EFFECT OF SOLVENT MEDIA IN ALTERING THE RATES OF DIELS-ALDER REACTIONS AND OTHER C-C BOND FORMING REACTIONS

BY

DIGANTA SARMA

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

Dr. ANIL KUMAR

(RESEARCH GUIDE)

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BY

DIGANTA SARMA

PHYSICAL CHEMISTRY DIVISION

NATIONAL CHEMICAL LABORATORY

PUNE 411008

INDIA

Dr. ANIL KUMAR

(RESEARCH GUIDE)

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DECLARATION

I hereby declare that the thesis entitled "**Effect of solvent media in altering the rates of Diels-Alder reactions and other C-C bond forming reactions**", submitted for the Degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the Physical Chemistry Division, National Chemical Laboratory, Pune from July, 2003 to February, 2007 under the supervision of Dr. Anil Kumar (Research guide). The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other University.

Date: 26th Feb. 2007
Physical Chemistry Division
National Chemical Laboratory
Pune-411008

Diganta Sarma
(Research student)

Dr Anil Kumar
Physical Chemistry Division

Tel: +91-20-25902278
Fax: +91-20-25902636
e-mail: a.kumar@ncl.res.in

National Chemical Laboratory
Dr Homi Bhabha Road
Pune – 411 008, INDIA

CERTIFICATE

Certified that the work incorporated in the thesis, "**Effect of solvent media in altering the rates of Diels-Alder reactions and other C-C bond forming reactions**", submitted by **Mr. Diganta Sarma**, for the degree of **Doctor of Philosophy**, was carried out by the candidate under my supervision in Physical Chemistry Division, National Chemical Laboratory, Pune, India. Materials obtained from other sources have been duly acknowledged in the thesis.

Date: 26th Feb. 2007
Place: Pune

Dr. Anil Kumar
(Research Guide)

Dedicated
To
My mother
&
Memories of my father

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evaluate my scientific problems and discussed the difficulties. They were always rational and fair in their criticism.

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Date: 26th Feb. 2007 *Diganta Sarma*

List of Abbreviations

AC	Activated complex
AR	Analytical grade
BPC	*N*-Butylpyridinium chloride
[BMIM]Cl	1-Butyl-3-methyl imidazolium chloride
[EMIM]BF_4	1-Ethyl-3-methyl imidazolium tetrafluoroborate
[BMIM][BF_4]	1-Butyl-3-methyl imidazolium tetrafluoroborate
[BM_2IM][BF_4]	1-Butyl-2,3-dimethyl imidazolium tetrafluoroborate
[BMIM][Lactate]	1-Butyl-3-methyl imidazolium lactate
[BMIM][PF_6]	1-Butyl-3-methyl imidazolium hexafluorophosphate
BINOL	1,1'-Bi-2-naphthol
BuOH	1-Butanol
cP	Centi poise
CDA	Chiral derivatizing agents
CSP	Chiral stationary phase
DCC	Dicyclohexyl carbodiimide
DiBuIM	1,3-Di butylimidazolium
DME	Dimethoxyethane
EMIC	1-Ethyl-3-methyl imidazolium chloride
[EMIM][CF_3SO_3]	1-Butyl-3-methyl imidazolium trifluoromethanesulfonate
[EMIM][NTf_2]	1-Butyl-3-methyl imidazolium trifluoromethanesulfonimide
EtOH	Ethanol
EWG	Electron Withdrawing Group
ERG	Electron Releasing Group
EAN	Ethyl ammonium nitrate
EG	Ethylene Glycol
FMO	Frontier Molecular Orbital
FM	Formamide
GC	Gas chromatography
GnCl	Guanidine chloride

HFP	1,1,1,6,6,6-Hexafluoro-2-propanol
HOMO	Highest Occupied Molecular Orbital
[HMI][BF_4]	1-Hexyl-3-methylimidazolium tetrafluoroborate
HBuIM	Hydrogen butylimidazolium
IS	Initial state
LPDE	Lithium Perchlorate Diethyl Ether
$Ln(OTf)_3$	Lanthanum Triflate
LUMO	Lowest Unoccupied Molecular Orbital
$LiClO_4$	Lithium Perchlorate
MM	Molecular Mechanical
MVK	Methyl Vinyl Ketone
MeOH	1-Methanol
MTPA	α-Methoxy-α-(trifluoromethyl)phenylaceticacid
[OMIM][BF_4]	1-Octyl-3-methyl imidazolium tetrafluoroborate
OTf	Trifluoromethanesulfonate (Triflate)
PrOH	1-Propanol
QM	Quantum Mechanical
SOI	Secondary Orbital Interactions
$Sc(OTf)_3$	Scandium Triflate
Sp	Solvophobicity parameter
S-I	Salting-in
S-O	Salting-out
TS	Transition State
TFE	1,1,1-Trifluoroethanol
TEA	Triethylamine
TON	Turn over number
VOC	Volatile Organic Compounds
$Yb(OTf)_3$	Ytterbium Triflate
α	Hydrogen bond donor ability
β	Hydrogen bond acceptor ability
π^*	Dipolarity-polarizability

s_o	Solubilities of nonelectrolyte in water
s	Solubilities of nonelectrolyte in electrolyte solution
c_s	Molar concentration of electrolyte
f_c	Activity coefficient
k	Salting constant

ABSTRACT

EFFECT OF SOLVENT MEDIA IN ALTERING THE RATES OF DIELS-ALDER REACTIONS AND OTHER C-C BOND FORMING REACTIONS

Conventionally most of the organic reactions are carried out in solution phase. The solution phase, that contains pure or mixed solvents, plays a pivotal role in determining the course of reactions and the amount of product formed. There are other parameters like temperature, pressure, concentration of reactants and stability of product that are also essential in governing the course of reactions. However, the change of a solvent in an organic reaction can bring about great changes in its kinetic profiles. There are several interesting properties of solvents, which may be considered significant in altering the reaction kinetics of organic reactions. The solvent media may promote the reaction rates by stabilizing the transition state. The polarity, dielectric constant, ionizing power, surface tension, viscosity, etc. of solvents can play crucial role in directing the kinetics of organic reactions in a specific manner.

The Diels-Alder reaction is one of the most important C-C bond forming reactions in organic chemistry to form cyclic structures. It is a class of cycloaddition reaction between a conjugated diene and an alkene, commonly termed the dienophile, to form a cyclohexene system. The remarkable importance of Diels-Alder reaction lies in the synthesis of natural products and physiologically active molecules. For a long time solvent polarity was believed to have no effect on the course of a Diels-Alder reaction due to involvement of isopolar activated complex. Berson, however, showed a clear relationship between the *endo/exo* product ratio and solvent polarity in the Diels-Alder reaction of cyclopentadiene and acrylates. Diels-Alder reactions in aqueous media were first carried out back in the 1930s, but no particular attention was paid to this fact until 1980, when Breslow and coworkers made the startling observation that the reaction of cyclopentadiene with butenone in water was more than 700 times faster than the same

reaction in 2,2,6-trimethylpentane; whereas the reaction rate in methanol is comparable to that in a hydrocarbon solvent. Such an unusual acceleration of the Diels-Alder reaction by water was attributed to the "hydrophobic effect", in which the hydrophobic interactions brought together the two nonpolar groups in the transition state.

Another important C-C bond formation reaction is Michael addition. The reaction is the addition of an enolate of a ketone or aldehyde (Michael donors) to an α,β-unsaturated carbonyl compound (Michael acceptors) at the β-carbon and involves conjugate addition. The reaction donors are active methylenes such as malonates and nitroalkanes, and the acceptors are activated olefins such as α,β-unsaturated carbonyl compounds.

The conventional organic solvents used in organic reactions are known to be environment pollutants. In view of the environmental pollution caused by the use of these volatile organic solvents, there is a greater need to replace them by environmentally benign solvents. In this regard ionic liquids have emerged as important substitutes for several organic solvents. Many ionic liquids have been developed for specific synthetic problems. For this reason, ionic liquids have been termed "designer solvent". Ionic liquids are considered green solvents in substituting many volatile organic solvents as they possess some special properties like: (1) They are nonvolatile, (2) They are nonflammable, (3) They have physicochemical properties that can be altered / controlled by judicious selection of the cation and/or anion and (4) Most importantly they can be recycled for a number of times without loss of activity.

Several parameters have been discussed to explain dramatic variation in reaction rates as well as stereoselectivities in the above mentioned solvent media. The possible origin of forces includes hydrophobic packing, solvent pressure, hydrogen bonding, hydrophobic hydration, and salting-out (S-O) and salting-in (S-I) effects, etc. However, no single parameter can explain the rate profiles of all reactions studied.

The present thesis deals with delineation and understanding of origins of possible forces responsible for rate acceleration and stereoselectivities in water, aqueous salt solutions and ionic liquids. These have been discussed in detail in seven separate chapters:

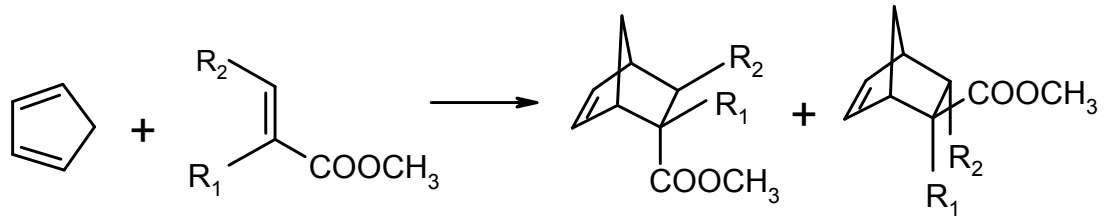
Chapter I describes a critical literature survey of the physical organic, green chemistry and asymmetric aspects of carbon-carbon bond forming reactions, in particular

Diels-Alder and Michael reactions. The frontier orbital description of cycloaddition as well as mechanistic aspects of Diels-Alder reaction has been discussed. The role of secondary orbital interaction in understanding the stereochemistry of Diels-Alder reactions has been introduced. Efforts have been made to explain the special role of water highlighting the possible factors like hydrophobic effect, hydrogen bonding, polarity, Lewis acid catalysis etc. for rate variation. Ionic liquids are emerging as potential green solvents over volatile organic solvents. Various Diels-Alder reactions carried out in ionic liquids have been emphasized. Asymmetric aspects of Diels-Alder and Michael reactions are also reported.

Chapter II deals with the objectives of the investigations carried out based on the literature survey. It also describes the organization of the thesis.

Chapter III is concerned with the competing role of secondary orbital interaction and hydrophobic effect in determining the stereoselectivity of Diels-Alder reactions.

In general, Diels-Alder reactions in water offer higher *endo/exo* ratios as compared to those in conventional organic solvents, but this is not the case for the reaction of cyclopentadiene with methyl *trans* crotonate (Scheme I). Secondary orbital interactions favor Diels-Alder reactions to be *endo* selective. But in this case hydrophobic effect of the methyl group influences the stabilization of the geometry of the transition states.

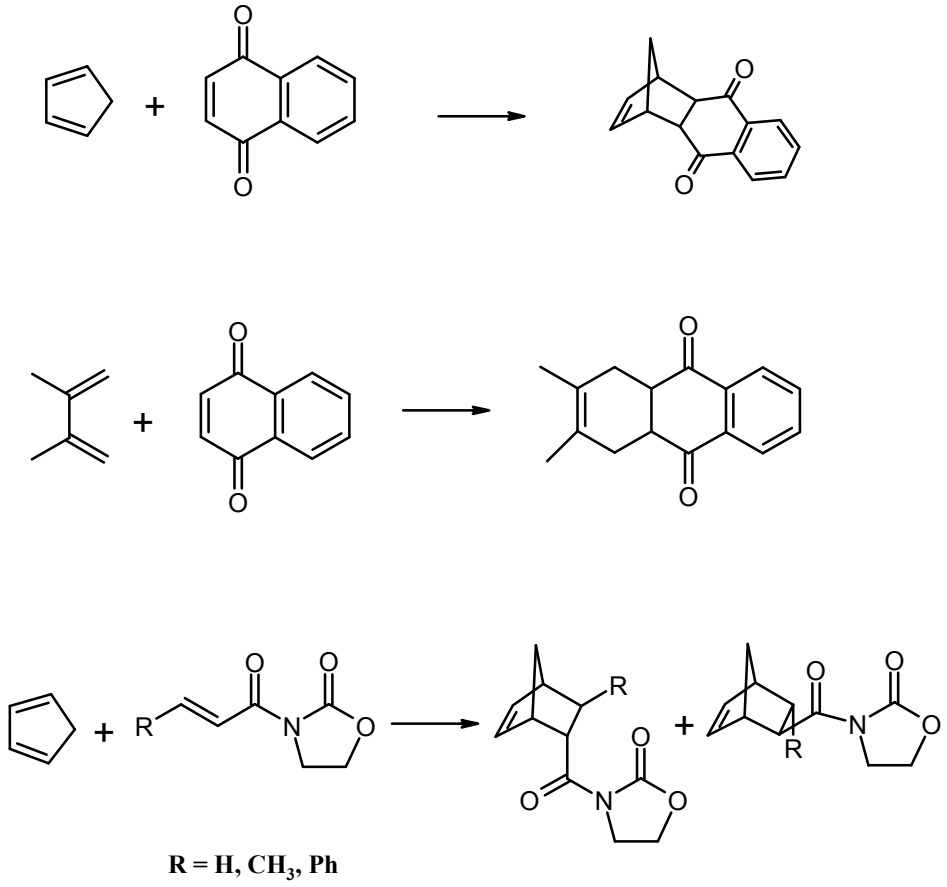


Scheme I: Diels-Alder reactions

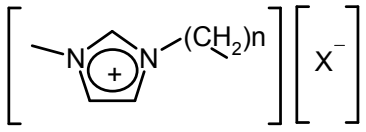
The effects of aqueous salt solutions on the reaction of cyclopentadiene and methyl *trans* crotonate have been investigated. The increase in *endo/exo* ratios with salting-in agents like GnCl, $LiClO_4$, urea etc and the decrease in *endo/exo* ratios with salting-out agents like LiCl, NaCl, NaBr, KCl, $MgCl_2$, $CaCl_2$ et. have been discussed in terms of hydrophobic effect.

The role of cosolvents on the stereoslectivity of Diels-Alder reaction between cyclopentadiene and methyl *trans* crotonate has also been examined.

Chapter IV discusses the Diels-Alder reactions of different dienes and dienophiles (Scheme II) in room temperature ionic liquids (Figure I). The reactions have



Scheme II: Diels-Alder reactions

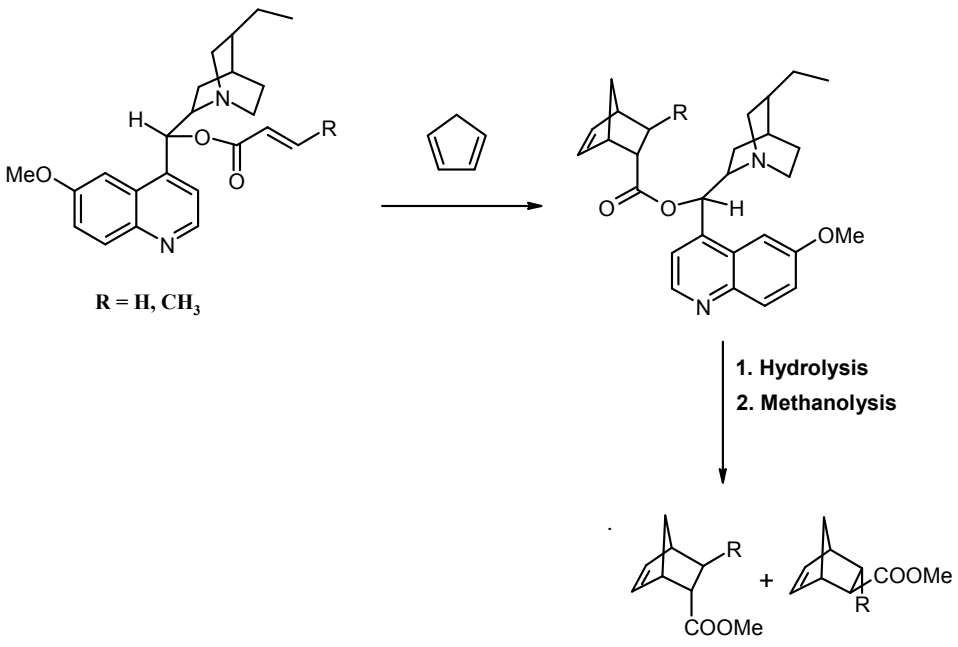


n=1 [EMIM]=1-ethyl-3-methylimidazolium X=BF_4, PF_6, Lactate,
n=3 [BMIM]=1-butyl-3-methylimidazolium TFA, NTf_2
n=7 [OMIM]=1-octyl-3-methylimidazolium

Figure I. Ionic liquids studied

also been carried out in the presence of rare earth metal triflates to reveal increase in yields and *endo/exo* products. It suggests enhancement in the catalytic power of the triflates in room temperature ionic liquids. It is possible to recover and reuse the ionic liquid phase with triflates to give comparative yields and stereoselectivities even after six cycles.

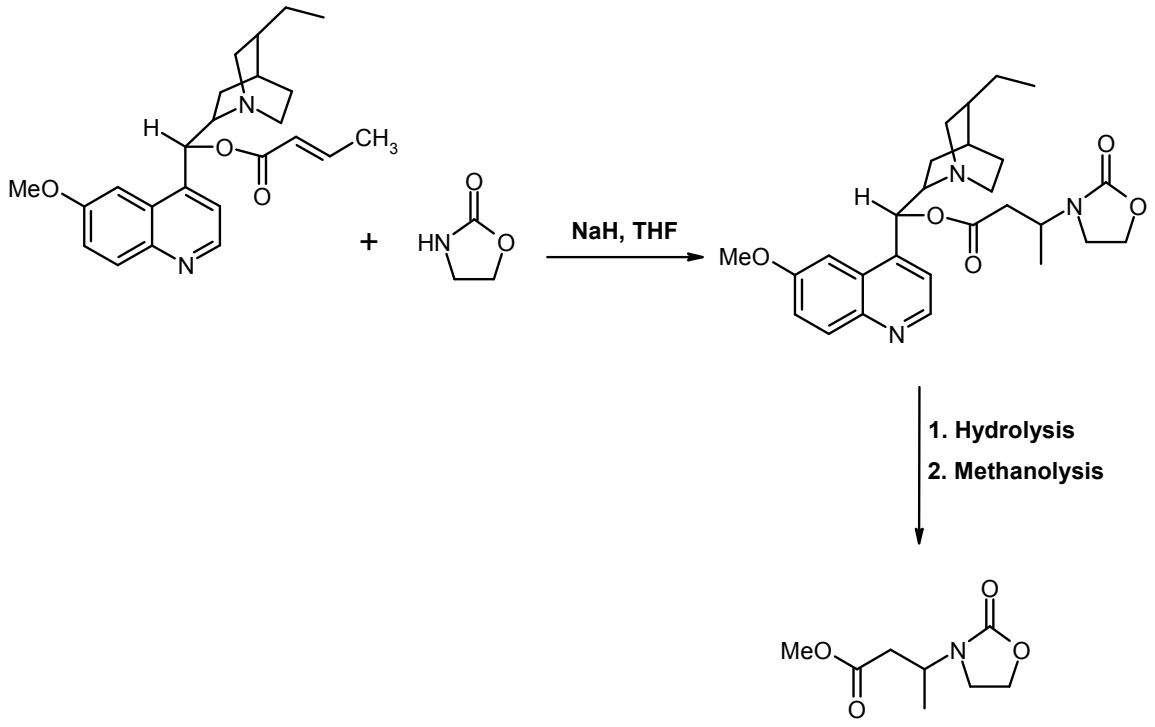
Chapter V emphasizes the role of solvents in asymmetric Diels-Alder and Michael reactions. Methodology is based on the use of quinine as a chiral auxiliary.



Scheme III: Asymmetric Diels-Alder reactions

Quinine derived dienophiles are used to carry out asymmetric Diels-Alder reactions. After the reaction the chiral auxiliary is removed by hydrolysis (Scheme III).

Quinine derived α,β-unsaturated compounds are used to carry out asymmetric Michael reactions (Scheme IV).



Scheme IV: Asymmetric Michael reactions

Chapter VI reveals the conclusions of the research work and future prospects of the studies.

Chapter VII is a detailed description of the experimental procedures to carry out Diels-Alder reactions in water, salt solutions and ionic liquids. Stereochemical assignments and solubility measurements are discussed in detail. Synthesis of different ionic liquids, dienophiles and compounds for asymmetric reactions are reported. NMR spectra for product confirmation and gas chromatographs for quantitative determination of the *endo/exo* ratios as well as enantiomeric excess are presented.

Thus the present work focuses on the possible origin of forces responsible for the rate enhancement in Diels-Alder reactions in water, aqueous salt solutions and ionic liquids. The effect of solvents on asymmetric Diels-Alder and Michael reactions are quantified through various solvent parameters.

CONTENTS

Chapter 1

INTRODUCTION

Chapter 1

Introduction

The efficient formation of C-C bonds forms the backbone of synthetic organic chemistry.

Although the well-known Kolbe synthesis was discovered in 1849 (the first observation was made in 1834 by Faraday), *for more than a century, C-C bond formation in aqueous media has been limited mainly to electrochemical processes and aldol condensation reactions. This is in contrast to the many enzymatic processes that by necessity must occur in an aqueous environment. In the last decade, there has been increasing recognition that organic reactions carried out in aqueous media (one of the green solvents) may offer advantages over those occurring in organic solvents.*

This chapter describes a critical literature survey of physical organic, green chemistry and asymmetric aspects of carbon-carbon bond forming reactions, particularly in Diels-Alder and Michael reactions.

1.1 Diels-Alder reaction

Diels-Alder reaction is one of the most important C-C bond forming reactions in organic chemistry to form cyclic structures. It is a class of cycloaddition reaction between a conjugated diene and an alkene, commonly termed the dienophile, to form a cyclohexene system (Figure 1.1). Otto Diels and Kurt Alder were awarded the Nobel Prize in Chemistry in 1950 for their works on this reaction. When one or more heteroatoms are present in the diene and/or dienophile framework, the cycloaddition is called a hetero-Diels-Alder reaction.

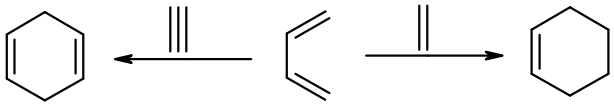
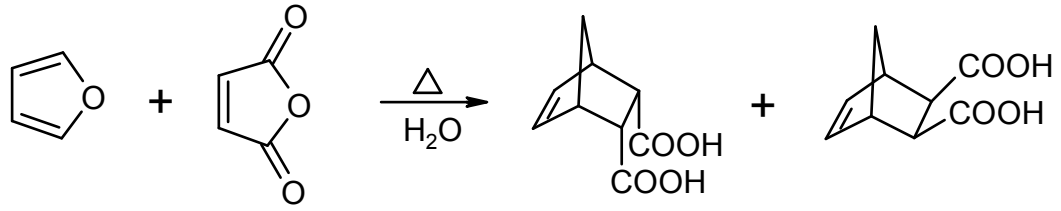


Figure 1.1

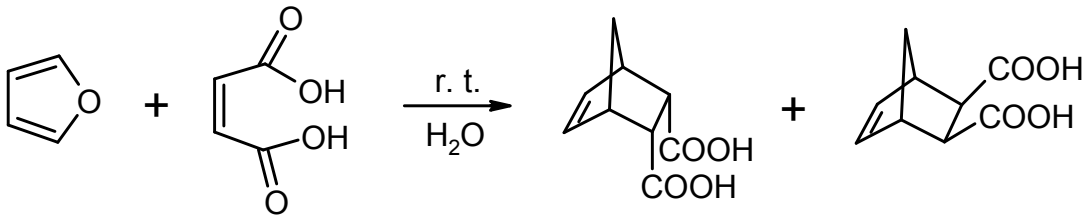
The reaction is classified as a $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition; '4' and '2' identify both the number of 'π' electrons involved in the electronic rearrangement and the number of atoms originating the unsaturated six-membered ring. The subscript 's' indicates that the reaction takes place suprafacially on both components.

Diels and Alder carried out the reactions of furan **(1)** with maleic anhydride **(2)** (Scheme 1.1) and with maleic acid **(4)** (Scheme 1.2) in water at high temperature and at room temperature, respectively.[1] The discovery of [4+2] π-cycloaddition reactions was followed by [2+2] π-, [4+4] π-, [3+2] π- cycloaddition reactions.[2]



1 **2** **3a** **3b**

Scheme 1.1



1 **4** **3a** **3b**

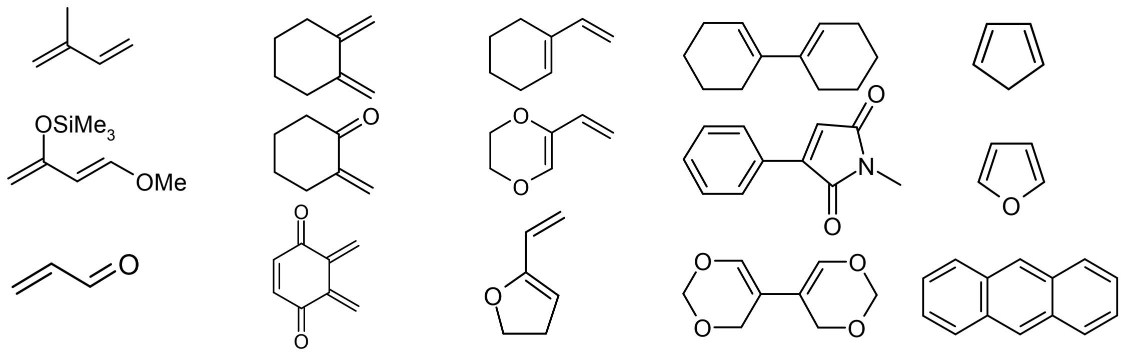
Scheme 1.2

1.1.1 Diene and dienophile

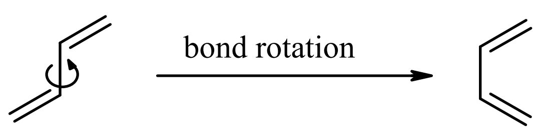
The diene component in Diels-Alder reaction can be open chain or cyclic and it can have many different kinds of substituents (Table 1.1).

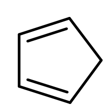
Table 1.1 Representative dienes

Open chain	Outer ring	Inner-outer ring	Across ring	Inner ring



One important feature of Diels-Alder reaction is that diene is required to be in the *s-cis* conformation in order for Diels-Alder reaction to work (Figure 1.2a). The s-*cis* conformation has both of the double bonds pointing on the same side of the C-C single bond that connects them. In solution, the C-C single bond in the diene that connects the two alkenes is constantly rotating, so at equilibrium there is usually some mixture of dienes in the s-*trans* conformation and some in the s-*cis* conformation. The ones that are at that moment in the s-*trans* conformation do not react; while the ones in the s-*cis* conformation can go on to react. Cyclic dienes that are permanently in the s-*cis* conformation are exceptionally good at Diels-Alder reactions-cyclopentadiene is a classic





“locked” s-*cis*
excellent diene

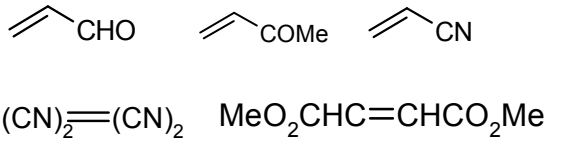
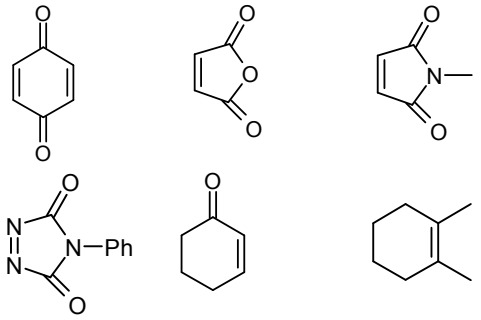
Figure 1.2a **Figure 1.2b**

example (Figure 1.2b). On the contrary, cyclic dienes that are permanently in the s-*trans* conformation and cannot adopt the s-*cis* conformation do not undergo Diels-Alder

reaction at all. The two ends of these dienes cannot get close enough to react with an alkene, and in any case, the product would have an improbable *trans* double bond in the new six membered ring.

In a typical Diels-Alder reaction, the dienophile has an electron-withdrawing group conjugated to the alkene (Table 1.2). Though common, this feature is not exclusive of Diels-Alder dienophiles. There must be some extra conjugation, at least a phenyl group or chlorine atom. The reaction between butadiene and a simple alkene (even ethylene) occurs in only poor yield.

Table 1.2 Representative dienophiles

Acyclic	Cyclic
	

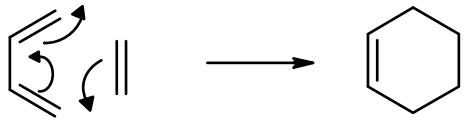
1.1.2 Mechanistic aspects

The process of bond breaking and bond formation in Diels-Alder reaction is considered to be concerted[3] but not necessarily synchronous.[4] However, the mechanism of Diels-Alder reaction has been a matter of debate. Especially the concertedness of the reaction, the existence of intermediates and the nature of the activated complex have been the subject of controversy.[3,5]

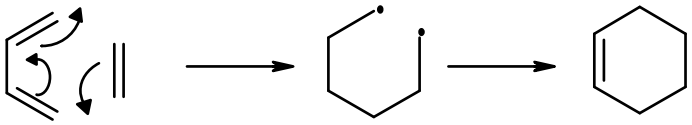
There are three possible mechanisms that have been considered for Diels-Alder reaction (Figure 1.3).[6] In mechanism ***a*** there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step. In mechanism ***b*** one

end of the diene fastens to one end of the dienophile first to give a diradical, and then, in a second step, the other ends become fastened. The third mechanism ***c*** is similar to mechanism **b**, but the initial bond and the subsequent bond are formed by movements of electron pairs and the intermediate is a diion..

Mechanism ***a***



Mechanism ***b***



Mechanism ***c***

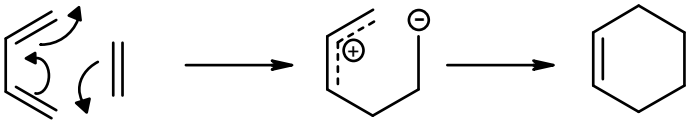
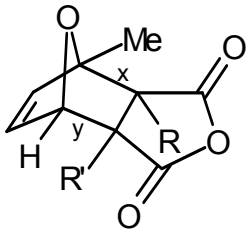


Figure 1.3

There have been many mechanistic investigations of Diels-Alder reaction. The bulk of the evidence suggests that most Diels-Alder reactions take place by the one-step cyclic mechanism **a**,[7,8,9] although it is possible that a biradical[10,11] or even a diion[12] mechanism may be taking place in some cases. The main evidence in support of mechanism **a** is as follows: (1) The reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration. (2) In general, the rates of Diels-Alder reactions depend very little on the nature of the solvent due to the involvement of isopolar activated complex.[13,14] This rules out a diion intermediate because polar solvents increase the rates of reactions that develop charges in the transition state. (3) It was shown that, in the decomposition of **5**,

the isotope effect k_I / k_{II} was equal to 1.00 within experimental error.[15,16] If bond x broke before bond y, then there should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of x and y is simultaneous.



I: R = H, R' = D
II: R = D, R' = H

5

The synchronous nature of the transition state in Diels-Alder reaction has also been a subject of controversy. When reactants are unsymmetrically substituted, when very reactive species are used or Lewis-acids are employed as catalysts, the reaction is less synchronous. Normal electron demand Diels-Alder reactions ($HOMO_{diene}$-$LUMO_{dienophile}$ interaction) are thought to have a higher degree of synchronous character than inverse electron demand Diels-Alder reactions ($HOMO_{dienophile}$-$LUMO_{diene}$ interaction)[17,18]. Eventually, this pattern may lead to one of the few examples of a stepwise or radical mechanism.[19,20]

A new development regarding the issue of concertedness has been formulated recently. On the basis of femtosecond-resolved mass spectroscopy, Zewail and coworkers suggested that Diels-Alder reactions did not have one single reaction pathway, but that several trajectories were simultaneously used.[21]

1.1.3 The frontier orbital description of cycloadditions

A cycloaddition reaction is allowed only when all overlaps between the highest-occupied molecular orbital (HOMO) of one reactant and the lowest-unoccupied

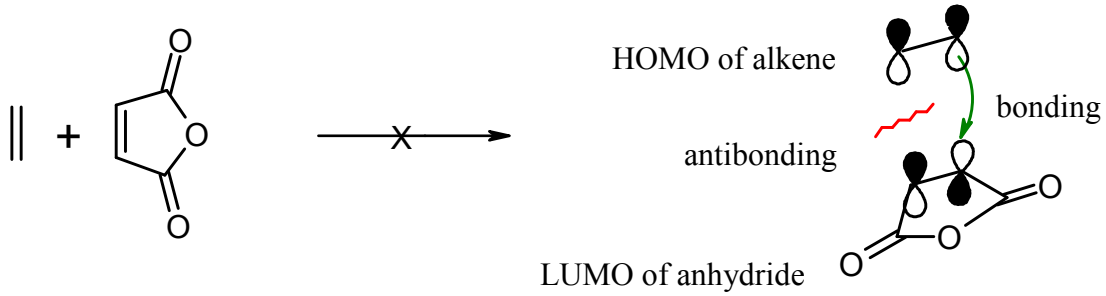


Figure 1.4

molecular orbital (LUMO) of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe. In case of [2+2]π-cycloaddition (Figure 1.4), lobes of HOMO in one molecule and that of LUMO in the other do not have corresponding signs and hence the reaction is thermally forbidden. On the other hand, Diels-Alder reaction (a [4+2] π-cycloaddition) is allowed, whether

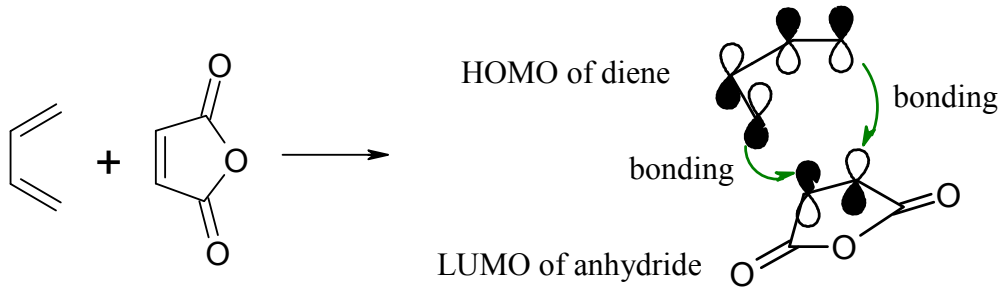


Figure 1.5

considered from either direction (Figure 1.5). The 1,4-lobes of butadiene HOMO match those in the LUMO of ethylene, the addition is thermally allowed.

Based on perturbation theory, Klopman[22] and Salem[23,24] have derived an expression for energy gain when the orbitals of one reactant interact with those of another. There are three terms that contribute to energy changes: the first is a closed shell repulsion (occupied orbitals of diene repel the occupied orbitals of dienophile), the second term is Coulombic repulsion and attraction (important for ionic reactions) and the third is the interaction of all filled orbitals with all the unfilled of correct symmetry (especially the HOMO of diene interacting with the LUMO of dienepholie that makes the largest contribution to equation 1.1). For a cycloaddition reaction the third term is defined as:

$$\Delta E = \sum_{r}^{occ}\sum_{s}^{unocc} - \sum_{r}^{unocc}\sum_{s}^{occ} \frac{2(\sum_{ab} c_{ra} c_{sb} \beta_{ab})^2}{E_r - E_s} \qquad (1.1)$$

where:

c_{ra} is the coefficient of atomic orbital a in molecular orbital r, where r refers to molecular orbitals of one molecule and s refers to those on the other.

E_r is the energy of molecular orbital r.

β_{ab} is the resonance integral; it is assumed to be proportional with the overlap integral S.

2 is the occupancy number (interaction involves two electrons).

According to frontier molecular orbital (FMO) theory the reactivity is correlated with the properties of highest filled and lowest vacant orbitals of the reacting molecules. The interaction energy described in equation (1.1) now is simplified to equation (1.2).

$$\Delta E = \frac{2(c^{diene}_{HOMO1} c^{dienophile}_{LUMO1} \beta_{11} + c^{diene}_{HOMO4} c^{dienophile}_{LUMO2} \beta_{24})^2}{E^{diene}_{HOMO} - E^{dienophile}_{LUMO}} +$$

$$\frac{2(c^{dienophile}_{HOMO1} c^{diene}_{LUMO1} \beta_{11} + c^{dienophile}_{HOMO2} c^{diene}_{LUMO4} \beta_{24})^2}{E^{dienophile}_{HOMO} - E^{diene}_{LUMO}} \qquad (1.2)$$

In practice it was noted that for numerous diene-dienophile, $E_{HOMO}^{diene} - E_{LUMO}^{dienophile}$ >> $E_{HOMO}^{dienophile} - E_{LUMO}^{diene}$, therefore ΔE becomes:

$$\Delta E = \frac{2(c_{HOMO1}^{diene} c_{LUMO1}^{dienophile} \beta_{11} + c_{HOMO4}^{diene} c_{LUMO2}^{dienophile} \beta_{24})^2}{E_{HOMO}^{diene} - E_{LUMO}^{dienophile}} \quad (1.3)$$

Thus, the larger are the coefficients and the smaller is the HOMO-LUMO energy gap, the lower is the activation energy for the respective Diels-Alder reaction (Figure 1.6).

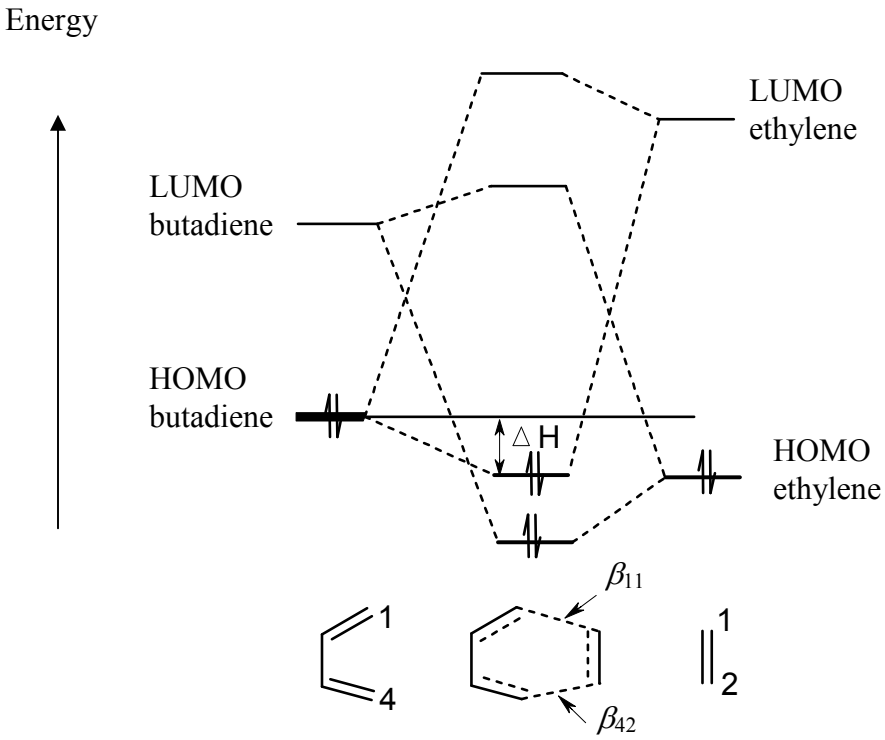


Figure 1.6 FMO interactions in Diels-Alder reactions.

1.1.4 Effect of substituents

An electron-releasing group (ERG) on the diene skeleton and electron withdrawing-group(s) (EWG) on dienophile make Diels-Alder reaction efficient and rapid. ERGs are "brining" up the diene's HOMO. EWGs are "brining" down the dienophile's LUMO (Figure 1.7). Because the energy gap is becoming smaller, ΔE is becoming larger (equation 1.3). The consequence of this effect is a dramatic increase in the rate of cycloaddition.

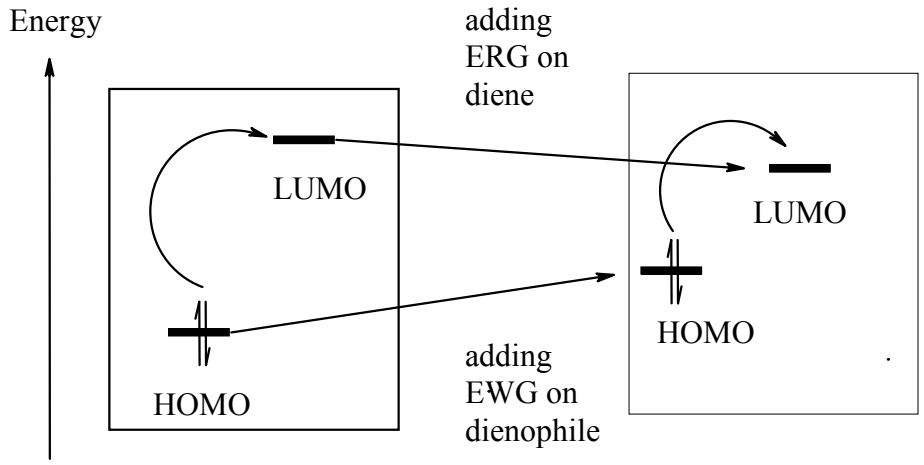
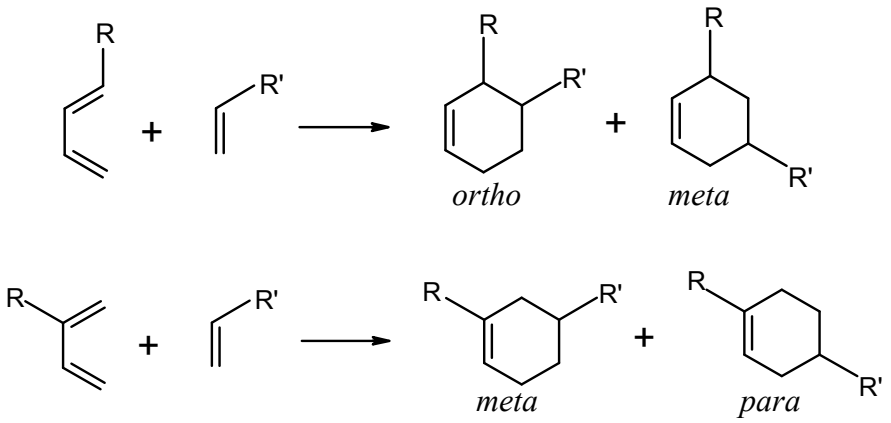


Figure 1.7 Substituents effect on the HOMO-LUMO energy gap.

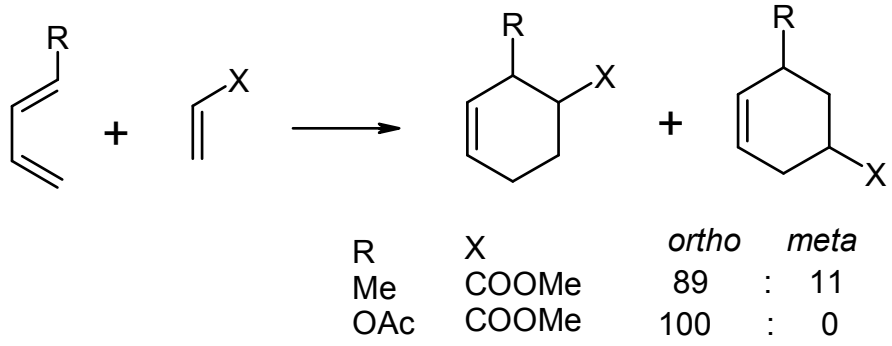
1.1.5 Regioselectivity

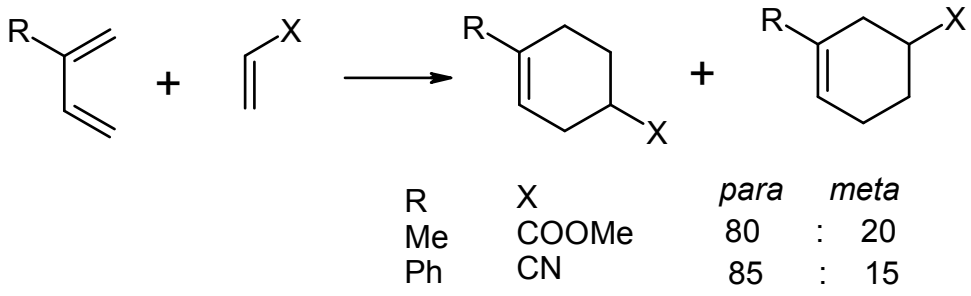
Diels-Alder reaction between an unsymmetrical diene and an unsymmetrical dienophile can lead to the formation of a mixture of regioisomers depending upon the relative orientation of the diene and the dienophile in the transition state. Dienes substituted in the 1-position can give a mixture of 1,2- (*ortho*-like) and 1,3- (*meta*-like) disubstituted cyclohexene. Similarly 2-substituted dienes can give a mixture of 1,3- (*meta*-like) and 1,4- (*para*-like) disubstituted cyclohexene (Scheme 1.3).



Scheme 1.3 Formation of regioisomers

Diels-Alder reaction is generally highly regoiselective and formation of *ortho* and *para* adducts predominate over *meta* adduct (Schemes 1.4 and 1.5).[25]





Schemes 1.4 and 1.5 Regioselectivity in Diels-Alder reactions

An acceptable explanation for the regioselectivity can be provided by examining the frontier orbitals of a dienophile and diene. If the reaction is uncatalyzed and there is a lack of strong solvent effect, a key factor in orienting the direction of the cycloaddition is the size of the coefficient on the individual atoms that are forming the new bonds. The new bonds are formed preferentially when "large-large" and "small-small" (Houk rule) overlap.[26] (Figure 1.8)

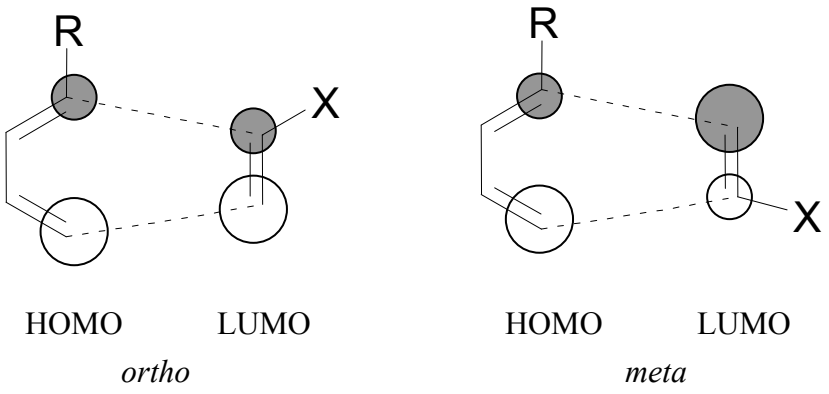
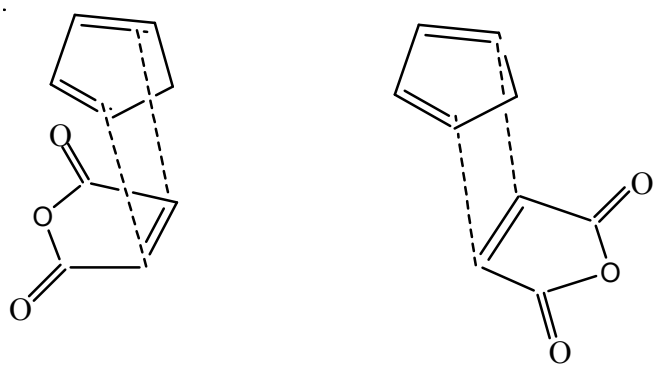


Figure 1.8 Orbital interactions leading to regoisomers

1.1.6 Diastereoselectivity

A cyclic diene may add to a dienophile, which is unsymmetrical about the C=C axis in two sterically distinct modes forming *endo* and *exo* isomers. They have the dienophile substituents respectively on the same side as the diene bridge and on the opposite side (Figure 1.9). In a wide variety of Diels-Alder reactions, the *endo* orientation is preferred. This is the basis of the *endo* rule or Alder *endo* rule.[27] According to Martin and Hill "*Endo* addition involves the tendency for dienophile substituents to be so oriented in the favored transition state that they lie directly above the residual unsaturation of the diene, whether for reasons of spatial orbital overlap or for reasons of steric accommodation. That transition state, which is best stabilized by spatial orbital overlap and simultaneously least destabilized by unfavorable steric repulsions has the

lowest free energy of all possible transition states, and consequently predominates in the kinetically determined product."[28]

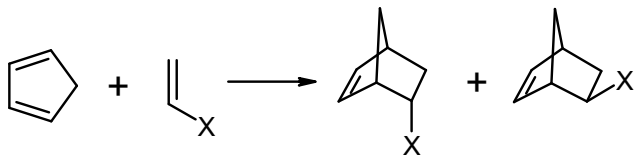


endo TS *exo* TS

Figure 1.9 Cyclopentadiene with maleic anhydride following Alder rule

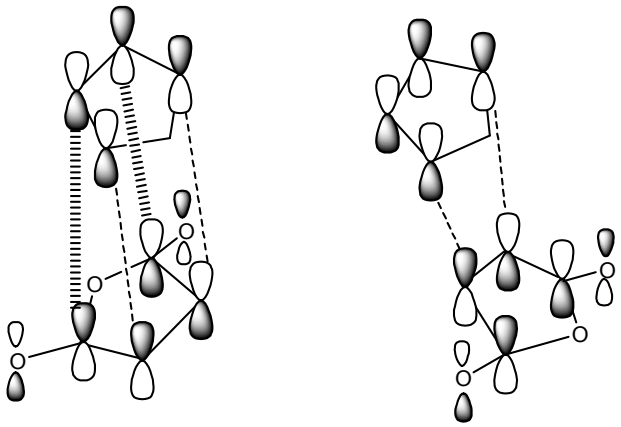
An *endo* transition is best observed in reactions with cyclic dienes such as cyclopentadiene where the *endo: exo* orientation is easily detected in the cycloadduct. Cyclopentadiene, for example, reacts to give an *endo* product (X group is 'under' the ring) and an *exo* product (X group is 'away' from the ring). As shown in Table 1.3, the *endo*-product is favored over the *exo*-product in every case.[28] In Table 1.3, both electron rich and electron poor alkenes exhibit *endo*-selectivity on reaction with cyclopentadiene.

Table 1.3 *Endo/exo* selectivity in Diels-Alder reactions of cyclopentadiene



X	*endo: exo*
COOH	75:25
COOMe	76:24
C≡N	60:40
OAc	81:19
CH_2OH	80:20

The Alder rule is explained by FMO theory, invoking secondary orbital interactions (SOI). A comparison of the *endo* transition state with the *exo* transition state (Figure 1.10) for the reaction of cyclopentadiene with maleic anhydride shows that in the *endo* transition state there is an additional bonding interaction between the carbonyl groups of the dienophile and the developing π-bond at the back of the diene.



endo *exo*

Figure 1.10

This interaction is absent in the *exo* transition state. This SOI stabilizes *endo* and lowers the energy of that transition state relative to *exo*.

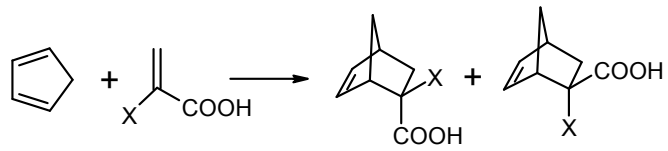
However, SOI hypothesis has been called into question by many researchers,[29-31] who have shown that the main arguments suggesting the existence of SOI are inconclusive. An *ab initio* study by Houk *et al.* has disproved the localization of a transition structure for the concerted mechanism leading to the major adduct, whereas the transition state corresponding to the stepwise pathway has been characterized.[32] Since these techniques have been successfully used in the characterization of the alternative mechanistic pathways of other cycloadditions,[3,33] it can be concluded that the formation of the *endo* adduct takes place through a stepwise mechanism. Considering that Woodward-Hoffmann rules are valid only for concerted reactions, SOI cannot be invoked for the cyclobutadiene dimerization.

The most striking corollaries of the hypothesis of SOI were obtained when an *exo* preference was predicted. Such a prediction was made for the [4+3]π- cycloaddition between butadiene and the allyl cation on the basis of $LUMO_{diene}$-$HOMO_{cation}$ repulsive interactions. However, both theoretical[34] and experimental results[35] agree with a stepwise mechanism. Therefore, SOI cannot play a role in the reaction of butadiene and allyl cation.

The assumed effects of SOI can instead be attributed to a combination of well-known interaction mechanisms such as solvent effects, steric interactions, hydrogen bonds and electrostatic forces (which will be discussed in detail in Chapter 3).[36]

In the addition of open-chain dienophiles to cyclic dienes, the *endo* rule is not always obeyed and the composition of the mixture obtained may depend on the precise structure of the dienophile and on the reaction conditions. Thus, in the addition of acrylic acid to cyclopentadiene the *endo* and *exo* products were obtained in the ratio 75: 25 but in the *α*-substituted acrylic acids, the product ratio varied depending on the nature of the group X (Table 1.4).[28]

Table 1.4 Proportion of *endo* and *exo* acids formed in addition of *α*-substituted acrylic acids to cyclopentadiene



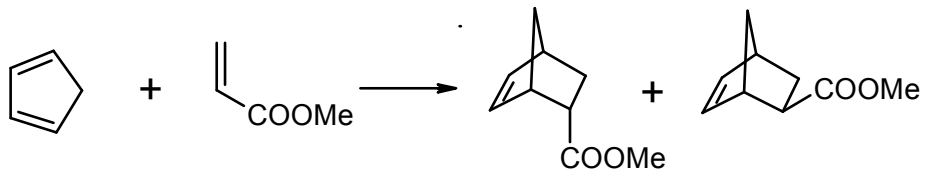
X	*% endo*	*% exo*
H	75	25
CH_3	35	65
C_2H_5	-	100
C_6H_5	60	40
Br	30	70

1.1.7 Effect of solvents

Conventionally most of the organic reactions are carried out in solution phase. The solution phase, that contains pure or mixed solvents, plays pivotal role in determining the course of reactions and amount of product formed. There are other parameters like temperature, pressure, concentration of reactants and stability of product that are also essential in governing the course of reactions. However, the change of a solvent in an organic reaction can bring about great changes in its kinetic profiles. There are several interesting properties of solvents, which may be considered significant in altering the reaction kinetics of organic reactions. The solvent media may promote or retard the reaction rates by stabilizing transition state. Polarity, dielectric constant, ionizing power, surface tension, viscosity, etc. of solvents can play crucial role in governing the kinetics of organic reactions in a specific manner.

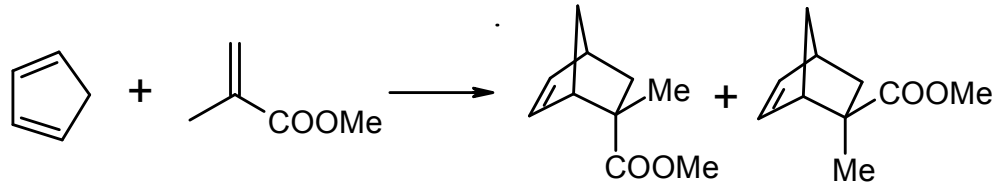
For a long time, solvent polarity was believed to have no effect on the course of a Diels-Alder reaction due to the involvement of isopolar activated complex.[6,13,14] Berson *et al.*, however, showed a clear relationship between *endo: exo* product ratio and solvent polarity in Diels-Alder reaction of cyclopentadiene **(6)** and acrylates[37] (Scheme 1.7-1.9). Thus, in the kinetically controlled addition of **6** to methyl acrylate **(7)**, methyl

methacrylate **(9)** and methyl *trans* crotonate **(11)** in different solvents, the proportion of *endo* product increased with the polarity of the solvent. In all cases mixtures of the *endo* and *exo* products were obtained. The reaction of **6** with **9** gave *exo* isomer as the predominant product under all experimental conditions. With **11** the *exo* adduct was predominant in some solvents (e.g. triethylamine at 30^0C) and the *endo* in others (ethanol, acetic acid) (Figure 1.11)



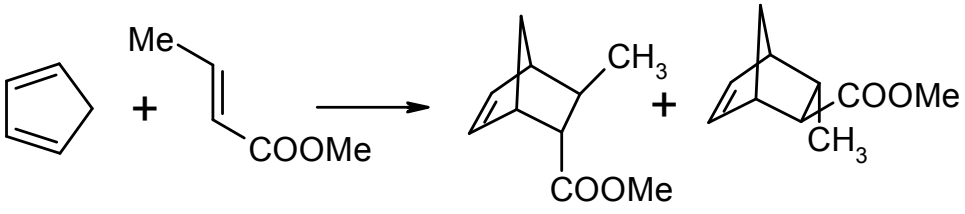
6 **7** **8a** **8b**

Scheme 1.7



6 **9** **10a** **10b**

Scheme 1.8



6 **11** **12a** **12b**

Scheme 1.9

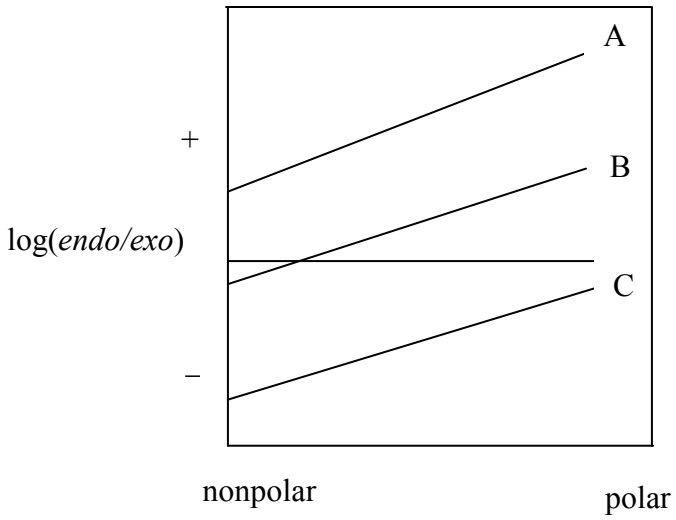
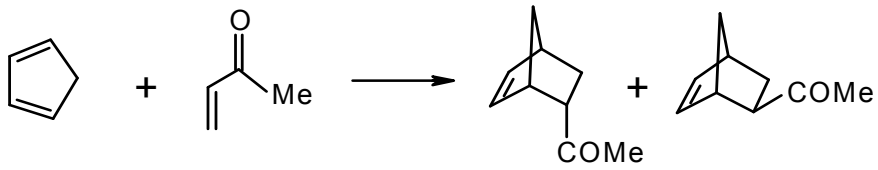


Figure 1.11 log (*endo/exo)* ratios as a function of polarities of solvents for the reactions of **6** with **7** (Scheme **1.7**) (curve A), with **11** (Scheme **1.9**) (curve B), with **9** (Scheme **1.8**) (curve C)

An empirical parameter Ω, a measure of solvent polarity, has been developed to explain the solvent effects on the variation in *endo: exo* ratios.[37] Later, A new solvent parameter, solvophobic power *Sp* developed by Abraham and coworkers was used to explain the rate variation in case of pure water, organic solvents and aqueous organic mixtures.[38] Schneider and Sangwan presented the first quantitative description of reaction rates as a function of *Sp*.[39] Since a single parameter could not explain the rate variation in a variety of solvent, a multiparameter approach was proposed involving a combination of various solvent parameters such as *Sp*, α (Hydrogen bond donor ability), β (Hydrogen bond acceptor ability), π^* *(*dipolarity-polarizability) etc. Cativiela *et al.* described the solvent effects using the various solvent parameters on rate profiles of Diels-Alder reactions in detail.[40]

1.1.8 Diels-Alder reactions promoted by water- hydrophobic effect

Diels-Alder reaction is one of the earliest examples of C-C bond formation reactions in aqueous media. Diels-Alder reactions in aqueous media were first carried out back in the 1930s.[41] But no particular attention was paid to this fact until 1980, when Rideout and Breslow[42] made the startling observation that the reaction of **6** with methyl vinyl ketone **(13)** (Scheme 1.10) in water was more than 700 times faster than the same



6 **13** **14a** **14b**

Scheme 1.10

reaction in 2,2,4-trimethylpentane. The reaction rate in methanol is comparable to that in a hydrocarbon solvent. Such an unusual acceleration of Diels-Alder reaction by water was attributed to the "hydrophobic effect",[43] in which the hydrophobic interactions brought together the two nonpolar groups in the transition state.

In addition, the hydrophobic binding of the diene and dienophile into a cyclodextrin cavity in water largely replaces the association because of the hydrophobic

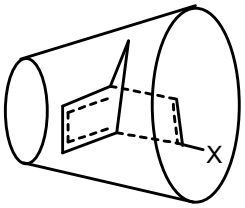
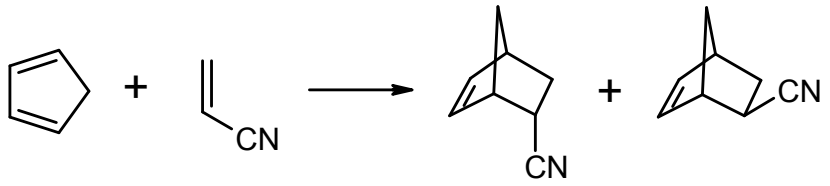


Figure 1.12 TS of Diels-Alder reaction in *β*-cyclodextrin cavity

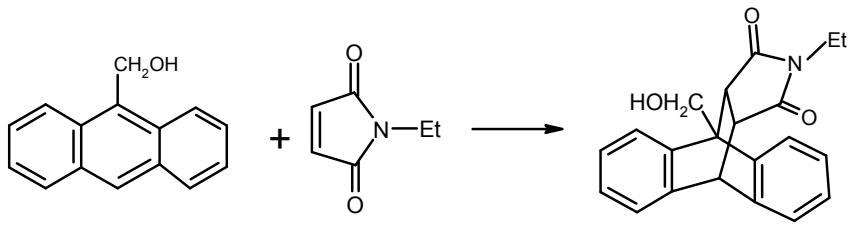
interaction. Therefore, the catalysis of Diels-Alder reactions with **6** occurs by mutual binding of the reagents in the cyclodextrin cavity, relative to the unassociated molecules. The use of β-cyclodextrin, which simultaneously forms an inclusion complex with the diene and dienophile (Figure 1.12), further enhances the rate of aqueous Diels-Alder reactions. On the other hand, the use of α-cyclodextrin decreases the rate of the reaction. This inhibition is explained by the fact that the relatively smaller cavity of α-cyclodextrin can only accommodate the binding of **6**, leaving no room for the dienophile.



6 **15** **16a** **16b**

Scheme 1.11

Diels-Alder reaction of **6** with acrylonitrile **(15)** (Scheme 1.11) shows only a small rate increase on changing the solvent from hydrocarbon to methanol but a much larger increase with water.[42] Again it seems likely that this large increase in water is not simply a polar effect in a reaction which shows little sensitivity to the polarity of the other two solvents but is a specific hydrophobic effect. The most striking evidence of this reaction comes from the study on Diels-Alder reaction of anthracene-9-carbinol **(17)** with *N*-ethylmaleimide **(18)** (Scheme 1.12).[42] This reaction is slower in polar solvents than it is in nonpolar hydrocarbon solvent, with the exception of water in which the rate is very fast. Only the hydrophobic effect seems capable of explaining this exceptional



17 **18** **19**

Scheme 1.12

behavior of water. In this case, the *β*-cyclodextrin became an inhibitor, rather than an activator, due to the even larger transition state, which cannot fit into its cavity.

Grieco *et al.* employed aqueous Diels-Alder reactions successfully in organic synthesis.[44-49] They extensively studied the reactivity of dienes containing hydrophilic carboxylates, or ammonium groups, as well as hetero Diels-Alder reactions of iminium ions in synthesising several bioactive natural products. Lubineau and coworkers further demonstrated the merits of water with respect to the rates and stereoselectivities of Diels-Alder reaction.[50-52]

The enhanced rates and selectivities of Diels-Alder reactions in water have been attributed to several other factors like hydrogen bonding, internal pressure etc. which will be discussed in detail in chapter 3.

1.2 The salting effect

The change in solubility of a nonelectrolyte in an aqueous solution, which results from the addition of an electrolyte, is known as the salting effect. Thus, there can either be an increase or a decrease in solubility of a nonelectrolyte with increasing concentrations of added electrolyte. They are known as salting-out and salting-in, respectively.[53-57] For the purpose of the definition, electrolytes and nonelectrolytes are the salts that have high and low solubilities, respectively. Mathematically, the influence of an electrolyte on the aqueous solubility of a nonelectrolyte can be expressed by the

physical equation for gases, commonly known as the Setschenow equation (Equation 1.4),[53] given below

$$\log s_o/s = \log f_c = kc_s \quad (1.4)$$

where s_o and s are the solubilities of the nonelectrolyte in water and electrolyte solution, respectively, c_s is the molar concentration of the electrolyte, f_c is the activity coefficient of the non electrolyte (expressed in concentration units), and k is the salting constant. A positive value for this constant indicates salting-out, and a negative value indicates salting-in behavior.

The effect of salts on kinetics of the protein denaturation and organic reactions in water has been discussed in terms of salting-out (rate-increasing) and salting-in (rate-inhibiting) phenomena.[58-60] It has been observed that salts like LiCl, NaCl, $CaCl_2$, $MgCl_2$, etc. are the salting-out agents in water, while guanidine chloride (GnCl), $LiClO_4$, urea, etc. the salting-in ones. Salting-out agents increase the hydrophobic effect, and they therefore decrease the solubility of hydrocarbons in water. Thus they increase the reaction rate as well as *endo/exo* ratios. Salting-in agents show opposite behavior. They increase the water solubility of hydrocarbons thereby, increasing the reaction rate as well as *endo/exo* ratios. Effect of ions on protein stability and organic reactions has been qualitatively ordered in a series known as Hofmeister series[61] as shown below:

Anions: $F^- \approx SO_4^{2-} > HPO_4^{2-} >$ acetate $> Cl^- > NO_3^- > Br^- > ClO_3^- > I^- > SCN^-$

Cations: $NH_4^+ > K^+ > Li^+ > Mg^{2+} > Ca^{2+} > Gn^+$

When salts like NaCl, LiCl etc. dissolve in water there is a volume contraction, electrostriction, as water collapses around the ions to solvate them.[60, 62] Thus there is less empty space for hydrocarbon solutes and the energy cost to create space for the hydrocarbons is greater. This can be thought of as the energy cost for cavitation, producing a hydrocarbon-sized hole in the solvent. Electrostriction increases the energy cost of cavitation.

On the other hand, when salts like GnCl, $LiClO_4$, etc dissolve in water that large ions (and the non-ionic molecule urea that is also a denaturant) break up the organized structure of water and make cavitation easier.[63]

In an effort to explain the rate accelerations of Diels-Alder reactions, it was suggested that the internal pressure[62,64] of the ionic solutions presses the diene and dienophile (hydrophobic packing) together to realize the reaction.[59] The rate data[65] for the reaction of **17** with **18** (Scheme 1.12) in 2 M solutions of several sodium and guanidine salts are observed to be linear with internal pressures of salt solutions.[66] The Diels-Alder reactions are accompanied by negative activation volumes, indicating a compact transition state.[67] Salts, like LiCl, NaCl, NaBr, etc., increase the internal pressure of water. The increased internal pressure in conjunction with the negative activation volume gives rise to the rate acceleration. The rate-declining effect by the guanidine salts can be explained in terms of reduced internal pressures and the negative activation volumes of Diels-Alder reactions.

An attempt was also made to divide the salting-out and -in zones on the basis of internal pressure.[68] In the case of the rate-enhancing salts, like LiCl, NaCl, etc., the phenomena of electrostriction caused by the volume contraction on dissolving an electrolyte in water assumes significance.[69,70] The electrostriction leads to a decrease in the solubilities of hydrocarbons, thus causing the salting-out and subsequently the rate enhancement. The antielectrostriction effect in GnCl or $LiClO_4$ gives rise to exactly the opposite effect. There are, however, opposing reports on the role of internal pressure.[71]

1.3 Effect of addition of co-solvents

The addition of hydrophilic cosolvents, for example alcohols in water, results in an additional rate enhancement in aqueous cosolvent media. Engberts *et al.* carried out the reaction of **6** with **13** (Scheme 1.10) over the whole mole fraction scale in MeOH-H_2O, EtOH-H_2O, 1-PrOH-H_2O and 1-BuOH-H_2O at 25°C.[72] The preference for the *endo* product was greatly enhanced in water: *endo:exo* = 10 (MeOH), 7 (t-BuOH) and 21 (H_2O). Similar results were obtained for ethyl vinyl ketone used as the dienophile.[72] Solvent effects on rate constants reveal differences in interactions of the solvent with the

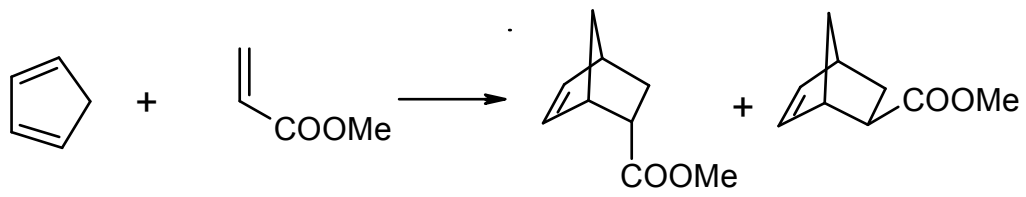
initial state (IS) and the activated complex (AC)**.** Pseudothermodynamic analysis allows a distinction between both effects. In this analysis, the difference in $\Delta^{\neq}G^{*}$ for reaction in the solvents S_1 and S_2, is combined with Gibbs activation energies for transfer of the substrate (S) from S_1 to S_2. The IS **(6 + 13)** is strongly destabilized in the water-rich region ($x(H_2O) > 0.8$). This effect is dominated by the contribution of the rather hydrophobic **6,** but the hydrophobicity of **13** is revealed by the positive $\Delta G^{0}_{1\rightarrow 2}$ as well. By contrast, there are only minor changes in $\Delta G^{0}_{1\rightarrow 2}$ for the AC over the whole solvent composition range. These results imply that the rate acceleration in water and in the water-rich mixtures is primarily caused by destabilization of the IS relative to the AC**.**[73] In the absence of substrate association, two factors are of major importance in determining this difference in solvation behavior of the IS and AC**.** The first is hydrogen-bonding; the AC is more polarized than the IS, and the polarized carbonyl moiety of the AC will be better stabilized by hydrogen-bonding than the carbonyl group of the IS. This enhanced hydrogen-bonding of water to the AC was also proposed on the basis of Monte Carlo simulations [74] and *ab initio* MO calculations [75] and is in line with the relatively high rates of Diels-Alder reactions in TFE (1,1,1-Trifluoroethanol) and HFP (1,1,1,6,6,6-Hexafluoro-2-propanol).

The second effect involves enforced hydrophobic interaction. The activation process of the concerted cycloaddition reaction involves a reduction of the hydrophobic surface area of the reaction partners, leading to a gain in Gibbs activation energy relative to nonaqueous solvents. This effect is not equivalent to "hydrophobic packing" of diene and dienophile in water, which may well lead to a complex with a geometry different from that of the AC**.** The term ‘enforced’ is employed to stress that the hydrophobic interactions are operative as they are an integral part of the activation process. Engberts and co-workers introduced the concept of enforced hydrophobic hydration. In this process the hydrophobicity of diene and dienophile is decreased during the process of activation. Diene and dienophile do not aggregate spontaneously under the reaction conditions. This observation is expressed by the term ‘enforced’. To account for the large effect of water on Diels-Alder reactions, the enforced hydrophobic binding process is more favorable in water than in conventional organic solvents. On the basis of the Gibbs energy associated with the direct diene-dienophile pair potential and the rearrangement of

water molecules accompanying the enforced hydrophobic hydration, it is possible to state that the reduction of the hydrophobic surface and hydrated volume during the activation process leads to a large gain of the entropy and a large loss of the enthalpy of water molecules.[76] The studies have shown that both an unfavorable enthalpy contribution and a larger favorable entropy contribution lead to the reduction of free energy of the activation process.

1.4 Lewis acid catalysis of Diels-Alder reaction

The coordination of a Lewis acid to the lone pair of electrons on the hetero atom of the dienophile makes the dienophile more electron deficient. The energy of the HOMO and LUMO of the dienophile is decreased compared to the uncomplexed dienophile and hence the $HOMO_{diene}$-$LUMO_{dienophile}$ energy gap is decreased. As a result of the decrease in the HOMO-LUMO gap the rate is enhanced. The most commonly employed Lewis acids are $BF_3.Et_2O$, $AlCl_3$, $TiCl_4$, $SnCl_4$, hydrolytically stable lanthanide triflates, lithium percholarates etc. The Lewis acid catalysed Diels-Alder reaction can be generally carried out at room temperature or at lower temperatures compared to the uncatalysed reaction which often require refluxing conditions in a benzene or toluene medium. Apart from the rate acceleration the catalysed reactions also show enhanced regio and stereoselectivities which can be ascribed to the changes in the coefficients of the MOs compared to the uncatalysed dienophile. Yates and Eaton reported the rate acceleration of Diels-Alder reactions of anthracene with various dienophiles catalysed by anhydrous aluminium chloride.[77] Sauer has investigated the effect of various Lewis acids on the *endo/exo* selectivity of the addition of **9** to **6**.[78,79] The reaction catalysed by anhydrous $AlCl_3$ showed much higher *endo* selectivity than the uncatalysed reaction (Scheme 1.13)



6 **9** **10a** **10b**

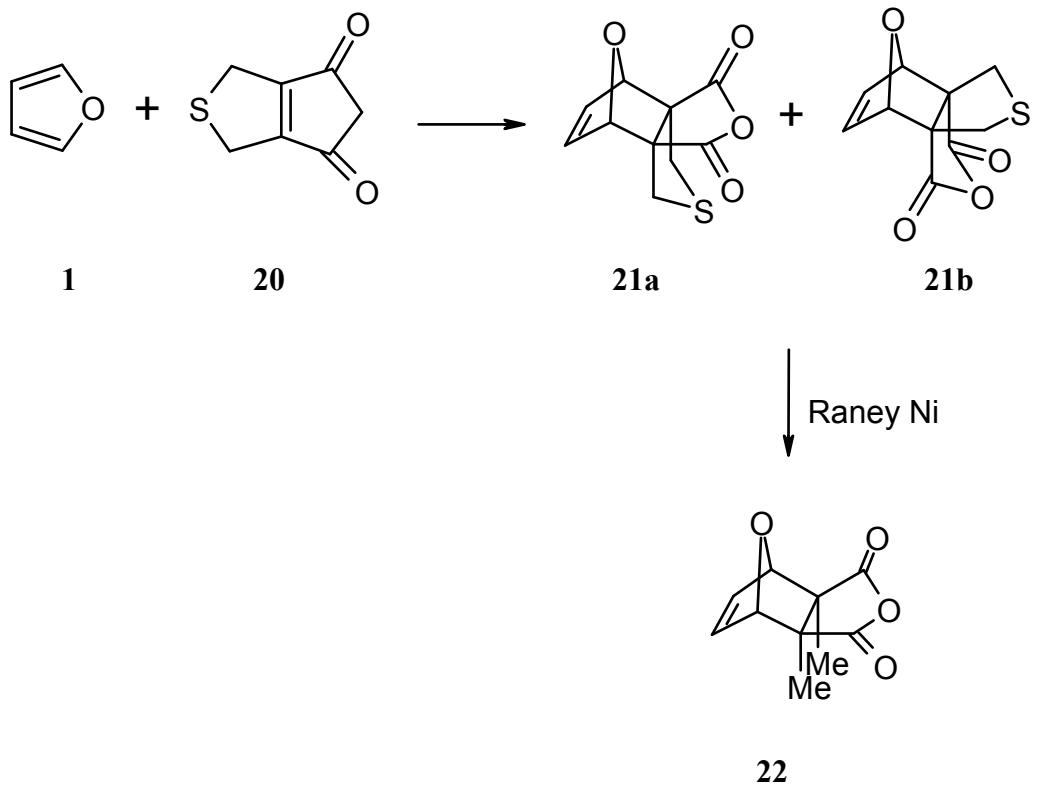
		endo: exo
0^0C, uncatalysed,	22.5%	82: 18
-78^0C, $AlCl_3.Et_2O$,	81%	97: 3

Scheme 1.13 Effect of Lewis acid catalysis on the selectivity of Diels-Alder reaction

A 5 M solution of lithium perchlorate in anhydrous diethyl ether (5 M LPDE) as reaction medium has been introduced by Winstein *et al.* for carrying out the ionization reaction of *p*-methoxyneophyl *p*-toluenesulphonate.[80] Later, the exhaustive investigations have been carried out by Pocker *et al.* on the use of LPDE during the ionization of triphenylmethyl chloride and many other reactions in 5 M LPDE.[81] The rate of ionization reaction was faster by 7 x 10^9 times in 5 M LPDE as compared to that in diethyl ether alone. The rearrangement of 1-phenylallyl chloride to cinnamyl chloride was also enhanced by 10^4 times in 5 M LPDE solution.[82] Similar rate accelerations were observed by Kumar and Pawar while examining various Diels-Alder recations in LPDE in concentration range up to 6.06 M.[83] The spectacular rate enhancement by LPDE-mediated organic reactions was ascribed to electrostatic catalysis by ionic aggregates.[84-86]

Sauer *et al* [87] were the first one to recognize the advantage of using a solution of 4 M LPDE for carrying out the Diels-Alder reaction between **6** and **7** (Scheme 1.7). They observed increased *endo* selectivity compared to that in ether. Later, Grieco *et al.* applied 5 M LPDE for carrying out several organic transformations.[88] Initially the effect of 5 M LPDE was explained on the basis of the pressure effect of the highly ionic medium on organic solutes. However, later investigations have shown clearly that lithium ion acts as

a Lewis acid in catalysing many reactions carried out in this medium.[71] Lithium perchlorate has also been used with other organic solvents like THF, acetone etc. to promote Diels-Alder reactions.[89-91] The most striking example of a Diels-Alder reaction carried out in 5 M LPDE is the addition of **1** to the maleic anhydride derivative **(20)** (Scheme 1.14). The cycloadduct is a crucial intermediate in the synthesis of cantharidin **(22)**.[88] In the absence of any catalyst this reaction proceeds only at high pressures as reported by Dauben.[92] The sluggishness of this reaction is due to the aromatic nature of furan and to the dienophile being a tetrasubstituted olefin. In LPDE medium the reaction proceeds smoothly at ambient conditions and gives the adducts in good yield.



1 **20** **21a** **21b** **22**

Scheme 1.14 Synthesis of cantharidin by Diels-Alder reaction

These reactions, if carried out in LPDE solutions of concentrations higher than 5 M, show a substantial decrease in these kinetic parameters. This decrease is attributed to the very high viscosity of LPDE solutions near saturation.[93] To quantify the effect of

LPDE, the reaction of **6** with ethyl acrylate was carried in LPDE solutions of different concentrations. A 26-time increase in the reaction rates was observed in 5 M LPDE compared to that in pure diethyl ether. However, the reaction rate began to fall above 5.5 M LPDE. The *endo: exo* ratio of 8.1:1 in 5 M LPDE, reduced to 5.2:1 in 6 M LPDE. The viscosity of 5 M LPDE increases by about 15 times as compared to that of pure diethyl ether. Further, the viscosity of 6.07 M LPDE is surprisingly enhanced by about 800 times as compared to pure diethyl ether.[94] This very high viscosity of 6.07 M LPDE retards the reaction rate above 5 M LPDE.

Based on the NMR spectroscopic studies Pocker and co-workers have shown that, lithium perchlorate forms a 1:2 etherate ($LiClO_4.2Et_2O$) below 4.25 M concentration and a mixture of 2:1 and 1:1 etherates above 4.25 M.[95] According to Kabalka and co-workers, based on spectroscopic and chemical evidence, the increased rates of reaction of certain Diels-Alder reactions and high selectivities are due to the mild Lewis acidity of the lithium ion in ether.[71] According to these authors, the strong and intrinsic Lewis acidity of lithium ion is moderated in diethyl ether due to its complexation with the solvent and the counter ion. Forman and Dailey[96] and Righetti and co-workers[97] have also shown that the rate enhancement of Diels-Alder reactions is due to Lewis acid catalysis by the lithium ion. Apart from the Lewis acidity of the lithium ion, the increased polarity of the medium also plays a role in the rate enhancement.[87] Various organic transformations using LPDE have been discussed by Sankararaman *et al.*[98]

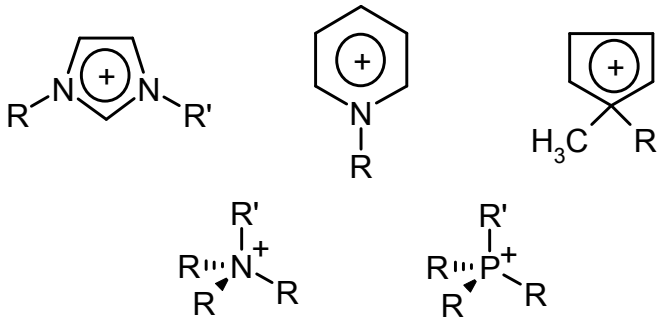
1.5 Ionic liquids

Today's environmental concerns demand clean reaction processes that do not use harmful organic solvents and minimize chemical waste. In view of environmental pollution caused by the use of volatile organic solvents, there is a greater need to replace them by environmentally benign solvents. In this regard, ionic liquids have emerged as important substitutes for several organic reactions.

Ionic liquids are salts composed wholly of ions (organic cation and organic or inorganic anion).[99] The ions are poorly coordinated, which results in these solvents being

liquid below 100^0C, or even at room temperature which are known as room temperature ionic liquids. At least one ion has a delocalized charge and one component is organic, which prevents the formation of a stable crystal lattice. Examples of some common cations and anions that are used to synthesize ionic liquids are listed in Figure 1.13.

Some typical cations



Some typical anions

$[AlCl_4]^-$, $[Al_2Cl_7]^-$, $[(CF_3SO_2)_2N]^-$, $[CF_3SO_2N]^-$,

$[CF_3COO]^-$, $[PF_6]^-$, $[BF_4]^-$, $[SbF_6]^-$, $[RSO_3]^-$

Figure 1.13 Typical cations and anions of ionic liquids

The Pollution Prevention Act of 1990 in the United States established a national policy to prevent or reduce pollution at its source whenever feasible. The Pollution Prevention Act also provided an opportunity to expand beyond traditional Environmental Protection Agency (EPA) programs and devise creative strategies to protect human health and the environment. Green chemistry is the use of chemistry for pollution prevention. More specifically, green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Green chemistry is a highly effective approach to pollution prevention because it applies innovative scientific

solutions to real-world environmental situations. The 12 principles of green chemistry, originally published by Paul Anastas and John Warner provide a road map for chemists to implement green chemistry.[100] Promoting this new approach to pollution prevention through the environmentally conscious design of chemical products and processes is the focus of EPA's Green Chemistry Program, an initiative under the EPA's Design for the Environment Program. The principles cover such concepts as:

(1) The design of processes to maximise the amount of raw material that ends up in the product.
(2) The use of safe, environmentally benign solvents where possible.
(3) The design of energy efficient processes.
(4) The best form of waste disposal, aiming not to create it in the first place.

Many ionic liquids have been developed for specific synthetic problems. For this reason, ionic liquids have been termed "designer solvents". Ionic liquids are considered green solvents in substituting many volatile organic solvents as they possess some special properties like:

(1) They are relatively nonvolatile and hence do not produce atmospheric volatile organic compounds (VOCs) and can be used in low-pressure (vacuum) environments.
(2) They are nonflammable.
(3) They possess good solvating power for a wide variety of organic and inorganic compounds.
(4) They can be considered both a polar and a noncoordinating solvent.
(5) They are the most complex and versatile of solvents in that they have the ability to interact via hydrogen bonding, π–π, n–π, dispersive, dipolar, electrostatic, and hydrophobic interactions.
(6) They can be immiscible with nonpolar organic solvents and/or water.
(7) They have physicochemical properties that can be altered / controlled by judicious selection of the cation and / or anion.
(8) Since ionic liquids can be synthesized by metathesis reaction, a range of task specific ionic liquids can be synthesized.
(9) Most importantly they can be recycled for a number of times without loss of activity.

Ionic liquids enjoy a plethora of applications in various domains of physical sciences. For example, they are used as "solvents" for organic, organometallic syntheses and catalysis, as electrolytes in electrochemistry, in fuel and solar cells, as lubricants, as a stationary phase for chromatography, as matrices for mass spectrometry, supports for the immobilization of enzymes, in separation technologies, as liquid crystals, templates for the synthesis of mesoporous, nano-materials and ordered films, materials for embalming and tissue preservation, etc.[101]

1.5.1 Physicochemical properties

Ionic liquids possess a unique array of physico-chemical properties that make them suitable in numerous task-specific applications in which conventional solvents are non-applicable or insufficiently effective. Such properties include:

1. Melting Point: The solid-liquid transition temperatures of ionic liquids can be below ambient and as low as 100^0C. The structure of an ionic liquid has a direct impact upon its properties, in particular the melting point and liquidus ranges. The charge, size and distribution of charge on the respective ions are the main factors that influence the melting points of the salts. The dominant force in ionic liquids is Coulombic attraction between ions. The Coulombic attraction term is given by equation 1.5:

$$E_c = Mz^+z^- / 4\pi\varepsilon_o r \qquad (1.5)$$

Where $z^+$and z^- are the ion charges and r is the inter-ion separation.

The overall lattice energies of ionic solids thus depend on (i) the product of the net ion charges, (ii) ion-ion separation, and (iii) packing efficiency of the ions (reflected in the Madelung constant, M). Thus, low-melting salts should be most preferred when the charges on the ions are ±1 and when the sizes of the ions are large, thus ensuring that the inter-ion separation (r) is also large. In addition, large ions permit charge delocalization, further reducing overall charge density.

Melting points of organic salts have an important relationship to the symmetry of organic cations.[102,103] Increasing symmetry in the ions increases melting points, by permitting more efficient ion-ion packing in the crystal cell. A change from spherical or high-symmetry ions such as Na^+ or $[NMe_4]^+$ to lower-symmetry ions such as imidazolium cations distorts the Coulombic charge distribution. In addition, cations such as the imidazolium cations contain alkyl groups that do not participate in charge delocalization.

2. Viscosity: The viscosity of ionic liquids is normally higher than that of common molecular solvents. Ionic liquid viscosities at room temperature range from a low of around 10 cP to values in excess of 500 cP. There are several factors affecting ionic liquid viscosities such as temperature, ion sizes, impurities etc.

a) Effect of temperature- Viscosities of ionic liquids decrease with the increase in temperature. For example, the viscosity of 1-butyl-3-methyl imidazolium hexafluorophosphate [BMIM][PF_6] decreases by about 27 % as the temperature changes from 293 K to 298 K.[104]

(b) Effect of impurities- Small amount of impurities can have a large effect on the viscosities of ionic liquids. A recent study[105] indicates that the chloride impurities in the ionic liquids increase the viscosity, while the presence of water or other cosolvents decreases the viscosity. The increase of viscosity with increasing concentration of chloride in [BMIM][BF_4] is related to an increase in the cohesive forces *via* hydrogen bonding between the chloride and the protons of the imidazolium ring.

(c) Effect of ion sizes: Within a series of non-haloaluminate ionic liquids containing the same cation, a change in the anion clearly affects the viscosity. The general order of increasing viscosity with respect to the anion is: $[(CF_3SO_2)_2N]^- < [BF_4]^- < [CF_3CO_2]^- < [CF_3SO_3]^- < [(C_2H_5SO_2)_2N]^- < [C_3F_7CO_2]^- < [CH_3CO_2]^- < [CH_3SO_3]^- < [C_4F_9SO_3]^-$. Obviously, this trend does not exactly correlate with anion size. This may be due to some other properties such as their ability to form weak hydrogen bonds with the cation. The viscosities of ionic liquids are also affected by the identity of the organic cation. For ionic liquids with the same anion, the trend is that larger alkyl substituents on the imidazolium cation give rise to more viscous fluids.

3. Conductivity: Since ionic liquids are composed entirely of ions, they are expected to possess very high conductivities. Conductivity of ionic liquids is mostly of the order of 10^{-1} Sm^{-1} at ambient temperatures, less conductive than concentrated aqueous electrolytes. The explanation for this observation was based on the reduction of available charge carriers due to ion pairing and/or ion aggregation and to the reduced ion mobility due to the large ion size. Parameters such as viscosity and density of liquid, ion size and degree of dissociation affect the conductivity. So it is rather difficult to estimate the contribution of each parameter to the conductivity of an ionic liquid. However, proportionality between the conductivity and inverse of the viscosity has been observed for several liquids in a wide temperature range.[106]

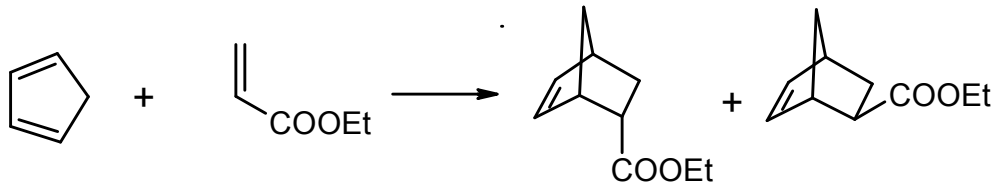
4. Polarity: Different combinations of anions and cations produce solvents with different polarities. No ionic liquids have shown themselves to be "super-polar"; regardless of the method used to assess their polarities, ionic liquids come within the range of molecular solvents. Most general measures of overall polarity place ionic liquids in the range of the short- to medium-chain alcohols.

Since measurement of dielectric constant requires a non conducting medium, it is not possible in the case of ionic liquids. Therefore, the polarity scales for ionic liquids have been suggested by using various methods such as absorption spectra, fluorescence spectra, refractive index, organic reactions as probe etc. More systematical polarity studies of 1-alkyl-3-methylimidazolium type ionic liquids have been reported by the Seddon research group.[107] In their research, the wavelength of maximum absorption (λmax) was measured and the molar transition energies (ENR) were calculated for solvatochromic dye Nile Red dissolved in the ionic liquids. In this case, the smaller value of ENR indicates stronger polarity a solvent has. The polarity of $[BMIM]^+$ type slats declines with the increasing size of anions NO_2^-, NO_3^-, BF_4^-, and PF_6^-. This is due to the dispersal of negative charge on the anion, and thus less charge is available for interactions with solute Nile Red.

1.5.2 Diels-Alder reactions in ionic liquids

Neutral ionic liquids have been found to be suitable solvents for Diels-Alder reaction. The first study was of the reaction of 6 with 7 and 13 in ethylammonium nitrate (EAN), $[EtNH_3][NO_3]$.[108] EAN gave *endo* selectivity enhancements for the reactions of **6** with **7** and **13**, and a rate enhancement for the former, relative to nonpolar organic solvents. Although Diels-Alder reactions are found to be faster in water than in room temperature ionic liquids,[108] EAN should be superior to water as a reaction medium in at least one respect: in general, neutral organic compounds are more soluble in EAN than in water. Therefore, unlike the situation with the latter, reactions can be performed on a synthetically useful scale in EAN under homogeneous conditions with perhaps greater reproducibility from run to run. Later on its (EAN) use was restricted due to its explosive nature.

Earle *et al*. compared the rates and selectivities of reactions between ethyl acrylate **(23)** and **6** (Scheme 1.15) in different ionic liquids.[109] They found that the reaction in $[BMIM][PF_6]$ was slightly faster than in water, but slower than in 5 M LPDE. The *endo*: *exo* selectivity in the ionic liquid was comparable to the LPDE (8:1).



6 **23** **24a** **24b**

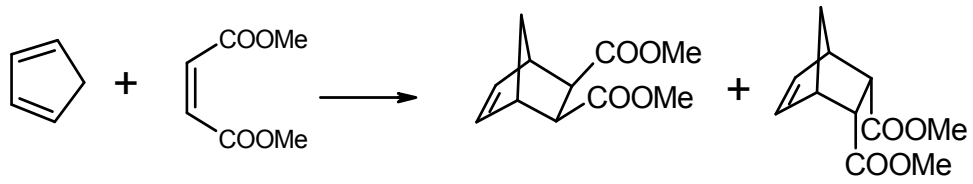
Scheme 1.15

Welton *et al.* tested different ionic liquids as solvents for the addition of **6** and **7** (Scheme 1.7). They were able to show that the used ionic liquids controlled the *endo: exo* ratios through a hydrogen bond interaction with the electron-withdrawing group of the

dienophile.[110] The effect was slightly weaker in these ionic liquids than EAN, and this may be due to stronger (N-H) hydrogen bonding leading to stronger solvophobic effects in EAN.

Chloroaluminate ionic liquids composed of $AlCl_3$ and organic cations can promote a variety of organic reactions. The composition of these chloroaluminate ionic liquids governs the acidity and basicity of solvent media, in which the reactions are carried out. Wilkes in a recent article outlined the historical development in the area of ionic liquids.[111]

The utility of room temperature chloroaluminate ionic liquids as solvent and catalyst for the synthetically important Diels-Alder reaction has been studied by Lee.[112] Diels-Alder reactions of **6** with **7** (Scheme 1.7) was investigated in $AlCl_3$:BPC (*N*-butylpyridinium chloride) and $AlCl_3$:EMIC (1-ethyl-3-methyl imidazolium chloride). A dramatic enhancement in *endo*: *exo* ratios (9:1) in the acidic melt (51 % $AlCl_3$) was noted as compared to 4.88:1 obtained in the basic melt (48 % $AlCl_3$). The observed *endo* selectivity enhancement in the 51 % melt is a direct result of the increase in Lewis/Bronsted acidity of the medium, while the observed 5:1 *endo: exo* product ratio in the basic melt is a reflection of the polarity of the medium. Efforts were also made to carry out the reaction of **6** with dimethyl maleate **(25)** with quite similar results (Scheme 1.16).



6 **25** **26a** **26b**

Scheme 1.16

Exo-selective reaction of **6** with **9** (Scheme 1.8) was converted into *endo*-selective by employing chloroaluminate ionic liquids as solvent media.[113] In 45 % $AlCl_3$:BPC 26 % *endo* products were observed. The *endo* products were enhanced by about 3 times in

60 % $AlCl_3$:BPC. When 60 % $AlCl_3$:EMIC was used, a 4 fold increase was observed in *endo* products than that in 45 % $AlCl_3$:EMIC. The applications of chloroaluminates as reaction media have been reviewed by Kumar and Sarma.[114]

Recently, Tiwari and Kumar have demonstrated experimentally that Diels-Alder reactions proceed faster in water than in ionic liquids.[115] Diels-Alder reactions of **6** and variety of acrylates were carried out in ionic liquids such as [EMIM][BF_4], [BMIM][BF_4], [BMIM][PF_6], [OMIM][PF_6] and [BMIM]I. They clearly demonstrated that water is a more powerful solvent than ionic liquids in promoting Diels-Alder reactions.

1.6 Rare earth metal triflates

Lewis acid catalysis has been of great interest in organic synthesis. While various kinds of Lewis acid-promoted reactions have been developed, and many have been applied in industry, these reactions must be generally carried out under strictly anhydrous conditions. The presence of even a small amount of water inhibits the reaction, because most Lewis acids immediately react with water rather than the substrates and decompose. This has restricted the use of Lewis acids in organic synthesis. However, it has been found that rare earth metal trifluoromethanesulfonates (triflates) such as $Sc(OTf)_3$, $Yb(OTf)_3$, etc. can be used as water-stable Lewis acids in water containing solvents.[116]

Lanthanide compounds are expected to act as strong Lewis acids because of their hard character and to have strong affinity toward carbonyl oxygens.[117] Among these compounds, lanthanide triflates are expected to be one of the strongest Lewis acids because of the electron-withdrawing trifluoromethanesulfonyl group. On the other hand, their hydrolysis is postulated to be slow, based on their hydration energies and hydrolysis constants. In fact, while most metal triflates are prepared under strict anhydrous conditions, lanthanide triflates are reported to be prepared in aqueous solution as shown below (Equation 1.6),

$$M_2O_3 + 6\ TfOH \longrightarrow 2\ M(OTf)_3 + 3H_2O \qquad (1.6)$$

M= Sc, Ln, etc. (*ca* 50% $TfOH/H_2O$)
Tf = trifluoromethanesulfonyl

Very interestingly, almost 100% of lanthanide triflates can be easily recovered from the aqueous layer after the reaction is completed and can be reused.(Figure 1.14)

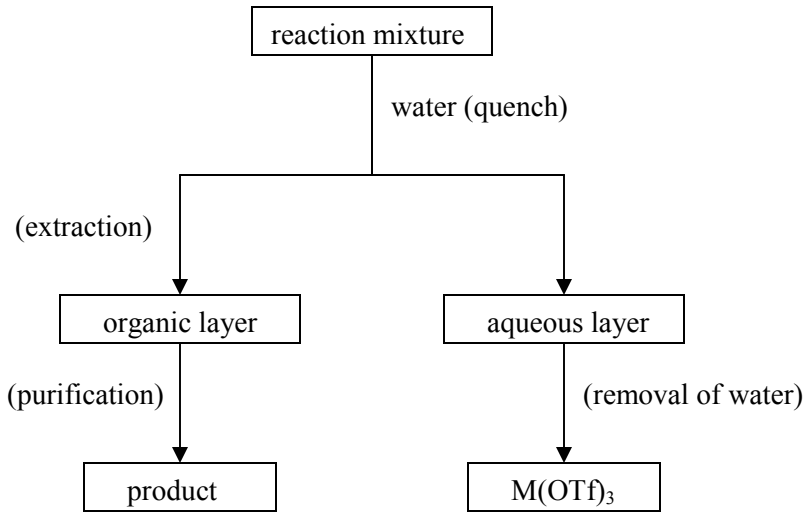
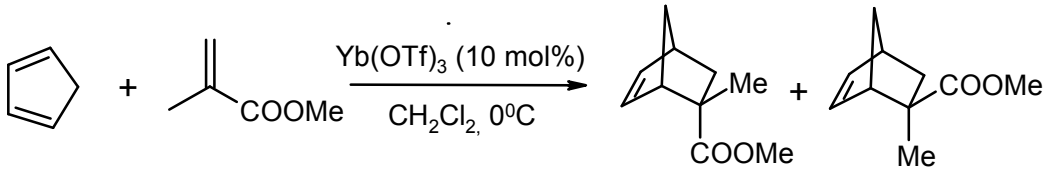


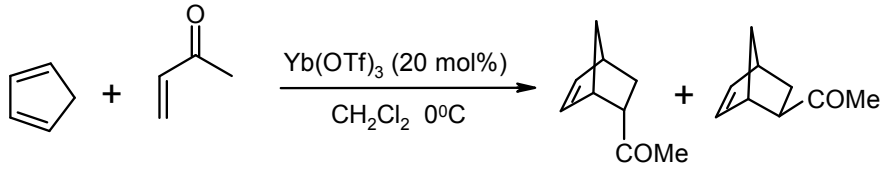
Figure 1.14 Recovery of the catalyst



6 **27** **28a** **28b**

endo:exo=7:93

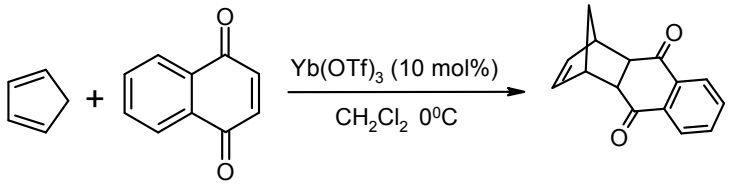
Scheme 1.17



6 **13** **14a** **14b**

endo:exo=90:10

Scheme 1.18



6 **29** **30**

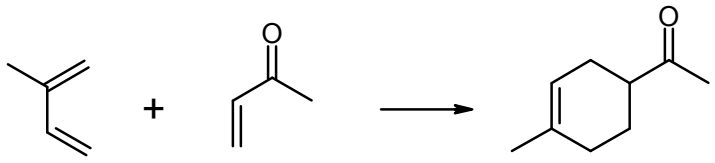
endo:exo=100:0

Scheme 1.19

Lanthanide triflates are found to be efficient catalysts in Diels-Alder reactions of carbonyl-containing dienophiles with **6** (Schemes 1.17-1.19).[118] A catalytic amount of

$Yb(OTf)_3$ is enough to promote the reactions to give the corresponding adducts in high yields.

In Diels-Alder reactions, $Sc(OTf)_3$ is more effective than the lanthanide triflates as a catalyst.[119] While in the presence of 10 mol% of $Y(OTf)_3$ or $Yb(OTf)_3$, only a trace amount of the adduct is obtained in Diels-Alder reaction of **13** with isoprene **(31)**, the reaction proceeds quite smoothly to give the adduct **32** in a 91% yield in the presence of 10 mol% of $Sc(OTf)_3$.



31 **13** **32**

Scheme 1.20

The present Diels-Alder reactions proceed even in aqueous media. Thus, naphthoquinone **(29)** reacts with **6** (Scheme 1.19) in THF-H_2O (9:1) at room temperature to give the corresponding adduct in a 93% yield with 100% *endo* selectivity. After the reaction is completed, the aqueous phase is concentrated to give the catalyst. The yields of the second and third runs are comparable to that of the first run.

1.7 Asymmetric synthesis

Asymmetric Synthesis deals with synthesis of chiral molecules, which are non-superimposable on its mirror images. The word *chiral* comes from the Greek word '*cheir',* which means hand. The chirality can also be referred in wider context. For example, a hand and a foot are chiral and fulfill the same criterion as a chiral molecule. A left hand is a mirror image of the right hand and these cannot be superimposed. Thus, hands are chiral. So, chirality is referred to as handedness. If an organic molecule is chiral,

it exists as a mixture of non-superimposable mirror image isomers, which are called *enantiomers*. They are given names (*R*) and (*S*) based on certain defined rules.

In 1894, Emil Fischer clearly outlined the concept of asymmetric synthesis based upon his experiments in the conversion of one sugar to its higher homolog via the cyanohydrin reaction, relating this process directly to the biochemical process for the production of optically active sugars in plants.[120] Many drugs and other chemicals come in these two forms, which often behave very differently; one may be active while the other is inactive or even harmful. Thalidomide is a frightening example. It is a chiral molecule, thus every dose of it contained two different forms of the drug. Both are made up of same atoms, but position of the atoms is different (disposition in space). Pregnant women in Europe in the early 1960s took it for the benefit (sedative in this case) of one form but their children suffered from the effects (teratogen in this case) of the other. Since then, the regulatory agency of all the countries framed a law that if a drug molecule is chiral, each enantiomeric form should be synthesized and tested separately before approval is given for its use. In other words, it should be shown that none of the form is harmful. This led to a major emphasis in the development of new methods (enantioselective reactions) for synthesis of one mirror image isomer (enantiomer) in a highly selective manner. In fact, three scientists- Dr. William S. Knowles, Prof. R. Noyori, and Prof. K.B. Sharpless shared the Nobel Prize in the year 2001 for their contribution in this area.

The most quoted definition of an asymmetric synthesis is that of Marckwald: "Asymmetric syntheses are those which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials, but with the avoidance of any separation."[121] Eliel proposed the following criteria for judging an asymmetric synthesis:[122]

1. The synthesis must be highly stereoselective: If we consider the synthesis of a substance (A_1), which can have another stereoisomer (A_2), starting from a pure compound (X), then following consequences may occur,

(1) $X \longrightarrow A_1\,(100\%)$

(2) $X \longrightarrow A_1\,(\text{excess}) + A_2 \quad \text{or} \quad A_2\,(\text{excess}) + A_1$

(3) $X \longrightarrow A_1\,(50\%) + A_2\,(50\%)$

In these cases, (1) is said to be 100% stereoselective, (2) is less stereoselective and (3) indicates that reaction has no stereochemical control.

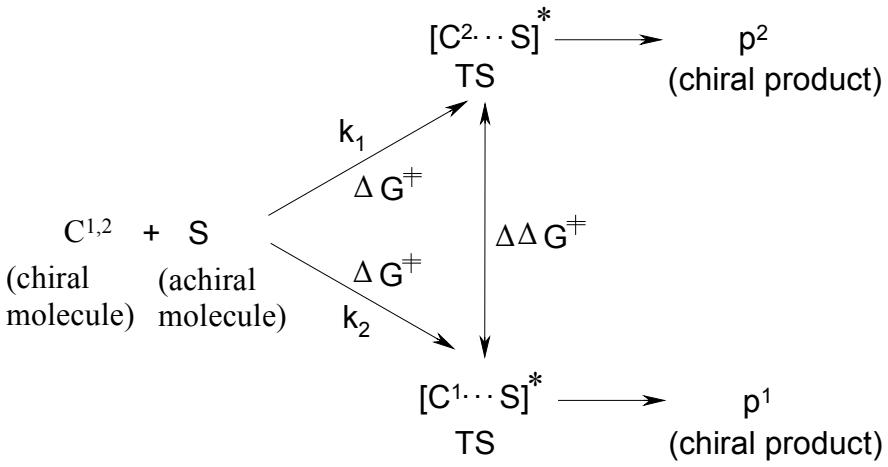
2. If the chiral auxiliary is an integral part of the starting material, the chiral center generated in the asymmetric synthesis must be readily separable from the auxiliary without racemization.

3. The chiral auxiliary or reagent must be recoverable in good yield and without racemization.

4. The chiral auxiliary or catalyst should be readily and inexpensively available in enantiomerically pure form.

In light of recent developments that are not addressed by the Markwald definition, a broader definition is appropriate: "Asymmetric Synthesis is a reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substance. The stereoslelectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substance."

Asymmetric synthesis has long been a coveted goal for organic chemists. Unfortunately, the extensive efforts attempting to design efficient asymmetric syntheses have not borne fruit in proportion to the efforts expended. The reasons for this are many, but the single most important reason lies in the lack of understanding and control of transition-state geometry. It is this phenomenon which solely dictates which reaction profile (p^1 or p^2) will predominate. The ratio p^1/p^2 is a function of the relative rate constants, k_l, k_2, leading to the respective diastereomeric transition states (Scheme 1.21). Thus, identical or comparable reaction rates for each process will result in racemic or only slightly enriched enantiomeric excess of the desired product, neither of which is of any value to the desired goals. Since the competing processes are dependent on the free energy of activation ($\Delta G^{\ddagger}$) for each of them, the magnitude of the differences in this term ($\Delta\Delta G^{\ddagger}$) will be solely responsible for the ratio of enantiomeric products (p^1, p^2). A $\Delta\Delta G^{\ddagger}$ value of approximately 2 kcal at 0^0C is considered necessary to provide one of the enantiomeric products (p^1 or p^2) in at least an 80% excess (90:10 mixture of enantiomers), and this ratio may be construed as synthetically useful.[123]



Scheme 1.21

1.7.1 Enantiomeric excess (*ee*)

Enantiomeric excess is defined as the excess of one enantiomer over the other, expressed as a percentage of the whole. It exists where one enantiomer is present more than the other in a chemical substance. Such a mixture of two enantiomers, unlike a racemic mixture, shows a net optical rotation. It is possible to determine the specific rotation of the mixture and then knowing the specific rotation of the enantiomer in excess we can determine the enantiomeric excess.

$$\text{Enantiomeric excess} = \frac{\text{Specific rotation of the mixture}}{\text{Specific rotation of the pure enantiomer in excess}} \times 100$$

The enantiomeric excess can be determined in another way if we know the amount of each enantiomer produced.

$$\text{Enantiomeric excess} = \frac{\text{moles of major enantiomer} \quad \text{moles of other enantiomer}}{\text{Total moles of both enantiomers}} \times 100$$

For mixtures of diastereomers the same treatment leads to diastereomeric excess (de). The term enantiomeric excess was first introduced in 1971 by Morrison and Mosher.[124]

The use of enantiomeric excess has established itself because of its historic ties with optical rotation. It has recently been suggested that the concept of *ee* should be replaced by that of enantiomeric ratio or *er* (S:R) or *q* (S/R) because determination of optical purity has been replaced by other techniques which directly measure R and S and because it simplifies many mathematical treatments. The same arguments are valid for changing *de* to diasteromeric ratio (*dr*).[125] Direct determination of these quantities is possible with NMR spectroscopy and chiral column chromatography.

NMR spectroscopic method: In the 1960s, a number of discoveries were made that facilitated the direct observation of diastereomeric and enantiomeric mixtures by NMR. The development of chiral derivatizing agents, lanthanide shift reagents, and chiral solvating agents made it possible to observe separate signals for enantiomers.

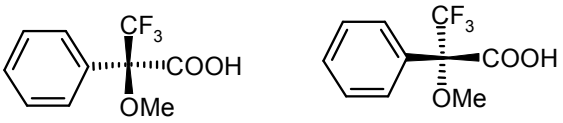
Chiral Derivatizing Agents (CDAs): The derivatization of a mixture of enantiomers with a chiral reagent produces diastereomers that may be analyzed by NMR spectroscopy. In order to be useful, a number of requirements must be met:

1. The CDA must be enantiomerically pure.
2. The reaction of the CDA with both enantiomers must go to completion under the reaction conditions.
3. The CDA must not racemize under the derivatization or analysis conditions, and its attachment should be mild enough so that the substrate does not racemize either.
4. The CDA should have a functional group that gives a singlet and that is remote from other signals for easy integration

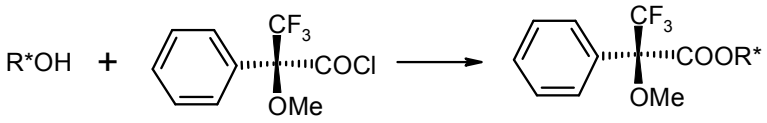
$$\text{Analyte (R + S) + CDA (R')} \longrightarrow \text{Diastereomeric derivatives R-R' + S-R'} \qquad (1.7)$$

Equation 1.7 illustrates the derivatization of a mixture of R and S enantiomers of analyte with an enantiomerically pure derivatizing agent R'. If the reaction is complete

for both enantiomers of analyte, the ratio of diastereomeric derivatives R-R' and S-R' will equal the ratio of enantiomers R and S of the analyte. Although a number of CDAs have been developed over the years, by far the most popular is Mosher's acid, α-methoxy-α-(trifluoromethyl)phenylaceticacid (MTPA) **(33)**. It is commercially available in either enantiomeric form, and is used for derivatization of alcohols and amines.



(R)- 33 **(S)- 33**



Scheme 1.22 Application of Mosher's acid.

Chromatographic method: A very commonly used method for the analysis of mixtures of enantiomers is chiral GC.[126,127] In addition to being quick and simple, this sensitive method is normally unaffected by trace impurities. The method is based on the principle that molecular association between the chiral stationary phase and the sample may lead to some chiral recognition and sufficient resolution of the enantiomers. The chiral stationary phase contains an auxiliary resolving agent of high enantiomeric purity. The enantiomers to be analysed undergo rapid and reversible diastereomeric interactions with the stationary phase and hence may be eluted at different rates (indicated as t_R, the retention time).

Another important method of determining enantiomeric excess is high performance liquid chromatography (HPLC). In HPLC, a large variety of analyte types have been resolved on columns packed with derivatized cellulose. Cellulose acetate, benzoate, and carbamate derivatives provide chiral stationary phases (CSPs) that will separate a very broad range of analyte types. Separation is achieved by donor-acceptor interactions, with inclusion phenomena sometimes playing a secondary role.

Microcrystalline cellulose triacetate, cyclodextrin- and crown ether-derived CSPs, as well as some chiral synthetic polymers, achieve enantiomeric separation primarily by forming host-guest complexes with the analyte; in these cases, donor-acceptor interactions are secondary.

1.7.2 Asymmetric induction

In asymmetric synthesis chirality can be induced in a reaction either by using external chiral agent or by using some chiral auxiliary, which is an integral part of the starting material. In the chiral auxiliary strategy (I) An enantiomerically pure compound (usually derived from a simple natural product like an amino acid), called a chiral auxiliary, is attached to the starting material, (II) A diastereoselective reaction is carried out, which, because of the enantiomeric purity of the chiral auxiliary, gives only one enantiomer of the product. (III) The chiral auxiliary is removed by, for example, hydrolysis, leaving the product of the reaction as a single enantiomer. The chiral auxiliaries can be recycled, so although stoichiometric quantities are needed, there is no waste.

1.8 Asymmetric Diels-Alder reaction

The historical development of the asymmetric Diels-Alder reaction begins with auxiliary- based methods for (covalently) modifying the cycloaddition reactants, and has now progressed through chiral (stoichiometric) catalysts, to true catalysts that are efficient in both enantioselectivity and turnover. Thus the development of Diels-Alder reaction is a microcosm of the field of asymmetric synthesis itself.[128]

Dienophile auxiliaries: In general, cycloadditions catalysed by Lewis acids proceed at significantly lower temperatures and with higher selectivities than their uncatalysed counterparts. Factors that contribute to the increased selectivity of the catalysed reactions include lower temperatures and more organized transition states. Coordination of a Lewis acid to the enone carbonyl not only activates the enone by electron withdrawal, it also

restricts conformational motion and thereby reduces the number of competing transition states. Figure 1.15 illustrates several chiral auxiliaries for dienophile modification that have been used in Diels-Alder reaction.

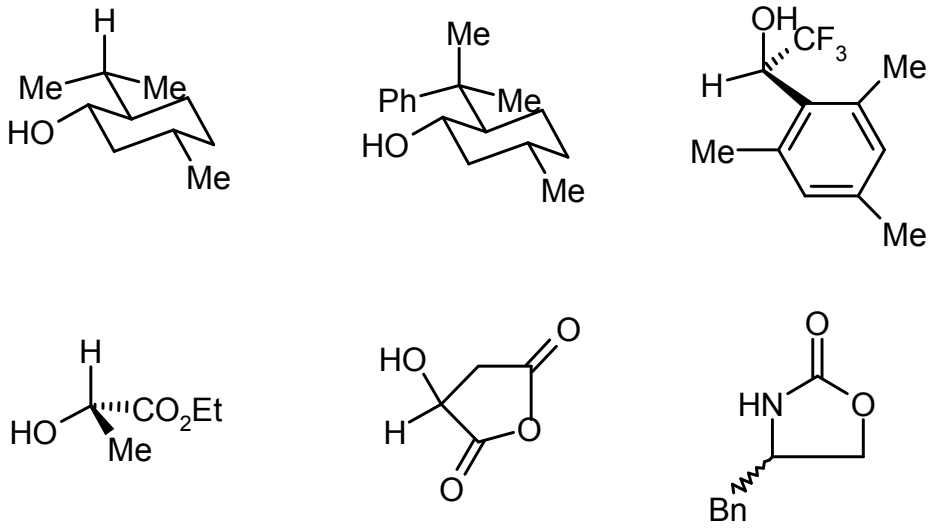
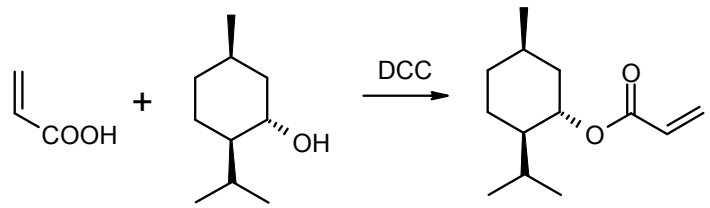


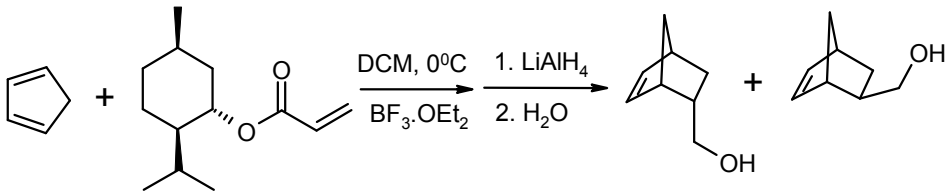
Figure 1.15 Dienophile chiral auxiliaries

One of the most common auxiliaries is menthol **(35)**, where an acrylic acid **(34)** derivative is attached to form a menthyl ester **(36)** (Scheme 1.23). The reaction of **6** with **36** (Scheme 1.24) gave **37a** and **37b**, after reduction of the ester products with lithium aluminium hydride, with good enantioselectivity.[124]



34 **35** **36**

Scheme 1.23

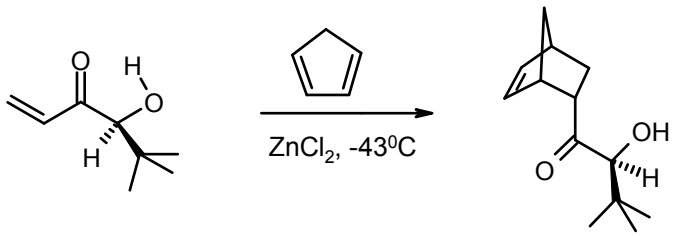


6 **36** **37a** **37b**

74% *ee*

Scheme 1.24

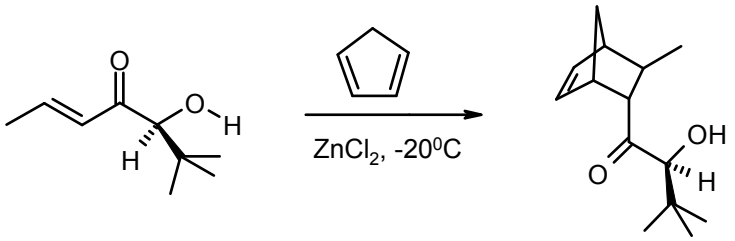
The compound **38** reacts with **6** in the presence of $ZnCl_2$ at -43^{0}C, affording exclusively *endo*-adduct **39**. Similarly, compound **40**, a homologue of **38**, undergoes a Diels-Alder reaction giving compound **41** with similar high stereoselectivity. (Schemes 1.25-1.26) [129,130]



38

39
endo:exo = 15:1
de > 100 for *endo*

Scheme 1.25

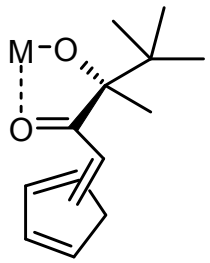


40

41
endo:exo = 15:1
de > 100 for *endo*

Scheme 1.26

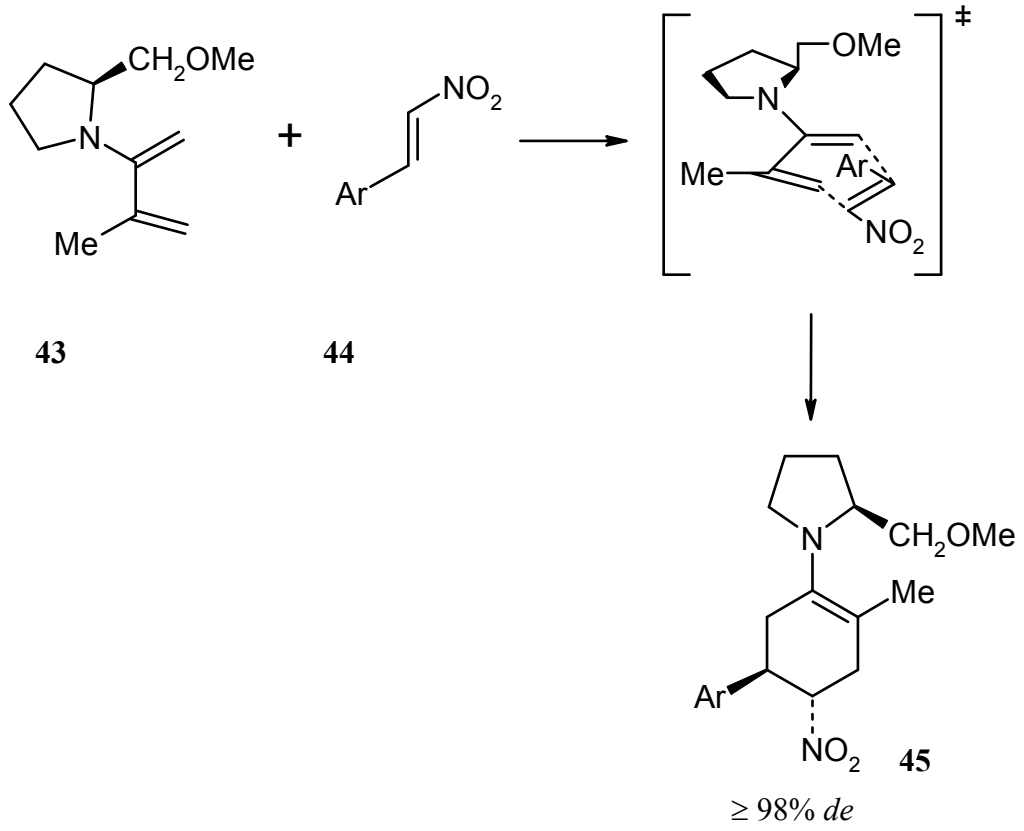
The high enantioselectivity shown in the above reactions can be attributed to two important factors. First, coordination of the Lewis acid with the α-hydroxy ketone moiety of dienophile **38** or **40** leads to the formation of a rigid five-membered chelate **42**. This chelate causes the differentiation of the two diastereotopic faces of the enone system. Second, arising from the established absolute configuration of **38** and **40**, within **42**, Diels-Alder reaction proceeds with the enone fragment at its *cisoid* position (*syn*-planar).



42

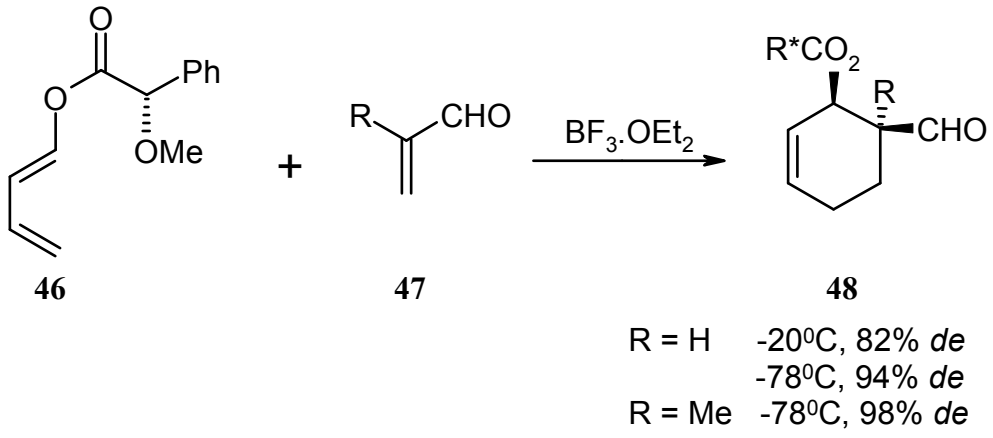
In Oppolzer's review, a variety of chiral auxiliaries related to **35** and other chiral alcohols were presented, giving the enantiomeric *endo* adducts with good to excellent selectivity.[131] Because of the different conditions (Lewis acid, temperature, solvent) used for each of these auxiliaries, it is difficult to determine the "most selective" auxiliary. Indeed, considerations such as easy of separability and reaction scale are important factors in selecting an auxiliary for any given application.

Diene auxiliaries: In comparison to the large amount of work on chiral dienophiles for the asymmetric Diels-Alder reaction, there have been very few reports of chiral auxiliaries for the diene component. This may be due to the lack of convenient methods for the synthesis of modified dienes. Scheme 1.27 illustrates an asymmetric cycloaddition of an enamine diene **(43)**.[132]



Scheme 1.27 Asymmetric Diels-Alder reaction of dienamine

A more generally useful chiral auxiliary was introduced by Trost.[133] The original diastereoselectivity reported for addition to acrolein was 82% at -20^{0}C (Scheme 1.28), but Thornton later reported 94% de at -78^{0}C.[134]



Scheme 1.28 Asymmetric Diels-Alder reaction of *o*-methylmandelate

Chiral catalysts: Quite a number of ligand/metal combinations have been evaluated as chiral catalysts for Diels-Alder reaction, with several being very successful. Much of the effort has been occupied in ligand synthesis and design, but the effort has largely been empirically driven (i.e., trial and error). Figure 1.16 shows several complexes that have been tested as catalysts in Diels-Alder reaction and which show both high diastereoselectivity and high enantioselectivity. Among the metals, the most commonly used are boron and titanium, but copper[135,136], magnesium[137], and lanthanides[138,139] have also found some use. Additional references and other Lewis acid catalysts can be found in recent reviews.[140,141]

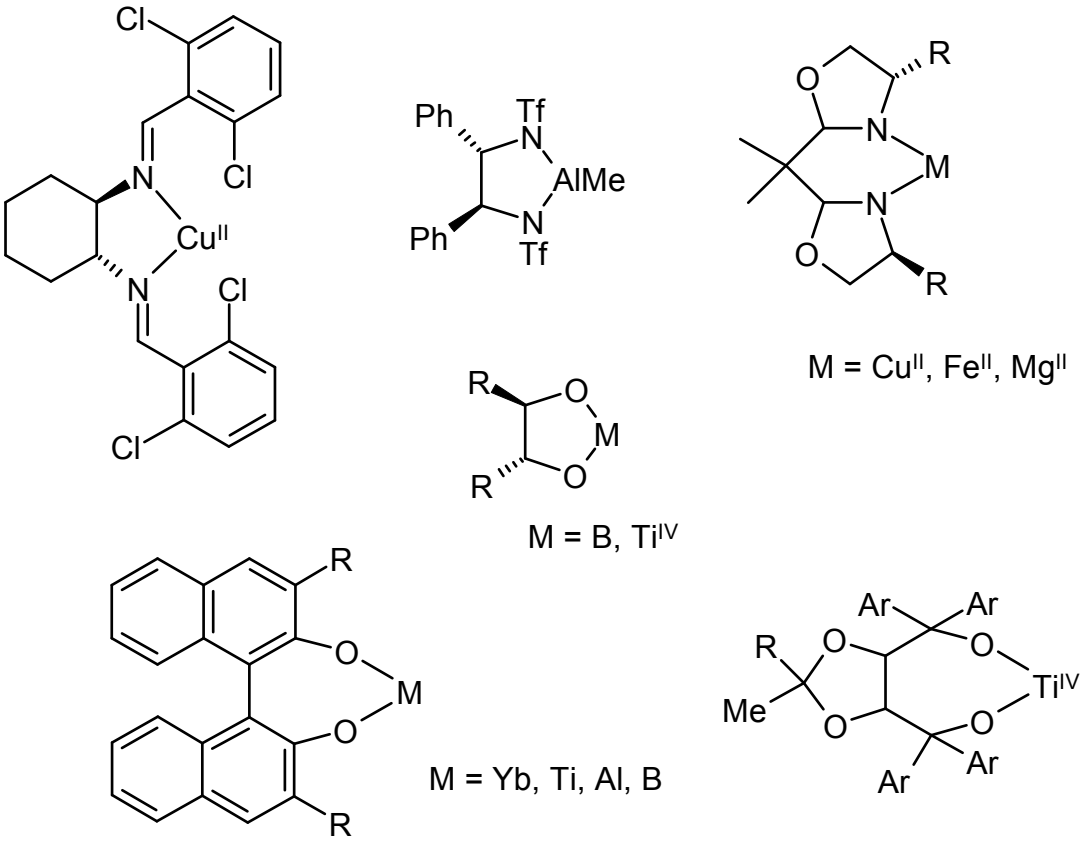
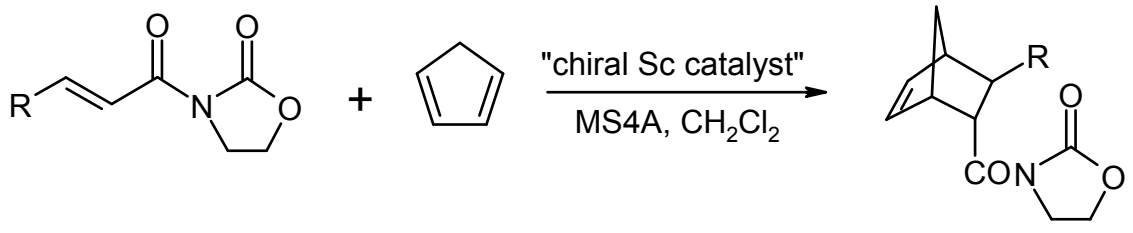


Figure 1.16 Chiral catalysts for asymmetric Diels-Alder reaction.

A chiral scandium catalyst **52**, prepared from scandium trifluoromethane sulphonate ($Sc(OTf)_3$), (R)-(+)-1,1'-bi-2-naphthol (BINOL), and a tertiary amine in dichloromethane, is quite effective in the enantioselective Diels-Alder reactions of acyl-

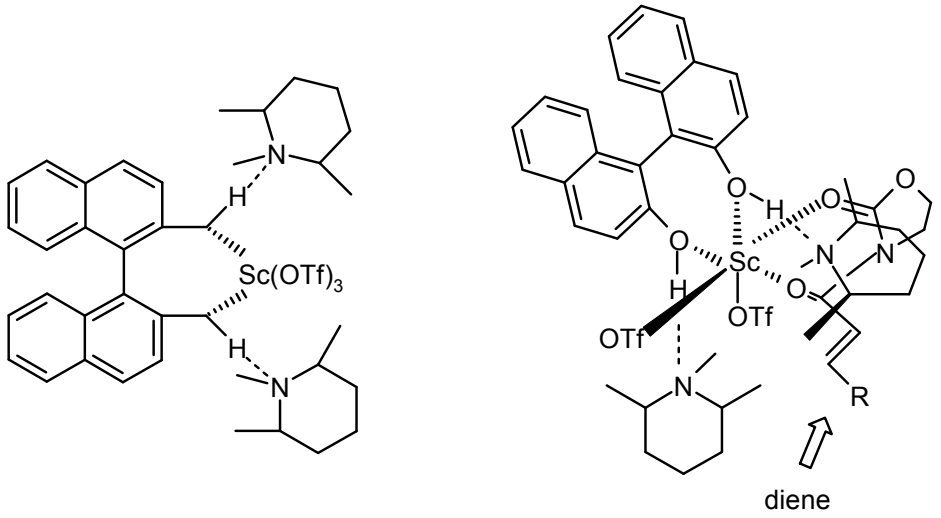
1,3-oxazolidin-2-ones with dienes. The corresponding Diels-Alder adducts are obtained in high yields with high diastereo- and enantioselectivities. (Scheme 1.29)[142]



49 **50** **51**

R = Me, 96% *ee*
R = Ph, 97% *ee*

Scheme 1.29

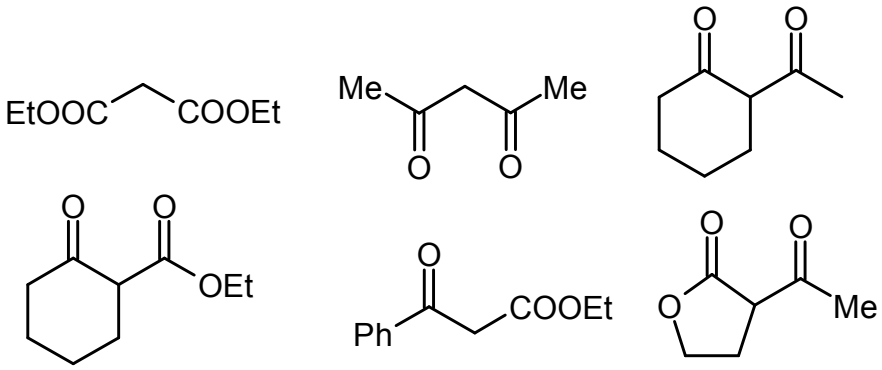


52 **53**

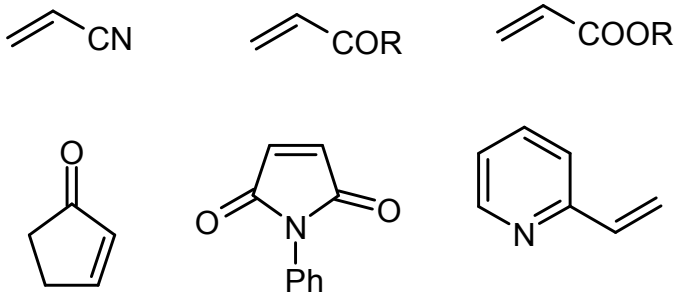
The sense of asymmetric induction in the present reactions has been rationalized by assuming an intermediate octahedral Sc(III)-dienophile complex, **53.** The axial chirality of (R)-BINOL is transferred to the amine, the *re* face of the acyl-1,3-oxazolidine-2-one is effectively shielded by the amine part, and a diene approaches the dienophile from the *si* face to afford the adduct in a high enantioselectivity.

1.9 Michael addition

Michael addition is one of the most useful methods for the mild formation of C-C bonds. The reaction is the addition of an enolate of a ketone or aldehyde (Michael donors) to an *α,β*-unsaturated carbonyl compound (Michael acceptors) at the *β* carbon and involves conjugate addition. The reaction donors are active methylenes such as malonates and nitroalkanes, and the acceptors are activated olefins such as *α,β*-unsaturated carbonyl compounds. Some of the examples of acceptors and donors are shown below (Figures 1.17a-1.17b):



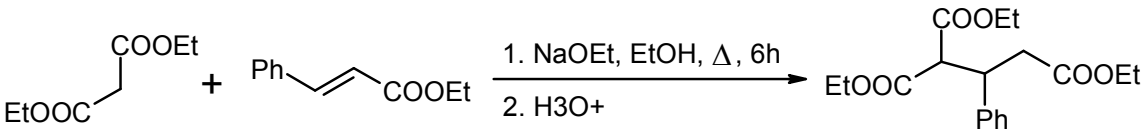
(a)



(b)

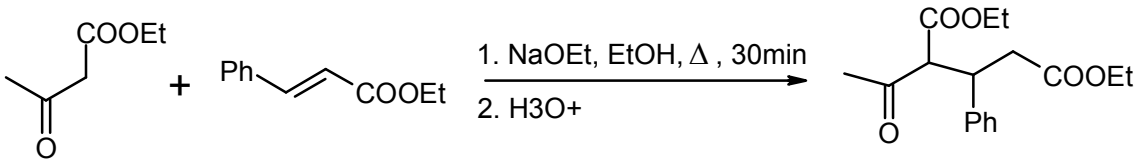
Figure 1.17 (a) Michael donors, (b) Michael acceptors.

The base-protonated additions of the sodium salts of malonates **(54)** and *β*-ketoesters **(57)** to ethyl cinnamate **(55)** is shown below (Schemes 1.30-1.31):[143]



54 **55** **56**

Scheme 1.30



57 **55** **58**

Scheme 1.31

The Michael reaction has traditionally been performed in protic solvents, with catalytic amounts of base. The mechanistic pathway is shown below (Figure 1.18):

Step1:

First, an acid-base reaction. Hydroxide functions as a base and removes the acidic α-hydrogen giving the reactive

Step2:

The nucleophilic enolate attacks the conjugated ketone at the electrophilic alkene **C** in a nucleophilic addition type process with the electrons being pushed through to the electronegative **O**, giving an intermediate enolate.

Step3:

An acid-base reaction. The enolate deprotonates a water molecule recreating hydroxide and the more favourable carbonyl group.

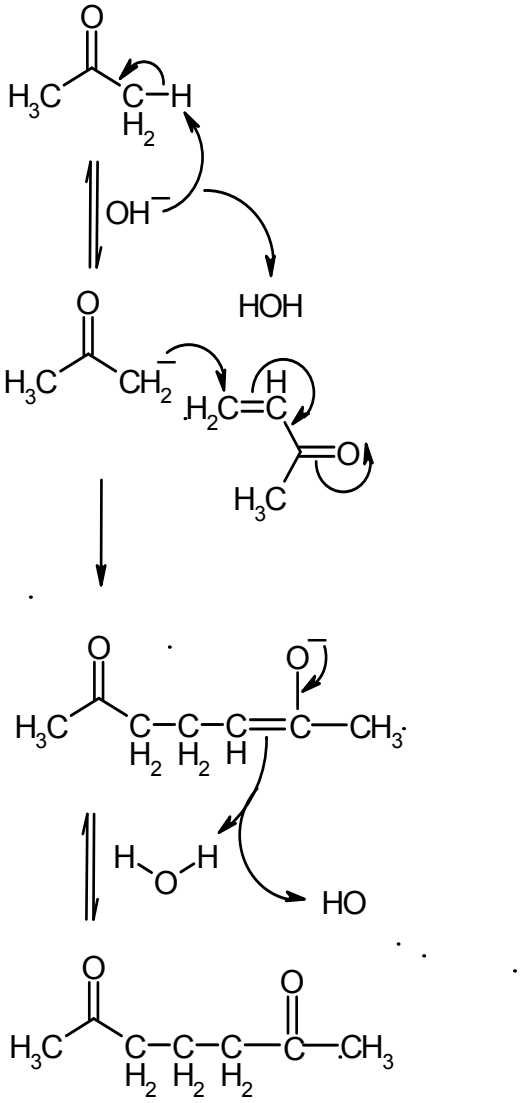


Figure 1.18 Mechanism of Michael addition

Although base catalysis of the Michael reaction is commonly known as a very efficient and high-yielding process, the strongly basic conditions are often a limiting factor since they can lead to a number of side- and subsequent reactions.[144] In order to circumvent strongly alkaline conditions, several alternatives have been developed in recent years that make use of weak Bronsted bases [e.g. $Ba(OH)_2$[145] or alkali metal fluorides[146]] or employ mild reaction conditions (e.g. basic zeolites[147], alumina[148], phase-

transfer catalysis[149], solid-phase catalysis[150]). However, the most valuable alternatives should be able to proceed under neutral reaction conditions.[151] Most notably, the application of transition-metal compounds as catalysts is a mild and efficient alternative to base catalysis of the Michael reaction.[152] Likewise, lanthanide compounds, which have become very popular for a number of carbon-carbon bond forming reactions in the past few years, are reported to catalyse the Michael reaction with high efficiency.[153]

1.9.1 The frontier orbital description

In a typical Michael acceptor, say, propenal, the electron deficiency is greater at the carbonyl carbon than at the β-carbon. However, FMO analysis reveals that the coefficient of the LUMO is greater at the β-carbon. Thus soft[154] nucleophiles should add to the β-carbon if the additions are under molecular orbital control.[155]

FMO analysis has been used to account for the transition state structure obtained from *ab initio* calulations of the reaction between a soft nucleophile (an enamine) and an alkenone.[156] Examining the two possible molecular orbital combinations, it was concluded that the $HOMO_{enamine}$ / $LUMO_{alkenone}$ combination is largely attractive and also minimizes the anti-bonding interactions (Figure 1.19).

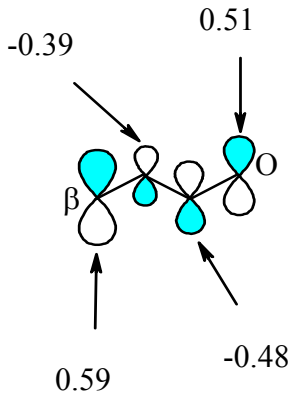


Figure 1.19 Orbital coefficients for the LUMO of propenal

1.9.2 Asymmetric Michael addition

The Michael addition is an important atom-economical method for diastereoselective and enantioselective C-C bond formation. A classical tandem sequence of Michael and aldol additions is the Robinson annulation. More recent research has focused on expanding the scope of asymmetric Michael additions. The most common methods involve chiral phase transfer catalysis, involving chiral quaternary ammonium salts derived from the cinchona alkaloids, and organocatalysis, which uses enamine or iminium activation with chiral secondary amines, usually derived from proline.

When a prochiral acceptor ($R_1CH=A$) and a prochiral donor ($R_2CH=D$) react, the stereoisomers are labeled as either *syn* or *anti* based on the relative configurations of R_1 and R_2 (Figure 1.20)

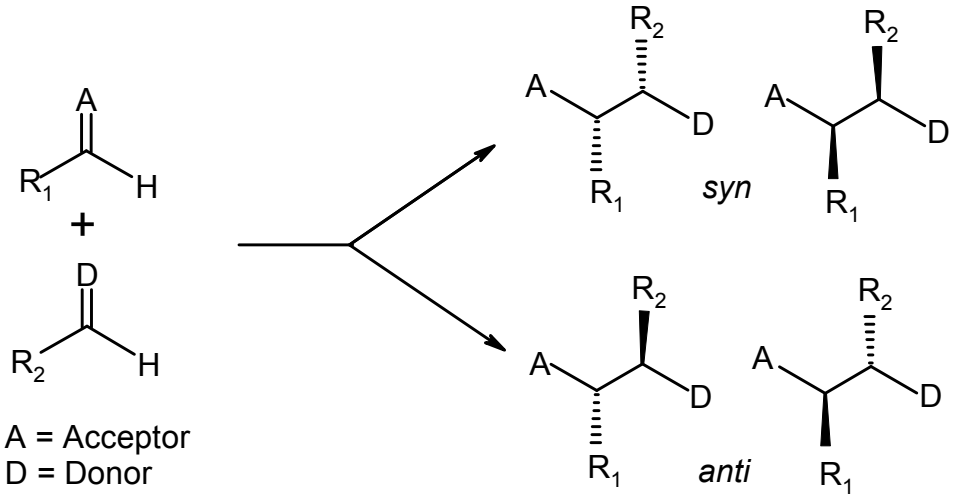
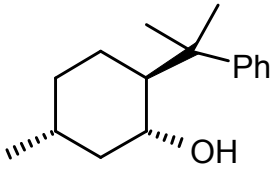
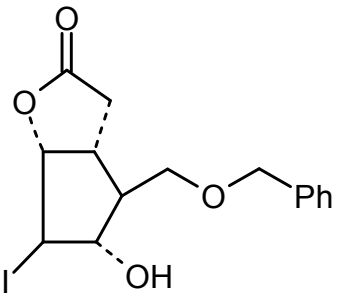


Figure 1.20 Adduct nomenclature for Michael addition.

***Chiral donors*:** The first auxiliary that furnished important lavels of asymmetric induction in a graet variety of condensations was (-)-8-phenylmenthol **(59)**. It was used for the preparation of the key prostaglandin intermediate **60** in optically pure form without resolution.[157]

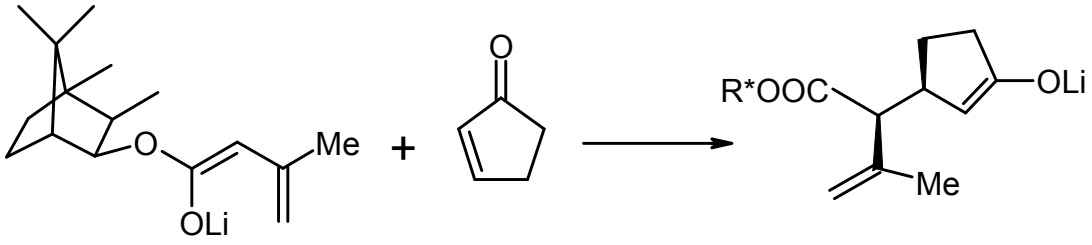


59



60

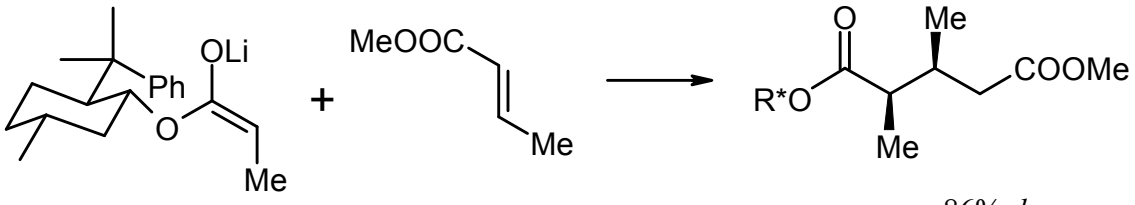
Oppolzer showed that the *Z*(*O*)-dienolate **(61)** adds to cyclopentenone **(62)** with 60% diastereoselectivity (Scheme 1.32).[158] Corey reported the asymmetric Michael addition of the E(*O*)-enolate of phenylmenthone propionate **(64)** to E-methyl crotonate **(11)** (Scheme 1.33). The product mixture was 90% *syn*, and the *syn* adducts were produced in a 95:5 ratio, for an overall selectivity of 86% for the illustrated isomer.[159]



60% *de*

61 **62** **63**

Scheme 1.32

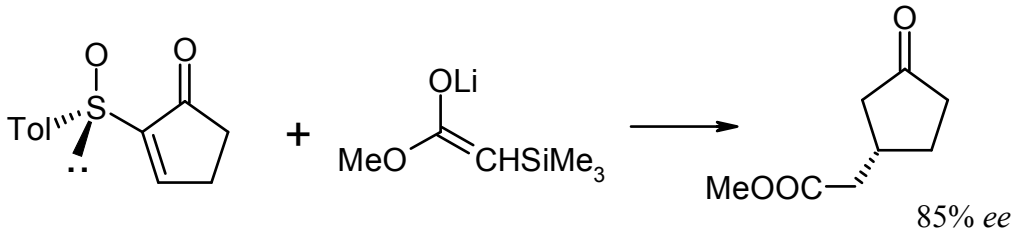


86% *de*

64 **11** **65**

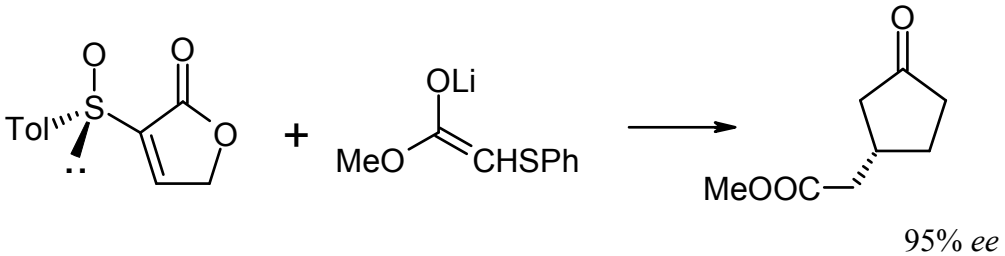
Scheme 1.33

***Chiral acceptors*:** It has been shown that enones having a chiral sulfoxide in the α-position are excellent receptors for conjugate addition of organometallics, and may also be used as Michael acceptors in enolate additions.[160] The lithium enolate of methyl trimethylsilyl acetate **(67)** adds to cyclopentenone **(66)** and cyclohexenone sulfoxides with good to excellent selectivity (Scheme 1.34).[161] After the Michael addition, the sulfoxide and trimethylsilyl groups are removed, and the selectivity is assessed by determining the enantiomeric purity of the β-substituted ketone. Similarly, lithium enolates of phenylthioacetate esters **(69)** add to five and six-membered lactones with high enantioselectivity (Scheme 1.35).[161]



66 **67** **68**

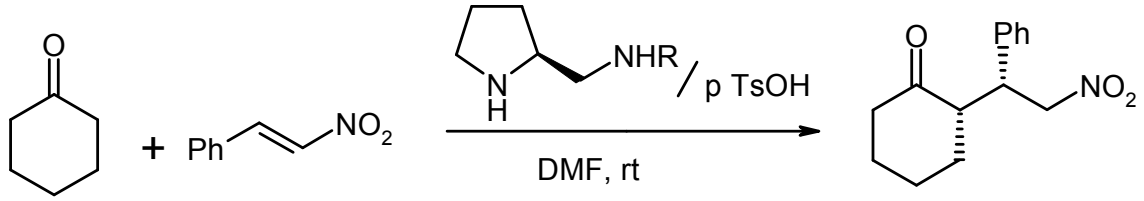
Scheme 1.34



66 **69** **68**

Scheme 1.35

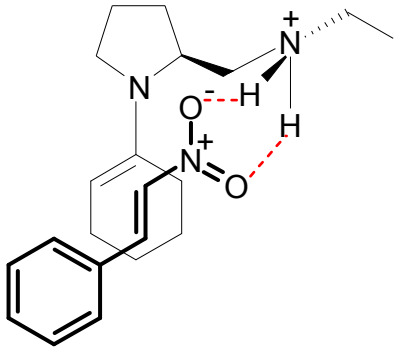
***Chiral catalyst*:** In the reaction between cyclohexanone **(70)** and nitrostyrene **(71)** (Scheme 1.36), the base proline is derivatized and works in conjunction with a protic acid such as p-toluenesulfonic acid.[162]



70 **71** **72**

Scheme 1.36

Syn addition is favored with 99% *ee*. In the transition state **73** believed to be responsible for this selectivity, the enamine (formed between the proline nitrogen and the cycloketone) and **71** are co-facial with the nitro group hydrogen bonded to the protonated amine in the proline side group.



73

Catalytic asymmetric Michael reactions using chiral amines,[163] alkaloids,[164,165] polymer bound alkaloids,[166,167] chiral crown ethers and bases,[168] optically active Co (II)

complexes,[169] natural proteins[170] and amino alcohols[171] as catalysts have been extensively studied. A breakthrough in catalytic asymmetric Michael addition reactions was achieved with the introduction of heterobimetallic catalysts. In a series of reports Shibasaki and coworkers[172] elaborated the utility of such heterobimetallic catalysts of BINOL–La (Al)-alkali metals in bringing about highly enantioselective Michael addition reactions.

Chapter 2

OBJECTIVES

Chapter 2

Objectives

In the recent years, great progress has been made in the field of green chemistry. Green chemistry encourages the design of products and processes that reduce or eliminate the use and generation of hazardous substances. The overall objective of this research effort is to concentrate on the use of green solvents in carrying out organic reactions. Although significant work has been carried out concerning the mechanistic details of Diels-Alder reaction, adequate studies have not so far being carried out to evaluate the exact mechanistic pathway. One of the goals of this research work is to investigate whether the selectivity of Diels-Alder reactions are governed by secondary orbital interactions or by some other forces. Now a days, ionic liquids are being used as alternative substitutes over volatile organic solvents for carrying out several organic transformations. But from the literature reports it is not clear which ionic liquid is useful in effective in promoting a specific Diels-Alder reaction. Development of suitable methodology to find out the specific combination of ionic liquid and Diels-Alder reaction is one of the important targets of research work. In asymmetric synthesis solvents are known to possess important roles in getting one isomer in excess over the other. Our aim is to explore the solvent effect in asymmetric C-C bond forming reactions.

Based on the literature survey discussed in chapter 1, we set our objectives as follows:

1. To delineate the origin of forces responsible for the spectacular rate accelerations and stereoselectivities of Diels-Alder reactions in water and aqueous salt solutions.
2. Although *endo* selectivity of Diels-Alder reaction can be explained on the basis of Alder *endo* rule, but there are some exceptions to this rule. Efforts will be made to suggest alternative forces in understanding the stereochemistry of Diels-Alder reactions.

3. Efforts will be made to propose the specific combination of ionic liquid and Diels-Alder reaction for achieving maximum output. A combined effect of Lewis acid catalysts and ionic liquids in governing Diels-Alder reactions will also be emphasised.
4. To explore the possibility of solvent effects in asymmetric C-C bond forming reactions.

Chapter 3

ROLE OF WATER AND AQUEOUS SALT SOLUTIONS

Chapter 3

Role of water and aqueous salt solutions

In the present chapter, the effect of pure water and aqueous salt solutions on rates and endo/exo stereoselectivities of Diels-Alder reactions of cyclopentadiene ***(6)*** *with methyl acrylate* ***(7)****, methyl methacrylate* ***(9)*** *and methyl trans crotonate* ***(11)*** *are discussed in detail. The observations are explained on the basis of hydrophobic effect. The competing role of secondary orbital interactions (SOI) as well as hydrophobic effects in determining the stereoselectivities of Diels-Alder reactions has also been described. Effect of cosolvents on the stereoselectivities of Diels-Alder reactions has also been examined.*

3.1 Origin of the *endo-exo* selectivity in Diels-Alder reactions

In a wide variety of Diels-Alder reactions, the *endo* orientation is preferred. This is the basis of the Alder *endo* rule. However, this hypothesis has been called into question by many researchers, who have shown that the main arguments suggesting the existence of SOI are inconclusive.

While the importance of SOI seems established, it cannot explain the predominantly *endo* cycloadditions of cyclopentadiene with the mono-olefins cyclopentene[173], norbornene[174], cyclopropene[175], and propene[176] –systems. In these systems no secondary orbital stabilization is possible. It indicates that inductive (van der Waals or dipolar) forces or favorable geometry for overlap may be of over-riding importance in determining the stereoselectivity. Another possibility is that the *exo* transition state is destabilized in these cases by steric repulsion of the methylene hydrogen of cyclopentadiene and the alkyl groups of the mono-olefins.[28]

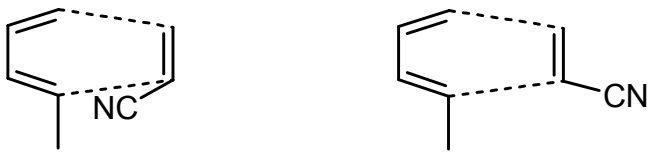
A combination of solvent effects, steric interactions, hydrogen bonds, electrostatic interactions, etc. can be used in the place of SOI.[36]

1. Solvent Effects. A major challenge exists in the elucidation of the origins of the *endo/exo* selectivity found in experimental studies of Diels-Alder cycloadditions carried out in solutions. It is well known that an increase in the solvent polarity induces an increase in the *endo/exo* ratio in a number of common Diels-Alder reactions.[37,40] The reaction of cyclopentadiene and acrylonitrile can be regarded as a typical example of an *endo* preference induced by the medium effect (Scheme 3.1). Experimental[177] as well as theoretical studies[75, 178] indicate that the polarity of the medium induces an increase in the *endo/exo* ratio of this reaction.

endo *exo*

Scheme 3.1

The Diels-Alder cycloaddition between acrylonitrile and piperylene follows a behavior pattern similar to that of the corresponding reaction with cyclopentadiene (Scheme 3.2). Thus, a preference for the *ortho-trans* adduct (corresponding to an *exo* approach) is found in benzene solution, whereas the *ortho-cis* product (formed via an *endo* transition state) is favored in polar solvents (e.g., methanol, ethanol, and acetone).



endo *exo*

Scheme 3.2

2. Steric Interactions: It is currently widely accepted that steric interactions can play a role in the *endo/exo* selectivity of Diels-Alder reactions. For example, the *endo* preference observed in the cycloadditions of cyclopentadiene with some alkenes (such as cyclopentene or *cis*-3,4-dichlorocyclobutene) is generally attributed to steric repulsion between the methylene group of the diene and the substituents of the dienophile.[179] However, it can be argued that the *endo* preference of Diels-Alder reactions of cyclopentadiene with a number of α,β-unsaturated carbonyl compounds could also be justified in terms of SOI (Figure 3.1).[6] Nevertheless, experimental data (shown in Table 3.1) indicate that a methyl group induces a greater *endo* preference than carbonyl-bearing substituents (COOH, CHO, $COOCH_3$).[180] This result seems in better accord with the larger size of the methyl group as deduced from experimental data on the *axial/equatorial* conformational equilibria in cyclohexane derivatives.[181]

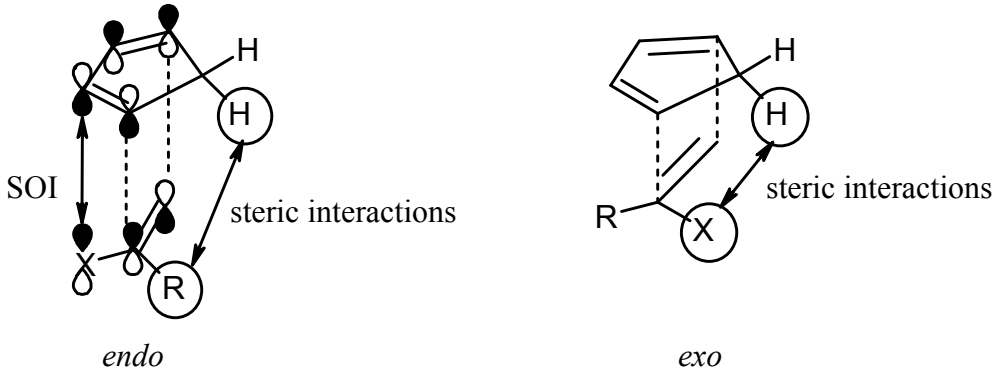


Figure 3.1 Alternative interactions proposed

Table 3.1 The % e*ndo* of the Diels-Alder reactions of **6** with various dienophiles

R	X	% *endo*
H	COOH	80.2
CH_3	COOH	29.2
H	CHO	74.4
CH_3	CHO	17
H	$COOCH_3$	74.3
CH_3	$COOCH_3$	30.1

3. Hydrogen Bonds: One of the most interesting cases of *endo/exo* selectivity is the preferential formation of the *endo* adduct (the only stereoisomer detected by NMR) in the cycloaddition reaction between butadiene and cyclopropene.[182] This result has been attributed to a stabilizing interaction between the central carbons of the diene and the methylene group of cyclopropene.[183,184] In a theoretical study it has been shown that the *endo/exo* selectivity can be attributed to a combination of electron delocalization and electrostatic forces. Such combined effects may be consistent with the existence of a hydrogen bond between the atoms involved (Figure 3.2).[185] Furthermore, crystallographic results have shown that the methylene group of cyclopropene is a strong C-H hydrogen bond donor, similar to acetylenic C-H groups.[186]

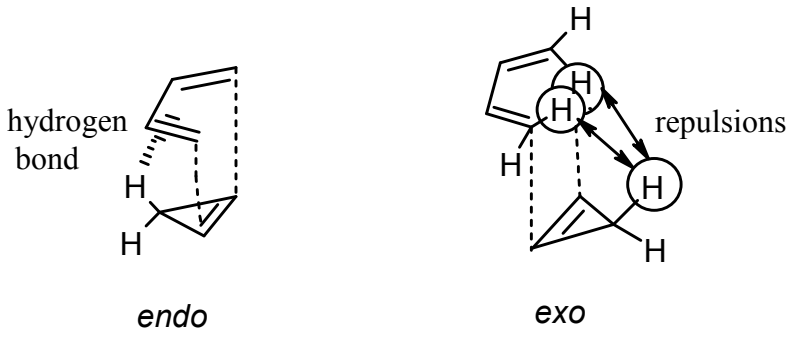
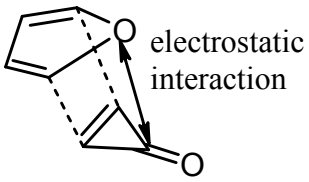


Figure 3.2 Alternative interactions proposed

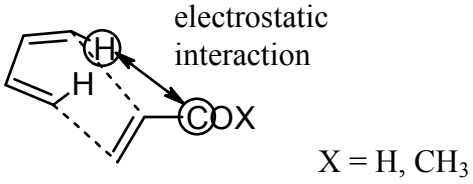
Another alternative explanation involves the existence of a destabilizing interaction in the *exo* transition state (Figure 3.2). It arises from the repulsion (due to electrostatic and/or van der Waals interactions) between a hydrogen atom of the methylene group of cyclopropene and the inner hydrogen atoms of butadiene (situated at a distance of 2.3 Å, according to HF/6-31G* calculations).[184]

4. Electrostatic Forces: The reaction of furan and cyclopropenone is an *exo* selective reaction. The high *exo* preference predicted by *ab initio* study [MP4SDQ/6-31G* energy calculations on MP2/6-31G*-optimized geometries (1.8 kcal mol^{-1})] has been attributed to the existence of a strong electrostatic stabilization between the furan oxygen and the

carbonyl carbon of cyclopropenone (Scheme 3.3).[187] The short distance between these atoms in the *exo* transition structure (2.7 Å) provides justification of the results obtained. The *endo/exo* selectivity predicted by theoretical calculations for other Diels-Alder reactions can also be explained in terms of electrostatic forces.[36] For example, the slight *endo* preferences calculated for the reactions of butadiene with simple α,β-unsaturated carbonyl compounds (such as acrolein[188] or methyl acrylate[189]) can be attributed to electrostatic repulsions existing in the *exo* transition states between the positive charges corresponding to the "in" hydrogens of butadiene and the carbonyl carbon of the dienophile (Scheme 3.4). This mechanistic interaction offers an alternative explanation to the hypothesis of SOI.



Scheme 3.3



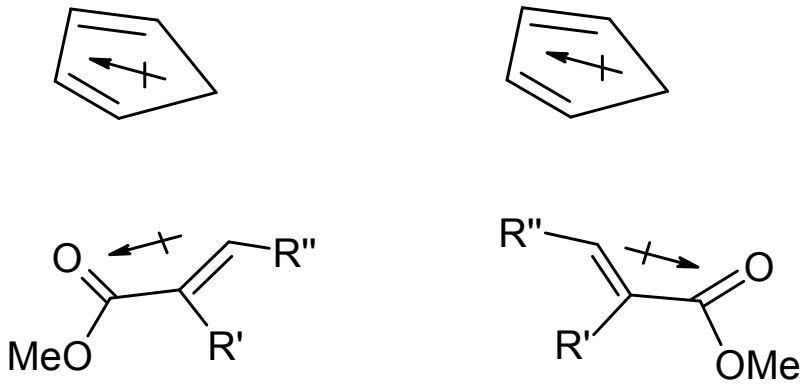
Scheme 3.4

3.2 *Endo*- and *exo*- selectivities of Diels-Alder reactions

In most Diels-Alder reactions, when the product distribution is under kinetic control, the *endo* adduct is preferentially, sometimes exclusively, formed. Alder proposed that *endo* addition was the consequence of a plane-to-plane orientation of diene and dienophile with "maximum accumulation of double bonds". Since this same orientation would promote stability in a molecular complex, it was suggested that complex formation between the reactants might be responsible for preferential *endo* addition. However, some Diels-Alder reactions violate Alder rule. In such cases Alder rule of "maximum

accumulation of unsaturation" is of minor importance in determining the ratios of products. The reaction of **6** with **7** (Scheme 1.7) obeys the rule in all solvents,[37,68] with **9** (Scheme 1.8) violates it in all solvents,[37] and with **11**[37] (Scheme 1.9) shows borderline behavior, conforming to the rule in polar solvents but not in non-polar solvents.

With all three dienophiles in the above-mentioned reactions, the *endo/exo* ratio increases as the solvent changes from nonpolar to polar. The observations can be explained if the transition state is assumed involving a bimolecular aggregate in which the diene and dienophile lie in parallel planes as shown in Figure 3.3. It is clear from the figure that the permanent electric dipole of the *endo* TS is greater than that of corresponding *exo* isomer since in the *endo* TS, the component dipoles point in roughly the same direction. Hence the net dipole moment is greater than the *exo* TS, where the component dipoles point in roughly opposite direction.



endo TS *exo* TS

Figure 3.3 Orientation and dipole moments of diene and dienophile in the *endo* and *exo* TS

3.3 Effect of water: Diels-Alder reaction of cyclopentadiene and methyl *trans* crotonate

Extensive work has been carried out on the *endo/exo* ratios obtaining for the reactions of **6** with **7** (Scheme 1.7) and with **9** (Scheme 1.8) carried out in aqueous salt solutions. However, the reaction of **6** and **11** (Scheme 1.9) shows borderline distribution of the *endo/exo* ratios against the solvent polarity scale. Hence, we thought it worthwhile to examine whether the distribution of the *endo* and *exo* products would also be similar in organic solvents and aqueous salt solutions. We studied the stereoselectivities of Diels–Alder reaction between **6** and **11** in water to demonstrate that hydrophobic packing effects can dominate the geometries of transition states. We measured the *endo*/*exo* ratios for the Diels-Alder reaction of cyclopentadiene **6** and **11** in water and in other organic solvents.[190] Berson *et al.* carried out the reaction of **6** with **11** in different organic solvents. The range of solvents covers nine aprotic substances (TEA, decalin, DME, DMF, pyridine, nitromethane, acetonotrile, acetone and DCM), two alcohols (methanol and ethanol) and one carboxylic acid (acetic acid). For all the solvents they obtained *endo: exo* ratios of 1: 1.[37,180] For this reaction, the convention *endo*/*exo* refers to $endo_{carboxy}/exo_{carboxy}$.

The $endo_{carboxy}/exo_{carboxy}$ ratios for the reaction of **6** with **11** (Table 3.2) show that the $endo_{carboxy}/exo_{carboxy}$ ratio obtained in water is lower than those obtained in other solvents (Figure 3.4). The reaction of **6** with **11** in water was expected to give a higher $endo_{carboxy}/ exo_{carboxy}$ ratio, similar to that of the reaction of **6** with methyl acrylate **7** (Scheme 1.7) or other Diels-Alder reactions discussed elsewhere.[59] In general, Diels-Alder reactions in water offer higher *endo*/*exo* ratios as compared to those in conventional organic solvents, but this was not the case for the reaction of **6** with **11**. This reaction, in n-heptane (a nonpolar solvent) gave an $endo_{carboxy}/exo_{carboxy}$ ratio lower than that in water. The highest $endo_{carboxy}/exo_{carboxy}$ ratio of 2.57, a twofold increase as compared to that in water was obtained when the reaction was carried out in the highly polar solvent, *N*-methylformamide. The $endo_{carboxy}/exo_{carboxy}$ value in 1-propanol, 1-butanol, ethanol, ethylene carbonate, methanol, formamide, ethylene glycol and DMSO

increases by 35%, 39%, 44%, 44%, 52%, 63%, 67% and 68%, respectively, as compared to that in water alone.

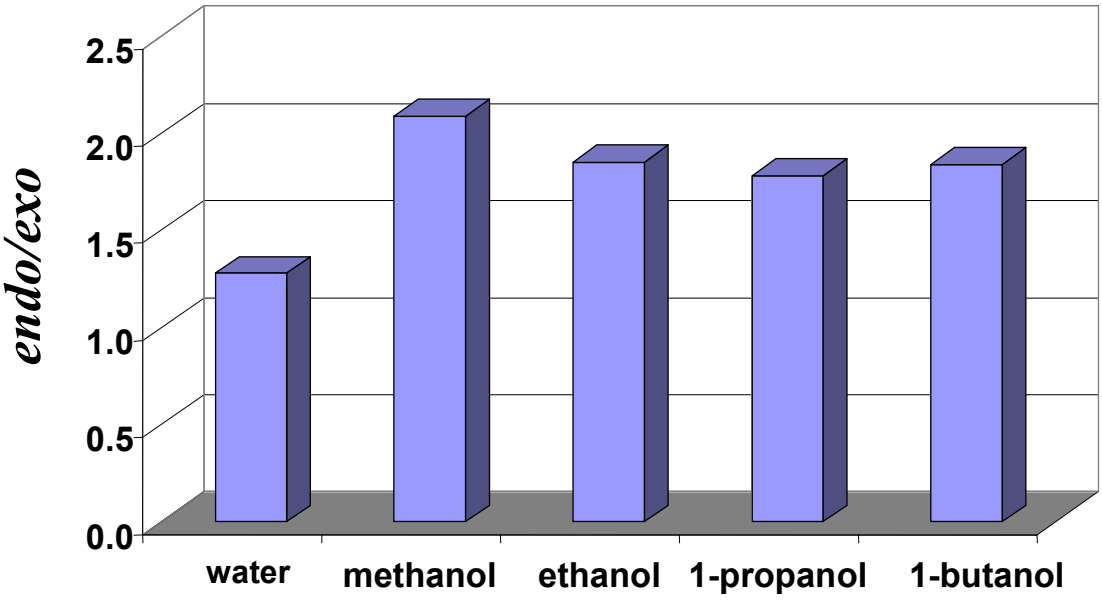


Figure 3.4 *Endo-exo* selectivities for the reaction of **6** with **11** in water and alcohols

The methyl group is more hydrophobic than the carboxylate group, so the hydrophobic packing of the methyl group in the transition state would lead to more $endo_{mt}$, corresponding to more $exo_{carboxy}$. This is exactly what one finds in this water-mediated reaction of **6** with **11**. This suggests that hydrophobic effects influence the stabilization of the geometry of the transition states. A similar change in the $endo_{carboxy}$/ $exo_{carboxy}$ selectivity was observed for the *exo*-selective reaction of **6** with **9** (Scheme 1.8) in water[191] (Table 3.2) and organic solvents.[37,180] In the absence of methyl group substitution, as in the reaction of **6** with **7** (Scheme 1.7), hydrophobic interactions become less important and SOIs direct the reaction to be $endo_{carboxy}$ selective leading to a higher $endo_{carboxy}/exo_{carboxy}$ ratio in water (Table 3.2).[37,68] The percentage yield observed for the

reaction of **6** with **11** was high (78%) as compared to that in organic solvents. Similar rate accelerations in aqueous media are observed for the reactions of **6** with **7** and with **9** also.

The $endo_{carboxy}/exo_{carboxy}$ values in water were checked after every 30 min before the completion of the reaction to yield the ratio as 1.28 ± 0.08 (an average of six readings) indicating that selective decomposition of either *endo* or *exo*-product did not take place.

Table 3.2 $Endo_{carboxy}/exo_{carboxy}$ ratios[a], for the reaction of **6** with **11** in different solvents and for the reactions of **6** with **7** and **9** in water alone.

Solvent	$endo_{carboxy}/exo_{carboxy}$	**% Yield (isolated)**
Water	1.28	78
Methanol	2.09	60
Ethanol	1.85	58
1-Propanol	1.78	55
1-Butanol	1.84	50
Ethylene carbonate	1.95	50
Reaction of **6** + **9** in water	0.40[b]	60
DMSO	2.29	62
Nitrobenzene	1.73	49
Formamide	2.09	69
N-Methylformamide	2.57	65
Ethylene glycol	2.14	68
n-Heptane	0.97	35
Reaction of **6** + **7** in water	1.97[c]	85

[a] Also implies the same as $exo_{mt}/endo_{mt}$.

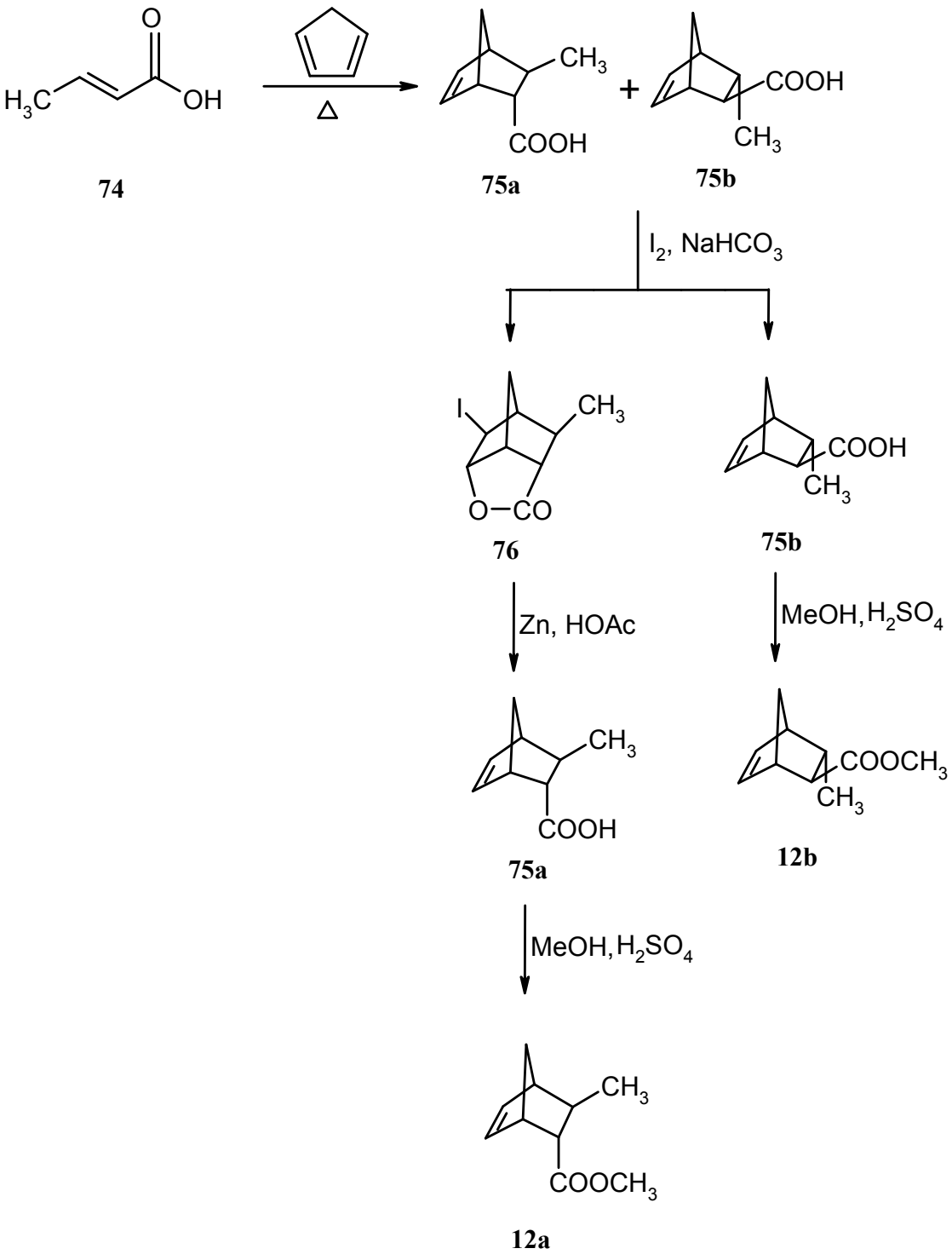
[b] From Ref. 191.

[c] From Ref. 68.

Also the separated *endo* and *exo* products were kept in water for the same time without any change suggesting that the *endo* product (56%) did not convert into the *exo* isomer (44%) and vice versa. In summary, it is possible to invoke the role of hydrophobic packing to explain the stereoselectivity of a Diels–Alder reaction in water.

3.4 Stereochemical assignment

The stereochemical assignments were made by condensing crotonic acid **(74)** with **6** and the resultant *endo* **(75a)** and *exo* bicylic acids **(75b)** were separated by iodolactonization method as reported earlier by Evans *et al.* (Scheme 3.5).[192] The iodolactone **(76)** was cleaved reductively with zinc and acetic acid to get pure *endo*-acid (**75a**) in high yield.[193] The bicyclic acids were then individually treated with methanol and conc. sulfuric acid under reflux for 18h to get the corresponding esters *endo*-2-carbomethoxy-*exo*-3- methylbicyclo[2,2,1]hept-5-ene (**12a**) and *exo*-2-carbomethoxy-*endo*-3-methylbicyclo[2,2,1]hept-5-ene (**12b**).



Scheme 3.5 Iodolactonization method for stereochemical assignment

3.5 The salting phenomena

The phrases "salting-out" and "salting-in" are generally used to denote, respectively, an increase and a decrease in the solubility of the nonelectrolyte with increasing concentration of electrolyte. As mentioned in the first chapter, compounds such as LiCl increase the hydrophobic effect, and they therefore decrease the solubility of hydrocarbons in water.[53] Thus LiCl is a "salting-out" agent; NaCl is another example. However, some salts increase the water solubility of hydrocarbons such as butane or benzene;[53] for instance, GnCl does so.[194] Breslow and Connors[195] used attractive terminology for calling LiCl-type salts as prohydrophobic agents, while GnCl and $LiClO_4$ as antihydrophobic ones. One can also call GnCl and $LiClO_4$ chaotropic and LiCl and NaCl antichaotropic agents.[63,196] Small ions such as Li^+ and $C1^-$ decrease hydrocarbon solubility, while large ions such as Gn^+, $C1O_4^-$, and I^- increase solubility. Thus LiCl has two components that work in the same direction, but with GnCl the increased water solubility of hydrocarbons is seen because the Gn^+ effect dominates the $C1^-$ effect. Guanidine salts with large anions are even more effective at solubilizing hydrocarbons.

Whenever a reaction is accelerated in water one can think of polarity, hydrophobic effect etc. as governing factors. However, simply seeing an increased rate of a reaction in water solution does not establish that a hydrophobic effect is involved. Better evidence for this comes from the use of special salting-in and salting-out agents. The reaction of **6** and **13** became faster in aqueous LiCl solution, but was found to be slightly slower in aqueous GnCl solution.[42] LiC1 increases the hydrophobic effect while GnCl (Guanidinium cation, Figure 3.4) decreases it. The reaction of anthracene-9-carbinol **(17)** and *N*-ethylmaleimide **(18)** (Scheme 1.12) is 2.5 times faster when 4.86 M LiCl is added, but 3 times slower on the addition of 4.86 M GnCl.[197] Such a contrast is expected if a hydrophobic effect is involved.

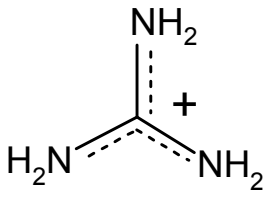


Figure 3.4 Structure of guanidinium cation

The contrast between salting-in and salting-out agents cannot be extended to solvents like ethylene glycol and formamide. Breslow *et al.* examined the solubility of benzene in formamide and in ethylene glycol, with and without additives. LiCl was still a salting-out agent, but so were $LiC1O_4$, GnC1, and even urea. Thus the additives that had decreased the hydrophobic effect in water were found to increase the solvophobic effect in these "water-like" solvents. All of these agents increased the rate of the Diels-Alder reaction of **6** with **13** in formamide and in ethylene glycol.

In a solution of benzene in water with added salting-out or salting-in agent, water was considered as a solvent, the benzene as solute, and the other agent as a solubility modifier. In principle, solubility modifiers can affect two different energy terms (Equation 3.1). (i) the energy required to produce a solvent cavity into which the solute (such as benzene) can go, and (ii) the energy of solute-medium solvation interaction.

$$\delta(\Delta G^{o})_{solution} = \delta(\Delta G^{o})_{cavitation} + \delta(\Delta G^{o})_{solute\ solvation} \qquad (3.1)$$

The salting-out process apparently affects the $(\Delta G^{o})_{cavitation}$ by electrostriction that squeezes out free space and makes cavity creation harder.[196] The salting-in agents such as GnCl and $LiClO_4$ make the cavitation easier by breaking the organized structure of water. It was assumed that they disrupt the structure of water by setting up new hydrogen bonds with water when a cavity is produced to accommodate the solute. This effect if true should be reflected in the surface tension data of salt solutions. The changes in the surface tension of water in GnCl and $LiClO_4$ are positive and smaller than in LiCl and NaCl, which indicates that the formation of cavities in these solutions is not favored with

increasing concentrations of GnCl and $LiClO_4$, unlike in the case of tetrabutylammonium salts. Thus, in such salt solutions the rate-decreasing effect originates from the solute-solvent interactions with dominating $\delta(\Delta G^o)$ solvation term.

The salting-in agent tetra-n-butylammonium chloride (Bu_4NCl) differs in that it lowers the surface tension of water. Thus, it probably contributes both to easier cavity formation and to direct solvation of the substrate. The findings that most salting-in agents switch to become salting-out agents in other polar solvents such as ethylene glycol and formamide but that Bu_4NCl does not switch in these solvents can be understood in terms of relative polarities. Bu_4N^+ ion is so nonpolar that it can preferentially solvate benzene in all three solvents, being less polar than any of them. Thus, it can have a negative $\delta(\Delta G^o)_{\text{solute solvation}}$ in all three solvents. However, Gn^+ ion and $C1O_4^-$ ion are more polar. It is assumed that they can solvate benzene better than water can, so $\delta(\Delta G^o)_{\text{solute solvation}}$ is negative in water. However, they are more polar than is ethylene glycol or formamide. In these solvents the second term of the equation 3.1 is not negative, since the solubility modifiers do not solvate benzene better than the organic solvents do. Now the surface-tension effects detected in these solvents produce an uncompensated $\delta(\Delta G^o)_{\text{cavitation}}$. The result is salting-out.

Guanidine salts like chloride, bromide, acetate and perchlorate inhibit Diels-Alder reaction rates and give rise to more *exo* products. But it has been shown by Kumar and Pawar that guanidine sulfate increases the rates and *endo* product formation of the reaction of **6** with **7.**[198] This contrasting effect of Gn_2SO_4 on the kinetics of the Diels–Alder reaction has been attributed to the dominant role of SO_4^{2-} ion over the guanidine cation.

3.6 Effect of aqueous salt solutions

The effect of salts on kinetics of Diels-Alder reactions has been discussed in terms several parameters like hydrophobic packing, solvent pressure, hydrogen bonding, hydrophobic hydration, and salting-out (S-O) and salting-in (S-I) effects, etc.[55,59] As part of our studies to delineate and quantify the origin of these forces, we have investigated

the reactions of **6** with **7** (Scheme 1.7) and with **9** (Scheme 1.8) in aqueous salt solutions.[68,191] Original contributions from Breslow and his group on the spectacular role of water and its salt solutions[42,65,199-202] and subsequent investigations from our group on the salt effect on the kinetics of Diels-Alder reactions have established that salts such as LiCl, NaCl, NaBr, KCl, $MgCl_2$, $CaCl_2$, and Na_2SO_4 enhance the rates and *endo*/*exo* ratios of Diels-Alder reactions in water, whereas guanidine chloride (GnCl) and $LiClO_4$ lower them.[203] Accordingly, LiCl, NaCl, $CaCl_2$, $MgCl_2$, etc. are the S-O agents, while GnCl, $LiClO_4$, urea, etc. are the S-I agents. These effects are discussed in detail elsewhere. The salt effects on the reactions of **6** with **7** and with **9** follow the expected results within the framework of Breslow's work on the salting effect and its relation with kinetic data of Diels-Alder reactions.[197-203] The salt effect on the *endo*/*exo* ratios for the reaction of **6** with **9** was less pronounced than that of **6** with **7**.

Here, we demonstrate a simple Diels-Alder reaction between **6** with **11** (Scheme 1.9) for which the salt effects on the *endo*/*exo* ratios are opposite to what Diels-Alder reactions in general exhibit.[204] It will be shown that "apparently contrasting" salt effects are actually normal effects with respect to the correct definitions of *endo* and *exo* stereoisomers.

In organic solvents, the reaction of **6** with **7** is *endo* selective, while that with **9** is *exo*-selective. The reaction of **6** with **11** in organic solvents gives the *endo*: *exo* ratio as nearly 1:1.[37,180] In case of **11**, the products are defined with respect to the stereochemistry of carboxylate as is the convention. Here, the conventional *endo*/*exo* refers to $endo_{carboxy}/exo_{carboxy}$. Thus, for this reaction, the $endo_{carboxy}/exo_{carboxy}$ ratio is equivalent to exo_{mt}/ $endo_{mt}$. The subscripts carboxy and mt stand for carboxylate and methyl group, respectively. It should be noted here that for the reaction involving **11**, *endo* and *exo* stereoisomers should be referred to with explicit use of carboxylate or methyl groups, as the case may be. A simple statement of *endo* and *exo* does not convey appropriate meanings of stereoisomers formed as a result of the reaction of **7** with **11**.

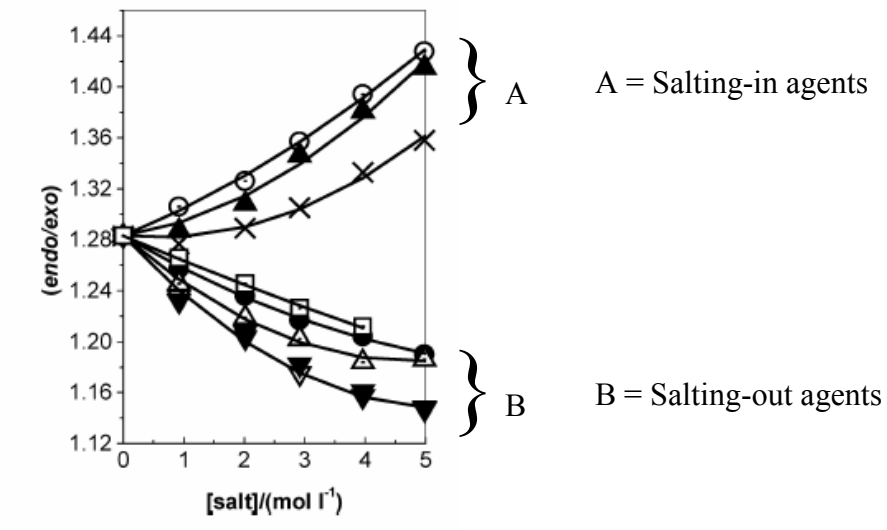


Figure 3.5 Plots of *(endo/exo)* vs. salt concentration for the reaction of **6** with **11** in KCl (□), LiCl (●), NaCl (Δ), $MgCl_2$ (▽), $CaCl_2$ (▼), urea (O), GnCl (▲), and $LiClO_4$ (X).

The $endo_{carboxy}/exo_{carboxy}$ ratios (the same ratio for $exo_{mt}/endo_{mt}$ is implied) shown in Figure 3.5 were obtained for the reaction of **6** with **11** carried out in aqueous solutions of LiCl, NaCl, KCl, $MgCl_2$, $CaCl_2$, GnCl, $LiClO_4$, and urea up to 5 M (except for KCl up to 4 M due to its restricted solubility in water). ^{1}H NMR and GC analyses were extensively used to determine the $endo_{carboxy}/exo_{carboxy}$ ratios of the adduct.[192] The precision of the $endo_{carboxy}/exo_{carboxy}$ ratios as determined from the average of triplicate reactions was observed as ±0.03. The maximum deviation at some salt concentration did not exceed ±0.05. An examination of Figure 3.5 shows that the salts such as LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ that are known to increase the $endo_{carboxy}/exo_{carboxy}$ ratios of simple reactions of **6** with **7** and with **9** showed opposite effects on the reaction of **6** with **11**.

As can be seen in the plots shown in Figure 3.5, LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ decrease the $endo_{carboxy}/exo_{carboxy}$ ratios from that in water ($endo_{carboxy}/exo_{carboxy}$ = 1.28) alone. This reaction in *n*-heptane, a nonpolar solvent, gave the $endo_{carboxy}/exo_{carboxy}$

ratio as 0.97. This decrease is monotonic in nature but shows the signs of tapering off at higher salt concentration possibly due to the solubility of these salts in the solutions. The $endo_{carboxy}/exo_{carboxy}$ ratios are consistently lower in these salts solutions when compared to that in water. $MgCl_2$ is the most effective salt in decreasing the $endo_{carboxy}/exo_{carboxy}$ ratios of this reaction, while KCl is the least effective.

When the reactions were performed in urea, GnCl, and $LiClO_4$, higher $endo_{carboxy}/exo_{carboxy}$ ratios of the products were obtained, as compared to that in water. As noted previously, these results are opposite to the trends obtained for the reactions of **6** with **7** (Figure 3.6) and **6** with **9** or other Diels-Alder reactions in general. $LiClO_4$ showed the least effect on the increase of $endo_{carboxy}/exo_{carboxy}$ ratios. This observation is again in contrast to the observations made in the cases of reactions of **6** with **7** and with **9**. GnCl, which was the least effective salt for the reactions of **6** with **7** and **6** with **9**, was noted to be the most effective of the three salts studied. Urea is the most effective agent for this reaction.

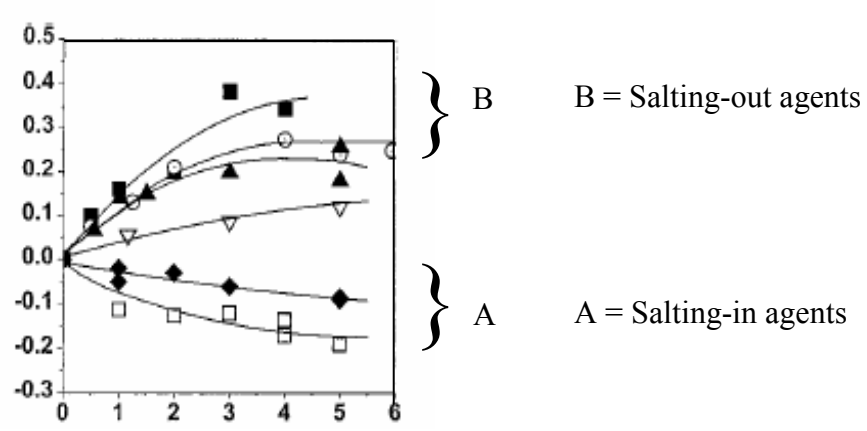


Figure 3.6 Plots of *(endo/exo)* vs. salt concentration for the reaction of **6** with **7** in LiCl (■), NaCl (O), NaBr (▲), $CaCl_2$ (▽), GnCl (♦) and $LiClO_4$ (□)

Intrigued by the above observations in water solutions, we decided to perform the reaction in other two self-associated solvents, namely ethylene glycol and formamide.

The reaction in ethylene glycol gave an $endo_{carboxy}/exo_{carboxy}$ ratio of 2.14, which was reduced to 1.18 in 5 M LiCl-ethylene glycol solution (Table 3.3). A gradual reduction in the $endo_{carboxy}/exo_{carboxy}$ ratios is seen from pure ethylene glycol to 1, 3, and 5 M LiCl solutions. On the other hand, this reaction gave higher $endo_{carboxy}/exo_{carboxy}$ ratio in 5 M $LiClO_4$-ethylene glycol as compared to that in ethylene glycol. The $endo_{carboxy}/exo_{carboxy}$ ratio of 2.09 obtained in pure formamide was lowered to 1.53 in 5 M LiCl solution of formamide. Further, when the reaction was carried out in 5 M $LiClO_4$-formamide, the $endo_{carboxy}/exo_{carboxy}$ ratio increased to 2.75.

As for conformity, LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ should have increased the $endo_{carboxy}/exo_{carboxy}$ ratios of this reaction as they did for the reactions of **6** with **7** and with **9**. These results indicate that these salts show a different behavior and no longer act

Table 3.3. $endo_{carboxy}/exo_{carboxy}$[a] ratios, for the reaction of **6** with **11** in ethylene glycol (EG), formamide (FM) and their salt solutions

Solvent system	$endo_{carboxy}/exo_{carboxy}$
EG	2.14
1 M LiCl-EG	1.08
3 M LiCl-EG	1.33
5 M LiCl-EG	1.18
1 M $LiClO_4$-EG	2.16
3 M $LiClO_4$-EG	2.57
5 M $LiClO_4$-EG	2.83
FM	2.09
5 M LiCl-FM	1.53
5 M $LiClO_4$-FM	2.75

[a] Also implies the same ratios for $exo_{mt}/endo_{mt}$.

as the S-O agents for the reaction of **7** with **11**. Similarly, $LiClO_4$, GnCl, and urea have increased the $endo_{carboxy}/exo_{carboxy}$ ratios and therefore no longer act as the S-I agents. This observation is noted in all three solvents.

The S-O and S-I phenomena are directly related to the solubility of reactants in a salt solution when compared to that in the pure solvent.[58,60,205,206] We attempted to confirm our observations on $endo_{carboxy}/exo_{carboxy}$ ratios by first measuring solubility of **11** in water, aqueous LiCl, and $LiClO_4$ (Table 3.4). The solubility of **11** in aqueous 5 M LiCl was substantially lower in aqueous 5 M LiCl than that in water alone, suggesting the role of LiCl as a S-O agent. On the other hand, the solubility of **11** in aqueous 5 M $LiClO_4$ was higher than that in water, indicating $LiClO_4$ to be a S-I agent. The solubility of **11** in 1 M LiCl-ethylene glycol is less than that noted in ethylene glycol alone, while **11** is more soluble in 1 M $LiClO_4$-ethylene glycol than in ethylene glycol itself. The infinite miscibility of **11** in formamide and its salt solutions did not allow us to measure its solubility in these media. The solubility data of **11** in water and ethylene glycol media demonstrate that LiCl should have increased the $endo_{carboxy}/exo_{carboxy}$ ratio due to the S-O, while $LiClO_4$ decreased them owing to the S-I effects. But this is not the case for the reaction of **6** with **11**. It is therefore clear that the reaction of **6** with **11** cannot be interpreted in terms of salting phenomena.

Table 3.4 Solubility of **11** in different solvent systems

Solvent system	Solubility of 11 (mM)
Water	36.70
aq 5 M LiCl	5.65
aq 5 M $LiClO_4$	39.10
EG	18.21
1 M LiCl-EG	11.70
1 M $LiClO_4$-EG	19.31

These interesting salt effects can be explained within the framework of hydrophobic packing as proposed by Breslow in the past.[59] Thus, accordingly, the lower $endo_{carboxy}/exo_{carboxy}$ values for this reaction in aqueous LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ as compared to in water shown above suggest that exo_{mt} is less than $endo_{mt}$ in water. Since the methyl group is more hydrophobic than the carboxylate group, the hydrophobic packing of the methyl group in the transition state would lead to higher $endo_{mt}$, which corresponds to higher $exo_{carboxy}$. These prohydrophobic salts enhance the hydrophobic packing of diene and dienophile as compared to water alone. This is exactly what we have noted in this investigation of the reaction of **6** with **11** in the above salt solutions. On the other hand, the antihydrophobic salts such as GnCl, $LiClO_4$, and urea decrease the hydrophobic packing resulting in lower $endo_{mt}$ corresponding to lower $exo_{carboxy}$. This suggests that hydrophobic effects dominate during the stabilization of the geometry of transition state rather than SOIs[6,207,208] as advocated in the past. For the past three decades, SOIs have been employed to explain the stereoselectivities of Diels-Alder reactions. However, the explanation of stereoselectivities of Diels-Alder reactions on this basis has been questioned.[36] It is established from the theoretical calculations that the atoms presumed to be involved in SOIs are situated relatively far (ca. 2.8 Å) in the corresponding transition-state structures.[36,209-213] This finding is against the existence of these interactions as the calculated geometries for transition-state structures of Diels-Alder reactions can lead to the estimation of the presence of other attractive effects.[214] Garcia *et al.* have deliberated on this issue to conclude that the hypothesis of SOIs is not necessary to explain the stereoselectivity ratios.[36] Accordingly, a combination of solvent effects, steric interactions, hydrogen bonds, electrostatic interactions, etc. can be used in their place.

A similar change in the $endo_{carboxy}/exo_{carboxy}$ selectivity has been observed for the reaction of **6** with **9** (Scheme 1.8); however, this reaction is *exo*-selective in water and its salt solutions.[191] In the absence of methyl group substitution, as in the reaction of **6** with **7** (Scheme 1.7), hydrophobic interactions become less important and SOI directs the reaction to be $endo_{carboxy}$ selective leading to a higher $endo_{carboxy}/exo_{carboxy}$ ratio in water (Table 3.2).[68]

It is important to state here that we have carried out Diels-Alder reactions of **6** with other dienophiles, but such types of salt effects both in aqueous and nonaqueous salt solutions were not observed. In summary, it is possible to invoke the role of hydrophobic packing over that of SOIs to explain the stereoselectivity ratio of a particular Diels-Alder reaction in aqueous salt solutions. The "apparent contrasting" salt effects could be interpreted in terms of hydrophobic effects.

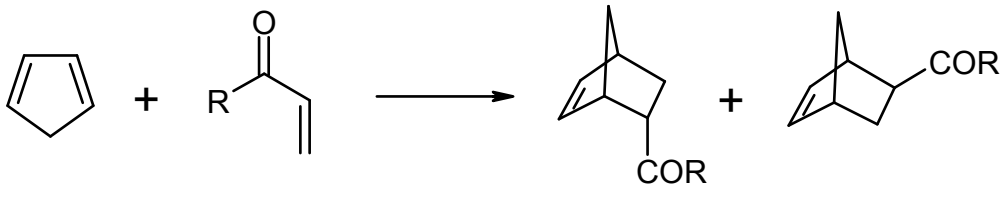
3.7 Diels-Alder reactions in aqueous media

Generally, the process of bond breaking and bond formation in the Diels-Alder reaction is considered to be concerted[3,215] but not necessarily synchronous.[4,59] In extreme cases the Diels-Alder reaction can even become a two-step process with a zwitterionic[12] or biradical[19] intermediate. The concertedness implies that there is only a small change in charge separation on going from the initial state to the activated complex. As a result the rates of many Diels-Alder reactions remain almost unaffected by the solvent.[6,13,14] The rate of some Diels-Alder reactions, however, can be strongly influenced by the medium.[216-219] This is especially true for aqueous media, where accelerations up to 13000 times (when compared to organic solvents) can be achieved.[72,73,220] This special effect of water has attained much attention ever since its discovery in 1980.[42] An extensive discussion of the origin of the remarkable acceleration induced by water has already been given by Engberts *et al*.[72,73,220] Evidence has been presented that there are two effects causing this aqueous rate enhancement: (1) Enforced hydrophobic interactions and (2) Hydrogen bonding to the activating group of the dienophile.

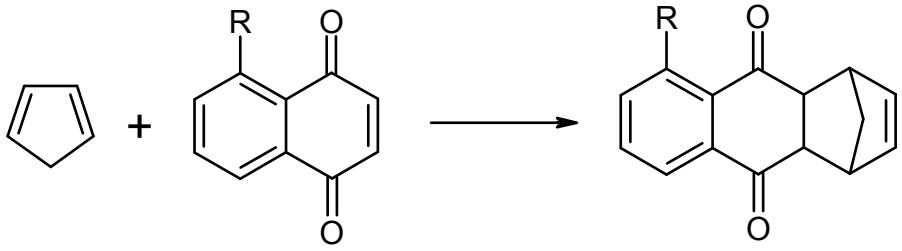
1. Enforced hydrophobic interactions: The reaction partners in a typical Diels-Alder reaction are usually poorly soluble in water. As a result the water molecules surrounding these reagents arrange themselves in hydrophobic hydration shells. The Diels-Alder reaction *forces* the reaction partners into close contact in the activated complex, leading to a reduction of the molecular surface area exposed to water. This causes the transition

state to be less destabilized than the initial state, resulting in a faster reaction in water as compared to nonaqueous solvents.[72,73,220]

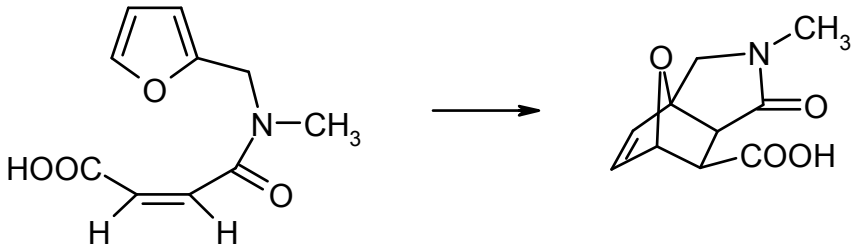
Intermolecular Diels-Alder reactions of **6** with alkyl vinyl ketones **(13, 77)** and 5-substituted-l,4-naphthoquinones **(79a-c)** as well as of the intramolecular Diels-Alder reaction of *N*-furfuryl-*N*-methylmaleamic acid **(81)** in aqueous media were reported by



6 **13, R=Me** **77, R=Et** **14a, R=Me** **78a, R=Et** **14b, R=Me** **78b, R=Et**



6 **79a, R=H** **79b, R=OH** **79c, R=OCH_3** **80a, R=H** **80b, R=OH** **80c, R=OCH_3**



81 **82**

Scheme 3.6

Engberts *et al.* (Scheme 3.6).[73] The second-order rate constants for the cycloaddition of dienophiles **13, 77** and **79a-c** with diene **6** in water are, respectively, about 200 and 5800 times larger than those in n-hexane. The intramolecular cycloaddition of **81** was found to be accelerated in water similarly. In order to analyze the origin of these unexpectedly large rate effects, they examined the effect of different substituents in the dienophiles on the observed medium effects.

A bimolecular reaction necessarily involves the formation of a direct, solvent-unseparated complex of both reactants during the activation process. If two relatively apolar reactants are involved in this process, and the medium is highly aqueous, the term "enforced pairwise hydrophobic interaction" is used. The term "enforced" is introduced, in order to distinguish this associative process from hydrophobic interactions between the reactants that do not lead to the activated complex; hydrophobic interactions can lead to solvent-separated complexes, and moreover, the geometry of the complexes formed might not lead to further reaction. In order to account for the large effect of water on the Diels-Alder reactions, the enforced solvophobic binding process needs to be more favorable in water than in conventional organic solvents.

In general, the Gibbs energy associated with enforced solvophobic interaction is given by equation 3.2.

$$\Delta G(R) = U_{DD}(R) + \delta G^{SI}(R) \qquad (3.2)$$

The first term represents the direct diene-dienophile pair potential, which is the work required in the process of bringing diene and dienophile from an infinite separation to a distance *R* in vacuum. The second term takes account of the solvent effect on the same associative process. The diene as well as the dienophile are quite polarizable molecules and will strongly interact in a solvent-unseparated complex. Now, Diels-Alder reactions are characterized by a large, negative volume of activation. The distance between the diene and the dienophile in the activated complex will be significantly smaller than *R,* and in highly aqueous media, the "enforced pairwise hydrophobic

interaction" will be accompanied by an additional decrease of the molecular volume that has to be hydrated.

During the activation process of Diels-Alder reaction, solute-solvent interactions are replaced by solute-solute interactions and the solvent molecules will rearrange themselves around the activated complex and in the bulk. Water has an extremely low molecular polarizability. As a consequence, London dispersion interactions between the reactants and the solvent molecules will be enthalpically much more favorable in conventional organic solvents than in water. Due to this contribution, the $\Delta^{\neq}H^{\Theta}$ for Diels-Alder reaction in water will be markedly smaller.

Hydrophobic packing between diene and dienophile, which is often suggested to be the major cause for the rate accelerations of Diels-Alder reactions in water[42,196,197,199] is difficult to reconcile with the large rate acceleration observed for the intramolecular cycloaddition of **81** in water, which is of the same magnitude as those found for the intermolecular Diels-Alder reactions. Instead, it was proposed that intramolecular Diels-Alder reactions are also accompanied by a significant decrease of the molecular volume and a concomitant decrease of the solvent-accessible surface during the activation process. Accordingly, enforced hydrophobic interactions provide a likely explanation for the rate enhancement.

2. Hydrogen bonding: Hydrogen bonding of the water molecules to the activating group in the dienophile (for normal electron-demand Diels-Alder reactions) cause rate enhancement in aqueous media. The role of this activating group is to withdraw electron density from the double bond, thereby lowering the LUMO energy of the dienophile and facilitating the interaction with the diene HOMO. When a hydrogen bond is formed to such an activating group, its electron withdrawing capacity is enhanced, which results in a further lowering of the LUMO energy, a smaller HOMO-LUMO gap, and thus a faster reaction.[221]

The importance of hydrogen bonding is also apparent from *ab initio* studies by Jorgensen *et al.*[74,222,223] They proposed that if enforced hydrophobic interactions were the only cause of acceleration, then the plots of Gibbs energies of transfer for both the activated complex and product should bear a resemblance. In view of the dissimilarity in

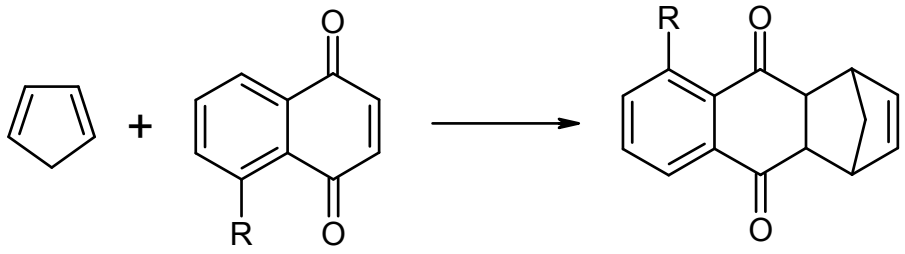
these plots, it was suggested that one or more additional factors could be involved in enhancing the reaction rates in water. For the reactions of **6** with **13** (Scheme 1.10) and with **15** (Scheme 1.11), the use of a sophisticated computational technique estimated the optimal interaction energies to be 1.5-2 kcal mol^{-1} more favorable for hydrogen bonding to the oxygen or nitrogen in the transition states. The computational results suggested that hydrogen bonding effects are very significant in addition to the hydrophobic component. This work on the role of hydrogen bonding on the reaction rates has also been confirmed by experimental kinetic data.[224] For the reaction of **6** with **13** in water and trifluoroethanol, a comparison between the Gibbs free energies of the initial states and the activated complex has shown that hydrogen bonding stabilizes the activated complex more than the initial state.

Water also influences the selectivity of Diels-Alder reaction. Studies of the effects of solvents on the regio-[225] and diastereofacial[226] selectivity of Diels-Alder reactions have provided evidence that these parameters are mainly influenced by the hydrogen-bond donating ability of the solvent which affects the orbital coefficients of the dienophile. Computer simulations suggest that hydrogen bonds affect the diastereofacial selectivity by influencing the *s-cis/s-trans* conformational equilibrium.[210] It has also been suggested that hydrogen bonding, by increasing the orbital coefficients, leads to a tighter transition state in which the asymmetric center already present has more interaction with the stereocenter that is being formed.[227] With regard to the regio- and diastereofacial selectivity, water behaves as anticipated on the basis of its hydrogen-bond donating capability.

With respect to the *endo-exo* selectivity, water is an outstanding solvent for Diels-Alder reaction since *endo/exo* ratios are almost invariably higher in water than in organic solvents.[42] Since a good hydrogen-bond donating solvent is often also a structured solvent, an intrinsic correlation between the *Sp* and α-parameter can exist for water.

The Diels-Alder reactions of 5-substituted naphthoquinones **(83a-e)** with **6** (Scheme 3.7) and the corresponding reaction of **6** with methyl vinyl ketone **(13)** and methyl vinyl sulfone **(85)** (Scheme 3.8) have been studied in most detail in water, n-hexane, acetonitrile, ethanol, 1-propanol, 1,1,1-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFP).[72] Large rate enhancements were observed in water for the

reactions of **83a-e** with **6:** $k_2(H_2O)/k_2$(n-hexane) amounts to 1180 **(83a),** 1651 **(83b),** 4583 **(83c),** 7250 **(83d)** and 12780 **(83e).** It is clear that the rate acceleration in water depends markedly on the nature of the dienophile. Another obvious conclusion that emerges from these data is, that an increase of the hydrogen-bonding donor capacity of the alcohols leads to a substantial increase of k_2: $k_{(HFP)}/k_{(EtOH)}$= 83 **(83a),** 68 **(83b),** 114 **(83c),** 99 **(83d)** and 154 **(83e).** However, the rate increase in water, which is definitely less acidic than HFP, is the highest of all solvents: $k(H_2O)/k(HFP)$= 1.91 **(83a),** 2.88 **(83b),** 2.93 **(83c),** 3.73 **(83d)** and 2.96 **(83e).** The small size of the water molecule and the availability of two OH donor sites, in combination with the cooperative H_2O-H_2O interactions, enhance the effectiveness of water as a H-bond donor solvent. For the slower Diels-Alder reaction of **6** with 1**3** and **85** essentially similar results are obtained, but the rate enhancements going to water as the solvent are smaller. The hydrogen-bonding effect is also less pronounced.

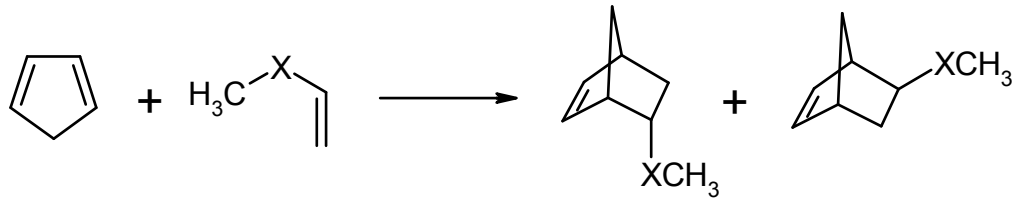


6

83a, R=NO_2
83b, R=$COCH_3$
83c, R=H
83d, R=CH_3
83e, R=OCH_3

84a, R=NO_2
84b, R=$COCH_3$
84c, R=H
84d, R=CH_3
84e, R=OCH_3

Scheme 3.7



6 **13 X=CO** **85 X=SO_2** **14a** **86a** **14b** **86b**

Scheme 3.8

Solvent effects on rate constants reveal differences in interactions of the solvent with the initial state (IS) and the activated complex (AC). The rate acceleration in water and in the water-rich mixtures is primarily caused by destabilization of the IS relative to the AC**.** In the absence of substrate association, hydrogen bonding is of major importance in determining this difference in solvation behavior of the IS and AC**.** The AC is more polarized than the IS**,** and the polarized carbonyl moiety of the AC will be better stabilized by hydrogen-bonding than the carbonyl group of the IS. This enhanced hydrogen-bonding of water to the AC was also proposed on the basis of Monte Carlo simulations[74] and *ab initio* MO calculations[75] and is in line with the relatively high rates of the Diels-Alder reactions in TFE and HFP. As argued by Jorgensen small charge variations in the AC relative to the IS will induce large differences in hydrogen-bonding. A detailed comparison of the solvent effects on the Diels-Alder reaction of **6** with 1**3** and **85**[220] led to the unexpected result that **85** is less hydrophobic than **13** despite the fact that the sulfonyl moiety is a weaker hydrogen-bond acceptor than the carbonyl group. This finding can be rationalized by assuming that **85** accepts four hydrogen bonds in water while the carbonyl group can accept only two hydrogen-bonds.

Using a combined quantum mechanical and molecular mechanical (QM/MM) potential, Gao *et al.*[228] have carried out Monte Carlo simulations to investigate the hydrophobic and hydrogen-bonding effects on Diels-Alder reactions in aqueous solution. Two prototypical systems were considered, including the reaction of **6** with **13** and the

reaction of **6** with isoprene **(31)** (Scheme 1.20). Analysis of the simulation results revealed that the hydrophobic effect is significant in both reactions. Since hydrogen bonding interactions are not involved in the reaction of **6** and **31**, the entire transition-state stabilization (4.6 ± 0.3 kcal mol^{-1}) can be attributed to the hydrophobic effect. In the reaction of **6** and **13**, enhanced hydrogen-bonding interaction and the hydrophobic effect contribute equally to the transition state stabilization (-3.5 ± 0.4 kcal mol^{-1}).

A combined effect of both enforced hydrophobic interactions and the hydrogen-bonding in stabilizing the transition state was attributed as origin of rate enhancement in several Diels-Alder reactions.

3.8 Effect of cosolvents on the stereoselectivity of Diels-Alder reactions

To study the effect of cosolvent media we carried out the Diels-Alder reaction of **6** with **11** in aqueous mixtures of different solvents. The solvents used for our study were methanol, ethanol, 1-propanol, 1-butanol, acetone and dioxane. The $endo_{carboxy}$/ $exo_{carboxy}$ ratios for the reaction of **1** with **11** carried out in the aqueous mixtures of solvents are shown in Table 3.5. It is interesting to observe that the $endo_{carboxy}$/$exo_{carboxy}$ ratios become almost double in aqueous methanol and ethanol as compared to in water alone ($endo_{carboxy}$ /$exo_{carboxy}$ in water 1.28 ± 0.02). However, the maxima in the $endo_{carboxy}$/ $exo_{carboxy}$ ratios are observed in 50 and 80% of methanol and ethanol mixtures, respectively (Figure 3.7). This effect is not witnessed in aqueous 1-propanol and 1-butanol, in which the $endo_{carboxy}$ /$exo_{carboxy}$ ratios increase without showing any peaks. The effect of 1-propanol on the $endo_{carboxy}$/$exo_{carboxy}$ ratios for this reaction is higher than that of 1-butanol. The drop in the $endo_{carboxy}$ /$exo_{carboxy}$ ratios for this reaction in the alcohol-rich solutions of both methanol and ethanol is quite sharp. These observations suggest that the aqueous lower alcohols can play significant role in altering the $endo_{carboxy}$ /$exo_{carboxy}$ ratios of this reaction. Similar effect of aqueous methanol on the reaction of **6** with **7** has been observed. The aqueous solutions of acetone and dioxane showed least but similar effect

on the $endo_{carboxy}$ /$exo_{carboxy}$ ratios observed for this reaction. From an earlier study, it is evident that the reactions of **6** with **13** in water alone offered an $endo_{carboxy}$:$exo_{carboxy}$ ratio of 22:1, which dropped to 10:1 in methanol. However, this fall in the $endo_{carboxy}$ / $exo_{carboxy}$ values obtained in aqueous alcohols was gradual rather than exhibiting peaks. It seems that the increase in carbon chain length of the alcohol decreases the *endo* product for the reaction of **6** with **11**.

Table 3.5 Effect of solvents and their aqueous mixtures

% solvent in water (v/v)	***endo/exo* ratio**					
	Methanol	**Ethanol**	**1-Propanol**	**1-Butanol**	**Acetone**	**Dioxane**
20	1.438	1.605	1.820	1.902	1.419	1.426
40	1.785	2.499	2.128	1.975	1.580	1.588
60	2.372	2.533	2.198	2.050	1.819	1.836
80	2.568	2.166	2.151	2.048	1.845	2.039
100	2.087	1.854	1.776	1.843	1.248	1.257

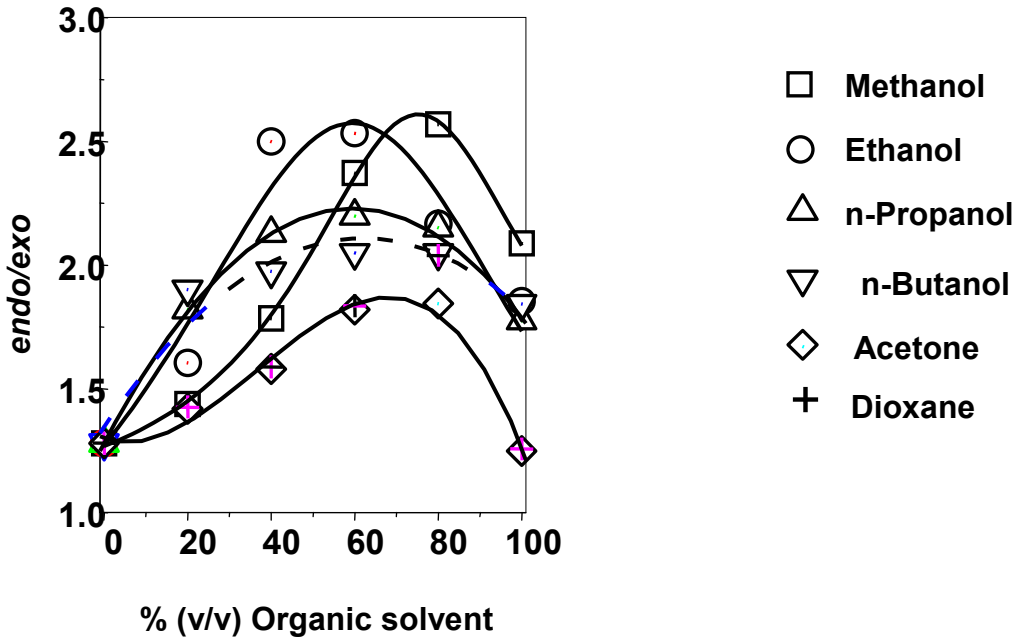


Figure 3.7 Plots of *endo/exo* vs. % (v/v) organic solvent in water for the reaction of **6** with **11**

3.9 Effect of temperature on the stereoselectivity of Diels-Alder reactions

By appropriate controls, the product mixtures in Diels-Alder reactions are shown to be kinetically determined. Consequently, if it is assumed that the formation of *endo* and *exo* products in a given run follow rate laws of the same form, the product ratio *endo/exo* is equal to the ratios of the specific rate coefficients k_{endo}/k_{exo}. Furthermore, the ground state reactants leading to a pair of *endo-exo* isomeric transition states are identical, so that log (k_{endo}/k_{exo}) directly proportional to the free energy difference between the two transition states. The temperature-dependence of the product ratio is expressed in Arrhenius form (equation 3.3),

$$\log (k_{endo}/k_{exo}) = \log (A_{endo}/A_{exo}) + (E_{endo}-E_{exo})/2.303\ RT \quad (3.3)$$

values for the ratios of the pre-exponential factors and for the differences in empirical activation energies from the intercepts and slopes of plots of log (k_{endo}/k_{exo}) vs. 1/T.

The differences in entropies of activation are given by the equation 3.4.

$$\Delta S_N^{\neq} - \Delta S_X^{\neq} = 2.303\ R \log (A_{endo}/A_{exo}) \quad (3.4)$$

The differences in enthalpies of activation are identical with the differences in Arhenius activation energies.

To study the effect of temperature Berson *et al.* carried out Diels-Alder reactions of **6** with **7**, **9** and **11** in different organic solvents. For the reactions of **6** with **9** and with **11** the *endo/exo* ratios were found to decrease with increasing temperature for all the solvents. But, opposite trend was observed for the reaction of **6** with **9**. The *endo/exo* ratios were found to increase with increasing temperature.

We carried out the reaction of **6** with **11** in aqueous mixtures of different organic solvents at various temperatures. The organic solvents used for our study were 1-propanol, dioxane, and two water like solvents ethylene glycol and formamide. As the temperature varies from 2^0C to 32^0C, the *endo/exo* ratio in 1-propanol increases from 1.363 to 1.720 (Table 3.6). Similarly, with increasing temperature the *endo/exo* ratio in ethylene glycol and formamide also increases. In case of dioxane the change in the *endo/exo* ratio with temperature is negligible. The reaction **6** and **11** in dioxane at 2^0C was not possible as the freezing point of dioxane is very low (12^0C) and so are for ethylene glycol and formamide. It is clear from the Table 3.6 that the change of the *endo/exo* ratios with temperature is not very significant.

We then next investigated the effect of temperature on the reaction of **6** with **11** employing aqueous mixtures of 1-propanol. We used four different compositions 20%, 40%, 60% and 80% of 1-propanol in water. In case of 20% 1-propanol (v/v), the *endo/exo* ratio was found to decrease with increasing temperature (Table 3.7). In this case the *endo/exo* ratio value of 1.835 at 2^0C was decreased to 1.818 at 32^0C. Opposite trend was obtained in case of 40% 1-propanol. The *endo/exo* ratio value of 2.099 at 2^0C was

increased to 2.138 at 32^0C. Again in case of 60% and 80% 1-propanol in water *endo/exo* ratios were found to increase with increasing temperature. The change in the *endo/exo* ratio with temperature was marginal. From this experiment no particular trend was observed.

Table 3.6 Effect of temperature on the reaction of **6** with **11** in different organic solvents

Temperature (^{0}C)	*endo/exo* ratio			
	1-Propanol	**Dioxane**	**Ethylene glycol**	**Formamide**
2	1.363	-	1.945[b]	2.281[b]
12	1.222	1.249[a]	1.963	2.259
22	1.591	1.246	2.009	2.325
32	1.720	1.243	2.066	2.480

[a] t = 15^0C
[b] t = 5^0C

It is however felt that the consideration of structures of aqueous alcohols as investigated in terms of the alcohol solvation can through light on this irregular behavior. The structure of water at around 40% alcohol solution is greatly altered as strong interactions take place between alcohol and water molecules. This situation can be very dominant in methanol where a sharp transition in the physical properties of water takes place in 40% alcohol solutions. This analysis requires a correlation between the *endo/exo*

Table 3.7 Effect of temperature on the stereoselectivity of **6** and **11**

Temperature (^{0}C)	***endo/exo* ratio in aqueous mixtures of 1-Propanol**			
	20	**40**	**60**	**80**
2	1.835	2.099	2.233	1.896
12	1.762	2.073	2.214	1.671
22	1.721	2.169	2.199	2.124
32	1.818	2.138	2.244	2.151

ratios of a Diels-Alder reaction and micro-structural changes occurring at intermittent compositions of aqueous alcohols.

In nutshell, the anomalous behavior of salt effects can be explained on the basis of hydrophobic effect. It has been shown that hydrophobic effects are dominant over secondary orbital interactions in determining the stereoselectivity ratios of a simple Diels-Alder reaction in water and aqueous salt solutions.

Chapter 4

ROLE OF TRIFLATES AND IONIC LIQUIDS

Chapter 4

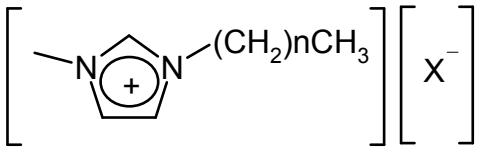
Role of triflates and ionic liquids

The present chapter describes the effects of various ionic liquids on rates and stereoselectivities of Diels-Alder reactions. Effects of rare earth metal triflates in conjunction with ionic liquids have also been investigated. An effort to examine the recylability of the ionic liquids-triflate media establishes the utility of this special combination in promoting Diels-Alder reactions.

4.1 Diels-Alder reactions in ionic liquids

Over the past decade, ionic liquids have become one of the fastest growing ‘‘green’’ media for chemists and engineers because of their advantageous physicochemical properties. However, little is known about how the use of an ionic liquid solvent can affect the reaction of solute species. With their unique characteristics, ionic liquids may induce solvent effects on a wide range of processes. A large number of reports have been published discussing the physico-chemical properties of ionic liquids. These properties include polarity, melting point, thermal stability, viscosity, density, ionic diffusion co-efficient, conductivity, refractive index, surface tension etc.[106, 229,230]

We studied the combined effect of triflates and ionic liquids in promoting Diels-Alder reactions. The ionic liquids selected for our study were 1-butyl-3-methylimidazolium [BMIM] salts of tetrafluoroborate $[BF_4]^-$, hexafluorophosphate $[PF_6]^-$ and lactate, 1-ethyl-3-methylimidazolium [EMIM] salts of tetrafluoroborate $[BF_4]^-$, trifluoromethanesulphonimide $[NTf_2]^-$, and trifluoroacetate $[TFA]^-$ and 1-octyl-3-methylimidazolium [OMIM] salt of tetrafluoroborate $[BF_4]^-$ (Figure 4.1). These ionic liquids are moisture stable and reaction product can be easily isolated by extracting it with diethyl ether.



n=1 [EMIM]=1-ethyl-3-methylimidazolium X=BF_4, PF_6, Lactate,
n=3 [BMIM]=1-butyl-3-methylimidazolium TFA, NTf_2
n=7 [OMIM]=1-octyl-3-methylimidazolium

Figure 4.1 Ionic liquids studied in this work

The criteria for selecting these seven different ionic liquids for our study are: (i) they have no Lewis acid character; hence they would not interfere with the catalytic activity of triflates, (ii) they are moisture stable, thus simplifying their handling, (iii) they allow simple and quantitative extraction of the products with diethyl ether.

We set our objectives as:

1. To study the effect of the increasing chain length of the alkyl chain attached to the cation on the course of Diels-Alder reactions,
2. As the chain length of the alkyl chain attached to the cation increases, viscosity of the ionic liquids also increases. It will therefore be of interest to unveil the effect of viscosity of ionic liquids on Diels-Alder reactions.
3. If we change the property of ionic liquids from hydrophilic to hydrophobic, how will be effected in the selectivity of Diels-Alder reactions. Ionic liquids such as [BMIM][BF_4] are hydrophilic in nature, whereas ionic liquids like [BMIM][PF_6] are known to possess hydrophobic nature.

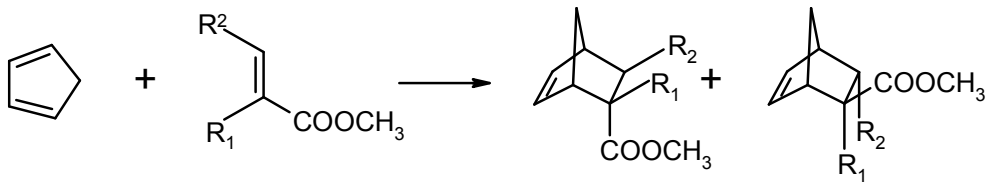
In the literature exist two reports on the use of [BMIM][BF_4] in carrying out the reaction of cyclopentadiene **6** with methyl acrylate **7** (Scheme 1.7) giving 85 and 97%

product with about 80% *endo* isomer.[229,231] The use of anions like $[PF_6]^-$, $[SbF_6]^-$ and $[CF_3COO]^-$ with $[BMIM]^+$ have resulted into high yields. We carried out the reaction of **6** with **7** in two relatively less viscous ionic liquids [EMIM][TFA] and [EMIM][NTf_2]. The reaction proceeded with 75 and 89% yield, respectively to give about 80% *endo* isomer (Table 4.1, entries 1, 2) as shown in this study.

Besides using organic solvents as reaction media[37] for the reaction of **6** and methyl methacrylate **9** (Scheme 1.8) only one study[113] employing chloroaluminates has been reported in the literature. The reaction is *exo* selective in organic solvents but was shown to give higher *endo* product in acidic chloroaluminates.[113] We carried out this reaction in [BMIM][BF_4], [EMIM][BF_4] and [OMIM][BF_4] to give about 26% yield with an average 30% of *endo* product (Table 4.1, entries 3-5). It was, therefore, not possible to obtain higher *endo* product by the use of these ionic liquids. The nature and size of organic cation did not affect the results in this case.

The reaction of **6** with methyl *trans* crotonate **11** (Scheme 1.9) in organic solvents offers nearly equal distribution of *endo* and *exo* stereoisomers.[37] This reaction did not proceed exceedingly well in [BMIM][BF_4] (Table 4.1, entry 6). This reaction in the acidic chloroaluminate has been reported to proceed with about 60% yield and 90% *endo* isomer.[113] The reason that the reaction proceeded with higher *endo* product may be because of $AlCl_3$ in the chloroaluminate ionic liquid. $AlCl_3$ alone has been shown in the past to give such a result. It appears that Lewis acid can only catalyse this reaction and the ionic liquid acts as a solvent medium.

Table 4.1 Diels-Alder reactions of **6** with **7**, **9** and **11** in ionic liquids[a]



6 **7** R_1=H, R_2= H **8a** **8b**
9 R_1=CH_3, R_2=H **10a** **10b**
11 R_1=H, R_2=CH_3 **12a** **12b**

R^1	R^2	Entry	Ionic liquids	Yield[b] %	*endo/exo*[b]
H	H	1	[EMIM][TFA]	75	78/22
		2	[EMIM][NTf_2]	89	80/20
CH_3	H	3	[BMIM][BF_4]	26	28/72
		4	[EMIM][BF_4]	29	31/69
		5	[OMIM][BF_4]	24	30/70
H	CH_3	6	[BMIM][BF_4]	13	55/45

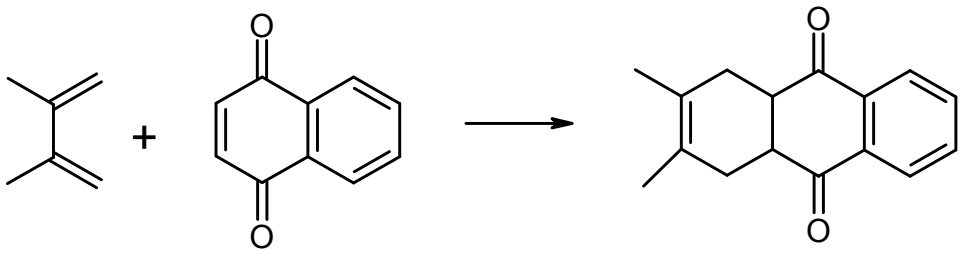
[a] 4.65 mmol of **6**; 1.16 mmol of dienophile; ionic liquid 2 mL; reaction time 24h.

[b] Calculated from GC; No increase in yield observed after the times reported.

The reaction of **6** with 1,4-naphthoquinone **(29)** (Scheme 1.19) was carried out in [BMIM][BF_4], [BMIM][PF_6], [EMIM][TFA] and [EMIM][NTf_2] to give about 77% yield in 30 min (Table 4.4, entry 1). A change in the ionic liquids did not bring about any variations in the yield obtained (Table 4.4, entries 4-6). A literature report suggests nearly the same yield in 30 min in 1-hexyl-3-methylimidazoliumtetrafluoroborate [HMIM][BF_4].[232]

Diels-Alder reaction of 2,3-dimethylbutadiene **(87)** and 1,4-naphthoquinone **29** (Scheme 4.1) has been carried out in organic solvent.[233] Allen and Bell carried out the

reaction of **87** with **29** in alcohol (ethanol) under refluxing condition for 5 h to get 96% yields. The reaction of **87** and **29** in [BMIM][BF_4], [BMIM][PF_6], [EMIM][TFA] and [EMIM][NTf_2] gave about 42-50% product in 6 h. Again a change in ionic liquids as a reaction medium did not have any noticeable effect on the yield (Table 4.5, entries 1, 4-6).

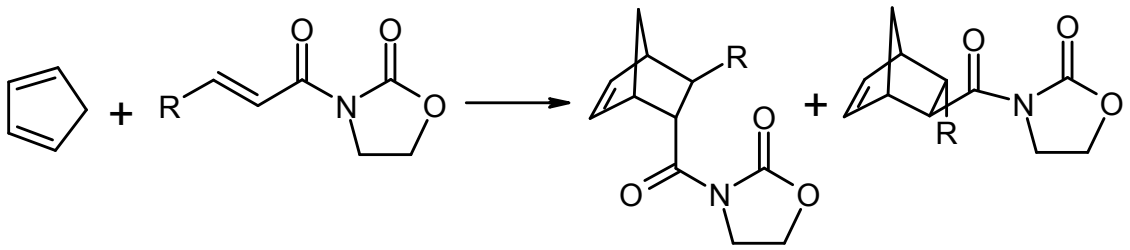


87 **29** **88**

Scheme 4.1

The reactions of **6** with acyl oxazolidinones were then investigated in different ionic liquids (Scheme 4.2). The reaction of acryloyl oxazolidinone **89** gave highest yields (82%) in [EMIM][NTf_2] and the lowest in [BMIM][Lactate] i.e. 70% in 3 h (Table 4.2, entries 11, 7). This reaction proceeded with 88% *endo* product in [BMIM][Lactate] though lowest in yield. Crotonyl oxazolidinione **91** reacted with **6** slowly in 24 h to give 14-20% yield with 77% *endo* isomer in all the ionic liquids studied herein (Table 4.3). Cinnamoyl oxazolidinone **93** reacted with **6** in ionic liquids to offer very little yield (≈10%) even after several hours.

Meracz and Oh carried out the reaction of **6** with **89** and with **91** in two different ionic liquids, hydrogen butylimidazolium tetrafluoroborate (HBuIM) and 1,3-di butylimidazolium tetrafluoroborate (DiBuIM).[234] The reactions proceeded well in HBuIM with excellent *endo/exo* ratios for **89**. However, for **91**, use of HBuIM or DiBuIM gave low yields but with high *endo-exo* selectivities.

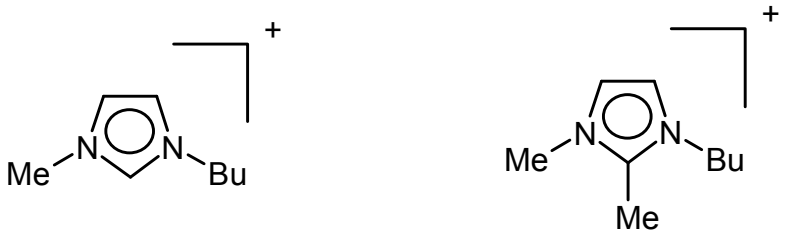


6	**89 R=H**	**90a**	**90b**
	91 R=CH_3	**92a**	**92b**
	93 R=Ph	**94a**	**94b**

Scheme 4.2

Literature reports also show similar rate acceleration of Diels-Alder reactions in ionic liquids. The reaction of **6** with **7** (Scheme 1.7) has been investigated in water,[68] salt solutions[68], LPDE[83] and ionic liquids.[108,112,113,229,231] The first study of Diels–Alder reaction in ionic liquid was performed by Jaeger and Tucker, using ethylammonium nitrate.[108] Ethylammonium nitrate was formed by the addition of conc. nitric acid to ethylamine. Water was removed by distillation to get the pure salt, which was liquid at ambient temperature. Jaeger and Tucker used this ionic liquid to enhance the reaction of **6** with **7** and methyl vinyl ketone **13** (Scheme 1.10).[108] The *endo* product and rate enhancement for these reactions in this ionic liquid has been compared with those obtained in water and in other organic solvents. Water has been used beneficially as a solvent for Diels-Alder reaction.[42,44] Dramatic rate and stereoselectivity enhancement have been observed in water relative to those obtained in conventional organic solvents. With encouraging results in ethylammonium nitrate it has been explored whether this ionic liquid shares some common solvent properties with aqueous medium that speed up these reactions. Ethylammonium nitrate resembles water in many respects. Like water, it possesses a high cohesive energy density.[235] Also, the standard free energies, enthalpies and entropies of solution for several nonpolar gases in ethylammonium nitrate parallel to those in water.[236] However, the use of ethylammonium nitrate could not be further argued in view of its explosive nature.[235]

Diels-Alder reactions are reported to show strong solvent dependence.[37,40,59] It has been proposed that improved reaction rates and selectivity arise from a number of factors, such as the polarity of the solvent,[37] or its solvophobicity.[59] Aggarwal *et al.* explored the role of hydrogen bonding in controlling the selectivity of Diels-Alder reactions in ionic liquids.[231] The *endo/exo* ratios for the reaction of **6** with **7** have been studied in ionic liquids containing $[BMIM]^+$ and $[BM_2IM]^+$ cations. The principal difference between $[BMIM]^+$ and $[BM_2IM]^+$ is that the ability of the latter to form hydrogen bond through the proton on the C^2 position of the imidazolium ring has been blocked (Figure 4.2).



$[BMIM]^+$ $[BM_2IM]^+$

Figure 4.2 Structure of $[BMIM]^+$ and $[BM_2IM]^+$ cations

The fastest rate of reaction has been observed in the most viscous ionic liquids.[231] The reaction slows down as the viscosity of the ionic liquid is reduced. When the *endo/exo* ratios for the above reaction, carried out in $[BMIM][BF_4]$ and $[BM_2IM][BF_4]$ are compared, it is observed that higher *endo/exo* ratios can be obtained in $[BMIM][BF_4]$

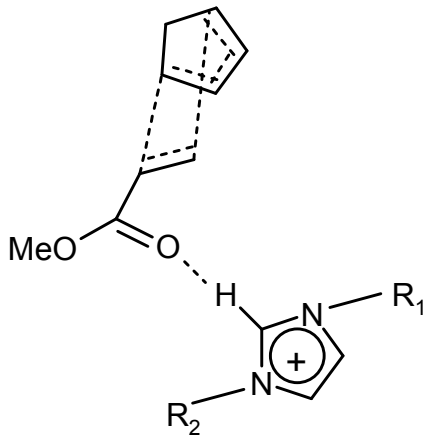


Figure 4.3 The hydrogen bond interaction of imidazolium cation in the TS of the reaction of **6** with **7** (Scheme 1.7)

than in $[BM_2IM][BF_4]$. This is attributed to the hydrogen bond donating ability through the proton on C^2 of the imidazolium ring as shown in Figure 4.3. The formation of a H-bond from the cation of the ionic liquid to the dienophile is a Lewis acid-base interaction.[237] The selectivity of the reaction is still enhanced when ionic liquids such as $[HO(CH_2)_2MIM][N(Tf)_2]$ and $[EtNH_3][NO_3]$ with strong hydrogen bond abilities are used. Since E_T^N values are dominated by ability of a solvent to hydrogen bond with the solute, the *endo/exo* ratios can be correlated with the E_T^N values of the ionic liquids.

The *endo*/*exo* ratio and associated acceleration of the Diels–Alder addition of **6** and **7** in ionic liquids is controlled by the ability of the liquid to hydrogen bond to the **7** as determined by two competing equilibria.[231] The cation can hydrogen bond to the anion (A) of the ionic liquid (Equation 4.1) or to the methyl acrylate (MA) (Equation 4.2).

$$[BMIM]^+ + A^- \overset{K_1}{\rightleftharpoons} [BMIM]^+ \text{.....} A^- \quad (4.1)$$

$$[BMIM]^+ + MA \overset{K_2}{\rightleftharpoons} [BMIM]^+ \text{.....} MA \quad (4.2)$$

In order to explore of possibility of hydrogen bonding, [BMIM]Cl was added to [BMIM][BF_4] and the reaction was repeated. The chloride anion is a better hydrogen bond acceptor than tetrafluoroborate. Therefore, one would anticipate that addition of [BMIM]Cl to [BMIM][BF_4] would lead to formation of an ionic liquid that was less able to coordinate to the methyl acrylate, thus reducing the *endo*/*exo* ratio [Equations (4.1) and (4.2)]. The salt [BMIM]Cl was chosen so that only one cation would be present in the system. Addition of [BMIM]Cl caused a reduction in the yield to 49%, with the remaining being unreacted starting material, suggesting a reduction in the rate of the reaction. This was matched by a reduction in the *endo* selectivity (*endo*/*exo* ratio = 3.7 as compared to that in pure [BMIM][BF_4] where *endo/exo* ratio = 4.6), showing that the addition of a more basic anion to the [BMIM][BF_4] does indeed lead to a reduction in the selectivity of the reaction.

Vidis *et al.* conducted the reaction of **6** with **7** in a series of ionic liquids with the same cation $[BMIM]^+$, and different anions, i.e., tetrafluoroborate $[BF_4]^-$, hexafluorophosphate $[PF_6]^-$, hexafluoroantimonate $[SbF_6]^-$, and bis(trifluoromethylsulfonyl)imide $[NTf_2]^-$.[229] They examined the effect of concentration of the reactants and ionic liquids on the stereoselectivity of the reaction. It was noted from their experiments that [BMIM][NTf_2] forms a single phase with the substrates (as do [BMIM][SbF_6] and [BMIM][CF_3COO]), whereas the other systems were biphasic. Cyclopentadiene **6** and methyl acrylate **7** in a 1.5: 1 ratio were added to between 1 and 8 mol equivalents of [BMIM][BF_4]. With the mol ratios of [BMIM][BF_4]: methyl acrylate below 6 the system was biphasic and at 6 and above the reaction system was homogeneous. A significant increase in the *endo/exo* ratio was observed when the reaction becomes homogeneous. Similar findings were observed for [BMIM][PF_6]. In two ionic liquids, which formed homogeneous systems throughout the substrate

concentration range investigated, [BMIM][NTf_2] and [BMIM][CF_3COO], the selectivity appeared to be independent of the solvent volume.

Vidis *et al.* from their work have shown that with increasing chain length of the alkyl chain attached to the cation the *endo/exo* selectivity decreases. For example, the selectivity decreases from 5.1 in 1,3-dimethylimidazolium $[NTf_2]^-$ to 3.9 in the 1-octyl-3-methylimidazolium salt. Similar trends were observed for other series of alkyl-substituted cations. In addition, it was observed that the presence of functional groups such as hydroxy, carboxyl, nitrile or benzyl groups increases the selectivity compared to an alkyl chain. Surprisingly, higher selectivities were observed in 1-alkyl-2,3-dimethylimidazolium ionic liquids than in their 1-alkyl-3-methylimidazolium analogues. This observation, in conjunction with the relatively high selectivities in the *N*-alkylpyridinium salts, indicates that the hydrogen bond donor properties of the cation do not satisfactorily account for selectivities. Based on the experimental evidence the following factors were proposed that govern the selectivity:

1. Hydrogen bond donor capacity of the cation can stabilise the transition state by bonding to the carbonyl oxygen in methyl acrylate.
2. Long substituents on the cation lead to lower selectivities, presumably due to steric interaction between the TS and the cation.
3. Strong electrostatic association between the ionic liquid ions leads to less interaction between the ionic liquid and the TS. This can be overcome by using functionalised ionic liquids with hydrogen bond donor moieties removed from the immediate proximity of the centre of charge of the cation or anion. Ionic liquid ions with highly delocalised or shielded centres of charge associate less closely with one-another.
4. The presence of a LUMO low energy promotes interaction between the TS and the ionic liquid, whereas a low-energy HOMO has the opposite effect.
5. The *endo* TS has a higher dipole moment than the *exo* one.[37] Thus, polarisable solvents can lower the energy of *endo* TS more than that of the *exo* TS.

The reaction **6** and **7** has also been carried out in chloroaluminate ionic liquids.[112,113] Room temperature chloroaluminate ionic liquids are polar, exhibit high solubility towards organic and inorganic solutes, and most importantly exhibit variable Lewis acidity.[113,114, 238-240] Selectivity and reactivity of Diets-Alder reactions are strongly influenced by the Lewis acidity of the medium. A combination of either *N*-1-butylpyridinium chloride or 1-ethyl-3-methylimidazolium chloride with $AlCl_3$ was used in different proportions to offer 95% *endo* product in the acidic chloroaluminate.[112,113] Acidic and basic nature of chloroaluminate ionic liquids can be easily tuned by changing the composition of the components of the ionic liquid. However, the moisture instability of chloroaluminates is a detrimental factor during the work.

Recently, Tiwari and Kumar have attempted to correlate the rates of Diels-Alder reactions of **6** with acrylates carried out in various ionic liquids with several solvent properties such as surface tensions, solvophobicities, $\delta_H(H^2)$, polarity parameter E_T^{30} and viscosities of solvent media.[115] The authors suggested that the rate constants of these reactions decrease with decrease in E_T^{30} values of ionic liquids. They have also proposed that the rate constants for these reactions decrease with increase in viscosities of ionic liquids possibly due to diffusion problems encountered by the reactants.

4.2 Effect of triflates in ionic liquids for promoting Diels-Alder reactions

Lewis acid catalysed C-C bond-forming reactions are now of great interest in organic synthesis. Lewis acids are used to catalyse a wide variety of reactions. The mechanism steps are:

1. Lewis acid forms a polar coordinate with a basic site on the reactant (such as an O or N).
2. Its electrons are drawn towards the catalyst, thus activating the reactant.

3. The reactant is then able to be transformed by a substitution or addition reaction.
4. The product dissociates and catalyst is regenerated.

Common Lewis acids include $AlCl_3$, $FeCl_3$ and BF_3. These reactions are usually carried out under strictly anhydrous conditions, because most Lewis acids immediately react with water rather than the substrates and are decomposed or deactivated. $AlCl_3$, for example, reacts violently with water. Typical solvents for fascilitating the use of $AlCl_3$ are dichloromethane and benzene. Unlike common Lewis acids that decompose readily in the presence of water, lanthanide triflates ($Ln(OTf)_3$, Ln = La, Ce, Eu, Yb etc.), yttrium triflate ($Y(OTf)_3$) and scandium triflate ($Sc(OTf)_3$ are stable in water and function well in aqueous media. Triflates are readily prepared from metal oxide (e.g. Sc_2O_3) and aqueous trifluoromethanesulfonic acid (Triflic acid, TfOH) solution. Triflic acid is a 'superacid' so its conjugate base ions are very stable. The metal triflate complex is strongly electrophilic, thus acts as a strong Lewis acid.

While the element Sc is in group 3 and lies above La and Y, its radius is appreciably smaller than those of any other rare earth elements. The chemical behavior of Sc is known to be intermediate between that of aluminium and lanthanides.[241] Sc has been uncommon probably due to the lack of rich sources and difficulties encountered during separation.

A variety of organic transformations have been successfully carried out in the presence of triflates, which were otherwise catalysed by common Lewis acids like $AlCl_3$, $FeCl_3$ etc. The examples of triflate catalysed reactions are Friedel-Crafts reactions (alkylation as well as acylation), Aldol condensations, Diels-Alder reactions (carbo as well as aza Diels-Alder), Michael additions, Mannich-type reactions, 1,3-Dipolar cycloadditions etc.

Although many Diels-Alder reactions have been carried out at high reaction temperatures without catalyst, heat-sensitive compounds in complex and multistep syntheses cannot be employed. Furthermore, Diels-Alder reactions are reversible, and the lowest possible temperatures are generally used. While Lewis acid catalysts allow reactions to proceed at room temperature or below with satisfactory yields, they are often

accompanied by diene polymerization. Excess amount of catalyst are often needed to catalyse carbonyl-containing dienophiles.[77,242] But, a small amount of triflate is sufficient to complete reactions in most cases. In addition, triflates can be recovered by simple extraction of product with diethyl ether after reactions are completed and can be reused. In the case of organic solvents most of the triflates are lost in the quenching step, recovery of catalyst is not possible. The concept of recoverable and recyclable transition-metal-based catalysts has become extremely important from both an environmental and economic viewpoint and various strategies have been employed for their immobilization on different supports.[243]

The benefits of lanthanide triflate catalysts can be summarised as:

1. stable in water, so reactions can be carried out in water or aqueous solutions. This reduces the need for toxic organic solvents and generates less toxic waste,
2. recoverable and hence reusable,
3. selective, often producing fewer by-products than standard methods,
4. some reactions can use greener non-chlorinated reagents, and reduce the number of synthesis steps,
5. less toxic and not corrosive, so safer and easier to handle,
6. mild reaction conditions are safer and reduce energy consumption.

Although triflate catalysed C–C bond formation reactions, have recently been received considerable attention due to their broad synthetic utility,[244] there are limitations in performing these catalytic reactions on a large scale due to their low turnover numbers (TONs are usually < 10–20). TON is defined as the number of moles of substrate that a mole of catalyst can convert before becoming inactivated. An ideal catalyst would have an infinite turnover number in this sense, because it wouldn't ever be consumed, but in actual practice turnover numbers vary from 100 to a million or more. To explore the possibility of repetitive use of catalyst, several polymer- or dendrimer-bound scandium catalysts have very recently been employed.[245-250] However, most supported scandium catalysts require complicated synthetic manipulations and, moreover, their catalytic activity still remains far from satisfactory.

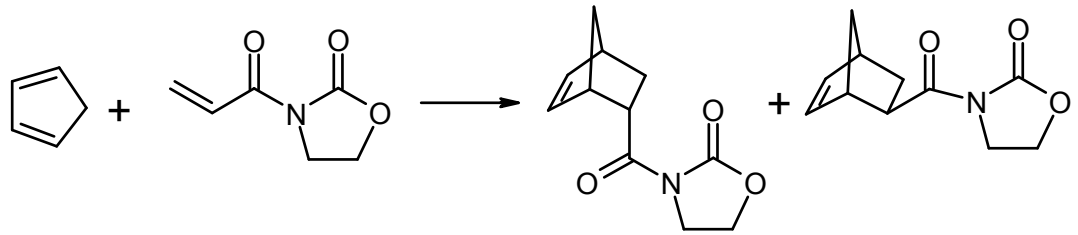
In view of the reports on acceleration of Diels-Alder reactions by rare earth metal triflates, we decided to see how triflates influence various Diels-Alder reactions in different ionic liquids shown in figure 4.1.

First, the reaction of cyclopentadiene **6** with acryloyl oxazolidinone **89** in [BMIM][BF_4] became very fast when catalysed by 2 mol% La(OTf)$_3$ to give 83% yield and 86% *endo* product (compare entry 2 with entry 1 in Table 4.2). The reaction time in the presence of La(OTf)$_3$ was reduced from 3 h to 30 min. Another triflate, Sc(OTf)$_3$ was more effective than La(OTf)$_3$ as the reaction proceeded with 86% yield and 91% *endo* product. Similar results were obtained in [BMIM][PF_6] catalysed by La(OTf)$_3$ and Sc(OTf)$_3$ (Table 4.2, entries 4-6). The reaction was three-time faster on catalysing it by triflates in [BMIM][Lectate] (Table 4.2, entries 7-9) to offer higher yields as compared to in the ionic liquids alone.

The reaction of **6** with **91** was greatly catalysed by 10 mol% La(OTf)$_3$ in [BMIM][BF_4] to give 62% product and 79% *endo* isomer in 10 h as compared to in ionic liquid alone (Table 4.3, entries 1, 2). A 74% product with 86% *endo* isomer (Table 4.3, entry 3) was obtained in this ionic liquid in the presence of 10 mol% Sc(OTf)$_3$. The reaction proceeded with similar results in other ionic liquids (Table 4.3, entries 4-9). The reactions were also carried out in [BMIM][BF_4] with 2, 5 and 10 mol% of triflates, out of which 10 mol% of triflate resulted into optimum yields and *endo* products. The reaction time for the catalysed reactions in ionic liquids was nearly halved for these reactions as compared to in ionic liquids alone.

Both the triflates in ionic liquids failed to promote the reaction of **6** with **93** with no change in the yields.

Table 4.2 Diels-Alder reactions of **6** with **89** in ionic liquids without and with rare earth metal triflates[a]



6 **89** **90a** **90b**

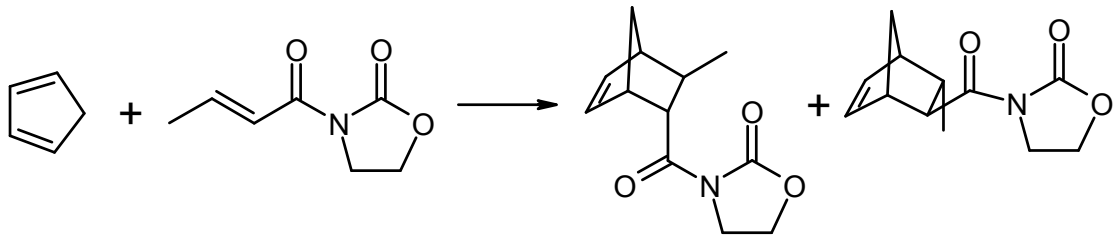
Ionic liquids	Entry	Catalyst	Time (h)	Yield[b] %	*endo/exo*[c]
[BMIM][BF_4]	1	-	3	79	85/15
	2	2 mol% $La(OTf)_3$	0.5	83	86/14
	3	2 mol% $Sc(OTf)_3$	0.5	86	91/09
[BMIM][PF_6]	4	-	3	75	86/14
	5	2 mol% $La(OTf)_3$	0.5	80	87/13
	6	2 mol% $Sc(OTf)_3$	0.5	83	88/12
[BMIM][Lactate]	7	-	3	70	88/12
	8	2 mol% $La(OTf)_3$	0.5	82	88/12
	9	2 mol% $Sc(OTf)_3$	0.5	86	90/10
[EMIM][TFA]	10	-	3	80	86/14
[EMIM][NTf_2]	11	-	3	82	87/13

[a] 2.83 mmol of **6**; 0.71 mmol of **89**; ionic liquid 2 mL.

[b] Isolated yield; No increase in yield observed after the times reported.

[c] Determined by ^{1}H NMR (300 MHz).

Table 4.3 Diels-Alder reactions of **6** with **91** in ionic liquids without and with rare earth metal triflates[a]



6 **91** **92a** **92b**

Ionic liquid	Entry	Catalyst	Time (h)	Yield[b] %	*endo/exo*[c]
[BMIM][BF_4]	1	-	24	14	77/23
	2	10 mol% $La(OTf)_3$	10	62	79/21
	3	10 mol% $Sc(OTf)_3$	10	74	86/14
[BMIM][PF_6]	4	-	24	18	77/23
	5	10 mol% $La(OTf)_3$	10	64	80/20
	6	10 mol% $Sc(OTf)_3$	10	81	82/18
[BMIM][Lactate]	7	-	24	19	77/23
	8	10 mol% $La(OTf)_3$	10	64	80/20
	9	10 mol% $Sc(OTf)_3$	10	90	82/18
[EMIM][TFA]	10	-	24	20	77/23
[EMIM][NTf_2]	11	-	24	21	78/22

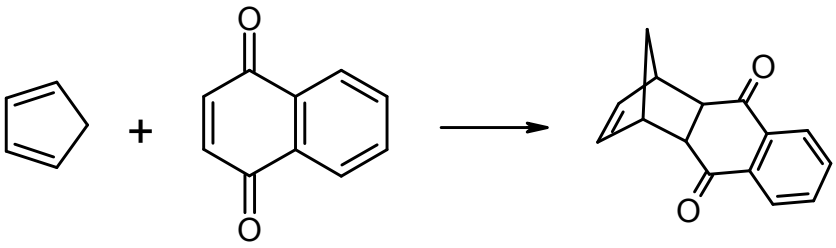
[a] 2.83 mmol of **6**; 0.71 mmol of **91**; ionic liquid 2 mL.

[b] Isolated yield; No increase in yield observed after the times reported.

[c] Determined by ^{1}H NMR (300 MHz).

The reaction of **6** with 1,4-naphthoquinone **29** was also accelerated by triflates in [BMIM][BF_4]. The reaction was completed just in 10 min when catalysed by 1 mol% of triflates to afford very good yield (Table 4.4, entries 2, 3). The reaction when carried out in higher concentration of triflates was noted to be too fast to follow.

Table 4.4 Diels-Alder reactions of **6** with **29** in ionic liquids without and with rare earth metal triflates[a]



6 **29** **30**

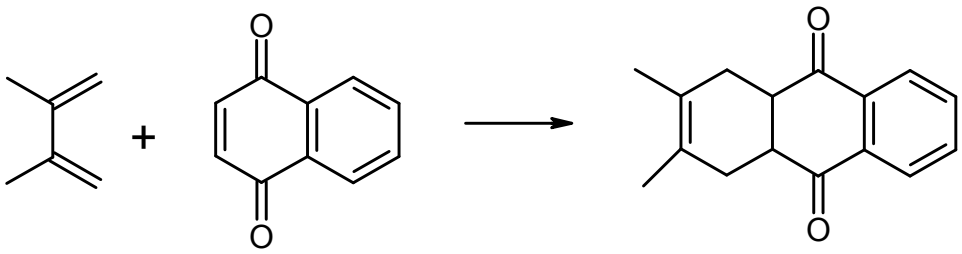
Ionic liquids	Entry	Catalyst	Time (min)	Yield[b] %
[BMIM][BF_4]	1	-	30	77
	2	1 mol% $La(OTf)_3$	10	82
	3	1 mol% $Sc(OTf)_3$	10	84
[BMIM][PF_6]	4	-	30	74
[EMIM][TFA]	5	-	30	78
[EMIM][NTf_2]	6	-	30	79

[a] 2.53 mmol of **6**; 0.63 mmol of **29**; ionic liquid 2 mL.

[b] Isolated yield; No increase in yield observed after the times reported; *endo: exo* = 100:0 determined by ^{1}H NMR (300 MHz).

Cyclipentadiene **6** reacted with 2,3-dimethyl-1,3-butadiene **87** in many ionic liquids to afford about 50% yield in 6 h (Table 4.5). A 2 mol% triflate catalysed the reaction to give quantitative yield just in 2h (Table 4.5, entries 2, 3).

Table 4.5 Diels-Alder reactions of **87** with **29** in ionic liquids without and with rare earth metal triflates[a]



87 **29** **88**

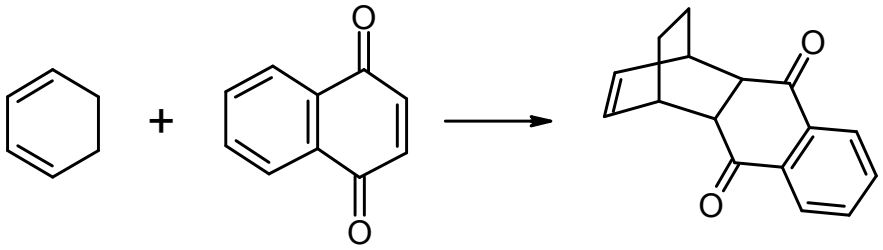
Ionic liquids	Entry	Catalyst	Time (h)	Yield[b] %
[BMIM][BF_4]	1	-	6	42
	2	2 mol% $La(OTf)_3$	2	>99
	3	2 mol% $Sc(OTf)_3$	2	>99
[BMIM][PF_6]	4	-	6	48
[EMIM][TFA]	5	-	6	49
[EMIM][NTf_2]	6	-	6	50

[a] 1.89 mmol of 87; 0.63 mmol of **29**; ionic liquid 2 mL.

[b] Calculated from GC; No increase in yield observed after the times reported.

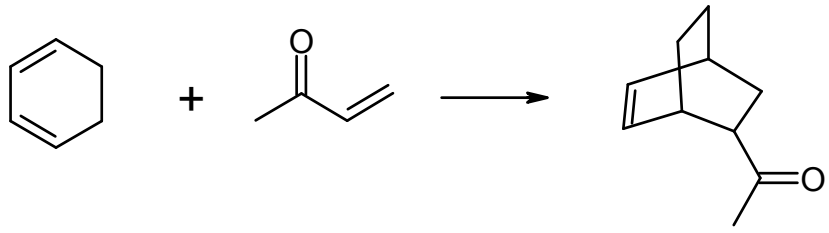
Song *et al.* employed $Sc(OTf)_3$ for catalysing Diels-Alder reactions in ionic liquids. The ionic liquids used were [BMIM][PF_6], [BMIM][SbF_6] and [BMIM][OTf].

They carried out the reaction of 1,3-dimethylbutadiene **(87)** with 1,4-naphthoquinone **(29)** (Scheme 4.1) in the presence of 10 mol% $Sc(OTf)_3$,[251] the amount used usually in conventional organic solvents.[119] The reaction using 10 mol% of catalyst was too fast to control. The reaction proceeded in seconds with sudden generation of heat and color change of the reaction mixture to dark brown. Therefore, they reduced the amount of catalyst gradually to 0.1 mol%, which was sufficient to complete the reaction. It was observed that the use of only 1 equiv. of the ionic liquid as an additive in CH_2Cl_2 solvent gives a satisfactory rate acceleration effect. The reaction rates were compared for both organic solvent (e.g. CH_2Cl_2) and ionic liquid (e.g. [BMIM][PF_6]). Similar rate acceleration as well as improvement of the *endo/exo* selectivity was observed for other substrates also. In [BMIM][PF_6], Diels-Alder reactions of 1,3-cyclohexadiene **(95)** with **29** (Scheme 4.3) and with **13** (Scheme 4.4) proceeded *endo* selectively, *endo:exo* = > 99:1 as compared to 94:6 in CH_2Cl_2 (Scheme 4.3).[119]



95 **29** **96**

Scheme 4.3



95 **13** **97**

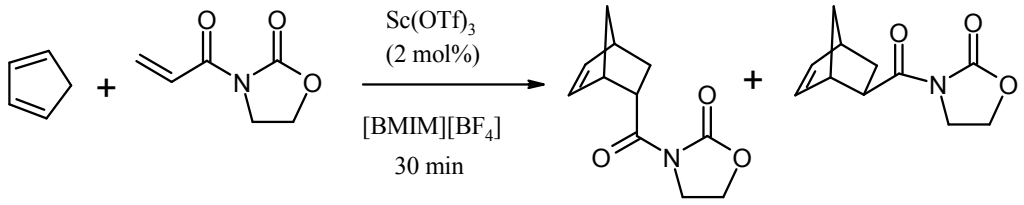
Scheme 4.4

Silvero *et al.* have very recently examined the effect of different Lewis acid catalysts on several Diels-Alder reactions including cyclopentadiene, **6** with methyl vinyl ketone, **13** in particular. In their exhaustive and comparative investigations, they observed that the triflates of Ce^{III}, Sc^{III} and Y^{III} salts were highly active when used in ionic liquid called [HMI][BF_4], where [HMI] stands for 1-hexyl-3-methylimidazolium.[232]

4.3 Recyclability

Considering the practical importance and wide applications of ionic liquids in organic synthesis and chemical industry it is essential to demonstrate efficient recycling of the ionic liquids. The results obtained in our experiment confirm that it is possible to recycle ionic liquid medium up to six runs without any loss of activity. Catalytic systems consisting of triflate and ionic liquid can also be recycled and reutilised after extraction of the products for at least six times without loss of activity and *endo/exo* selectivity. A representative example of recyclability process is shown in the Table 4.6. Both the yields and *endo/exo* product ratio remained unchanged up to six runs. This shows that the recycling can offer very effective results in this case. Our results are also supported by earlier reports.[251] Song *et al.* carried out Diels-Alder reactions in different ionic liquids. The recovered ionic liquid phase containing the catalyst was reused several times without any loss of activity even after the eleventh use.

Table 4.6 Recovery and reuse of the ionic liquid phase containing $Sc(OTf)_3$[a]



6 **89** **90a** **90b**

Run	Yield[b]%	*endo/exo*[c]
1	86	88/12
2	84	86/14
3	81	87/13
4	83	88/12
5	80	87/13
6	82	86/14

[a] 2.83 mmol of **6**; 0.70 mmol of **89**; ionic liquid 2 mL.

[b] Isolated yield.

[c] Determined by ^{1}H NMR (300 MHz).

Thus from these observations it is clear that Diels-Alder reactions carried out in ionic liquids can be further accelerated by rare earth metal triflates. Scandium triflate is found to be more effective in catalysing Diels-Alder reactions than lanthanide triflate. It is possible to achieve good yields even after six recycles of ionic liquids with triflates.

Chapter 5

ASYMMETRIC C-C BOND FORMING REACTIONS

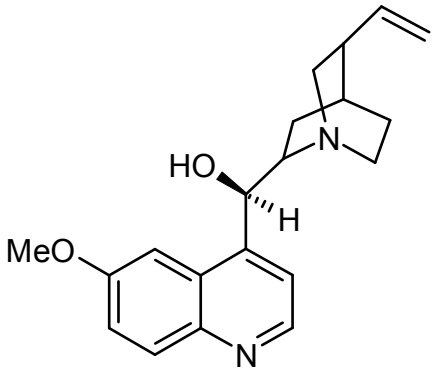
Chapter 5

Asymmetric C-C bond forming reactions

The present chapter emphasizes the role of various solvents on asymmetric C-C bond forming reactions. The chapter is divided into two parts- Part A deals with the effect of solvents on asymmetric Diels-Alder reactions whereas Part B is concerned with the solvents effect on asymmetric Michael reactions.

Part A. Asymmetric Diels-Alder reactions

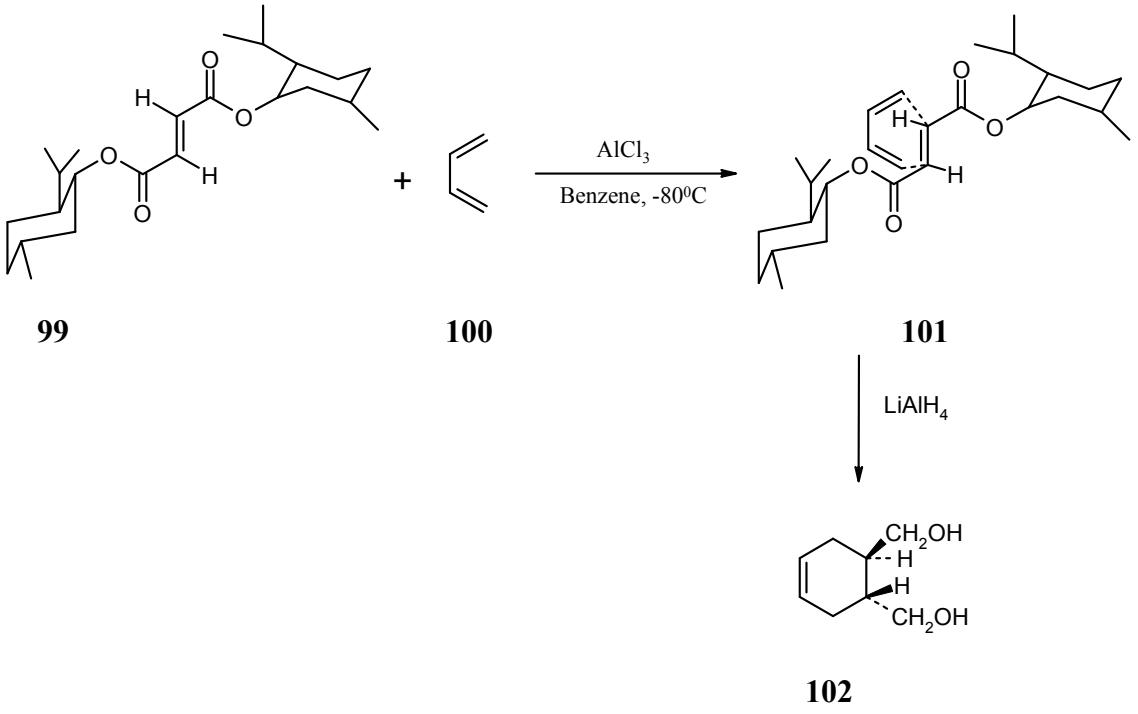
In asymmetric synthesis chirality can be induced in a reaction either by using external chiral agent or by using some chiral auxiliary, which is an integral part of the starting material. We used chiral auxiliary approach where quinine **(98)** was used as



98

chiral inducer. Quinine is a natural white crystalline alkaloid having antipyretic, anti-malarial with analgesic and anti-inflammatory properties and a bitter taste. Quinine was extracted from the bark of the South American cinchona tree, isolated and named in 1817 by French researchers Pierre Joseph Pelletier and Joseph Caventou. The name was derived from the original Quechua (Native American) word for the cinchona tree bark, "Quina" or "Quina-Quina", which roughly means "bark of bark" or "holy bark". Cinchona trees remain the only practical source of quinine. Several efficient total syntheses of quinine have been achieved,[252] but none of them can compete in economic terms with isolation of the alkaloid from natural sources.

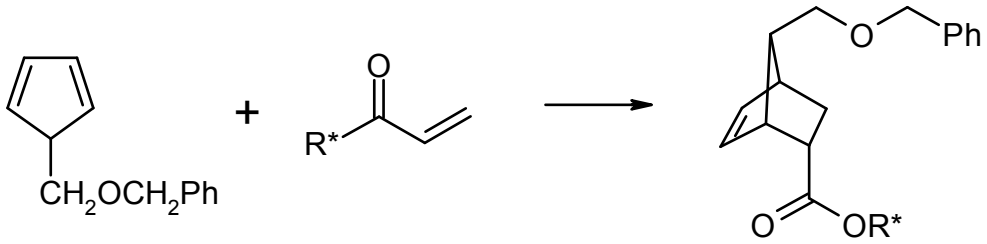
Asymmetric Diels-Alder reactions using chiral auxiliary was first introduced by Walborsky *et al.*[253] They used menthol as chiral auxiliary. The reaction of dimenthyl fumarate **(99)** and 1,3-butadiene **(100)** in presence of catalytic amount of $AlCl_3$ gave **102** , after reduction of the product **101** with lithium aluminium hydride, with 57% enantioselectivity (Scheme 5.1).



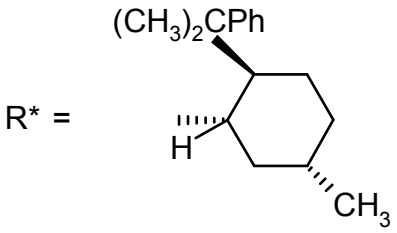
99 **100** **101** **102**

Scheme 5.1

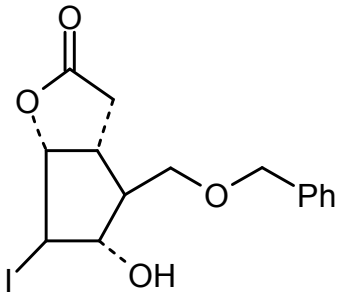
Later on, it was found that Lewis acids (e.g. $AlCl_3$) can catalyse Diels-Alder reaction, allowing to run it in very mild conditions, often below 0^0C.[77] The activation process occurs by coordination of the carbonyl group of dienophile to the Lewis acid.[254,255] The mildness of the catalytic reaction allowed very high levels of diasteromeric excess (<95%) with menthyl acrylate or menthyl fumarate as a diene.[253,256] Corey developed an asymmetric Diels-Alder approach to prostaglandin synthesis.[157] Treatment of the optically pure acrylate **104** with 5-benzyloxymethyl cyclopentadiene **(103)** afforded an 89% of the *endo* adduct **105**. This reaction was used for the synthesis of the key prostaglandin intermediate **60** in optically pure form.



103 **104** **105**



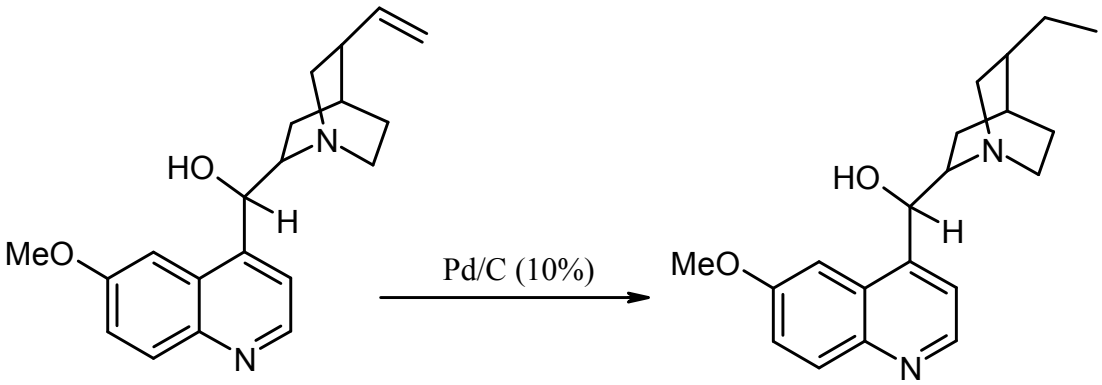
Scheme 5.2



60

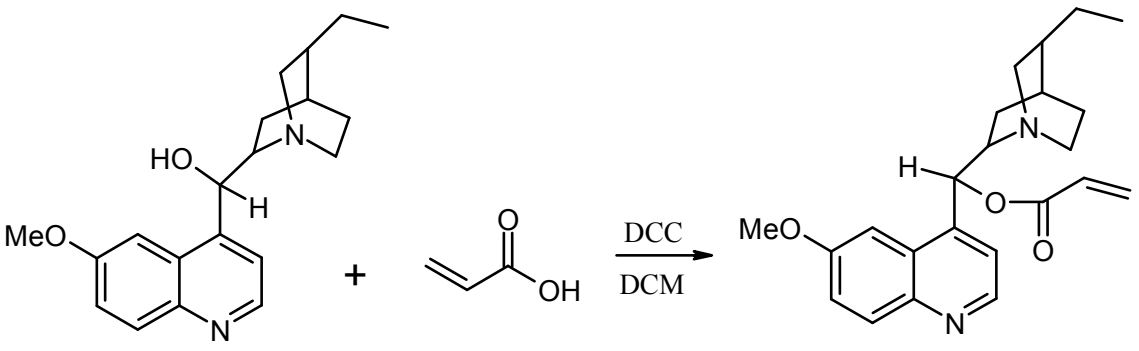
Many natural products can be prepared at an early stage of the synthetic scheme by taking advantage of an asymmetric Diels-Alder reaction. For example, loganine has been obtained from a Diels-Alder reaction on a crotonate of a terpene derivative. The cycloadduct was prepared with very high enantioselectivity.[257] Chiral auxiliaries of various kinds have been subsequently developed for thermal or catalytic Diels-Alder reactions.[128,141,192,258-266]

We carried out Diels-Alder reactions of cyclopentadiene **6** and chiral dienophiles derived from quinine. Terminal double bond attached to the aza-bicyclic ring of quinine **98** was first reduced by 10% Pd/C to avoid the possibility of the same to act as dienophile (Scheme 5. 3). Acrylic caid **(34)** was then attached to the hydroxyl group of hydroquinine **(106)** by esterification reaction (Scheme 5.4). Same treatment with crotonic acid **(74)**



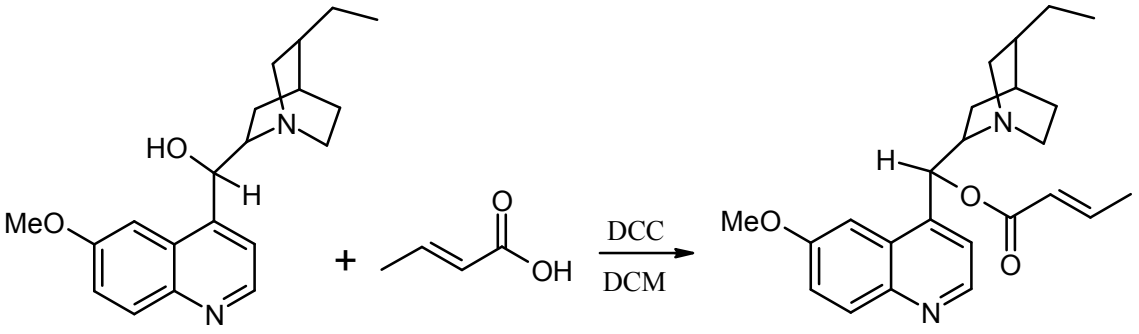
98 **106**

Scheme 5.3



106 **34** **107**

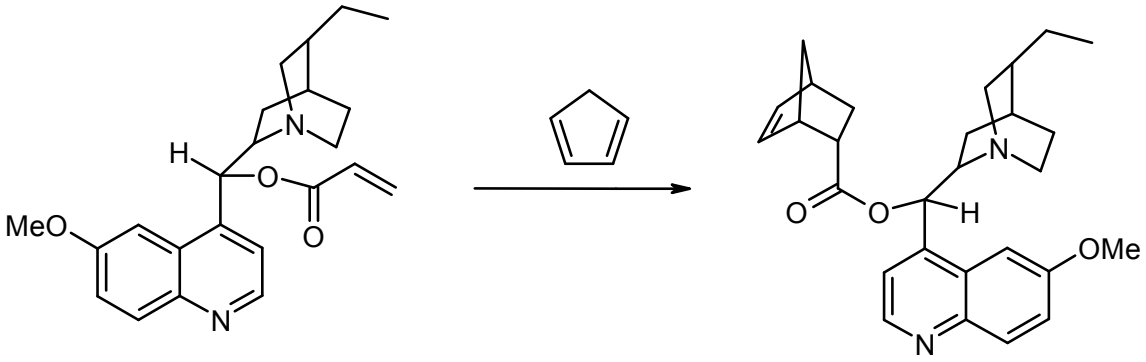
Scheme 5.4



106 **74** **108**

Scheme 5.5

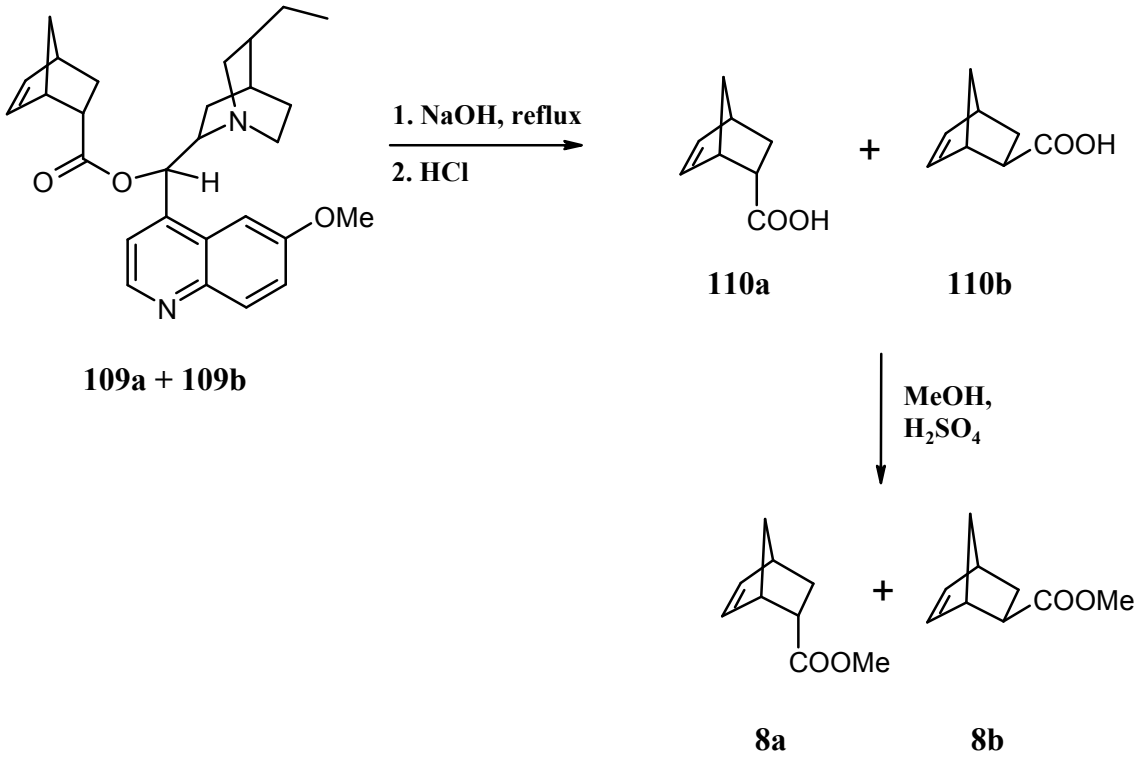
afforded **108** (Scheme 5.5). After getting the chiral dienophiles (**107** and **108**) we carried out asymmetric Diels-Alder reactions in different solvent media. The aim of our work was to explore the solvent effect on asymmetric Diels-Alder reactions of quinine derived chiral auxiliary. Since our work is mainly concentrated on the use of green solvents, the reaction of cyclopentadiene **6** and **107** (Scheme 5.6) was first carried out in water, and ionic liquids. The *endo-exo* products **(109a, 109b)** were hydrolysed to get the bicyclic



107 **109a + 109b**

(Mixture of *endo*- and *exo* products)

Scheme 5.6



109a + 109b **110a** **110b**

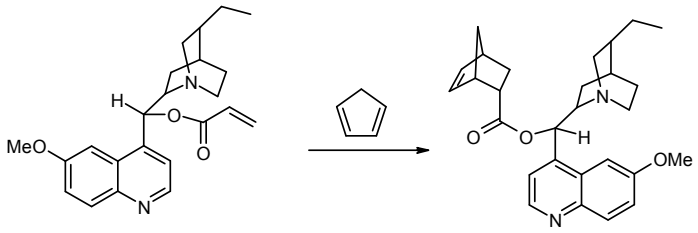
8a **8b**

Scheme 5.7

acids **(110a, 110b)** as well as to recover the catalyst. The resultant acids were then treated with methanol in the presence of conc. sulfuric acid to get the methyl esters (Scheme 5.7). The enantiomeric excess (*ee*) of the final *endo-exo* esters were obtained from gas chromatograph using chiral column.

The reaction of **6** and **107** (Scheme 5.7) in water afforded 65% yield with 79% *endo* selectivity (Table 5.1). The enantiomeric excess obtained was 15%. The same reaction was carried out in two different ionic liquids [BMIM][BF_4] and [EMIM][NTf_2]. Although good yields as well as selectivity were observed, the enantioselectivities obtained were very low.

Table 5.1 Asymmetric Diels-Alder reaction of **6** and **107** in water and ionic liquids



Solvent	**% Yield**[a]	***endo/exo***[b]	**% *ee***[b]
Water	65	79/21	15
[BMIM][BF_4]	62	84/16	10
[EMIM][NTf_2]	66	82/18	11

[a] Isolated yield

[b] From GC

Since enantioselctivities obtained in these green solvent media were very less, we then next carried out the reaction of **6** with **107** in conventional organic solvents. (Table 5.2)

Table 5.2 Asymmetric Diels-Alder reaction of **6** and **107** in organic solvents

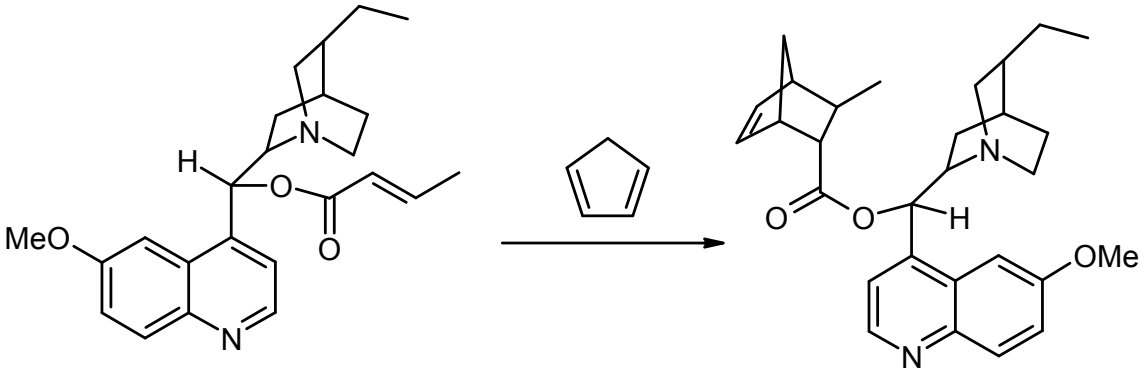
Solvent	**% Yield**[a]	***endo/exo***[b]	**% *ee***[c]
Toluene	60	79/21	30
CCl_4	55	78/22	29
p-Xylene	54	77/23	27
DCM	70	90/10	19
Diethyl ether	52	78/22	18
THF	61	78/22	16
1,4-Dioxane	50	85/15	8
Methanol	72	90/10	25
1-Butanol	62	86/14	21
Methanol: water (1:1)	75	87/13	17
THF: water (1:1)	62	85/15	15
THF: water (1:4)	75	87/13	20
THF: water (4:1)	64	84/16	17
Dioxane: water (1:1)	61	90/10	24
5 M LPDE	73	89/11	25
1 M $LiClO_4$-THF	65	83/17	17

[a] Isolated yield

[b] From GC

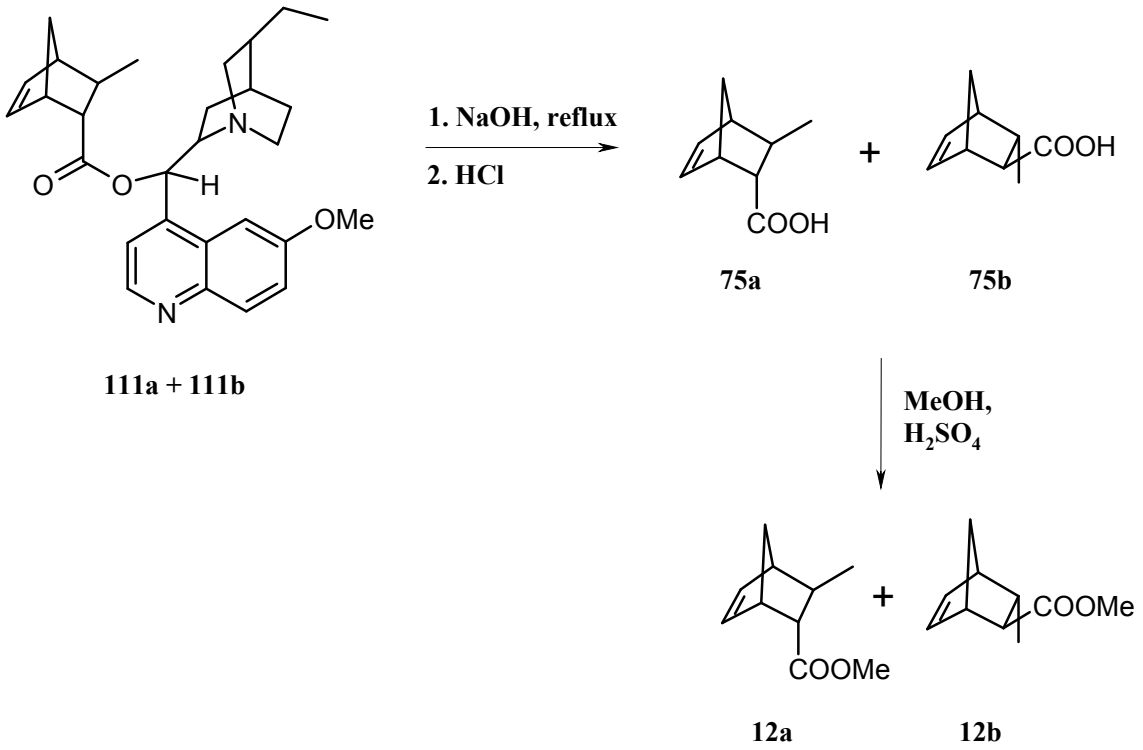
Effect of cosolvents on the asymmetric aspects of Diels-Alder reaction were also studied, but no particular trend was observed. The literature reports have shown that enantioselectivity in Diels-Alders reactions can be enhanced by the application of external high pressure.[267-270] We carried out the Diels-Alder reaction of **6** with **107** in 5 M LPDE solution, since 5 M LPDE is known to possess internal pressure of 16 kbar.[271] This internal pressure is equivalent and a substitute to the external high pressure used for the synthesis of cantharidin, a natural product.[88] We did not observe any exceptional benefit by the use of 5 M LPDE and so is for 1 M LP-THF (it also possesses high internal pressure). The enantioselectivities obtained were 25% in 5 M LPDE and 17% in 1 M LP-THF respectively.

In order to study the effect of substituents on asymmetric Diels-Alder reactions, we carried out the reaction of **6** with **108** (Scheme 5.8) in water, ionic liquids and different organic solvents. The product was hydrolysed to get the bicyclic acids (112a, 112b), followed by treatment with methanol and conc. sulfuric acid.



108 **111a + 111b**

Scheme 5.8

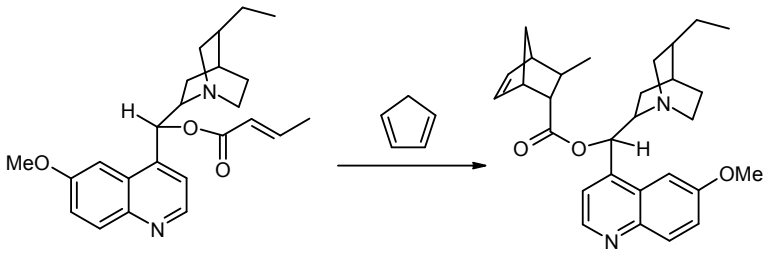


111a + 111b **75a** **75b** **12a** **12b**

Scheme 5.9

The reaction of **6** and **108** was first carried out in two green solvents water and ionic liquids. Although *endo-exo* selectivities obtained were satisfactory, the enantioselectivities were very low (Table 5.3). Therefore, we next employed conventional organic solvents to carry out the reaction of **6** and **108**. It is clear from the Table 5.3 that nonpolar solvents (except dioxane) are better solvents for asymmetric Diels-Alder reaction. Among the solvents studied toluene gave the highest enantioselectivity (38%), whereas the percentage *ee* obtained in dioxane was only 6%. In methanol the percentage *ee* obtained was 24%, whereas 19% *ee* was obtained in highly polar solvent water. At this stage, it is however not possible to state that polarity of solvents plays any role here.

Table 5.3 Asymmetric Diels-Alder reaction of **6** and **108** in water, ionic liquids and organic solvents



Solvent	% Yield[a]	*endo/exo*[b]	% *ee*[c]
Water	37	73/27	19
[BMIM][BF_4]	32	67/33	13
Toluene	30	59/41	38
p-Xylene	29	60/40	28
CCl_4	26	74/26	24
Dioxane	22	78/22	6
Methanol	40	81/19	24
THF: water (1:4)	38	65/35	21
5 M LPDE	41	81/19	21

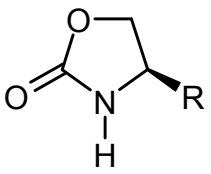
[a] Isolated yield

[b] From GC

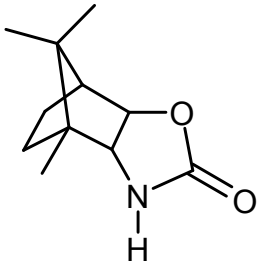
At this point it is not clear the exact role of solvents in asymmetric Diels-Alder reactions. However, there must be some solvent properties which are playing role in the transition state to form one isomer in excess (although not very high) over the other.

Part B. Asymmetric Michael reaction

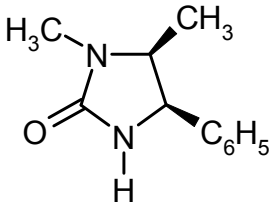
One of the most popular and reliable methods of asymmetric Michael reaction has proved to be *via* stoichiometric chiral auxiliaries. Following this methodology, several optically pure β -substituted carbonyl derivatives have been synthesized *via* asymmetric Michael additions to chiral oxazolidinones,[272-275] ester,[276,277] amide[278,279] or imide derivatives.[280,281] Thus, Evans's oxazolidinones **l12a,b** and related chiral auxiliaries like **l12c,** (4*R*,5*S*)-l,5-dimethyl-4-phenyl-2-imidazolidinone **(113),** trityloxymethyl-γ-butyrolactam **(114)** or 8-phenylmenthol **(115)** have been linked to α,β-unsaturated acids to allow asymmetric conjugate addition of several nucleophiles (Figure 5.1).



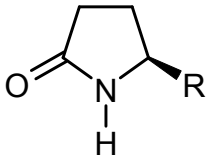
112a, R= $CH_2C_6H_5$
112b, R= C_6H_5



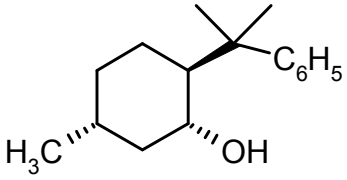
112c



113



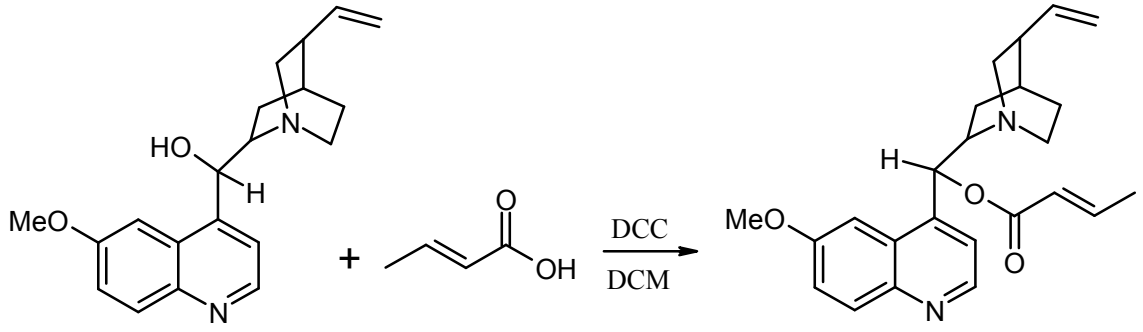
114, R= $CH_2OC(C_6H_5)_3$



115

Figure 5.1

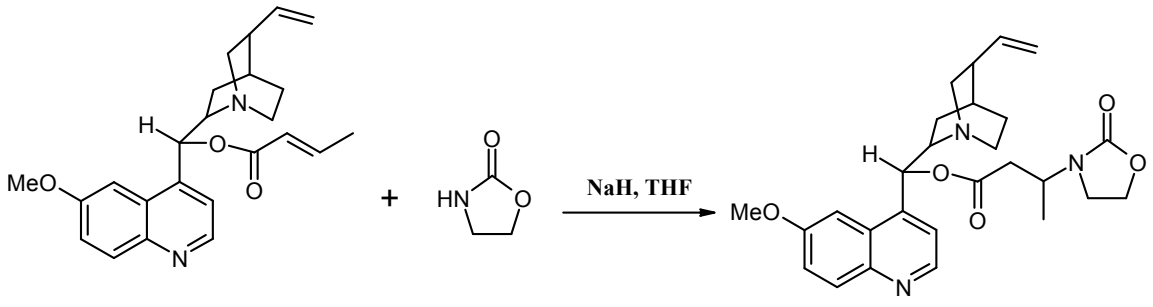
We carried out Michael addition of 2-oxazolidinone to chiral *α,β*-unsaturated carbonyl compounds derived from quinine **98** in different solvent media. Crotonic acid **74** was first attached to the hydroxyl group of **98** by esterification reaction (Scheme 5.10).



98 **74** **116**

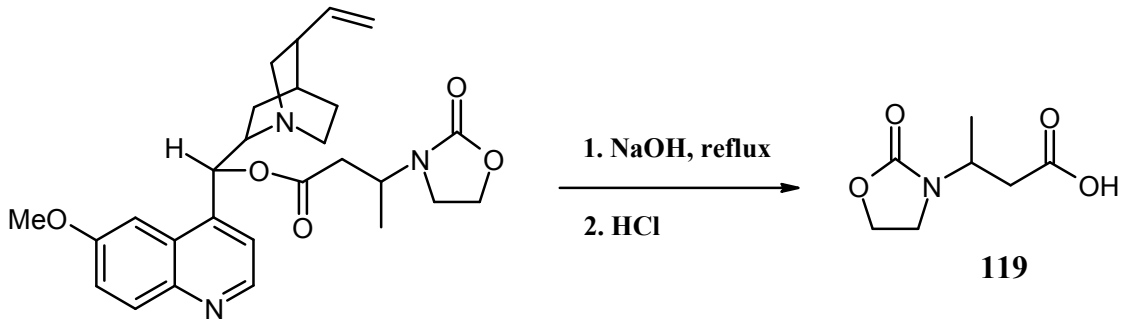
Scheme 5.10

In the next step asymmetric Michael reaction of 2-oxazolidinone **(117)** and chiral *α,β*-unsaturated carbonyl compounds **(116)** derived from **98** was carried out in presence of a base (Scheme 5.11). The product **118** was then hydrolysed to get the acid adduct **119** as well as to get the catalyst back (Scheme 5.12). The resultant acid **119** was then treated with methanol in presence of conc. sulfuric acid to get the methyl ester **120** (Scheme 5.12). The enantiomeric excess (*ee*) of the final methyl ester **120** was obtained from gas chromatograph using chiral column which was found to be 34%. Comparable enantioslectivities were obtained in other organic solvents like diethyl ether, toluene etc. It was not possible to use water as solvent media because in water **116** readily undergoes ester hydrolysis in presence of a base. Again, literature report shows that ionic liquids get protonated in presence of base, so they are no longer inert solvents.[282] Several side

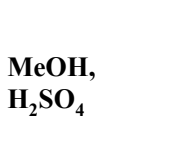


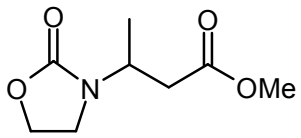
116 **117** **118**

Scheme 5.11



118 **119**





120

34% *ee*

Scheme 5.12

reaction products are possible in presence of base. To avoid these possibilities, ionic liquids were not chosen for our experiment. Lowering of reaction temperature sometimes help in getting high enantioselectivities. But we did not observe any enhancement of enantioselectivities while carrying out the reaction at -20^0C and -78^0C respectively. Our observations are supported by the literature report.[283] Shirakawa and Kobayashi carried out asymmetric Michael additions in different solvents. They observed negligible solvent effect on stereoselectivity.

Through this work, we have shown that stereocontrol can be obtained to some extent in the conjugate addition of oxazolidinone to chiral crotonate derived from optically pure quinine. The chiral auxiliaries can be recycled, so although stoichiometric quantities are needed, there is no waste.

Chapter 6

SUMMARY AND CONCLUSIONS

Chapter 6

Summary and conclusions

In this Ph. D. dissertation an attempt has been made to investigate the origin of forces responsible for spectacular rate enhancement as well as stereoselectivity changes for Diels-Alder reactions in various green solvents. The green solvents used were water, aqueous salt solutions and ionic liquids. Diels-Alder reactions are found to be faster in water as compared to those in organic solvents. Unusual acceleration of Diels-Alder reaction by water was attributed to the "hydrophobic effect", in which the hydrophobic interactions brought together the two nonpolar groups in the transition state. Any additives which increase the hydrophobic effect also increase the reaction rate and *endo/exo* ratios. Salts are known to alter the hydrophobicity of the medium. Salts are of two types- salting-out agents and salting-in agents. Salting-out agents increase the hydrophobic effect, thereby increasing the reaction rate as well as *endo/exo* ratios. The opposite phenomenon is observed in case of salting-in agents. The reaction rate and *endo/exo* ratios go on decreasing with increasing concentration of salting-in agents. Diels-Alder reactions are in general *endo* selective. According to Alder *endo* rule there is an additional bonding interaction, known as secondary orbital interaction present in the *endo* transition state. This interaction is absent in the *exo* transition state. This secondary orbital interaction stabilizes *endo* and lowers the energy of that transition state relative to *exo*. But there are some exceptions to this *endo* rule. For example, the reaction of cyclopentadiene and methyl methacrylate is an *exo* selective reaction whereas the reaction of cyclopentadiene and methyl *trans* crotonate shows borderline behavior. The reaction of cyclopentadiene and methyl *trans* crotonate has been carried out in water and in other organic solvents. The $endo_{carboxy}/exo_{carboxy}$ ratios for this reaction show that the $endo_{carboxy}/exo_{carboxy}$ ratio obtained in water is lower than those obtained in other solvents. This reaction in water was expected to give a higher $endo_{carboxy}/ exo_{carboxy}$ ratio, similar to that of the reaction of cyclopentadiene with methyl acrylate or other Diels-Alder reactions. In general, Diels-Alder reactions in water offer higher *endo*/*exo* ratios as

compared to those in conventional organic solvents, but this was not the case for the reaction of cyclopentadiene with methyl *trans* crotonate. This anomalous observation has been explained on the basis of hydrophobic effect. It has been suggested that hydrophobic effects influence the stabilization of the geometry of the transition states. The reaction of cyclopentadiene and methyl *trans* crotonate has also been carried out in presence of salt solutions. The *endo/exo* ratios were found to decrease with increasing concentration of salting-out agents, whereas opposite behavior was observed for salting-in agents. This anomalous observation has also been explained on the basis of hydrophobic effect.

Due to the environmental hazards caused by volatile organic solvents, ionic liquids are being used as potential alternatives. Diels-Alder reactions have been carried out in different ionic liquids. Rare earth metal triflates as Lewis acid catalysts have been used in conjunction with ionic liquids. This new catalytic system (ionic liquid and triflate) has been found to be more effective in Diels-Alder reactions.

In asymmetric synthesis chirality can be induced in a reaction either by using external chiral agent or by using some chiral auxiliary, which is an integral part of the starting material. Efforts have been made to carry out asymmetric Diels-Alder and Michael reactions of quinine derived chiral auxiliaries. Asymmetric Diels-Alder and Michael reactions have been carried out in different solvent media. Solvents are found to play significant role in getting one isomer in excess over the other.

The research work carried out during this period can be concluded as follows:

1. Hydrophobic effect dominates over secondary orbital interactions to explain the stereoselectivity ratio of a particular Diels-Alder reaction in aqueous salt solutions.
2. Ionic liquids in conjunction with rare earth metal triflates are more effective in catalysing Diels-Alder reactions.
3. Nature of solvent exerts a strong influence on the enantiomeric composition of cycloadduct in asymmetric Diels-Alder reactions and addition products in Michael reactions.

Chapter 7

EXPERIMENTAL SECTION

Chapter 7

Experimental section

This chapter describes the detail procedure of the experiments carried out during the investigations.

7.1 Reaction of cyclopentadiene (6) and methyl *trans* crotonate (11)

The change of stereoselectivity of the Diels-Alder reaction between **6** and **11** was investigated. The reaction was carried out in different solvent media like pure water, organic solvents and their aqueous salt solutions. The salts chosen were LiCl, NaCl, $MgCl_2$, $CaCl_2$, KCl, urea, $LiClO_4$ and GnCl.

A typical procedure to carry out a Diels-Alder reaction of **6** with **11** (Scheme 1.9) is given below.

6 was freshly cracked from its dimer (Merck) just before its use. **11** was prepared by heating freshly crystallized *trans*-crotonic acid **(74)** with methanol and sulfuric acid for 18 h by the procedure given elsewhere.[37] After concentration of the mixture and its subsequent dilution with water and extraction with ether the organic portion was washed with bicarbonate and water, dried over anhydrous sodium sulfate. The product was distilled at 118^0C. The salts used in the investigation were of AR grade and were dried in an oven at 150^0C for 5 h before their use. Their aqueous solutions were made in deionized water. Ethylene glycol (Aldrich, purity > 99+%, spectrophotometric grade) and formamide (Aldrich, purity > 99+%, spectrophometric grade) were used in the investigation.

In a typical run, freshly cracked **6** (1.27 g, 1.58 mmol) was transferred into 5 mL of solvent. Then **11** (0.48 g, 4.80 mmol) was dissolved in 5 mL of the solvent. The solution containing **6** was added to the solution containing **11**. The reaction mixture was magnetically stirred at 27^0C for about 12 h. Ethyl acetate was added to the reaction

mixture, organic layer was separated, washed with water, brine solution, dried over anhydrous sodium sulfate. Solvent was then removed to get the crude product. The products were purified by column chromatography using 10% ethyl acetate in hexane as eluent.

The *endo*- and *exo*-products were characterized using NMR.[177,180]

7.2 Stereochemical Assignment

Crotonic acid **(74)** (3 g, 34.88 mmol) was condensed with **6** (6.91 g, 104.64 mmol) thermally, and the resultant *endo* and *exo* bicyclic acids **(75a, 75b)** were separated by iodolactonization (Scheme 3.5).[192] To a solution of 0.50 g (3.29 mmol) of mixture of *endo* and *exo* (adduct) acid **(75a + 75b)** in 20mL CH_2Cl_2 was added saturated solution of sodium bicarbonate (aq. 15 mL). After 10 min, iodine (1.25 g, 4.93 mmol) was added to rapidly stirred two phase reaction mixture at 0^0 C, protected from light and stirred for 10 h at 0^0 C. The mixture was then diluted with CH_2Cl_2 and sodium thiosulfate was added to reduce the excess iodine. Organic layer was separated, washed with water, brine solution, dried over anhydrous sodium sulfate. Solvent was then removed to get the iodolactone **(76)**.

The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether to get the *exo* carboxy isomer **(75b)**, contaminated by any unreacted crotonic acid.

The iodolactone **76** was cleaved reductively with zinc and acetic acid to the pure *endo*-acid **(75a)** in high yield.[193] Zinc dust (0.82 g, 123.07 mmol) was slowly added to a solution of **76** (0.70 g, 2.52 mmol) in 5 mL of glacial acetic acid. After three hours, the mixture was filtered, the solid was washed with hot water, and the combined filtrates were further diluted with water and extracted with ether. The ether was extracted with 5% sodium bicarbonate solution, which on acidification yielded *endo* acid **(75a)** as white solid, m.p. 105-106.8^{0}C.

The bicyclic acids **(75a** and **75b)** were then individually treated with methanol and conc. sulfuric acid under reflux for 18 h to get the corresponding esters *endo*-2-carbomethoxy-*exo*-3-methylbicyclo[2,2,1]hept-5-ene **(12a)** and *exo*-2-carbomethoxy-*endo*-3-methylbicyclo[2,2,1]hept-5-ene **(12b)**. ^{1}H NMR spectra of the mixture of *endo*

and *exo* as well as pure *endo* ester were recorded. Chemical shifts are expressed in δ units relative to tetramethylsilane (TMS) signal as internal reference in $CDCl_3$.

NMR, 200 MHz, $CDCl_3$

endo-2-carbomethoxy-*exo*-3-methyl- and *exo*-2-carbomethoxy-*endo*-3-methylbicyclo[2,2,1]hept-5-ene **(12a, 12b)** : δ 3.62 (s, *endo*-2-OCH_3), 1.17 (d, *exo*-3-CH_3), 3.67 (s, *exo*-2-OCH_3), 0.90 (d, *endo*- 3-CH_3).

endo-2-carbomethoxy-*exo*-3-methylbicyclo[2,2,1]hept-5-ene **(12a)** : δ 6.26 (dd, 1H), 5.98 (dd, 1H), 3.59 (s, 3H), 3.07 (br s, 1H), 2.43 (br s, 1H), 2.34 (t, 1H), 1.75-1.83 (m, 1H), 1.39-1.54 (m, 2H), 1.17 (d, 3H).

The products were analysed by gas chromatograph (Varian CP 3800) using a CP SIL 5CB column. The retention times for *endo* and *exo* products were 8.411 m and 8.278 m, respectively. GC analyses of the individual isomers were also taken and were found to be 8.633 m for the *endo* and 8.249 m for the *exo* ester. GC and NMR were also used to check the dimerization of **6**, which was found to be negligible.

The reaction was carried out three times and each value of the *endo*/*exo* ratio plotted in Figure 3.5 is an average quantity.

7.3 Solubility of methyl *trans* crotonate (11)

The solubility of **11** in solvents and their salt solutions was measured using a Varian Cary 50 UV visible spectrophotometer. Each solution was equilibrated for 3 h at 25^0C. The bottom layer was removed, diluted and absorbance measured at 210 nm for water medium. In the case of ethylene glycol, the absorbance was measured at 208 nm. The changes in ionic concentrations produced negligible effect on the absorptivity of **11**. The measurements made in triplicate were averaged with a maximum of deviation of 0.05 mM in solubility value.

7.4 Synthesis of substrates

Synthesis of acyl oxazolidinones (89, 91, 93) are given below:

7.4.1 Preparation of *N*-acryloyl-2-oxazolidinone (89)

To a solution of acrylic acid **(34)** (1.08 g, 14.94 mmol) and triethylamine (2.91 g, 28.74 mmol) in dry THF was added acryloyl chloride (1.26 g, 13.79 mmol) at -20^{0}C. A white solid was formed instantaneously. The mixture was stirred at -20^{0}C for 1 h. Lithium chloride (0.55 g, 13.19 mmol) was added followed by 2-oxazolidinone (1 g, 11.49 mmol).[284] The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by addition of 0.2 N HCl (2 equiv), and THF was removed *in vacuo.* The residue was partitioned between ethyl acetate and 0.2 N HCl. The organic layer was washed subsequently with 0.2 N HCl, brine, 1 M sodium bicarbonate, and brine. The organic solution was then dried over sodium sulfate and filtered. Ethyl acetate was removed *in vacuo*. Product was purified by column chromatography using 30% ethyl acetate in pet ether. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.5 (dd, 1H), 6.5 (d,1H), 5.83 (d, 1H), 4.39 (t, 2H), 4.04 (t, 2H).

7.4.2 Preparation of *N*-crotonyl-2-oxazolidinone (91)

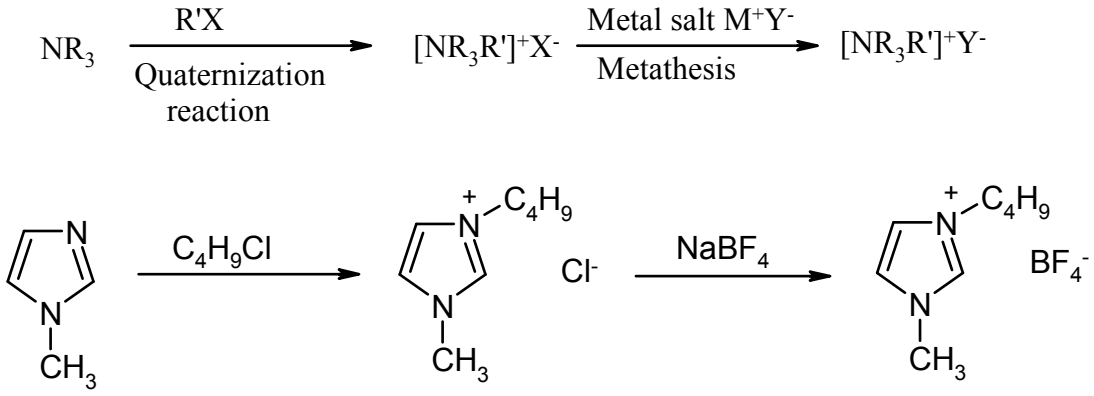
To a solution of crotonic acid **(74)** (6.43 g, 74.71 mmol) and triethylamine (14.51 g, 143.66 mmol) in dry THF was added crotonyl chloride (7.24 g, 68.96 mmol) at -20^{0}C. A white solid was formed instantaneously. The mixture was stirred at -20^{0}C for 1 h. Lithium chloride (2.66 g, 63.22 mmol) was added followed by 2-oxazolidinone (5 g, 57.47 mmol). The mixture was allowed to warm to room temperature and stirred for 4 h. Work-up procedure is same for the preparation of **89**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.28 (dd, 2H), 4.5 (t, 2H), 4.16 (t, 2H), 2.06 (d, 3H).

7.4.3 Preparation of *N*-cinnamoyl-2-oxazolidinone (93)

To a solution of cinnamic acid (2.21 g, 14.95 mmol) and triethylamine (2.91 g, 28.74 mmol) in dry THF was added cinnamoyl chloride (2.31 g, 13.79 mmol) at -20^{0}C. A white solid was formed instantaneously. The mixture was stirred at -20^{0}C for 1 h. Lithium chloride (0.55 g, 13.19 mmol) was added followed by 2-oxazolidinone (1 g, 11.49 mmol). The mixture was allowed to warm to room temperature and stirred for 4 h. Work-up procedure is same for the preparation of **89**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.64 (m, 2H), 7.59 (m, 2H), 7.39 (t, 3H).

7.5 Synthesis of ionic liquids

The ionic liquids were synthesized according to the procedure given in the literature.[109,285-288] The generalized schemes to synthesize ionic liquids are as shown below.



Scheme 7.1 Typical synthetic scheme of ionic liquids

7.5.1 Synthesis of 1-butyl-3-methyl imidazolium chloride [BMIM]Cl

The 1-methyl imidazole (5 g, 60.98 mmol) obtained from Merck was taken in three neck round bottom flask fitted with a water condenser and a gas inlet. 1-chlorobutane (9.03 g, 97.56 mmol) (Merck) was added to the reaction vessel with continuous magnetic stirring under nitrogen. The reaction mixture was heated until two phases were formed. The top phase, containing the unreacted starting material, was decanted and ethyl acetate (A. R. grade 300 mL) was added to the vessel. The reaction mixture was washed with ethyl acetate thrice. The product was slightly yellow. The product was recrystallized from acetonitrile and dried under vacuum at 80^{o}C for 6 h to yield pure crystalline [BMIM]Cl. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.0 (s, 1H), 7.3 (d, 2H), 4.4 (t, 2H), 4.1(s, 3H), 1.9(m, 4H), 1.4(m, 4H), 1.0 (t, 3H).

7.5.2 Synthesis of 1-butyl-3-methyl imidazolium tetrafluoroborate [BMIM][BF_4]

A solution of [BMIM]Cl (4.09 g, 23.42 mmol) in acetone (50 mL) at room temperature was added to sodium tetrafluoroborate (2.57 g, 23.42 mmol). After 24 h stirring, the resulting NaCl precipitate was then filtered through a plug of celite and volatiles were removed by rotary evaporation to a yellowish clear liquid. The product was dried for 6 h under high vacuum. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.13 (s, 1H), 7.68 (d, 2H), 4.30 (t, 2H), 4.04 (s, 3H), 1.99 (m, 2H), 1.47 (m, 2H), 1.03 (t, 3H).

7.5.3 Synthesis of 1-butyl-3-methyl imidazolium hexaflurophosphate [BMIM][PF_6]

The same procedure was used as for [BMIM][BF_4]. A solution of [BMIM]Cl (5.72 g, 32.87 mmol) in acetone (50 mL) at room temperature was added to sodium

hexafluorophosphate (5.52 g, 32.87 mmol). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.80 (s, 1H), 7.42 (d, 2H), 4.22 (t, 2H), 3.99 (s, 3H), 1.88 (m, 2H), 1.40 (m, 2H), 1.01 (t, 3H).

7.5.4 Synthesis of 1-butyl-3-methyl imidazolium lactate [BMIM][Lactate]

The same procedure was used as for [BMIM][BF_4]. A solution of [BMIM]Cl (2.24 g, 12.83 mmol) in acetone (25 mL) at room temperature was added to sodium L-Lactate (1.44 g, 12.83 mmol). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.99 (s, 1H), 6.92 (d, 2H), 3.43 (t, 2H), 3.20 (s, 3H), 3.04 (m, 2H), 1.10 (m, 2H), 0.62 (m, 5H), 0.21 (t, 3H).

7.5.5 Synthesis of 1-butyl-3-methyl imidazolium tetrafluoroborate [EMIM]Br

The same procedure was used as for [BMIM]Cl. Under vigorous stirring freshly distilled 1-bromoethane (15.24 g, 121.95 mmol) was added dropwise over 1 h to 1-methyl imidazole (5 g, 60.98 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.08 (s, 1H), 7.54 (d, 2H), 4.23 (q, 2H), 3.95 (s, 3H), 1.43 (t, 3H).

7.5.6 Synthesis of 1-ethyl-3-methyl imidazolium tetrafluoroborate [EMIM][BF_4]

The same procedure was used as for [BMIM][BF_4]. A solution of [EMIM]Br (2 g, 10.47 mmol) in acetone (25 mL) at room temperature was added to sodium tetrafluoroborate (1.15 g, 10.47 mmol). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.19 (s, 1H), 7.01 (d, 2H), 3.62 (q, 2H), 3.28 (s, 3H), 0.82 (t, 3H).

7.5.7 Synthesis of 1-ethyl-3-methyl imidazolium trifluoroacetate [EMIM][TFA]

Trifluoroacetic acid (3.93 g, 34.48 mmol) was slowly added to a stirred slurry of freshly prepared silver (I) oxide (4 g, 17.24 mmol) in 50mL distilled water over 10 min. To avoid photodegradation of silver (I) oxide, the reaction mixture was fully covered with aluminum foil. Until the silver (I) oxide was completely reacted, a solution of [EMIM]Br (6.59 g, 34.48 mmol) in 50mL distilled water was added to the reaction mixture and stirred at room temperature for 2 h. The yellow precipitate of silver (I) bromide was filtered off, and the solvent was removed at 65^0C under vacuum. The resulting salt is a brown liquid. It was then dried for 6 h under high vacuum. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.88 (s, 1H), 8.05 (d, 2H), 4.57 (q, 2H), 4.24 (s, 3H), 1.72 (t, 3H).

7.5.8 Synthesis of 1-ethyl-3-methylimidazolium bis((trifluoromethyl) sulfonyl) amide [EMIM][NTf_2]

[EMIM]Br (10 g, 52.36 mmol) was dissolved in 30 mL of distilled water and lithium bis((trifluoromethyl)sulfonyl)amide (15.03 g, 52.36 mmol) in 10 mL distilled water was added with vigorous stirring. After 1 h, the phases were allowed to separate and the upper aqueous phase was decanted. Distilled water was added to the ionic liquid phase and the mixture was stirred for 15 m. The solution was extracted by 100 mL of CH_2Cl_2, and the extract was concentrated and dried for 2 h at 60^0C under high vacuum. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.36 (s, 1H), 6.88 (d, 2H), 3.70 (q, 2H), 3.41 (s, 3H), 1.02 (t, 3H).

7.5.9 Synthesis of 1-octyl-3-methyl imidazolium tetrafluoroborate [OMIM][BF_4]

The same procedure was used as for [BMIM][BF_4]. A solution of [OMIM]Cl (2 g, 8.69 mmol) in acetone (25 mL) at room temperature was added to sodium tetrafluoroborate (0.96 g, 8.69 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.34 (d, 2H), 4.17 (m, 2H), 3.95 (s, 3H), 1.88 (m, 2H), 1.28 (m, 10H), 0.89 (t, 3H).

7.6 Reaction of 6 with 89

Compound **6** (0.14 g, 2.13 mmol) was added dropwise to a well stirred mixture of acryloyl oxazolidinone (0.1 g, 0.71 mmol) and $Sc(OTf)_3$ (0.01 g, 0.02 mmol) in [BMIM][BF_4] (2 mL), and the reaction mixture was stirred at room temperature for 30 m. The crude was extracted with diethyl ether (3x10 mL), solvent was removed in rotavapour. The product was purified by column chromatography over silica gel.

7.7 Reaction of 6 and 91

The same procedure was used as discussed above. **6** (0.14 g, 2.13 mmol) was added dropwise to a well stirred mixture of **91** (0.10 g, 0.71 mmol) and $Sc(OTf)_3$ (0.03 g, 0.07 mmol) in [BMIM][BF_4] (2 mL), and the reaction mixture was stirred at room temperature for 10 h.

7.8 Reaction of 6 and 1,4-naphthoquinone (29)

Compound **6** (0.50 g, 7.59 mmol) was added dropwise to a well stirred mixture of **29** (0.30 g, 1.89 mmol) and $Sc(OTf)_3$ (0.01 g, 0.02 mmol) in [BMIM][BF_4] (2 mL), and the reaction mixture was stirred at room temperature for 10 m. The crude was extracted with diethyl ether (3x10 mL), solvent was removed in rotavapour. The product was

purified by column chromatography over silica gel. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (m, 2H), 7.68 (m, 2H), 5.94 (m, 2H), 3.62 (m, 2H), 3.43 (m, 2H), 1.51 (m, 2H).

7.9 Reaction of 2,3-dimethylbutadiene (87) and 29

Compound **87** (0.47 g, 5.67 mmol) was added dropwise to a well stirred mixture of **29** (0.30 g, 1.89 mmol) and $Sc(OTf)_3$ (0.02 g, 0.04 mmol) in [BMIM][BF_4] (2 mL), and the reaction mixture was stirred at room temperature for 2 h. The crude was extracted with diethyl ether (3x10 mL), solvent was removed in rotavapour. The product was purified by column chromatography over silica gel. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.02 (m, 2H), 7.73 (m, 2H), 3.34 (m, 2H), 2.39 (t, 2H), 2.16 (t, 2H), 1.62 (s, 6H).

7.10 Reaction of 6 with 7 and 9

Compound **6** (0.31 g, 4.64 mmol) was added dropwise to a well stirred mixture of dienophile (0.01 g, 1.16 mmol) in [BMIM][BF_4] (2 mL), and the reaction mixture was stirred at room temperature for 2 h. The crude was extracted with diethyl ether (3x10 mL), solvent was removed in rotavapour. The product was purified by column chromatography over silica gel.

Stereoselectivities

Endo/exo ratios for the reactions of 6 with acyl oxazolidinones (**89**, **91** and **93**) were determined by ^{1}H NMR. *Endo/exo* ratios for the reactions of **6** with **7**, **9** and **11** were determined by GC. Products were characterized using NMR data.[14a,b] *Endo/exo* products for the reaction of **6** with **11** were separated by iodolactonization method[15] and comparing with the reported NMR spectra.[16] Percentage yield for the reaction of **87** and **29** was estimated by GC.

7.11 Synthesis of chiral auxiliaries

The chiral auxiliaries for asymmetric Diels-Alder and Michael reactions were synthesised as follows:

7.11.1 Synthesis of dihydroquininyl acrylate (107)

To a solution of dihydroquinine **106** (0.50 g, 1.53 mmol) and acrylic acid **34** (0.22 g, 3.07 mmol) in CH_2Cl_2 (20 mL) at 0 °C, under nitrogen atmosphere, was added DCC (0.64 g, 3.07 mmol) in one portion. After 10 min the temperature was raised to r.t. and stirring was continued for 12 h. The dicyclohexylurea formed was filtered and the precipitate washed with CH_2Cl_2 (10 mL). The filtrate was washed with sat. sodium bicarbonate (10 mL), dried with Na_2SO_4 and concentrated at reduced pressure to furnish the crude product, which was purified by column chromatography over silica gel. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.7 (d, 1H), 7.97 (d, 1H), 7.45 (m, 2H), 7.39 (d, 1H), 7.33 (m, 1H), 6.59 (m, 1H), 6.25 (m, 1H), 5.88 (d, 1H), 3.96 (s, 3H), 3.34 (m, 1H), 2.37 (m, 4H), 1.34 (m, 8H), 0.83 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 11.44, 13.64, 20.40, 27.01, 28.91, 36.69, 39.38, 53.06, 55.10, 59.77, 68.75, 101.13, 113.35, 118.16, 120.71, 128.17, 130.48, 141.27, 143.30, 145.63, 149.55, 157.11, 170.44.

7.11.2 Synthesis of dihydroquininyl crotonate (109)

To a solution of **106 (**2 g, 6.14 mmol) and crotonic acid (1.06 g, 12.28 mmol) in CH_2Cl_2 (30 mL) at 0 °C, under nitrogen atmosphere, was added DCC (2.50 g, 12.28 mmol) in one portion. After 10 m the temperature was raised to r.t. and stirring was continued for 12 h. The solution was extracted with CH_2Cl_2 (10 mL), washed with sat. sodium bicarbonate (10 mL), dried with Na_2SO_4 and concentrated at reduced pressure to furnish the crude product, which was purified by column chromatography over silica gel. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.67 (d, 1H), 7.98 (d, 1H), 7.49 (m, 2H), 7.39 (d, 1H), 7.33 (m, 1H), 7.04 (m, 1H), 5.92 (d, 1H), 3.96 (s, 3H), 3.30 (m, 3H), 3.18 (m, 1H), 1.93

(m, 8H), 1.29 (m, 4H), 0.80 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 11.56, 13.87, 17.87, 22.15, 24.77, 27.08, 36.33, 42.50, 56.03, 57.61, 58.49, 72.05, 101.05, 117.89, 122.0, 122.76, 126.71, 131.36, 142.66, 144.37, 146.33, 146.90, 158.02, 164.09.

7.11.3 Synthesis of quininyl crotonate (116)

The same procedure was used as discussed for **109** with the change that quinine **98** was employed instead of **106**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.67 (d, 1H), 7.96 (d, 1H), 7.37 (m, 2H), 7.29 (d, 1H), 7.01 (m, 1H), 6.62 (m, 1H), 5.82 (d, 2H), 4.97 (m, 2H), 3.96 (s, 3H), 3.70 (m, 1H), 3.18 (m, 3H), 2.68 (m, 2H), 1.86 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 13.74, 17.67, 22.57, 27.11, 38.30, 41.94, 55.27, 55.77, 58.43, 59.84, 72.60, 100.99, 114.33, 118.08, 121.69, 128.40, 131.20, 140.82, 143.19, 144.19, 145.83, 148.85, 157.63, 164.69.

7.12 Reaction of 6 and 107

Compound **6** (0.34 g, 5.21 mmol) was added dropwise to a well stirred mixture of **107** (0.50 g, 1.31 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at room temperature for 12 h. The crude was extracted with CH_2Cl_2 (3x10 mL), solvent was removed in rotavapour. The product was purified by column chromatography over silica gel.

7.13 Reaction of 6 and 109

The same procedure was used as for the reaction of **6** and **107**. Compound **6** (0.33 g, 5.04 mmol) was added dropwise to a well stirred mixture of **109** (0.50 g, 1.26 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at room temperature for 12 h.

7.14 Michael addition of 2-oxazolidinone (117) to quininyl crotonate (116)

117 (0.22 g, 2.53 mmol) was added to a well stirred suspension of sodium hydride (0.06 g, 2.53 mmol) in THF (20 mL) at 0^0C under nitrogen environment. After 10 min. temperature was raised to room temperature, **116** (1 g, 2.53 mmol) in THF (10 mL) was added to the solution. Stirring was continued for 12 h. Saturated ammonium chloride solution was added to the reaction mixture, extracted with CH_2Cl_2, dried with Na_2SO_4 and concentrated at reduced pressure to furnish the crude product **118**, which was purified by column chromatography over silica gel. The product was then hydrolysed, followed by treatment with methanol and conc. sulfuric acid to get the methyl ester **120**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.26 (t, 3H), 3.62 (s, 3H), 3.50 (t, 3H), 2.50 (d, 2H), 1.19 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 16.86, 37.65, 39.73, 45.62, 50.89, 61.18, 158.70, 170.21.

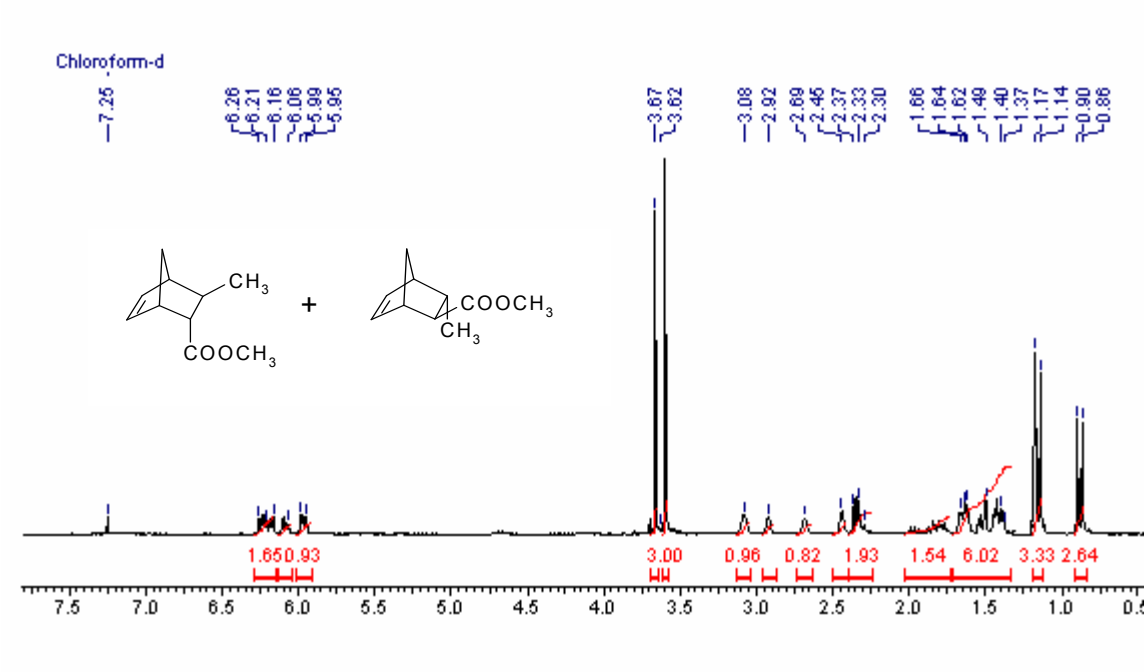


Figure 7.1 ^{1}H NMR of mixture of **12a** and **12b**

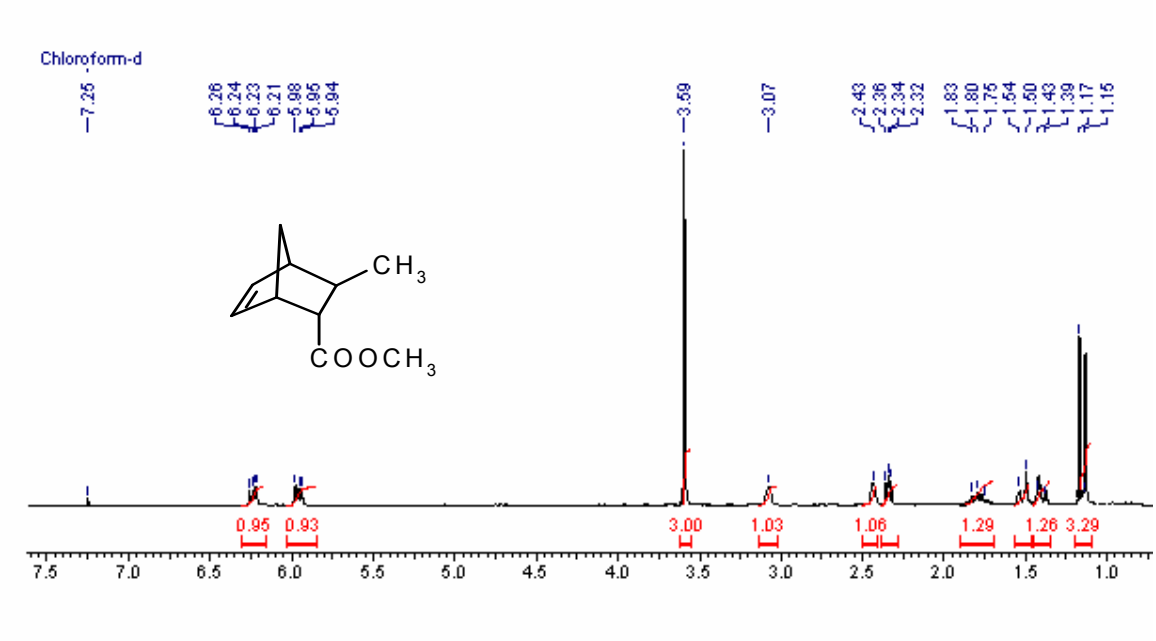


Figure 7.2 ^{1}H NMR of **12a**

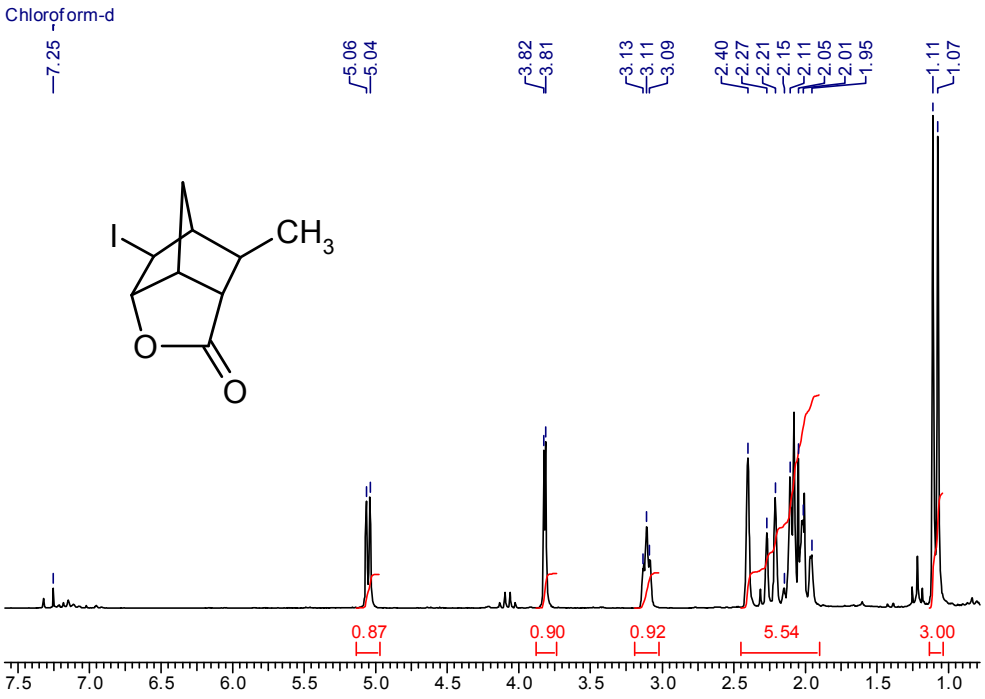


Figure 7.3 ^{1}H NMR of **76**

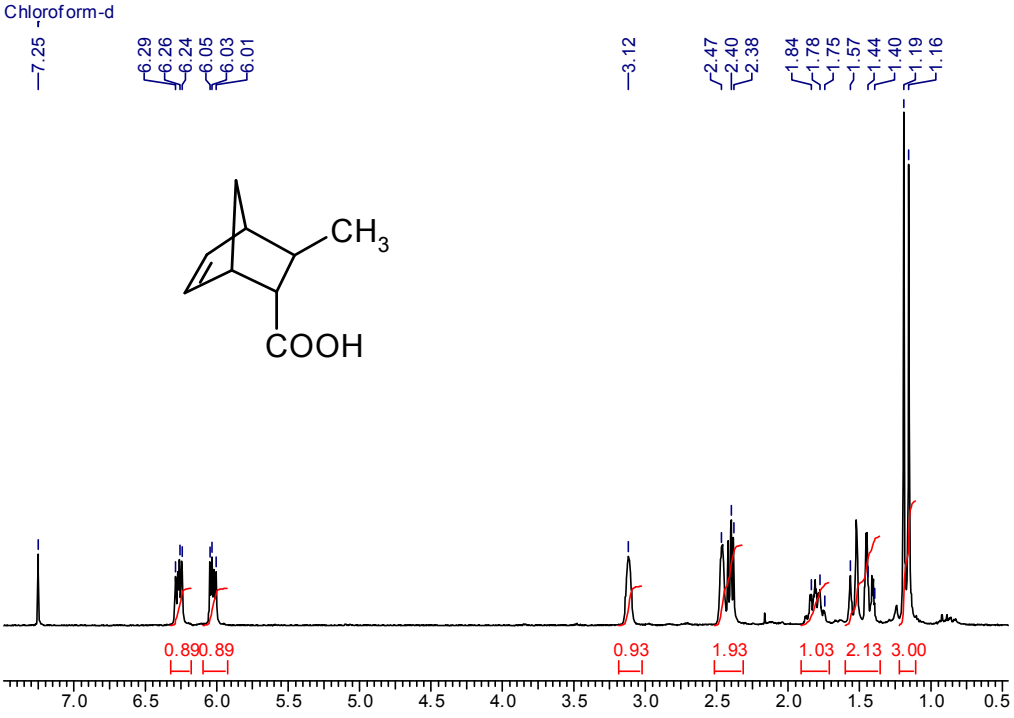


Figure 7.4 ^{1}H NMR of **75a**

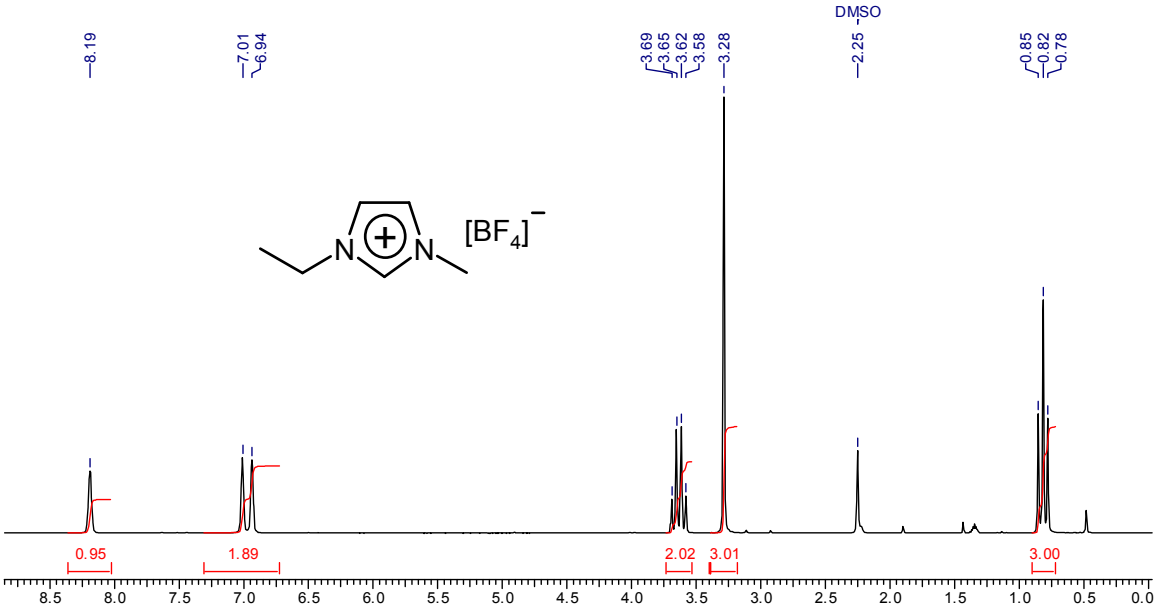


Figure 7.5 ^{1}H NMR of [EMIM][BF_4]

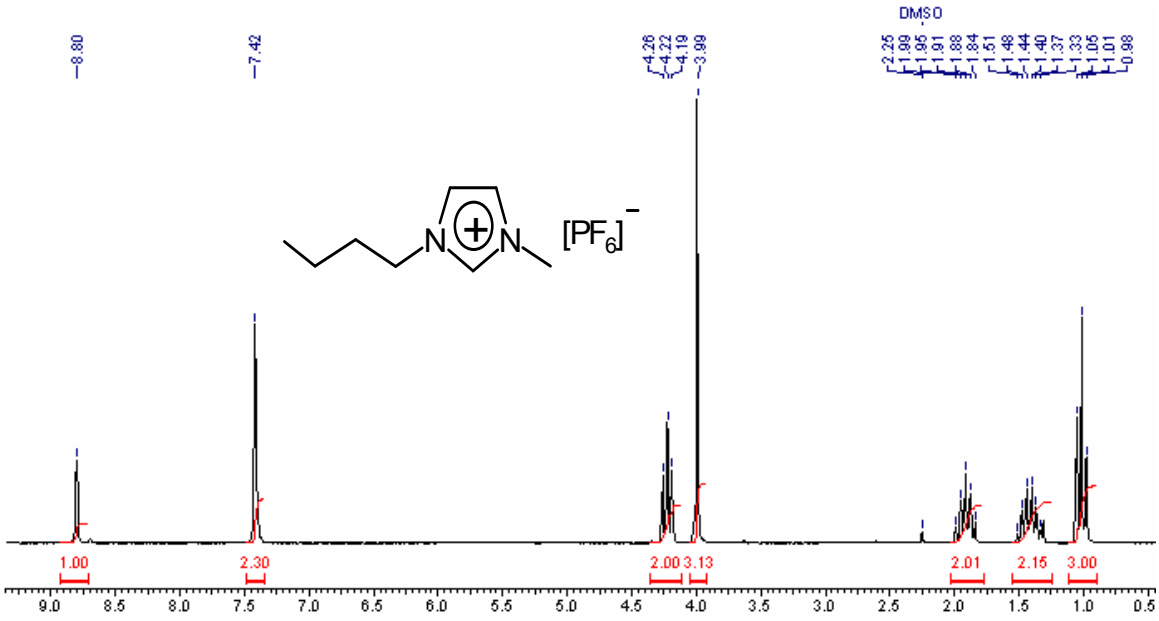


Figure 7.6 ^{1}H NMR of [BMIM][PF_6]

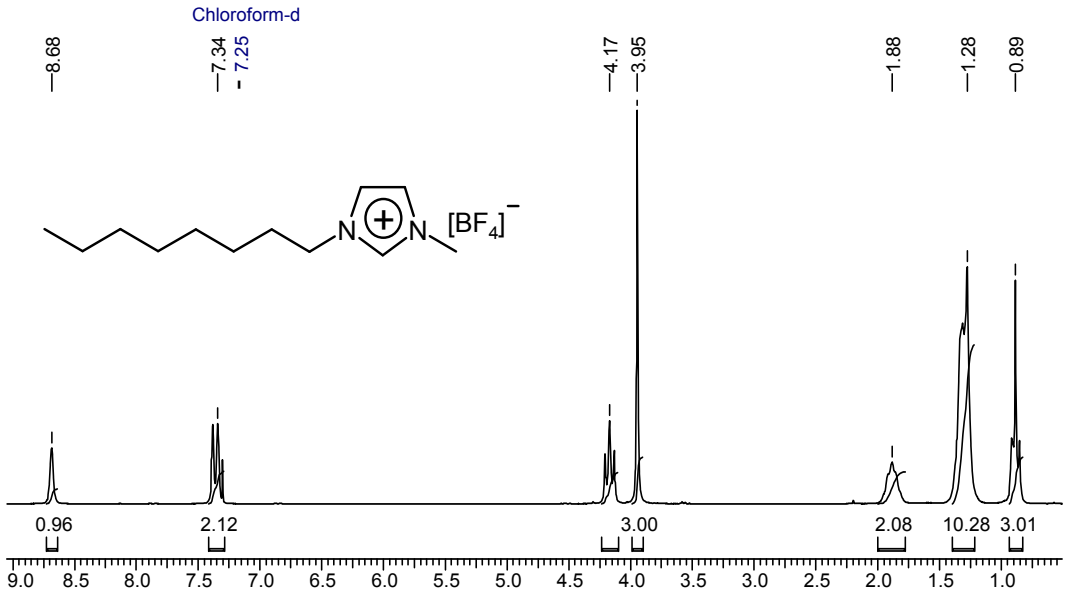


Figure 7.7 ^{1}H NMR of [OMIM][BF_4]

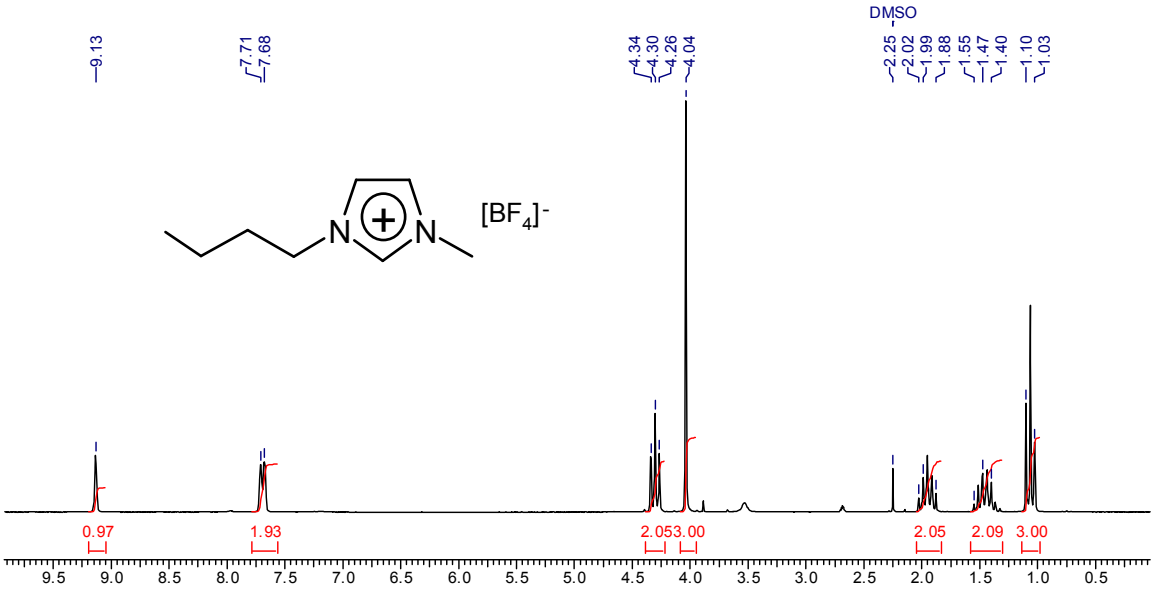


Figure 7.8 ^{1}H NMR of [BMIM][BF_4]

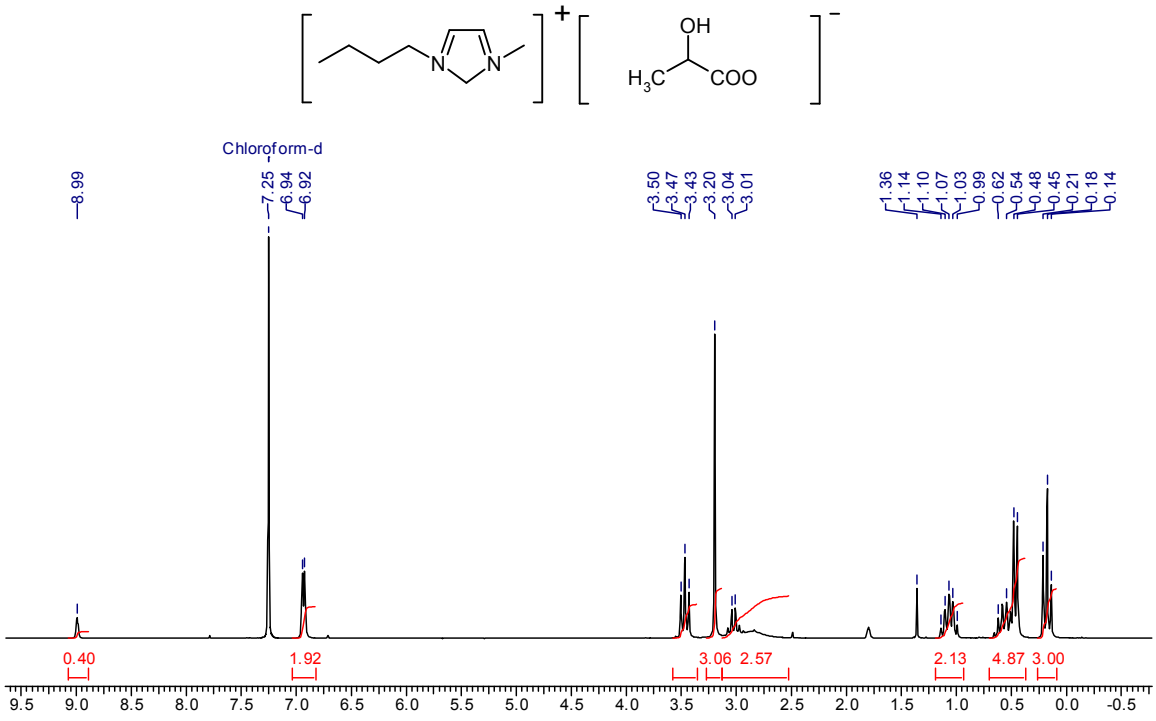


Figure 7.9 ^{1}H NMR of [BMIM][Lactate]

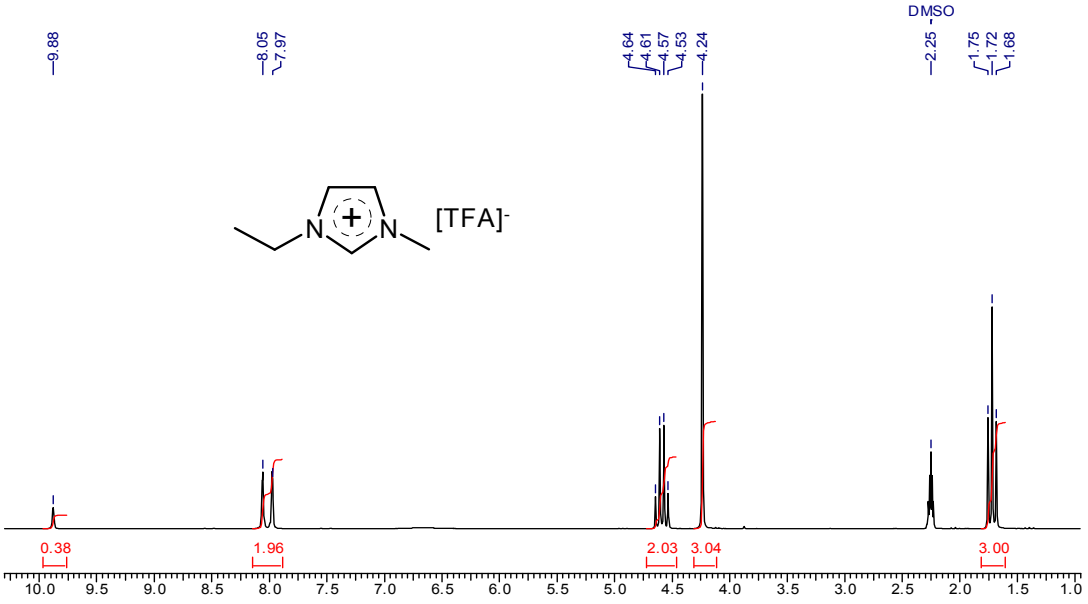


Figure 7.10 ^{1}H NMR of [EMIM][TFA]

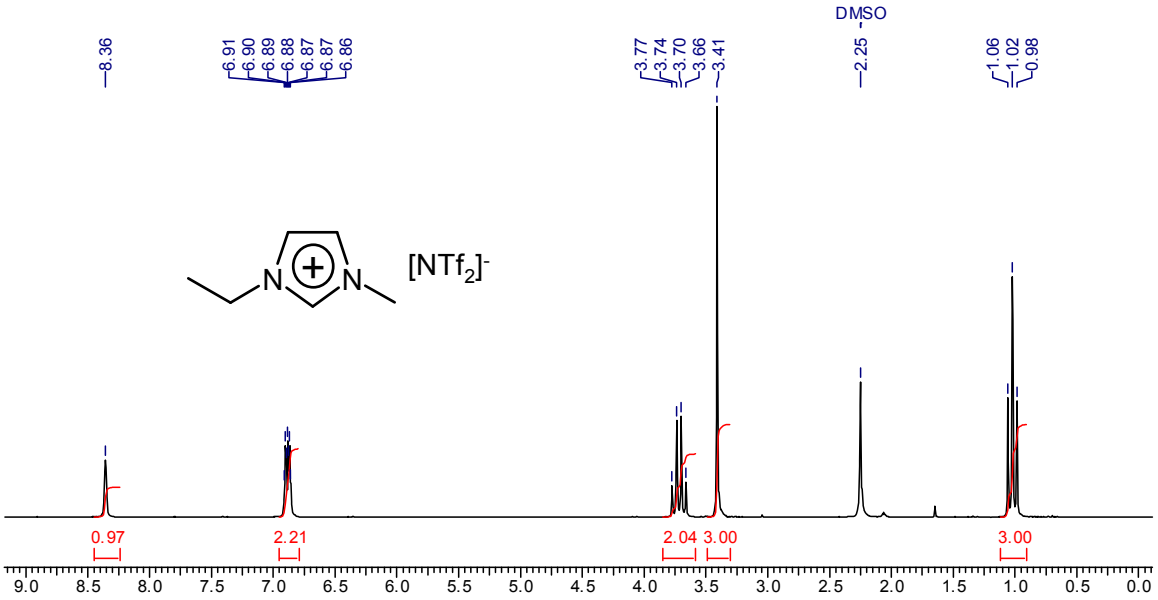


Figure 7.11 ^{1}H NMR of [EMIM][NTf$_2$]

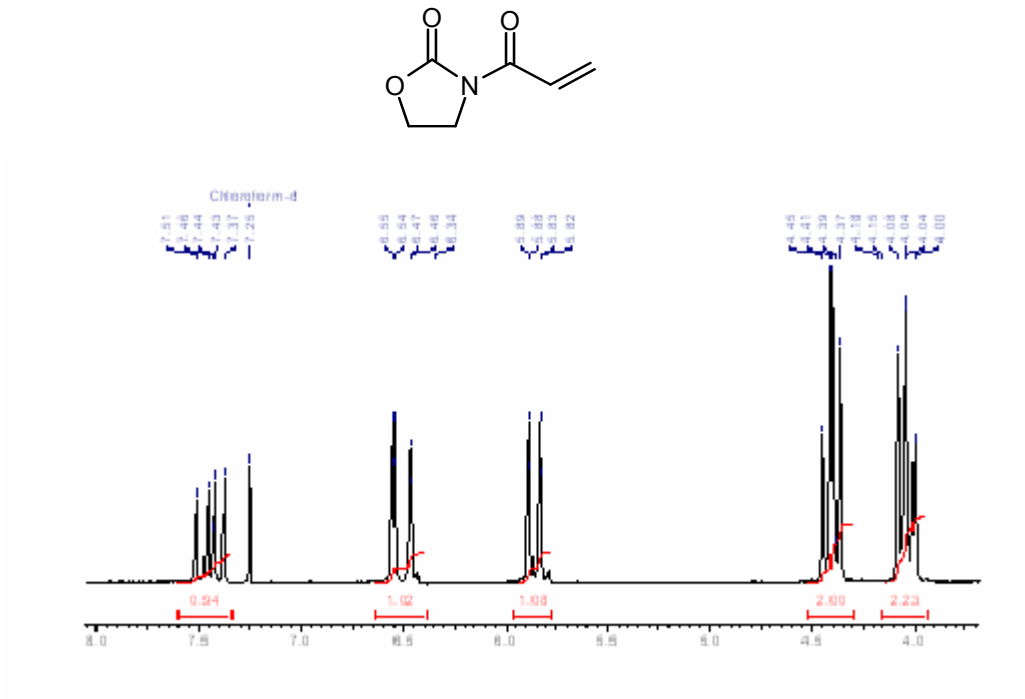


Figure 7.12 ^{1}H NMR of **89**

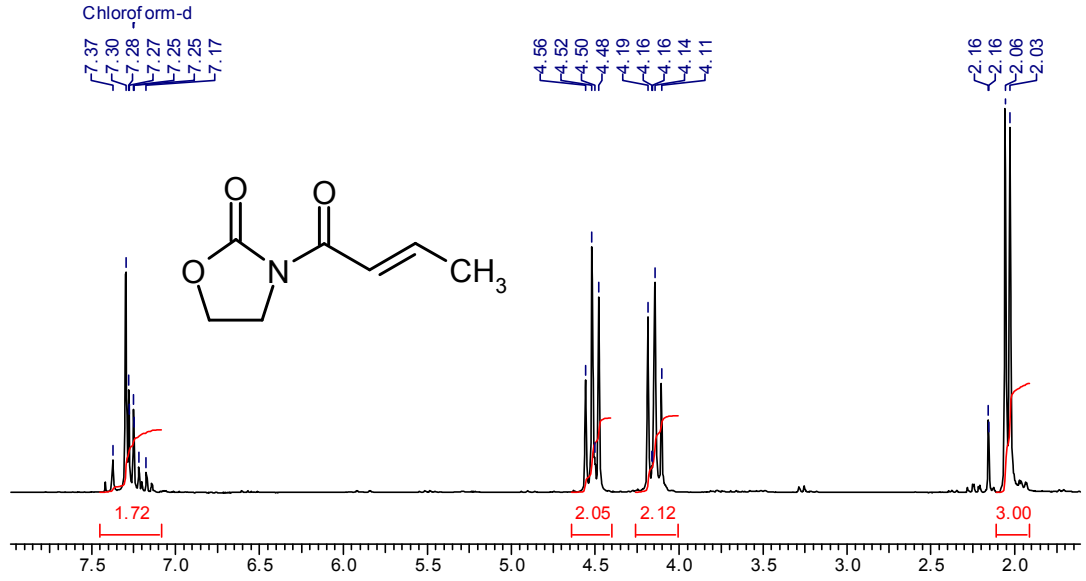


Figure 7.13 ^{1}H NMR of **91**

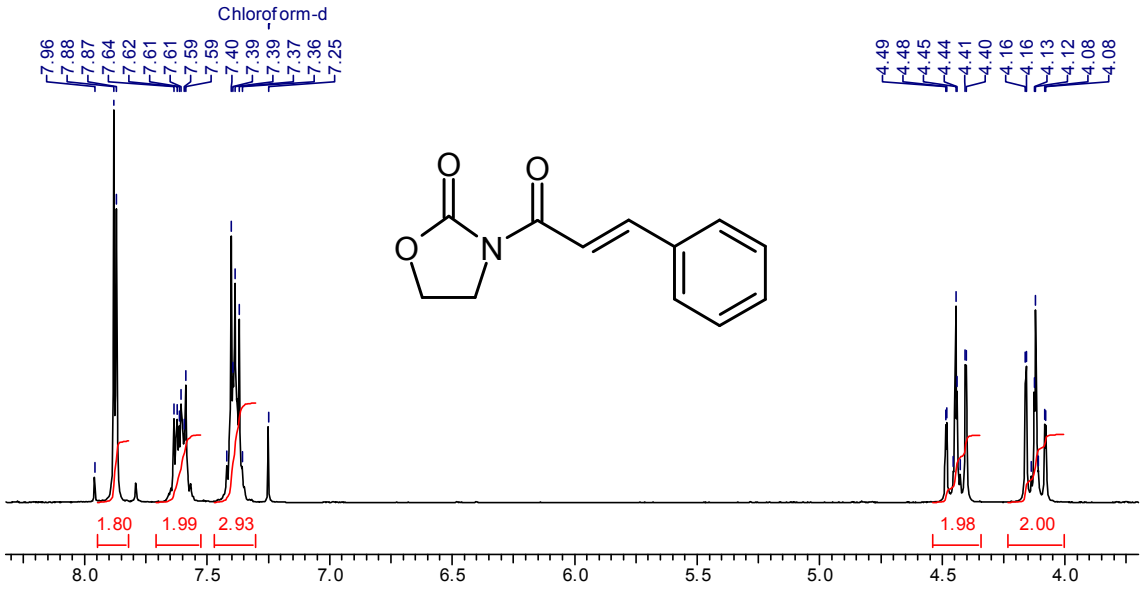


Figure 7.14 ^{1}H NMR of **93**

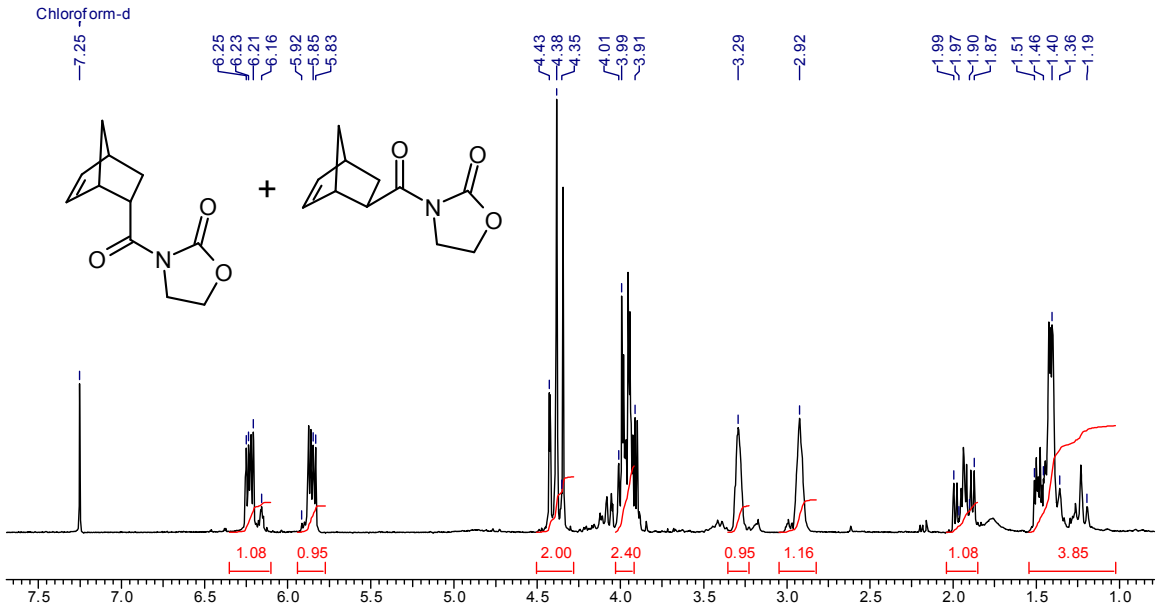


Figure 7.15 ^{1}H NMR of mixture of **90a** and **90b**

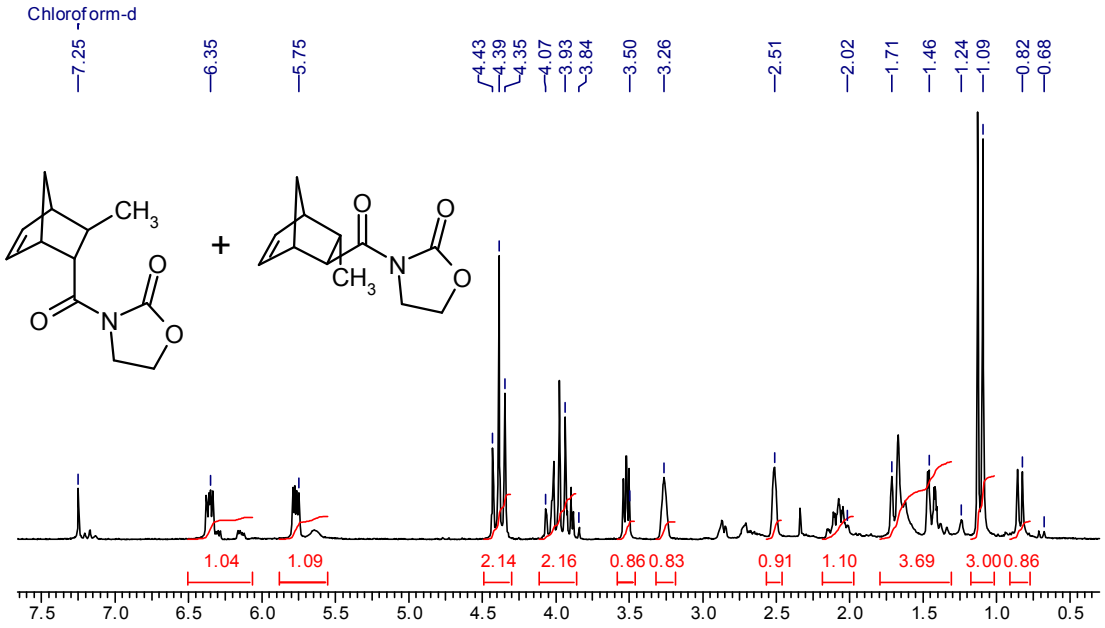


Figure 7.16 ^{1}H NMR of mixture of **92a** and **92b**

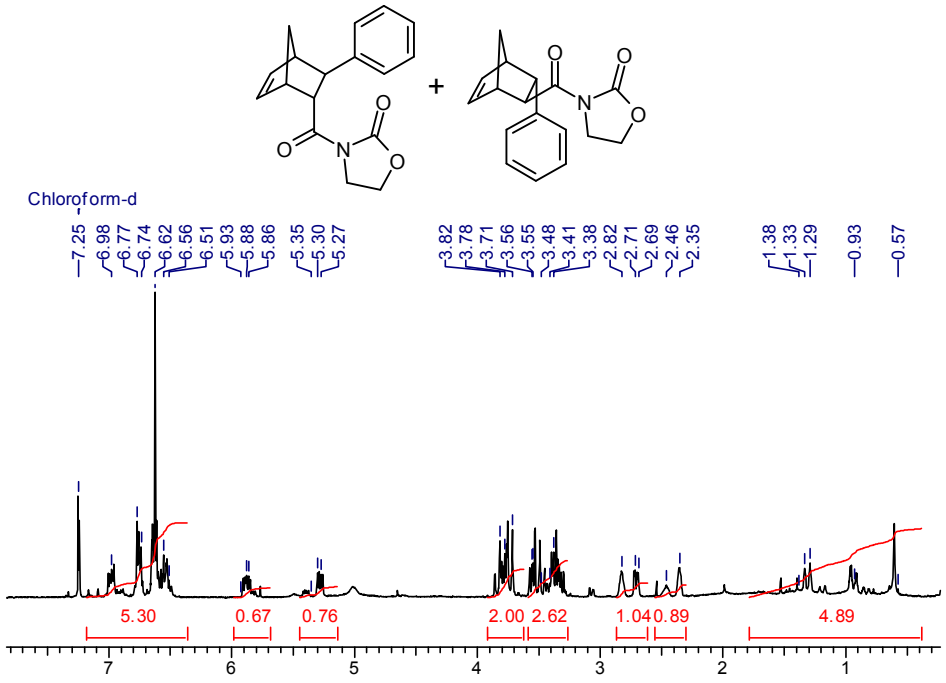


Figure 7.17 ^{1}H NMR of mixture of **94a** and **94b**

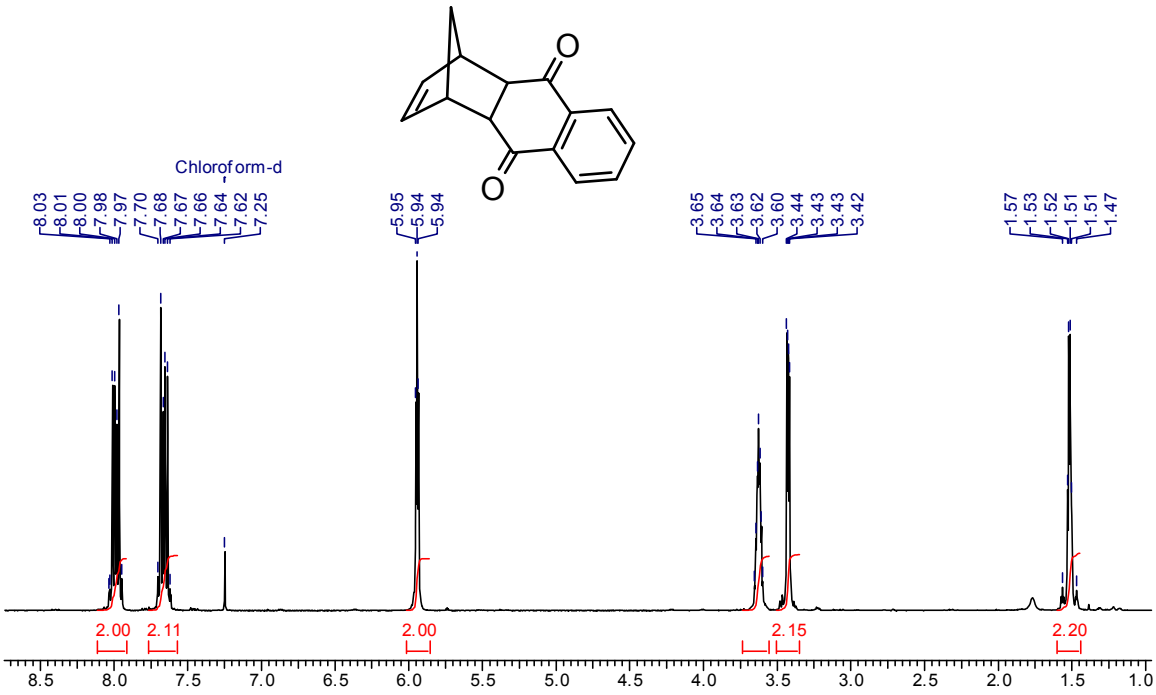


Figure 7.18 ^{1}H NMR of **30**

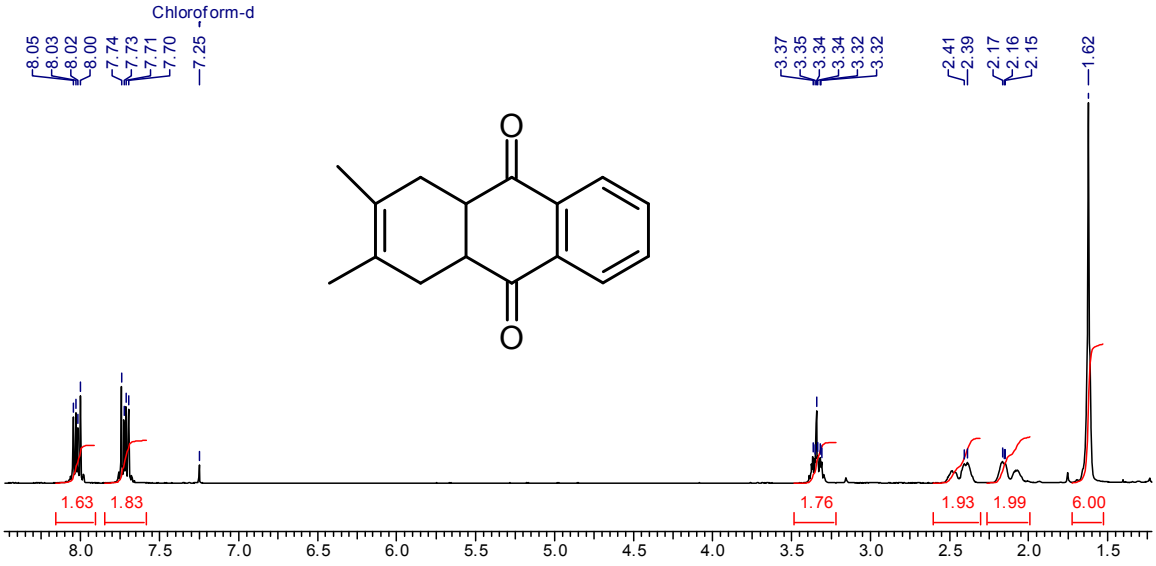


Figure 7.19 ^{1}H NMR of **88**

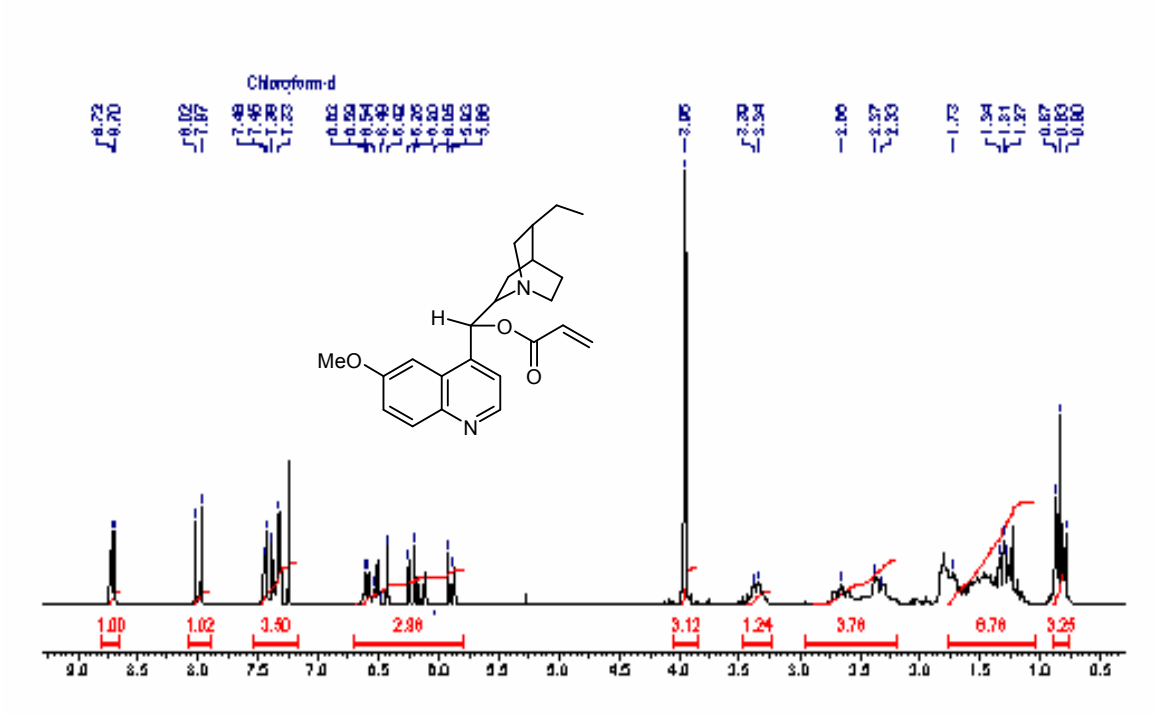


Figure 7.20 ^{1}H NMR of **107**

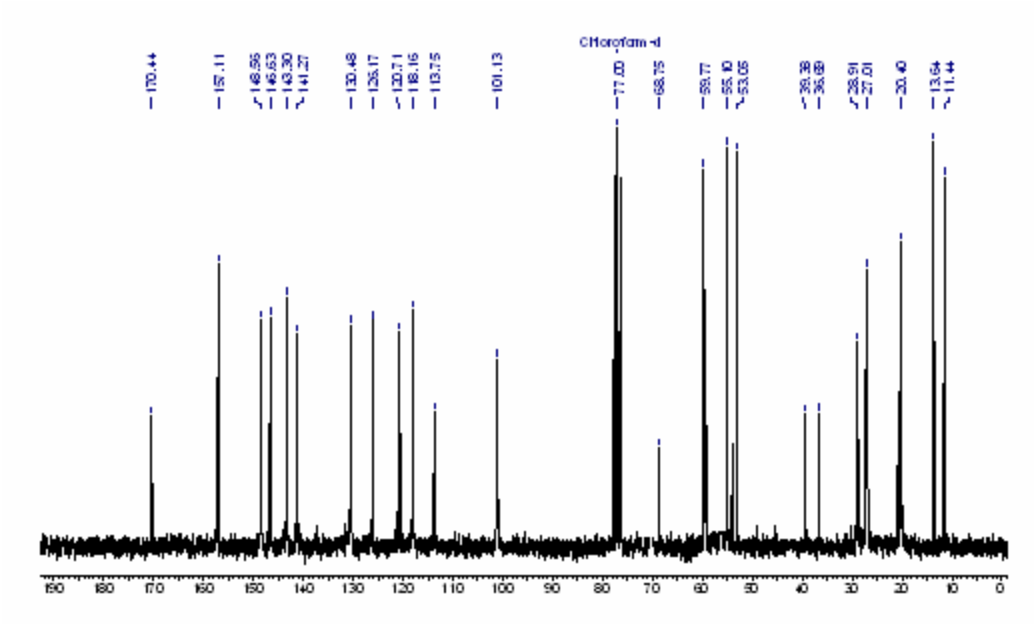


Figure 7.21 ^{13}C NMR of **107**

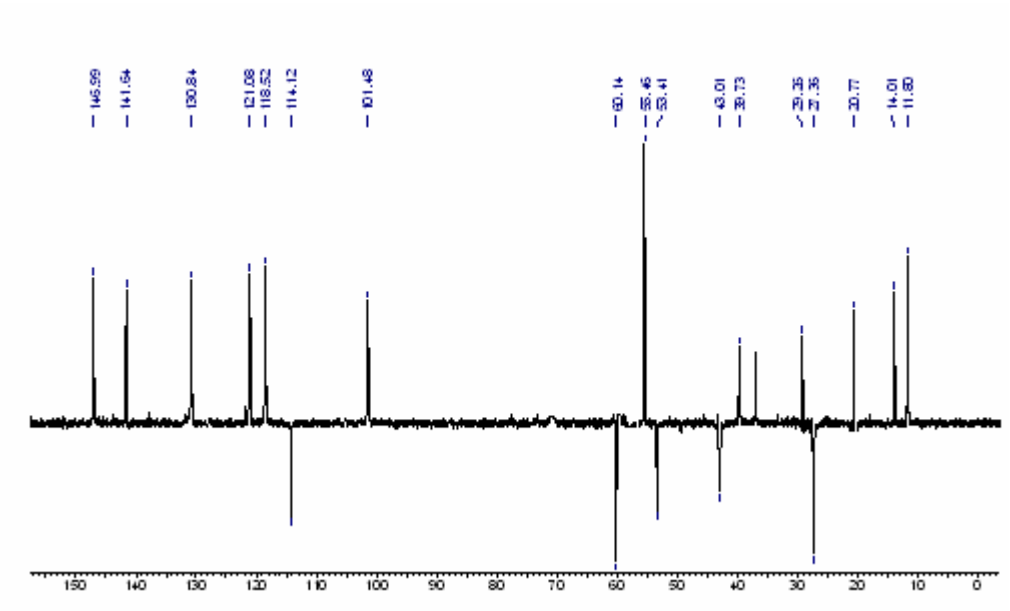


Figure 7.22 DEPT NMR of **107**

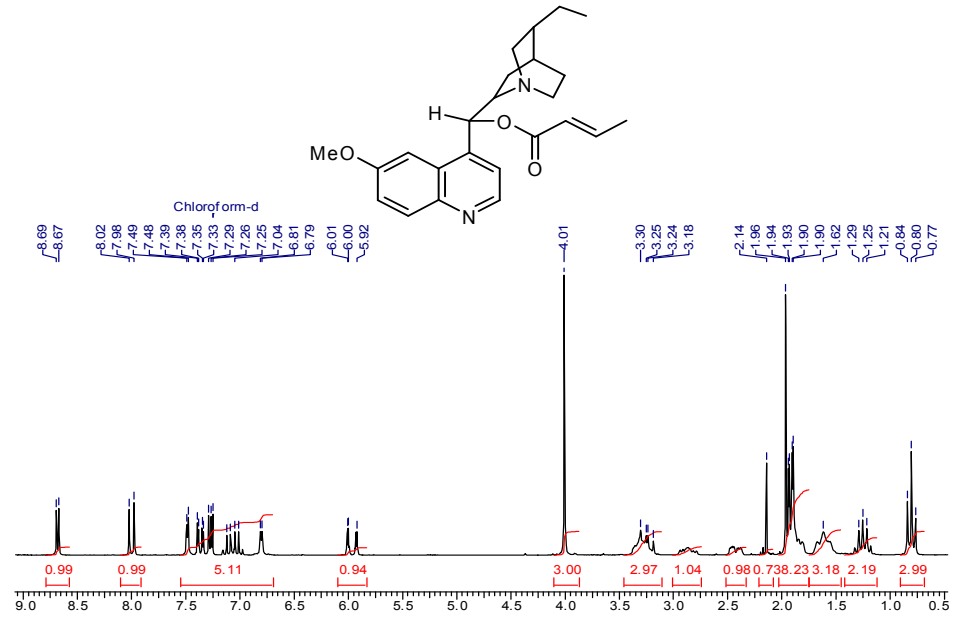


Figure 7.23 ^{1}H NMR of **108**

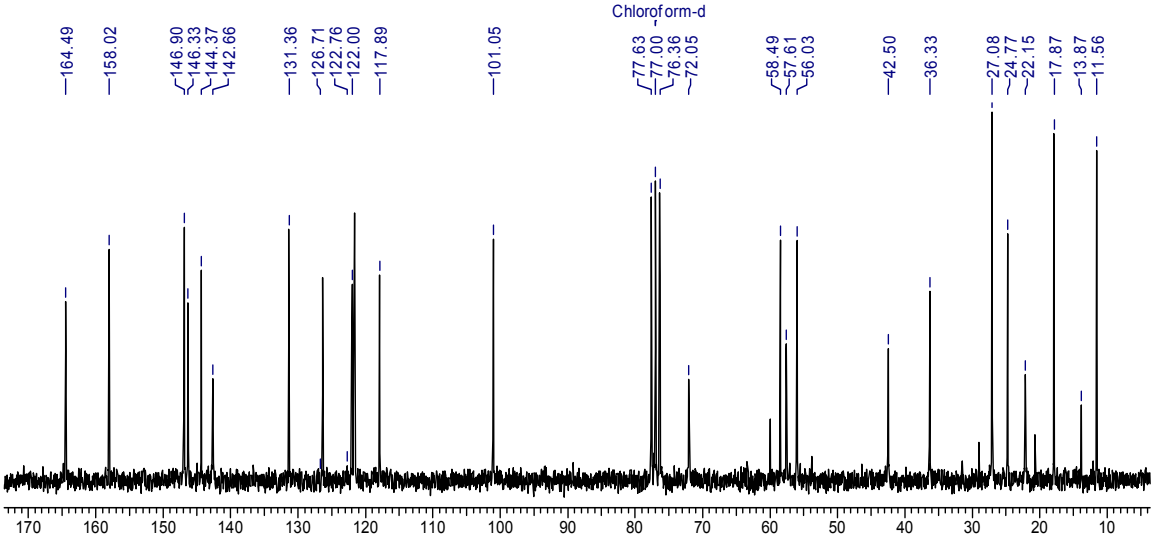


Figure 7.24 ^{13}C NMR of **108**

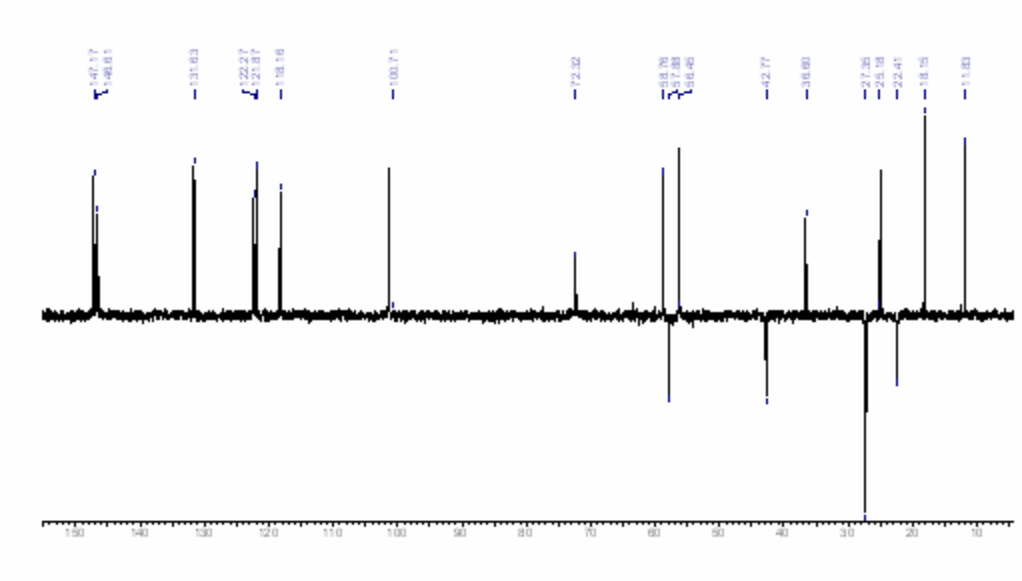


Figure 7.25 DEPT NMR of **108**

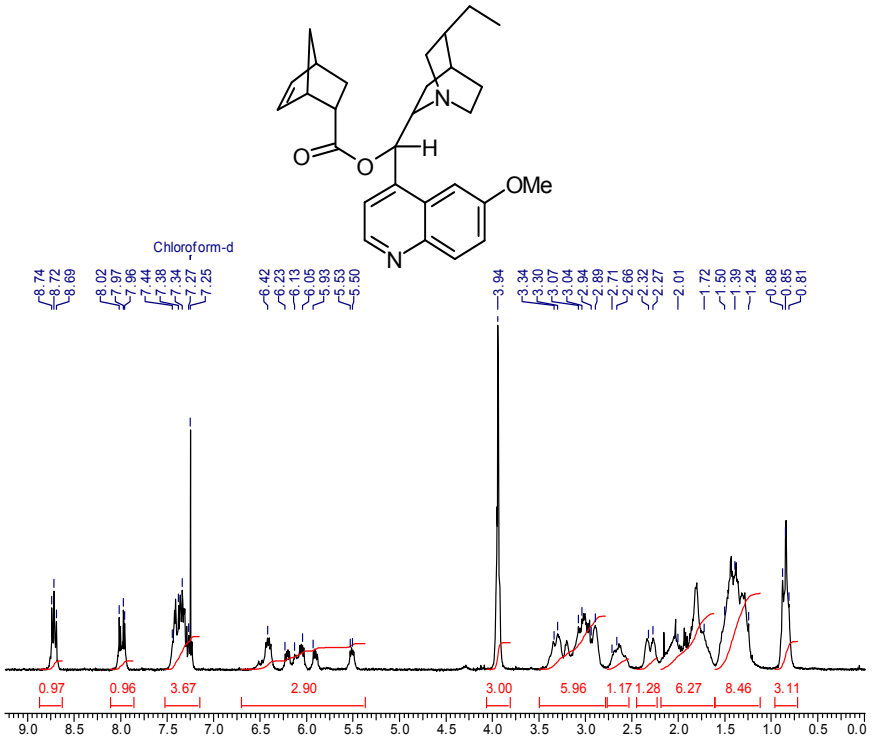


Figure 7.26 ^{1}H NMR of **109a + 109b**

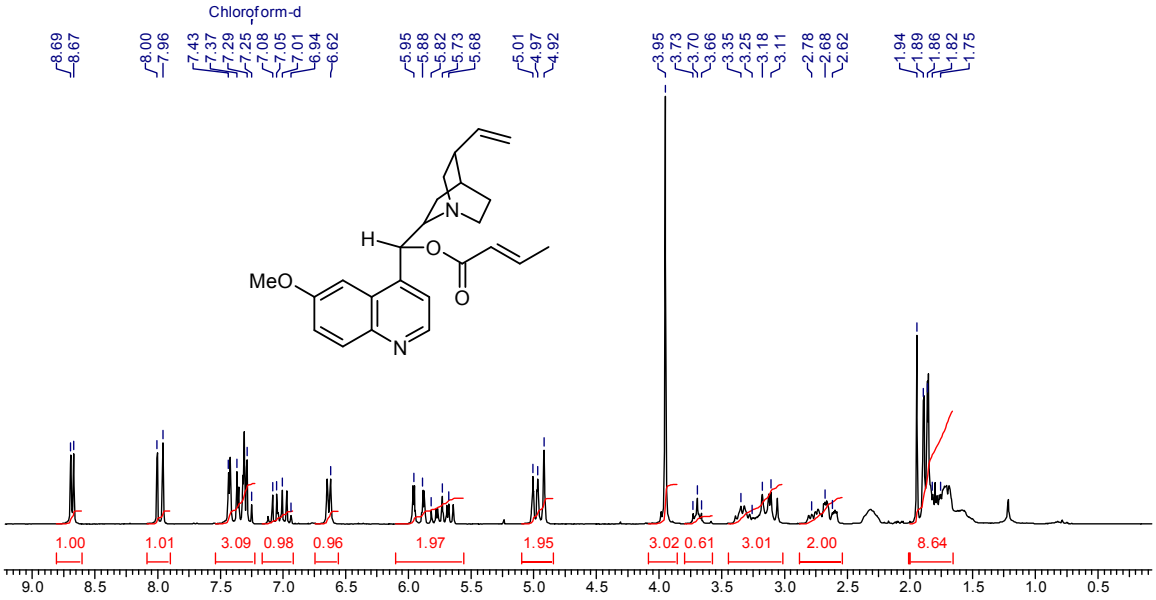


Figure 7.27 ^{1}H NMR of **116**

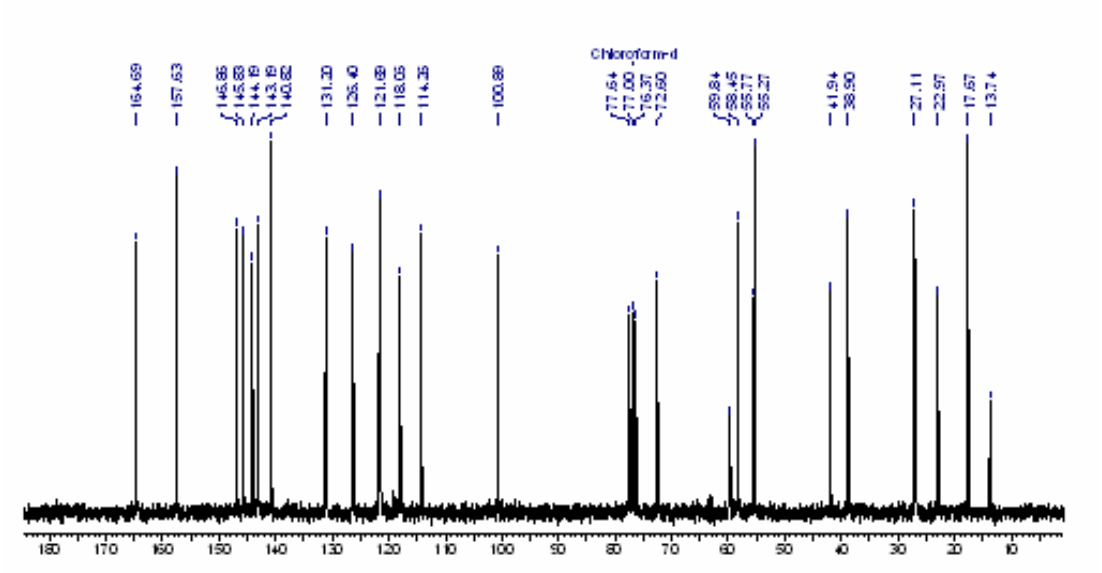


Figure 7.28 ^{13}C NMR of **116**

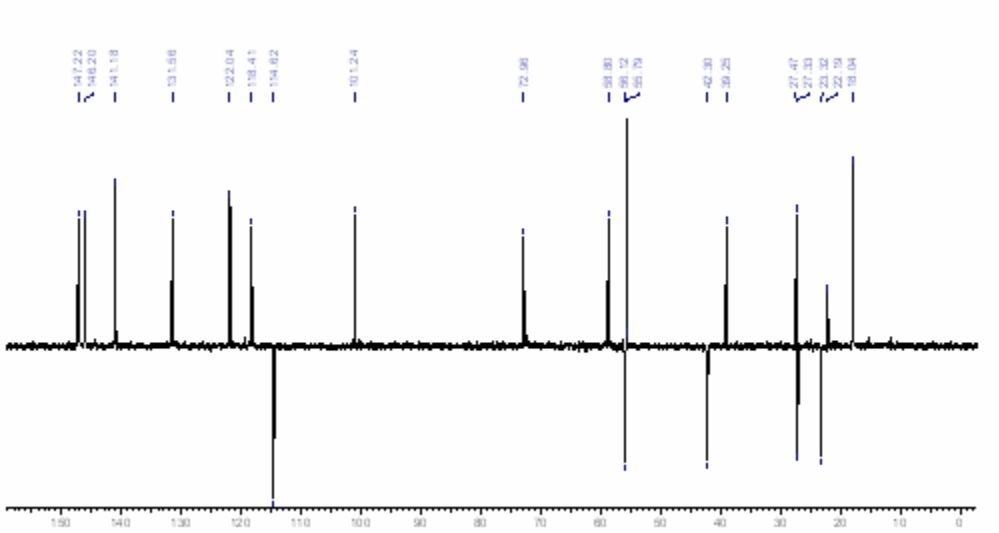


Figure 7.29 DEPT NMR of **116**

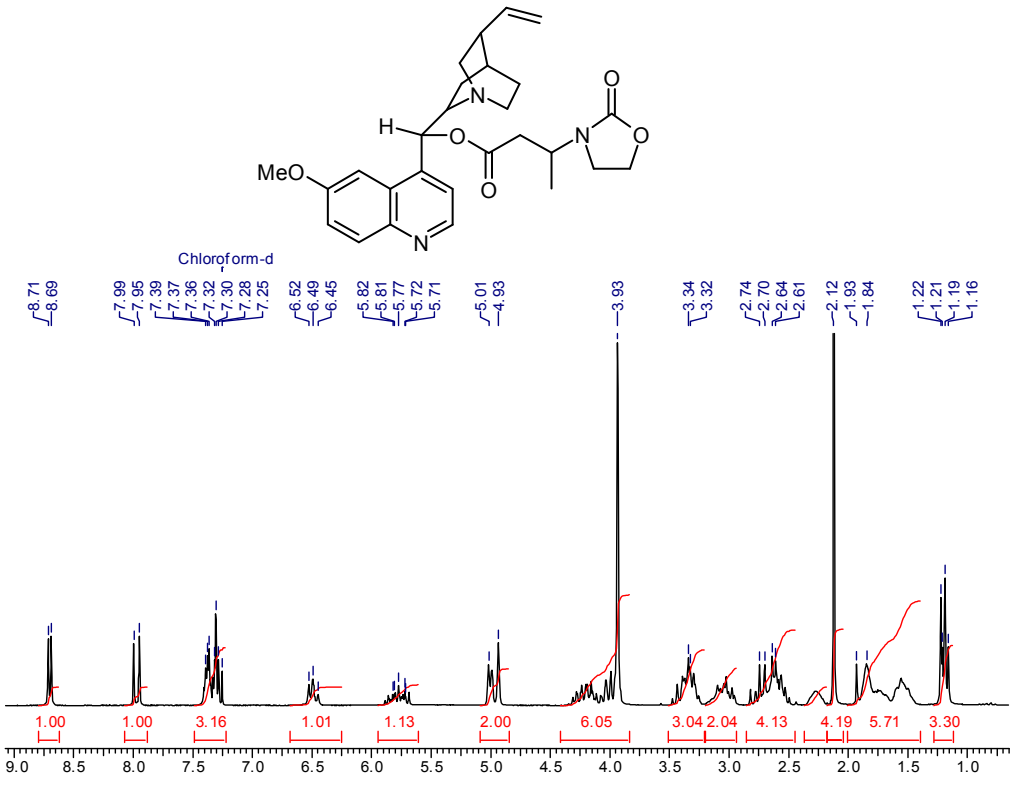


Figure 7.30 ^{1}H NMR of **118**

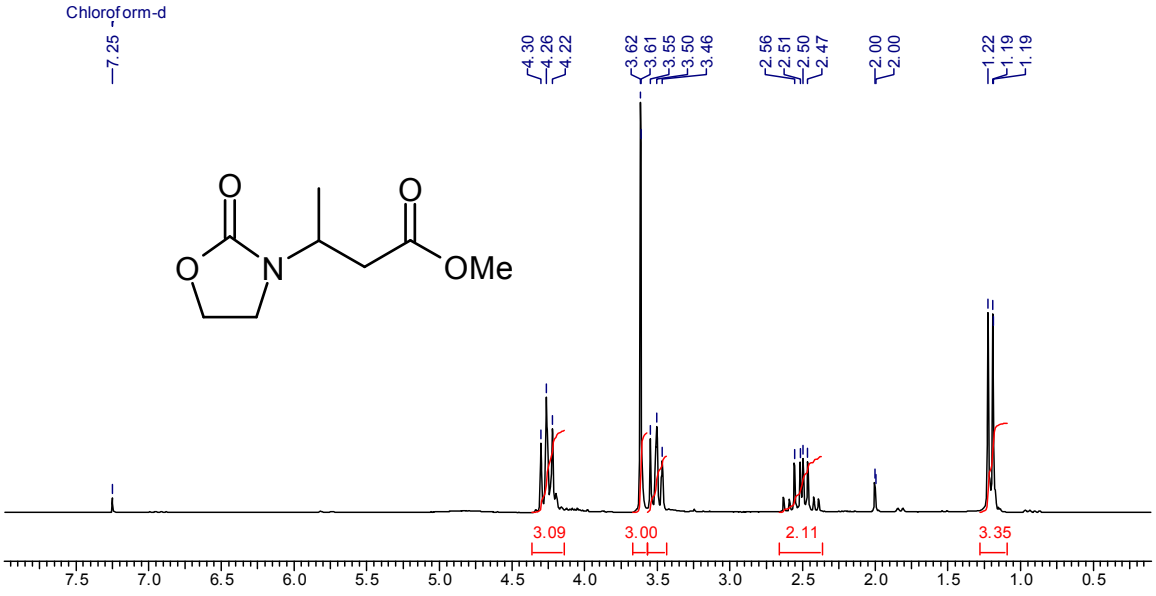


Figure 7.31 ^{1}H NMR of **120**

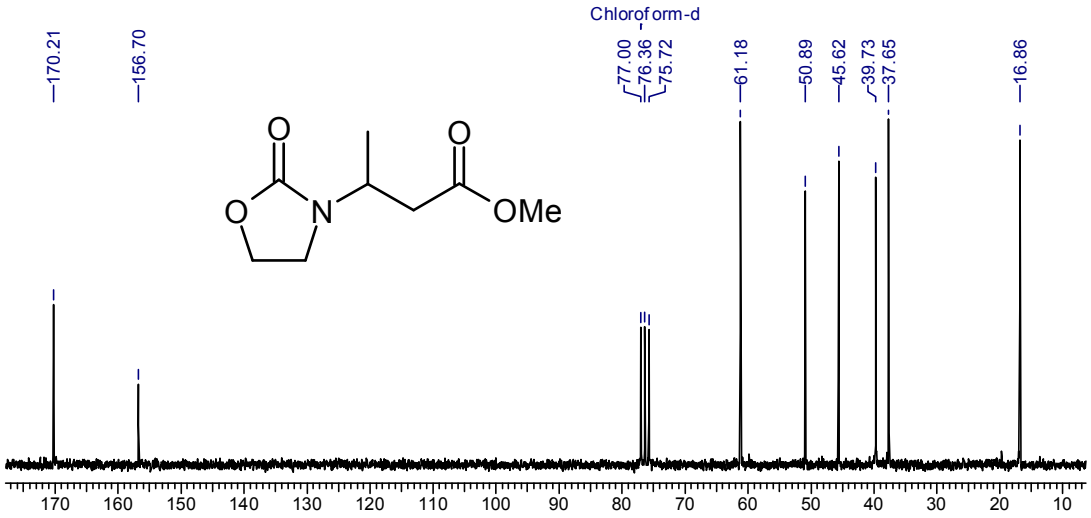


Figure 7.32 ^{13}C NMR of **120**

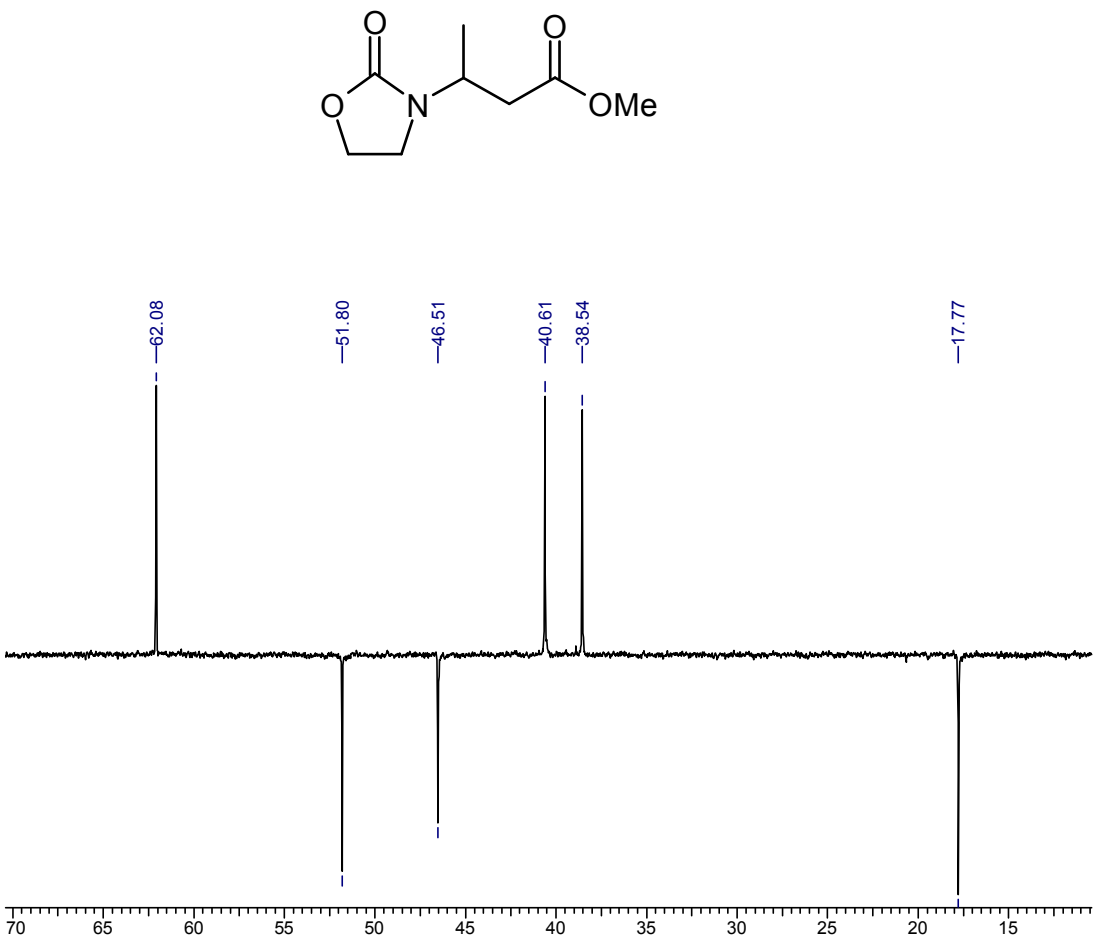
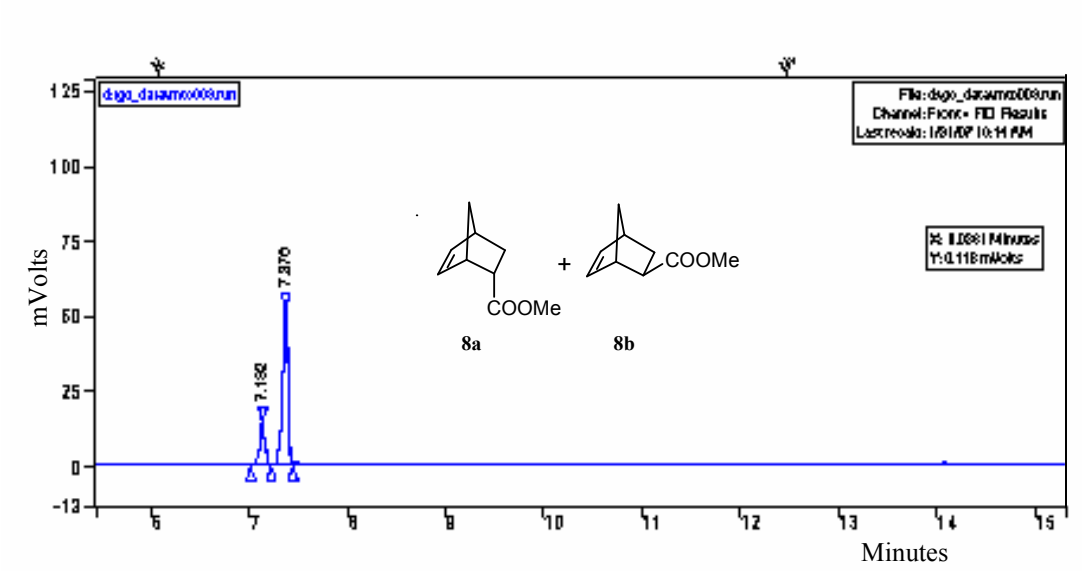


Figure 7.33 DEPT NMR of **120**




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Front = FID              Run Time     : 16.485 min
```

** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		21.1956	7.132	0.000	53771	BV	3.4
2		78.8044	7.376	0.000	199918	VB	3.5
	Totals:	100.0000		0.000	253689		

```
Total Unidentified Counts :     253688 counts

Detected Peaks: 6           Rejected Peaks: 4      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -18 microVolts          LSB:     1 microVolts

Noise (used): 41 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 2.0  uL     Position: 1

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```
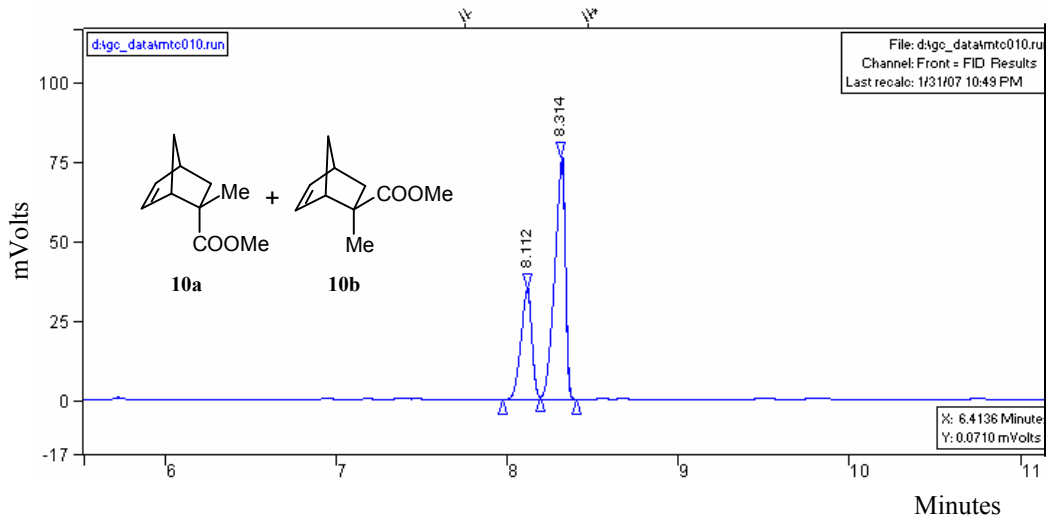

Figure 7.34 *Endo/exo* ratio of the products **8a** and **8b**.




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Front = FID              Run Time     : 16.485 min
```

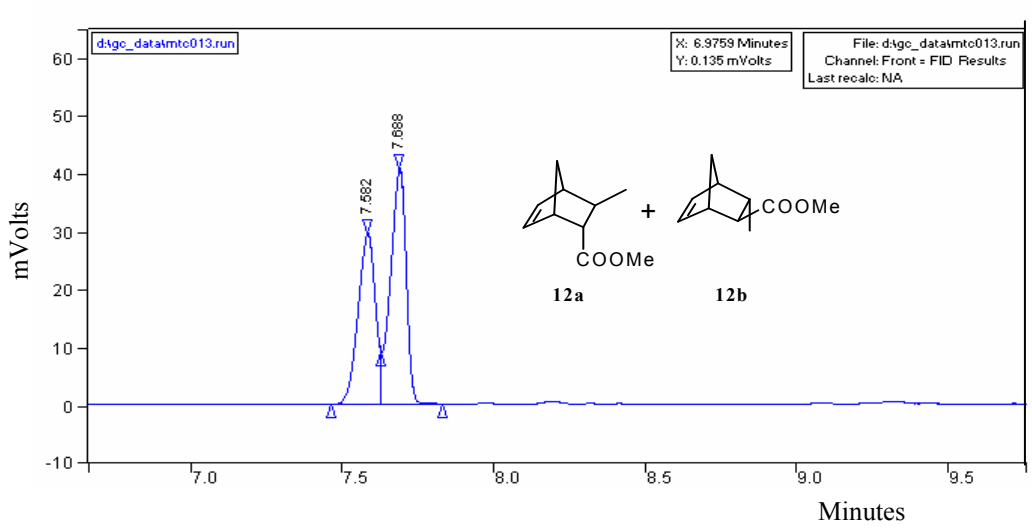
** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		31.9661	8.112	0.000	156583	BV	4.2
2		68.0339	8.314	0.000	333257	VB	4.1
	Totals:	100.0000		0.000	489840		

```
Total Unidentified Counts :     489840 counts

Detected Peaks: 2           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 2 microVolts          LSB:     1 microVolts

Noise (used): 51 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 1.0  uL     Position: 1

********************************************************************************
```

Figure 7.35 *Endo/exo* ratio of the products **10a** and **10b**.




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Front = FID              Run Time     : 11.590 min
```

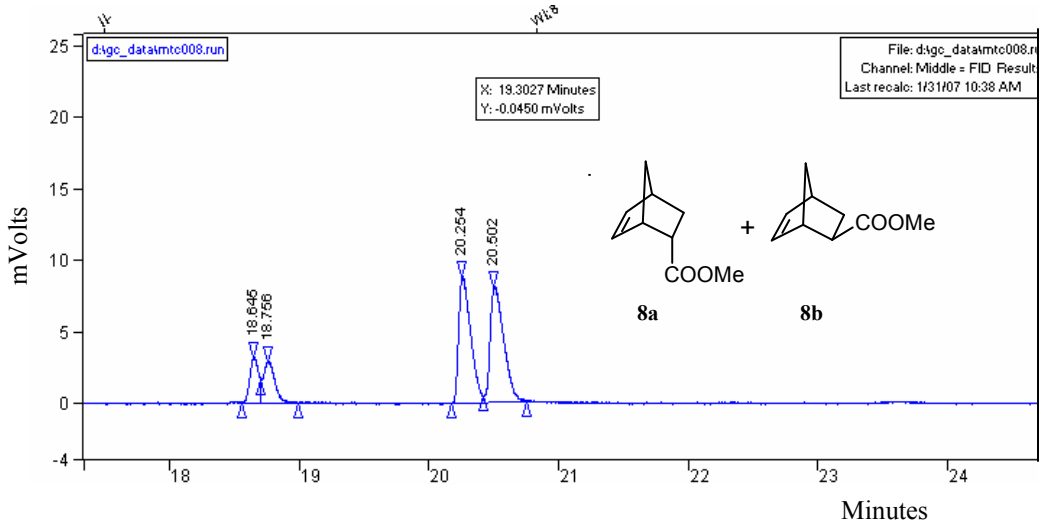
** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		44.9863	7.582	0.000	120171	BV	3.9
2		55.0137	7.688	0.000	146957	VB	3.4
	Totals:	100.0000		0.000	267128		

```
Total Unidentified Counts :     267128 counts

Detected Peaks: 2           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -39 microVolts          LSB:     1 microVolts

Noise (used): 334 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 1.0  uL     Position: 1

*********************************************************************
```

Figure 7.36 *Endo/exo* ratio of the products **12a** and **12b**.




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Middle = FID             Run Time     : 32.718 min
```

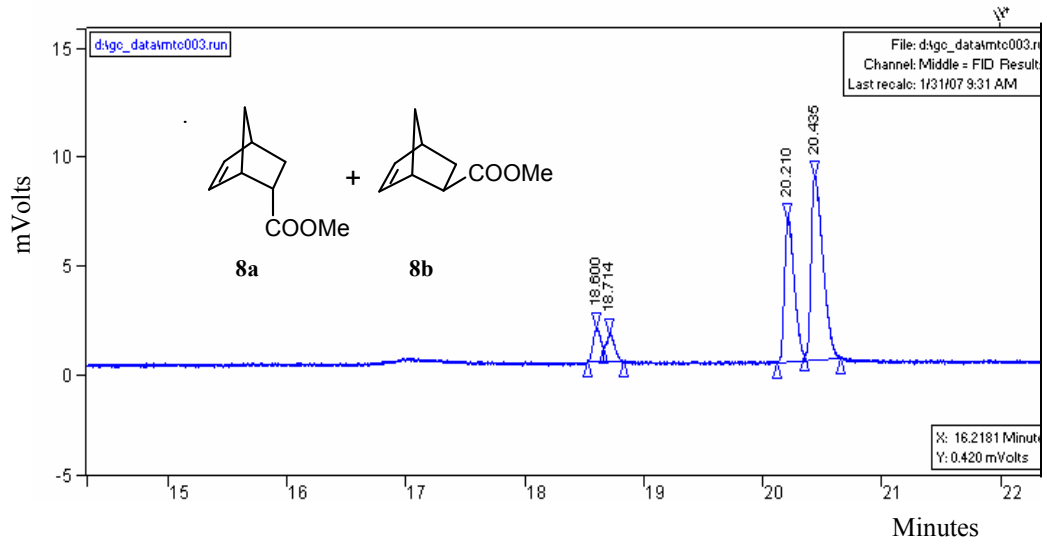
** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		10.3462	18.645	0.000	15361	BV	5.3
2		11.7719	18.756	0.000	17477	VB	6.5
3		38.3106	20.254	0.000	56878	BV	6.1
4		39.5713	20.502	0.000	58750	VB	6.8
	Totals:	100.0000		0.000	148466		

```
Total Unidentified Counts :     148465 counts

Detected Peaks: 5           Rejected Peaks: 1      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -261 microVolts          LSB:     1 microVolts

Noise (used): 118 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 2.0  uL     Position: 2

********************************************************************************
```

Figure 7.37 GC chromatogram for racemic **8a** and **8b.**




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Middle = FID             Run Time     : 32.717 min
```

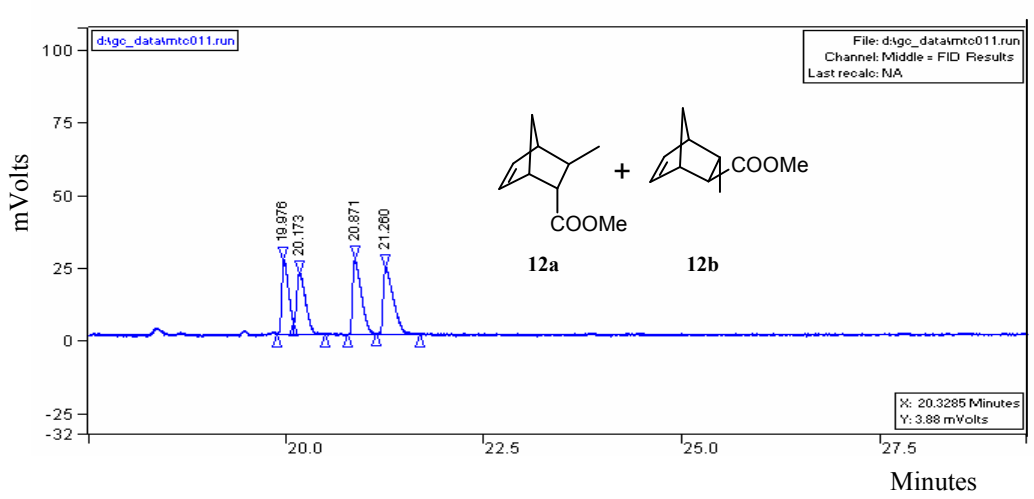
** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		6.6002	18.600	0.000	7310	BV	4.9
2		5.5963	18.714	0.000	6198	VB	5.5
3		34.6998	20.210	0.000	38433	BV	5.5
4		53.1037	20.435	0.000	58817	VB	6.6
	Totals:	100.0000		0.000	110758		

```
Total Unidentified Counts :     110760 counts

Detected Peaks: 4           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -1044 microVolts          LSB:     1 microVolts

Noise (used): 213 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 2.0  uL     Position: 2

********************************************************************
```

Figure 7.38 GC chromatogram for chiral **8a** and **8b.**




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Middle = FID             Run Time     : 32.718 min
```

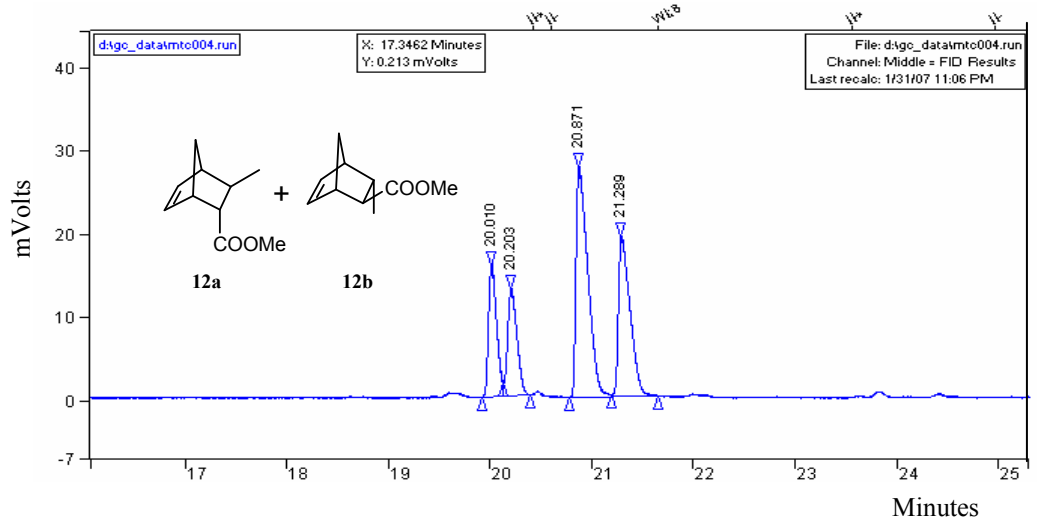
** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		21.1876	19.975	0.000	154660	BV	5.9
2		22.5202	20.170	0.000	164387	VB	7.3
3		27.5976	20.871	0.000	201450	BV	7.4
4		28.6945	21.260	0.000	209457	VB	8.4
	Totals:	99.9999		0.000	729954		

```
Total Unidentified Counts :     729953 counts

Detected Peaks: 4           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -3089 microVolts          LSB:     1 microVolts

Noise (used): 1431 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 2.0  uL     Position: 2

**********************************************************************
```

Figure 7.39 GC chromatogram for racemic **12a** and **12b.**




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Middle = FID             Run Time     : 32.717 min
```

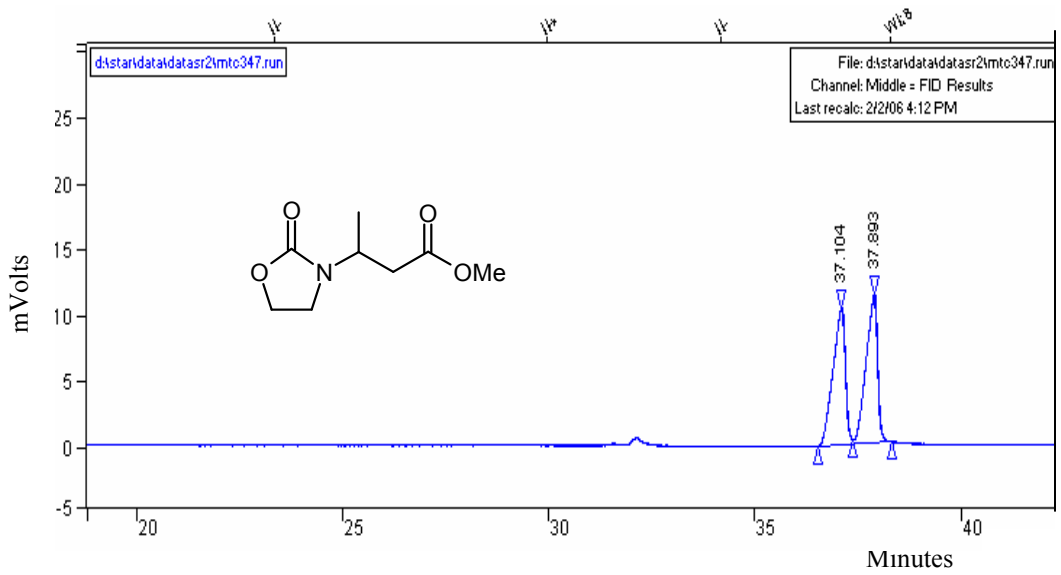
** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		16.2560	20.010	0.000	89141	BV	5.3
2		15.1297	20.203	0.000	82965	VB	6.1
3		40.6592	20.871	0.000	222958	BV	7.6
4		27.9551	21.289	0.000	153294	VB	7.5
	Totals:	100.0000		0.000	548358		

```
Total Unidentified Counts :     548357 counts

Detected Peaks: 4           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: -583 microVolts          LSB:     1 microVolts

Noise (used): 209 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 2.0  uL     Position: 2

*********************************************************************
```

Figure 7.40 GC chromatogram for chiral **12a** and **12b.**




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Middle = FID             Run Time     : 42.443 min
```

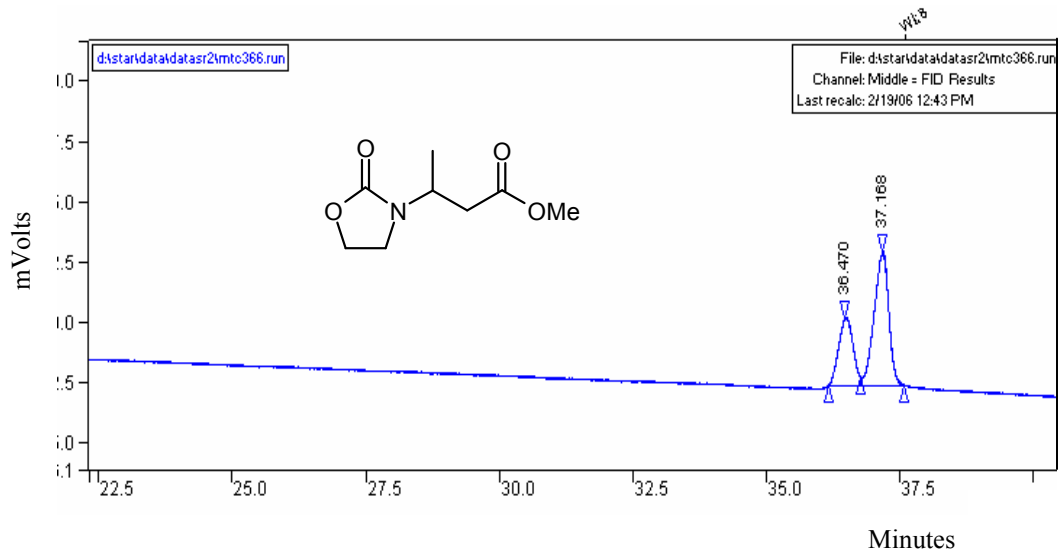
** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		49.7092	37.104	0.000	216580	BV	18.9
2		50.2908	37.893	0.000	219114	VB	17.9
	Totals:	100.0000		0.000	548358		

```
Total Unidentified Counts :     435694 counts

Detected Peaks: 2           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 64 microVolts          LSB:     1 microVolts

Noise (used): 209 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 2.0  uL     Position: 2

********************************************************************************
```

Figure 7.41 GC chromatogram for racemic **120.**




```
Operator   :                          Detector Type: 3800 (10 Volts)
Workstation:                          Bus Address  : 44
Instrument : Varian Star #1           Sample Rate  : 10.00 Hz
Channel    : Middle = FID             Run Time     : 42.443 min
```

** Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)
1		33.3525	36.470	0.000	52937	BV	18.0
2		66.6475	37.168	0.000	105783	VB	17.6
	Totals:	100.0000		0.000	548358		

```
Total Unidentified Counts :     158721 counts

Detected Peaks: 2           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 26 microVolts          LSB:     1 microVolts

Noise (used): 69 microVolts - monitored before this run

Vial: 1        Injection Number: 1     Volume: 2.0  uL     Position: 2

********************************************************************************
```

Figure 7.42 GC chromatogram for chiral **120.**

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List of publications

1. **Sarma, D**.; Kumar, A. "Hydrophobic interactions are dominant over secondary orbital interactions for a simple Diels-Alder reaction in salt solutions", *Org. Lett.* **2006,** 8, 2199-2202.

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1. Kumar, A.; **Sarma, D.** "Recent Applications of Chloroaluminate Ionic Liquids in Promoting Organic Reactions" ACS Symposium Series 902", **2005**, 350-370, Editors: Rogers, R. D.; Seddon, K. R.

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1. 'Enhanced Catalytic Performance of Triflates in Ionic Liquids: Diels-Alder reactions'
   Poster presented at the "**7th Tetrahedron Symposium, Challenges in Organic Chemistry**" at Kyoto Research Park, Kyoto, Japan during 25-26th May, 2006.

2. 'Anomalous Salting Effect on a simple Diels-Alder Reaction in Water',
   Poster presented at the "**7th National Symposium in Chemistry**" at Indian Association for the Cultivation of Science (IACS), Kolkata, India during 4-6th February, 2005.