

3.4 Physical Data

Melting points were determined in vacuum-sealed capillaries on a Kofler hot stage apparatus and were uncorrected. Optical rotations were obtained in the stated solvent at ambient temperature with a Rudolph Autopol III polarimeter.

Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were taken on a Bruker Advance DPX-300 spectrometer. Flourine nuclear magnetic resonance (^{19}F NMR) spectra were taken on a Bruker Advance DPX-200 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance of $CDCl_3$ (7.27 ppm for proton, 77.0 ppm for carbon) as the internal standard. NMR data are reported as chemical shift (multiplicity, number of protons, coupling constant in Hz). Multiplicity is designated using the following abbreviation: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), app (apparent).

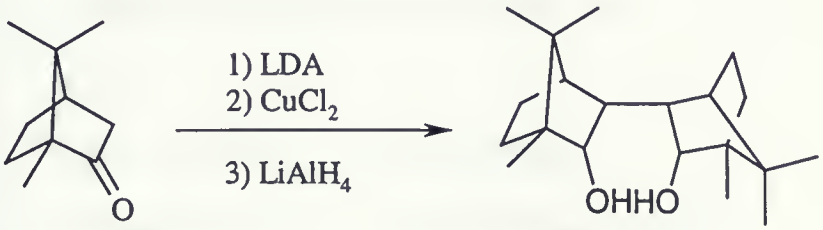
Infrared spectra were measured on a Mattson Research Series FT-IR spectrometer and are reported in wavenumbers (cm^{-1}) with polystyrene as standard.

Mass spectra were recorded on a Kratos Concept IS spectrometer operating in EI or FAB mode and are reported as m/z values for the parent peak and the major fragments.

Gas chromatography (GC) was performed on an HP 6890 gas chromatograph using Chiraldex G-PM (permethylated ß-cyclodextrin); Chiraldex G-TA (trifluoroacetylated ß-cyclodextrin) or Chiraldex B-PB (permethyl β-cylodextrin). Specifics concerning the GC operating conditions (flow rates, gases used, retention times, etc.) are reported in the appropriate section for each compound.

3.5 Synthetic Protocols

The preparation of (1R,1'R,2R,2'R,3S,3'S,4R,4"R)-3,3'-Bi(1,7,7-trimethylbicyclo [2.2.1]heptan-2-ol)



12a

To a solution of (R)-camphor (100 mg, 0.66 mmol) in dry toluene (1.0 ml) under Argon at 0^0C was added dropwise LDA (0.46 ml of 1.5M solution in hexane) with stirring for 1h. To the resulting solution, cooled to -78^{0}C, was added a solution of $CuCl_2$ (0.093 g, 0.69 mmol) in dry pyridine (5 ml) and TMEDA (1.0 ml) by cannula under argon. After the mixture was stirred at -78^{0}C for 24h, it was allowed to warm to room temperature. The mixture was transferred by syringe to a previously cooled (-78 ^{0}C) suspension of LAH (0.049 g, 1.3 mmol) in dry THF (1.5 mL) and stirred at 0^0C for 24h. Quenching excess LAH by slowly adding H_2O, diluting with CH_2Cl_2, treatment with aqueous 1N HCl, drying (Na_2SO_4), filtration, and evaporation in vacuo gave a viscous yellow oil. Chromatographic purification (silica gel, hexane/ethylacetate (97.5:2.5)) furnished title compound (50.3mg, 50%) as colorless crystals.

m.p. 176-178^{0}C

$[\alpha]_D$: +71.1 (c=0.18, MeOH)

IR(KBr): 2883 (m), 2946 (s), 3355 (s, b) cm^{-1}

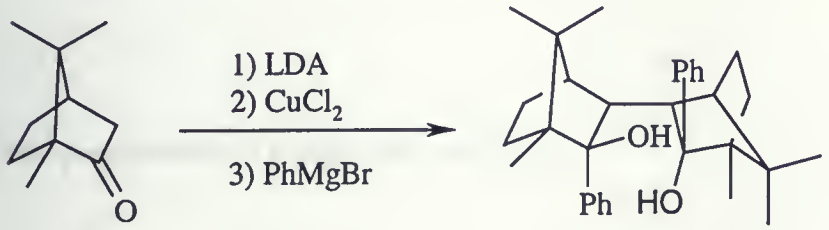
^{1}H NMR: (300 MHz, $CDCl_3$) δ 0.8 (s, 3H, CH_3), 0.9 (s, 3H, CH_3), 0.95 (m, 2H, CH_2), 1.2 (s, 3H, CH_3), 1.5 (ddd, J=10.4, 10.4, 2.4Hz, 1H, CH_2), 1.65 (s, 1H, CH0, 1.7 (m, 1H, CH_2), 2.1 (dd, J=4.8, 2.2Hz, 1H, CH), 2.45 (d, J=2.98Hz, 1H, OH), 3.75 (m, 1H, CHOH)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 83.3, 51.7, 50.1, 49.5, 47.4, 34.3, 30.2, 22.7, 22.2, 12.2

MS(EI): m/z (rel) 306 (1.6), 288 (22.7), 152 (41.9)

HRMS: calculated for $C_{20}H_{34}O_2$ 306.2558, Found: 306.2574

The preparation of diphenyl BIBOL



8 **46**

To a solution of (R)-camphor (100 mg, 0.66 mmol) in dry toluene (1.0 ml) under argon at 0^0C was added dropwise LDA (0.46 mL of a 1.5M solution in hexane) with stirring for 1h. To the resulting solution, cooled to -78^0C, was added a solution of $CuCl_2$ (0.093 g, 0.69 mmol) in dry pyridine (5 ml) and TMEDA (1.0 ml) by cannula under argon. After the mixture was stirred at -78^0C for 24h, it was allowed to warm to room temperature. Next, a pre-prepared Grignard reagent-phenyl magnisium bromide (6.57 mL, 1M solution in THF) was added to previous mixture through cannula and stirred at 0^0 C to room temperature for

24h. Quenching excess Grigrind reagent by slowly adding saturated NH_4Cl, dilution with CH_2Cl_2, treatment with aqueous 1N HCl (3x10 mL), drying (Na_2SO_4), filtration, and evaporation *in vacuo* gave a viscous yellow oil. Chromatographic purification (silica gel, hexane/AcOEt 98:2.) furnished title compound (98mg, 32.6%) as colorless liquid.

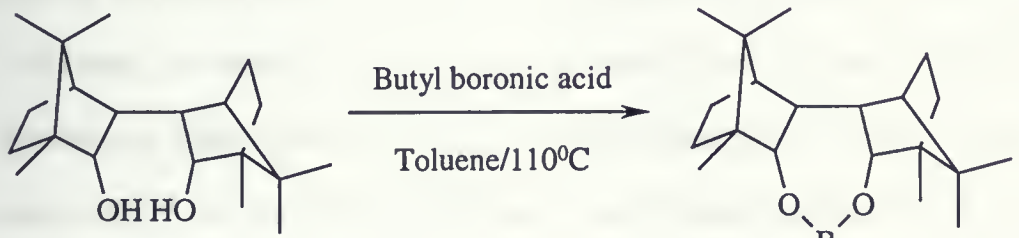
^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.37-6.93 (m, 10H), 3.14 (s, 2H), 2.09-2.08 (d, J=4.37Hz, 2H). 1.91-1.89 (m, 2H), 1.40 (s, 6H), 1.42-1.37 (m, 4H), 1.14-1.09 (m, 4H), 0.92 (s, 6H), 0.66 (s, 6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 145.7, 128.0, 127.3, 127.2, 87.1, 55.6, 54.6, 51.5, 50.5, 331.4, 30.2, 23.9, 23.4, 10.4

MS(FAB): m/z: 105 (100%), 438 (28.9%), 457 (1.6%)

HRMS: calculated for $C_{32}H_{42}O_2$ 458.3191, Found: 458.31921

The preparation of n-Butyl Boron-BIBOL



12a **51**

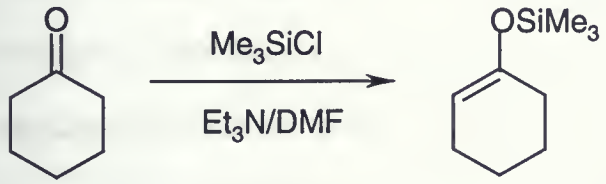
To a flask containing BIBOL (60 mg, 0.196 mmol) and toluene (3mL), was added n-butyl boronic acid (18 mg, 0.18 mmol) and pre-actived 4A molecule sieves. The resulting mixture was refluxed at 111°C for 15h. The crude product was purified by chromatography (silica gel, hexane / ethylacetate 98:2) to afford 45 mg (61.6% yield).

TLC: R_f= 0.85 (hexane)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.57-4.55 (d, J=7.599, 1H), 3.97-3.94 (d, J=7.32, 1H), 2.40-2.22 (m, 2H), 1.78-1.71 (m, 4H), 1.50-1.43 (m, 2H), 0.92-0.87 (m, 4H), 0.81-0.77(m, 5H)

MS(FAB) m/z: 55(100%), 95(67%), 271(12.2), 287(7.2%), 371(5.8%)

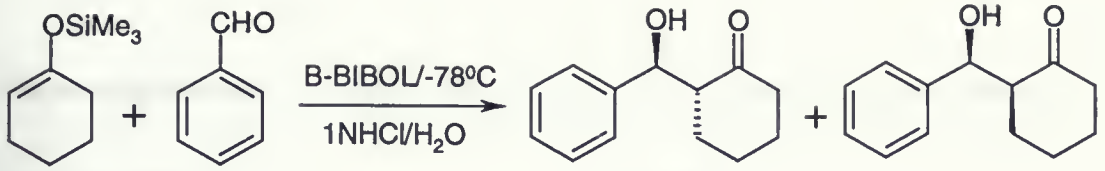
The preparation of trimethylsilly cyclohexanone enolate[60]



73

Triethyl amine (18 ml, 0.225 mmol) was added to a dried round bottom flask equipped with a stirring bar, followed by DMF (20ml), and trimethylsily chloride (8 mL, 0.612 mmol). The mixture was stirred until a yellow precipitate appeared. After adding cyclohexanone (5.3 mL, 0.05 mmol), the reaction was allowed to reflux for 4 hours and then cooled down to room temperature, diluted with hexane (150 ml) and washed with saturated sodium bicarbonate solution (3 x 100 ml). The organic layer was collected and dried with sodium sulfate, concentrated on a rotavap. The title compound was collected through fraction distillation under high vacumm (28^0C-29^0C / 6mmHg) to yield 7.06g (82%yield)

General procedure of catalytic asymmetric Mukaiyama type aldol reaction for (2S)-2-[(S)-hydroxy(phenyl)methyl]cyclohexanone



71a **71b**

Activated molecular sieves (4A, *ca.*20 mg) in a small round bottom flask were flame-dried under high vacuum. Boron-BIBOL catalyst (5.5 mg, 0.012 mmol) was added under dried argon. Trimethylsilyl cyclohexanone enol ether (85 uL, 0.5 mmol) and CH_2Cl_2 (1mL) was added and the mixture was cooled to -78^{0}C. Benzaldehyde (54 uL, 0.5 mmol) was added to the cold mixture dropwise and stirred at -78^{0}C for 4h. The reaction was warmed to room temperature and quenched with saturated amnion chloride solution (2mL). The biphasic mixture was stirred at rt. for 1h. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vauo* to afford the crude aldol adducts. The residue was purified by column chromatography on silica gel with hexane and ethylacetate (9:1)

m.p.: 104-105^{0}C

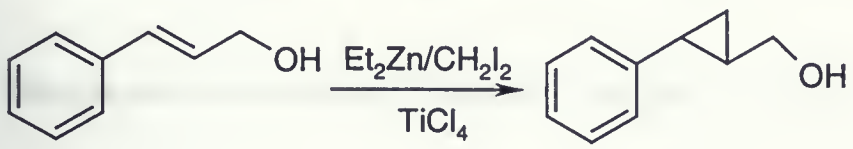
TLC: R_f=0.31 (hexane / ethylacatate, 3/1)

^{1}H NMR: (300 MHz, $CDCl_3$) 7.36-7.22 (m, 5H), 5.39 (m, 1H), 3.05 (d, J=2.0Hz, 1H, OH), 2.62-2.57 (m, 1H), 2.48-2.43 (m, 1H), 1.76-1.60 (m, 3H), 1.56-1.44 (m, 1H)

^{13}C NMR: (75 MHz, $CDCl_3$) 128.1, 126.9, 125.7, 70.5, 57.1, 2.6, 27.9, 25.9, 24.8

MS(FAB): 205 (M+1, 4), 204 (M, 25), 186 (M-H_2O, 52), 185 (17), 157, 107 (34), 106 (30), 1105 (40), 98 (100), 97 (22), 91 (10), 83 (26), 79 (3), 78 (11), 77 (58), 70 (54), 55 (32), 51 (22)

General procedure for making the racemic trans-(3-Phenylcyclopropyl0methanol



49

To a solution of CH_2I_2 (160 uL, 2 mmol) in CH_2Cl_2 (8 mL) at 0^0C was added dropwise Et_2Zn (100 uL, 1 mmol). The resulting solution was stirred at 0^0C for 15 min and a white precipitate was formed. The solution was cooled to -78^0C and a solution of cinnamyl alcohol (140 mg, 1.05 eq.) in 5 mL of CH_2Cl_2 was added. The resulting homogeneous solution was stirred at -20^0C for 15min and $TiCl_4$ (16 uL, 0.15 mmol) was then added. After 3h of stirring at -20^0c, the resulting solution was cooled to -40^0C and poured into a saturated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$ and concentrated under a reduced pressure. The crude residue was purified by flash chromatography (20% ethylacetate / hexanes) to afford 133 mg (90% yield) of the desired alcohol.

TLC: R_f=0.23 (20% ethylacetate / hexanes)

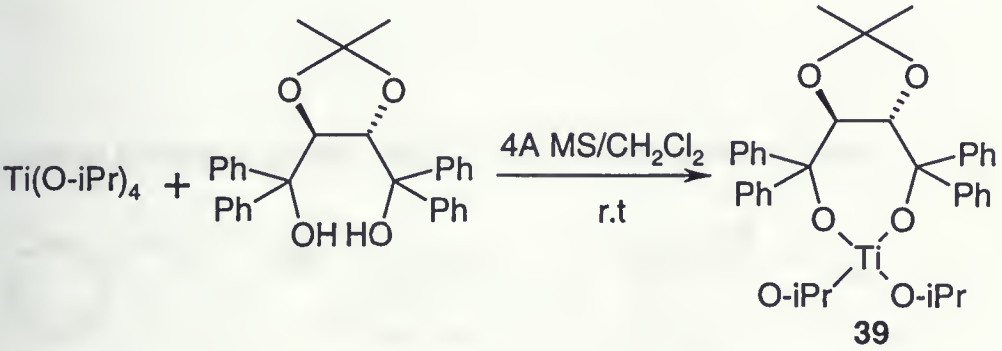
$[\alpha]_D$: +70 (c 1.9, EtOH)

^1H NMR: (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.20-7.15 (m, 2H), 7.10-7.07 (m, 2H), 3.67-3.59 (m, 2H), 1.86-1.82 (m, 1H), 1.75 (s, (br), 1H), 1.51-1.43 (m, 1H), 1.01-0.92 (m, 2H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 142.5, 128.3, 125.8, 125.6, 66.3, 25.2, 21.2, 13.8,

HRMS: calculated for $C_{10}H_{12}O$ 148.0888, Found: 148.0880

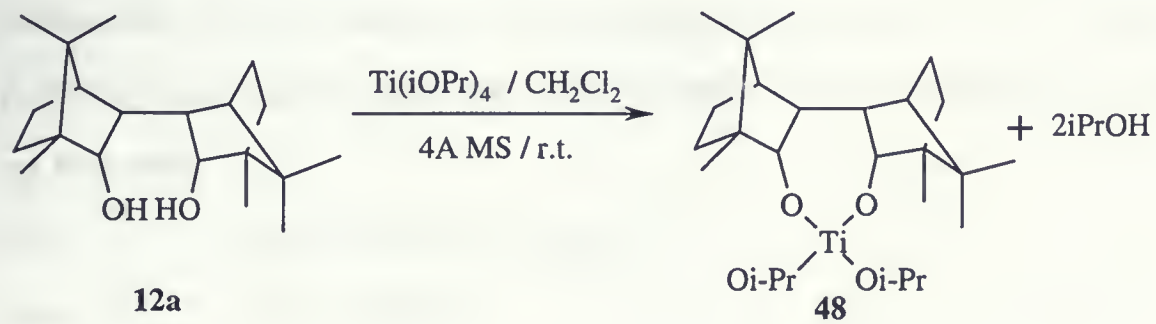
General procedure for the synthesis of the Ti(Oi-Pr)$_2$(TADDOL) catalyst



39

To a mixture of (4R, 5R)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-,5-dimethanol (TADDOL) (140 mg, 0.29 mmol) and 4A molecular sieves (1g) in CH_2Cl_2 (5 mL) was added $Ti(Oi\text{-}Pr)_4$ (74 uL, 0.25 mmol). After 1.5h of stirring at room temperature, the solvent was removed under reduced pressure and residue was left under high vacuum for 2h.

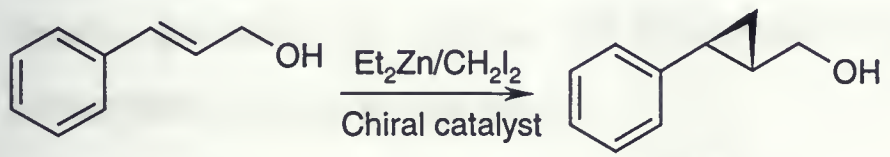
The preparation of the Ti(Oi-Pr)$_2$-BIBOL catalyst



12a **48**

To a mixture of (1R,1'R,2R,2'R,3S,3'S,4R,4'R)-3,3'-Bi(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol) (BIBOL) (20 mg, 0.065 mmol) and 4A molecular. sieves (100 mg) in CH_2Cl_2 (1mL) was added $Ti(Oi\text{-}Pr)_4$ (17.71 uL, 0.06 mmol). After 1.5h of stirring at room temperature, the solvent was removed under reduced pressure and residue was left under high vacuum for 2h.

General procedure for the catalytical asymmetric cyclopropanation



49

To a solution of CH_2I_2 (160 uL, 2 mmol) in CH_2Cl_2 (5mL) was added dropwise Et_2Zn (100 uL, 1 mmol). The resulting solution was stirred at 0^0C for 15min and a white precipitate was formed. The solution was cooled to -40^0C and a solution of the catalyst in CH_2Cl_2 (5 mL) was added immediately followed by a solution of cinnamyl alcohol. After 90min of stirring at 0^oC, the resulting solution was cooled to -40^0C and poured into 30 mL of a saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was washed with EtOAc (3 x 5mL). The combined organic layers were washed with saturated aqueous NH_4Cl, saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc / hexanes) to afford the desired product (120 mg, 80% yield).

TLC: R_f=0.23 (20% EtOAc/hexanes)

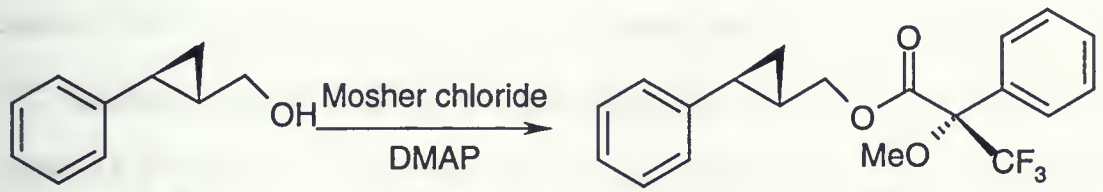
$[\alpha]_D$: +70 (c 1.9, EtOH)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.20-7.15 (m, 2H), 7.10-7.07 (m, 2H), 3.67-3.59 (m, 2H), 1.86-1.82 (m,1H), 1.75 (s, (br0, 1H), 1.51-1.43 (m, 1H), 1.01-0.92 (m, 2H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 142.5, 128.3, 125.8, 125.6, 66.3, 25.2, 21.2, 13.8,

HRMS: calculated for $C_{10}H_{12}O$ 148.0888, Found: 148.0880

General procedure for making [(1S,2R)-2-phenylcyclopropyl]methyl(2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



49 **50**

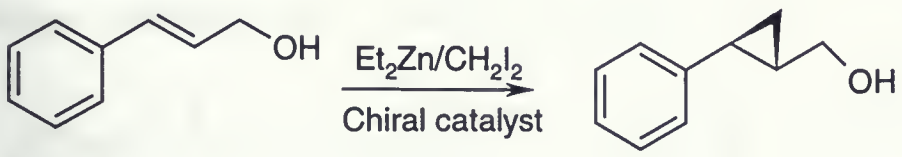
To a mixture of 3-phenylcyclopropyl-methanol (5 mg, 0.03 mmol) and 4-dimethylamnio pyridine (8 mg, 0.065 mmol) and a stirring bar was sealed in a 5 mL *via* with CH_2Cl_2. After cooling down to 0^0C, 8 ul (S)-(+)-α-methoxy, α-trifluoromethyl phenyl acetyl chloride was added and stirred for 3h. The reaction was quenched by 1N HCl (3ml), extracted by saturated sodium bicarbonate solution (2 x 5mL), dried with sodium sulfate, purified by flash chromatography (5% ethyl acetate / hexane) to afford title compound.

TLC: R_f=0.75 (Hexane)

^{1}H NMR: (300 MHz, $CDCl_3$) 7.49-6.92 (m, 10H), 4.58-4.20 (m, 2H), 3.56 (s, 3H), 2.00-1.95 (m, 1H), 1.59-1.56 (m, br, 2H), 1.08-1.06 (m, 2H)

^{19}F NMR: (200 MHz, $CDCl_3$) 71.38, 71.46 (CF_3)

General procedure for making (+)-(1S,2S)-2-Phenylcyclopropylmethanol by using chiral dioxaborolane



49

To a stirred solution of diethylzinc (50 uL, 0.49 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0^0C was added diiodomethane (80 uL, 0.98 mmol). The mixture was stirred at 0^0C for 10min (white precipitate was formed), and a pre-formed solution of dioxaborolane (0.25 mmol) and cinnamyl alcohol (30 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was rapidly added *via* cannula. The resulting mixture was stirred at room temperature for 2h and then cooled to 0^0C. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was washed with ethyl acetate (3 x20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatoography on silica gel (20% EtOAc/hexanes) to produce the desired cyclopropylmethanol (32.5 mg, 95%).

TLC: R_f 0.23 (20% EtOAc / hexanes)

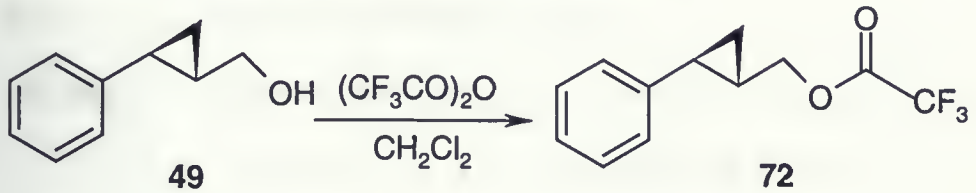
$[\alpha]_D$: +70 (c 1.9, EtOH)

^1H NMR: (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.20-7.15 (m, 2H), 7.10-7.07 (m, 2H), 3.67-3.59 (m, 2H), 1.86-1.82 (m, 1H), 1.75 (s, (br), 1H), 1.51-1.43 (m, 1H), 1.01-0.92 (m, 2H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 142.5, 128.3, 125.8, 125.6, 66.3, 25.2, 21.2, 13.8,

HRMS: calculated for $C_{10}H_{12}O$ 148.0888, Found: 148.0880

General procedure for making the [(1S,2R)-2-phenylcyclopropyl]methyl trifluoromethylpropanoate for chiral GC analysis.



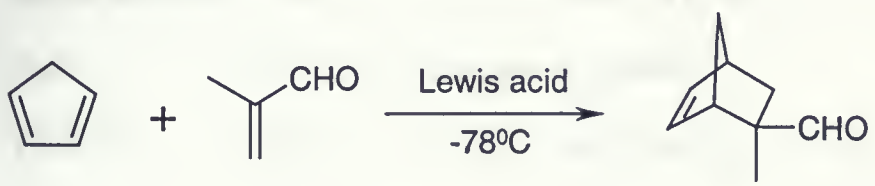
49 72

To a solution of the crude allylic alcohol (10 mg) in CH_2Cl_2 was added trifluoroactic anhydride (0.25 mL). After 30min of stirring at room temperature, another additional portion of trifluoroacetic anhydride (0.25 mL) was added. After 30min, the reaction mixture was diluted with CH_2Cl_2, and the resulting homogeneous solution was quenched with saturated $NaHCO_3$, separated and dried over Na_2SO_4 for GC analysis.

TLC: R_f= 0.8 (hexane)

^{1}H NMR: ($CDCl_3$, 300MHz) δ 7.29-7.08 (m, 5H), 4.37-4.32 (d, J=15.3, 2H), 2.00-2.00 (m, 1H), 1.50 (br, 1H+H_2O), 1.17-1.05 (dd, 2H)

General procedure for making 2-methylbicyclo[2.21]hept-5-ene-2-carbaldehyde by using Lewis acid or Chiral Boron-BIBOL catalyst



52

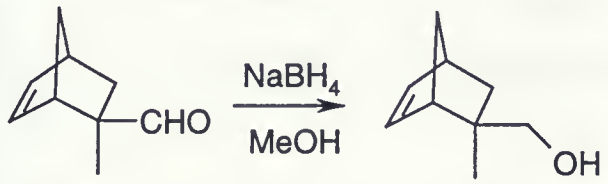
To a dried flask which contained Boron-BIBOL (5 mg, 0.0134 mmol) was dried under high vacuum for 1h., dried CH_2Cl_2 (1 mL) was added and the solution was cooled to -78^{0}C. Fresh distilled cyclopentadiene (26 mg, 0.40 mmol) was added and followed by 2-methylacrolein

(11 uL, 0.134 mmol). The resulting solution was stirred for 1h. The reaction was quenched with water(5 mL), extracted with CH_2Cl_2 (2 x 5mL), dried over Na_2SO_4 , concentrated to afford colorless crystals (15 mg, 83%yield).

TLC: R_f =0.55 (10% EtOAc/hexane)

^{1}H NMR: ($CDCl_3$, 300 MHz), δ 9.77 (s, 1H), 6.34-6.29 (q, 1H), 6.13-6.11 (q, 1H), 2.95 (s, 1H), 2.91 (s, 1H), 2.29-2.24 (dd, 1H), 1.40-1.41 (d, J=1.407Hz, 2H), 1.03 (s, 3H), 0.79-0.76 (d, 1H)

The preparation of (2-methylbicyclo[2.21]hept-5-en-2-yl)methanol



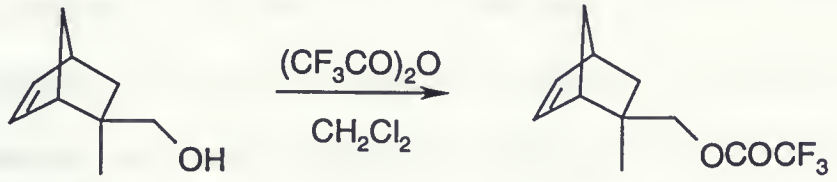
52 **73**

Aldehyde **69** (15 mg, 0.108 mmol) was dissolved in MeOH (2 mL) at 0^0C, three portion excess amount sodium boronhydride (200 mg) was added in. The reaction was stirred at 0^0C for 30min and then worked up with 6M HCl and CH_2Cl_2. The organic layer was dried over sodium sulfate and concentrated to give white oil. (15 mg, 98% yield)

TLC: R_f =0.33 (30% ethyl acetate/hexane)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.18-6.16 (m, 1H), 6.14-6.11 (m, 1H), 3.64 (s, 1H), 2.80 (s, 1H), 2.58 (s, 1H), 1.64-1.37 (m, 2H), 0.95 (s, 3H), 0.85-0.78 (m, 1H)

The preparation of (2-methylbicyclo[2.21]hept-5-en-2-yl)methy trifluoroacetate



73 **74**

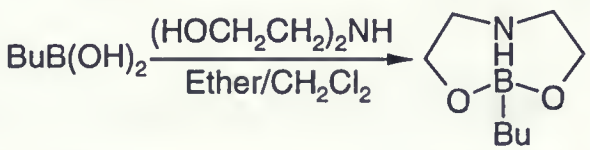
To the alcohol **82** (15 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL), excess amount trifluoroacetatic anhydride (50 uL) was added. The mixture was stirred at 0^0C for 30min and worked up with saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was dried over sodium sulfate and the resulting solution is ready for GC analysis.

TLC: R_f=0.8 (10% ethyl acetate/hexane)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.22-6.11 (m, 2H), 4.38 (s, 2H), 2.86 (s, 1H), 2.62 (s, 1H), 2.86 (s, 1H), 2.2.62 (s, 1H), 1.57-11.54 (m, 2H), 0.97 (s, 3H), 0.94-0.89 (m, 1H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 137.2, 135.8, 72.7, 48.2, 47.9, 43.5, 37.7, 23.2

The preparation of [(2-)-N,O,O'[2,2'-Iminobis[ethanolato]]]-2-butyl boron



67

A mixture of butylboronic acid (0.5 g, 5 mmol) and diethanolamine (0.55 g, 5 mmol) were dissolved in dry ether (10 mL) and dry dichloromethane (5 mL). 3A Molecular sieves (1 g) was added. The resulting heterogeneous solution was stirred for 2h under argon. The solid

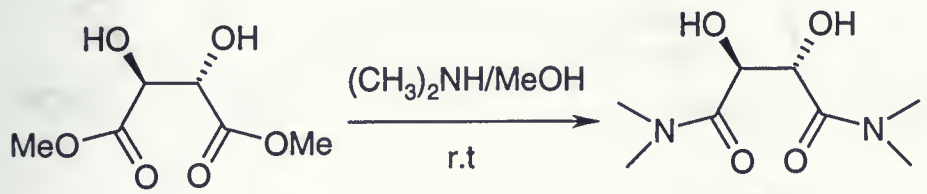
was then triturated with dichloromethane and filtered. The filtrate was concentrated under reduced pressure to yield the crude diethanolamine complex which was purified by recrystallization. The white solid was dissolved in hot dichloromethane (2 mL) followed by ether (5 ml) to induce recrystallization of the complex. The mixture was then cooled to 0^0C and the solid collected on a Buchner funnel and washed with ether (2 x 3 mL). The product was dried under vacuum (0.2 mmHg) to afford the title compound (0.77 g, 90%) as a white crystalline solid.

m.p.: 145-148^{0}C.

^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.98-4.80(m, 1H, NH), 3.98 (s (br), 2H), 3.88 (s (br),2H, 3.26 (s (br),2H), 2.79 (s (br), 2H), 1.37-1.21 (m, 4H), 0.88 (t, 3H, J=7Hz), 0.48-0.44 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 62.5, 51.4, 28.1, 26.5, 18.4(br),14.1.

The preparation of (R,R)-(+)-N,N,N',N',-Tetramethyltartaric acid diamide[53]



75

To a mixture of (L)-dimethyl tartrate (6.18 g, 30 mmol) in freshly distilled methanol (6 mL) was added liquid, anhydrous, cold (-78 ^{0}C) dimethylamine (approximately 4.5 mL, 70 mmol). The mixture was swirled briefly, and then allowed to stand in a hood for 3 days with a drying tube in place. After seeding and cooling in a refrigerator overnight, the massive crystals were collected by suction filtration. The filtrate was concentrated, seeded, and cooled

to yield a second crop. The combined crystals were washed with cold methanol (-30 ^{0}C) and dried under reduced pressure at 70-100 ^{0}C (oil bath). The diamide thus obtained was sufficiently pure to be used in the synthesis. The yield was 5.7 g (93%). Recrystallization from methanol / ethylacetate furnished an analytically pure sample.

m.p.: 189-190^{0}C

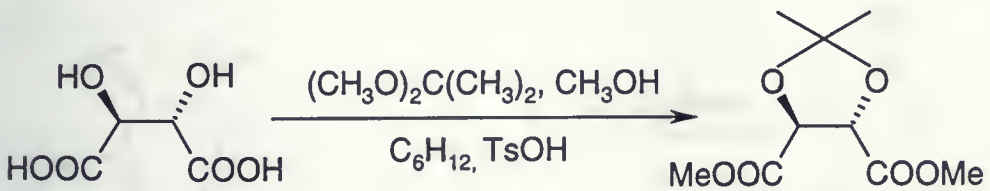
$[\alpha]_D$: +43^0 (95% ethanol, c 3.0)

TLC: R_f=0.50 (10% methanol / ethylacetate)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.65 (s, 2H), 4.21 (s (br), 2H), 3.13 (s, 6H), 3.01 (s, 6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 170.8, 69.8, 36.9, 36.1.

The preparation of (R,R)-(+) dimethyl 2,3-O-isopropylidene-L-tartrate[64]



56

A mixture of L-tartaric acid (110 g, 67 mmol), 2,2-dimethoxypropane (19 ml, 0.15 mol), anhydrous methanol (4 ml), and p-toluenesulfonic acid monohydrate (400 mg, 2.1 mmol) was stirred and heated under reflux for two hours until a dark red homogeneous solution was obtained. Additional 2,2-dimethoxypropane (10 ml, 77 mmol) and cyclohexane were then added to the above solution and the flask was fitted with a vigreux column. The mixture was heated again under reflux and the acetone-cyclohexane and methanol-cyclohexane azeotropes were slowly removed by distillation. After addition of another portion of 2,2-

dimethoxypropane (3 ml, 25 mmol) followed by heating and reflux for an additional 15 min, the mixture was cooled to room temperature and anhydrous potassium carbonate (0.1 g, 0.72 mmol) was added. The mixture was stirred until the reddish color was abated to give a yellow solution. Volatile material was removed *in vacuo* and the residue was fractionally distilled under vacuum (b.p. 94-101 ^{0}C / 0.5 mmHg) to afford ketal ester (11 g, 80%) as a pale yellow oil.

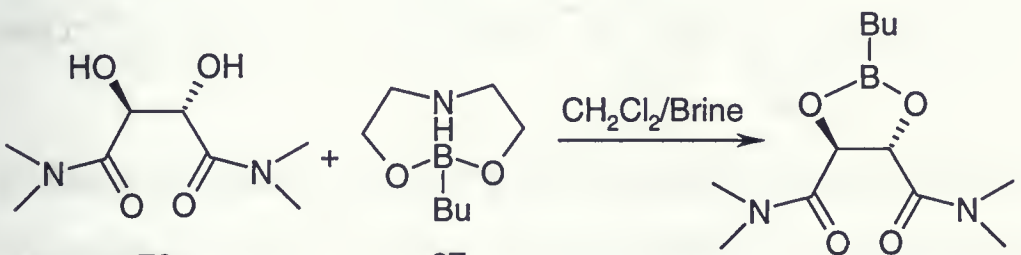
$[\alpha]_D$: -48.4 (neat)

TLC: R_f=0.43 (hexane:ethylacetate=2:1)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.79 (s, 2H), 3.81 (s, 6H),1.47 (s,6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 170.4, 114.2, 77.3, 53.2, 26.7

The preparation of (R,R)-(-)-2-Butyl-N,N,N',N',- tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide



76 **67** **77**

The butylboronate diethanolamine complex (77 mg, 0.45 mmol) and (R,R)-(+)-N,N,N',N',-tetramethyltartaric acid diamide (119 mg, 0.583 mmol) were dissolved in dichloromethane (2.5 ml). Brine (1 ml) was added and the resulting biphasic solution was stirred under argon at room temperature for 30 min. The two layers were separated and the aqueous layer was extracted with dichloromethane (1 ml). The combined organic layers were washed with brine (1 ml), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure

and dried under vacuum (0.2 mmHg) to afford the title compound (113 mg, 93%) as a pale yellow oil:

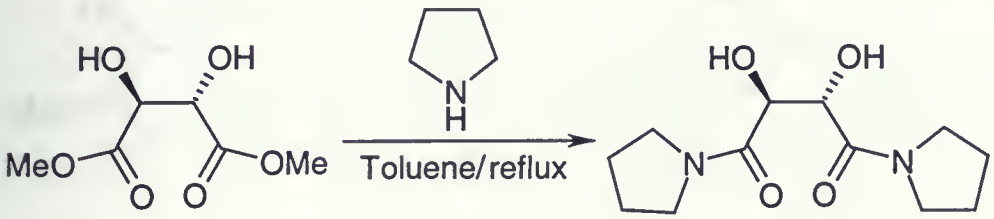
$[\alpha]_D$: -104.4 (c 1.70, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$) δ 5.53 (s, 2H), 3.20(s, 6H), 1.41-1.29 (m, 4H), 0.87 (t, J=7Hz, 3H), 0.85 (t, J=8Hz, 2H);

^{13}C NMR: (75 MHz, $CDCl_3$) δ 168.2, 75.6, 36.9, 35.7, 25.0, 13.6, 9.87(br);

HRMS: calculated for $C_{12}H_{23}BN_2O_4$: 270.1751. Found: 270.1746.

The preparation of (R,R)-(+)-1,4-dioxo-1,4-dipyrrolidin-1-ylbutane-2,3-diol



62

A mixture of (L)-dimethyl tartrate (800 mg, 4.5 mmol) and pyrrolidine (958 mg, 13.5 mmol) of pyrrolidine in 1ml dry toluene was heated at 111^{0}C. After stirring and reluxing for 6h, the reaction was cooled down to room temperature and treated ethylacetate (about 2 mL), the mixture was left in a refrigerator overnight, the crystals were collected by suction filtration and washed with cold ethyl acetate (4 x 5 mL). The filtrate was concentrated, seeded and cooled to yield a second crop of crystallized material. The combined crystals was dried under high vacuum. The yield was 1.04 g (90.3%)

m.p.: 120-122^{0}C

$[\alpha]_D$: +30.5 (95% ethanol, c 2.0)

TLC: R_f=0.33 (10% methanol / ethylacetate)

IR(KBr): 3413, 2989, 2949, 2880, 1641, 1460, 1382, 1235, 1108cm^{-1}

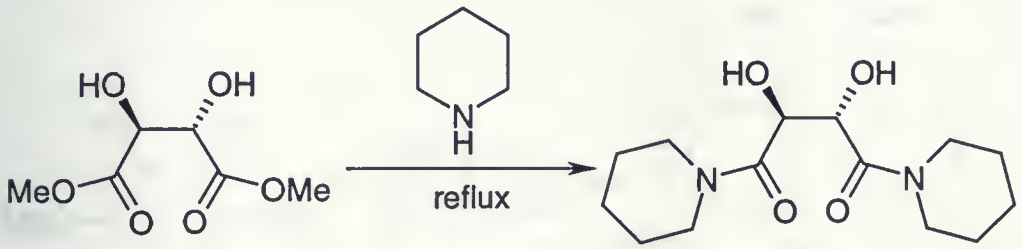
^1H NMR: (300 MHz, $CDCl_3$) δ 4.53 (s, 2H), 4.30 (br, 2H),.3.88-3.38 (m, 8H), 2.09-1.84 (m, 8H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 169.9, 71.2, 47.2, 47.1, 26.6, 24.2

MS(FAB): m/z: 257 (100%, M+1), 186 (65.8%), 158 (55.4%), 98 (65%), 72 (43%)

HRMS(FAB): calculated for $C_{12}H_{21}N_2O_4$: 257.1512 (MH^+). Found: 257.1519.

The preparation of (R,R)-(+)-1,4-dioxo-1,4-dipiperidrin-1-ylbutane-2,3-diol



65

A mixture of (L)-dimethyl tartrate (800 mg, 4.5 mmol) and piperidine (1.148 g, 13.5 mmol) in dry toluene (1 mL) was heated to 110^{0}C. After stirring and refluxing overnight, the reaction was cooled down to room temperature treated with ethyl acetate (about 2 mL). The mixture was left to stand in a refrigerater overnight. The crystals produced were collected by suction filtration and washed with cold ethylacetate (3 x 5 mL). The filtrate was concentrated, subjected to column chromatography on silica gel (methanol / ethylacetate, 1:9) to provide additional diol. The combined yield was 613 mg (48%).

m.p.: 134-135^{0}C

$[\alpha]_D$: +15.95 (95% ethanol, c 2.0)

TLC: R_f= 0.5 (10% methanol / ethylacetate)

IR(KBr): 3412, 3021, 2936, 2859, 1640, 1479, 1372, 1247cm^{-1}

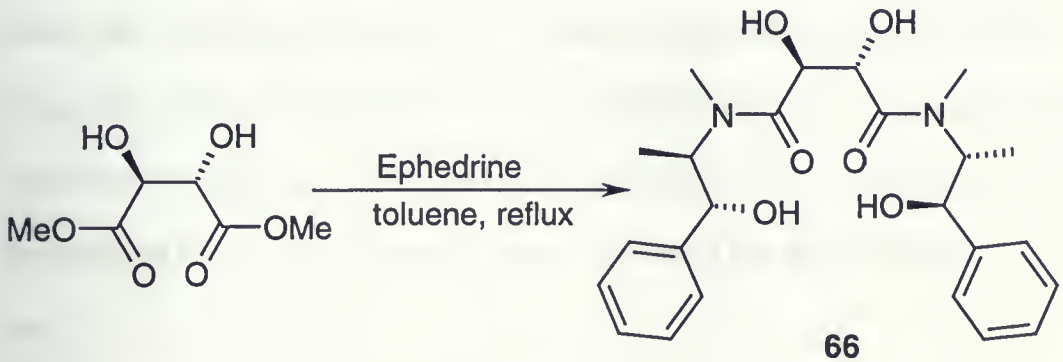
^1H NMR: (300 MHz,$CDCl_3$) δ 4.47 (S, 2H), 3.88-3.56 (m,8H), 3.34 (br, 2H), 1.65-1.63 (m, 12H)

^{13}C NMR: (75 MHz $CDCl_3$) δ 170.9, 70.6, 47.4, 44.4, 26.59, 25.9, 24.8

MS (FAB): m/z: 285 (100%, M+1), 200 (100%), 172 (70%), 112(90%), 84 (52%)

HRMS(FAB): Calculated for $C_{14}H_{25}N_2O_4$: 285.1748(MH^+)., Found: 285.1765

The preparation of Diephedrine tartaric acid diamide



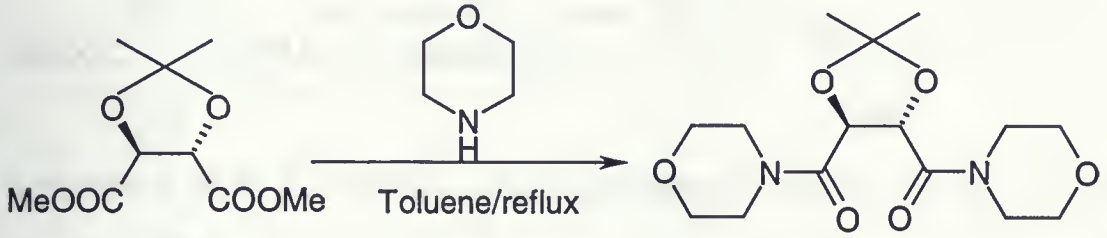
66

A mixture of L-tartrate (100 mg, 0.56 mmol) and L-ephedrine (370 mg, 22.45 mmol) in dry toluene (1 mL) was stirred and refluxed overnight. The mixture was then cooled down to room temperature and concentrated, subjected to column chromatography on silica gel (ethylacetate) to provide the product. The yield was 188.2 mg (75.7%)

TLC: R_f=0.35 (ethyl acetate)

^1H NMR: (300MHz, $CDCl_3$) δ 7.28-7.36 (m, 10H), 4.90-4.89 (d, 2H), 4.54-4.45 (t, 2H), 4.02 (s, 2H), 2.68 (s, 6H), 1.26-1.24 (d, 6H), 3.30 (br, 2H)

The Preparation of 4-{[(4R,5R0-2,2-dimthyl-5-(morpholin-4-ylcarbonyl)-1,3-dioxolan-4-yl]carbonyl}morpholine



56 **58**

A mixture of (R,R)-(+) dimethyl 2,3-O-isopropylidene-L-tartrate (50 mg, 0.23 mmol) and morpholine (80 mg, 0.92 mmol) in dry toluene (0.5 mL) was stirred and heated under reflux overnight. The reaction was allowed to stand at room temperature to yield white crystals. The crude product was collected by suction filtration and washed with cold 50% hexane / ethylacetate (5 mL). The crude product was dissolved in CH_2Cl_2, decolorized with Norrit and recrystalized from 50% hexane / ethylacetate. The yield was 66 mg. (88%)

m.p.: 174-175^{0}C

TLC: R_f=0.6 (ethylacetate)

$[\alpha]_D$: -19 (95% ethanol, c 2.0)

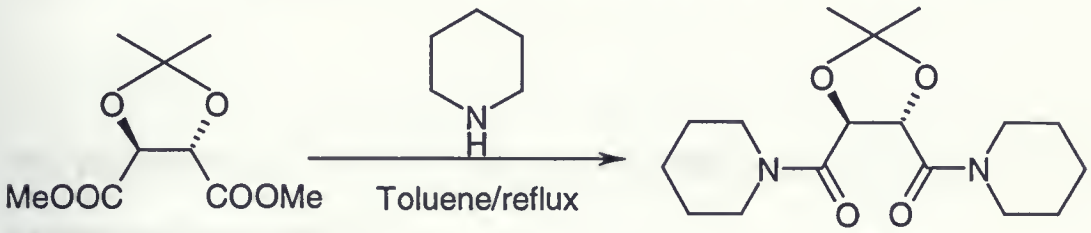
IR(KBr): 2993, 2931, 2860, 1655, 1477, 1375cm^{-1}

^{1}H NMR: (300 MHz,$CDCl_3$) δ 5.36 (s, 2H), 3.82-3.33 (m, 16H), 1.44 (s, 6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 167.0, 112.3, 75.1, 66.9, 46.2, 42.7, 26.4

MS (FAB): m/z: 329 (100%, M+1), 114 (47%), 156 (27%), 70 (23.5%), 214 (13.9%), 271 (7.1%)

The Preparation of (R,R)-(-)-Dipiperidine tartaric acid diamide acetonide?



56 60

A mixture of (R,R)-(+) dimethyl 2,3-O-isopropylidene-L-tartrate (500 mg, 2.3 mmol) and piperidine (800 mg, 9.4 mmol) in dry toluene (1 mL) was stirred and refluxed overnight. The mixture was allowed to stand in the freezer overnight to yield white crystals. The crude product was collected using suction filtration and washed with 50% cold hexane / ethylacetate. The product was dissolved in CH_2Cl_2, decolorized with Norrit and recrystalized from 50% hexane / ethylacetate. The yield was 633 mg (85%).

m.p.: 110-111^{0}C

$[\alpha]_D$: -18.22 (95% ethanol, C 2.0)

TLC: R_f=0.6 (ethyl acetate)

IR (KBr): 2992, 2934, 2861, 1640, 1463, 1374, 1248, 1163, 1063cm^{-1}

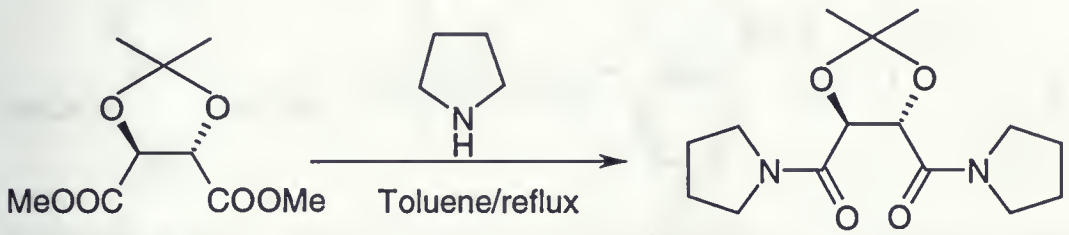
^{1}H NMR: (300 MHz, $CDCl_3$) δ 5.31 (s, 2H), 3.72-3.46 (m, 8H), 1.64-1.57 (m, 12H), 1.44 (s, 6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 167.2, 112.2, 75.7, 47.1, 43.8, 26.9, 25.9, 24.9

MS (FAB): m/z: 325 (100%, M+1), 112 (59.5%), 84 (36.8%), 69 (24%), 212 (17.7%)

HRMS(FAB): Calculated for $C_{17}H_{29}N_2O_4$: 325.2173(MH^+), Found: 325.2175

The preparation of 1-{[(4R,5R)-2,2-dimethyl-5-(pyrrolidin-1-ylcarbonyl)-1,3-dioxolan-4-yl]carbonyl}pyrrolidine



56 57

A mixture of the acetonide of tartrite (500 mg, 2.3 mmol) and pyrrolidine (800 mg, 11.3 mmol) in 1mL dry toluene was stirred and refluxed overnight. The mixture was allowed to stand in the freezer overnight to yield white crystals. The crude product was collected using suction filtration, decolorized with Norrit and recrystallized from 50% hexane / ethylacetate. Yield and washed with 50% cold hexane / ethylacetate. The product was dissolved in $CH_2Cl_2$is 612 mg (90%).

m.p.: 142-143^{0}C

$[\alpha]_D$: -44.2 (95% ethanol, c 2.0)

TLC: R_f=0.33 (ethyl acetate)

IR (KBr): 2984, 2878, 1641, 1453, 1371, 1337, 1225, 1162cm^{-1}

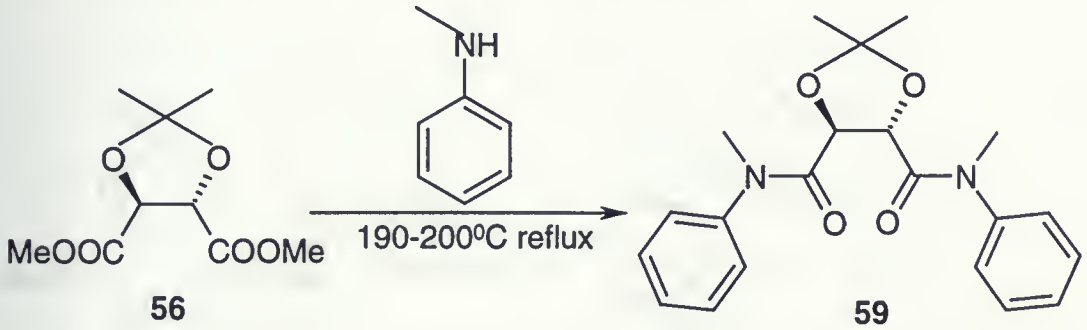
^{1}H NMR: (300 MHz, $CDCl_3$) δ 5.10 (s, 2H), 3.78-3.64 (m, 4H), 3.56-3.47 (t, 4H), 2.06-1.70 (m, 8H), 1.49 (s, 6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 167.3, 112.6, 46.9, 46.6, 26.7, 26.4, 24.4

MS (FAB): m/z: 297 (100%), 140 (28.3%), 198 (17.9%), 70 (20.6%), 239 (6%)

HRMS(FAB): Calculated for $C_{15}H_{25}N_2O_4$: 297.1744(MH^+), Found: 297.1746

The preparation of (R,R)-(-)-di-N-methyl analine tartaric acid diamide



56 59

A mixture of the acetonide of L-dimethyl tartrate (600 mg, 2.75 mmol) and N-methyl aniline (1.0 g, 9.33 mmol) in sea sand bath was stirred and refluxed overnight at 190-200 ^{0}C. The reaction was cooled to room temperature and then concentrated. The product was purified by silica gel with 20% ethylacetate / hexane. The yield was 607 mg (60.6%).

TLC: R_f=0.40 (50% hexane / ethyl acetate)

m.p.: 77-78^{0}C

$[\alpha]_D$: -109.4 (95% ethanol, c 2.0)

IR(KBr): 3061, 2986, 2934, 1659, 1593, 1497, 1454, 1396 cm^{-1}

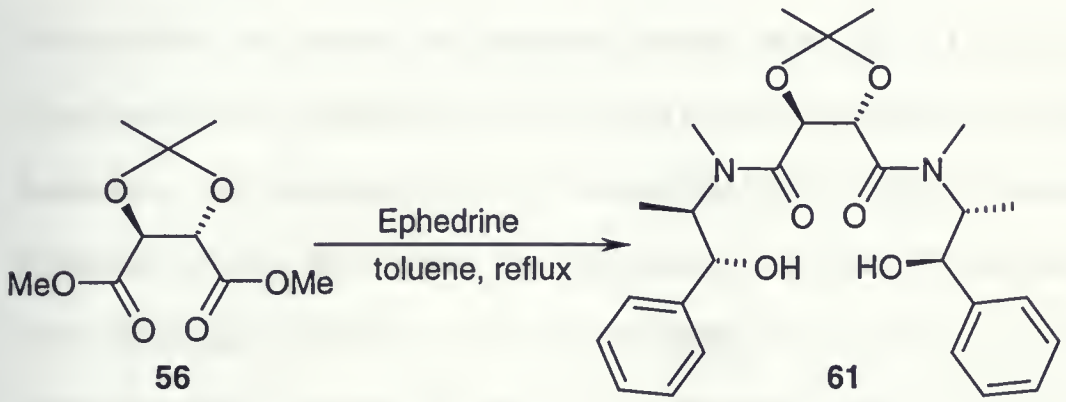
^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.62-7.28 (m, 10H), 4.75 (s, 2H), 3.26 (s, 6H), 1.24 (s, 6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 168.3, 143.0, 129.8, 128.3, 127.7, 112.4, 75.9, 38.4, 26.6

MS (FAB): m/z: 369 (100%, m+1), 134 (80%), 176 (46%), 107 (33%), 148 (43%)

HRMS(FAB): Calculated for $C_{21}H_{25}N_2O_4$: 369.1797(MH^+), Found: 369.1798

The preparation of (R,R)-(-)-di-epherdrine tartaric acid diamide



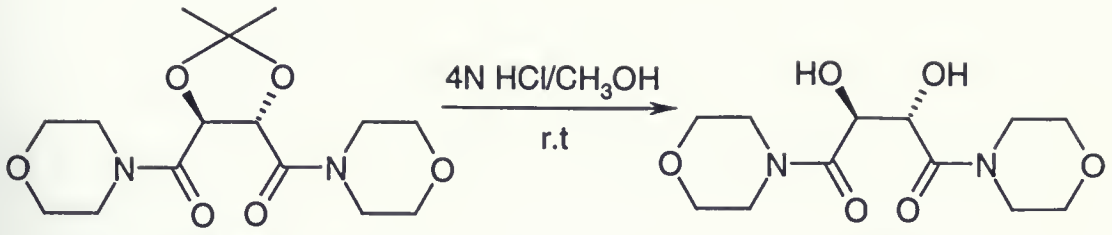
A mixture of acetonide of L-dimethyl-tartrate (50 mg, 0.23 mmol) and L-ephedrine (80 mg, 0.46 mmol) in dry toluene (1 mL) was stirred and refluxed overnight. The mixture was then cooled down to room temperature and concentrated. The product was separated by silica gel with 20% ethyl acetate/hexane, yield 104.8 mg (95%).

TLC: R_f=0.30 (50% EtOAc / Hexane)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.41-7.21 (m, 10H), 5.21 (s, 2H), 4.41-4.35 (t, 2H), 3.59-3.60 (d, 2H), 2.95 (s, 6H), 1.29 (s, 6H), 1.23-1.25 (d, 6H)

MS (FAB): m/z: 485 (m+1, 27%), 467 (15.5%), 377 (7.9%), 292 (16%), 148 (100%), 117 (13.9%), 91 (11.7%)

The preparation of (R,R)-(+)-1,-dimorpholin-4-yl-1,4-dioxobutane-2,3-diol



58 63

To a solution of the acetonide of dimorphorine diamide **56** (80 mg, 0.24 mmol) in methanol (1ml) was added 4N hydrochoric acid (2mL), and the resulting mixture was stirred at room temperature. The homogenious solution was neutralized by the addition of saturated sodium bicarbonate solution, then washed with ethyl acetate (2 x 5mL). The aqueous layer was concentrated under reduced pressure, then dried under high vacuum to get a white solid.. Dichloromethane (3 x10 mL) was used to extract the product from above white solid, then heating filtrated, recrystalized by addition ethyl acetate (5 mL) to afford the title compound. The filtrate was purified by flash chromatography on silica gel with 5% methanol / ethyl acetate. The combined yield is 63 mg (91%).

m.p.: 80-82^{0}C

$[\alpha]_D$: +26.9 (95% ethanol, c =2)

TLC: R_f=0.45 (10% methanol / ethyl acetate)

IR (KBr): 3410.5, 2957.1, 2961.0, 1632.1, 1474.5, 1398.9, 1272.9, 1245.4, 1112.2

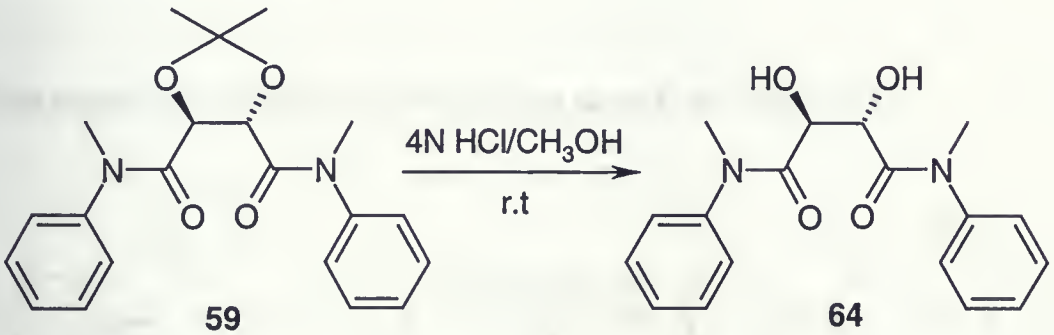
^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.26 (s, 2H), 3.73-3.68 (m, 16H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 170.4, 70.5, 67.1, 46.8, 3.5

MS (FAB): m/z: 289 (m+1, 100%), 174 (50.9%), 202 (45%), 114 (43.3%), 70 (17.6)

HRMS(FAB): Calculated for $C_{12}H_{21}N_2O_6$: 289.1408(MH^+), Found: 289.1412.

The preparation of (R,R)-(+)-2,3-dihydroxy-N,N'-dimethyl-N,N'-diphenylbutanediamide



To a solution of the acetonide of N-methyl analine tartaric acide diamide **58** (30 mg, 0.0815 mmol) in methanol (1mL) was added 4N hydrochoric acid (2mL), and the resulting mixture was stirred at room temperature. The homogeneous solution was neutralized by the addition of saturated sodium bicarbonate solution, then washed with ethyl acetate (2 x 5mL). The aqueous layer was concentrated under reduced pressure, and dried under high vacuum to afford white solid. Dichloromethane (3 x5 mL) was used to extract the product from white solid, then heating filtrated, recrystalized by the addition of ethyl acetate (5mL) to afford the title compound. The filtrate was purified by flash chromatography on silica gel using pure ethyl acetate. The combined yield is 25mg (93.5%).

m.p.: 54^0C

$[\alpha]_D$: +78.5 (95% ethanol, c=2)

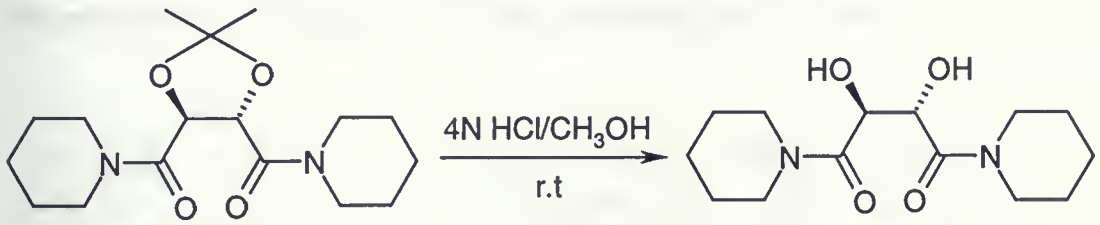
TLC: R_f=0.30 (ethyl acetate)

^{1}H NMR: (300 MHz $CDCl_3$) δ 7.30-7.22 (m, 6H), 6.92-6.95 (d, J=6.486Hz, 4H), 3.50 (s, 2H), 3.24 (s, 6H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 170.4, 141.8, 130.3, 128.6, 127.4, 69.9, 39.1

MS (FAB): m/z: 329 (100%), 194 (96.3%), 134 (95.3%), 55 (60.1%), 222 (52.2%), 107 (48.6%)

The preparation of (R,R)-(+)-Dipiperidine tartaric acid diamide 63



60 65

To a solution of the acetonide of di piperiline tartaric acide diamide (40 mg, 0.123 mmol) in methanol (1 mL) was added 4N hydrochoric acid (2 mL), and the resulting mixture was stirred at room temperature. The homogenous solution was neutralized by saturated sodium bicarbonate solution, washed with ethyl acetate (2 x 5mL). The aqueous layer was concentrated under reduced pressure, dried under high vacuum to afford white solid. Dichloromethane (3 x 5 mL) was used to extract the product from white solid, then heating filtrated, recrystalized by the addition of ethyl acetate to afford the title compound. The filtrate was purified by flash chromatography on silica gel using 5% methanol / ethyl acetate. The combining yield is 33mg (94.3%).

m.p.: 134-135^{0}C

$[\alpha]_D$: +15.95 (95% ethanol, c 2.0)

TLC: R_f= 0.5 (10% methanol / ethyl acetate)

IR(KBr): 3412, 3021, 2936, 2859, 1640, 1479, 1372, 1247cm^{-1}

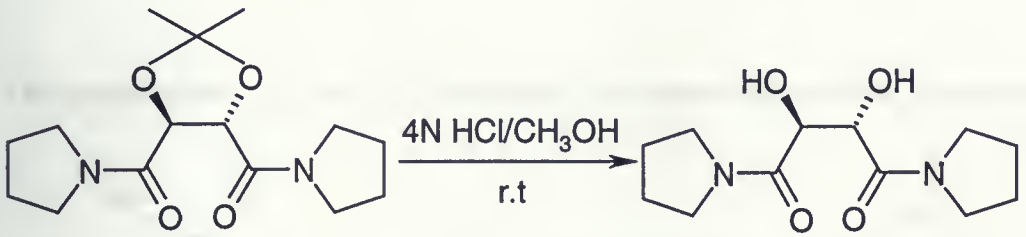
^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.48 (S, 2H), 3.88-3.56 (m, 8H), 3.34 (br, 2H), 1.65-1.63 (m, 12H)

^{13}C NMR: (75MHz, $CDCl_3$) δ 170.9, 70.6, 47.4, 44.4, 26.6, 25.9, 24.9

MS (FAB): m/z: 285 (100%,M+1), 200 (100%), 172 (70%), 112(90%), 84 (52%)

HRMS(FAB): calculated for $C_{14}H_{25}N_2O_4$: 285.1748(MH^+), Found: 285.1765

The preparation of (R,R)-(+)-Dipyrrolidine tartaric acid diamide



57 62

To a solution of the acetonide of pyrrolidine tartaric acid diamide (50 mg, 0.169 mmol) in methanol (1mL) was added 4N hydrochoric acid (2mL), and the resulting mixture was stirred at room temperature. The homogenous solution was neutralized by saturated sodium bicarbonate solution, washed with ethyl acetate (2 x 5mL). The aqueous layer was concentrated under reduced pressure, dried under high vacuum to afford white solid. Dichloromethane (3 x 5 mL) was used to extract the product from white solid, heating filtrated, recrystalized by the addition of ethyl acetate to afford the title compound. The filtrate was purified by flash chromatography on silica gel using pure 5% methanol / ethyl acetate. The combined yield is 41mg (95.3%).

m.p.: 120-122^{0}C

$[\alpha]_D$: +30.5 (95% ethanol, c 2.0)

TLC: R_f=0.33 (10% methanol / ethylacetate)

IR(KBr): 3413, 2989, 2949, 2880, 1641, 1460, 1382, 1235, 1108 cm^{-1}

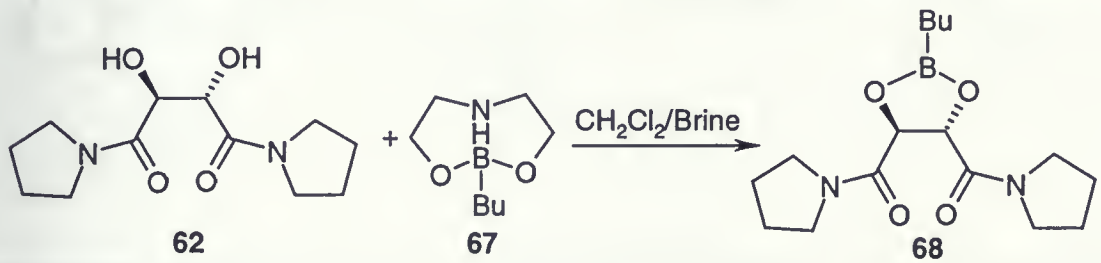
^1H NMR: (300 MHz, $CDCl_3$) δ 4.53 (s, 2H), 4.30 (br, 2H),.3.88-3.38 (m, 8H), 2.09-1.84 (m, 8H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 169.9, 71.2, 47.2, 47.1, 26.6, 24.2

MS (FAB): m/z: 257 (100%, M+1), 186 (65.8%), 158 (55.4%), 98 (65%), 72 (43%)

HRMS(FAB): calculated for $C_{12}H_{21}N_2O_4$: 257.1512(MH^+). Found: 257.1519.

The preparation of (R,R)-(-)-2-Butyl-dipyrrolidine-dioxaborolane-4,5-dicarboxamide



The butylboronate diethanolamine complex (77 mg, 0.45 mmol) and (R,R)-(+)-dipyrrolidine tartaric acid diamide (122 mg, 0.476 mmol) were dissolved in dichloromethane (2.5mL). Brine (1ml) was then added and the resulting biphasic solution was stirred under argon at room temperature for 30 min. The two layers were separated and the aqueous layer was extracted with dichloromethane (1mL). The combined organic layers were washed with brine (1mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and dried under vacuum (0.2 mmHg) to afford the title compound (143 mg, 98%) as a pale yellow oil:

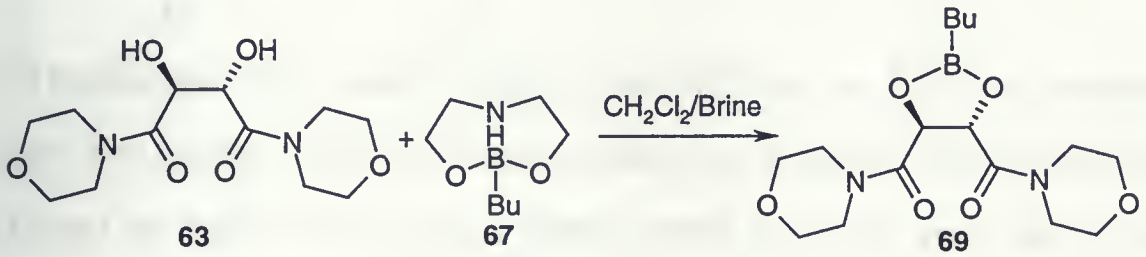
$[\alpha]_D$: -90.6 (c 2, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$) δ 5.30 (s, 2H), 3.77-3.45 (m, 8H) 2.03-1.83 (m, 8H), 1.38-1.25 (m, 4H), 0.88-0.84 (m, 5H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 167.8, 75.1, 46.9, 46.7, 26.5, 24.6, 14.2.

HRMS: calculated for $C_{16}H_{27}BN_2O_4$: 322.2064. Found: 322.2061.

The preparation of (R,R)-(-)-2-Butyl-dimorpherine-dioxaborolane-4,5-dicarboxamide



The butylboronate diethanolamine complex (12 mg, 0.07 mmol) and (R,R)-(+)-dimorpherine tartaric acid diamide (28.5 mg, 0.1 mmol) were dissolved in dichloromethane (1 mL). Brine (0.5 mL) was added and the resulting biphasic solution was stirred under argon at room temperature for 30 min. The two layers were separated and the aqueous layer was extracted with dichloromethane (1 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and dried under vacuum (0.2 mmHg) to afford the title compound (21.8 mg, 87.9%) as a pale yellow oil:

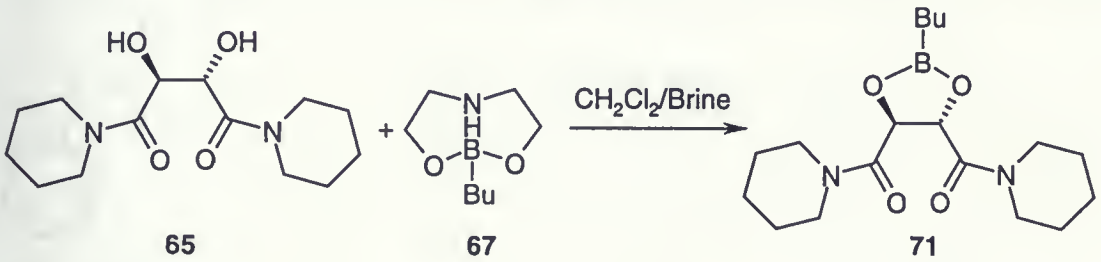
$[\alpha]_D$: -78.5 (c 1.7, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 5.57 (s, 1H), 5.36 (s, 1H), 4.03-3.45 (m, 16H), 1.49-1.30 (m, 4H), 0.95-0.70 (m, 5H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 167.45, 75.71, 67.29, 67.11, 47.63, 26.93, 14.23

HRMS: calculated for $C_{16}H_{27}BN_2O_4$: 322.2064. Found: 322.2061.

The preparation of (R,R)-(-)-2-Butyl-dipiperidine-dioxaborolane-4,5-dicarboxamide



65 67 71

The butylboronate diethanolamine complex (11mg, 0.062mmol) and (R,R)-(+)-dimorpherine tartaric acid diamide (22mg, 0.077mmol) were dissolved in dichloromethane (1mL). Brine (0.5 mL) was added and the resulting biphasic solution was stirred under argon at room temperature for 30min. The two layers were separated and the aqueous layer was extracted with dichloromethane (1mL). The combined organic layers were washed with brine (1mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and dried under vacuum (0.2 mmHg) to afford the title compound (20.1 mg, 92.6%) as a pale yellow oil:

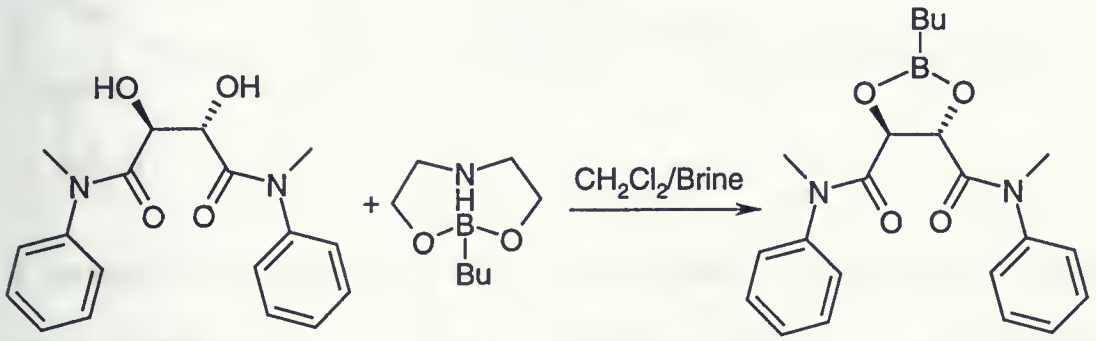
$[\alpha]_D$: -70.8 (c 1.7, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 5.56 (s, 2H), 3.75-3.39 (m, 20H), 1.49-1.26 (m, 4H), 0.99-0.68 (m, 5H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 170.82, 70.58, 47.33, 47.13, 44.30, 44.15, 26.99, 26.58, 26.24, 25.92, 25.64, 24.89, 24.79, 14.26

HRMS: calculated for $C_{18}H_{31}BN_2O_4$: 350.2567. Found: 350.23786.

The preparation of (R,R)-(-)-2-Butyl-di-N-methyl analine-dioxaborolane-4,5-dicarboxamide



64 **67** **70**

The butylboronate diethanolamine complex **53** (2.8mg, 0.01675mmol) and (R,R)-(+)-N-methyl analine tartaric acid diamide **62** (7.1mg, 0.0216mmol) were dissolved in dichloromethane (1 mL). Brine (0.5 mL) was added and the resulting biphasic solution was stirred under argon at room temperature for 30 min. The two layers were separated and the aqueous layer was extracted with dichloromethane (1 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and dried under vacuum (0.2 mmHg) to afford the title compound (6 mg, 90.9%) as a pale yellow oil:

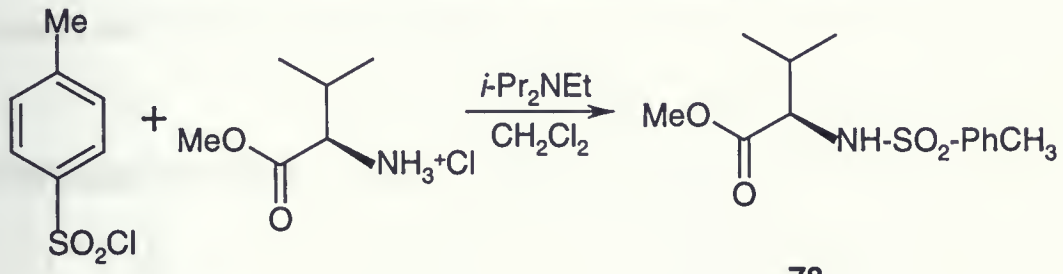
$[\alpha]_D$: -90.8 (c 1.7, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.45-7.15 (m, 10H), 4.95 (s, 2H), 3.22 (s, 6H), 1.31-1.27 (m, 4H), 0.89-0.82 (m, 5H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ 169.22, 142.71, 13.19, 128.62, 127.57, 76.36, 38.36, 26.22, 25.52, 14.26, 10.39

HRMS: calculated for $C_{22}H_{27}BN_2O_4$: 394.2003, Found: 394.2058.

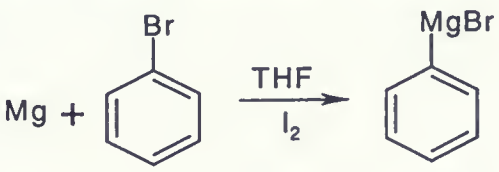
The preparation of L-methyl N-[(4-methylphenyl)sulfonyl]-valinate



78

A mixture of L-valine hydrochloride (1.68 g, 10 mmol), 4-dimethyl amonion pyridine (10 mg) in dichloromethane (10 mL) and *i*-Pr_2NEt (3.5 ml) was stirred for 10 min to dissolve. A clear light yellow solution was present. Another solution of 10 ml CH_2Cl_2 which was dissolved 2.0 g (10.5 mmol) p-toluene sulfonyl chloride was allowed to add to the prior flask through cannula dropwise. The resulting solution was string overnight. 1M HCL (30 mL) was used to quench the reaction and the organic layer was separated, washed with dichloromethane (3 x 10 mL) and saturated sodium bicarbonate (20 mL), dried over sodium sulfate, concentrated to get white solid. The product was carried forward to the synthetic step without further purification.

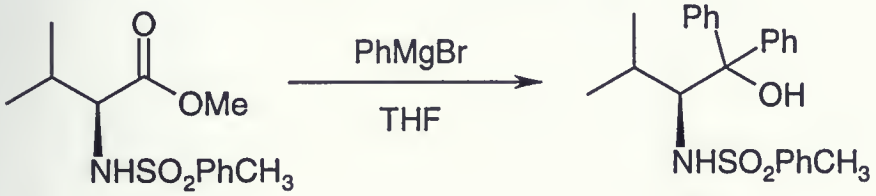
The preparation of phenyl magnesium bromide



79

To a mixture of magnesium (2.9g, 120 mmol) and iodine (two pieces) in THF (20 mL) was added a solution of bromobenzene (10.5 mL, 100 mmol) in THF (50 mL) dropwise via a cannula. Heating the reaction resulted in a color change from white to black. Stirring was continued for a further 2 hours at 35 ^{0} C. The mixture was cooled to room temperature and directly used in the next synthetic step.

The preparation of chiral diphenyl valine amino achohol



80

The solution of valine tosyl amide (2g, 10.5mmol) in 5ml THF was added into Grignard solution dropwise through cannula. The resulting mixture was stirred overnight then quenched with saturated amnion chloride (7mL). The unreactive magnesium was decanted and the solvent was evaporated under a reduced pressure. The mixture was acidified with 1M HCl, worked up with dichloromethane and saturated sodium chloride, dried with sodium sulfate, concentrated to give the crude white product. Recrystalized from 15ml isopropanol/hexane (heating may necessary), white needle crystal was collected. Yield is 2.3g (78%).

m.p.: 148-150^{0}C

TLC: R_f=0.44 (hexane:ethyl acetate=7:3)

$[\alpha]_D$: +23.15 (95% ethanol)

IR(KBr): 3515.7, 303.2, 2879.9, 2963.4, 194.7, 1911.1, 1795.8, 1598.6, 1496.8

^{1}H NMR: (300 MHz, $CDCl_3$) 7.46-7.24 (m, 5H), 7.17-7.08 (m, 5H), 4.42-4.69 (d, J=9.45Hz, 1H), 4.46-4.43 (d, J=9.72, 1H), 2.59 (br, 1H), 2.38 (s, 3H), 2.16-1.98 (m, 1H), 0.99-0.97 (d, J=6.86Hz, 3H), 0.79-0.77 (d, J=6.67Hz, 3H)

^{13}C NMR: (75 MHz, $CDCl_3$) 1145.3, 144.9, 142.9, 139.1, 129.7, 128.8, 128.6, 127.6, 127.3, 127.1, 126.1, 126.2, 82.6, 6.7, 29.3, 23.3, 21.8, 17.9.

MS(FAB): m/z:226 (100%), 260 (82.7%), 392 (74.6%), 91 (71.9%), 155 (49.3%), 183 (42.3%)

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REFERENCES

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