DIELS-ALDER REACTION OF CINNAMOYL DIENOPHILES AND TERPENE DIENES AND ITS APPLICATION TOWARDS THE SYNTHESIS OF NATURAL PRODUCTS

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FACULTY OF SCIENCE
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DIELS-ALDER REACTION OF CINNAMOYL DIENOPHILES AND TERPENE DIENES AND ITS APPLICATION TOWARDS THE SYNTHESIS OF NATURAL PRODUCTS

ABSTRACT

The Lewis acid, $AlBr_3$, was found to effectively catalyse the Diels-Alder reaction between cinnamoyl dienophile, *trans*-chalcone and terpene diene, (*E*)-ocimene to give the cycloadduct product of [(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl](phenyl)methanone in high yield (72%) and with excellent regio- (100:0) and diastereoselectivity (95:5). The effectiveness of the $AlBr_3$ towards Diels-Alder reactions between various dienophiles and dienes was also evaluated. The acyclic dienes such as isoprene, 2,3-dimethylbutadiene and myrcene underwent Diels-Alder reaction with *trans*-chalcone, affording the corresponding adducts in relatively good yields (73-82%) and with excellent regioselectivity (90:10). A chiral titanium complex with 2 equivalents of FMOC-L-Phe-OH exhibited a significant enantioselectivity (61% ee) in the study of asymmetric Diels-Alder reaction of *trans*-chalcone and isoprene but unfortunately producing low yield (21%). A series of (±)-panduratin A derivatives were prepared by using $AlBr_3$ as catalyst. Eighteen (±)-panduratin A derivatives were successfully synthesised with yields between 9 to 71%. The natural products, fislatifolione, isofislatifolione, fislatifolic acid, panduratins H and I were synthesised *via* thermal, catalyst and chiral complex-induced Diels-Alder reactions. The thermal-induced Diels-Alder reaction afforded the natural products in moderate yields (28-39%) and with moderate regioselectivities (67:33 to 77:23), but only fislatifolione and isofislatifolione were successfully synthesised through catalyst and chiral complex-induced Diels-Alder reactions.

Keywords: Diels-Alder reaction, cinnamoyl dienophile, terpene diene, asymmetric Diels-Alder reaction, natural products.

TINDAK BALAS DIELS-ALDER CINNAMOYL DIENOPHILES DAN TERPENE DIENES DAN PENGGUNAANNYA TERHADAP SINTESIS PRODUK SEMULAJADI

ABSTRAK

Asid Lewis, $AlBr_3$ didapati secara berkesan memangkinkan tindak balas Diels-Alder antara cinnamoyl dienophile, *trans*-chalcone dan terpene diene, (*E*)-ocimene untuk memberikan produk cycloadduct, [(1*RS*,2*SR*,6*RS*)-3-metil-2-(3-metilbut-2-en-1-yl)-6-fenilsikloheks-3-en-1-yl](fenil)methanon dalam hasil tinggi (72%) dan dengan regio- (100:0) dan diastereoselektiviti yang sangat baik (95:5). Keberkesanan $AlBr_3$ terhadap tindak balas Diels-Alder antara pelbagai dienophile dan diene juga dinilai. Diene asiklik seperti isoprena, 2,3-dimetilbutadiena dan myrcene mengalami tindak balas Diels-Alder dengan *trans*-chalcone, memberikan tambahan yang sepadan dalam hasil yang agak baik (73-82%) dan dengan regioselektiviti yang sangat baik (90:10). Kompleks titanium kiral dengan 2 setara FMOC-L-Phe-OH mempamerkan enantioselektif yang ketara (61% ee) dalam kajian tindak balas Diels-Alder asimetri *trans*-chalcone dan isoprena tetapi malangnya hasil adalah rendah (21%). Satu siri derivatif (±)-panduratin A disediakan dengan menggunakan $AlBr_3$ sebagai pemangkin. Lapan belas jenis derivatif (±)-panduratin A berjaya disintesis dengan hasil di antara 9 hingga 71%. Produk semula jadi, fislatifolione, isofislatifolione, asid fislatifolik, panduratin H dan I telah disintesis melalui tindak balas Diels-Alder yang disebabkan oleh haba, pemangkin dan kompleks kiral. Tindak balas Diels-Alder yang disebabkan oleh haba menghasilkan produk semula jadi dalam hasil sederhana (28-39%) dan dengan regioselektiviti yang sederhana (67:33 hingga 77:23), tetapi hanya fislatifolione dan isofislatifolione berjaya disintesis melalui tindak balas Diels-Alder yang disebabkan oleh pemangkin dan kompleks kiral.

Kata kunci: tindak balas Diels-Alder, cinnamoyl dienophile, terpene diene, tindak balas Diels-Alder asimetri, produk semula jadi.

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α	:	alpha
$\mathring{A}$	:	angstrom
β	:	beta
^{o}C	:	degree Celsius
δ	:	delta (chemical shift in ppm)
%	:	percent
π	:	pi
ψ	:	psi
σ	:	sigma
^{1}H	:	proton-1
^{13}C	:	carbon-13
1,10-phen	:	1,10-phenanthroline
AcOH	:	acetic acid
AgNP	:	silver(0) nanoparticles
AgOTf	:	silver(I) trifluoromethanesulfonate
Al-HMS	:	aluminium hexagonal molecular silica
anhyd.	:	anhydrous
aq	:	aqueous
Ar	:	argon gas
$B(C_6F_5)_3$	:	tris(pentafluorophenyl)borane(III)
Bn_2-L-Phe-OH	:	*N*,*N*-dibenzyl-L-phenylalanine
Boc	:	*tert*-butyloxycarbonyl group
BOC-L-Pro-OH	:	*N*-(*tert*-butoxycarbonyl)-L-proline
$B(OPh)_3$	:	triphenyl borate
br d	:	broad doublet

br s	:	broad singlet
calcd.	:	calculated
conc. HCl	:	concentrated hydrochloric acid
COSY	:	homonuclear correlation spectroscopy
CuOTf	:	copper(I) trifluoromethanesulfonate
$Cu(OTf)_2$	:	copper(II) trifluoromethanesulfonate
d	:	doublet
DA	:	Diels-Alder
DCE	:	1,2-dichloroethane
dd	:	doublet of doublets
ddd	:	doublet of doublet of doublets
DIBAL	:	diisobutylaluminium hydride
DIPEA	:	*N*,*N*-diisopropylethylamine
DMA	:	dimethylacetamide
DMF	:	dimethylformamide
DMP	:	Dess-Martin periodinane
DMSO	:	dimethyl sulfoxide
dq	:	doublet of quartets
d.r.	:	diastereomeric ratio
dt	:	doublet of triplets
EDG	:	electron-donating groups
ee	:	enantiomeric excess
EOM	:	methyl ethyl ether group
EOM-Cl	:	chloromethyl ethyl ether
equiv	:	equivalent
etc.	:	et cetera (and others)

EWG	:	electron-withdrawing groups
F	:	fluorine atom
FMO	:	frontier molecular orbitals
Fmoc	:	fluorenylmethyloxycarbonyl group
Fmoc-Cl	:	9-fluorenylmethoxycarbonyl chloride
FMOC-L-Ala-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-alanine
FMOC-L-Cys-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-cysteine
FMOC-L-Cys(Trt)-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-*S*-trityl-L-cysteine
FMOC-L-His(Trt)-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-*N*-trityl-L-histidine
FMOC-L-Leu-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-leucine
FMOC-L-Nle-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-norleucine
FMOC-L-Phe-IPA	:	isopropyl {[(9H-fluoren-9-yl)methoxy]carbonyl}-L-phenylalaninate
FMOC-L-Phe-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine
FMOC-L-Phe-ol	:	(9H-fluoren-9-yl)methyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate
FMOC-L-Pro-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-proline
FMOC-L-Ser-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-serine
FMOC-L-Ser(Trt)-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-O-trityl-L-serine
FMOC-L-Trp-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-tryptophan
FMOC-L-Tyr(tBu)-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-*O-tert*-butyl-L-tyrosine
FMOC-L-Tyr-OH	:	*N*-(9-fluorenylmethoxycarbonyl)-L-tyrosine
$Ga(OTf)_3$	:	gallium(III) trifluoromethanesulfonate
h	:	hour
H	:	hydrogen atom
HATU	:	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate

HMBC	:	heteronuclear multiple bond correlation
HOMO	:	highest occupied molecular orbital
HPLC	:	high-performance liquid chromatography
HRMS (ESI)	:	high-resolution mass spectrometry (electrospray ionisation)
HSQC	:	heteronuclear single quantum coherence
Hz	:	hertz
i.e.	:	id est (that is)
J	:	coupling constant in Hz
kbar	:	kilobar
LA	:	Lewis acid
L-Phe-OH	:	L-phenylalanine
L-Phe-ol	:	(*S*)-(-)-2-amino-3-phenyl-1-propanol
LUMO	:	lowest unoccupied molecular orbital
m	:	multiplet
m	:	*meta*
M	:	molar
Me	:	methyl group
MEM	:	methoxyethane group
mg	:	milligram
MHz	:	megahertz
min	:	minute
mL	:	milliliter
mmol	:	millimoles
mol%	:	mole percent
MOM	:	methoxymethyl group
MS	:	molecular sieves

m/z	:	mass-to-charge ratio
N	:	normality
N_2	:	nitrogen gas
n-BuLi	:	*n*-butyllithium
n.d.	:	non-detected
nm	:	nanometer
NMR	:	nuclear magnetic resonance
o	:	*ortho*
p	:	*para*
pCH_3Ph	:	*p*-methylphenyl group
*p*ClPh	:	*p*-chlorophenyl group
PTSA	:	*p*-toluenesulfonic acid
p-TsOH	:	*p*-toluenesulfonic acid
Ph-L-Phe-OH	:	*N*-phenyl-L-phenylalanine
py	:	pyridine
R-BINOL	:	(*R*)-(+)-1,1'-binaphthalene-2,2'-diol
R-BINOL-EOM	:	(*R*)-(+)-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene
R-Br_2-BINOL	:	(*R*)-(+)-3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol
R-Br_2-BONOL-EOM	:	(*R*)-(+)-3,3'-dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene
ref.	:	reference
resp.	:	respectively
R-$(Hex)_2$-BINOL	:	(*R*)-(+)-3,3'-dihexyl-[1,1'-binaphthalene]-2,2'-diol
R-$(Hex)_2$-BINOL-EOM	:	(*R*)-(+)-3,3'-dihexyl--2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene
r.r.	:	regioisomeric ratio
r.t.	:	room temperature

R-(Trip)$_2$-BINOL	:	(*R*)-(+)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol
R-(Trip)$_2$-BINOL-EOM	:	(*R*)-(+)-3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene
R-VANOL	:	(*R*)-3,3′-diphenyl-2,2′-bi-1-naphthalol
s	:	singlet
(-)-SALEN	:	(*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine
sat.	:	saturated
sept	:	septet
SEM	:	2-(trimethylsilyl)ethoxymethyl group
(*S*)-VANOL	:	(*S*)-3,3′-diphenyl-2,2′-bi-1-naphthalol
t	:	triplet
(-)-TADDOL	:	(−)-*trans*-α,α'-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
td	:	triplet of doublets
Temp.	:	temperature
TFA	:	trifluoracetic acid
TfOH	:	trifluoromethanesulfonic acid
THF	:	tetrahydrofuran
TLC	:	thin layer chromatography
TMS	:	tetramethylsilane
uv	:	ultraviolet
VANOL	:	3,3'-diphenyl-2,2'-bi-1-naphthalol
Yb(OTf)$_3$	:	ytterbium(III) trifluoromethanesulfonate

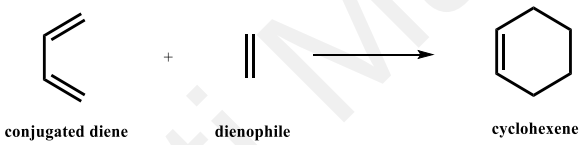
LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 General Introduction of Diels-Alder Reaction

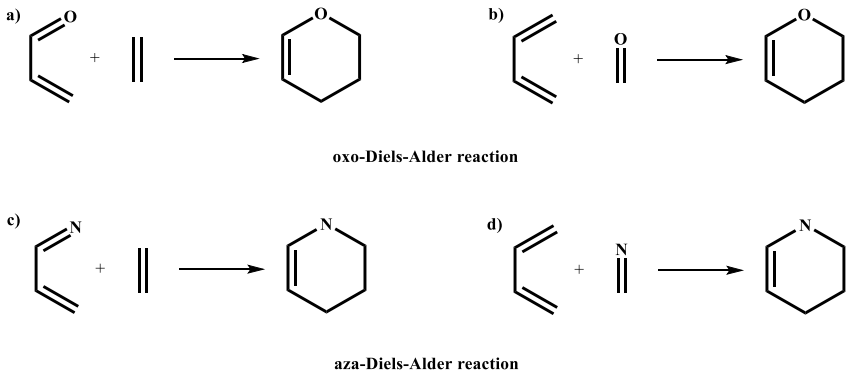
1.1.1 Background

The Diels–Alder (DA) reaction is a chemical reaction between a conjugated diene and an alkene, commonly termed the dienophile to form a cyclohexene (Scheme 1.1). Two new carbon-carbon bonds are formed in the reaction. This reaction was first described by Otto Diels and Kurt Alder in 1928, for which they were awarded the Nobel Prize in Chemistry in 1950. Since its discovery in 1928, more than 17000 papers have been published concerning synthetic, mechanistic and theoretical aspects of the reaction (Fringuelli & Taticchi, 2002).



Scheme 1.1: Diels-Alder reaction.

When one or more heteroatoms are present in the diene and/or dienophile system, the cycloaddition is called a hetero-Diels-Alder reaction. For example, carbonyl groups can be a dienophile to successfully react with dienes to yield dihydropyran rings, a reaction known as the oxo-Diels-Alder reaction (Schemes 1.2a & b), and imines can be used, either as the dienophile or at various sites in the diene, to form various *N*-heterocyclic compounds through the aza-Diels-Alder reaction (Schemes 1.2c & d).



Scheme 1.2: Oxo- and aza-Diels-Alder reactions.

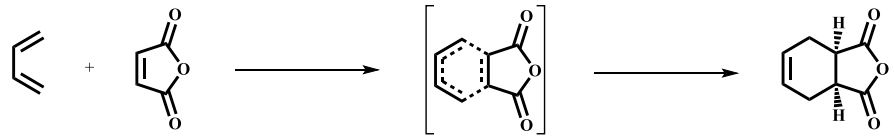
DA reaction can be accelerated using a catalyst or conducted at high temperatures. This reaction can be inter- or intramolecular. DA reaction is a reversible reaction, known as the retro-Diels-Alder reaction.

1.1.2 Mechanism

DA reaction is a concerted pericyclic reaction with the bond-forming and bond-breaking processes assumed to occur through a cyclic-like six-membered transition state. It is classified as a [π4s + π2s] cycloaddition, proceeding through a suprafacial/suprafacial interaction of a 4π electron system (the diene structure) with a 2π electron system (the dienophile structure), an interaction that leads to a transition state without an additional orbital symmetry-imposed energetic barrier and allows the DA reaction to take place with relative ease.

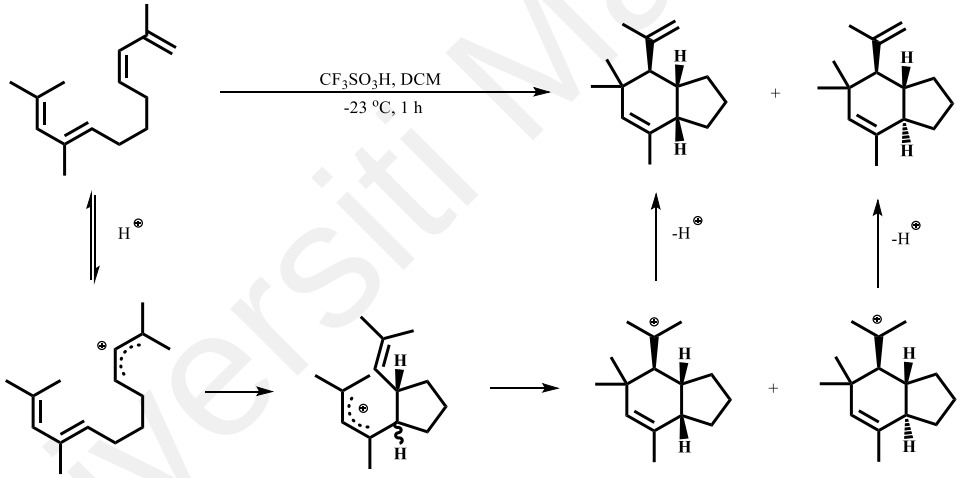
A concerted synchronous transition state (Dewer et al., 1986) (the formation of new bonds occurs simultaneously) and a concerted asynchronous transition state (Angell et al., 1986) (the formation of one σ bond proceeds the other) have been suggested, and the pathway of the reaction depends on the nature of the reagents and the experimental conditions. Most DA reactions, particularly under thermal condition and those involving apolar dienes and dienophiles, are thought to undergo the concerted mechanism (Scheme 1.3) (Fringuelli & Taticchi, 2002). The reaction between 1,3-butadiene and

ethene is a prototype of concerted synchronous reactions that have been investigated both experimentally and theoretically (Houk et al., 1986).



Scheme 1.3: Concerted mechanism (Fringuelli & Taticchi, 2002).

Conjugated cations, anions and radicals also can undergo the DA reaction. In such a case, the two σ bonds are formed in two separate steps and this is called stepwise mechanism (Scheme 1.4) (Gorman & Gassman, 1995; de Pascual-Teresa & Houk, 1996; Fringuelli & Taticchi, 2002).



Scheme 1.4: Stepwise mechanism (Fringuelli & Taticchi, 2002).

DA reaction can proceed through either normal electron demand or inverse electron demand. Frontier molecular orbitals (FMO) theory can used to explain the difference. For the normal electron demand DA reaction, the more important of the two HOMO-LUMO interactions is that between the electron-rich diene's ψ_2 (electron-donating substituent on diene) as the highest occupied molecular orbital (HOMO) with the electron-deficient dienophile's π^* (electron-withdrawing substituent on dienophile) as the lowest unoccupied molecular orbital (LUMO) (Figure 1.1a). The HOMO-LUMO energy gap is

close enough that the roles can be reversed by switching electronic effects of the substituents on the two components. In an inverse electron demand DA reaction, electron-withdrawing substituents on the diene (as LUMO) lower the energy of its empty ψ_3 orbital and electron-donating substituents on the dienophile (as HOMO) raise the energy of its filled π orbital sufficiently that the interaction between these two orbitals becomes the most energetically significant stabilising orbital interaction (Figure 1.1b).

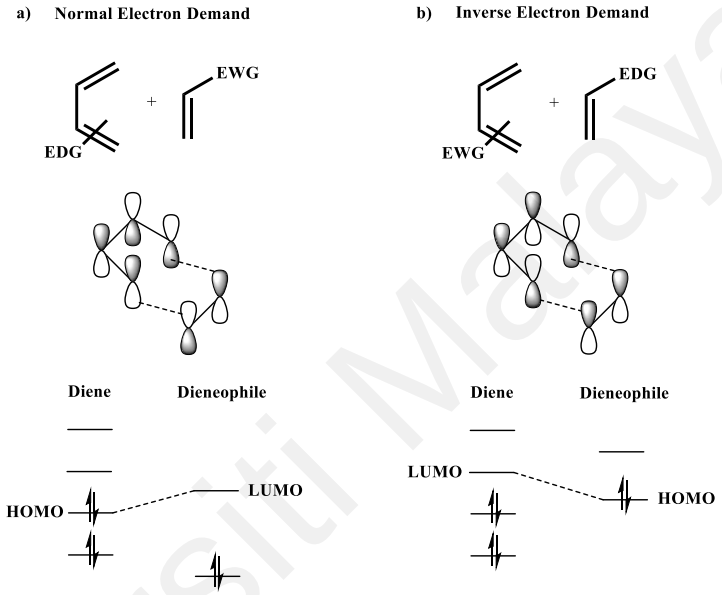


Figure 1.1: Normal and inverse electron demand Diels-Alder reactions (Adopted from www.wikipedia.org/wiki/Diels–Alder_reaction).

The reactivity of a DA reaction depends on the HOMO-LUMO energy separation of components: the lower the energy difference, the easier reaction occurs. Electron-withdrawing substituents lower the energy of both HOMO and LUMO, while electron-donating groups increase their energies. Normal electron demand DA reactions are accelerated by electron-donating substituents in the diene and by electron-withdrawing substituents in the dienophile. Inverse electron demand DA reactions are influenced by electronic effects of the substituents in the opposite way. Lewis acids can greatly accelerate the cycloaddition. One of the examples is the $AlCl_3$-catalysed reaction of cycloalkenones with 1,3-butadienes (Fringuelli et al., 1993). The coordination of the

carbonyl oxygen by Lewis acid increases the electron-withdrawing effect of the carbonyl group on the carbon-carbon double bond and lowers the LUMO dienophile energy.

1.1.3 The Dienophile

Dienophiles are molecules possessing a double or triple bond. The simplest dienophile, ethene, is poorly reactive. Dienophiles can possess many different types of substituents and form *cis* and *trans* conformers (Figure 1.2). Both conformers can form adducts in the DA reaction. The electronic effects of the substituents in the dienophile influence the rate of cycloaddition. Electron-withdrawing substituted dienophiles accelerate the reaction with electron-donating substituted dienes (normal electron demand DA reaction) (Fringuelli et al., 1993), whereas electron-donating groups in the dienophiles accelerate the cycloaddition with dienes having electron-withdrawing groups undergoing inverse electron demand DA reaction (Bodwell & Pi, 1997).

Figure 1.2: *Trans* and *cis* form dienophiles.

1.1.4 The Diene

The diene component of the DA reaction can be either cyclic or open-chain (Figure 1.3). Cyclic dienes are generally more reactive than the open-chain ones. The dienes can carry many different types of substituents but must be able to exist in the *cis* conformation to react, since this is the only conformer that can participate in the DA reaction (Sauer, 1966). A bulky substituent at the C2 or C3 position can increase reaction rate by destabilising the *trans* conformation and forcing the diene into the reactive *cis* conformation. For example, 2-*tert*-butyl-buta-1,3-diene is 27 times more reactive than simple butadiene (Carey & Sundberg, 2007). Conversely, dienes having bulky

substituents at both C2 and C3 are less reactive because the steric interactions between the substituents destabilise the *cis* conformation. Dienes with bulky terminal substituents (C1 and C4) decrease the rate of reaction, presumably by impeding the approach of the diene and dienophile (Craig et al., 1961).

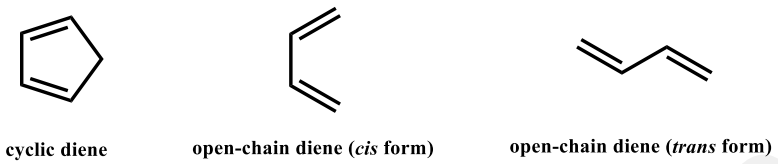
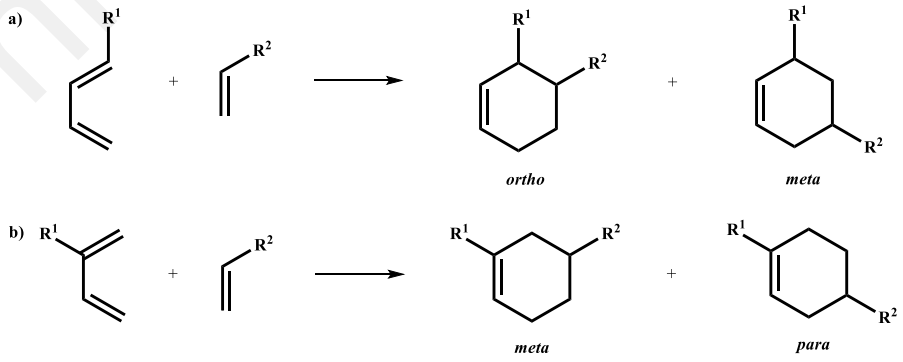


Figure 1.3: Cyclic and open-chain (*cis* and *trans* forms) dienes.

The electronic effects of the substituents in the diene influence the rate of cycloaddition. Electron-donating and electron-withdrawing groups activate the diene in normal and inverse electron demand DA reactions, respectively.

1.1.5 Regioselectivity

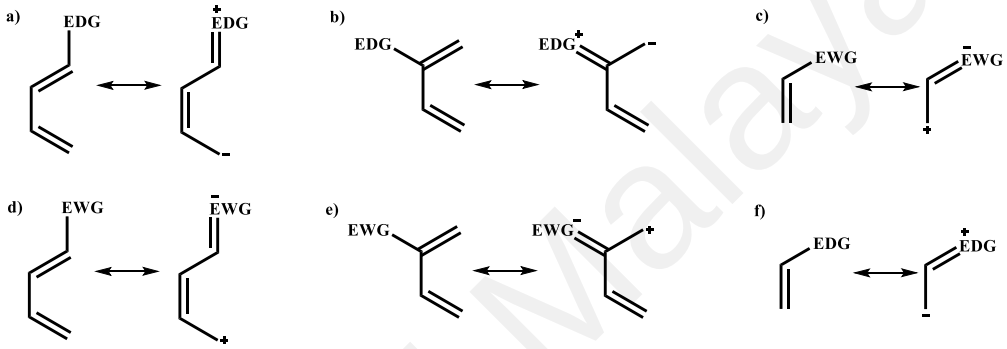
When an unsymmetrical diene reacts with an unsymmetrical dienophile, two regioisomer adducts can be formed depending on the orientation of the substituents in the adduct (Angell et al., 1986). The regioisomer adducts are usually named by using the classic nomenclature of disubstituted benzenes: *ortho*, *meta* and *para* (Scheme 1.5).



Scheme 1.5: Regioisomer adducts in Diels-Alder reaction.

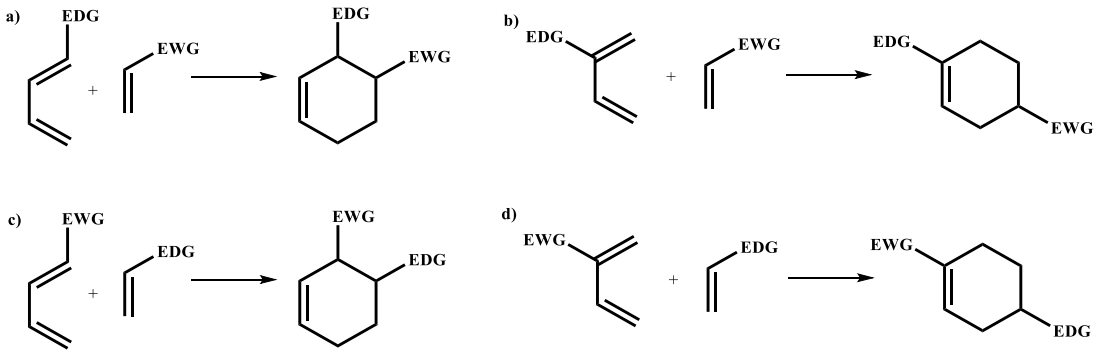
The regioselectivity of the DA reaction depends on the number and nature of substituents on diene and dienophile and on the reaction conditions (catalyst, temperature,

pressure, solvent, *etc.*). Generally, 1- and 2-substituted butadienes react with monosubstituted dienophiles to give mainly *ortho* and *para* adducts, respectively. It is termed *ortho-para* rule. Both normal and inverse electron demand DA reactions follow the *ortho-para* rule. The regioselectivity of DA reactions can explain based on the electronic effects of the substituents which orient the attack of reagent species by generating partial positive and negative charges in the dienes and dienophiles depicted in Scheme 1.6 (Kahn et al., 1986).



Scheme 1.6: Partial positive and negative charges in the dienes and dienophiles (Adopted from www.wikipedia.org/wiki/Diels–Alder_reaction).

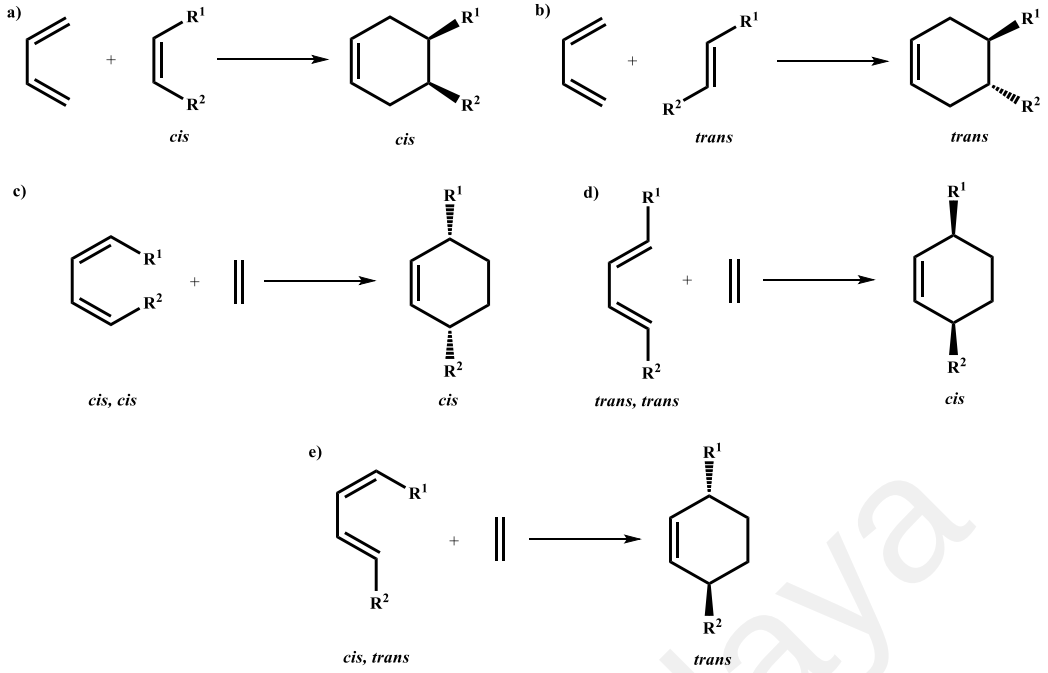
In a normal DA demand scenario, a diene bearing an electron-donating group (EDG) at C1 has its largest HOMO coefficient at C4 (Scheme 1.6a), while the dienophile with an electron-withdrawing group (EWG) at C1 has the largest LUMO coefficient at C2 (Scheme 1.6c). Pairing these two coefficients gives the *ortho* product as seen in case a in the Scheme 1.7. A diene substituted at C2 as in case b below has the largest HOMO coefficient at C1 (Scheme 1.6b), giving rise to the *para* product. Similar analyses for the corresponding inverse demand scenarios give rise to the analogous products as seen in cases c and d (Scheme 1.7). Generally, the more powerful the electronic effect of the substituents, the more regioselective the reaction.



Scheme 1.7: Regioselectivity of Diels-Alder reaction (Adopted from www.wikipedia.org/wiki/Diels–Alder_reaction).

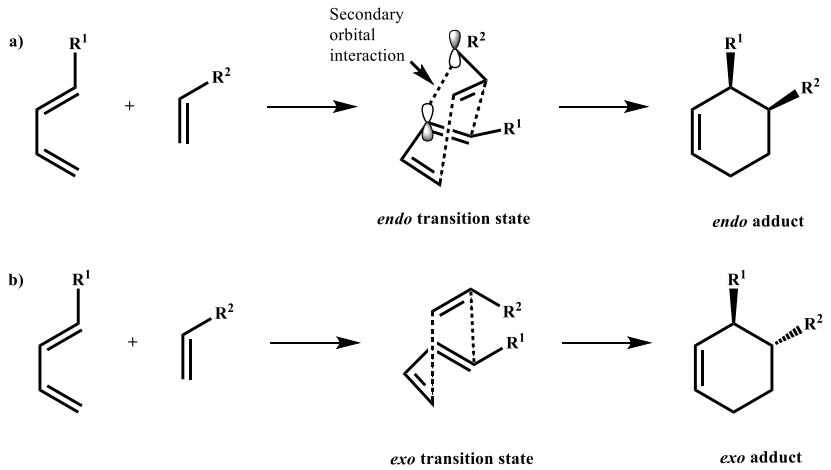
1.1.6 Stereoselectivity

DA reactions are suprafacial reactions and this manner of bond formation preserves in the cycloadduct the relative stereochemistry of the substituents at C1 and C4 and C1 and C2 of the parents diene and dienophile, respectively. For example, substituents in a *cis* (*trans*, resp.) (Schemes 1.8a & b) relationship on the double bond of the dienophile give rise to substituents that are *cis* (*trans*, resp.) on those same carbons with respect to the cyclohexene ring. Likewise, *cis*, *cis*- and *trans*, *trans*-disubstitued dienes (Schemes 1.8c & d) give *cis* substituents at these carbons of the product whereas *cis*, *trans*-disubstituted diene gives *trans* substituents (Scheme 1.8e).



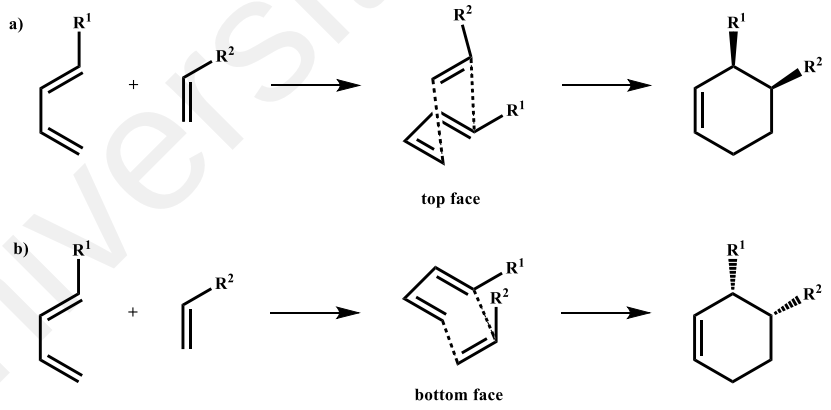
Scheme 1.8: Stereoselectivity of Diels-Alder reaction.

The relative stereochemistry of the substituents in the newly created stereogenic centers of the DA adduct is fixed by two possible suprafacial approaches named *endo* and *exo*. In the *endo* approach (Scheme 1.9a), the most significant substituent on the dienophile is oriented towards the diene π system. In the alternative *exo* approach shown in Scheme 1.9b, it is oriented away from it. The *exo* addition mode is preferred because it has less steric repulsive interaction than the *endo* approach. However, the *endo* adduct is usually the major product. The *endo* transition state is more stable than *exo* transition state due to the interactions between the π systems of the dienophile and the diene. This interaction is described as secondary orbital interaction (Ginsburg, 1983; Wannere et al., 2006). The *endo* preference is known as the Alder *endo* rule. *Endo* selectivity is typically higher for rigid dienophiles such as maleic anhydride and benzoquinone, for others, such as acrylates and crotonates, selectivity is not very pronounced (Houk & Lusku, 1971). Often, as with highly substituted dienes or very bulky dienophiles, steric effects can override the normal *endo* selectivity and leading to the *exo* isomer being preferred. The adducts formed by *endo-exo* approaches are diastereomeric in natural.



Scheme 1.9: *Endo* and *exo* approaches for Diels-Alder reaction.

Beside *endo*-*exo* approaches, cycloaddition of a dienophile occurs at the same rate to the top and bottom face of a diene to give a 50:50 mixture of adducts depicted in Scheme 1.10 (Oppolzer, 1991). The stereochemistry of the substituents of the newly formed stereogenic centers in the adducts are non-superimposable mirror images. The formed adducts are enantiomeric in nature.

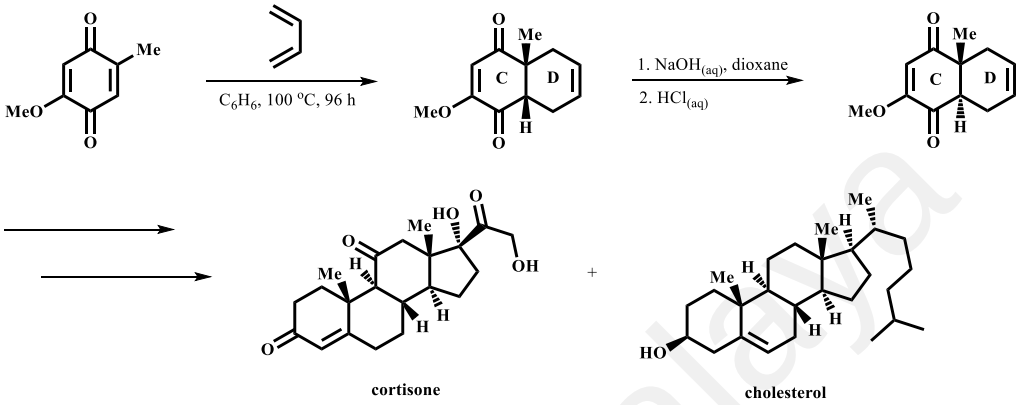


Scheme 1.10: Top and bottom approaches for Diels-Alder reaction.

1.1.7 Application

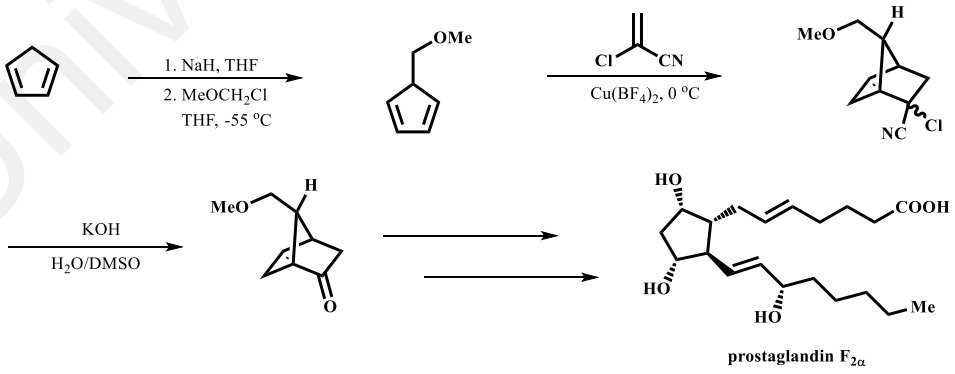
The DA reaction is amongst the best-known organic reactions that is widely used to construct, in a regio- and stereo-controlled way, a six-membered ring with up to four stereogenic centers. With these advantages, the reaction is a popular synthetic tool for constructing simple and complex molecules.

The first application of Diels–Alder reaction in total synthesis was illustrated by R. B. Woodward's synthesis of the steroid hormones of cortisone and cholesterol (Scheme 1.11) (Woodward et al., 1952). The reaction of butadiene with the quinone furnished the C and D rings of the steroid skeleton with the desired regiochemistry.



Scheme 1.11: Total synthesis of the steroid hormones of cortisone and cholesterol (Woodward et al., 1952).

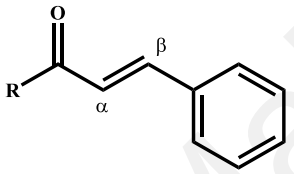
Another example is synthesis of prostaglandin F2α by E. J. Corey as shown in Scheme 1.12 (Corey et al., 1969) where a DA reaction was utilised early in the synthesis to establish the relative stereochemistry of three contiguous stereocenters on the prostaglandin cyclopentane core.



Scheme 1.12: Total synthesis of the prostaglandins F2α (Corey et al., 1969).

1.2 Cinnamoyl Dienophiles

Cinnamoyl dienophiles refer to organic compounds with the general structure (O=CR)-C^{α}=C^{β}-Ph (Figure 1.4). The alkene in these compounds is conjugated with a carbonyl group while another site is attached to a phenyl ring. Cinnamoyl dienophile can be further subclassified according to the nature of the carbonyl group. Cinnamic acid and cinnamide are types of cinnamoyl dienophile that consist of an alkene conjugated to carboxylic acid and amide, respectively. While cinnamaldehyde and cinnamate consist of an alkene conjugated to an aldehyde and ester, respectively.



R= OH (cinnamic acid)
R= NH_2 (cinnamide)
R= H (cinnamaldehyde)
R= OMe (methyl cinnamate)
R= Me (4-phenylbut-3-en-2-one)
R= Ph (chalcone)

Figure 1.4: General structure of cinnamoyl dienophiles.

Cinnamoyl dienophiles can be prepared through an aldol condensation (Iranpoor & Kazemi, 1998), Knoevenagel condensation (Mase & Horibe, 2013), Perkin reaction (Sevenard, 2003) and Meyer–Schuster rearrangement (Engel & Dudley, 2006).

Cinnamoyl dienophiles are electrophilic at both the carbonyl carbon as well as the β-carbon. Depending on conditions, either site can be attacked by nucleophiles. Due to their extended conjugation, cinnamoyl dienophiles are prone to polymerisation. Again because of their electrophilic character, the alkene portion of cinnamoyl dienophiles are good dienophiles in Diels–Alder reactions. They can be further activated by Lewis acids, which bind to the carbonyl oxygen. Cinnamoyl dienophiles are good ligands for low-valent metal complexes, examples being (benzylideneacetone)iron tricarbonyl and tris(dibenzylideneacetone)dipalladium(0). Cinnamoyl dienophiles are readily

hydrogenated and hydrogenation can occur on the carbonyl or the alkene (conjugate reduction) selectively, or both functional groups.

1.3 Terpene Dienes

Terpenes are a large and diverse class of organic compounds, produced by a variety of plants, particularly conifers, and by some insects. They often have a strong odour and may protect the plants that produce them by deterring herbivores and by attracting predators and parasites of herbivores (Trapp & Croteau, 2001). Terpenes are hydrocarbons, terpenoids are modified terpenes that contain additional functional groups, usually oxygen-containing. In nature, terpenes occur predominantly as hydrocarbons, alcohols and their glycosides, ethers, aldehydes, ketones, carboxylic acids and esters (Breitmaier, 2006).

The building block of terpene is a five-carbon isoprene unit (Figure 1.5). The isopropyl part of isoprene is defined as the head, and the ethyl residue as the tail. Terpene has a molecular formula of $(C_5H_8)_n$ (n dictates the number of units involved) and can be visualised as the result of linking isoprene units "head to tail" to form chains, which can be arranged to form rings. This is the isoprene rule found by Leopold Ružička in 1953 (Ruzicka, 1953). Terpenes are classified by the number of isoprene units in the molecule; a prefix in the name indicates the number of terpene units needed to assemble the molecule where are hemi- (1 unit), mono- (2 unit), sesqui- (3 unit), di- (4 unit), sester- (5 unit), tri- (6 unit), sesquar- (7 unit), tetraterpenes (8 unit) and polyterpenes (> 8 unit). In mono-, sesqui-, di- and sesterterpenes, the isoprene units are linked to each other from head-to-tail; tri- and tetraterpenes contain one tail-to-tail connection in the center.

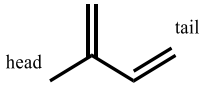


Figure 1.5: Chemical structure of isoprene unit.

There are two metabolic pathways that produce terpenes: the Mevalonic acid pathway and the 2-C-methyl-D-erythritol 4-phosphate/1-deoxy-D-xylulose 5-phosphate pathway (MEP/DOXP pathway). Isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) are the end-products in both pathways and are the precursors of terpenes.

Terpenes have desirable properties for use in food, cosmetics, pharmaceuticals, pesticide and biotechnology industries (Eggersdorfer, 2000; Isman, 2000; Koziol et al., 2014; Koyama & Heinbockel, 2020). In addition, terpenes are also major biosynthetic building blocks. Terpenes such as ocimene, myrcene, *etc*. have been used in the synthesis of targeted and natural compounds for many years (Chee et al., 2010; Pasfield et al., 2013; Cong et al., 2010; Bañuelos et al., 2010; Li et al., 2016).

1.4 Natural Products Derived from Diels-Alder Reaction between Cinnamoyl Dienophiles and Terpene Dienes

Terpene dienes are major biosynthetic building blocks for many natural products. One of the biosynthesis processes mimic the DA cycloaddition reaction. Amongst the more well-known examples are panduratin A (**1**) and its derivatives, panduratins C (**2**), H (**3**) and I (**3a**) (Figure 1.6) (Cheenpracha et al., 2006; Win et al., 2008). Panduratin A (**1**) was first isolated from the rhizomes of *Boesenbergia rotunda* (or *Boesenbergia pandurate* at earlier time) (Tuntiwachwuttikul et al., 1984). It has a wide range of promising biological activities, such as anticancer (Yun et al., 2005), anti-inflammatory (Tuchinda et al., 2002), antibacterial (Park et al., 2005), antiangiogenic (Lai et al., 2015), antioxidant (Salama et al., 2013), anti-HIV (Cheenpracha et al., 2006) and competitive dengue-2 virus NS3 protease inhibitory activity (Kiat et al., 2006). Panduratin A (**1**) and its derivatives **2**, **3** & **3a** possessed cyclohexenyl skeleton which is biosynthetically derived from substituted chalcone or cinnamate with (*E*)-ocimene, respectively.

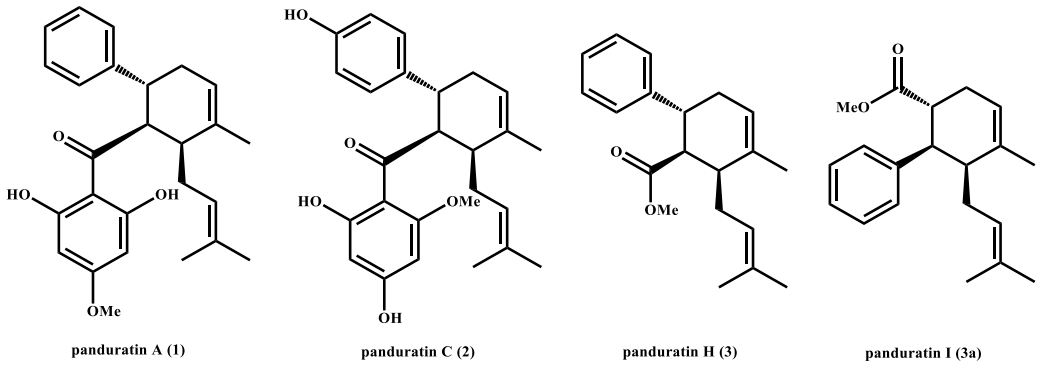


Figure 1.6: Chemical structures of padurantin A (1) and its derivatives 2, 3 & 3a.

Nicolaioidesin C (**4**) (Figure 1.7) was isolated from the roots of *Renealmia nicolaioides* (Gu et al., 2002). It showed cytotoxic activity against prostate cancer cells and cathepsin inhibitory activity in vitro (Deb Majumdar et al., 2011). In addition, nicolaioidesin C (**4**) also exhibited potent preferential cytotoxicity against PANC-1 human pancreatic cancer cells under nutrition deprived conditions (Nguyen et al., 2017). Similar with panduratin A (**1**), nicolaioidesin C (**4**) is a cyclohexenyl chalcone natural product which biosynthetically derived from substituted chalcone with terpene diene, myrcene.

Fislatifolic acid (**5**), fislatifolione (**6**) and its regioisomer, isofislatifolione (**6a**) (Figure 1.7) were isolated from the stem bark of *Fissistigma latifolium* (Geny et al., 2017). (+)-Fislatifolic acid (**5**) shows micromolar activity as a dual Bcl-xL/Mcl-1 inhibitor and cytotoxic activity against A549 and MCF7 cancer cell lines (Tiamas et al., 2018). Fislatifolic acid (**5**), fislatifolione (**6**) and isofislatifolione (**6a**) are cyclohexenyl chalcone natural products which biosynthetically derived from cinnamic acid or ketone with myrcene, respectively.

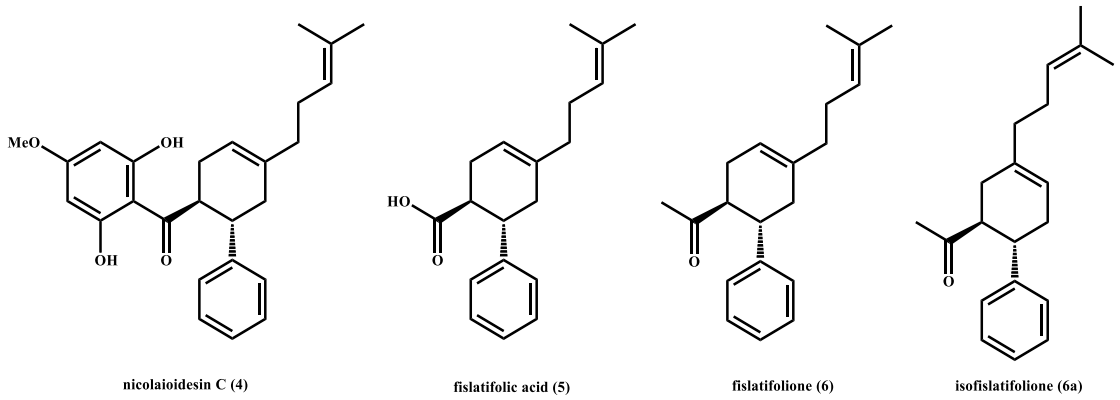


Figure 1.7: Chemical structures of nicolaioidesin C (4), fislatifolic acid (5), fislatifolione (6) and isofislatifolione (6a).

CHAPTER 2: LITERATURE REVIEW

2.1 Normal Diels-Alder Reaction between Cinnamoyl Dienophiles and Terpene Dienes

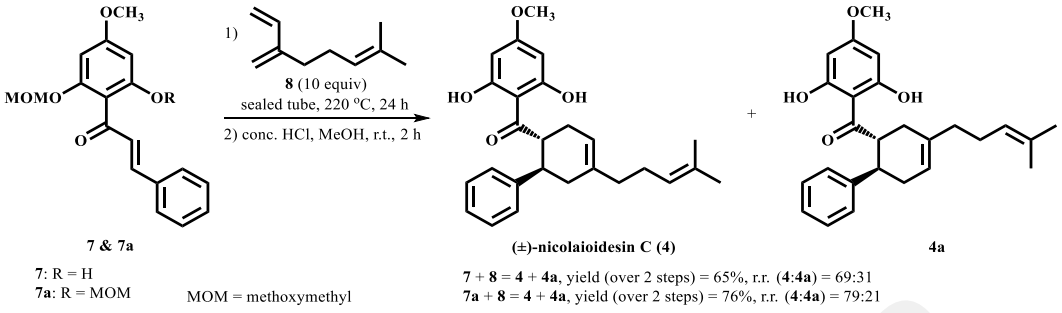
Several strategies have been reported in the literature for DA reactions between cinnamoyl dienophiles and terpene dienes. The synthetic strategies can be divided into thermal promotion, high-pressure promotion and catalyst promotion.

2.1.1 Thermal Promotion

The thermal-promoted DA reaction is the most commonly used strategy for construction of the cyclohexene skeleton. Many groups (Lee, Rahman & Coster) have used this strategy for the synthesis of prenylflavonoid-related DA natural products and their analogues.

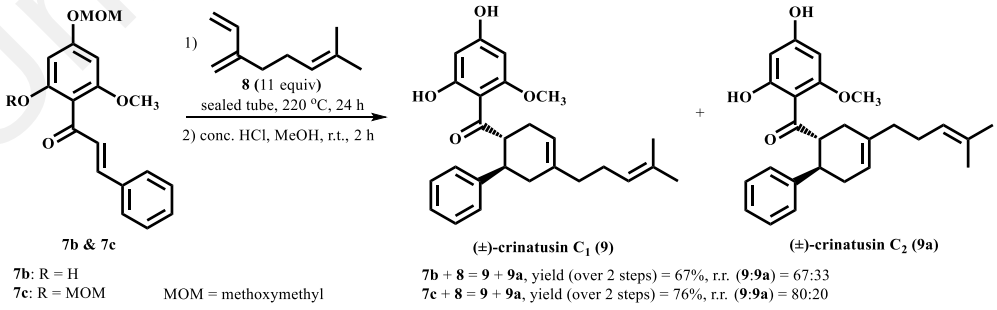
In 2008, Jung and Lee (2008) reported the synthesis of the naturally occurring dihydrochalcones (±)-nicolaioidesin C (**4**), (±)-crinatusin C_1 (**9**) and (±)-crinatusin C_2 (**9a**), through thermal DA cycloadditions between methoxymethyl (MOM)-protected chalcones **7** & **7a-c** and myrcene (**8**), followed by MOM deprotection. In their study, (*E*)-1-(2-hydroxy-4-methoxy-6-methoxymethoxyphenyl)-3-phenylpropenone (**7**) (mono-MOM-protected chalcone) and (*E*)-1-(4-methoxy-2,6-bismethoxymethoxyphenyl)-3-phenylpropenone (**7a**) (di-MOM-protected chalcone) reacted with myrcene (**8)** in benzene in a sealed tube at 220 °C for 24 h followed by the cleavage of MOM ether with concentrated HCl in methanol at room temperature for 2 h gave the expected (±)-nicolaioidesin C (**4**) together with its unnatural regioisomer **4a** in 65% and 76% yield (over 2 steps), respectively (Scheme 2.1). Interestingly, both dienophiles **7** & **7a** gave different regioselectivity. (*E*)-1-(2-hydroxy-4-methoxy-6-methoxymethoxyphenyl)-3-phenylpropenone (**7**) gave the ratio of (±)-nicolaioidesin C (**4**) and its regioisomer **4a** in

69:31 whereas (*E*)-1-(4-methoxy-2,6-bismethoxymethoxyphenyl)-3-phenylpropenone (**7a**) improved the selectivity to 79:21. This is probably due to bulky two MOM ethers.



Scheme 2.1: Synthesis of (±)-nicolaioidesin C (4) and its unnatural regioisomer 4a.

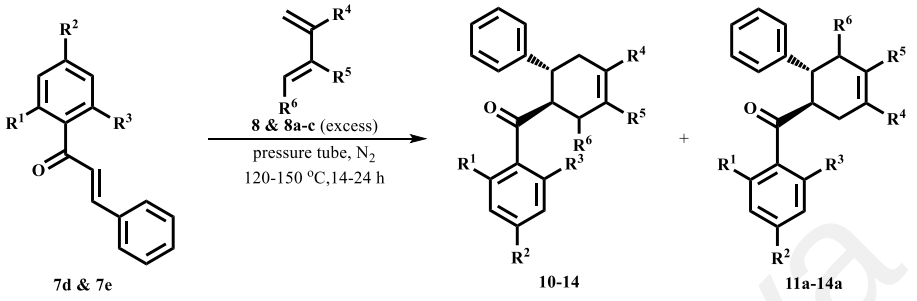
For the synthesis of (±)-crinatusins C_1 (**9**) and C_2 (**9a**), (*E*)-1-(2-hydroxy-6-methoxy-4-methoxymethoxyphenyl)-3-phenylpropenone (**7b**) (mono-MOM-protected chalcone) and (*E*)-1-(2-methoxy-4,6-bismethoxymethoxyphenyl)-3-phenylpropenone (**7c**) (di-MOM-protected chalcone) were used to react with myrcene (**8**) in similar conditions (Scheme 2.2). (*E*)-1-(2-Hydroxy-6-methoxy-4-methoxymethoxyphenyl)-3-phenylpropenone (**7b**) afforded the two natural products **9** & **9a** in 67% (over 2 steps) and regioisomeric ratio in 67:33 whereas the DA yield and regioisomeric ratio for (*E*)-1-(2-methoxy-4,6-bismethoxymethoxyphenyl)-3-phenylpropenone (**7c**) were 76% (over 2 steps) in 80:20.



Scheme 2.2: Synthesis of (±)-crinatusins C_1 (9) and C_2 (9a).

Two years later, Rahman and co-worker (Chee et al., 2010) applied high temperature to the DA reactions between 2′,4′,6′-trimethoxychalcone (**7d**) or 4′-methoxychalcone (**7e**)

with 2,3-dimethyl-1,3-butadiene (**8a**), isoprene (**8b**), (*E*)-ocimene (**8c**) and myrcene (**8**) (Scheme 2.3). The DA reactions gave excellent yields and the regioisomeric ratios (*meta*/*para*) are 2:3.



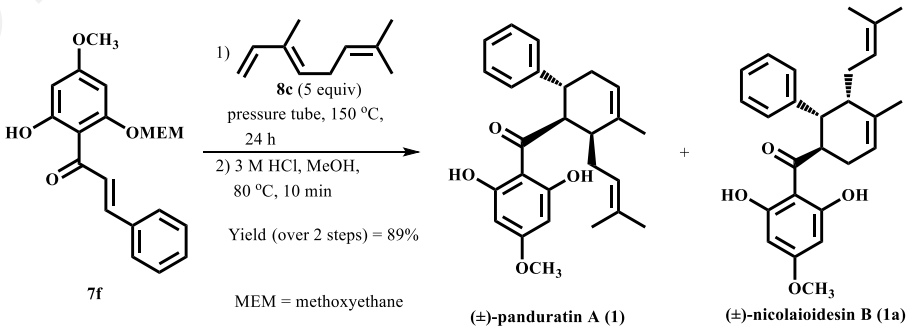
7d: $R^1 = R^2 = R^3 = OCH_3$
7e: $R^1 = R^3 = H$; $R^2 = OCH_3$

8a: $R^4 = R^5 = CH_3$; $R^6 = H$
8b: $R^4 = R^6 = H$; $R^5 = CH_3$
8c: $R^4 = H$; $R^5 = CH_3$; $R^6 = CH_2CH{=}C(CH_3)_2$
8: $R^4 = R^6 = H$; $R^5 = CH_2CH_2CH{=}C(CH_3)_2$

10: $R^1 = R^2 = R^3 = OCH_3$; $R^4 = R^5 = CH_3$; $R^6 = H$, yield = 93%
11 (*meta*) & **11a** (*para*): $R^1 = R^2 = R^3 = OCH_3$; $R^4 = R^6 = H$; $R^5 = CH_3$; yield = 86%, r.r. (**11**:**11a**) = 2:3
12 (*meta*) & **12a** (*para*): $R^1 = R^2 = R^3 = OCH_3$; $R^4 = H$; $R^5 = CH_3$; $R^6 = CH_2CH{=}C(CH_3)_2$, yield = 99%, r.r. (**12**:**12a**) = 2:3
13 (*meta*) & **13a** (*para*): $R^1 = R^3 = R^4 = H$; $R^2 = OCH_3$; $R^5 = CH_3$; $R^6 = CH_2CH{=}C(CH_3)_2$, yield = 96%, r.r. (**13**:**13a**) = 2:3
14 (*meta*) & **14a** (*para*): $R^1 = R^2 = R^3 = OCH_3$; $R^4 = R^6 = H$; $R^5 = CH_2CH_2CH{=}C(CH_3)_2$, yield = 89%, r.r. (**14**:**14a**) = 2:3

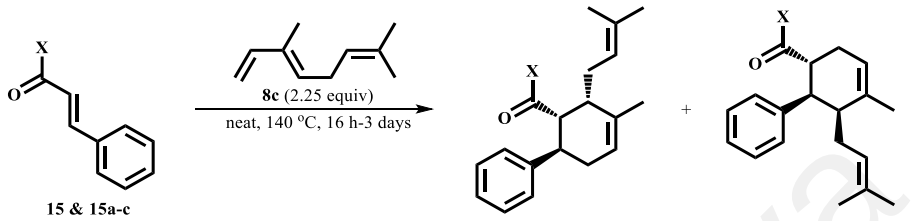
Scheme 2.3: Thermal-induced Diels-Alder reactions of substituted 4-methoxychalcones 7d & 7e with different dienes 8 & 8a-c.

By using similar conditions, the mixture of (±)-panduratin A (**1**) and its regioisomer (±)-nicolaioidesin B (**1a**) was synthesised by DA reaction between 2′-hydroxy-4′-methoxy-6′-ethoxymethoxychalcone (**7f**) and (*E*)-ocimene (**8c**), followed by methoxyethane (MEM) deprotection (Scheme 2.4). The two processes gave (±)-panduratin A (**1**) and (±)-nicolaioidesin B (**1a**) as a mixture in 89% yield.



Scheme 2.4: Synthesis of (±)-panduratin A (1) and (±)-nicolaioidesin B (1a).

Coster's group (Pigott et al., 2014) examined the DA reactions of cinnamate analogues **15** & **15a-c** with (*E*)-ocimene (**8c**) under thermal conditions in 2014 (Scheme 2.5). Among of cinnamate analogues **15** & **15a-c**, (*E*)-*N*-methoxy-*N*-methylcinnamide (**15b**) gave the highest regioselectivity with the regioisomeric ratio (*meta*/*para*) of < 2:> 98.

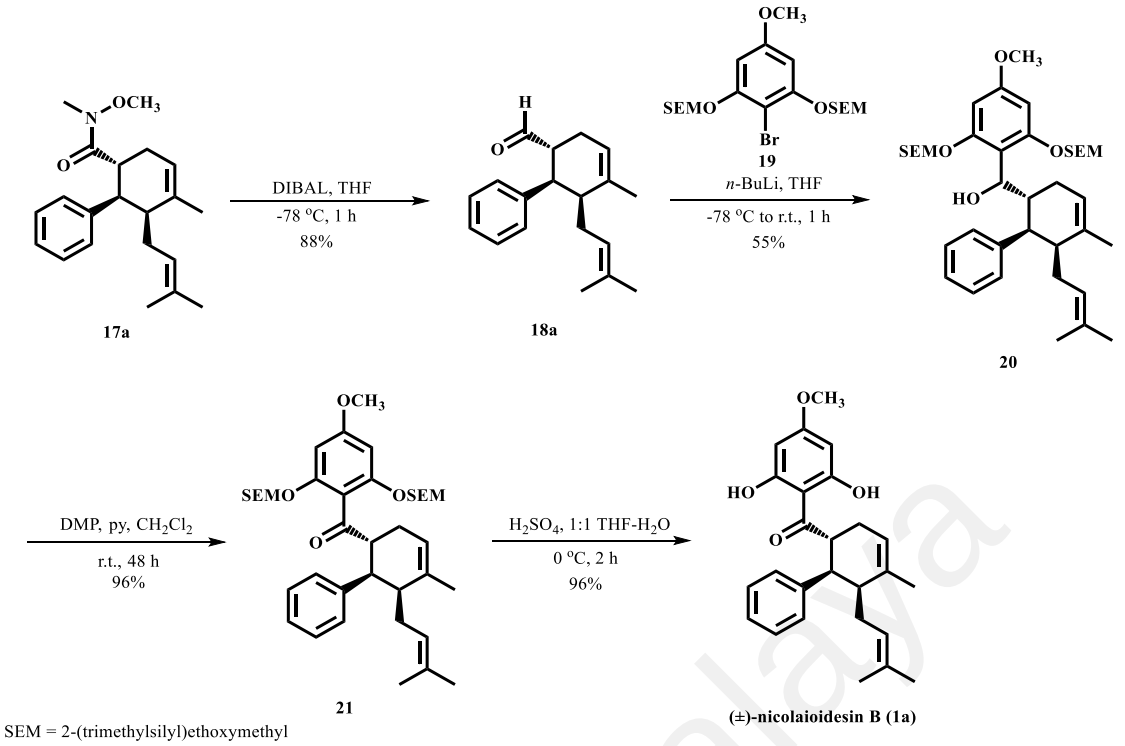


15: X = OCH_3
15a: X = OC_6F_5
15b: X = $N(CH_3)OCH_3$
15c: X = H

3 (*meta*) & **3a** (*para*): X = OCH_3, yield = 97%, r.r. (**3**:**3a**) = 25:75
16 (*meta*) & **16a** (*para*): X = OC_6F_5, yield = 96%, r.r. (**16**:**16a**) = 33:67
17 (*meta*) & **17a** (*para*): X = $N(CH_3)OCH_3$, yield = 70%, r.r. (**17**:**17a**) = < 2:> 98
18 (*meta*) & **18a** (*para*): X = H, yield = trace, r.r. (**18**:**18a**) = n.d.

Scheme 2.5: Thermal-induced Diels-Alder reactions of cinnamate derivatives 15 & 15a-c with (*E*)-ocimene (8c).

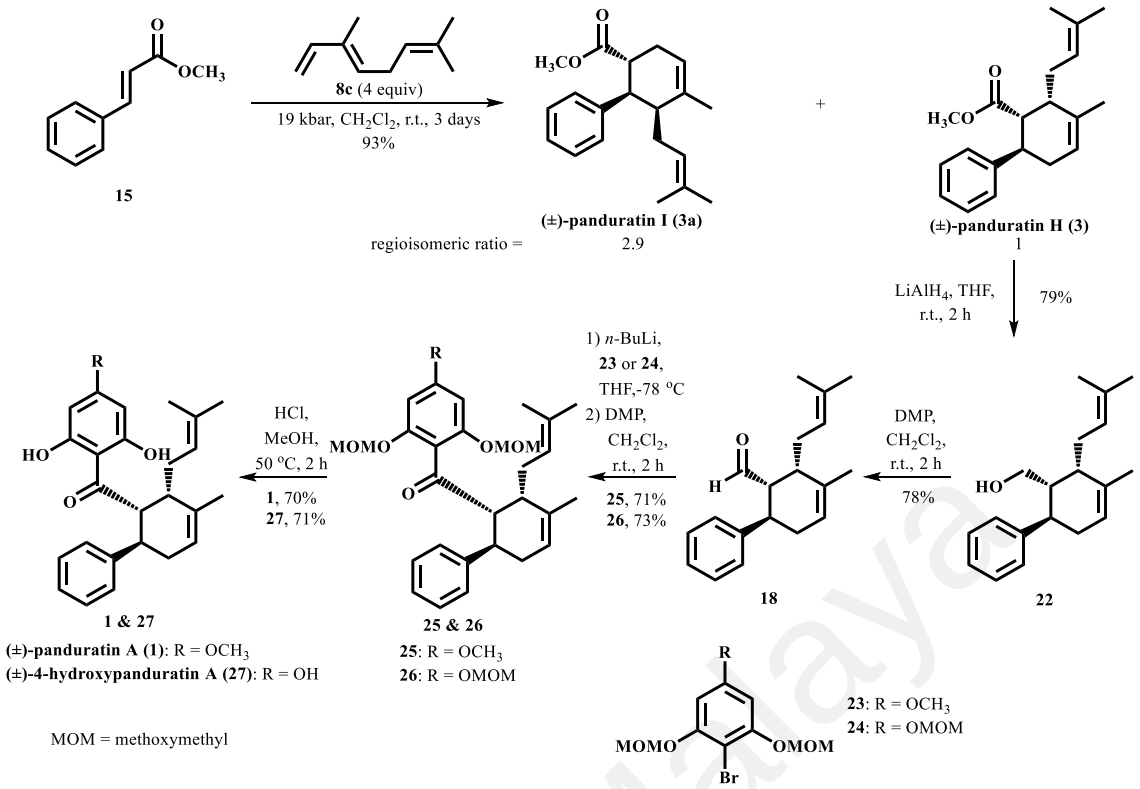
For the process of natural product synthesis, as opposed to Lee & Rahman's synthesis strategy in which a late-stage DA reaction was employed to synthesise the cyclohexene core, Coster's group used a different early-stage high temperature induced cycloaddition strategy, followed by the construction of the side chain through further transformations. This strategy allows late-stage diversification to different natural products and analogues through the variation of building blocks. By using this method, they transformed the *para*-adduct **17a** from *N*-methoxy-*N*-methylcinnamide (**15b**) into the natural product (±)-nicolaioidesin B (**1a**) in four further steps (Scheme 2.6).



Scheme 2.6: Coster's synthesis of (±)-nicolaioidesin B (1a).

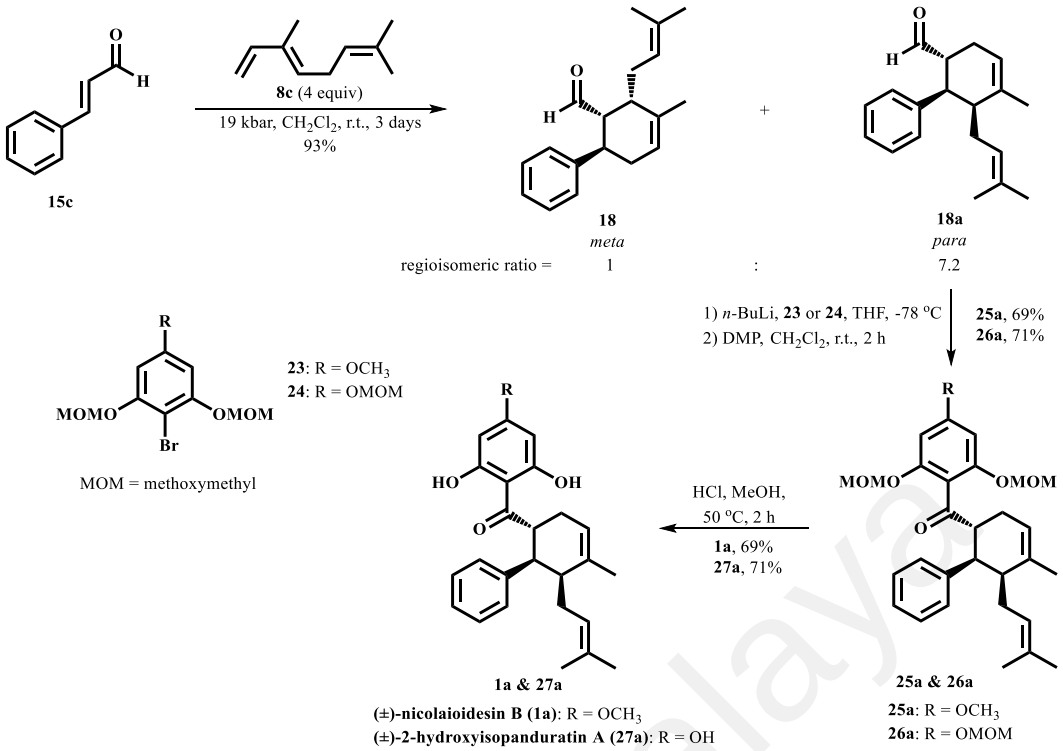
2.1.2 High-pressure Promotion

The application of high-pressure-induced DA reaction to synthesise prenylflavonoid and related DA natural products has been reported by McLeod and co-workers (Pasfield et al., 2013) in 2013. The cycloaddition between methyl cinnamate (**15**) and (*E*)-ocimene (**8c**) was carried out in dichloromethane at 19 kbar at room temperature, natural products, (±)-panduratin H (**3**) and its regioisomer (±)-panduratin I (**3a**) were obtained in a 1:2.9 ratio with 93% yield after three days under this condition. (±)-Panduratin H (**3**) was further converted to further natural products, (±)-panduratin A (**1**) and (±)-4-hydroxypanduratin A (**27**) within 5 steps (Scheme 2.7).



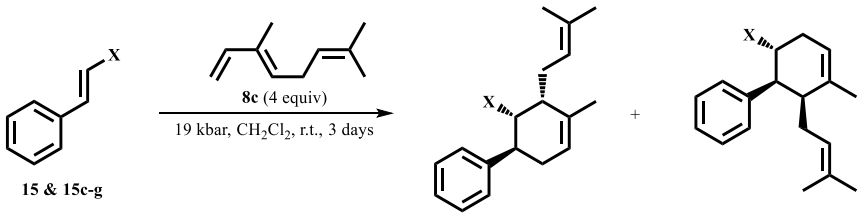
Scheme 2.7: Synthesis of (±)-panduratins A (1), H (3) and I (3a) and (±)-4-hydroxypanduratin A (27).

Cinnamaldehyde (**15c**) was also used as a reactant for the synthesis of nicolaioidesin B (**1a**) and 2-hydroxyisopanduratin A (**27a**). Cinnamaldehyde (**15c**) was reacted with (*E*)-ocimene (**8c**) in high-pressure condition to afford a separable 1:7.2 mixture of the two DA regioisomers **18** & **18a**. Ultimately, the *para*-adduct **18a** was then transformed into the desired natural products **1a** & **27a** in 3 steps (Scheme 2.8).



Scheme 2.8: Synthesis of (±)-nicolaioidesin B (1a) and (±)-2-hydroxyisopanduratin A (27a).

Furthermore, to explore the influence of structure on cycloaddition regioselectivity, various dienophiles **15** & **15c-g** with differing electronic and steric attributes were paired with (*E*)-ocimene (**8c**) in the high-pressure DA reaction (Scheme 2.9). In all cases the reactions afforded *para*-regioisomer **3a**, **18a** & **28a-31a** as the major product. Stronger activating groups, such as the aldehyde or nitrile groups, provided slightly higher ratios favoring *para*-regioisomer. However, substitution of the ethyl ester for the more electron-withdrawing 2,2,2-trifluoroethyl ester, a strong inductive electron-withdrawing group, provided the DA adducts in a similar ratio.



15 & 15c-g

15d: X = CN
15e: X = COOtBu
15c: X = CHO
15f: X = COOEt
15: X = $COOCH_3$
15g: X = $COOCH_2CF_3$

3, 18 & 28-31
meta

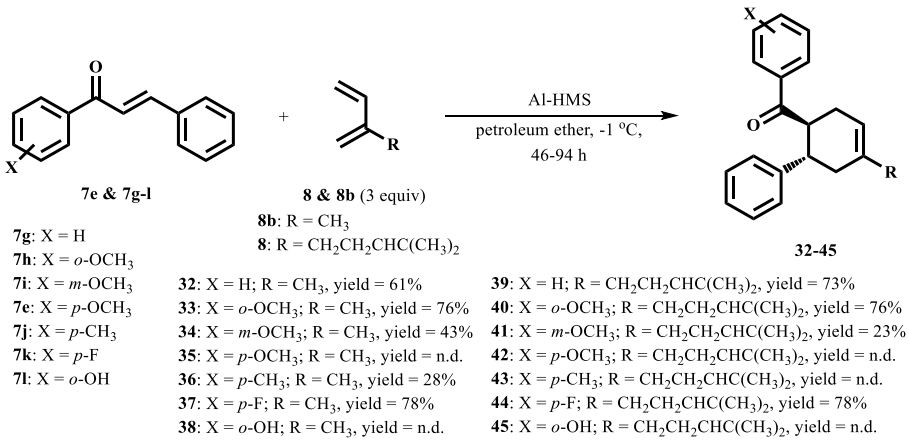
3a, 18a & 28a-31a
para

28 (*meta*) & **28a** (*para*): X = CN, r.r. (**28**:**28a**) = 1:9.5
29 (*meta*) & **29a** (*para*): X = COOtBu, r.r. (**29**:**29a**) = 1:8.9
18 (*meta*) & **18a** (*para*): X = CHO, r.r. (**18**:**18a**) = 1:7.2
30 (*meta*) & **30a** (*para*): X = COOEt, r.r. (**30**:**30a**) = 1:3.1
3 (*meta*) & **3a** (*para*): X = $COOCH_3$, r.r. (**3**:**3a**) = 1:2.9
31 (*meta*) & **31a** (*para*): X = $COOCH_2CF_3$, r.r. (**31**:**31a**) = 1:2.4

Scheme 2.9: High-pressure-induced Diels-Alder reactions of different dienophiles 15 & 15c-g with (*E*)-ocimene (8c).

2.1.3 Catalyst Promotion

In 2008, Corbett and Weavers (2008) utilised aluminium hexagonal molecular silica (Al-HMS) catalyst formed from tetraethyl orthosilicate and aluminium isopropoxide in the presence of hexadecylamine as catalyst in the DA reaction of *trans*-chalcone (**7g**) with isoprene (**8b**) at -1 ^{o}C for 46 h, which gave 61% yield (Scheme 2.10). The NMR spectral revealed that the DA product was almost entirely one regioisomer. In addition, this catalyst could eliminate problems with diene polymerisation that are always encountered during the reaction that involves Lewis Acids. Ultimately, they employed the catalyst to prepare new adducts of isoprene (**8b**) and myrcene (**8**) with various substituted chalcones **7e** & **7g-l** in moderate to good yield (Scheme 2.10).



7e & 7g-l

7g: X = H
7h: X = *o*-OCH_3
7i: X = *m*-OCH_3
7e: X = *p*-OCH_3
7j: X = *p*-CH_3
7k: X = *p*-F
7l: X = *o*-OH

8 & 8b (3 equiv)

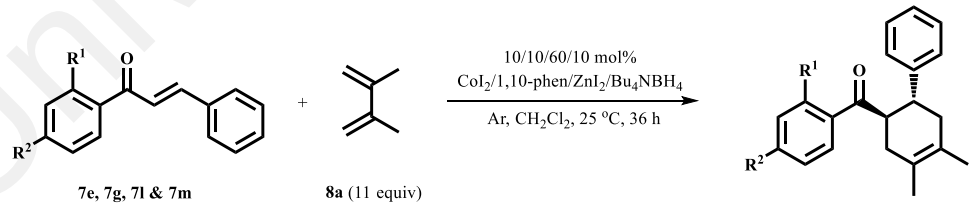
8b: R = CH_3
8: R = $CH_2CH_2CHC(CH_3)_2$

32-45

32: X = H; R = CH_3, yield = 61%
33: X = *o*-OCH_3; R = CH_3, yield = 76%
34: X = *m*-OCH_3; R = CH_3, yield = 43%
35: X = *p*-OCH_3; R = CH_3, yield = n.d.
36: X = *p*-CH_3; R = CH_3, yield = 28%
37: X = *p*-F; R = CH_3, yield = 78%
38: X = *o*-OH; R = CH_3, yield = n.d.
39: X = H; R = $CH_2CH_2CHC(CH_3)_2$, yield = 73%
40: X = *o*-OCH_3; R = $CH_2CH_2CHC(CH_3)_2$, yield = 76%
41: X = *m*-OCH_3; R = $CH_2CH_2CHC(CH_3)_2$, yield = 23%
42: X = *p*-OCH_3; R = $CH_2CH_2CHC(CH_3)_2$, yield = n.d.
43: X = *p*-CH_3; R = $CH_2CH_2CHC(CH_3)_2$, yield = n.d.
44: X = *p*-F; R = $CH_2CH_2CHC(CH_3)_2$, yield = 78%
45: X = *o*-OH; R = $CH_2CH_2CHC(CH_3)_2$, yield = n.d.

Scheme 2.10: Aluminium hexagonal molecular silica (Al-HMS)-catalysed Diels-Alder reactions of substituted chalcones 7e & 7g-l with isoprene (8b) and myrcene (8).

In the same year, Porco and co-workers (Cong et al., 2008) developed the methodology to construct the cyclohexenyl chalcone nucleus employing electron-rich 2′-hydroxychalcone dienophiles. A heterogeneous catalyst mixture composed of cobalt(II) iodide, 1,10-phenanthroline, zinc(II) iodide and tetrabutylammonium borohydride (10/10/60/10 mol%) was developed. This catalyst gave an excellent yield in the DA reaction of 2′-hydroxychalcone (**7l**) and 2,3-dimethylbutadiene (**8a**), but the yield was lower when 2′-hydroxychalcone (**7l**) was replaced by other dienophiles of **7e**, **7g** & **7m** (Scheme 2.11).



7e, 7g, 7l & 7m

7l: R^1 = OH; R^2 = H
7g: R^1 = R^2 = H
7e: R^1 = H; R^2 = OCH_3
7m: R^1 = H; R^2 = OH

8a (11 equiv)

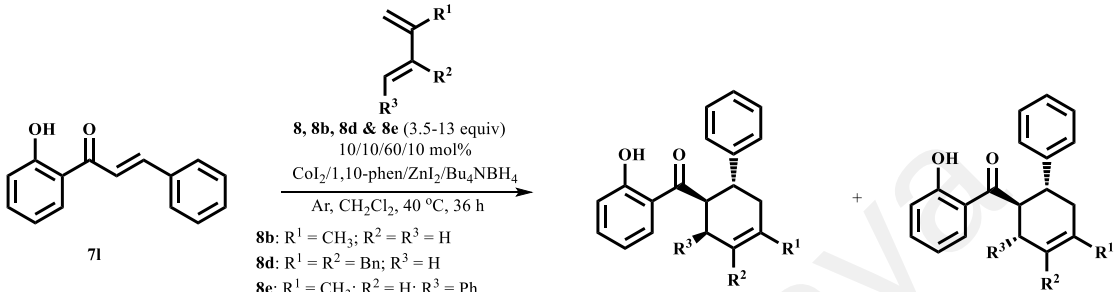
46-49

46: R^1 = OH; R^2 = H, yield = 95%
47: R^1 = R^2 = H, yield = 38%
48: R^1 = H; R^2 = OCH_3, yield = 55%
49: R^1 = H; R^2 = OH, yield = < 2%

Scheme 2.11: Diels-Alder reactions of different dienophiles 7e, 7g, 7l & 7m with 2,3-dimethylbutadiene (8a).

However, excellent yield was observed when the 2,3-dimethylbutadiene (**8a**) was replaced with other dienes such as isoprene (**8b**), 2,3-dibenzyl-1,3-butadiene (**8d**),

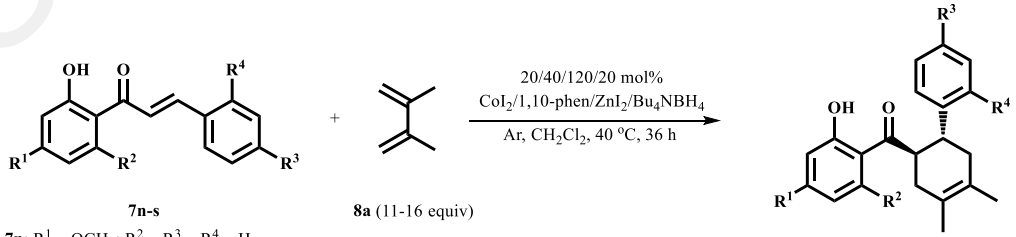
1-phenyl-3-methyl-1,3-butadiene (**8e**) and myrcene (**8**) (Scheme 2.12). Single regioisomers **38** & **45** were observed for isoprene (**8b**) and myrcene (**8**), respectively. For 1-phenyl-3-methyl-1,3-butadiene (**8e**), single regioisomers **51** & **51a** and 1:1.5 *endo*/*exo* ratio was obtained.



38: $R^1 = CH_3$; $R^2 = R^3 = H$, yield = 97%
50: $R^1 = R^2 = Bn$; $R^3 = H$, yield = 99%
51 (*endo*) & **51a** (*exo*): $R^1 = CH_3$; $R^2 = H$; $R^3 = Ph$, yield = 97%, d.r. (**51**:**51a**) = 1:1.5
45: $R^1 = CH_2CH_2CH=C(CH_3)_2$; $R^2 = R^3 = H$, yield = 96%

Scheme 2.12: Diels-Alder reactions of 2′-hydroxychalcone (7l) with different dienes 8, 8b, 8d & 8e.

In addition, several highly electron-rich 2′-hydroxychalcones **7n-s** were also investigated (Scheme 2.13). For these dienophiles **7n-s**, a 20/40/120/20 mol% CoI_2/1,10-phen/ZnI_2/Bu_4NBH_4 catalyst loading was found to be optimal. Lower yields were obtained with additional alkoxy substitution of the chalcone (**7n**, **7p** & **7r**). The corresponding acetylated 2′-hydroxychalcones **7o**, **7q** & **7s** maintained high reactivity likely due to their less electron-rich character.

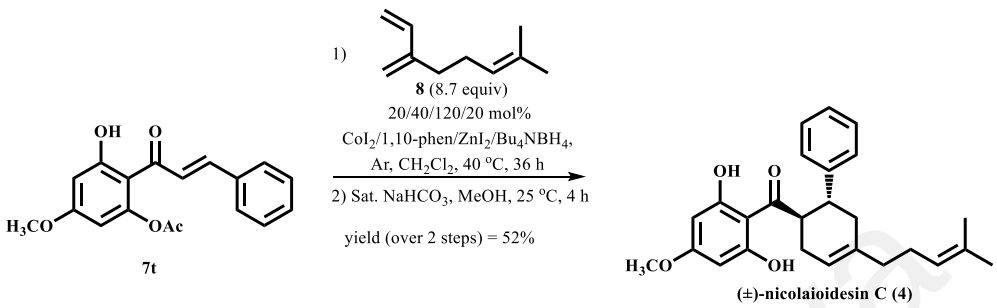


7n: $R^1 = OCH_3$; $R^2 = R^3 = R^4 = H$
7o: $R^1 = OAc$; $R^2 = R^3 = R^4 = H$
7p: $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$
7q: $R^1 = R^2 = OAc$; $R^3 = R^4 = H$
7r: $R^1 = R^3 = R^4 = OCH_3$; $R^2 = H$
7s: $R^1 = R^3 = R^4 = OAc$; $R^2 = H$

52: $R^1 = OCH_3$; $R^2 = R^3 = R^4 = H$, yield = 68%
53: $R^1 = OAc$; $R^2 = R^3 = R^4 = H$, yield = 84%
54: $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$, yield = 33%
55: $R^1 = R^2 = OAc$; $R^3 = R^4 = H$, yield = 72%
56: $R^1 = R^3 = R^4 = OCH_3$; $R^2 = H$, yield = 18%
57: $R^1 = R^3 = R^4 = OAc$; $R^2 = H$, yield = 61%

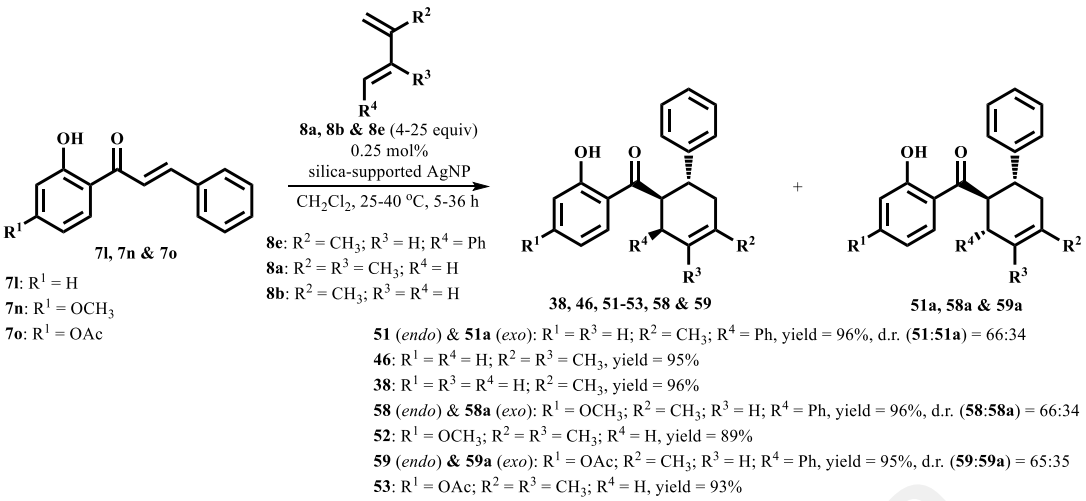
Scheme 2.13: Diels-Alder reactions of electron-rich 2′-hydroxychalcones 7n-s with 2,3-dimethylbutadiene (8a).

Ultimately, they used the same amount of catalyst in the DA reaction between acylated chalcone **7t** and myrcene (**8**), followed by saponification, providing adduct (±)-nicolaioidesin C (**4**) in 52% as a single regioisomer (Scheme 2.14).



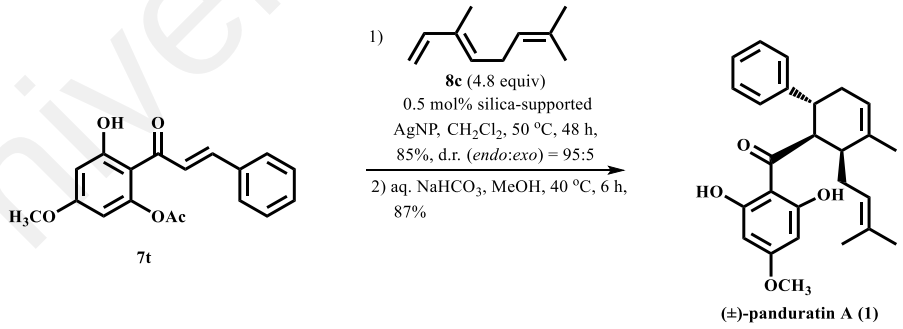
Scheme 2.14: Synthesis of (±)-nicolaioidesin C (4).

Two years later, due to the unsuccessful synthesis of panduratin A (**1**) by using the previous catalyst mixture (CoI_2, 1,10-phenanthroline, ZnI_2 and Bu_4NBH_4). Porco and co-workers (Cong et al., 2010) developed a new catalyst, silver(0) nanoparticles (AgNP), formed from reduction of silver tetrafluoroborate by tetrabutylammonium borohydride and immobilised on silica. The silica-supported AgNP could effectively catalyse the cycloaddition of 2′-hydroxychalcone (**7l**) and its analogous **7n** & **7o** with several dienes such as 1-phenyl-3-methyl-1,3-butadiene (**8e**), 2,3-dimethylbutadiene (**8a**) and isoprene (**8b**) (Scheme 2.15). The catalyst afforded the desired cycloadduct of **38**, **46**, **51-53**, **58**, **59**, **51a**, **58a** & **59a** in 86-96% yield as a single regioisomer and *endo*/*exo* ratio in 66:34 to 65:35.



Scheme 2.15: Silica-supported AgNP-catalysed Diels-Alder reactions of different dienophiles 7l, 7n & 7o with different dienes 8a, 8b & 8e.

Ultimately, the AgNP was used in the total synthesis of (±)-panduratin A (**1**). The DA reaction of acetylated chalcone **7t** and (*E*)-ocimene (**8c**) catalysed by silica-supported AgNP, predominantly afforded the desired *endo*-cycloadduct in excellent yield along with a small amount (approximately 5%) of an *exo*-stereoisomer corresponding to the natural product (±)-nicolaioidesin A (**1b**). The final deacetylation of the *endo*-cycloadduct afforded (±)-panduratin A (**1**) in 74% yield (Scheme 2.16).



Scheme 2.16: Synthesis of (±)-panduratin A (1).

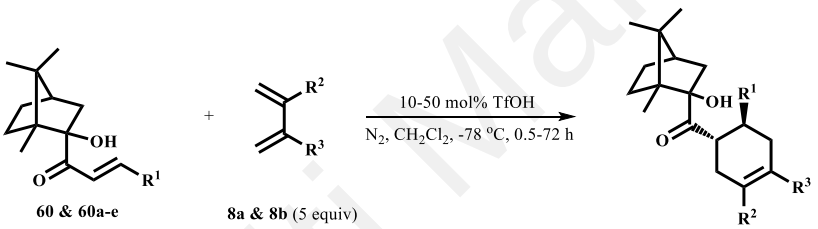
2.2 Enantioselective Diels-Alder Reaction between Cinnamoyl Dienophiles and Terpene Dienes

The synthetic methodologies for enantioselective DA reaction between cinnamoyl dienophiles and terpene dienes can be divided into chiral auxiliary methods (substrate-

controlled asymmetric induction) and chiral catalyst methods (catalyst-controlled asymmetric induction).

2.2.1 Chiral Auxiliary Method

In 2010, Palomo and co-workers (Bañuelos et al., 2010) studied the chiral auxiliary, (1*R*)-(+)-champhor in asymmetric DA reaction. Several dienophiles, (1*R*)-(+)-champhor derived α′-hydroxy enones **60** & **60a-e** with isoprene (**8b**) and 2,3-dimethylbutadiene (**8a**) were carried out in the presence of 10-50 mol% triflic acid as catalyst at -78 °C in dichloromethane to afford the desired adducts **61-68** in 53-95% yield with diastereomeric ratio (d.r.) > 98:2 (Scheme 2.17).



60 & 60a-e

60: $R^1 = CH_3$
60a: $R^1 = C_6H_{11}$
60b: R^1 = tBu
60c: R^1 = Ph
60d: $R^1 = p CH_3Ph$
60e: $R^1 = p$ClPh

8a & 8b (5 equiv)

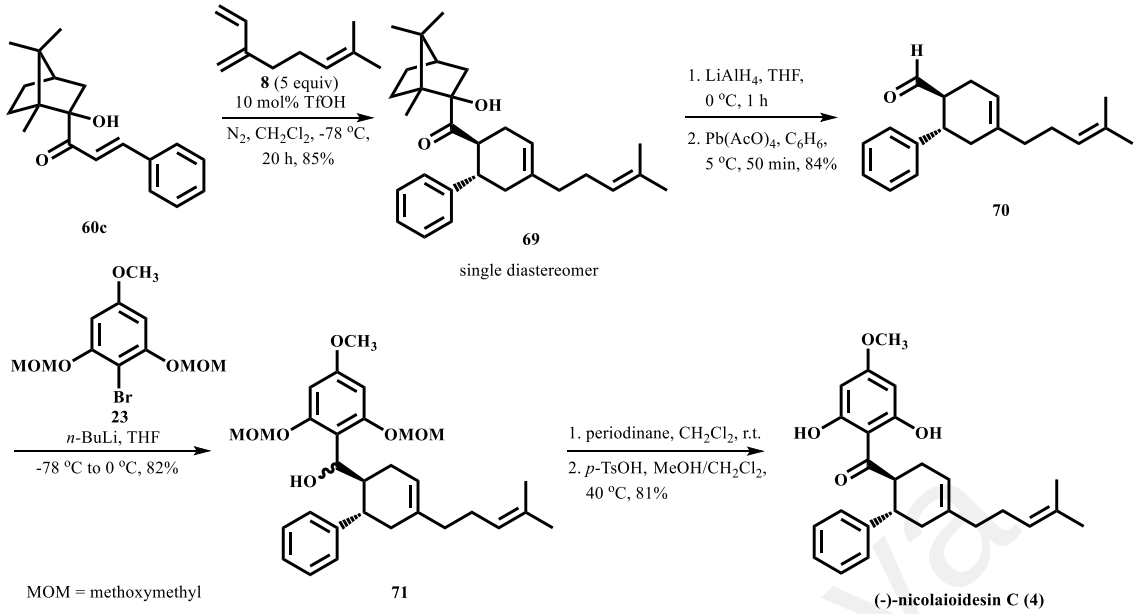
8b: R^2 = H; $R^3 = CH_3$
8a: $R^2 = R^3 = CH_3$

61-68

61: $R^1 = R^3 = CH_3$; R^2 = H, yield = 93%, d.r. = > 98:2
62: $R^1 = R^2 = R^3 = CH_3$, yield = 95%, d.r. = > 98:2
63: $R^1 = C_6H_{11}$; R^2 = H; $R^3 = CH_3$, yield = 57%, d.r. = > 98:2
64: $R^1 = C_6H_{11}$; $R^2 = R^3 = CH_3$, yield = 60%, d.r. = > 98:2
65: R^1 = tBu; $R^2 = R^3 = CH_3$, yield = 53%, d.r. = > 98:2
66: R^1 = Ph; R^2 = H; $R^3 = CH_3$, yield = 85%, d.r. = > 98:2
67: $R^1 = p CH_3Ph$; $R^2 = R^3 = CH_3$, yield = 90%, d.r. = > 98:2
68: $R^1 = p$ClPh; $R^2 = R^3 = CH_3$, yield = 95%, d.r. = > 98:2

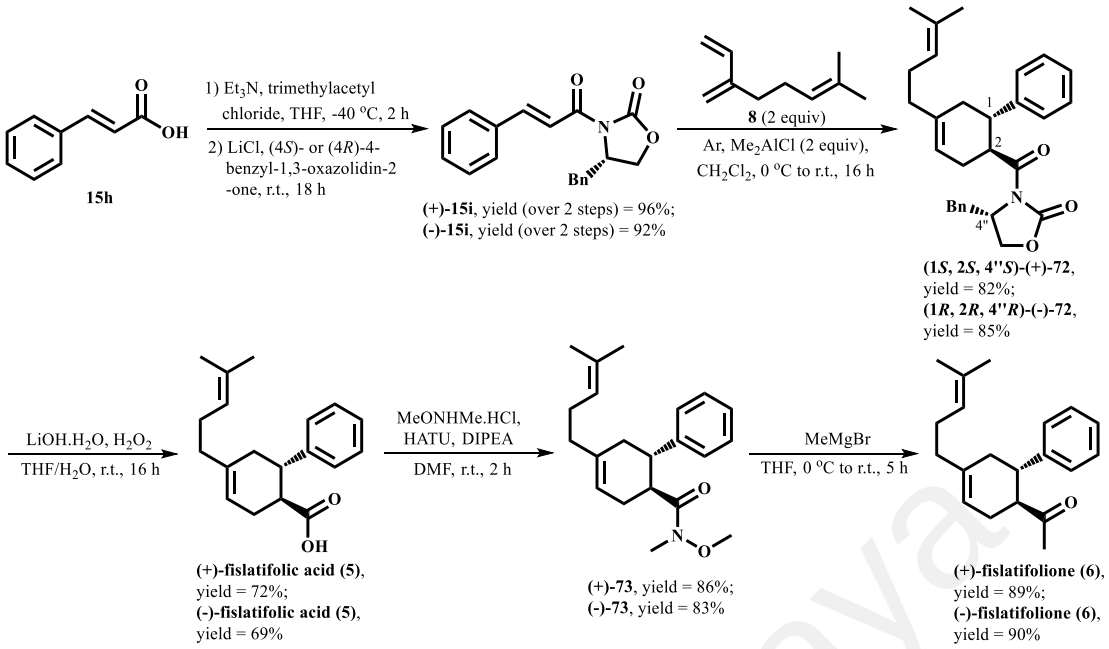
Scheme 2.17: TfOH-catalysed Diels-Alder reactions of (1*R*)-(+)-champhor derived α′-hydroxy enones 60 & 60a-e with isoprene (8b) and 2,3-dimethylbutadiene (8a).

In addition, they also used the chiral champhor auxiliary in the enantioselective total synthesis of (-)-nicolaioidesin C (**4**) (Scheme 2.18). The DA reaction of (1*R*)-(+)-champhor derived α′-hydroxy enone **60c** and myrcene (**8**) in the presence of 10 mol% triflic acid at -78 °C in CH_2Cl_2 to afford the corresponding adduct **69** as single diastereomer in 85% yield. Ultimately, the DA adduct **69** could be transformed into the natural product (-)-nicolaioidesin C (**4**) in five further steps.

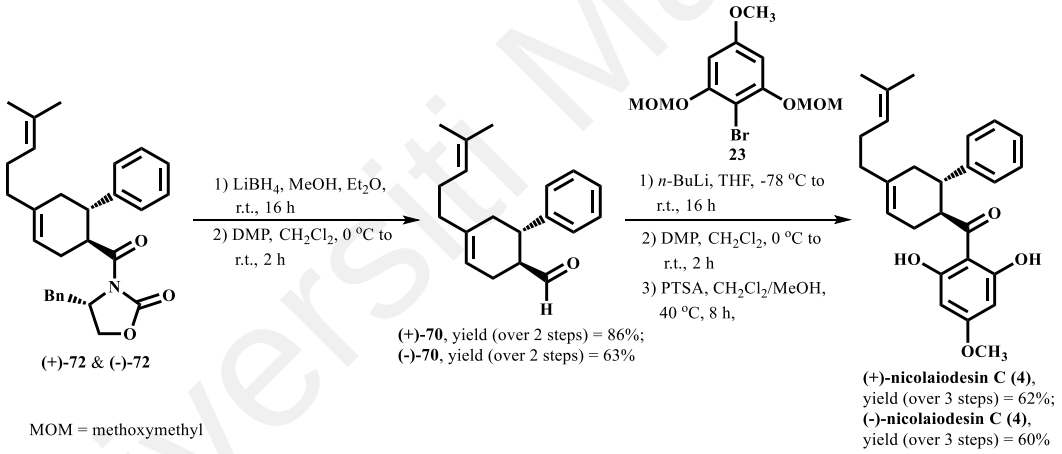


Scheme 2.18: Synthesis of (-)-nicolaioidesin C (4).

Alternatively, chiral Evans oxazolidinone was also used as chiral auxiliary in the enantioselective synthesis of cyclohexenyl chalcone natural products by other researchers. Roussi's group (Tiamas et al., 2018) utilised chiral Evans oxazolidinone auxiliary in the enantioselective total synthesis of both enantiomers of three myrcene-derived cyclohexenyl chalcone natural products, fislatifolic acid (**5**), fislatifolione (**6**) and nicolaidesin C (**4**). The dienophiles (+)-**15i** & (-)-**15i** in the reaction were prepared by a peptidic coupling reaction between *trans*-cinnamic acid (**15h**) and either (4*S*)- or (4*R*)-4-benzyl-1,3-oxazolidin-2-one. These corresponding dienophiles (+)-**15i** & (-)-**15i** were then separately reacted with myrcene (**8**) in presence of Me_2AlCl (2 equiv) to form the desired (+)- and (-)-adducts **72** in 82 and 85% yield, respectively with complete regio- and diastereocontrol (>95:5, as measured by ^1H NMR spectroscopy). The formed adducts (+)-**72** & (-)-**72** could be transformed into the natural products, (+)- and (-)-fislatifolic acids (**5**), (+)- and (-)-fislatifoliones (**6**) and (+)- and (-)-nicolaidesins C (**4**) in further steps (Schemes 2.19 & 2.20).



Scheme 2.19: Synthesis of (+)- and (-)-fislatifolic acid (5) and fislatifolione (6).

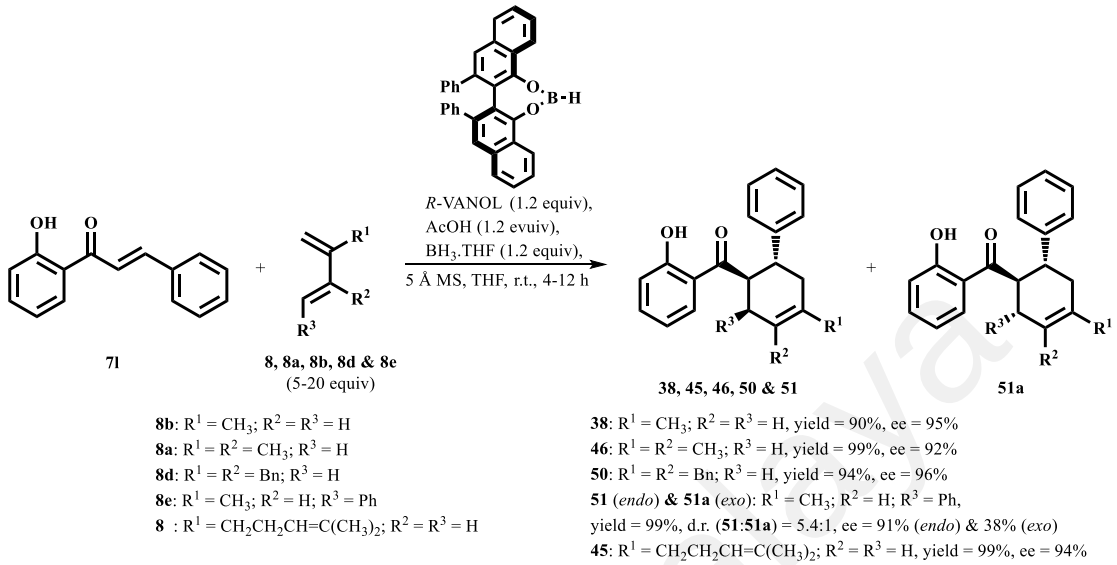


Scheme 2.20: Synthesis of (+)- and (-)-nicolaiodesin C (4).

2.2.2 Chiral Catalyst Method

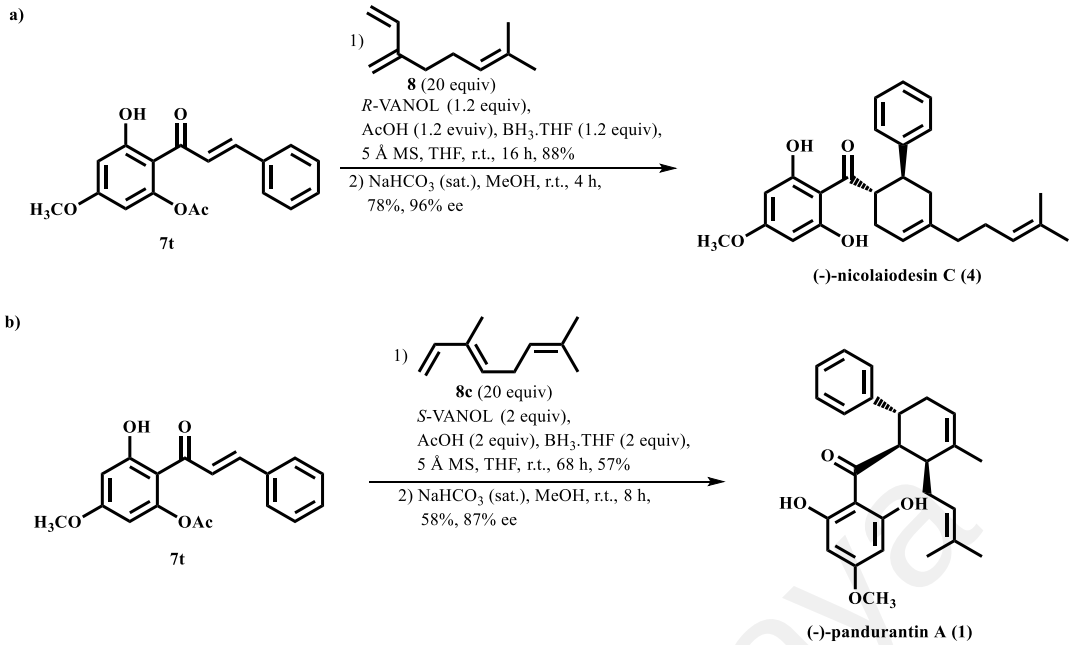
In 2016, Lei and co-workers (Li et al., 2016) used a chiral VANOL-boron Lewis acid complex in the enantioselective DA cycloadditions of 2′-hydroxychalcone (**7l**) with various dienes such as isoprene (**8b**), 2,3-dimethylbutadiene (**8a**), 2,3-dibenzyl-1,3-butadiene (**8d**), 1-phenyl-3-methyl-1,3-butadiene (**8e**) and myrcene (**8**) (Scheme 2.21). All the substituted dienes **8**, **8a**, **8b**, **8d** & **8e** were converted to the corresponding adducts **38**, **45**, **46**, **50**, **51** & **51a** in excellent yields with high ee values. Single regioisomers were

observed for unsymmetrical 2-substituted and 1,3-disubstituted dienes **8**, **8b** & **8e**, and the *endo*/*exo* diastereoselectivity for 1-phenyl-3-methyl-1,3-butadiene (**8e**) was 5.4:1.



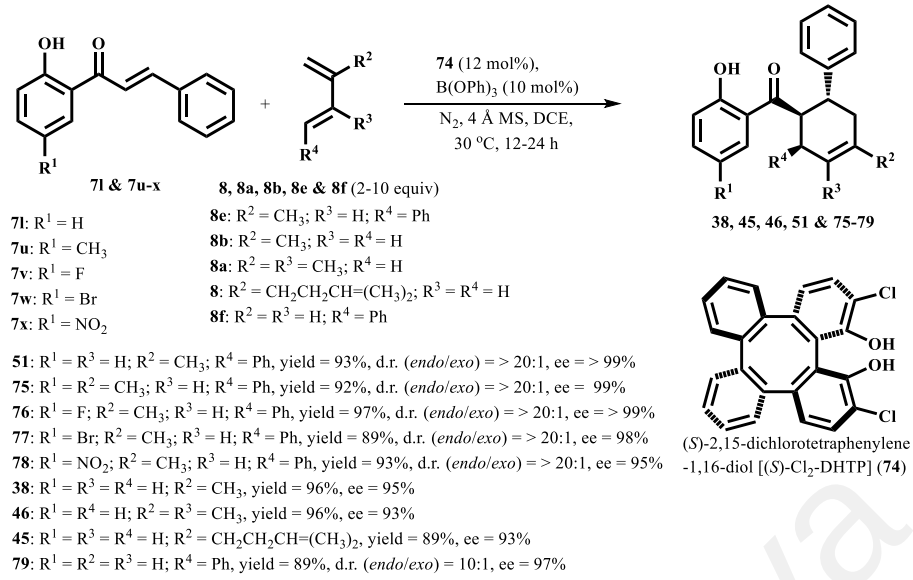
Scheme 2.21: Chiral VANOL-boron Lewis acid complex-catalysed Diels-Alder reactions of 2′-hydroxychalcone (7l) with different dienes 8, 8a, 8b, 8d & 8e.

Encouraged by the effective asymmetric DA reactions with a wide variety of substrates, Lei and co-workers applied the complex to the enantioselective total synthesis of (-)-nicolaiodesin C (**4**) and (-)-panduratin A (**1**) (Scheme 2.22). The dienophile, 2′-hydroxy-4′-methoxy-6′-acetylchalcone (**7t**) was reacted with myrcene (**8**) under the optimised reaction conditions, and then the acetyl group was removed to afford (-)-nicolaiodesin C (**4**) with 69% yield (over 2 steps) and 96% ee. (-)-Panduratin A (**1**) was obtained from the same reaction sequence, starting from DA cycloaddition of 2′-hydroxy-4′-methoxy-6′-acetylchalcone (**7t**) with (*E*)-ocimene (**8c**) to give the target molecule **1** in 33% yield (over 2 steps) and 87% ee.



Scheme 2.22: Synthesis of a) (-)-nicolaiodesin C (4) and b) (-)-panduratin A (1).

Four years later, Chang's group (Chai et al., 2020) produced a similar chiral boron complex by reacting (*S*)-2,15-dichlorotetraphenylene-1,16-diol [(*S*)-Cl_2-DHTP] (**69**) with $B(OPh)_3$. This chiral hydroxytetraphenylene boron complex can effectively catalyse enantioselective DA reactions of substituted 2′-hydroxychalcones **7l** & **7u-x** and dienes **8, 8a, 8b, 8e** & **8f** under mild reaction conditions (Scheme 2.23). The corresponding adducts **38, 45, 46, 51** & **75-79** were obtained in high yields and excellent diastereo- and enantioselectivities. Unfortunately, the DA reactions involving (*E*)-chalcone, (*E*)-3-phenyl-1-(pyridine-2-yl)prop-2-en-1-one or (*E*)-2-(3-phenylprop-2-enoyl)pyridine-1-oxide were unsuccessful, which suggested that the hydroxy group is necessary for the reaction.



51: $R^1 = R^3 = H$; $R^2 = CH_3$; R^4 = Ph, yield = 93%, d.r. (*endo*/*exo*) = > 20:1, ee = > 99%
75: $R^1 = R^2 = CH_3$; $R^3 = H$; R^4 = Ph, yield = 92%, d.r. (*endo*/*exo*) = > 20:1, ee = 99%
76: R^1 = F; $R^2 = CH_3$; $R^3 = H$; R^4 = Ph, yield = 97%, d.r. (*endo*/*exo*) = > 20:1, ee = > 99%
77: R^1 = Br; $R^2 = CH_3$; $R^3 = H$; R^4 = Ph, yield = 89%, d.r. (*endo*/*exo*) = > 20:1, ee = 98%
78: $R^1 = NO_2$; $R^2 = CH_3$; $R^3 = H$; R^4 = Ph, yield = 93%, d.r. (*endo*/*exo*) = > 20:1, ee = 95%
38: $R^1 = R^3 = R^4 = H$; $R^2 = CH_3$, yield = 96%, ee = 95%
46: $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$, yield = 96%, ee = 93%
45: $R^1 = R^3 = R^4 = H$; $R^2 = CH_2CH_2CH=(CH_3)_2$, yield = 89%, ee = 93%
79: $R^1 = R^2 = R^3 = H$; R^4 = Ph, yield = 89%, d.r. (*endo*/*exo*) = 10:1, ee = 97%

Scheme 2.23: Chiral hydroxytetraphenylene boron complex-catalysed Diels-Alder reactions of substituted 2′-hydroxychalcones 7l & 7u-x with different dienes 8, 8a, 8b, 8e & 8f.

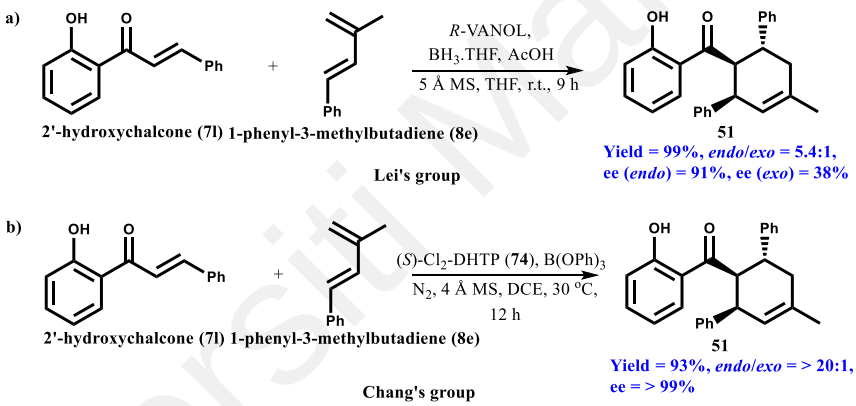
2.3 Aims and Objectives

Many naturally occurring compounds such as panduratin A (**1**), nicolaioidesin C (**4**), fislatifolic acid (**5**) and many more possess a wide range of promising biological activities, such as anticancer, anti-inflammatory, antibacterial, antiangiogenic, antioxidant and anti-HIV. However, the natural products are present in very small amounts in natural sources, making large-scale extraction impractical. It is therefore necessary to find synthetic methods to obtain larger quantities of the natural products. In addition, derivatisation would also be desirable to better explore biological activities. Formation of the natural products can be envisioned *via* DA reactions between cinnamoyl dienophiles and terpene dienes.

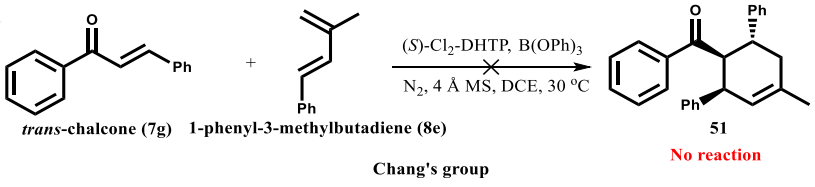
According to the literature, several methods such as thermal, high-pressure, catalyst and chiral auxiliary can be used to promote the DA reactions between cinnamoyl dienophiles and terpene dienes. Among these methods, thermal and high-pressure methods have no enantioselective selectivity, while the chiral auxiliary method is an

indirect synthesis method. The catalyst method seems to be the best because of operational simplicity, directness and high regio-, diastereo- and enantioselectivities.

Although the high yield and excellent regio-, diastereo- and enantioselectivity catalytic systems toward cinnamoyl dienophiles and terpene dienes have been developed by Lei's (Li et al., 2016) and Zhang's (Chai et al., 2020) groups (Scheme 2.24), the scope of dienophile reactivity thus far has been limited to the 2′-hydroxychalcones. Simpler chalcones such as those without 2-hydroxy functionality remained unreactive (Scheme 2.25). Thus, it would be beneficial to develop new catalysts that could catalyse the DA reactions with a broader range of cinnamoyl compounds.



Scheme 2.24: Diels-Alder reaction between 2′-hydroxychalcone (7l) with 1-phenyl-3-methylbutadiene (8e) catalysed by a) Lei's and b) Chang's groups catalytic systems.



Scheme 2.25: Diels-Alder reaction between *trans*-chalcone (7g) with 1-phenyl-3-methylbutadiene (8e) catalysed by Chang's group catalytic system.

Lewis acids are the most commonly used catalyst in the DA reaction. In this project, the best Lewis acid catalyst for DA reaction between cinnamoyl dienophiles and terpene dienes will first be identified through screening a series of Lewis acids commonly used

in DA reactions. Subsequently, the effectiveness of the selected Lewis acid catalyst towards DA reactions between various dienophiles and dienes will be evaluated and a method for enantioselective DA reaction between cinnamoyl dienophile and terpene diene will be developed. Finally, the developed Lewis acid catalyst and chiral Lewis acid complex will be applied in the approach of total synthesis of selected natural products or their derivatives such as panduratin A (**1**), fislatifolione (**6**) and fislatifolic acid (**5**).

2.4 Objectives of Study

The objectives of this study are as follows:

1. To identify a Lewis acid that can effectively catalyse the DA reaction between cinnamoyl dienophile and terpene diene.
2. To evaluate the effectiveness of the selected Lewis acid catalyst towards DA reactions between various dienophiles and dienes.
3. To develop a method for enantioselective DA reaction between cinnamoyl dienophile and terpene diene.
4. To apply the developed Lewis acid catalyst and chiral Lewis acid complex in the approach of total synthesis of selected natural products or their derivatives.

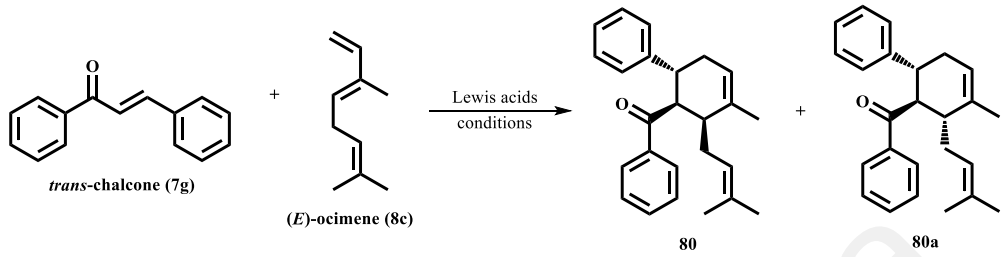
CHAPTER 3: METHODOLOGY

3.1 Materials and Methods

All chemicals and solvents were used as received without further purification unless stated. Analytical TLC was carried out on Merck precoated aluminum silica gel sheets (Kieselgel 60 F254). TLC visualisation was accomplished under UV lamp (254 nm). NMR spectra (^{1}H, ^{13}C, COSY, HSQC & HMBC) were obtained using JOEL ECA 400 (400 MHz) and Bruker Avance III HD 400 (400 MHz) NMR spectrometers with TMS as the internal standard. All measurements were recorded in solution in $CDCl_3$ or CD_3OD. Chemical shifts are reported in ppm relative to $CDCl_3$, CD_3OD or TMS. Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet; d = doublet; t = triplet; sept = septet; m = multiplet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; td = triplet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet; br d = broad doublet), coupling constant and integration. All ^{13}C NMR spectra were recorded with complete proton decoupling. HRMS (ESI) analyses were performed using Agilent 6500 Q-TOF (ESI) spectrometer with Agilent Zorbax C-18 column. Melting points were determined with a Stuart SMP30 melting point apparatus. Enantiomeric purity was determined by chiral HPLC analysis on a Chiralcel IC or OD column (150 x 4.6 mm, 5 μm), eluting with *n*-hexane/isopropanol (98%/2% or 90%/10%) at a flow rate of 0.5 mL min^{-1}. The sample injection volumes were 1-10 μL. The detection wavelength was set at 254 nm and the total analysis time was 15-20 min. The DFT calculations were performed using the HyperChem Professional 8.0 software.

3.2 Experimental Procedure

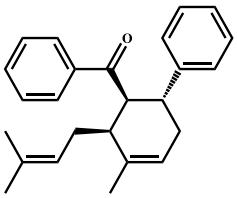
3.2.1 General Procedure A for Screening and Optimisation of Lewis Acid-Catalysed Diels-Alder Reaction



A Lewis acid (10-50 mol%) was added to a solution of *trans*-chalcone (**7g**) (0.5 mmol) in anhyd. solvent (1 mL) at r.t. (28 °C) under N_2 atmosphere. (*E*)-Ocimene (**8c**) (2.5 mmol) was added, and the mixture was stirred at r.t. or 50 ºC for 24 h or until all the *trans*-chalcone (**7g**) was consumed based on TLC analysis. The mixture was then poured into ice-water acidified with 3 N aq HCl to pH 2-3. The resulting mixture was extracted thrice with EtOAc, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% EtOAc-hexane) to give adduct **80**. The structure of **80** was confirmed by ^1H, ^{13}C, COSY, HSQC, HMBC NMR and HRMS spectroscopic techniques. No pure sample was obtained for the adduct **80a** due to the low quantity of the adduct formed. However, some key peaks of the adduct **80a** can still be identified in the ^1H NMR spectrum of the crude product. Based on the key peaks, adduct **80a** was recognised to be a stereoisomer (*endo*/*exo*) of the adduct **80**. The 95:5 ratio of adducts **80** and **80a** was determined from the ^1H NMR spectrum of the crude product.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (80)

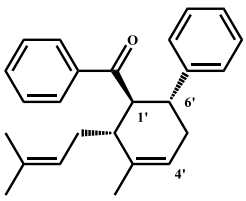
Compound **80** was prepared using general procedure A employing 30 mol% $AlBr_3$ in toluene at r.t. for 3 h.



Pale brown solid; yield: 124 mg (72%); mp = 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 6 H), 1.70 (s, 3 H), 1.97-2.09 (m, 2 H), 2.11-2.18 (m, 1 H), 2.34-2.39 (m, 2 H), 3.36 (td, *J* = 10.5, 6.4 Hz, 1 H), 4.08 (dd, *J* = 10.5, 5.0 Hz, 1 H), 4.74 (t, *J* = 6.9 Hz, 1 H), 5.41 (br s, 1 H), 6.99 (t, *J* = 6.9 Hz, 1 H), 7.09-7.14 (m, 4 H), 7.32 (t, *J* = 7.8 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 22.8, 25.6, 28.7, 35.0, 36.9, 42.8, 50.3, 121.3, 123.7, 125.7, 127.0, 127.9, 128.3, 128.4, 131.9, 132.5, 136.5, 137.4, 146.3, 200.6; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{29}O$: 345.2218, found: 345.2225.

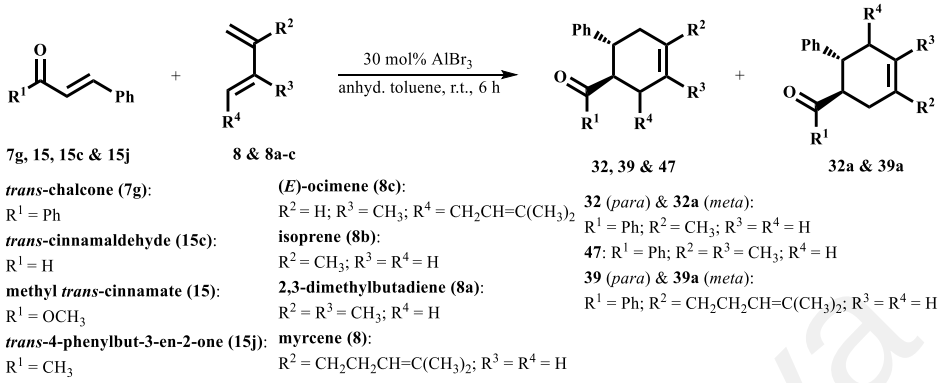
[(1*RS*,2*RS*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (80a)

Compound **80a** was prepared using general procedure A employing 30 mol% $AlBr_3$ in toluene at r.t. for 3 h.



^{1}H NMR (400 MHz, $CDCl_3$) (some key peaks): δ = 3.08 (H-6′, td, *J* = 11.6, 4.8 Hz, 1H), 3.76 (H-1′, dd, *J* = 11.6, 10.0 Hz, 1H), 5.65 (H-4′, br d, *J* = 4.8 Hz, 1H).

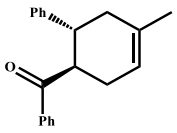
3.2.2 General Procedure B for Diels-Alder Reactions of Various Dienophiles 7g, 15, 15c & 15j and Dienes 8 & 8a-c



A 1.0 M solution of $AlBr_3$ in CH_2Br_2 (30 mol%) was added to a solution of dienophile **7g**, **15**, **15c** & 1**5j** (0.5 mmol) in anhyd. toluene (1 mL) at r.t. (28 °C) under N_2 atmosphere. Diene **8** & **8a-c** (2.5 mmol) was added, and the mixture was stirred at r.t for 6 h. The mixture was then poured into ice-water acidified with 3 N aq HCl to pH 2-3. The resulting mixture was extracted thrice with EtOAc, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% EtOAc-hexane) to give adduct **32**, **39** & **47**. For unsymmetrical 2-substituted dienes, isoprene (**8b**) and myrcene (**8**), no pure sample was obtained for the adducts **32a** & **39a** due to low quantity of the adducts formed. However, some key peaks of the adducts **32a** & **39a** can still be identified in the ^{1}H NMR spectrum of the crude products. Based on the key peaks, adducts **32a** & **39a** were recognised to be a regioisomer (*para*/*meta*) of the adducts **32** & **39**, respectively. The 90:10 ratio of adducts **32** & **32a** and **75** & **75a** was determined from the ^{1}H NMR spectrum of the crude products.

[4-Methyl-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (32)

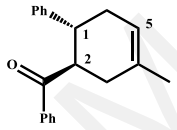
Compound **32** was prepared using general procedure B employing *trans*-chalcone (**7g**) as the dienophile and isoprene (**8b**) as the diene. The ^{1}H NMR spectroscopic data for adduct **32** agreed with that reported in the literature (Corbett & Weavers, 2008).



Pale yellow solid; yield: 101 mg (73%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 3 H), 2.15-2.35 (m, 4 H), 3.26 (td, *J* = 10.4, 7.2 Hz, 1 H), 3.87 (td, *J* = 10.6, 5.6 Hz, 1 H), 5.43 (br s, 1 H), 6.99 (t, *J* = 7.2 Hz, 1 H), 7.06-7.13 (m, 4 H), 7.30 (t, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 2 H).

[3-Methyl-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (32a)

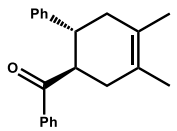
Compound **32a** was prepared using general procedure B employing *trans*-chalcone (**7g**) as the dienophile and isoprene (**8b**) as the diene.



^{1}H NMR (400 MHz, $CDCl_3$) (some key peaks): δ = 3.17 (H-1, td, *J* = 10.4, 5.2 Hz, 1 H), 3.96 (H-2, td, *J* = 10.4, 5.6 Hz, 1 H), 5.48 (H-5, br d, *J* = 4.0 Hz, 1 H).

[3,4-Dimethyl-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (47)

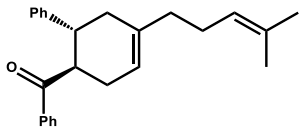
Compound **47** was prepared using general procedure B employing *trans*-chalcone (**7g**) as the dienophile and 2,3-dimethylbuta-1,3-diene (**8a**) as the diene. The ^{1}H NMR spectroscopic data for adduct **47** agreed with that reported in the literature (Cong et al., 2008).



Pale yellow solid; yield: 119 mg (82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 6 H), 2.24-2.33 (m, 4 H), 3.30 (ddd, *J* = 10.8, 9.2, 7.2 Hz, 1 H), 4.01 (ddd, *J* = 10.8, 10.8, 5.6 Hz, 1 H), 7.05 (m, 1 H), 7.17 (m, 4 H), 7.36 (m, 2 H), 7.46 (m, 1 H), 7.81 (d, *J* = 7.2 Hz, 2 H).

(4-(4-Methylpent-3-en-1-yl)-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (39)

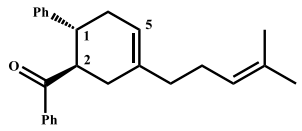
Compound **39** was prepared using general procedure B employing *trans*-chalcone (**7g**) as the dienophile and myrcene (**8**) as the diene. The ^{1}H NMR spectroscopic data for adduct **39** agreed with that reported in the literature (Corbett & Weavers, 2008).



Pale yellow solid; yield: 138 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 1.63 (s, 3 H), 1.95-2.06 (m, 4 H), 2.17-2.38 (m, 4 H), 3.23 (td, *J* = 10.8, 6.4 Hz, 1 H), 3.87 (td, *J* = 10.6, 5.6 Hz, 1 H), 5.06 (t, *J* = 6.8 Hz, 1 H), 5.44 (br d, *J* = 3.6 Hz, 1 H), 6.98 (t, *J* = 7.2 Hz, 1 H), 7.05-7.13 (m, 4 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 2 H).

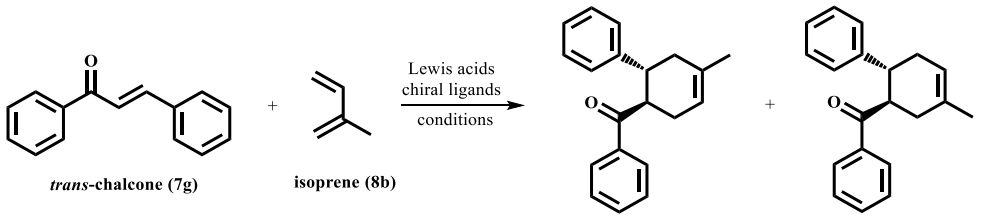
(3-(4-Methylpent-3-en-1-yl)-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (39a)

Compound **39a** was prepared using general procedure B employing *trans*-chalcone (**7g**) as the dienophile and myrcene (**8**) as the diene.



^{1}H NMR (400 MHz, $CDCl_3$) (some key peaks): δ = 3.17 (H-1, td, *J* = 10.4, 5.6 Hz, 1 H), 3.93 (H-2, td, *J* = 10.4, 5.2 Hz, 1 H), 5.50 (H-5, br d, *J* = 4.4 Hz, 1 H).

3.2.3 General Procedure C for Screening of Chiral Complexes



chiral ligands

1. *R*-BINOL (L1)
2. (-)-TADDOL (L2)
3. (-)-SALEN (L3)
4. (-)-BOX (L4)
5. FMOC-L-Phe-OH (L5)
6. FMOC-L-Tyr(tBu)-OH (L6)
7. *R*-Br_2-BINOL (L7)
8. *R*-$(Hex)_2$-BINOL (L8)
9. *R*-$(Trip)_2$-BINOL (L9)
10. 2-naphthol (L10)
11. (-)-linalool (L11)
12. FMOC-L-Leu-OH (L12)
13. FMOC-L-Trp-OH (L13)
14. FMOC-L-Tyr-OH (L14)
15. FMOC-L-Ser(Trt)-OH (L15)
16. FMOC-L-His(Trt)-OH (L16)
17. FMOC-L-Pro-OH (L17)
18. BOC-L-Pro-OH (L18)
19. FMOC-L-Nle-OH (L19)
20. FMOC-L-Ala-OH (L20)
21. FMOC-L-Cys(Trt)-OH (L21)
22. Ph-L-Phe-OH (L22)
23. Bn_2-L-Phe-OH (L23)
24. FMOC-L-Phe-ol (L24)
25. FMOC-L-Phe-IPA (L25)

i) Method 1: Lewis Acid without Chiral Ligand

A Lewis acid (0.15-0.25 mmol) was added to a solution of *trans*-chalcone (**7g**) (0.2-0.5 mmol) in anhyd. solvent (1.0-2.0 mL) at r.t. (28 °C) under N_2 atmosphere and the mixture was stirred at r.t. for 0.5 h. Isoprene (**8b**) (1.0-2.5 mmol) was added, and the mixture was stirred at r.t for 6-48 h. After the completion of the reaction, the reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give **32** and **32a** as mixture. The ^{1}H NMR spectroscopic data for adducts **32** & **32a** agreed with previously reported (See the ^{1}H NMR data of adducts **32** & **32a** at chapter 3.2.2). This method was applied to the reactions in entries 1, 3, 16 & 38, Table 4.6.

ii) Method 2: Lewis Acid with Chiral Ligand

A Lewis acid (0.1-0.5 mmol) was added to a solution of chiral ligand (0.1-0.6 mmol) in anhyd. solvent (0.65-1.6 mL) at r.t. (28 °C) under N_2 atmosphere and the mixture was stirred at r.t. for 1 h. A solution of *trans*-chalcone (**7g**) (0.1-0.25 mmol) in anhyd. solvent (0.15-0.4 mL) was added, and the mixture was stirred at r.t. for 0.5 h. Isoprene (**8b**) (0.5-1.25 mmol) was added, and the mixture was stirred at r.t for 1-72 h. After the completion

of the reaction, the reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give **32** and **32a** as mixture. The ^{1}H NMR spectroscopic data for adducts **32** & **32a** agreed with previously reported (See the ^{1}H NMR data of adducts **32** & **32a** at chapter 3.2.2). This method was applied to the reactions in entries 2, 4-14, 17-19, 30, 35-37, 39, 74-81 & 83, Table 4.6.

For the reactions entries 18, 19, 30, 74, 76-79, 81 & 83, Table 4.6, the complexation conditions of Lewis acid with chiral ligand changed from 1 h at r.t. to 3 h at 80 ºC. For the reaction entry 75, Table 4.6, the complexation reaction time of Lewis acid with chiral ligand changed from 1 h to 4 h. For reaction entry 80, Table 4.6, the complexation conditions of Lewis acid with chiral ligand changed from 1 h at r.t. to 17 h at 80 ºC.

iii) Method 3: Lewis acid with Two Different Type of Chiral Ligands

A 1.0 M solution of Et_2AlCl in *n*-hexane (0.25 mmol) was added to a solution of *R*-BINOL (**L1**) (0.25 mmol) in anhyd. CH_2Cl_2 (2 mL) at r.t. (28 °C) under N_2 atmosphere and the mixture was stirred at r.t. for 1 h. Then, the mixture was added to FMOC-L-Tyr(tBu)-OH (**L6**) (0.25 mmol), and the mixture was stirred at r.t. for another 1 h. A solution of *trans*-chalcone (**7g**) (0.25 mmol) in anhyd. CH_2Cl_2 (1 mL) was added, and the mixture was stirred at r.t. for 0.5 h. Isoprene (**8b**) (1.25 mmol) was added, and the mixture was stirred at r.t for 24 h. After the completion of the reaction, the reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give **32** and **32a** as mixture. The ^{1}H NMR spectroscopic data for adducts **32** & **32a** agreed with previously reported (See the ^{1}H NMR data of adducts **32** & **32a** at chapter 3.2.2). This method was applied to the reaction in entry 15, Table 4.6.

iv) Method 4: Lewis Acid with Chiral Ligand in the Presence of *n*-BuLi or Et_3N

n-BuLi or Et_3N (0.2-0.8 mmol) was added to a solution of chiral ligand (0.1-0.8 mmol) in anhyd. toluene (0.65-1.3 mL) at r.t. (28 °C) under N_2 atmosphere and the mixture was stirred at r.t. for 0.5 h. Then, a 1.0 M solution of $TiCl_4$ in toluene (0.1-0.4 mmol) was added, and the mixture was stirred at r.t. for 1 h. A solution of *trans*-chalcone (**7g**) (0.1-0.2 mmol) in anhyd toluene (0.15-0.3 mL) was added, and the mixture was stirred at r.t. for 0.5 h. Isoprene (**8b**) (0.5-1.0 mmol) was added, and the mixture was stirred at r.t. for 1-48 h. After the completion of the reaction, the reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give **32** and **32a** as mixture. The ^{1}H NMR spectroscopic data for adducts **32** & **32a** agreed with previously reported (See the ^{1}H NMR data of adducts **32** & **32a** at chapter 3.2.2). This method was applied to the reactions in entries 20-29, 31-34, 40-51, 70 & 71, Table 4.6.

For the reactions entries 20-29 & 31, Table 4.6, the complexation conditions of Lewis acid with deprotonated chiral ligand changed from 1 h at r.t. to 3 h at 80 °C.

v) Method 5: Lewis Acid with Chiral Ligand in the Presence of $NaHCO_3$ or NaOH

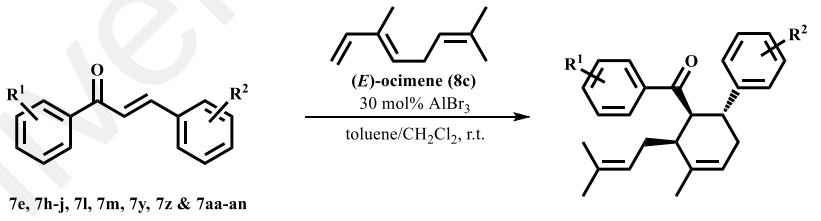
A solution of $NaHCO_3$ or NaOH (5.0 mmol) in distilled water (14 mL) was added to a solution of chiral ligand (5.0 mmol) in methanol (140 mL) and the mixture was stirred at r.t. for 17 h. The mixture was then concentrated under reduced pressure and further dried under high vacuum. The formed sodium salt of chiral ligand (0.2-0.8 mmol) was dissolved in anhyd. solvent (1.3-1.95 mL) at r.t. (28 °C) under N_2 atmosphere, then Lewis acid (0.2-0.4 mmol) was added, and the resulting mixture was stirred at r.t. for 2 h. A solution of *trans*-chalcone (**7g**) (0.2 mmol) in anhyd solvent (0.3-0.45 mL) was added, and the mixture was stirred at r.t. for 0.5 h. Isoprene (**8b**) (1.0 mmol) was added, and the mixture was stirred at r.t. or 75 °C for 24-72 h. After the completion of the reaction, the

reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give **32** and **32a** as mixture. The ^{1}H NMR spectroscopic data for adducts **32** & **32a** agreed with previously reported (See the ^{1}H NMR data of adducts **32** & **32a** at chapter 3.2.2). This method was applied to the reactions in entries 52-69, 72, 73 & 82, Table 4.6.

For the reaction entry 63, Table 4.6, the complexation reaction time of Lewis acid with sodium salt of chiral ligand changed from 2 h to 0.5 h. For the reactions entry 82, Table 4.6, the complexation conditions of Lewis acid with sodium salt of chiral ligand changed from 2 h at r.t. to 3 h at 80 ºC.

3.2.4 General Procedure for the Synthesis of Selected Natural Products or their Derivatives

3.2.4.1 General Procedure D for the Synthesis of (±)-Panduratin A Derivatives 13 & 80b-r



7e, 7h-j, 7l, 7m, 7y, 7z & 7aa-an → **13 & 80b-r**

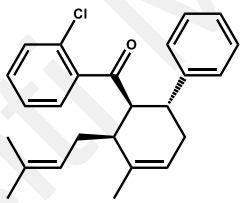
7l: R^1 = 2'-OH; R^2 = H
7h: R^1 = 2'-CH_3O; R^2 = H
7y: R^1 = 2'-Cl; R^2 = H
7z: R^1 = 3'-Cl; R^2 = H
7aa: R^1 = 3'-OH; R^2 = H
7i: R^1 = 3'-CH_3O; R^2 = H
7ab: R^1 = 4'-Cl; R^2 = H
7ac: R^1 = 4'-Br; R^2 = H
7j: R^1 = 4'-CH_3; R^2 = H
7m: R^1 = 4'-OH; R^2 = H
7e: R^1 = 4'-CH_3O; R^2 = H
7ad: R^1 = H; R^2 = 3-NO_2
7ae: R^1 = H; R^2 = 4-Br
7af: R^1 = H; R^2 = 4-Cl
7ag: R^1 = H; R^2 = 4-CH_3
7ah: R^1 = H; R^2 = 4-CH_3O
7ai: R^1 = H; R^2 = 4-NO_2
7aj: R^1 = 4'-CH_3O; R^2 = 4-Br
7ak: R^1 = 4'-CH_3O; R^2 = 4-CH_3
7al: R^1 = 4'-CH_3O; R^2 = 4-NO_2
7am: R^1 = 4'-Cl; R^2 = 4-CH_3O
7an: R^1 = 4'-CH_3; R^2 = 4-CH_3O
80b: R^1 = 2'-Cl; R^2 = H
80c: R^1 = 3'-Cl; R^2 = H
80d: R^1 = 3'-CH_3O; R^2 = H
80e: R^1 = 4'-Cl; R^2 = H
80f: R^1 = 4'-Br; R^2 = H
80g: R^1 = 4'-CH_3; R^2 = H
13: R^1 = 4'-CH_3O; R^2 = H
80h: R^1 = H; R^2 = 3-NO_2
80i: R^1 = H; R^2 = 4-Br
80j: R^1 = H; R^2 = 4-Cl
80k: R^1 = H; R^2 = 4-CH_3
80l: R^1 = H; R^2 = 4-CH_3O
80m: R^1 = H; R^2 = 4-NO_2
80n: R^1 = 4'-CH_3O; R^2 = 4-Br
80o: R^1 = 4'-CH_3O; R^2 = 4-CH_3
80p: R^1 = 4'-CH_3O; R^2 = 4-NO_2
80q: R^1 = 4'-Cl; R^2 = 4-CH_3O
80r: R^1 = 4'-CH_3; R^2 = 4-CH_3O

A 1.0 M solution of $AlBr_3$ in CH_2Br_2 (30 mol%) was added to a solution of the appropriate *trans*-chalcone **7e**, **7h-j**, **7l**, **7m**, **7y, 7z** & **7aa-an** (0.5 mmol) in anhyd toluene or CH_2Cl_2 (1 mL) at r.t. (28 °C) under N_2 atmosphere. (*E*)-Ocimene **(8c)** (2.5 mmol) was

added, and the mixture was stirred at r.t for 24 h or until all the chalcone was consumed based on TLC analysis. The mixture was then poured into ice-water acidified with 3 N aq HCl to pH 2-3. The resulting mixture was extracted thrice with EtOAc, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5-20% EtOAc-hexane) to give adduct **13** & **80b-r**. The structures of **13 & 80b-r** were confirmed by ^1H, ^{13}C NMR and HRMS spectroscopic techniques.

(2-Chlorophenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl]methanone (80b)

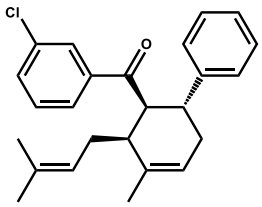
Compound **80b** was prepared using general procedure D employing 2′-chlorochalcone (**7y**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Yellow oil; yield: 32 mg (17%); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 1.58 (s, 3 H), 1.68 (s, 3 H), 2.11-2.22 (m, 2 H), 2.25-2.32 (m, 2 H), 2.39-2.46 (m, 1 H), 3.34 (td, *J* = 9.8, 7.1 Hz, 1 H), 3.96 (dd, *J* = 10.2, 4.2 Hz, 1 H), 4.97 (t, *J* = 6.6 Hz, 1 H), 5.40 (br s, 1 H), 7.04-7.08 (m, 1 H), 7.14-7.30 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 23.1, 25.8, 29.0, 33.8, 37.4, 40.6, 55.3, 121.0, 123.6, 126.0, 126.6, 127.7, 128.2, 129.4, 130.8, 131.5, 131.5, 132.0, 136.9, 139.0, 145.7, 202.7; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{28}{}^{35}ClO$: 379.1829, found: 379.1831.

(3-Chlorophenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl]methanone (80c)

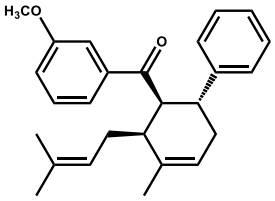
Compound **80c** was prepared using general procedure D employing 3′-chlorochalcone (**7z**) as the dienophile, toluene as the solvent and 3 h as the reaction time.



White solid; yield: 140 mg (74%); mp = 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 6 H), 1.72 (s, 3 H), 1.97-2.08 (m, 2 H), 2.10-2.18 (m, 1 H), 2.35-2.39 (m, 2 H), 3.34 (td, *J* = 10.5, 6.4 Hz, 1 H), 4.01 (dd, *J* = 10.7, 4.9 Hz, 1 H), 4.70 (t, *J* = 6.8 Hz, 1 H), 5.42 (br s, 1 H), 6.99-7.04 (m, 1 H), 7.10-7.15 (m, 4 H), 7.27 (t, *J* = 7.8 Hz, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.73 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.7, 25.6, 28.7, 34.9, 37.0, 43.0, 50.6, 121.4, 123.7, 125.9, 126.0, 127.1, 128.1, 128.4, 129.8, 132.3, 132.4, 134.8, 136.3, 139.1, 146.0, 199.2; HRMS (ESI): m/z [M + H]$^+$ calcd. for $C_{25}H_{28}{}^{35}ClO$: 379.1829, found: 379.1833.

(3-Methoxyphenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl]methanone (80d)

Compound **80d** was prepared using general procedure D employing 3′-methoxychalcone (**7i**) as the dienophile, CH_2Cl_2 as the solvent and 6 h as the reaction time.

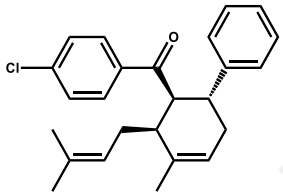


White solid; yield: 97 mg (52%); mp = 70-72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 3 H), 1.44 (s, 3 H), 1.74 (s, 3 H), 2.00-2.12 (m, 2 H), 2.13-2.21 (m, 1 H), 2.37-2.44 (m, 2 H), 3.38 (td, *J* = 10.6, 6.4 Hz, 1 H), 3.74 (s, 3 H), 4.08 (dd, *J* = 11.0, 4.9 Hz, 1 H), 4.79 (t, *J* = 7.1 Hz, 1 H), 5.44 (br s, 1 H), 6.99-7.05 (m, 2 H), 7.12-7.17 (m, 4 H), 7.28 (t, *J* = 7.8 Hz, 1 H), 7.32 (s, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 37.1, 43.0, 50.6, 55.3, 112.5, 119.0, 120.5, 121.3, 123.8,

125.8, 127.1, 128.3, 129.4, 131.9, 136.6, 138.9, 146.4, 159.8, 200.3; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{31}O_2$: 375.2324, found: 375.2312.

(4-Chlorophenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl]methanone (80e)

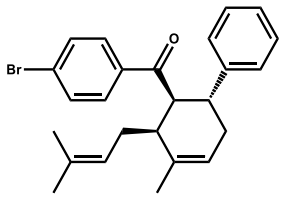
Compound **80e** was prepared using general procedure D employing 4′-chlorochalcone (**7ab**) as the dienophile, toluene as the solvent and 3 h as the reaction time.



White solid; yield: 133 mg (70%); mp = 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 6 H), 1.72 (s, 3 H), 1.97-2.07 (m, 2 H), 2.10-2.18 (m, 1 H), 2.35-2.40 (m, 2 H), 3.34 (td, *J* = 10.7, 6.4 Hz, 1 H), 4.03 (dd, *J* = 11.2, 4.9 Hz, 1 H), 4.72 (t, *J* = 7.1 Hz, 1 H), 5.43 (br s, 1 H), 7.00-7.05 (m, 1 H), 7.08-7.16 (m, 4 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 7.74 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 37.0, 43.0, 50.5, 121.4, 123.7, 125.9, 127.1, 128.4, 128.8, 129.4, 132.2, 135.8, 136.5, 138.9, 146.2, 199.4; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{28}{}^{35}ClO$: 379.1829, found: 379.1830.

(4-Bromophenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl]methanone (80f)

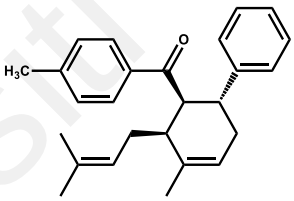
Compound **80f** was prepared using general procedure D employing 4′-bromochalcone (**7ac**) as the dienophile, toluene as the solvent and 3 h as the reaction time.



Pale brown solid; yield: 119 mg (56%); mp = 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 6 H), 1.72 (s, 3 H), 1.97-2.08 (m, 2 H), 2.09-2.18 (m, 1 H), 2.34-2.41 (m, 2 H), 3.34 (td, *J* = 10.6, 6.3 Hz, 1 H), 4.02 (dd, *J* = 11.0, 4.9 Hz, 1 H), 4.72 (t, *J* = 7.3 Hz, 1 H), 5.43 (br s, 1 H), 7.00-7.05 (m, 1 H), 7.09-7.16 (m, 4 H), 7.49 (d, *J* = 8.6 Hz, 2 H), 7.66 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 37.0, 43.0, 50.5, 121.4, 123.7, 125.9, 127.1, 127.6, 128.4, 129.5, 131.8, 132.2, 136.2, 136.4, 146.1, 199.6; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{28}{}^{79}BrO$: 423.1324, found: 423.1325.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl](4-tolyl)methanone (80g)

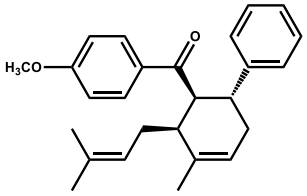
Compound **80g** was prepared using general procedure D employing 4′-methylchalcone (**7j**) as the dienophile, toluene as the solvent and 3 h as the reaction time.



Pale brown solid; yield: 111 mg (62%); mp = 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.42 (s, 3 H), 1.72 (s, 3 H), 1.97-2.10 (m, 2 H), 2.11-2.19 (m, 1 H), 2.32 (s, 3 H), 2.33-2.41 (m, 2 H), 3.36 (td, *J* = 10.6, 6.4 Hz, 1 H), 4.06 (dd, *J* = 11.1, 4.9 Hz, 1 H), 4.76 (t, *J* = 7.1 Hz, 1 H), 5.42 (br s, 1 H), 6.99-7.05 (m, 1 H), 7.12-7.16 (m, 6 H), 7.71 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 21.5, 22.9, 25.7, 28.9, 35.1, 37.0, 42.9, 50.3, 121.3, 123.8, 125.7, 127.1, 128.1, 128.3, 129.2, 131.8, 135.1, 136.7, 143.2, 146.5, 200.3; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{31}O$: 359.2375, found: 359.2370.

(4-Methoxyphenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl]methanone (13)

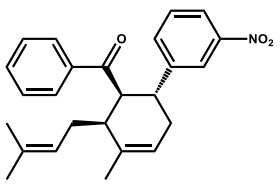
Compound **13** was prepared using general procedure D employing 4′-methoxychalcone (**7e**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Pale yellow solid; yield: 32 mg (17%); mp = 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.42 (s, 3 H), 1.72 (s, 3 H), 1.98-2.10 (m, 2 H), 2.12-2.19 (m, 1 H), 2.34-2.41 (m, 2 H), 3.36 (td, *J* = 10.6, 6.4 Hz, 1 H), 3.78 (s, 3 H), 4.04 (dd, *J* = 11.1, 4.9 Hz, 1 H), 4.77 (t, *J* = 7.1 Hz, 1 H), 5.42 (br s, 1 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 6.99-7.04 (m, 1 H), 7.12-7.13 (m, 4 H), 7.80 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.9, 25.7, 28.9, 35.1, 37.1, 43.1, 50.1, 55.4, 113.6, 121.3, 123.9, 125.7, 127.1, 128.3, 130.2, 130.8, 131.8, 136.8, 146.5, 163.0, 199.1; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{31}O_2$: 375.2324, found: 375.2322.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-(3-nitrophenyl)cyclohex-3-en-1-yl](phenyl)methanone (80h)

Compound **80h** was prepared using general procedure D employing 3-nitrochalcone (**7ad**) as the dienophile, toluene as the solvent and 3 h as the reaction time.

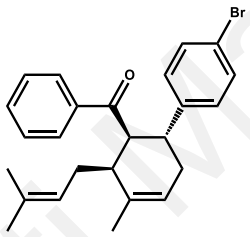


Pale brown oil; yield: 125 mg (64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 6 H), 1.73 (s, 3 H), 1.97-2.04 (m, 1 H), 2.06-2.16 (m, 2 H), 2.38-2.50 (m, 2 H), 3.51 (td, *J* = 11.0, 6.4 Hz, 1 H), 4.11 (dd, *J* = 11.2, 4.9 Hz, 1 H), 4.73 (t, *J* = 7.3 Hz, 1 H), 5.43 (br s, 1 H),

7.29 (t, *J* = 8.3 Hz, 1 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.46 (t, *J* = 7.3 Hz, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.3 Hz, 2 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 8.03 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.7, 25.6, 28.7, 35.0, 36.9, 43.1, 50.7, 120.8, 121.0, 121.9, 123.3, 127.9, 128.6, 129.1, 132.3, 132.9, 133.8, 136.8, 137.1, 148.3, 148.7, 200.3; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{28}NO_3$: 390.2069, found: 390.2057.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-(4-bromophenyl)cyclohex-3-en-1-yl](phenyl)methanone (80i)

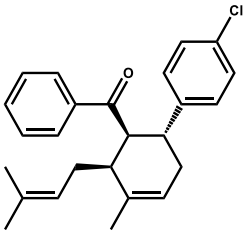
Compound **80i** was prepared using general procedure D employing 4-bromochalcone (**7ae**) as the dienophile, toluene as the solvent and 3 h as the reaction time.



Pale brown solid; yield: 131 mg (62%); mp = 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.40 (s, 3 H), 1.71 (s, 3 H), 1.96-2.05 (m, 2 H), 2.08-2.16 (m, 1 H), 2.32-2.42 (m, 2 H), 3.34 (td, *J* = 10.7, 6.3 Hz, 1 H), 4.03 (dd, *J* = 11.2, 4.9 Hz, 1 H), 4.72 (t, *J* = 7.1 Hz, 1 H), 5.41 (br s, 1 H), 7.02 (d, *J* = 8.3 Hz, 2 H), 7.24 (d, *J* = 8.3 Hz, 2 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.79 (d, *J* = 7.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 36.6, 43.0, 50.5, 119.4, 121.1, 123.6, 128.0, 128.6, 128.9, 131.4, 132.1, 132.7, 136.7, 137.3, 145.5, 200.4; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{28}{}^{79}BrO$: 423.1324, found: 423.1309.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-(4-chlorophenyl)cyclohex-3-en-1-yl](phenyl)methanone (80j)

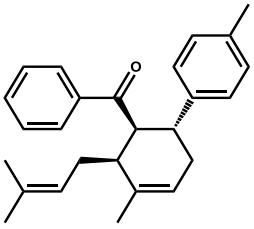
Compound **80j** was prepared using general procedure D employing 4-chlorochalcone (**7af**) as the dienophile, toluene as the solvent and 3 h as the reaction time.



White solid; yield: 131 mg (69%); mp = 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 6 H), 1.71 (s, 3 H), 1.96-2.05 (m, 2 H), 2.09-2.16 (m, 1 H), 2.31-2.42 (m, 2 H), 3.35 (td, *J* = 10.7, 6.4 Hz, 1 H), 4.03 (dd, *J* = 11.2, 4.9 Hz, 1 H), 4.73 (t, *J* = 7.3 Hz, 1 H), 5.41 (br s, 1 H), 7.05-7.10 (m, 4 H), 7.34 (t, *J* = 7.3 Hz, 2 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 37.0, 43.0, 50.5, 121.4, 123.7, 125.9, 127.1, 128.4, 128.8, 129.4, 132.2, 135.9, 136.5, 138.9, 146.2, 199.4; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{28}{}^{35}ClO$: 379.1829, found: 379.1825.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-(4-tolyl)cyclohex-3-en-1-yl](phenyl)methanone (80k)

Compound **80k** was prepared using general procedure D employing 4-methylchalcone (**7ag**) as the dienophile, toluene as the solvent and 3 h as the reaction time.

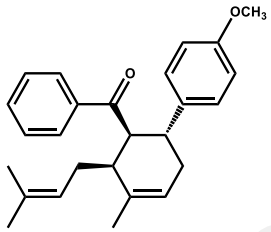


Pale yellow solid; yield: 79 mg (44%); mp = 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.40 (s, 3 H), 1.71 (s, 3 H), 1.97-2.14 (m, 3 H), 2.16 (s, 3 H), 2.34-2.40 (m, 2 H), 3.33 (td, *J* = 10.7, 6.4 Hz, 1 H), 4.07 (dd, *J* = 11.2, 5.0 Hz, 1 H), 4.74 (t, *J* = 7.3 Hz, 1 H), 5.42 (br s, 1 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 7.34 (t, *J* = 7.3 Hz, 2 H), 7.44 (t, *J* = 7.3 Hz, 1 H), 7.81 (d, *J* = 7.3 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 20.9, 22.8, 25.7, 28.8, 35.1, 36.6, 42.8, 50.5, 121.4, 123.8, 127.0, 128.0, 128.5,

129.1, 131.9, 132.5, 135.1, 136.6, 137.6, 143.3, 200.7; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{31}O$: 359.2375, found: 359.2372.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-(4-methoxyphenyl)cyclohex-3-en-1-yl](phenyl)methanone (80l)

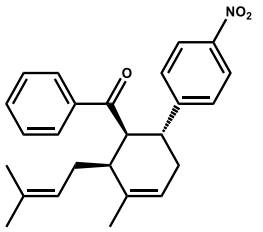
Compound **80l** was prepared using general procedure D employing 4-methoxychalcone (**7ah**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Yellow oil; yield: 32 mg (17%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.40 (s, 3 H), 1.71 (s, 3 H), 1.97-2.10 (m, 2 H), 2.11-2.18 (m, 1 H), 2.32-2.39 (m, 2 H), 3.32 (td, *J* = 10.5, 6.4 Hz, 1 H), 3.64 (s, 3 H), 4.03 (dd, *J* = 11.2, 4.9 Hz, 1 H), 4.75 (t, *J* = 7.3 Hz, 1 H), 5.42 (br s, 1 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 7.35 (t, *J* = 7.3 Hz, 2 H), 7.44 (t, *J* = 7.3 Hz, 1 H), 7.80 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 36.2, 42.8, 50.7, 55.1, 113.8, 121.4, 123.8, 128.0, 128.0, 128.5, 131.9, 132.5, 136.6, 137.6, 138.4, 157.5, 200.7; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{31}O_2$: 375.2324, found: 375.2324.

[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-(4-nitrophenyl)cyclohex-3-en-1-yl](phenyl)methanone (80m)

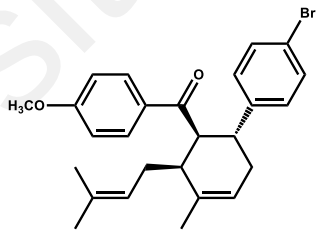
Compound **80m** was prepared using general procedure D employing 4-nitrochalcone (**7ai**) as the dienophile, CH_2Cl_2 as the solvent and 3 h as the reaction time.



Pale brown solid; yield: 138 mg (71%); mp = 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 6 H), 1.72 (s, 3 H), 1.96-2.04 (m, 2 H), 2.07-2.14 (m, 1 H), 2.34-2.40 (m, 1 H), 2.46-2.50 (m, 1 H), 3.49 (td, *J* = 11.0, 6.4 Hz, 1 H), 4.10 (dd, *J* = 11.2, 4.9 Hz, 1 H), 4.71 (t, *J* = 7.1 Hz, 1 H), 5.42 (br s, 1 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.35 (t, *J* = 7.3 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.79 (d, *J* = 7.3 Hz, 2 H), 7.99 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.7, 25.6, 28.7, 34.8, 37.2, 43.2, 50.6, 120.7, 123.2, 123.7, 127.9, 127.9, 128.6, 132.4, 133.0, 136.8, 137.0, 146.1, 154.6, 200.2; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{25}H_{28}NO_3$: 390.2069, found: 390.2056.

(4-Methoxyphenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-(4-bromophenyl)cyclohex-3-en-1-yl]methanone (80n)

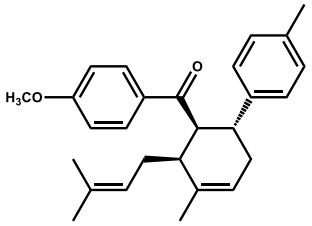
Compound **80n** was prepared using general procedure D employing 4′-methoxy-4-bromochalcone (**7aj**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Pale yellow oil; yield: 50 mg (22%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.42 (s, 3 H), 1.71 (s, 3 H), 1.96-2.04 (m, 2 H), 2.09-2.16 (m, 1 H), 2.31-2.40 (m, 2 H), 3.33 (td, *J* = 10.5, 6.4 Hz, 1 H), 3.79 (s, 3 H), 3.98 (dd, *J* = 11.2, 4.9 Hz, 1 H), 4.75 (t, *J* = 7.1 Hz, 1 H), 5.40 (br s, 1 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.9, 25.7, 28.8, 35.1, 36.6, 43.2, 50.2, 55.4, 113.7, 119.3, 121.1, 123.7, 128.9, 130.2, 130.5, 131.4, 131.9, 136.9, 145.6, 163.2, 198.9; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{30}{}^{79}BrO_2$: 453.1429, found: 453.1414.

(4-Methoxyphenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-(4-tolyl)cyclohex-3-en-1-yl]methanone (80o)

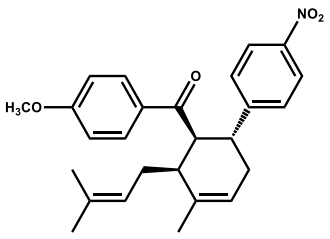
Compound **80o** was prepared using general procedure D employing 4′-methoxy-4-methylchalcone (**7ak**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Yellow oil; yield: 19 mg (10%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.42 (s, 3 H), 1.71 (s, 3 H), 1.97-2.09 (m, 2 H), 2.11-2.20 (m, 1 H), 2.16 (s, 3 H), 2.32-2.39 (m, 2 H), 3.32 (td, *J* = 10.6, 6.4 Hz, 1 H), 3.78 (s, 3 H), 4.01 (dd, *J* = 11.1, 4.9 Hz, 1 H), 4.77 (t, *J* = 7.1 Hz, 1 H), 5.41 (br s, 1 H), 6.82 (d, *J* = 8.9 Hz, 2 H), 6.93 (d, *J* = 8.1 Hz, 2 H), 7.02 (d, *J* = 8.1 Hz, 2 H), 7.80 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 20.9, 22.9, 25.7, 28.9, 35.2, 36.6, 43.1, 50.2, 55.4, 113.6, 121.4, 123.9, 126.9, 129.0, 130.2, 130.8, 131.7, 135.0, 136.8, 143.5, 163.0, 199.2; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{27}H_{33}O_2$: 389.2481, found: 389.2479.

(4-Methoxyphenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-(4-nitrophenyl)cyclohex-3-en-1-yl]methanone (80p)

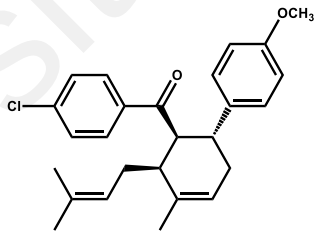
Compound **80p** was prepared using general procedure D employing 4′-methoxy-4-nitrochalcone (**7al**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Yellow oil; yield: 36 mg (17%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.42 (s, 3 H), 1.73 (s, 3 H), 1.97-2.06 (m, 2 H), 2.08-2.15 (m, 1 H), 2.34-2.41 (m, 1 H), 2.43-2.51 (m, 1 H), 3.49 (td, *J* = 11.0, 6.4 Hz, 1 H), 3.79 (s, 3 H), 4.05 (dd, *J* = 11.5, 4.9 Hz, 1 H), 4.75 (t, *J* = 7.1 Hz, 1 H), 5.42 (br s, 1 H), 6.84 (d, *J* = 9.0 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 7.78 (d, *J* = 9.0 Hz, 2 H), 8.00 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 37.3, 43.4, 50.4, 55.5, 113.8, 120.7, 123.4, 123.7, 127.9, 130.2, 130.2, 132.2, 137.0, 146.1, 154.8, 163.4, 198.7; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{30}NO_4$: 420.2175, found: 420.2172.

(4-Chlorophenyl)[(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-(4-methoxyphenyl)cyclohex-3-en-1-yl]methanone (80q)

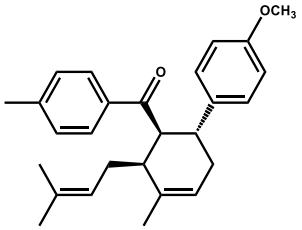
Compound **80q** was prepared using general procedure D employing 4′-chloro-4-methoxychalcone (**7am**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Pale yellow oil; yield: 22 mg (11%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 6 H), 1.71 (s, 3 H), 1.96-2.08 (m, 2 H), 2.10-2.17 (m, 1 H), 2.32-2.38 (m, 2 H), 3.29 (td, *J* = 10.6, 6.4 Hz, 1 H), 3.64 (s, 3 H), 3.97 (dd, *J* = 11.1, 4.9 Hz, 1 H), 4.71 (t, *J* = 7.1 Hz, 1 H), 5.42 (br s, 1 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.6 Hz, 2 H), 7.73 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 22.8, 25.7, 28.8, 35.0, 36.1, 43.0, 50.7, 55.1, 113.8, 121.5, 123.8, 128.0, 128.8, 129.4, 132.1, 135.9, 136.4, 138.2, 138.9, 157.6, 199.5; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{26}H_{30}{}^{35}ClO_2$: 409.1934, found: 409.1935.

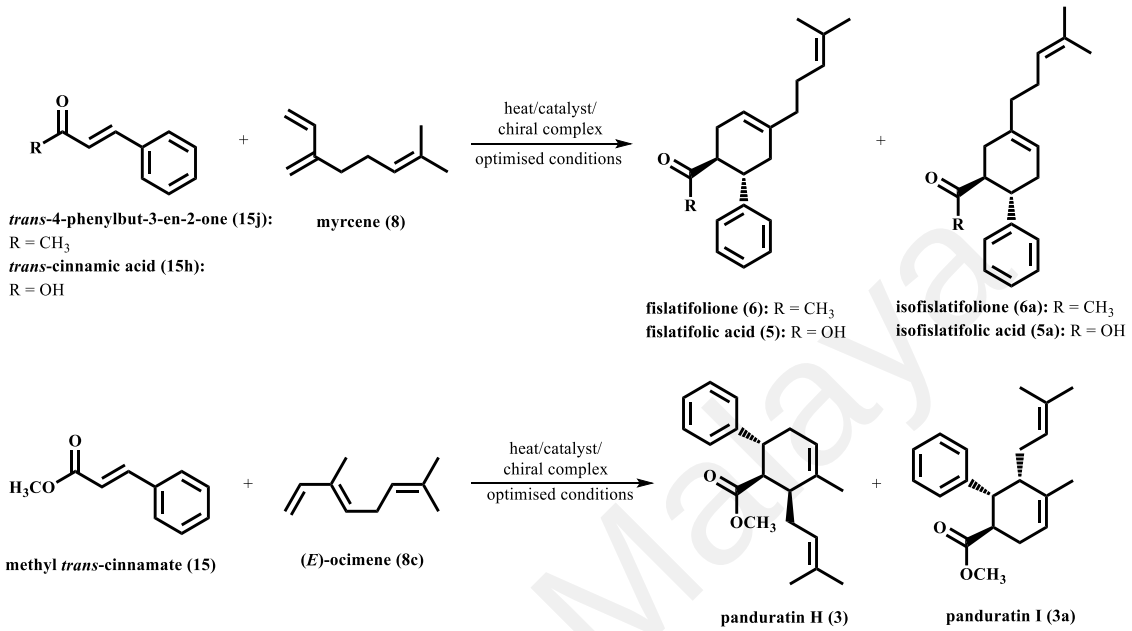
[(1*RS*,2*SR*,6*RS*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-(4-methoxyphenyl)cyclohex-3-en-1-yl](4-tolyl)methanone (80r)

Compound **80r** was prepared using general procedure D employing 4′-methyl-4-methoxychalcone (**7an**) as the dienophile, toluene as the solvent and 24 h as the reaction time.



Yellow oil; yield: 17 mg (9%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.42 (s, 3 H), 1.71 (s, 3 H), 1.96-2.08 (m, 2 H), 2.11-2.18 (m, 1 H), 2.32 (s, 3 H), 2.32-2.39 (m, 2 H), 3.31 (td, *J* = 10.5, 6.4 Hz, 1 H), 3.65 (s, 3 H), 4.01 (dd, *J* = 11.0, 4.9 Hz, 1 H), 4.76 (t, *J* = 7.1 Hz, 1 H), 5.41 (br s, 1 H), 6.67 (d, *J* = 8.6 Hz, 2 H), 7.06 (d, *J* = 8.6 Hz, 2 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 7.71 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 21.6, 22.9, 25.7, 28.9, 35.1, 36.2, 42.9, 50.6, 55.1, 113.8, 121.4, 123.9, 128.0, 128.1, 129.2, 131.8, 135.2, 136.7, 138.5, 143.2, 157.5, 200.3; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{27}H_{33}O_2$: 389.2481, found: 389.2482.

3.2.4.2 General Procedure E for the Synthesis of Fislatifolione (6), Isofislatifolione (6a), Fislatifolic Acid (5), Isofislatifolic Acid (5a), Panduratin H (3) and Panduratin I (3a)

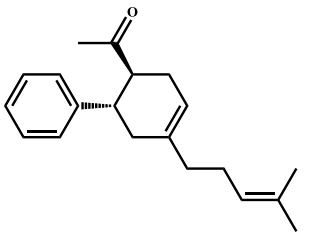


i) Thermal Condition

A mixture of cinnamoyl dienophile **15**, **15h** & **15j** (0.2 mmol) and diene **8** & **8c** (1.0 mmol) was dissolved in toluene (0.4 mL) and the mixture was stirred at 150 ºC for 24 h. The mixture was then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1-20% EtOAc-hexane) to give adducts **3** & **3a**, **5** & **5a** and **6** & **6a** as mixtures, respectively. A pure sample of each adduct was obtained by second column chromatography separation.

Fislatifolione (6)

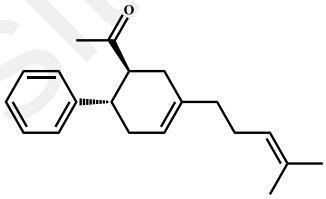
Compound **6** was prepared using general procedure E (i) employing *trans*-4-phenylbut-3-en-2-one (**15j**) as the dienophile and myrcene (**8**) as the diene. The ^{1}H NMR spectroscopic data for adduct **6** agreed with that reported in the literature (Geny et al., 2017).



Pale yellow oil; yield: 15 mg (26%); ^{1}H NMR (400 MHz, $CDCl_3$): 1.60 (s, 3 H), 1.69 (s, 3 H), 1.84 (s, 3 H), 1.95-2.02 (m, 2 H), 2.04-2.12 (m, 2 H), 2.15-2.22 (m, 2 H), 2.24-2.28 (m, 2 H), 2.94-3.05 (m, 2 H), 5.10 (t, *J* = 6.4 Hz, 1 H), 5.48 (br s, 1 H), 7.17-7.21 (m, 3 H), 7.26-7.31 (m, 2 H).

Isofislatifolione (6a)

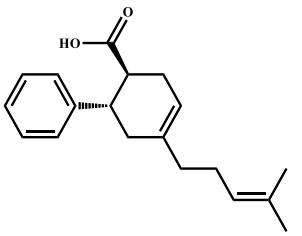
Compound **6a** was prepared using general procedure E (i) employing *trans*-4-phenylbut-3-en-2-one (**15j**) as the dienophile and myrcene (**8**) as the diene. The ^{1}H NMR spectroscopic data for adduct **6a** agreed with that reported in the literature (Geny et al., 2017).



Pale yellow oil; yield: 7 mg (13%); ^{1}H NMR (400 MHz, $CDCl_3$): 1.62 (s, 3 H), 1.71 (s, 3 H), 1.83 (s, 3 H), 1.98-2.38 (m, 8 H), 2.91-3.07 (m, 2 H), 5.12 (t, *J* = 6.8 Hz, 1 H), 5.51 (br s, 1 H), 7.17-7.20 (m, 3 H), 7.26-7.31 (m, 2 H).

Fislatifolic acid (5)

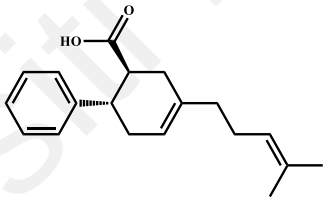
Compound **5** was prepared using general procedure E (i) employing *trans*-cinnamic acid (**15h**) as the dienophile and myrcene (**8**) as the diene. The ^{1}H NMR spectroscopic data for adduct **5** agreed with that reported in the literature (Geny et al., 2017).



Pale yellow oil; yield: 13 mg (22%); ^{1}H NMR (400 MHz, $CDCl_3$): 1.60 (s, 3 H), 1.69 (s, 3 H), 1.98-2.00 (m, 2 H), 2.07-2.09 (m, 2 H), 2.12-2.29 (m, 2 H), 2.36-2.40 (m, 2 H), 2.82 (td, *J* = 7.2, 5.2 Hz, 1 H), 3.03 (td, *J* = 7.2, 3.6 Hz, 1 H), 5.09 (t, *J* = 6.4 Hz, 1 H), 5.48 (br s, 1 H), 7.17-7.21 (m, 3 H), 7.26-7.31 (m, 2 H).

Isofislatifolic acid (5a)

Compound **5a** was prepared using general procedure E (i) employing *trans*-cinnamic acid (**15h**) as the dienophile and myrcene (**8**) as the diene. The structure of **5a** was confirmed by ^{1}H, ^{13}C, COSY, HSQC, HMBC NMR and HRMS spectroscopic techniques.

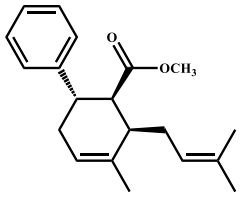


Pale yellow oil; yield: 7 mg (13%); ^{1}H NMR (400 MHz, $CDCl_3$): 1.61 (s, 3 H), 1.70 (s, 3 H), 2.00-2.04 (m, 2 H), 2.08-2.14 (m, 2 H), 2.19-2.25 (m, 1 H), 2.28-2.40 (m, 3 H), 2.87 (td, *J* = 10.8, 5.6 Hz, 1 H), 2.98 (td, *J* = 10.6, 5.6 Hz, 1 H), 5.11 (t, *J* = 6.8 Hz, 1 H), 5.49 (br s, 1 H), 7.17-7.21 (m, 3 H), 7.25-7.30 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 25.7, 26.3, 32.1, 33.5, 37.3, 42.2, 46.0, 120.2, 123.9, 126.5, 127.4, 128.4, 131.8, 135.6, 143.9, 179.7; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{19}H_{25}O_2$: 285.1855, found: 285.1842.

Panduratin H (3)

Compound **3** was prepared using general procedure E (i) employing methyl *trans*-cinnamate (**15**) as the dienophile and (*E*)-ocimene (**8c**) as the diene. The ^{1}H NMR

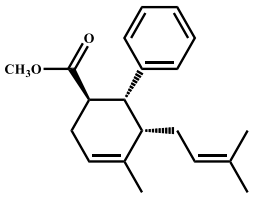
spectroscopic data for adduct **3** agreed with that reported in the literature (Win et al., 2008).



Pale yellow oil; yield: 4 mg (6%); ^{1}H NMR (400 MHz, $CDCl_3$): 1.60 (s, 3 H), 1.67 (s, 3 H), 1.78 (s, 3 H), 2.00-2.47 (m, 5 H), 3.08 (dd, *J* = 12.0, 5.2 Hz, 1 H), 3.19 (ddd, *J* = 11.1, 10.8, 6.0 Hz, 1 H), 3.41 (s, 3 H), 5.06 (t, *J* = 6.8 Hz, 1 H), 5.42 (br s, 1 H), 7.14-7.19 (m, 3 H), 7.24-7.28 (m, 2 H).

Panduratin I (3a)

Compound **3a** was prepared using general procedure E (i) employing methyl *trans*-cinnamate (**15**) as the dienophile and (*E*)-ocimene (**8c**) as the diene. The ^{1}H NMR spectroscopic data for adduct **3a** agreed with that reported in the literature (Win et al., 2008).



Pale yellow oil; yield: 13 mg (22%); ^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (s, 3 H), 1.57 (s, 3 H), 1.74 (s, 3 H), 1.86-2.46 (m, 5 H), 3.18 (ddd, *J* = 10.5, 9.8, 6.0 Hz, 1 H), 3.33 (dd, *J* = 11.4, 5.6 Hz, 1 H), 3.49 (s, 3 H), 4.81 (t, *J* = 7.2 Hz, 1 H), 5.45 (br s, 1 H), 7.13-7.19 (m, 3 H), 7.24-7.28 (m, 2 H).

ii) Catalyst Condition

A 1.0 M solution of $AlBr_3$ in CH_2Br_2 or $TiCl_4$ in toluene (0.06-0.4 mmol) was added to a solution of cinnamoyl dienophile **15**, **15h** & **15j** (0.2 mmol) in anhyd. toluene or

CH_2Cl_2 (0.4 mL) at r.t. (28 °C) under N_2 atmosphere. Diene **8** & **8c** (1.0 mmol) was added, and the mixture was stirred at r.t for 0.5-24 h. After the completion of the reaction, the reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give the desired adducts. The ^{1}H NMR spectroscopic data for the adducts agreed with previously reported [See the ^{1}H NMR data of the adducts at chapter 3.2.4.2 (i)].

iii) Chiral Complex Condition

a) Method 1 [2 equivalents of FMOC-L-Phe-OH (L5) with 1 equivalent of $TiCl_4$ in the Presence of $NaHCO_3$]

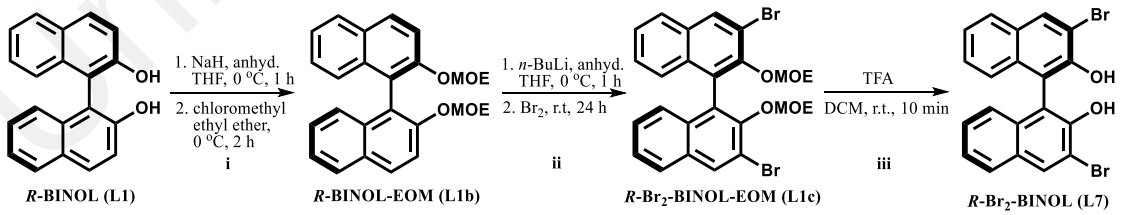
A solution of $NaHCO_3$ (5.0 mmol) in distilled water (14 mL) was added to a solution of FMOC-L-Phe-OH (**L5**) (5.0 mmol) in methanol (140 mL) and the mixture was stirred at r.t. for 17 h. The mixture was then concentrated under reduced pressure and further dried under high vacuum. The formed sodium salt of FMOC-L-Phe-OH (0.4 mmol) was dissolved in anhyd. toluene (1.3 mL) at r.t. (28 °C) under N_2 atmosphere, then a 1.0 M solution of $TiCl_4$ (0.2 mmol) was added, and the resulting mixture was stirred at r.t. for 2 h. A solution of cinnamoyl dienophile **15**, **15h** & **15j** (0.2 mmol) in anhyd toluene or CH_2Cl_2 (0.3 mL) was added, and the mixture was stirred at r.t. for 0.5 h. Diene **8** & **8c** (1.0 mmol) was added, and the mixture was stirred at r.t. for 24 h. After the completion of the reaction, the reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give the desired adducts. The ^{1}H NMR spectroscopic data for the adducts agreed with previously reported [See the ^{1}H NMR data of the adducts at chapter 3.2.4.2 (i)].

b) Method 2 [1 equivalent of *R*-BINOL (L1) with 1 equivalent of $TiCl_4$ in the Presence of *n*-BuLi]

A 2.0 M solution of *n*-BuLi in *n*-hexane (0.4-0.8 mmol) was added to a solution of *R*-BINOL (**L1**) (0.2-0.4 mmol) in anhyd. toluene (1.3 mL) at r.t. (28 °C) under N_2 atmosphere and the mixture was stirred at r.t. for 0.5 h. Then, a 1.0 M solution of $TiCl_4$ in toluene (0.2-0.4 mmol) was added, and the mixture was stirred at 80 °C for 3 h. A solution of cinnamoyl dienophile **15**, **15h** & **15j** (0.2 mmol) in anhyd. toluene or CH_2Cl_2 (0.3 mL) was added, and the mixture was stirred at r.t. for 0.5 h. Diene **8** & **8c** (1.0 mmol) was added, and the mixture was stirred at r.t. for 24 h. After the completion of the reaction, the reaction mixture was quenched with 5 mL of methanol and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to give the desired adducts. The ^{1}H NMR spectroscopic data for the adducts agreed with previously reported [See the ^{1}H NMR data of the adducts at chapter 3.2.4.2 (i)].

3.2.5 Synthesis of Chiral Ligands

3.2.5.1 Synthesis of (*R*)-(+)-3,3'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (*R*-Br_2-BINOL) (L7)



i) (*R*)-(+)-2,2'-Bis(ethoxymethoxy)-1,1'-binaphthalene (*R*-BINOL-EOM) (L1b): A solution of *R*-BINOL (**L1**) (5.0 mmol) in anhyd. THF (20 mL) was added to a mixture of NaH (15.0 mmol) and anhyd. THF (10 mL) at 0 °C under N_2 atmosphere and the mixture was stirred at 0 °C for 1 h. Then, chloromethyl ethyl ether (12.5 mmol) was added, and

the mixture was stirred at 0 °C for 2 h. After the completion of the reaction, saturated NH_4Cl solution was added to the reaction mixture until no evolution of gas was observed. The reaction mixture was extracted thrice with CH_2Cl_2. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% EtOAc-hexane) to afford the desired compound, (*R*)-(+)-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1b**). The ^1H NMR spectroscopic data for compound **L1b** agreed with that reported in the literature (Park et al., 2011).

Pale yellow oil; yield: 1083 mg (54%); $[\alpha]_D^{29}$ = +64.4 (c 0.13, Ethanol), literature (Park et al., 2011) $[\alpha]_D^{22}$ = +51.7 (c 0.47, Ethanol); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 6 H), 3.21-3.35 (m, 4 H), 4.94 (d, *J* = 7.2 Hz, 2 H), 5.05 (d, *J* = 6.8 Hz, 2 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 7.13 (t, *J* = 8.4 Hz, 2 H), 7.26 (t, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.8 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.87 (d, *J* = 8.8 Hz, 2 H).

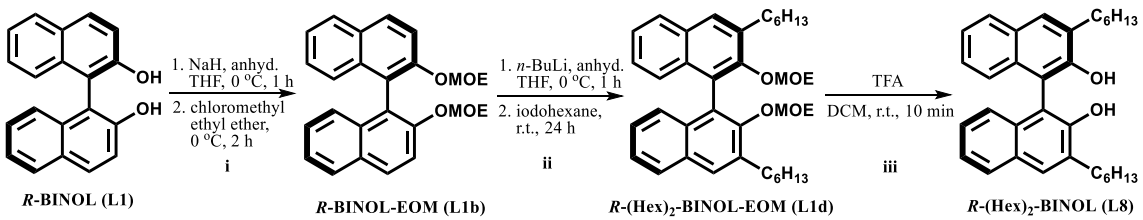
ii) (*R*)-(+)-3,3'-Dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (*R*-Br_2-BONOL-EOM) (L1c): A 2.0 M solution of *n*-BuLi in *n*-hexane (7.5 mmol) was added to a solution of (*R*)-(+)-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1b**) (2.5 mmol) in anhyd. THF (10 mL) at -78 °C under N_2 atmosphere and the mixture was stirred at 0 °C for 1 h. After that, the reaction was cooled to -78 °C and bromine (6.25 mmol) was added dropwise. The yellowish-brown reaction mixture was allowed to warm to r.t. and stirred for 24 h. Subsequently, the reaction mixture was quenched with 10 mL of saturated $Na_2S_2O_3$ solution and extracted thrice with EtOAc. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% EtOAc-hexane) to afford the desired compound, (*R*)-(+)-3,3'-dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1c**).

Pale brown solid; yield: 672 mg (48%); $[\alpha]_D^{29}$ = +65.9 (c 0.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.52 (t, *J* = 6.8 Hz, 6 H), 2.58 (dq, *J* = 9.2, 7.2 Hz, 2H), 2.94 (dq, *J* = 8.8, 6.8 Hz, 2 H), 4.76 (d, *J* = 6.0 Hz, 2 H), 4.83 (d, *J* = 5.6 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 7.21 (t, *J* = 8.0 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 8.19 (s, 2 H).

iii) (*R*)-(+)-3,3'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (*R*-Br$_2$-BINOL) (L7): (*R*)-(+)-3,3'-Dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1c**) (1.0 mmol) was dissolved in CH_2Cl_2 (30 mL). Trifluoroacetic acid (2 mL) was added dropwise, and the mixture was stirred at r.t. for 10 min. After the completion of the reaction, saturated $NaHCO_3$ solution was added to the reaction mixture until no evolution of gas was observed. The reaction mixture was extracted thrice with CH_2Cl_2. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The desired compound, (*R*)-(+)-3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol **(L7**) was obtained without further purification. The ^{1}H NMR spectroscopic data for compound **L7** agreed with that reported in the literature (Wu et al., 2004).

Pale brown solid; yield: 422 mg (95%); $[\alpha]_D^{29}$ = +101.5 (c 0.50, THF), literature (Wu et al., 2004) $[\alpha]_D^{25}$ = +104.7 (c 1.0, THF); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.48 (s, 2 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 7.24 (t, *J* = 7.2 Hz, 2 H), 7.31 (t, *J* = 6.8 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 8.18 (s, 2 H).

3.2.5.2 Synthesis of (*R*)-(+)-3,3'-Dihexyl-[1,1'-binaphthalene]-2,2'-diol [*R*-(Hex)$_2$-BINOL] (L8)



i) (*R*)-(+)-2,2'-Bis(ethoxymethoxy)-1,1'-binaphthalene (*R*-BINOL-EOM) (L1b): Prepared according to the procedure in chapter 3.2.5.1 (i).

ii) (*R*)-(+)-3,3'-Dihexyl-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene [*R*-(Hex)$_2$-BINOL-EOM] (L1d): Prepared according to the procedure in chapter 3.2.5.1 (ii), using iodohexane instead of bromine. The crude product was purified by column chromatography (silica gel, 5% EtOAc-hexane) to afford the desired compound, (*R*)-(+)-3,3'-dihexyl-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1d**).

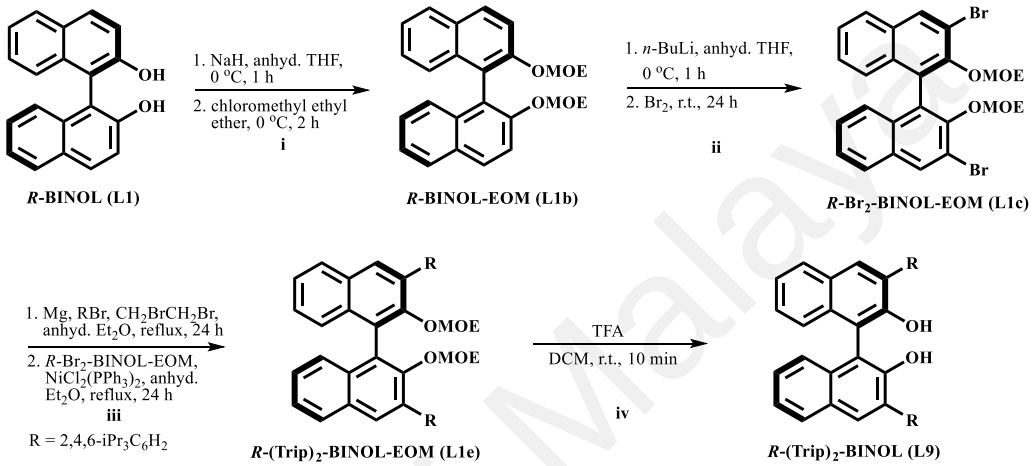
Pale brown oil; yield: 1013 mg (71%); $[\alpha]_D^{29}$ = -141.8 (c 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 6.8 Hz, 6 H), 0.83 (t, *J* = 6.8 Hz, 6 H), 1.22-1.33 (m, 8 H), 1.35-1.42 (m, 4 H), 1.63-1.80 (m, 4 H), 2.72-2.85 (m, 4 H), 2.88-2.95 (m, 2 H), 3.22 (dq, *J* = 9.2, 7.2 Hz, 2 H), 4.37 (d, *J* = 5.6 Hz, 2 H), 4.53 (d, *J* = 6.0 Hz, 2 H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 8.4 Hz, 2 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.71 (s, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H).

iii) (*R*)-(+)-3,3'-Dihexyl-[1,1'-binaphthalene]-2,2'-diol [*R*-(Hex)$_2$-BINOL] (L8): Prepared according to the procedure in chapter 3.2.5.1 (iii), using (*R*)-(+)-3,3'-dihexyl-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1d**) instead of (*R*)-(+)-3,3'-dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1c**). The crude product was purified by column chromatography (silica gel, 5% EtOAc-hexane) to afford the desired compound, (*R*)-(+)-3,3'-dihexyl-[1,1'-binaphthalene]-2,2'-diol (**L8**). The structure of **L8** was confirmed by ^{1}H, ^{13}C NMR and HRMS spectroscopic techniques.

Brown oil; yield: 91%; $[\alpha]_D^{29}$ = +52.1 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 6 H), 1.29-1.39 (m, 8 H), 1.41-1.48 (m, 4 H), 1.69-1.84 (m, 4 H), 2.86 (t, *J* = 7.6 Hz, 4 H), 5.11 (s, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 7.20 (t, *J* = 7.2 Hz, 2 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.77 (s, 2 H), 7.80 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 14.1, 22.7, 29.3, 29.6, 30.9, 31.8,110.7, 123.8, 124.0, 126.4, 127.7, 129.5, 129.9, 131.6, 132.1, 151.8; HRMS (ESI): m/z $[M - H]^+$ calcd. for $C_{32}H_{37}O_2^+$: 453.2789 found: 453.2783.

3.2.5.3 Synthesis of (*R*)-(+)-3,3'-Bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol [*R*-(Trip)$_2$-BINOL] (L9)



i) (*R*)-(+)-2,2'-Bis(ethoxymethoxy)-1,1'-binaphthalene (*R*-BINOL-EOM) (L1b): Prepared according to the procedure in chapter 3.2.5.1 (i).

ii) (*R*)-(+)-3,3'-Dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (*R*-Br$_2$-BONOL-EOM) (L1c): Prepared according to the procedure in chapter 3.2.5.1 (ii).

iii) (*R*)-(+)-3,3'-Bis(2,4,6-triisopropylphenyl)-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene [*R*-(Trip)$_2$-BINOL-EOM] (L1e): A solution of 1-bromo-2,4,6-triisopropylbenzene (6.0 mmol) in anhyd. Et_2O (10 mL) was added to magnesium (12 mmol) at r.t. (28 °C) under N_2 atmosphere. 1,2-Dibromoethane (20 µL) was added as an activator. After complete addition, the reaction mixture was refluxed for 24 h. After the completion of the reaction, it was cooled to room temperature. The reaction mixture was slowly added to a suspension of (*R*)-(+)-3,3'-dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1c**) (1.0 mmol) and $NiCl_2(Ph_3P)_2$ (0.1 mmol) in anhyd. Et_2O (5 mL).

The resultant brown solution was heated at reflux for 24 h. Subsequently, the brown solution was cooled to room temperature and quenched with 1 M solution of HCl (5 mL). The reaction mixture was extracted thrice with Et_2O. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to afford the desired compound, (*R*)-(+)-3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1e**).

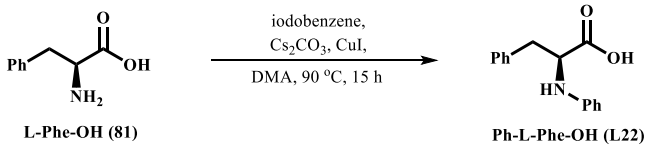
Pale yellow solid; yield: 630 mg (78%); $[\alpha]_D^{29}$ = +141.8 (c 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.40 (t, *J* = 7.2 Hz, 6 H), 0.90 (d, *J* = 6.8 Hz, 6 H), 1.10 (d, *J* = 7.2 Hz, 6 H), 1.13 (d, *J* = 6.8 Hz, 6 H), 1.19 (d, *J* = 6.8 Hz, 6 H), 1.22 (d, *J* = 6.8 Hz, 12 H), 2.32 (dq, *J* = 9.2, 7.2 Hz, 2 H), 2.41 (dq, *J* = 9.2, 7.2 Hz, 2 H), 2.76 (sept, *J* = 6.8 Hz, 4 H), 2.87 (sept, *J* = 7.2 Hz, 2 H), 4.16 (d, *J* = 5.2 Hz, 2 H), 4.18 (d, *J* = 5.2 Hz, 2 H), 7.00 (d, *J* = 11.2 Hz, 4 H), 7.21-7.35 (m, 6 H), 7.71 (s, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H).

iv) (*R*)-(+)-3,3'-Bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol [*R*-(Trip)$_2$-BINOL] (L9): Prepared according to the procedure in chapter 3.2.5.1 (iii), using (*R*)-(+)-3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1e**) instead of (*R*)-(+)-3,3'-dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene (**L1c**). The crude product was purified by column chromatography (silica gel, 1% EtOAc-hexane) to afford the desired compound, (*R*)-(+)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol (**L9**). The ^{1}H NMR spectroscopic data for compound **L9** agreed with that reported in the literature (Zhang et al., 2014).

Pale yellow solid; yield: 539 mg (78%); $[\alpha]_D^{29}$ = +72.5 (c 0.99, $CHCl_3$), literature (Knipe & Smith, 2014) $[\alpha]_D^{20}$ = +68.9 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8 Hz, 6 H), 1.01 (d, *J* = 6.8 Hz, 6 H), 1.04 (d, *J* = 6.8 Hz, 6 H), 1.13 (d, *J* = 6.8 Hz, 6 H), 1.24 (d, *J* = 7.2 Hz, 12 H), 2.62 (sept, *J* = 6.8 Hz, 2 H), 2.78 (sept, *J* = 6.8 Hz, 2 H),

2.89 (sept, *J* = 6.8 Hz, 2 H), 4.85 (s, 2 H), 7.06 (d, *J* = 6.8 Hz, 4 H), 7.19-7.24 (m, 4 H), 7.28-7.32 (m, 2 H), 7.69 (s, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H).

3.2.5.4 Synthesis of *N*-Phenyl-L-phenylalanine (Ph-L-Phe-OH) (L22)

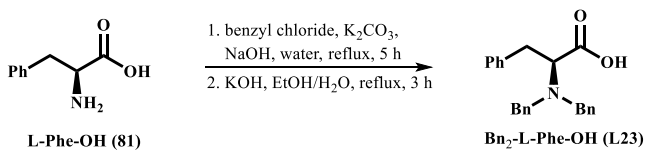


L-Phe-OH (81) → Ph-L-Phe-OH (L22)

L-phenylalanine (**81**) (0.5 mmol), Cs_2CO_3 (0.75 mmol) and CuI (0.05 mmol) were dissolved in DMA (2 mL). Iodobenzene (0.5 mmol) was added, and the mixture was stirred at 90 °C for 15 h. After the completion of the reaction, it was cooled to room temperature. Dilute HCl solution was added to the reaction mixture until pH < 7. The reaction mixture was extracted thrice with CH_2Cl_2. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% MeOH-CH_2Cl_2) to afford the desired compound, *N*-phenyl-L-phenylalanine (**L22**). The ^{1}H NMR spectroscopic data for compound **L22** agreed with that reported in the literature (Ma et al., 1998).

White solid; yield: 112 mg (93%); $[\alpha]_D^{29}$ = +18.5 (c 0.03, Acetone), literature (McKerrow et al., 2010) $[\alpha]_D^{22}$ = +3.0 (c 1.0, Acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.09 (dd, *J* = 13.6, 6.8 Hz, 1 H), 3.19 (dd, *J* = 13.6, 6.0 Hz, 1 H), 4.29 (t, *J* = 6.4 Hz, 1 H), 6.64-6.68 (m, 3 H), 7.10-7.17 (m, 2 H), 7.22-7.31 (m, 5 H).

3.2.5.5 Synthesis of *N*,*N*-Dibenzyl-L-phenylalanine (Bn_2-L-Phe-OH) (L23)

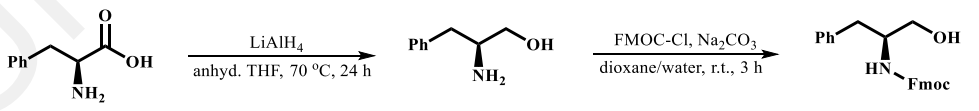


L-Phe-OH (81) → Bn_2-L-Phe-OH (L23)

L-phenylalanine (**81**) (2.5 mmol), K_2CO_3 (6.25 mmol) and NaOH (5.0 mmol) were dissolved in water (50 mL). Benzyl chloride (12.5 mmol) was added, and the resulting mixture was refluxed for 5 h. After the completion of the reaction, the mixture was cooled to room temperature and extracted with EtOAc. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. KOH (30 mL of 5% in EtOH/H_2O in 1:1) was added to the crude product and the mixture was refluxed for 3 h. After the completion of the reaction, it was cooled to room temperature and extracted thrice with EtOAc. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% EtOAc-hexane) to afford the desired compound, *N*,*N*-dibenzyl-L-phenylalanine (**L23**). The ^{1}H NMR spectroscopic data for compound **L23** agreed with that reported in the literature (Raza et al., 2015).

Pale yellow solid; yield: 535 mg (62%); $[\alpha]_D^{29}$ = -26.7 (c 0.50, Methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.98 (dd, *J* = 14.4, 8.4 Hz, 1 H), 3.24 (dd, *J* = 14.6, 6.4 Hz, 1 H), 3.65-3.74 (m, 5 H), 7.05-7.24 (m, 15 H)

3.2.5.6. Synthesis of (9H-Fluoren-9-yl)methyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (FMOC-L-Phe-ol) (L24)



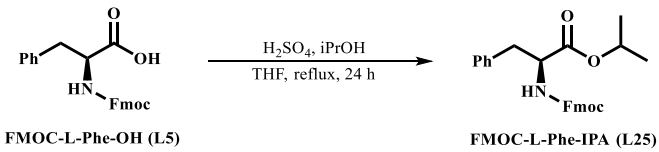
L-Phe-OH (81) **L-Phe-ol (82)** **FMOC-L-Phe-ol (L24)**

L-phenylalanine (**81**) (5.0 mmol) was dissolved in anhyd. THF (20 mL). A 1.0 M solution of $LiAlH_4$ in THF (10.0 mmol) was added, and the mixture was stirred in 70 °C for 24 h. After the completion of the reaction, it was cooled to room temperature. 2 N NaOH solution was added to the reaction mixture until no evolution of gas was observed. The reaction mixture was extracted thrice with CH_2Cl_2. The organic layer was collected,

dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was dissolved in dioxane (30 mL) and then added fluorenylmethyloxycarbonyl chloride (Fmoc-Cl) (5.5 mmol) and a solution of Na_2CO_3 (11 mmol) in distilled water (30 mL). The mixture was stirred in r.t for 3 h. The reaction mixture was extracted thrice with EtOAc. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 30% EtOAc-hexane) to afford the desired compound, (9H-fluoren-9-yl)methyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (**L24**). The ^{1}H NMR spectroscopic data for compound **L24** agreed with that reported in the literature (Horwell et al., 1991).

White solid; yield: 822 mg (44%); $[\alpha]_D^{29}$ = -40.2 (c 0.10, Methanol), literature (Horwell et al., 1991) $[\alpha]_D^{20}$ = -40.8 (c 0.55, Methanol); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.71 (dd, *J* = 13.4, 8.8 Hz, 1 H), 2.94 (dd, *J* = 13.6, 6.0 Hz, 1 H), 3.55 (d, *J* = 6.0 Hz, 2 H), 3.83-3.91 (m, 1 H), 4.14 (t, *J* = 7.2 Hz, 1 H), 4.21 (dd, *J* = 10.0, 7.2 Hz, 1 H), 4.35 (dd, *J* = 10.4, 6.8 Hz, 1 H), 7.16-7.21 (m, 1 H), 7.26-7.27 (m, 4 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.40 (t, *J* = 6.8 Hz, 2 H), 7.61 (d, *J* = 7.6 Hz, 2 H), 7.81 (d, *J* = 7.6 Hz, 2 H).

3.2.5.7 Synthesis of Isopropyl {[(9H-fluoren-9-yl)methoxy]carbonyl}-L-phenylalaninate (FMOC-L-Phe-IPA) (L25)



FMOC-L-Phe-OH (L5) FMOC-L-Phe-IPA (L25)

FMOC-L-phenylalanine **(L5)** (2.5 mmol) was dissolved in a mixture of 2-propanol (50 mL) and THF (10 mL). Concentrated H_2SO_4 (1 mL) was added dropwise to the solution and the mixture was refluxed for 24 h. After the completion of the reaction, it was cooled to room temperature. Saturated $NaHCO_3$ solution was added to the reaction mixture until no evolution of gas was observed and the reaction mixture was extracted thrice with

EtOAc. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% EtOAc-hexane) to afford the desired compound, isopropyl {[(9H-fluoren-9-yl)methoxy]carbonyl}-L-phenylalaninate (**L25**). The structure of **L25** was confirmed by ^{1}H, ^{13}C NMR and HRMS spectroscopic techniques.

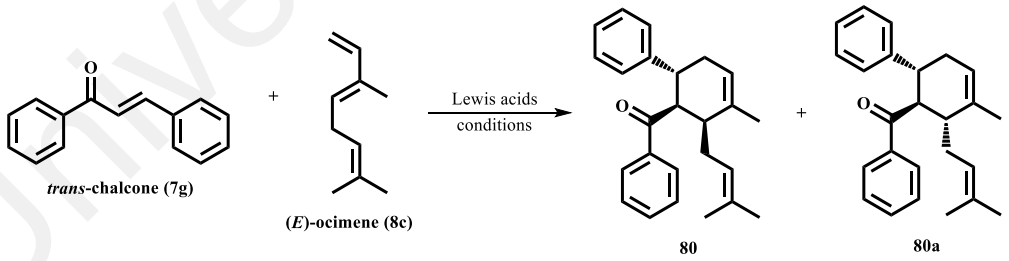
White solid; yield: 868 mg (81%); mp = 109-110 °C; $[\alpha]_D^{29}$ = +23.2 (c 0.99, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.4 Hz, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 3.09 (dd, *J* = 13.4, 5.6 Hz, 1 H), 3.13 (dd, *J* = 13.4, 5.6 Hz, 1 H), 4.21 (t, *J* = 6.8 Hz, 1 H), 4.33 (dd, *J* = 10.8, 6.8 Hz, 1 H), 4.44 (dd, *J* = 10.6, 6.8 Hz, 1 H), 4.62 (dt, *J* = 8.0, 6.0 Hz, 1 H), 5.02 (sept, *J* = 6.4 Hz, 1 H), 5.28 (d, *J* = 8.0 Hz, 1 H), 7.12 (d, *J* = 6.8 Hz, 2 H), 7.22-7.33 (m, 5 H), 7.40 (t, *J* = 7.2 Hz, 2 H), 7.57 (t, *J* = 6.8 Hz, 2 H), 7.77 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 21.8, 38.3, 47.2, 54.8, 66.9, 69.4, 120.0, 125.1, 125.1, 127.0, 127.7, 128.5, 129.4, 135.8, 141.3, 143.8, 143.9, 155.5, 171.0; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{27}H_{28}NO_4$: 430.2013, found: 430.1979.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Screening and Optimisation of Lewis Acids toward Diels-Alder Reaction of Cinnamoyl Dienophile and Terpene Diene

The reaction between a commercially available cinnamoyl dienophile [*i.e.*, *trans*-chalcone (**7g**)] and a terpene diene [*i.e.*, (*E*)-ocimene (**8c**)] was chosen as a model study for the DA reaction. This is because chalcones and (*E*)-ocimene (**8c**) are biosynthetic building blocks for the bioactive natural products, such as panduratins. Besides that, the DA reaction between *trans*-chalcone (**7g**) and (*E*)-ocimene (**8c**) had never been studied by other researchers. By referring to the literature (Brion, 1982; Fringuelli et al., 1983; Liu et al., 1994; Cong et al., 2010; Fang et al., 2013; Zhou et al., 2015), a series of Lewis acids commonly used in DA reactions were selected for this DA study. The study was done with 19 different types of Lewis acid as catalysts under 27 different reaction conditions to determine the best catalyst and reaction condition for this reaction. The results are tabulated in Table 4.1.

Table 4.1: Screening and optimisation of Lewis acids[a].



Entry	Catalyst	Catalyst loading (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	None	-	CH_2Cl_2	r.t.	24	-
2	AgOTf	30	CH_2Cl_2	r.t.	24	trace
3	$AgBF_4$	30	CH_2Cl_2	r.t.	24	-
4[c]	AgNP	30	CH_2Cl_2	r.t.	24	trace
5	$BF_3.Et_2O$	30	CH_2Cl_2	r.t.	24	-
6	$B(C_6F_5)_3$	30	toluene	r.t.	24	-
7	CoI_2	30	CH_2Cl_2	r.t.	24	-
8[d]	CuOTf	30	CH_2Cl_2	r.t.	24	-
9	$Cu(OTf)_2$	30	CH_2Cl_2	r.t.	24	-
10	$FeCl_3$	30	CH_2Cl_2	r.t.	24	trace

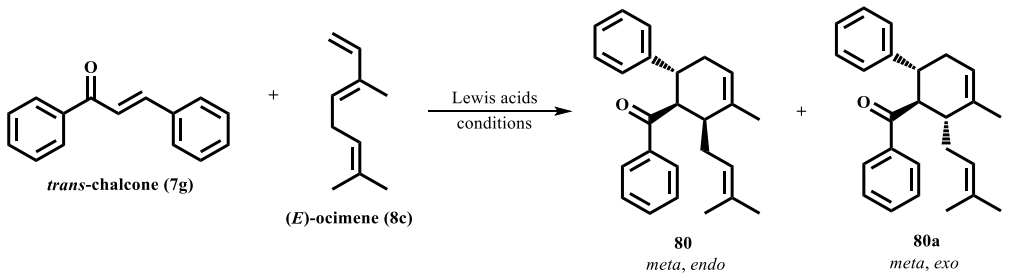
Table 4.1, continued. Screening and optimisation of Lewis acids[a].

Entry	Catalyst	Catalyst loading (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
11	$Ga(OTf)_3$	30	CH_2Cl_2	r.t.	24	trace
12	$MgBr_2.Et_2O$	30	CH_2Cl_2	r.t.	24	trace
13	$SnCl_2$	30	CH_2Cl_2	r.t.	24	trace
14[e]	$SnCl_4$	30	CH_2Cl_2	r.t.	24	trace
15	$Ti(iPrO)_4$	30	CH_2Cl_2	r.t.	24	-
16	$Yb(OTf)_3$	30	CH_2Cl_2	r.t.	24	-
17	ZnI_2	30	CH_2Cl_2	r.t.	24	trace
18[f]	$TiCl_4$	30	CH_2Cl_2	r.t.	24	45
19[g]	$AlCl_3$	30	CH_2Cl_2	r.t.	6	53
20[h]	$AlBr_3$	30	CH_2Cl_2	r.t.	3	67
21[h]	$AlBr_3$	10	CH_2Cl_2	r.t.	24	-
22[h]	$AlBr_3$	10	CH_2Cl_2	50	24	trace
23[h]	$AlBr_3$	20	CH_2Cl_2	r.t.	24	19
24[h]	$AlBr_3$	50	CH_2Cl_2	r.t.	3	16
25[h]	$AlBr_3$	30	THF	r.t.	24	trace
26[h]	$AlBr_3$	30	DCE	r.t.	3	61
27[h]	$AlBr_3$	30	toluene	r.t.	3	72

[a] Reaction conditions: **7g** (0.5 mmol), **8c** (2.5 mmol), catalyst, anhyd. solvent (1.0 mL), r.t. (r.t. = 28 °C). [b] Isolated yield for the *endo*-isomer. A 95:5 diastereoselective ratio was determined from the ^{1}H NMR of the crude product. No regioisomer was observed. [c] See ref. (Cong et al., 2010) for catalyst preparation. [d] CuOTf-toluene complex. [e] $SnCl_4$ (1.0 M) in CH_2Cl_2. [f] $TiCl_4$ (1.0 M) in CH_2Cl_2. [g] $AlCl_3$ (1.0 M) in nitrobenzene. [h] $AlBr_3$ (1.0 M) in CH_2Br_2.

The reaction between *trans*-chalcone (**7g**) and (*E*)-ocimene (**8c**) was carried out in the presence of various Lewis acids as catalysts in dichloromethane or toluene at room temperature (entries 2-20, Table 4.1). Most of the Lewis acid catalysts did not show encouraging results. The low reactivity of these catalysts may be the reason. However, three types of Lewis acid catalysts used gave significant yields (entries 18-20, Table 4.1). $AlBr_3$ gave the highest yield among those Lewis acids and the reaction was completed within 3 hours (entry 20, Table 4.1).

The ^{1}H NMR spectra revealed the products of the DA reaction to be the adducts of [(1*RS*,2*SR*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (**80**) and [(1*RS*,2*RS*,6*RS*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl](phenyl)methanone (**80a**) with the ratio 95:5 (Scheme 4.1).



Scheme 4.1: Diels-Alder reaction between *trans*-chalcone (7g) and (*E*)-ocimene (8c) catalysed by Lewis acids.

Both adducts **80** & **80a** have never been reported before. The structure of adduct **80** (Figure 4.1) was established from its spectral data, making use of homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments in combination with ^{1}H and ^{13}C NMR spectroscopic data.

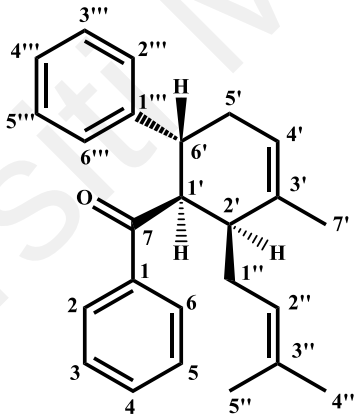


Figure 4.1: The structure of adduct 80.

The ^{1}H NMR spectrum of **80** (Table 4.2) displayed signals due to three aliphatic methines [δ_H 4.08 (H-1′), 2.11-2.18 (H-2′), 3.36 (H-6′)], two allylic methylenes [δ_H 1.97-2.09, 2.34-2.39 (H_2-5′), 1.97-2.09, 2.34-2.39 (H_2-1″)], two olefinic methines [δ_H 4.74 (H-2″), 5.41 (H-4′)], three vinyl methyls [δ_H 1.38 (H_3-4″), 1.38 (H_3-5″), 1.7 (H_3-7′)], two phenyl rings [δ_H 7.32 (H-3, 5), 7.40 (H-4), 7.79 (H-2, 6), 6.99 (H-4‴), 7.09-7.14 (H-2‴, 6‴, H-3‴, 5‴)]. These data were similar to those of the reported compound, panduratin A (**1**), except the signals due to trisubstituted phenyl ring in panduratin A (**1**) was replaced

with the signals of a phenyl ring [δ_H 7.32 (H-3, 5), 7.40 (H-4), 7.79 (H-2, 6)]. On the other hand, the ^{13}C NMR spectrum of **80** (Table 4.2) indicated 25 carbon signals including twelve aromatic carbons (δ_C 125.7, 127.0, 127.9, 128.3, 128.4, 132.5, 137.4, 146.3), three methines (δ_C 36.9, 42.8, 50.3), two methylenes (δ_C 28.7, 35.0), two olefinic methines (δ_C 121.3, 123.7), three methyls (δ_C 17.7, 22.8, 25.6), two olefinic quaternary carbons (δ_C 131.9, 136.5) and one ester carbonyl carbon (δ_C 200.6).

Table 4.2: ^{1}H and ^{13}C NMR data of adduct 80.

Position	^{1}H NMR	^{13}C NMR
1		137.4
2,6	7.79 (d, *J* = 7.8 Hz)	128.4
3,5	7.32 (t, *J* = 7.8 Hz)	128.3
4	7.40 (t, *J* = 7.3 Hz)	132.5
7		200.6
1′	4.08 (dd, *J* = 10.5, 5.0 Hz)	50.3
2′	2.11-2.18 (m)	42.8
3′		136.5
4′	5.41 (br s)	121.3
5′	1.97-2.09 (m), 2.34-2.39 (m)	35.0
6′	3.36 (td, *J* = 10.5, 6.4 Hz)	36.9
7′	1.70 (s)	22.8
1″	1.97-2.09 (m), 2.34-2.39 (m)	28.7
2″	4.74 (t, *J* = 6.9 Hz)	123.7
3″		131.9
4″	1.38 (s)	25.6
5″	1.38 (s)	17.7
1‴		146.3
2‴, 6‴	7.09-7.14 (m)	127.0
3‴, 5‴	7.09-7.14 (m)	127.9
4‴	6.99 (t, *J* = 6.9 Hz)	125.7

In the structure of adduct **80**, the phenone group was placed at C-1′ in the cyclohexene ring as a result of correlations between H-1′ (δ_H 4.08) and C-7 (δ_C 200.6), C-2′ (δ_C 42.8),

C-6′ (δ_C 36.9), and C-1″ (δ_C 28.7) in the HMBC spectrum (Figure 4.2). Similarly, the phenyl group was located at C-6′ in the cyclohexene ring on the basis of the observed HMBC spectrum correlations between H-6′ (δ_H 3.36) and C-1′ (δ_C 50.3), C-5′ (δ_C 35.0), C-2′ (δ_C 42.8), C-1‴ (δ_C 146.3), and C-2‴/6‴ (δ_C 127.0). The multiplicity of proton signal of position 1′ (H-1′) can be used to determine the orientation of prenyl group in the adduct **80** (regioselectivity). The multiplicity of signal due to H-1′ is doublet of doublets (dd) indicated that there is a proton on each side of the position C-1′. This indicated that the prenyl group is next to position C-1′ which is C-2′. HMBC correlation between H-2′ (δ_H 2.11-2.18) and C-1′ (δ_C 50.3), C-3′ (δ_C 136.5), C-7′ (δ_C 22.8), C-1″ (δ_C 28.7), and C-2″ (δ_C 123.7) gave further support for this conclusion and then this adduct **80** can be confirmed as a *meta*-regioisomer.

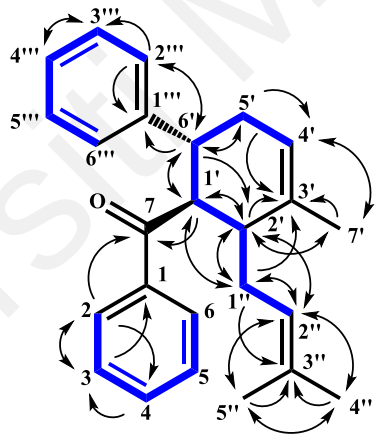


Figure 4.2: Selected COSY (blue & bold) and HMBC (arrows) correlations of adduct 80.

The relative stereochemistry of **80** was determined from the coupling constants of proton signal of position 1′ (H-1′) (Figure 4.3). The small coupling constant (J = 5.0 Hz) and large coupling constant (J = 10.5 Hz) of the signal due to H-1′ indicated that the H-1′ has a *cis* and a *trans* relationships with the adjacent protons (H-2′ & H-6′), respectively. Since *trans*-chalcone (**7g**) was used in this DA reaction, so, the H-1′ and H-6′ must be in a *trans* relationship. Furthermore, the H-1′ is oriented *cis* with the H-2′. So, adduct **80** was indicated as an *endo*-selective DA adduct. In addition, by comparing the multiplicity

and coupling constant of the signal due to H-1′ with those in panduratins A (**1**) (Tuntiwachwuttikul et al., 1984) and N (**1c**) (Nguyen et al., 2017) and nicolaioidesins A (**1b**) and B (**1a**) (Gu et al., 2002) (Table 4.3), the relative regio- and stereochemistries of adduct **80** were found to be similar to those of panduratin A (**1**).

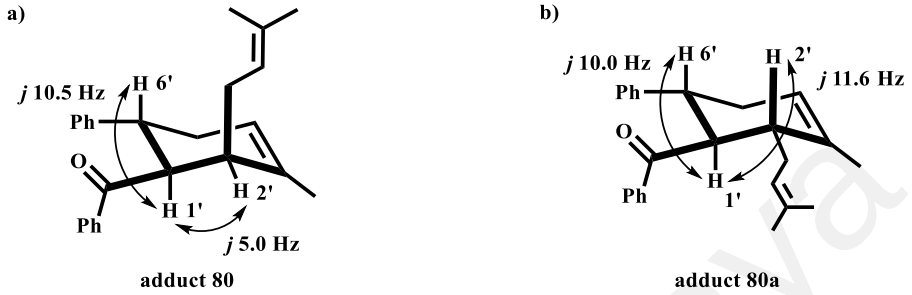
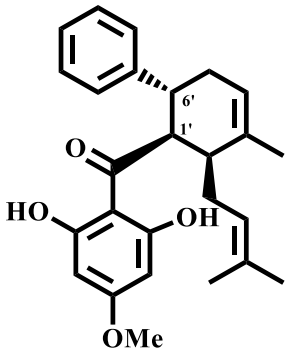
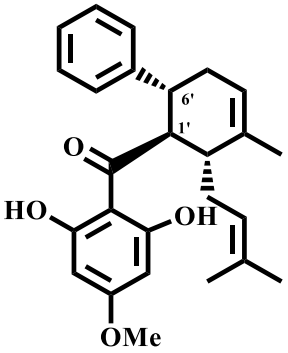


Figure 4.3: The chair conformations of a) adduct 80 and b) adduct 80a.

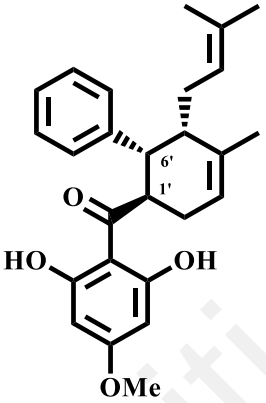
Table 4.3: Comparing the multiplicities and coupling constants of some proton signals in adducts 80 and 80a with those in panduratins A (1) and N (1c) and nicolaioidesins A (1b) and B (1a).



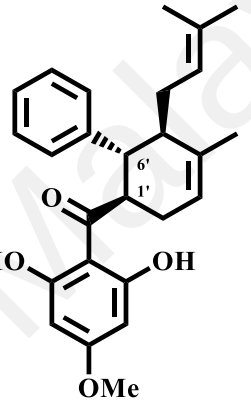
panduratin A (1)



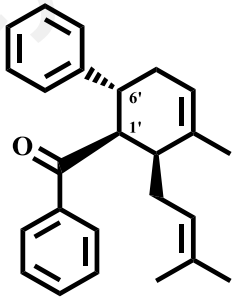
nicolaioidesin A (1b)



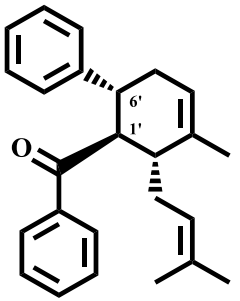
nicolaioidesin B (1a)



panduratin N (1c)



adduct 80



adduct 80a

Position	Panduratin A (1) (Tuntiwachwuttikul et al., 1984)	Nicolaioidesin A (1b) (Gu et al., 2002)	Nicolaioidesin B (1a) (Gu et al., 2002)	Panduratin N (1c) (Nguyen et al., 2017)	Adduct 80	Adduct 80a
H-1′	4.78 (dd, *J* = 11.0, 4.4 Hz)	4.38 (dd, *J* = 11.0, 11.0 Hz)	4.76 (ddd, *J* = 11.0, 11.0, 6.1 Hz)	4.65 (ddd, *J* = 11.3, 11.0, 4.5 Hz)	4.08 (dd, *J* = 10.5, 5.0 Hz)	3.76 (dd, *J* = 11.6, 10.0 Hz)
H-6′	3.45 (ddd, *J* = 11.0, 11.0, 6.3 Hz)	3.07 (ddd, *J* = 11.0, 11.0, 4.7 Hz)	3.57 (dd, *J* = 11.0, 5.1 Hz)	3.14 (dd, *J* = 11.0, 10.9 Hz)	3.36 (td, *J* = 10.5, 6.4 Hz)	3.08 (td, *J* = 11.6, 4.8 Hz)

A pure sample of adduct **80a** was not obtained due to the formation in smaller amounts. Therefore, no clear NMR spectrum was obtained for adduct **80a**. However, some key peaks of the adduct **80a** can still be identified in the ^{1}H NMR spectrum of the crude product. The regions, multiplicities and integrations of the signals due to H-1′ (δ_H 3.76, dd, 1H), H-4′ (δ_H 5.65, br d, 1H) and H-6′ (δ_H 3.08, td, 1H) in adduct **80a** are similar to those of adduct **80**. A significant difference between both adducts **80** & **80a** was observed in the coupling constant of signal of H-1′. Adduct **80a** has two large coupling constants (J = 11.6, 10.0 Hz) in the signal of H-1′ whereas adduct **80** has a small and a large coupling constants (J = 10.5, 5.0 Hz) in the signal of H-1′ (Table 4.3).

Two large coupling constants in the signal of H-1′ indicated that the H-1′ in adduct **80a** has *trans* relationship with the adjacent protons (H-2′ & H-6′) (Figure 4.3). Therefore, adduct **80a** was established to be a stereoisomer of the adduct **80**. Furthermore, the relative regio- and stereochemistries of adduct **80a** can confirmed by comparing the multiplicity and coupling constant of the signal of H-1′ with those observed in panduratins A (**1**) (Tuntiwachwuttikul et al., 1984) and N (**1c**) (Nguyen et al., 2017) and nicolaioidesins A (**1b**) and B (**1a**) (Gu et al., 2002) (Table 4.3). So, adduct **80a** was ascribed as the *meta*- and *exo*-selective DA adduct (Figure 4.4).

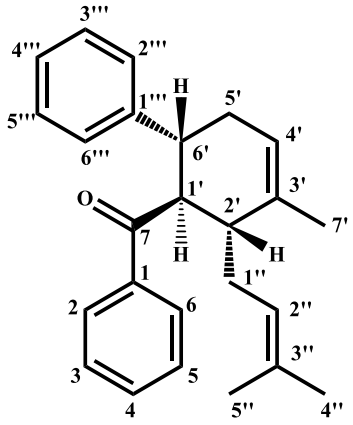


Figure 4.4: The structure of adduct 80a.

Diaxial interactions play a significant role in predicting the stability of compounds. *Trans*-diaxial interactions generally result in lower energy and greater stability compared to *cis*-diaxial interactions. The structure of adduct **80a** should be more stable than that of adduct **80** because adduct **80a** only has *trans*-diaxial interactions.

The amount of catalyst loading also appeared to be important in obtaining the highest yield of **80** (entries 20-24, Table 4.1) from the reaction. A 30 mol% catalyst loading was found to be the best amount of loading for the reaction. Catalyst loadings lower than 30 mol% (10 & 20 mol%) gave low yield with the starting material, *trans*-chalcone (**7g**) remaining in the reaction mixture (entries 21 & 23, Table 4.1). Applying heat to the reaction (entry 22, Table 4.1) or higher amount of catalyst loading used at 50 mol% yield (entry 24, Table 4.1) also did not increase the yield of the product. No starting material of the *trans*-chalcone (**7g**) in the DA reactions was observed after the reaction when 30 mol% and 50 mol% catalyst loadings were employed. Even though both reactions were completed, the DA yield at 50 mol% catalyst loading obtained was much lower than that of 30 mol% catalyst loading. This could be attributed to the polymerisation of product **80** when a higher loading of catalyst was applied. The polymerisation of the C=C bond in adduct 80 can be induced by $AlBr_3$ (Kennedy, 1972).

In the context of solvents used for the reaction (entries 20 & 25-27, Table 4.1), toluene was found to give the highest yield (entry 27, Table 4.1). This may be because the solubility of *trans*-chalcone (**7g**) in toluene was higher than that of other solvents, since *trans*-chalcone (**7g**) can form π-π stacking interactions with toluene. In contrast to toluene, THF (entry 25, Table 4.1) gave the lowest product yield. According to literature (Derouault et al., 1977), when $AlBr_3$ was dissolved in THF, THF acted as a donor ligand to form a pentacoordinated complex, $AlBr_3.2THF$ (Scheme 4.2). No DA product was obtained when THF used as solvent, plausibly due to the full occupancy of the THF to

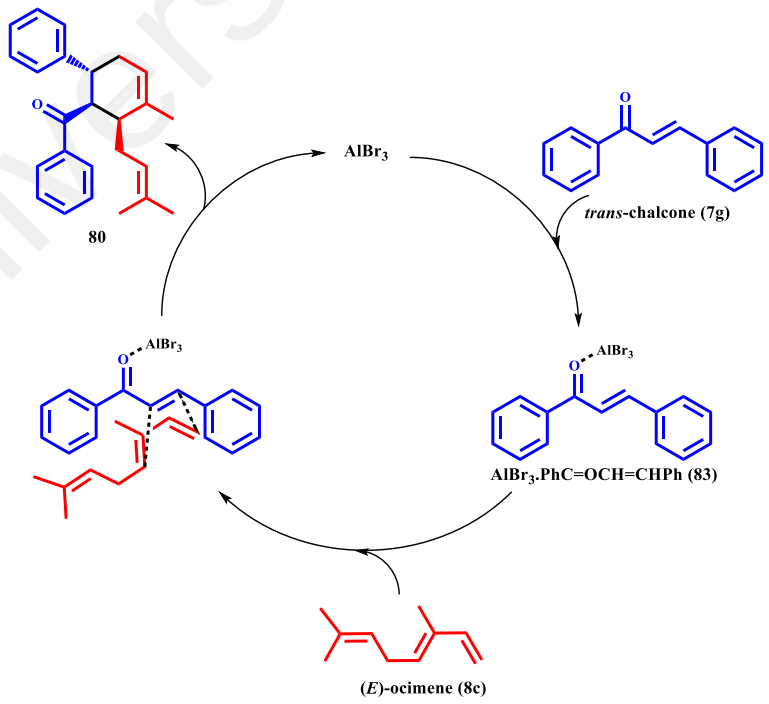
the metal core to form complex $AlBr_3$.2THF leading to poor or no space occupancy and coordination for the *trans*-chalcone (**7g**)**.** Complexation between the Lewis acid and dienophile [*i.e.*, *trans*-chalcone (**7g**)] is vital to lower the LUMO energy of the dienophile for DA reaction to occur at a reasonable reaction rate.

$$Al_2Br_6 + THF \longrightarrow AlBr_3.THF$$

$$AlBr_3.THF + THF \longrightarrow AlBr_3.2THF$$

Scheme 4.2: The complexation of $AlBr_3$ with THF.

Based on the above experimental results, the reaction mechanism of Diels-Alder reaction between *trans*-chalcone (**7g**) and (*E*)-ocimene (**8c**) catalysed by $AlBr_3$ was proposed, as shown in Scheme 4.3. Complexation between $AlBr_3$ and *trans*-chalcone (**7g**) led to the formation complex $AlBr_3$.PhC=OCH=CHPh (**83**) whereby the *trans*-chalcone (**7g**) is activated for reaction with the (*E*)-ocimene (**8c**). After the DA reaction, the adduct **80** dissociated from the $AlBr_3$ in order to make the catalyst available for another cycle.



Scheme 4.3: Proposed mechanism of Diels-Alder reaction between *trans*-chalcone (7g) and (*E*)-ocimene (8c) catalysed by $AlBr_3$.

4.2 Effectiveness of the Selected Lewis Acid Catalyst towards Diels-Alder Reactions between Various Dienophiles 7g, 15, 15c & 15j and Dienes 8 & 8a-c

Using the optimised reaction conditions (entry 27, Table 4.1) (In order to allow the reaction to complete, the reaction time was extended from 3 h to 6 h), several reactions were carried out with a variety of dienophiles **7g**, **15**, **15c & 15j** and dienes **8 & 8a-c**. In this study, *trans*-chalcone (**7g**) was reacted with 3 different types of acyclic diene **8**, **8a & 8b**. In addition, 3 different types of cinnamoyl dienophiles **15**, **15c & 15j** were reacted with (*E*)-ocimene (**8c**). The results of these reactions are shown in Table 4.4.

Table 4.4: Diels-Alder reactions of various dienophiles 7g, 15, 15c & 15j and dienes 8 & 8a-c[a].

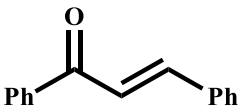
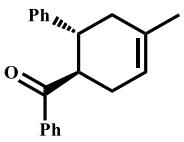
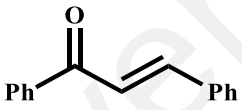
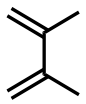
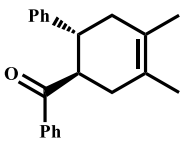
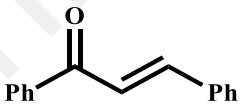
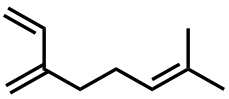
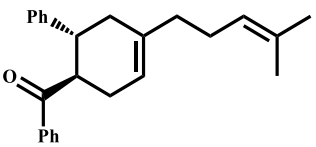
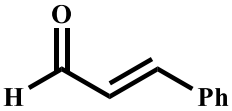
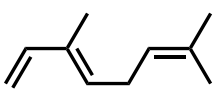
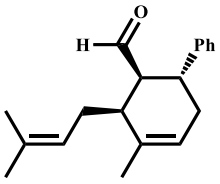
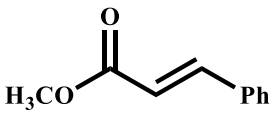
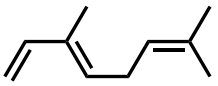
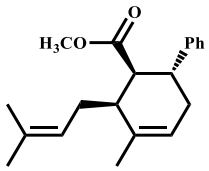
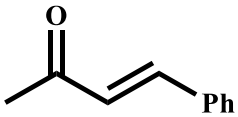
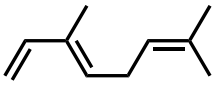
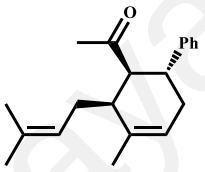
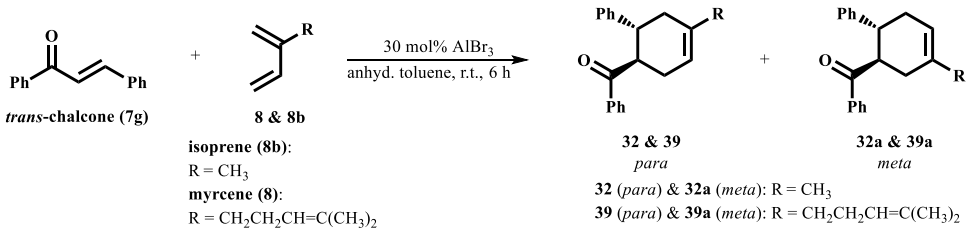
Entry	Dienophile	Diene	Product	Yield (%)[b]
1	 **7g**	 **8b**	 **32**	73[c,d]
2	 **7g**	 **8a**	 **47**	82
3	 **7g**	 **8**	 **39**	80[c,d]
4	 **15c**	 **8c**	 **18**	-

Table 4.4, continued. Diels-Alder reactions of various dienophiles 7g, 15, 15c & 15j and dienes 8 & 8a-c[a].

Entry	Dienophile	Diene	Product	Yield (%)[b]
5	 **15**	 **8c**	 **3**	-
6	 **15j**	 **8c**	 **84**	-

[a] Reaction conditions: **7g**, **15**, **15c** & **15j** (0.5 mmol), **8** & **8a-c** (2.5 mmol), $AlBr_3$ (1.0 M) in CH_2Br_2 (30 mol%), anhyd. toluene (1.0 mL), r.t., 6 h. [b] Isolated yield. [c] A 90:10 *para*:*meta* regioisomeric ratio was determined from the ^1H NMR of crude product. [d] Isolated yield for the *para*-regioisomer.

All three acyclic dienes [isoprene (**8b**), 2,3-dimethylbutadiene (**8a**) & myrcene (**8**)] reacted with *trans*-chalcone (**7g**) under the optimised reaction conditions to give the corresponding DA adducts in relatively good yields (73-82%) (entries 1-3, Table 4.4). For the unsymmetrical dienes, isoprene (**8b**) and myrcene (**8**) (entries 1 & 3, Table 4.4), two DA adducts **32**/**39** & **32a**/**39a** were formed in a ratio of 90:10 (Scheme 4.4). The ^1H NMR spectra of two adducts **32**/**39** & **32a**/**39a** compared with the reported compounds in the literature (Corbett & Weavers, 2008), indicated the adducts **32**/**39** & **32a**/**39a** to be regioisomers with the *para*-regioisomer **32**/**39** being the main observed product.



Scheme 4.4: Diels-Alder reactions of *trans*-chalcone (7g) with isoprene (8b) and myrcene (8).

In subsequent attempts, three other types of cinnamoyl dienophiles [*trans*-cinnamaldehyde (**15c**), methyl *trans*-cinnamate (**15**) and *trans*-4-phenylbut-3-en-2-one (**15j**)] were used in place of the *trans*-chalcone (**7g**) in the DA reaction (entries 4-6, Table 4.4). Unfortunately, even under the optimised conditions, none of the desired DA adducts **3**, **18** & **84** were obtained from these dienophiles **15**, **15c** & **15j**. This may be due to the lower reactivity of the dienophiles **15**, **15c** & **15j** compared to *trans*-chalcone (**7g**). The substituent on C=C bond in *trans*-chalcone (**7g**), PhC=O is a stronger electron-withdrawing group than that in dienophiles **15**, **15c** & **15j** (HC=O, CH_3OC=O & CH_3C=O). The stronger electron-withdrawing ability, the lower the LUMO energy of dienophile, making the DA reaction easier to occur. This hypothesis can be supported by the DFT calculations, as shown in Table 4.5. The LUMO energy of *trans*-chalcone (**7g**) and $AlBr_3$-*trans*-chalcone (**7g**) complex is lower than that of other dienophiles **15**, **15c** & **15j** and $AlBr_3$-dienophile complexes, indicating that *trans*-chalcone (**7g**) is more reactive than other dienophiles **15**, **15c** & **15j**.

Table 4.5: LUMO energy of various dienophiles and $AlBr_3$-dienophile complexes.

Dienophile	LUMO energy (eV)	LUMO energy (eV) ($AlBr_3$-dienophile complex)
trans-chalcone (**7g**)	5.833	-2.909
trans-cinnamaldehyde (**15c**)	5.987	3.607
methyl *trans*-cinnamate (**15**)	6.256	4.268
trans-4-phenylbut-3-en-2-one (**15j**)	6.501	3.784

4.3 Development of a Method for Enantioselective Diels-Alder Reaction of Cinnamoyl Dienophile and Terpene Diene

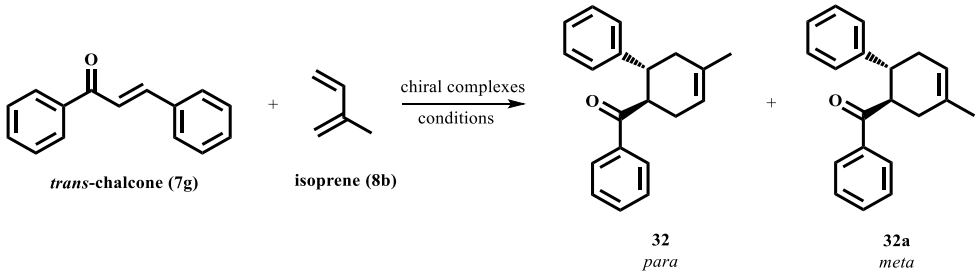
A model study on the enantioselectivity of the DA cycloaddition reaction was carried out using *trans*-chalcone (**7g**) and isoprene (**8b**) as reactants. Isoprene (**8b**) was used in this study since it does not form the *exo*/*endo* adducts in the DA reaction compared with

(*E*)-ocimene (**8c**). This is to simplify the isolation step. In this study, a variety of chiral complexes were synthesised and used to study enantioselectivity. The chiral complexes in this study were generated in situ using chiral ligand with Lewis acid and directly applied to the DA reaction without any characterisation. This is due to the formed chiral Lewis acid complex which are moisture sensitive. The chiral ligands can be recovered during the DA product isolation step. Eighteen commercially available ligands **L1-6** & **L10-21** and seven synthetic chiral ligands **L7-9** & **L22-25** were selected for this study (Figure 4.5). The chiral ligands used in this study can be divided into conventional chiral ligands such as *R*-BINOL (**L1**), (-)-TADDOL (**L2**), (-)-SALEN (**L3**) and (-)-BOX (**L4**) which are commonly used in the asymmetrical Diels-Alder reaction and new type chiral ligands such as α-amino acids **L5**, **L6** & **L12-21** which are never used in the asymmetrical Diels-Alder reaction. Most α-amino acids have chirality and can form a stable coordination complex with Lewis acids (Redshaw et al., 2005; Bína et al., 2005). Therefore, they have potential in the study of asymmetrical Diels-Alder reactions.

In this study, the DA reaction between *trans*-chalcone (**7g**) and isoprene (**8b**) produced two products, *para*- **32** and *meta*-regioisomers **32a** of which *para*-regioisomer **32** is the major product (Scheme 4.5). The enantiomeric *excess* (*ee*) value of adduct **32** was determined by chiral HPLC analysis on a Chiralcel IC column, eluting with *n*-hexane/isopropanol (98%/2%) at a flow rate of 0.5 mL min^{-1} and calculated according to the following equation:

$$ee\ (\%) = \frac{[\text{area of curve of enantiomer A}]-[\text{area of curve of enantiomer B}]}{[\text{area of curve of enantiomer A}]+[\text{area of curve of enantiomer B}]} \times 100\% \qquad (4.1)$$

Through the optical rotation measurement, enantiomer A was identified as the (+)-enantiomer while enantiomer B was the (-)-enantiomer. The results of this study are displayed in Table 4.6.



trans-chalcone (7g) isoprene (8b) **32** *para* **32a** *meta*

Scheme 4.5: Diels-Alder reaction between *trans*-chalcone (7g) and isoprene (8b) catalysed by chiral complexes.

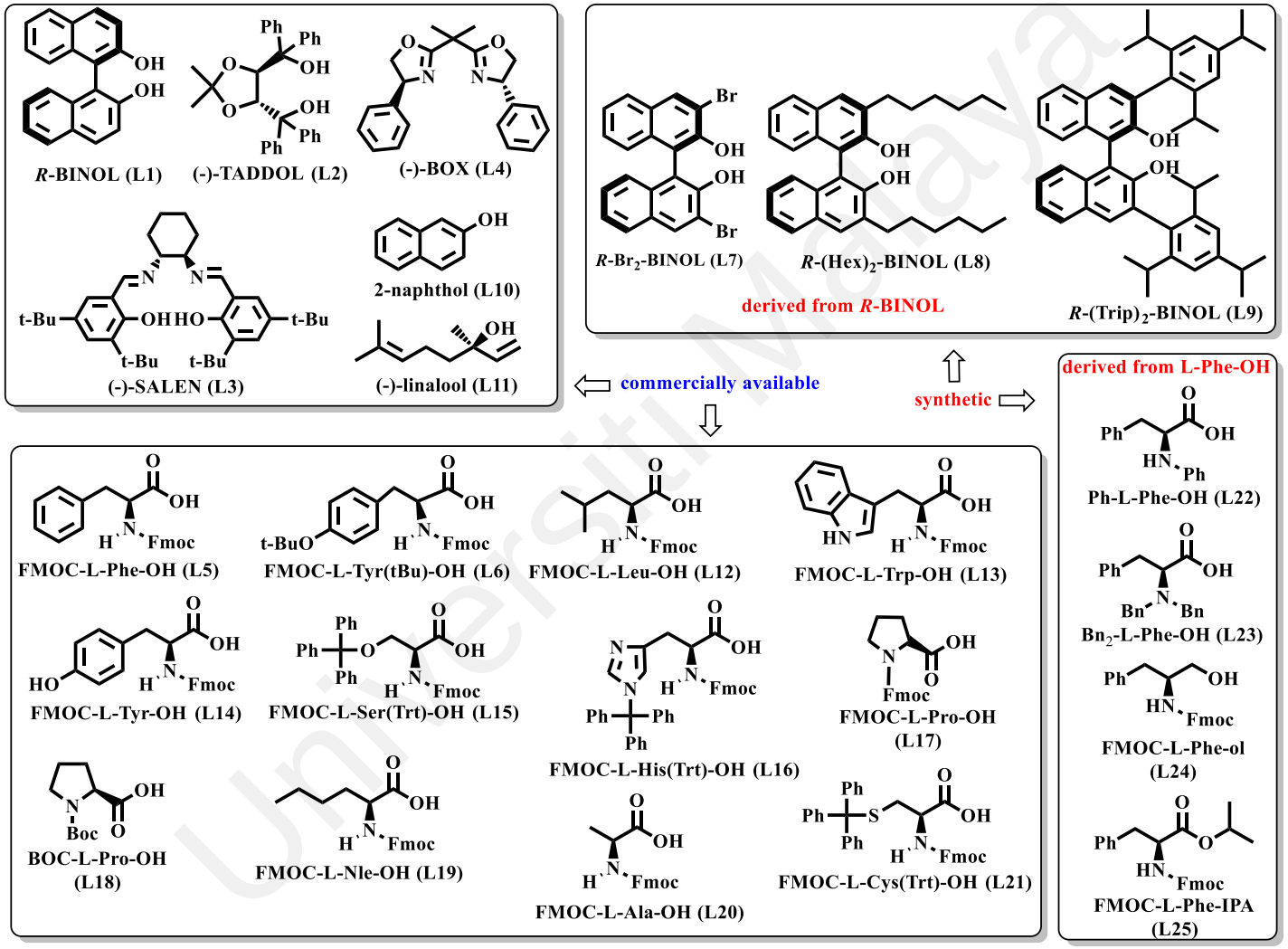
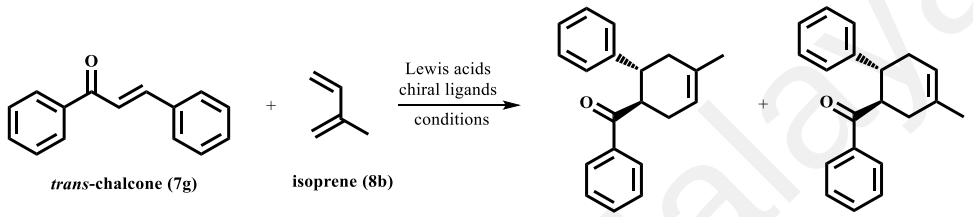


Figure 4.5: Ligands (L1-25) used in this study.

Table 4.6: Screening of chiral complexes.



Entry	Lewis acid (LA)	Ligand	Ratio (LA: Ligand)	Base	LA loading (equiv)	Solvent	Solvent amount (mL)	Temp.	Time (h)	Yield (32+32a) (%)[e]	32 (%)[f]	32a (%)[f]	ee (%)[g]
1[a,h]	$AlBr_3$	-	-	-	0.3	toluene	1	r.t.	6	73	90	10	-
2[b,i]	Me_3Al	*R*-BINOL (**L1**)	1:1	-	1	toluene	2	r.t.	50	trace	-	-	-
3[b,h]	Et_2AlCl	-	-	-	1	CH_2Cl_2	2	r.t.	24	39	93	7	-
4[b,i]	Et_2AlCl	*R*-BINOL (**L1**)	0.5:1	-	0.5	CH_2Cl_2	2	r.t.	24	8	96	4	1
5[b,i]	Et_2AlCl	*R*-BINOL (**L1**)	1:1	-	1	CH_2Cl_2	1.5	r.t.	24	41	95	5	0
6[b,i]	Et_2AlCl	*R*-BINOL (**L1**)	1:1	-	1	CH_2Cl_2	2	r.t.	24	42	96	4	0
7[b,i]	Et_2AlCl	*R*-BINOL (**L1**)	1:1	-	1	toluene	2	r.t.	72	49	88	12	3
8[b,i]	Et_2AlCl	*R*-BINOL (**L1**)	1.5:1	-	1.5	CH_2Cl_2	2	r.t.	6	84	97	3	-4
9[b,i]	Et_2AlCl	*R*-BINOL (**L1**)	2:1	-	2	CH_2Cl_2	2	r.t.	3.5	74	94	6	-6
10[b,i]	Et_2AlCl	(-)-TADDOL (**L2**)	1:1	-	1	CH_2Cl_2	2	r.t.	3	87	93	7	-4
11[b,i]	Et_2AlCl	(-)-SALEN (**L3**)	1:1	-	1	CH_2Cl_2	2	r.t.	24	-	-	-	-
12[b,i]	Et_2AlCl	(-)-BOX (**L4**)	1:1	-	1	CH_2Cl_2	2	r.t.	24	-	-	-	-
13[b,i]	Et_2AlCl	FMOC-L-Phe-OH (**L5**)	1:1	-	1	CH_2Cl_2	2	r.t.	24	7	94	6	1
14[b,i]	Et_2AlCl	FMOC-L-Phe-OH (**L5**)	1:2	-	1	CH_2Cl_2	2	r.t.	24	20	93	7	4
15[b,j]	Et_2AlCl	*R*-BINOL (**L1**) + FMOC-L-Tyr(tBu)-OH (**L6**)	1:1:1	-	1	CH_2Cl_2	3	r.t.	24	31	94	6	0
16[c,h]	$TiCl_4$	-	-	-	1	toluene	1.6	r.t.	6	36	96	4	-
17[c,i]	$TiCl_4$	*R*-BINOL (**L1**)	1:1	-	1	toluene	1.6	r.t.	4	73	96	4	1
18[c.i.k]	$TiCl_4$	*R*-BINOL (**L1**)	1:1	-	1	toluene	1.6	r.t.	4	100	96	4	2

Table 4.6, continued. Screening of chiral complexes.

Entry	Lewis acid (LA)	Ligand	Ratio (LA: Ligand)	Base	LA loading (equiv)	Solvent	Solvent amount (mL)	Temp.	Time (h)	Yield (32+32a) (%)[e]	32 (%)[f]	32a (%)[f]	ee (%)[g]
19[c,i,k]	$TiCl_4$	*R*-BINOL (**L1**)	1:2	-	1	toluene	1.6	r.t.	24	100	95	5	13
20[c,k,l]	$TiCl_4$	*R*-BINOL (**L1**)	1:1	*n*-BuLi	1	toluene	1.6	r.t.	24	75	95	5	20
21[c,k,l]	$TiCl_4$	*R*-BINOL (**L1**)	1:1.25	*n*-BuLi	1	toluene	1.6	r.t.	24	67	95	5	14
22[c,k,l]	$TiCl_4$	*R*-BINOL (**L1**)	1:1.5	*n*-BuLi	1	toluene	1.6	r.t.	24	69	97	3	12
23[c,k,l]	$TiCl_4$	*R*-BINOL (**L1**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	9	96	4	-4
24[d,k,l]	$TiCl_4$	*R*-Br_2-BINOL (**L7**)	1:1	*n*-BuLi	1	toluene	0.8	r.t.	24	31	97	3	10
25[d,k,l]	$TiCl_4$	*R*-Br_2-BINOL (**L7**)	1:1.5	*n*-BuLi	1	toluene	0.8	r.t.	24	20	96	4	4
26[d,k,l]	$TiCl_4$	*R*-$(Hex)_2$-BINOL (**L8**)	1:1	*n*-BuLi	1	toluene	0.8	r.t.	24	66	86	14	-3
27[d,k,l]	$TiCl_4$	*R*-$(Hex)_2$-BINOL (**L8**)	1:1.5	*n*-BuLi	1	toluene	0.8	r.t.	24	14	93	7	4
28[d,k,l]	$TiCl_4$	*R*-$(Trip)_2$-BINOL (**L9**)	1:1	*n*-BuLi	1	toluene	0.8	r.t.	24	45	98	2	-2
29[d,k,l]	$TiCl_4$	*R*-$(Trip)_2$-BINOL (**L9**)	1:1.5	*n*-BuLi	1	toluene	0.8	r.t.	24	19	95	5	-8
30[d,i,k]	$TiCl_4$	*R*-BINOL (**L1**), *R*-$(Trip)_2$-BINOL (**L9**)	1:1:1	-	1	toluene	0.8	r.t.	24	53	97	3	9
31[c,k,l]	$TiCl_4$	*R*-BINOL (**L1**), 2-naphthol (**L10**)	1:1:1	*n*-BuLi	1	toluene	1.6	r.t.	24	43	93	7	3
32[c,l]	$TiCl_4$	(-)-TADDOL (**L2**)	1:1	*n*-BuLi	1	toluene	1.6	r.t.	24	17	93	7	-2
33[c,l]	$TiCl_4$	(-)-linalool (**L11**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	36	95	5	1
34[c,l]	$TiCl_4$	(-)-linalool (**L11**)	1:3	*n*-BuLi	1	toluene	1.6	r.t.	24	-	-	-	-
35[c,i]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:1	-	1	toluene	1.6	r.t.	1	73	95	5	1
36[c,i]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	-	1	toluene	1.6	r.t.	3	70	97	3	-1
37[c,i]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:3	-	1	toluene	1.6	r.t.	1	69	95	5	-1
38[c,h]	$TiCl_2(iPrO)_2$	-	-	-	1	toluene	1.6	r.t.	48	14	93	7	-
39[c,i]	$TiCl_2(iPrO)_2$	FMOC-L-Phe-OH (**L5**)	1:2	-	1	toluene	1.6	r.t.	48	-	-	-	-
40[c,l]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:1	*n*-BuLi	1	toluene	1.6	r.t.	1	89	96	4	-1
41[c,l]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	30	95	5	9
42[c,l]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:3	*n*-BuLi	1	toluene	1.6	r.t.	24	-	-	-	-
43[c,l]	$TiCl_4$	FMOC-L-Leu-OH (**L12**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	11	93	7	1

Table 4.6, continued. Screening of chiral complexes.

Entry	Lewis acid (LA)	Ligand	Ratio (LA: Ligand)	Base	LA loading (equiv)	Solvent	Solvent amount (mL)	Temp.	Time (h)	Yield (32+32a) (%)[e]	32 (%)[f]	32a (%)[f]	ee (%)[g]
44[c,l]	$TiCl_4$	FMOC-L-Trp-OH (**L13**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	14	96	4	1
45[c,l]	$TiCl_4$	FMOC-L-Tyr-OH (**L14**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	20	96	4	0
46[c,l]	$TiCl_4$	FMOC-L-Tyr(tBu)-OH (**L6**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	11	94	6	1
47[c,l]	$TiCl_4$	FMOC-L-Ser(Trt)-OH (**L15**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	8	96	4	-4
48[c,l]	$TiCl_4$	FMOC-L-His(Trt)-OH (**L16**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	21	96	4	0
49[c,l]	$TiCl_4$	FMOC-L-Pro-OH (**L17**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	-	-	-	-
50[c,l]	$TiCl_4$	BOC-L-Pro-OH (**L18**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	24	-	-	-	-
51[c,l]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	Et_3N	2	toluene	1.6	r.t.	48	1	100	0	0
52[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:1	$NaHCO_3$	1	toluene	1.6	r.t.	24	100	94	6	0
53[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	24	21	95	5	61
54[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1.5	toluene	1.6	r.t.	24	6	94	6	26
55[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	2	toluene	1.6	r.t.	24	6	94	6	26
56[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:1.5	$NaHCO_3$	1	toluene	1.6	r.t.	24	5	95	5	49
57[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:1.5	$NaHCO_3$	2	toluene	1.6	r.t.	24	2	100	0	-37
58[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:1.6	$NaHCO_3$	1.25	toluene	1.6	r.t.	24	1	96	4	12
59[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	CH_2Cl_2	2.4	r.t.	24	-	-	-	-
60[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	THF	1.6	r.t.	24	-	-	-	-
61[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	toluene	2.4	r.t.	24	trace	-	-	-
62[c,m]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	toluene	1.6	75	24	trace	-	-	-
63[c,m,n]	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	24	8	86	14	4
64[c,m]	$TiCl_4$	FMOC-L-Trp-OH (**L13**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	24	3	92	8	-4
65[c,m]	$TiCl_4$	FMOC-L-Nle-OH (**L19**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	48	-	-	-	-
66[c,m]	$TiCl_4$	FMOC-L-Ala-OH (**L20**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	48	1	99	1	-1

Table 4.6, continued. Screening of chiral complexes.

Entry	Lewis acid (LA)	Ligand	Ratio (LA: Ligand)	Base	LA loading (equiv)	Solvent	Solvent amount (mL)	Temp.	Time (h)	Yield (32+32a) (%)[e]	32 (%)[f]	32a (%)[f]	ee (%)[g]
67[c,m]	$TiCl_4$	FMOC-L-Tyr(tBu)-OH (**L6**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	24	33	91	9	1
68[c,m]	$TiCl_4$	FMOC-L-Cys(Trt)-OH (**L21**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	24	66	95	5	1
69[c,m]	$TiCl_2(iPrO)_2$	FMOC-L-Phe-OH (**L5**)	1:1	$NaHCO_3$	1	toluene	1.6	r.t.	72	-	-	-	-
70[c,l]	$TiCl_4$	Ph-L-Phe-OH (**L22**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	48	trace	-	-	-
71[c,l]	$TiCl_4$	Bn_2-L-Phe-OH (**L23**)	1:2	*n*-BuLi	1	toluene	1.6	r.t.	48	7	96	4	0
72[c,m]	$TiCl_4$	Bn_2-L-Phe-OH (**L23**)	1:2	NaOH	1	toluene	1.6	r.t.	24	-	-	-	-
73[c,m]	$TiCl_4$	Bn_2-L-Phe-OH (**L23**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	48	11	93	7	1
74[c,i,k]	$TiCl_4$	FMOC-L-Phe-ol (**L24**)	1:1	-	1	toluene	1.6	r.t.	24	75	95	5	0
75[c,i,o]	$TiCl_4$	FMOC-L-Phe-ol (**L24**)	1:2	-	1	toluene	1.6	r.t.	72	5	89	11	-7
76[c,i,k]	$TiCl_4$	FMOC-L-Phe-ol (**L24**)	1:2	-	1	toluene	1.6	r.t.	48	4	91	9	0
77[c,i,k]	$TiCl_4$	FMOC-L-Phe-ol (**L24**)	1:2	-	1.5	toluene	1.6	r.t.	48	3	91	9	-1
78[c,i,k]	$TiCl_4$	FMOC-L-Phe-IPA (**L25**)	1:1	-	1	toluene	1.6	r.t.	3	82	95	5	0
79[c,i,k]	$TiCl_4$	FMOC-L-Phe-IPA (**L25**)	1:2	-	1	toluene	1.6	r.t.	18	73	93	7	-3
80[c,i,p]	$TiCl_4$	FMOC-L-Phe-IPA (**L25**)	1:2	-	1	toluene	1.6	r.t.	24	86	93	7	0
81[c,i,k]	$TiCl_4$	*R*-BINOL (**L1**), FMOC-L-Phe-OH (**L5**)	1:1:1	-	1	toluene	1.6	r.t.	24	70	95	5	2
82[c,k,m]	$TiCl_4$	*R*-BINOL (**L1**), FMOC-L-Phe-OH (**L5**)	1:1:1	$NaHCO_3$	1	toluene	1.6	r.t.	72	18	91	9	9
83[c,i,k]	$TiCl_4$	*R*-BINOL (**L1**), FMOC-L-Phe-ol (**L24**)	1:1:1	-	1	toluene	1.6	r.t.	72	53	92	8	12

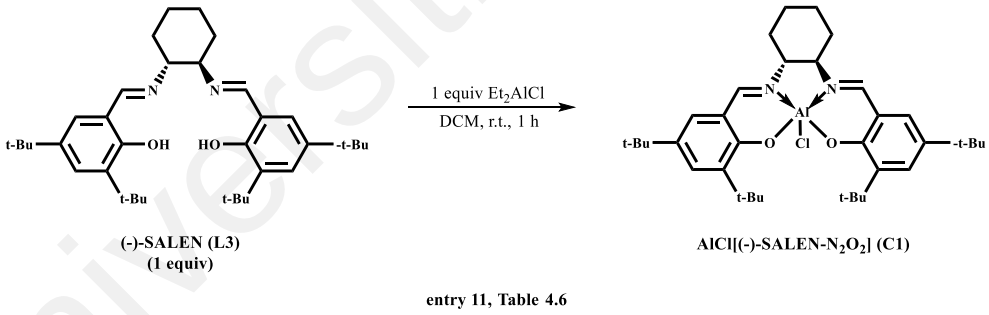
[a] Reaction conditions: **7g** (0.5 mmol), **8b** (2.5 mmol), anhyd. solvent. [b] Reaction conditions: **7g** (0.25 mmol), **8b** (1.25 mmol), anhyd. solvent. [c] Reaction conditions: **7g** (0.20 mmol), **8b** (1.0 mmol), anhyd. solvent. [d] Reaction conditions: **7g** (0.1 mmol), **8b** (0.5 mmol), anhyd. solvent. [e] Isolated yield for mixture of **32** and **32a**. [f] Determined from the ^{1}H NMR of crude product. [g] ee value for **32**. [h] **Method 1**: Lewis acid, *trans*-chalcone (**7g**), toluene or CH_2Cl_2, r.t., 0.5 h; isoprene (**8b**). [i] **Method 2:** Ligand, Lewis acid, toluene or CH_2Cl_2, r.t., 1 h; *trans*-chalcone (**7g**), toluene or CH_2Cl_2, r.t., 0.5 h; isoprene (**8b**). [j] **Method 3**: *R*-BINOL (**L1**), Et_2AlCl, CH_2Cl_2, r.t., 1 h; FMOC-L-Tyr(tBu)-OH (**L6**), r.t., 1 h; *trans*-chalcone (**7g**), CH_2Cl_2, r.t., 0.5 h; isoprene (**8b**). [k] The complexation conditions of Lewis acid with chiral ligand or deprotonated chiral ligand changed from 1 h at r.t. to 3 h at 80 °C. [l] **Method 4**: Ligand, *n*-BuLi/Et_3N, toluene, r.t., 0.5 h; $TiCl_4$, r.t., 1 h; *trans*-chalcone (**7g**), toluene, r.t., 0.5 h; isoprene (**8b**). [m] **Method 5**: Sodium salt of ligand, $TiCl_4$, solvent, r.t., 2 h; *trans*-chalcone (**7g**), solvent, r.t., 0.5 h; isoprene (**8b**). [n] The complexation reaction time of Lewis acid with sodium salt of chiral ligand changed from 2 h to 0.5 h. [o] The complexation reaction time of Lewis acid with chiral ligand changed from 1 h to 4 h. [p] The complexation condition of Lewis acid with chiral ligand changed from 1 h at r.t. to 17 h at 80 °C.

From entry 27, Table 4.1, $AlBr_3$ was identified as the best Lewis acid to catalyse the DA cycloaddition reaction to afford significant product yield. Subsequently, the enantioselective reaction study was carried out with an aluminium-based chiral ligand complex. In this study, $AlBr_3$ was replaced with organoaluminium such as Me_3Al or Et_2AlCl as the Lewis acid since it is easier for these Lewis acids to form complexes with organic ligands (Lebedev et al., 2019; Bigi et al., 1985; Ternel et al., 2013). The chiral ligands (**L1-25**) used in this study can be divided into four groups, namely OH group, COOH group, NH group and N-donor group.

Complexations of the OH group ligands to the aluminium-based Lewis acids were conducted. Initially, *R*-BINOL (**L1**) was complexed with Me_3Al and used as the chiral complex in this reaction study. However, this chiral complex showed disappointing results with only trace product observed (entry 2, Table 4.6). Fortunately, complexing Et_2AlCl with *R*-BINOL (**L1**) in place of Me_3Al, gave a moderate DA adduct of about 49% yield (entry 7, Table 4.6). Although this complex produced significant DA yield, a similar result was not given for the ee value of DA product.

Based on the above finding (entry 7, Table 4.6), in all subsequent reactions, Et_2AlCl was used as the Lewis acid source. It is found that varying the amount and type of solvent used resulted in no effect or improvement to the yield or ee value of the DA product (entries 5 & 6, Table 4.6). Different ratios of Et_2AlCl to *R*-BINOL (**L1**) were used, ranging from 0.5:1 to 2:1 to determine whether these variations will result in any effect on the enantioselectivity of the reactions (entries 4, 6, 8 & 9, Table 4.6). However, none of the combinations used showed any significant changes to the ee value of the DA product. Only when 1.5:1 and 2:1 ratios of Et_2AlCl to *R*-BINOL (**L1**) used showed very small (negligible) ee value at -4% and -6%, respectively (entries 8 & 9, Table 4.6).

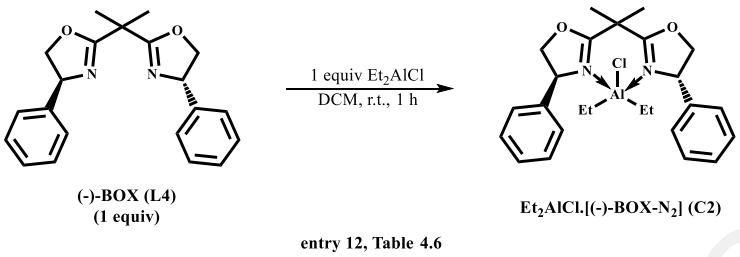
Since the use of *R*-BINOL (**L1**) did not give good enantioselectivity when complexed with Et_2AlCl, another chiral ligand, (-)-TADDOL (**L2**) was used instead. (-)-TADDOL (**L2**)-mediated reaction gave a good DA yield but poor ee value (entry 10, Table 4.6). In subsequent attempt, another type of chiral ligand, (-)-SALEN (**L3**) (N_2O_2 donor) was reacted with Et_2AlCl to form a chiral aluminium complex and applied to DA reaction. By referring to a literature (Madhavan & Weck, 2008), the scheme for the complexation of Et_2AlCl with (-)-SALEN (**L3**) is proposed in Scheme 4.6. The pentacoordinated chiral aluminium complex, AlCl[(-)-SALEN-N_2O_2] (**C1**) resulted in 0% DA yield (entry 11, Table 4.6). This may be due to the full occupancy of the chiral ligand **L3** to the metal core to form complex **C1** leading to poor or no space occupancy and coordination for the *trans*-chalcone (**7g**). The failure to coordinate the *trans*-chalcone (**7g**) to the chiral complex **C1** resulted in the LUMO energy of *trans*-chalcone (**7g**) not being lowered which could help in promoting the DA reaction.



Scheme 4.6: Proposed scheme for the complexation of Et_2AlCl with 1 equivalent of (-)-SALEN (L3) (entry 11, Table 4.6).

The N donor chiral ligand, (-)-BOX (**L4**) used to form chiral aluminium complex with Et_2AlCl. By reference to literature (Nishimoto et al., 2019), the scheme for the complexation of Et_2AlCl with (-)-BOX (**L4**) is proposed in Scheme 4.7. The formed chiral aluminium complex, Et_2AlCl.[(-)-BOX-N_2] (**C2**) gave 0% of DA product yield (entry 12, Table 4.6). This may be due to the complete occupancy of the chiral ligand **L4** to the Al core to form complex **C2,** resulting poor or no space occupancy and coordination for the

trans-chalcone (**7g**). The complexation between the complex **C2** and *trans*-chalcone (**7g**) is crucial to lower the LUMO energy of the dienophile [*trans*-chalcone (**7g**)] for DA reaction to occur at a reasonable reaction rate.



Scheme 4.7: Proposed scheme for the complexation of Et_2AlCl with 1 equivalent of (-)-BOX (L4) (entry 12, Table 4.6).

Attempts on using COOH-type chiral ligand, FMOC-L-amino acid as chiral ligand to induce selectivity in the DA reaction were also carried out. The FMOC-L-amino acid, FMOC-L-Phe-OH (**L5**) was used as a potential chiral ligand and reacted with Et_2AlCl in a 1:1 and a 2:1 ratio. These complexes were then used in the DA reaction. However, both the complexes gave low yields and poor enantioselectivity in the DA product (entries 13 & 14, Table 4.6).

Since the attempts of using a single type of chiral ligand to enhance the ee value were unsuccessful, the attempt to use a combination of two different types of chiral ligands complex in the reaction was applied. Two different chiral ligands, *R*-BINOL (**L1**) and FMOC-L-Tyr(tBu)-OH (**L6)** were reacted with Et_2AlCl and applied to the DA reaction. Although the formed complex produced DA adduct in about 31% yield, it did not provide any significant ee value for the DA product (entry 15, Table 4.6).

Since attempts with aluminium-based complexes failed to show good enantioselectivity, attempts to make titanium-based Lewis acid complexes with different chiral ligands were conducted and applied in the DA reaction. First, the chiral ligands with OH group were tried to use in this study. According to literature (Suttil et al., 2012;

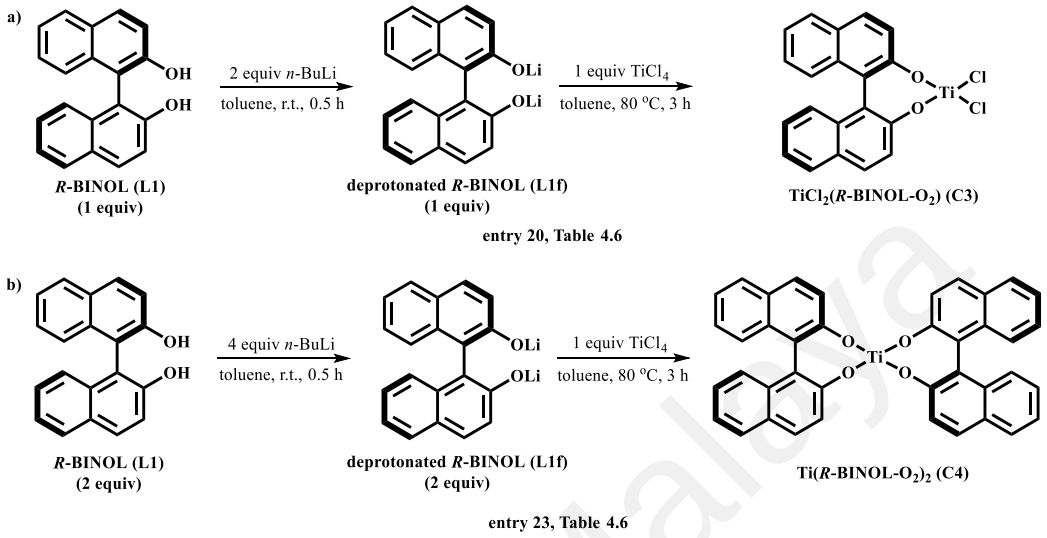
Han et al., 2012; Blackmore, 2008), the ligands with OH group can be directly or indirectly (OH group is first deprotonated by a base) complexed with titanium chloride to form titanium alkoxides.

The chiral ligand with OH group, *R*-BINOL (**L1**) was reacted with $TiCl_4$ at r.t for 1 hour to form a complex which was then used in the DA reaction. Although the DA reaction resulted in high yield, the enantioselectivity observed was poor (entry 17, Table 4.6), possible due to the non-forming chiral titanium complex or the inability of the formed chiral titanium complex to induce enantioselectivity to the DA product**.**

In the subsequent attempt, heating was applied. However, the result remained the same (entry 18, Table 4.6). Fortunately, when the amount of *R*-BINOL (**L1**) used was increased to 2 equivalents, the DA reaction began to exhibit a some enantioselectivity at about 13% ee (entry 19, Table 4.6). Based on the above results (entries 17-19, Table 4.6), the chiral complexes formed by the reaction of *R*-BINOL with $TiCl_4$ were observed to not yield a significant ee value for the DA product. The lack of formation of chiral titanium complexes by *R*-BINOL with $TiCl_4$ may be one of the reasons.

To accelerate the formation of chiral titanium complexes, the chiral ligands were deprotonated before reacting with $TiCl_4$. In subsequent attempts, *R*-BINOL (**L1**) was first deprotonated by reaction with *n*-BuLi at r,t, for 0.5 h and then reacted with $TiCl_4$ at 80 ^oC for 3 h to form the chiral titanium complex. Different ratios between $TiCl_4$ and deprotonated *R*-BINOL (**L1f**) ranging from 1:1 to 1:2 were used and their effects on the DA product yield and enantioselectivity were observed (entries 20-23, Table 4.6). The complex formed from 1 equivalent deprotonated *R*-BINOL (**L1f**) with $TiCl_4$ gave DA product yield at 75% (entry 20, Table 4.6) while 9% DA product yield for the complex formed from 2 equivalent deprotonated *R*-BINOL (**L1f**) with $TiCl_4$ (entry 23, Table 4.6). The large difference DA product yields for the two complexes indicated two different

structures of chiral titanium complexes were formed. By reference to literature (Kanazawa et al., 2016), the schemes for the complexation of $TiCl_4$ with 1 or 2 equivalents deprotonated *R*-BINOL (**L1f**) are proposed in Scheme 4.8.



Scheme 4.8: Proposed schemes for the complexation of $TiCl_4$ with a) 1 equivalent of deprotonated *R*-BINOL (L1f) (entry 20, Table 4.6) and b) 2 equivalents of deprotonated *R*-BINOL (L1f) (entry 23, Table 4.6).

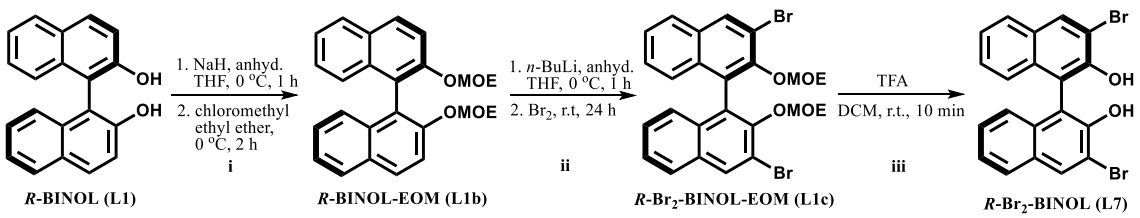
The DA yield for the complex Ti(*R*-BINOL-O_2)$_2$ (**C4**) (entry 23, Table 4.6) was observed to be lower than that $TiCl_2$(*R*-BINOL-O_2) (**C3**) (entry 20, Table 4.6), indicating that the reactivity of the complex **C4** to be lower than complex **C3**. The Cl anionic moieties in the complex **C3** were more electronegative than the alkoxy anionic moieties in complex **C4**, resulting in a higher Lewis acidity in the complex **C3** and helped to reduce the LUMO energy of the dienophile to give better DA yield (Mikami et al., 2003). At different ratios between $TiCl_4$ to deprotonated *R*-BINOL (**L1f**), the complex formed from $TiCl_4$ with 1 equivalent of deprotonated *R*-BINOL (**L1f**) (**C3**) had the highest ee value for DA product at 20% (entry 20, Table 4.6).

Compared with the previous reaction (entry 18, Table 4.6), the complex formed from deprotonated *R*-BINOL (**L1f**) with $TiCl_4$ (entry 20, Table 4.6) was found to exhibit higher enantioselectivity for the DA product (20% ee value) than that formed from *R*-BINOL

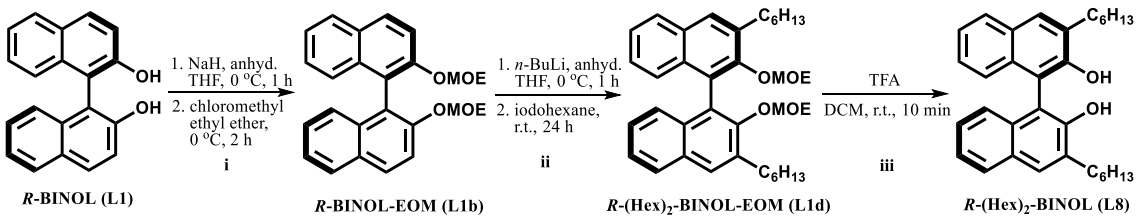
(**L1**) with $TiCl_4$ (entry 18, Table 4.6) (2% ee value). This is probably due to the chiral titanium complex is easier to be formed by using deprotonated *R*-BINOL (**L1f**) than *R*-BINOL (**L1**). Thus, in subsequent reactions, the ligands were first deprotonated before reacting with $TiCl_4$.

The chiral titanium complex **C3** gave better yield with significant enantioselectivity at 20%. Thus, in subsequent attempts, various complexes formed with $TiCl_4$ and chiral ligands derived from *R*-BINOL (**L1**) were used. Three types of chiral ligands derived from *R*-BINOL (**L1**) [*R*-Br_2-BINOL (**L7**), *R*-$(Hex)_2$-BINOL (**L8**) and *R*-$(Trip)_2$-BINOL (**L9**)] were used.

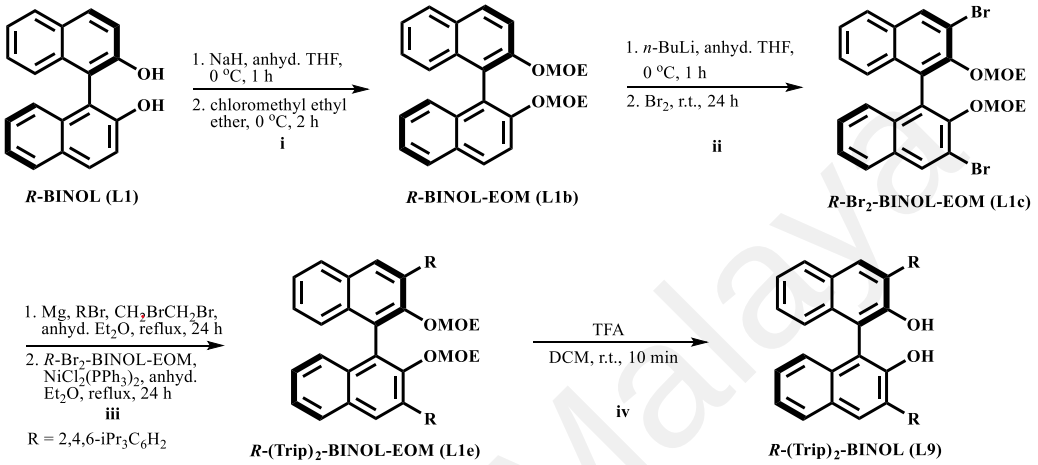
The *R*-Br_2-BINOL (**L7**) ligand was synthesised first by protecting *R*-BINOL (**L1**) with chloromethyl ethyl ether (EOM-Cl) in the presence of NaH to yield *R*-BINOL-EOM (**L1b**). Next, the *R*-BINOL-EOM (**L1b**) was reacted with *n*-BuLi followed by bromination, which was then deprotected with TFA (Scheme 4.9). *R*-$(Hex)_2$-BINOL (**L8**) was synthesised *via* coupling reaction between *R*-BINOL-EOM (**L1b**) with iodohexane in the presence of *n*-BuLi followed by EOM deprotection (Scheme 4.10). *R*-$(Trip)_2$-BINOL (**L9**) was synthesised using *R*-Br_2-BINOL-EOM (**L1c**) as the starting material followed by coupling reaction with a Grignard reagent of 2,4,6-triisopropylphenylmagnesium bromide in the presence of $Ni(PPh_3)_2Cl_2$. Subsequent deprotection of the EOM group gave the desired product **L9** (Scheme 4.11).



Scheme 4.9: Formation of *R*-Br_2-BINOL (L7).



Scheme 4.10: Formation of *R*-(Hex)$_2$-BINOL (L8).



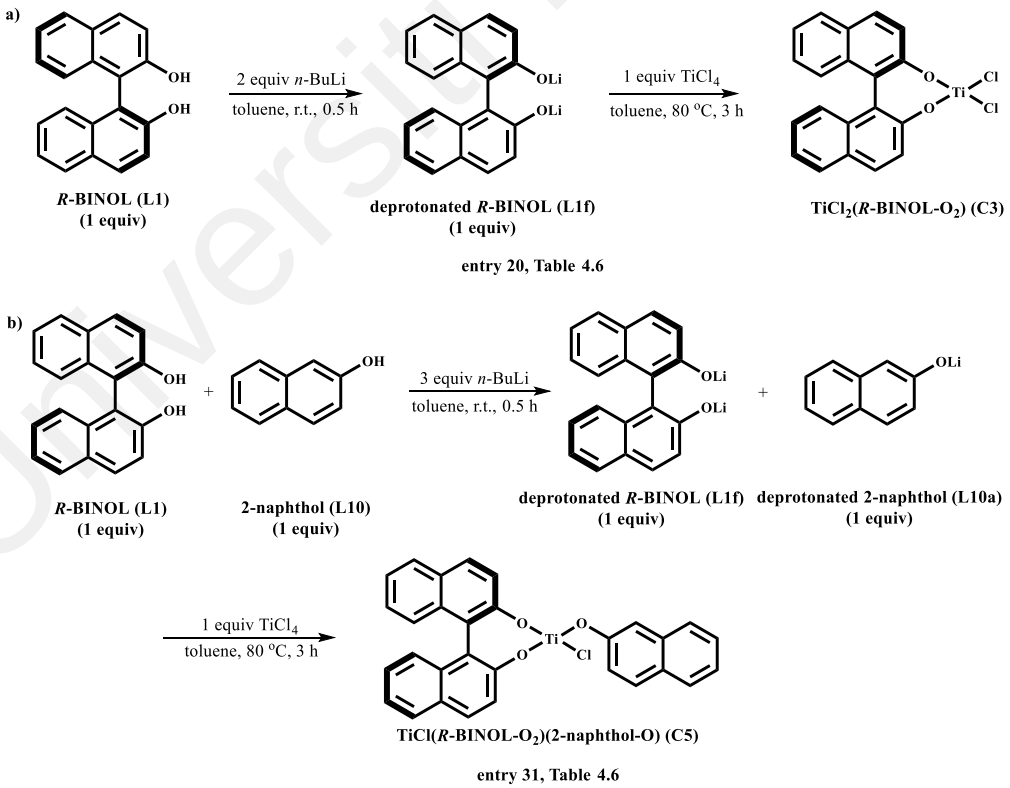
Scheme 4.11: Formation of *R*-(Trip)$_2$-BINOL (L9).

The three chiral ligands **L7-9** were initially deprotonated through a reaction with *n*-BuLi at r.t for 0.5 h and subsequently reacted with $TiCl_4$ in ratio of 1:1 and 1.5:1 at 80 °C for 3 h to form the chiral titanium complexes. The formed chiral titanium complexes were subjected to the DA reaction between *trans*-chalcone (**7g**) and isoprene (**8b**). These chiral titanium complexes gave various DA product yields (31-66% DA product yields for complex with 1 equivalent chiral ligand & 14-20% DA product yields for complex with 1.5 equivalents chiral ligand), possibly due to the nature of the chiral ligand. Compared to the chiral titanium complexes formed from *R*-BINOL (**L5**) (entries 20 & 22, Table 4.6) (75% DA product yield for complex with 1 equivalent *R*-BINOL (**C3**) & 69% DA product yield for complex with 1.5 equivalents *R*-BINOL), all these chiral titanium complexes (entries 24-29, Table 4.6), whether with 1 or 1.5 equivalents of chiral ligands **L7-9** were found to yield lower DA product yields [31% DA product yield for complex with 1 equivalent *R*-Br_2-BINOL (**L7**), 20% DA product yield for complex with

1.5 equivalents *R*-Br_2-BINOL (**L7**), 66% DA product yield for complex with 1 equivalent *R*-$(Hex)_2$-BINOL (**L8**), 14% DA product yield for complex with 1.5 equivalents *R*-$(Hex)_2$-BINOL (**L8**), 45% DA product yield for complex with 1 equivalent *R*-$(Trip)_2$-BINOL (**L9**), 19% DA product yield for complex with 1.5 equivalents *R*-$(Trip)_2$-BINOL (**L9**)]. This is probably due to the larger size of the three chiral ligands **L7-9** than *R*-BINOL (**L1**). The bulky ligands hinder the coordination of chiral titanium complexes with *trans*-chalcone (**7g**). Failure to coordinate *trans*-chalcone (**7g**) with the chiral complexes resulted in the LUMO energy of *trans*-chalcone (**7g**) not being lowered which could help in promoting the DA reaction. In addition, all these complexes, either with 1 or 1.5 equivalents of chiral ligands **L7-9,** gave DA product with low ee values (entries 24-29, Table 4.6).

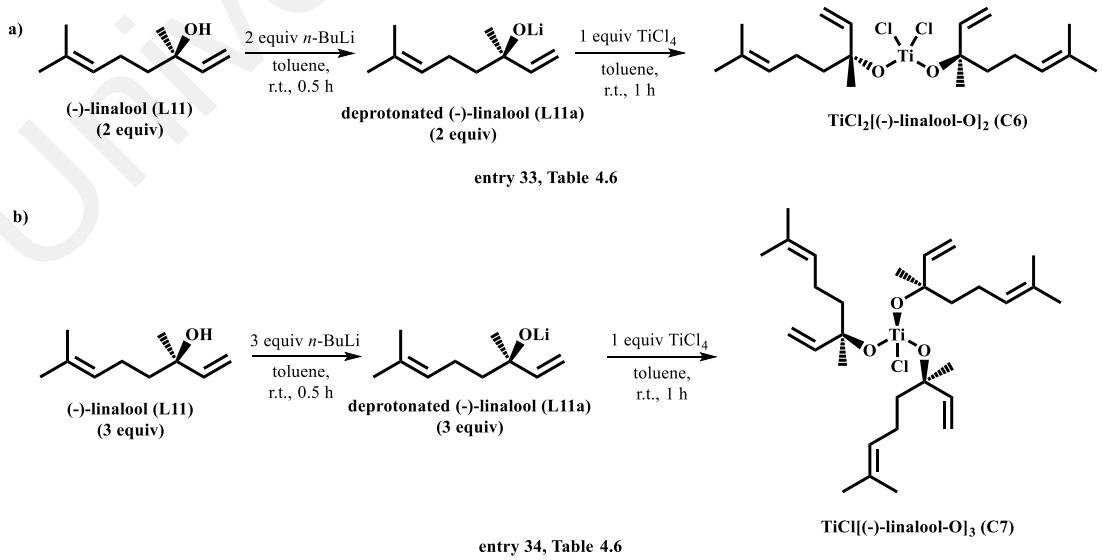
Since the use of single type of *R*-BINOLs complexed to $TiCl_4$ failed to induce good enantioselectivity, a combination comprising two different types of *R*-BINOLs [*R*-BINOL (**L1**) and *R*-$(Trip)_2$-BINOL (**L9**)] as ligands complexed to $TiCl_4$ was tested in the DA reaction. In this reaction, *R*-BINOL (**L1**) and *R*-$(Trip)_2$-BINOL (**L9**) were directly complexed to $TiCl_4$ without any deprotonation. However, the formed complex only gave 53% yield with 9% ee value in DA adduct (entry 30, Table 4.6). When compared with reaction of entry 19 in Table 4.6, which had similar chiral ligand:Lewis acid ratio, the observed DA yield for the chiral complex formed from a combination of 1 equivalent *R*-BINOL (**L1**) and 1 equivalent *R*-$(Trip)_2$-BINOL (**L9**) with $TiCl_4$ (entry 30, Table 4.6) (53% DA product yield) was lower than that formed from 2 equivalents *R*-BINOL (**L1**) with $TiCl_4$ (entry 19, Table 4.6) (100% DA product yield). This may be attributed to the larger size of *R*-$(Trip)_2$-BINOL (**L9**) diminishing the possibility of the complexation between formed complex and *trans*-chalcone (**7g**) from taking place. The failure of *trans*-chalcone (**7g**) coordinated to the formed complex resulted in no decrease in the LUMO energy of *trans*-chalcone (**7g**) and then gave lower DA yield.

Subsequently, a combination of one chiral ligand, *R*-BINOL (**L1**) and one non-chiral ligand, 2-naphthol (**L10**) in a titanium complex (this complex was synthesised by first reacting *R*-BINOL (**L1f**) and 2-naphthol (**L10a**) with *n*-BuLi at r.t. for 0.5 h, followed by a reaction with $TiCl_4$ at 80 °C for 3 h) was tested in the DA reaction (Scheme 4.12). This combination gave 43% yield and 3% ee value of the DA product (entry 31, Table 4.6). Compared to the complex $TiCl_2$(*R*-BINOL-O_2) (**C3**) in reaction entry 20, Table 4.6, the yield of the DA reaction using this complex, TiCl(*R*-BINOL-O_2)(2-naphthol-O) (C5) was found to have decreased (75% DA yield for complex **C3** & 43% DA yield for complex **C5**). Plausibly, the complex **C5** is less reactive than **C3** due to the fewer Cl atoms in **C5** (Cl atom is more electronegative than alkoxy group, the more Cl atoms in complex, the higher Lewis acidity of the complex). The enantioselectivity of the reaction was also observed to decrease from 20% to 3%.



Scheme 4.12: Proposed schemes for the complexation of $TiCl_4$ with a) 1 equivalent of deprotonated *R*-BINOL (L1f) (entry 20, Table 4.6) and b) a combination of 1 equivalent of deprotonated *R*-BINOL (L1f) and 1 equivalent of deprotonated 2-napthol (L10a) (entry 31, Table 4.6).

Beside *R*-BINOL (**L1**), other OH-type chiral ligands such as (-)-TADDOL (**L2**) and (-)-linalool (**L11)** have also been used. Slightly different from *R*-BINOL, (-)-TADDOL (**L2**) and (-)-linalool (**L11**) were first deprotonated by reacting with *n*-BuLi at r.t. for 0.5 h and then reacted with $TiCl_4$ at r.t. for 1 h to form the chiral titanium complexes. (-)-TADDOL (**L2**)-mediated reaction gave low DA yield with no significant enantioselectivity (entry 32, Table 4.6). Deprotonated (-)-linalool (**L11a**) reacted with $TiCl_4$ in the ratios of 2:1 and 3:1 to form the respective complexes, $TiCl_2$[(-)-linalool-O]$_2$ (**C6)** & TiCl[(-)-linalool-O]$_3$ (**C7**) and were used in the DA reaction (Scheme 4.13). Both complexes **C6** & **C7** gave different DA yields where 2 equivalents of (-)-linalool (**L11**) (**C6**) gave moderate yield, 36% (entry 33, Table 4.6) while no DA product was obtained when 3 equivalents of (-)-linalool (**L11**) (**C7**) was used (entry 34, Table 4.6). The results seem to indicate that the reactivity of titanium complexed with 3 equivalents of (-)-linalool (**L11**) (**C7**) to be weaker than that complexed with 2 equivalents (**C6**). Presumably, the lower reactivity of this complex (**C7**) is due to the lower Cl atoms content in the complex. In addition, complex **C6** did not give any significant ee value for the DA product.



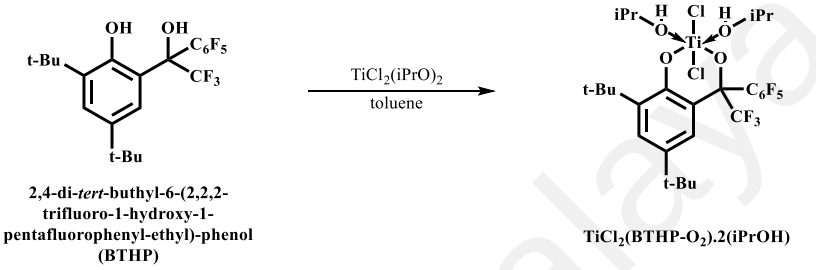
Scheme 4.13: Proposed schemes for the complexation of $TiCl_4$ with a) 2 equivalents of deprotonated (-)-linalool (L11a) (entry 33, Table 4.6) and b) 3 equivalents of deprotonated (-)-linalool (L11a) (entry 34, Table 4.6).

COOH group chiral ligands were also chosen for this enantioselective study. No examples of the reaction of $TiCl_4$ with COOH group chiral ligands have been reported in the literature. However, there are some examples of mono-, di- or triorganotitanium chlorides reacting with COOH group chiral ligands in the literature. According to the literature (Pérez et al., 2005; Stamatatos et al., 2011), ligands with COOH group can be directly or indirectly (COOH group is first deprotonated by a base) complex with organotitanium chlorides to form organotitanium carboxylates.

First, attempts were made to synthesise chiral titanium complexes directly from COOH-type chiral ligands with $TiCl_4$. *N*-Protected L-amino acid, FMOC-L-Phe-OH (**L5**) reacted with $TiCl_4$ in three different ratios, *i.e.*, 1:1, 2:1 and 3:1 respectively. All chiral complexes used gave similar yields in the DA product (73, 70 and 69% DA yields) and poor enantioselectivity (1, -1, and -1% ee values) (entries 35-37, Table 4.6). Possibly, in this case, the FMOC-L-amino acid did not complex with the titanium as anticipated.

Since the direct synthesis of the chiral titanium complex with $TiCl_4$ and FMOC-L-Phe-OH (**L5)** failed, another titanium-based Lewis acid, $TiCl_2(iPrO)_2$ was attempted for use. Two equivalents of FMOC-L-Phe-OH (**L5**) were reacted with $TiCl_2(iPrO)_2$ and this formed complex was applied to the DA reaction. Although there are no examples of $TiCl_2(iPrO)_2$ reacting with COOH-type chiral ligands in the literature, there are examples of $TiCl_2(iPrO)_2$ reacting with OH-type chiral ligands (Tuskaev et al., 2015). When $TiCl_2(iPrO)_2$ reacted with OH-type chiral ligand, the chiral ligand was bonded to Ti atom through O atoms and isopropanol were released. After that, the isopropanol reacted with the formed complex, dichlorotitanium(ligand)$_2$ to form a six coordinated complex, dichlorotitanium(ligand)$_2$.2iPrOH (Scheme 4.14). Based on this example, a scheme for the complexation of $TiCl_2(iPrO)_2$ with 2 equivalents of FMOC-L-Phe-OH (**L5**) was proposed, as shown in Scheme 4.15. No DA product was observed when this complex

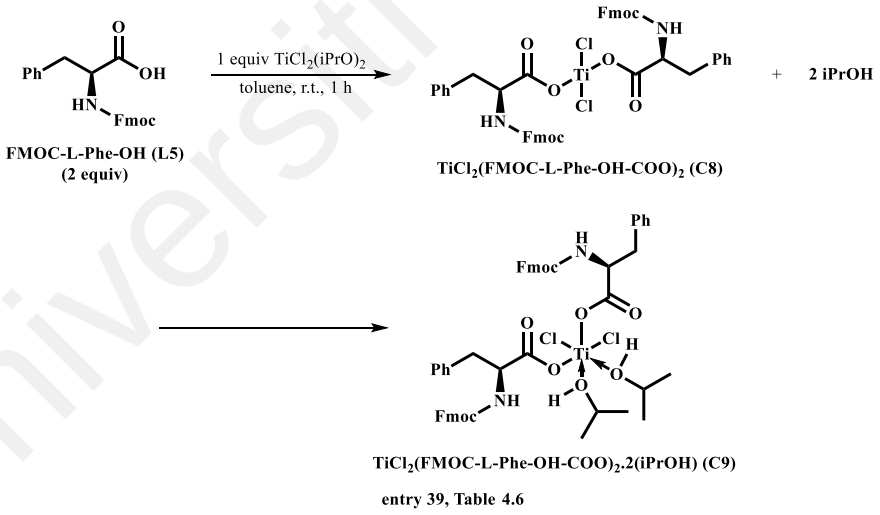
$TiCl_2$(FMOC-L-Phe-OH-COO)$_2$.2iPrOH (**C9**) was used (entry 39, Table 4.6). Possibly, due to the full occupancy of the two Cl atoms and four O atoms from two FMOC-L-Phe-OH (**L5**) and two isopropanol on the Ti core resulted in poor or no space for occupancy and coordination with the *trans*-chalcone (**7g**). Since this coordination between *trans*-chalcone (**7g**) and the chiral complex **C9** failed to occur, the LUMO energy of *trans*-chalcone (**7g**) was not lowered to enable better DA reaction.



2,4-di-*tert*-buthyl-6-(2,2,2-trifluoro-1-hydroxy-1-pentafluorophenyl-ethyl)-phenol (BTHP)

$TiCl_2$(BTHP-O_2).2(iPrOH)

Scheme 4.14: Synthesis of Ti(IV) complex with 2,4-di-*tert*-buthyl-6-(2,2,2-trifluoro-1-hydroxy-1-pentafluorophenyl-ethyl)phenol (Tuskaev et al., 2015).



$TiCl_2$(FMOC-L-Phe-OH-COO)$_2$ (C8)

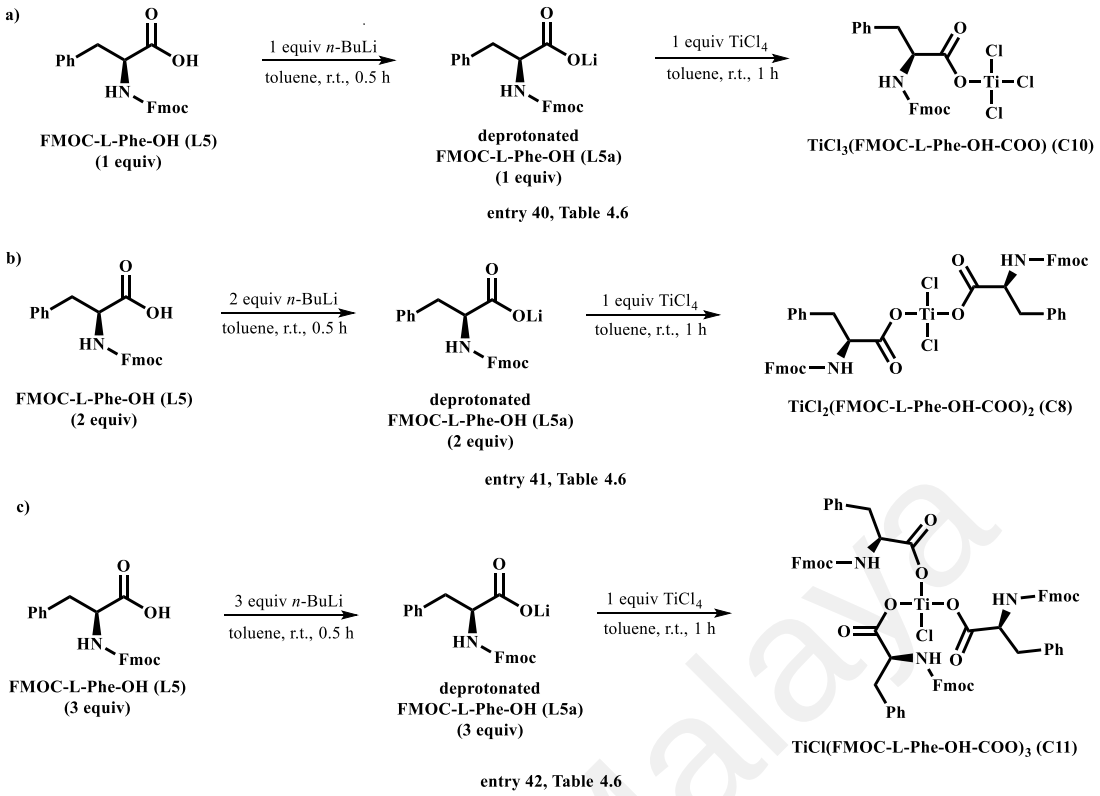
$TiCl_2$(FMOC-L-Phe-OH-COO)$_2$.2(iPrOH) (C9)

entry 39, Table 4.6

Scheme 4.15: Proposed scheme for the complexation of $TiCl_2(iPrO)_2$ with 2 equivalents of FMOC-L-Phe-OH (L5) (entry 39, Table 4.6).

Direct synthesis of chiral titanium complex using $TiCl_4$ with FMOC-L-Phe-OH (**L5**) seemed to be unsuccessful (entries 35-37, Table 4.6). To facilitate complex formation with $TiCl_4$, in the subsequent attempts, FMOC-L-Phe-OH (**L5**) was first deprotonated by reacting with *n*-BuLi at r.t. for 0.5 h. The resulting deprotonated FMOC-L-Phe-OH (**L5a**)

was then reacted with $TiCl_4$ in the ratios of 1:1, 2:1 and 3:1 (Ligand: Lewis acid) at r.t. for 1 h. The formed chiral titanium complexes were subsequently applied to the DA reaction. Based on the great difference of DA yields in the reactions (entries 40-42, Table 4.6), FMOC-L-Phe-OH (**L5**) was speculated to be successfully complexed with titanium atom and formed three different chiral titanium complexes **C8**, **C10** & **C11**. The proposed schemes for the complexation of $TiCl_4$ with 1-3 equivalents deprotonated FMOC-L-Phe-OH (**L5a**) are depicted in Scheme 4.16. The DA yields with these titanium complexes **C8**, **C10** & **C11** decreased when higher amount of FMOC-L-Phe-OH (**L5**) was used [89% DA yield with titanium complexed with 1 equivalent of FMOC-L-Phe-OH (**L5**) (**C10**), 30% DA yield with titanium complexed with 2 equivalents of FMOC-L-Phe-OH (**L5**) (**C8**) and no product observed with titanium complexed with 3 equivalents of FMOC-L-Phe-OH (**L5**) (**C11**)]. Possibly, this is related to the lower number of Cl atoms in the titanium complex. On the bright side, the chiral titanium complexed with 2 equivalents of FMOC-L-Phe-OH (**L5**) (**C8**) (entry 41, Table 4.6) gave better enantioselectivity at 9% as compared to those with 1 or 3 equivalents of FMOC-L-Phe-OH (**L5**) (**C10** & **C11**) (entries 40 & 42, Table 4.6).



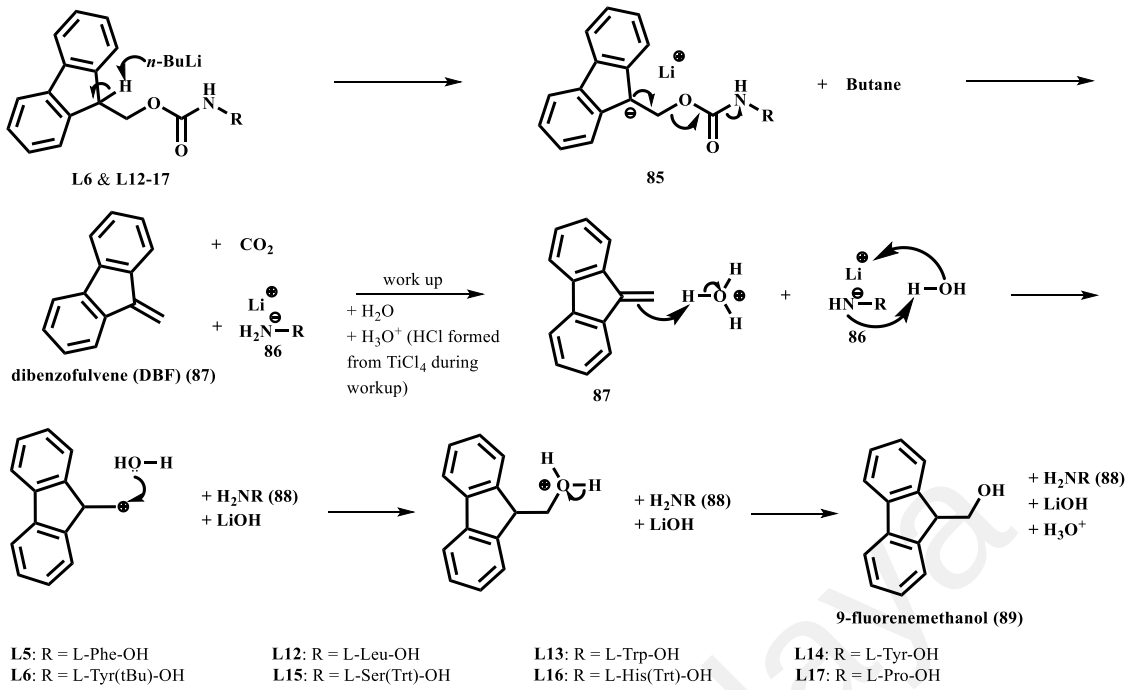
Scheme 4.16: Proposed schemes for the complexation of $TiCl_4$ with a) 1 equivalent of deprotonated FMOC-L-Phe-OH (L5a) (entry 40, Table 4.6), b) 2 equivalents of deprotonated FMOC-L-Phe-OH (L5a) (entry 41, Table 4.6) and c) 3 equivalents of deprotonated FMOC-L-Phe-OH (L5a) (entry 42, Table 4.6).

Encouraged by this observation (entry 41, Table 4.6), a series of FMOC/BOC-L-amino acid chiral ligands **L6** & **L12-18** were first deprotonated by reaction with *n*-BuLi at r.t. for 0.5 h and then reacted with $TiCl_4$ at r.t. for I h to form the chiral titanium complexes. The formed complexes were subjected to DA reaction. Unfortunately, none of these used complexes gave any enantioselectivity with significant ee values (entries 43-49, Table 4.6).

During the DA product isolation step, the fragment of FMOC-L-amino acids, 9-fluorenemethanol (**89**) was detected. After calculating the amount of recovered FMOC-L-amino acids (the complexes formed by $TiCl_4$ with deprotonated FMOC-L-amino acids are moisture-sensitive, FMOC-L-amino acids were recovered in the isolation step), the chiral FMOC-L-amino acid ligands **L5**, **L6** & **L12-17** were found to undergo varying

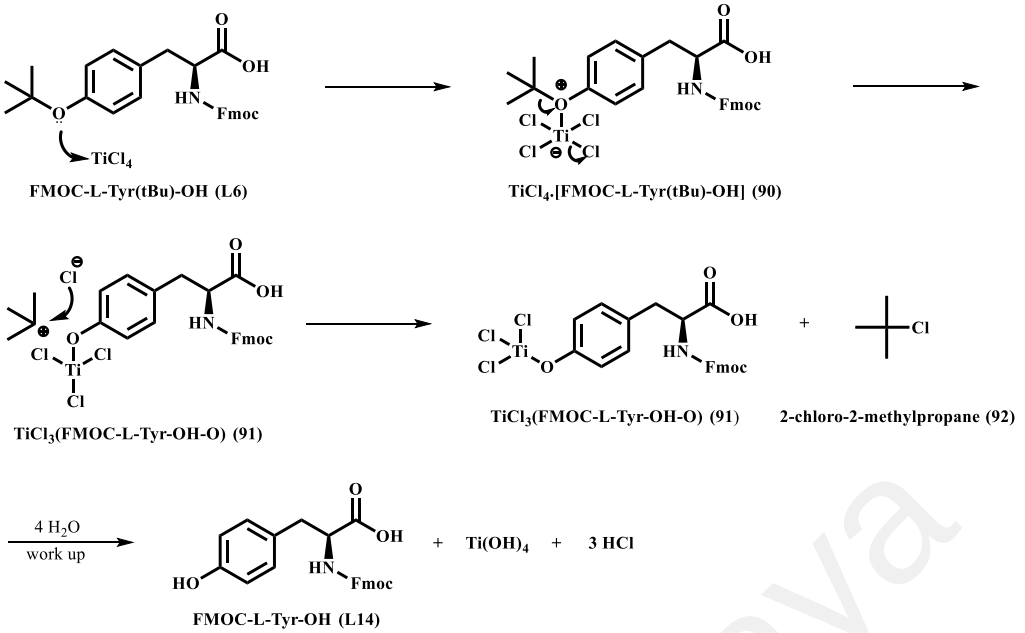
degrees of FMOC deprotection. The FMOC deprotection might be due to the use of a strong, nucleophilic base (*n*-BuLi) in the reaction.

Typically, the FMOC group is cleaved with piperidine, no report on the use of *n*-BuLi to cleave the FMOC group. Based on the piperidine-induced FMOC deprotection mechanism (Luna et al., 2016; Ralhan et al., 2015), the *n*-BuLi-induced FMOC deprotection mechanism was proposed, as shown in Scheme 4.17. First, *n*-BuLi abstracted the acidic proton at the 9-position of the fluorene ring system to form a lithium FMOC-L-amino acid salt (**85**) and butane. Consequently, salt **85** underwent a β-elimination process to give a lithium deprotected L-amino acid salt (**86**), dibenzofulvene (DBF) (**87**) and CO_2. The lithium deprotected L-amino acid salt (**86**) then reacted with water to produce deprotected L-amino acid (**88**) and LiOH during work up. Meanwhile, dibenzofulvene (**87**) underwent hydration under acidic condition (HCl formed from reaction between $TiCl_4$ and H_2O during work up process) to form 9-fluorenemethanol (**89**). Generally, the product of the hydration of dibenzofulvene is expected to be a tertiary alcohol, as the tertiary carbocation is more stable than the primary carbocation. However, in this reaction, the product obtained is primary alcohol, 9-fluorenemethanol. This may be due to steric hindrance between the tertiary carbocation and the OH group (Carpino, 1987).

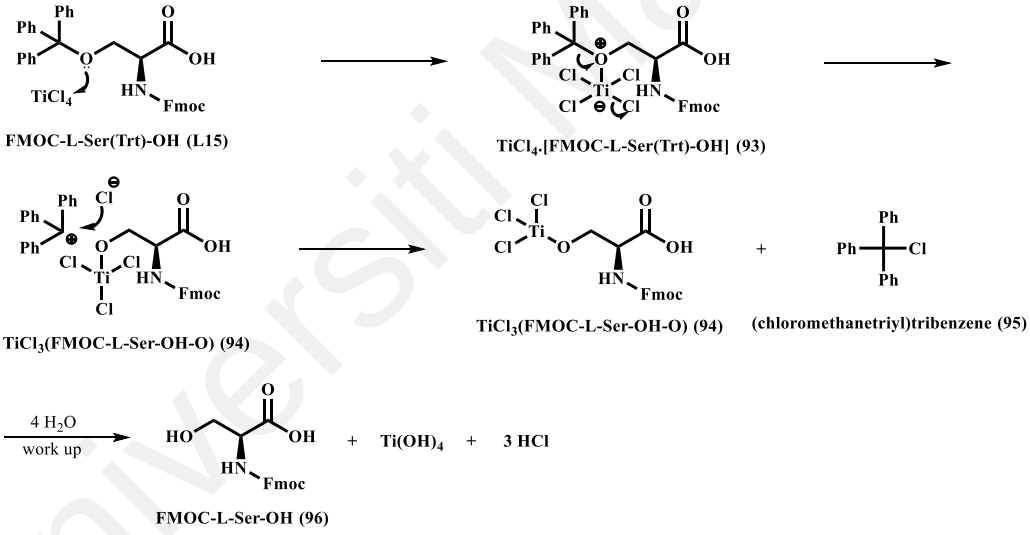


Scheme 4.17: Proposed mechanism of *n*-BuLi-induced FMOC deprotection.

Besides that, for the FMOC-L-Tyr(tBu)-OH (**L6**) and FMOC-L-Ser(Trt)-OH (**L15**) ligands, debutylation and detritylation happened during the DA reaction. This decomposition process may be induced by $TiCl_4$. The proposed mechanisms of debutylation of FMOC-L-Tyr(tBu)-OH (**L6**) and detritylation of FMOC-L-Ser(Trt)-OH (**L15**) are shown below in Schemes 4.18 & 4.19. Electron pairs on O-butyl/trityl atom attacked the central Ti atom to form Ti complex $TiCl_4$.[FMOC-L-Tyr(tBu)-OH] (**90**)/$TiCl_4$.[FMOC-L-Ser(Trt)-OH] (**93**). Consequently, the complex **90**/**93** dissociated to give a titanium alkoxide $TiCl_3$(FMOC-L-Tyr-OH-O) (**91**)/$TiCl_3$(FMOC-L-Ser-OH-O) (**94**), t-butyl/trityl cation and Cl anion. Following which, the t-butyl/trityl cation reacted with Cl anion to form 2-chloro-2-methylpropane (**92**)/(chloromethanetriyl)tribenzene (**95**) as byproduct. Finally, the alcohol FMOC-L-Tyr-OH (**L14**)/FMOC-L-Ser-OH (**96**) was liberated along with $Ti(OH)_4$ and HCl upon hydrolysis of the titanium alkoxide **91**/**94** in the workup process.

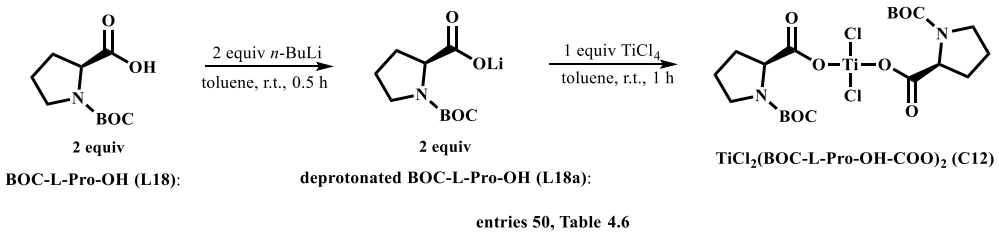


Scheme 4.18: Proposed mechanism of debutylation of FMOC-L-Tyr(tBu)-OH (L6).



Scheme 4.19: Proposed mechanism of detritylation of FMOC-L-Ser(Trt)-OH (L15).

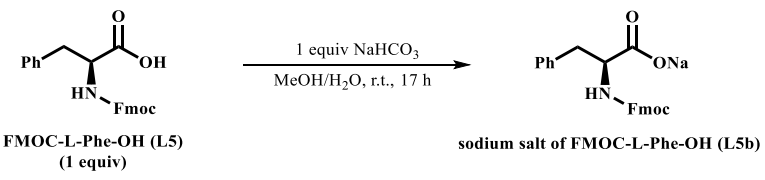
Although BOC deprotection was not observed with the BOC-L-Pro-OH (**L18**) ligand, complex $TiCl_2$(BOC-L-Pro-OH-COO)$_2$ (**C12)** (Scheme 4.20) did not yield any DA product (entry 50, Table 4.6). Presumably, the complex **C12** was not strong enough to induce the DA reaction.



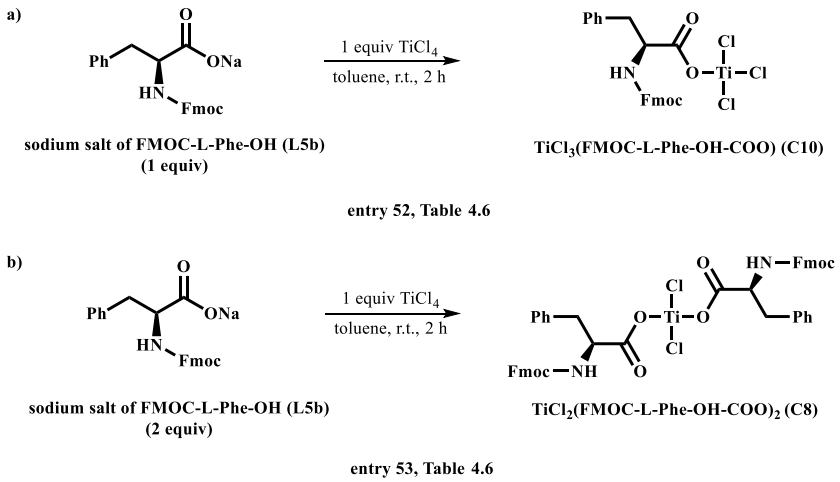
Scheme 4.20: Proposed scheme for the complexation of $TiCl_4$ with 2 equivalents of deprotonated BOC-L-Pro-OH (L18a) (entry 50, Table 4.6).

The FMOC group is essential to provide the required steric element to induce chirality. To prevent FMOC deprotection, Et_3N was then used in place of *n*-BuLi in the ligand deprotonation reaction. Unfortunately, the FMOC deprotection seemed to increase with Et_3N (entry 51, Table 4.6).

Subsequently, *n*-BuLi was replaced by a softer base, $NaHCO_3$ in the ligand deprotonation reaction. The sodium salt of FMOC-L-Phe-OH (**L5b**) was prepared beforehand by mixing FMOC-L-Phe-OH (**L5**) with an equivalent amount of $NaHCO_3$ in MeOH and water (Scheme 4.21) at r.t. for 17 h. The sodium salt of FMOC-L-Phe-OH (**L5b**) was then reacted with $TiCl_4$ in ratios 1:1 and 2:1 at r.t. for 2 h to make the chiral titanium complexes. The differences of DA yields and ee values in the reactions (entries 52 & 53, Table 4.6) indicated two different chiral titanium complexes were formed. By referring to literature (Baranwal et al., 2011), the schemes for the complexation of $TiCl_4$ with 1 and 2 equivalents sodium salt of FMOC-L-Phe-OH (**L5b**) were proposed (Scheme 4.22). Fortuitously, titanium complex **C8** (2 equivalents FMOC-L-Phe-OH to Ti) afforded the desired DA adduct with a significantly improved enantioselectivity at 61% ee, albeit lower yield (entry 53, Table 4.6).



Scheme 4.21: Formation of sodium salt of FMOC-L-Phe-OH (L5b).

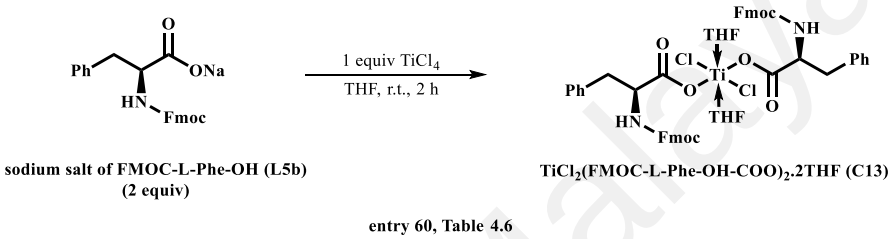


Scheme 4.22: Proposed schemes for the complexation of $TiCl_4$ with a) 1 equivalent of sodium salt of FMOC-L-Phe-OH (L5b) (entry 52, Table 4.6) and b) 2 equivalents of sodium salt of FMOC-L-Phe-OH (L5b) (entry 53, Table 4.6).

Due to low DA product yield with the chiral titanium complex **C8** (entry 53, Table 4.6), various other conditions were tested to improve the yield of reaction. First, the loading amount of the chiral titanium complex **C8** was increased from 1 equivalent to 1.5 and 2 equivalents (entries 54 & 55, Table 4.6). However, increasing the loading amount failed to increase the yield and ee value of the DA reaction. Reducing the ratio of FMOC-L-Phe-OH (**L5)** on the titanium from 2 equivalents to 1.5 and 1.6 equivalents (entries 56-58, Table 4.6) also did not increase the yield or enantioselectivity of the reaction. In these reactions (entries 53-58, Table 4.6), gradual formation of white solid following the addition of $TiCl_4$ to the solution of sodium salt of FMOC-L-Phe-OH (**L5b**) was observed. This white solid could possibly be insoluble chiral titanium complex **C8** in toluene. This poor solubility may be the reason for the low yield observed in these experiments.

To address the solubility problem, toluene was replaced by other solvents such as dichloromethane and THF in subsequent attempts. Replacing toluene with dichloromethane (entry 59, Table 4.6) did not give any significant improvement, the titanium complex **C8** seemed to be less soluble in dichloromethane than in toluene. Although titanium complex **C8** showed good solubility in THF, no DA product was

obtained (entry 60, Table 4.6). This is possibly due to the THF acting as donor ligand and reacted with the complex **C8** to form a six-coordinated complex, $TiCl_2$(FMOC-L-Phe-OH-COO)$_2$.2THF (**C13**) (Scheme 4.23) (Manzer et al., 1982). The full occupancy of the two Cl atoms and four O atoms from two FMOC-L-Phe-OH (**L5**) and two THF on the Ti core resulted in poor or no space for occupancy and coordination with the *trans*-chalcone (**7g**). The failure of the coordination of *trans*-chalcone (**7g**) to complex **C13** resulted in no reduction in the LUMO energy of *trans*-chalcone (**7g**) for a better DA reaction.



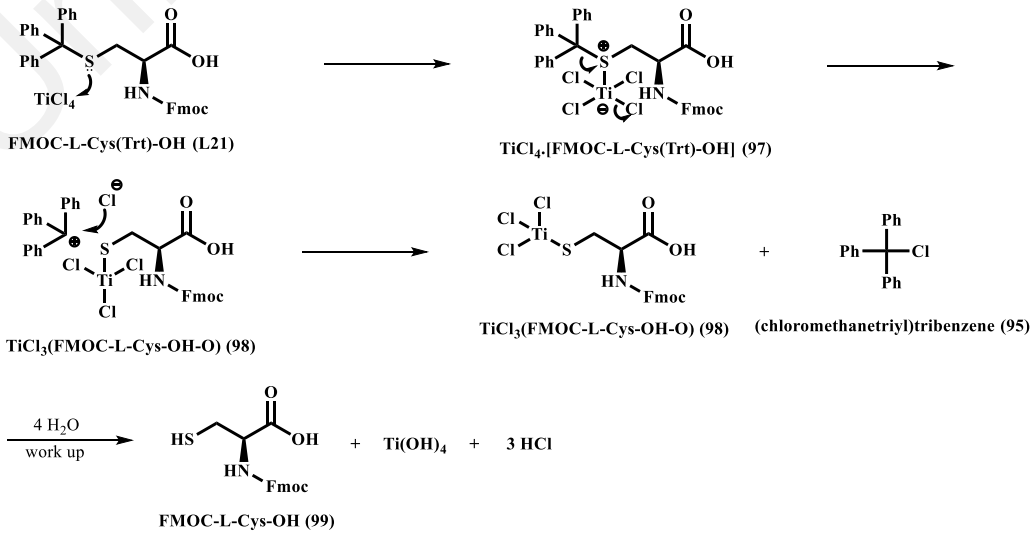
Scheme 4.23: Proposed scheme for the complexation of $TiCl_4$ with 2 equivalents of sodium salt of FMOC-L-Phe-OH (L5b) in THF (entry 60, Table 4.6).

Since changing solvents did not improve the yield, the volume of toluene used was increased (2.4 mL) (entry 61, Table 4.6) and the reaction temperature was increased (75 °C) (entry 62, Table 4.6). However, these conditions did not improve the yield of reaction.

To test the effect of different complexation time of sodium salt of FMOC-L-Phe-OH (**L5b**) with $TiCl_4$ on the DA reaction, the complexation time of sodium salt of FMOC-L-Phe-OH (**L5b**) with $TiCl_4$ for the above reaction (entry 53, Table 4.6) was shortened from 2 h to 0.5 h. The formed complex (entry 63, Table 4.6) gave low DA yield and the ee value was much lower (4% ee value) when compared to the complex (entry 53, Table 4.6) which was conducted at 2 h complexation time (61% ee value). Since the complexes in these two reactions (entries 53 & 63, Table 4.6) formed by the same reagent [$TiCl_4$, sodium salt of FMOC-L-Phe-OH (**L5b**)] under the same conditions (room temperature, toluene) except complexation time, the large difference in ee values between these two

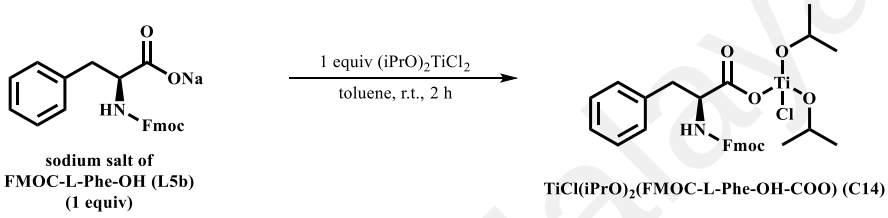
reactions may be due to the different amounts of chiral titanium complex in the reactions. The longer the complexation time, the more chiral titanium complex was formed, resulting in higher enantioselectivity for the DA reaction.

Since various conditions failed to increase the yield of DA reaction for the chiral titanium complex **C8** (entry 53, Table 4.6), other types of FMOC-L-amino acids **L6, L13** & **L19-21** were explored. The sodium salt of FMOC-L-amino acids were first prepared by reacting the FMOC-L-amino acids **L6**, **L13** & **L19-21** with $NaHCO_3$ at r.t. for 17 h. The resulting sodium salt of FMOC-L-amino acids were then reacted with $TiCl_4$ in a 2:1 ratio (Ligand: Lewis acid) at r.t. for 2 h to form the chiral titanium complexes. Unfortunately, other FMOC-L-amino acid ligands **L6, L13** & **L19-21** used did not show enantioselectivity with any significant ee values (entries 64-68, Table 4.6). This could be attributed to the low or non-solubility of these complexes in toluene (entries 64-66, Table 4.6) and ligands decomposition by $TiCl_4$ [debutylation occurred for FMOC-L-Tyr(tBu)-OH (**L6**) and detritylation occurred for FMOC-L-Cys(trt)-OH (**L21**)] (entries 67 & 68, Table 4.6). The proposed detritylation mechanism of FMOC-L-Cys(Trt)-OH (**L21**) in Scheme 4.24 is similar to that of FMOC-L-Ser(Trt)-OH (**L15**) shown in Scheme 4.19, but the final product is a thiol, FMOC-L-Cys-OH (**99**), instead of alcohol **96**.



Scheme 4.24: Proposed mechanism of detritylation of FMOC-L-Cys(Trt)-OH (L21).

$TiCl_2(iPrO)_2$ was also used in the complex formation with the sodium salt of FMOC-L-Phe-OH (**L5b**). Referring to the literature (Baranwal et al., 2011), the scheme for the complexation of $TiCl_2(iPrO)_2$ with 1 equivalent of sodium salt of FMOC-L-Phe-OH is proposed in Scheme 4.25. The complex, $TiCl(iPrO)_2$(FMOC-L-Phe-OH-COO) (**C14**), formed by the reaction between $TiCl_2(iPrO)_2$ and the sodium salt of FMOC-L-Phe-OH (**L5b**) at r.t. for 2 h, did not give any DA yield (entry 69, Table 4.6). This may be due to the reactivity of the complex **C14** not being strong enough to induce the DA reaction.



sodium salt of FMOC-L-Phe-OH (L5b) (1 equiv)

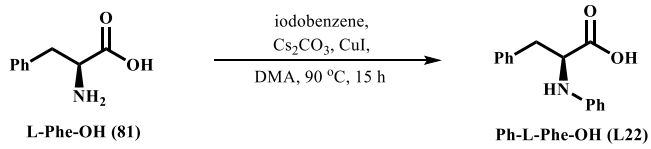
$TiCl(iPrO)_2$(FMOC-L-Phe-OH-COO) (C14)

entry 69, Table 4.6

Scheme 4.25: Proposed scheme for the complexation of $TiCl_2(iPrO)_2$ with 1 equivalent of sodium salt of FMOC-L-Phe-OH (L5b) (entry 69, Table 4.6).

The low DA yield obtained when using titanium complexed with 2 equivalents of FMOC-L-Phe-OH (**L5**) (**C8**) (entry 53, Table 4.6) may be due to the low solubility of the complex **C8** in toluene. Attempts to modify FMOC-L-Phe-OH (**L5**) into a more soluble chiral ligand in toluene were conducted. Four different types of chiral ligands **L22-25** derived from L-Phe-OH (**L5)** were synthesised. Amongst these four ligands **L22-25**, $(Bn)_2$-L-Phe-OH (**L23**) and FMOC-L-Phe-IPA (**L25**) showed good solubility in toluene as compared to FMOC-L-Phe-OH (**L5**). These chiral ligands **L22-25** were then complexed with $TiCl_4$ and subjected to the DA reaction.

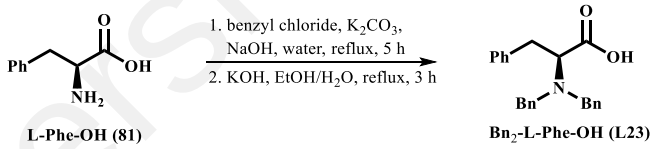
Ph-L-Phe-OH **(L22**) was used as a chiral ligand in the initial reaction which was synthesised *via* C-N coupling reaction between L-Phe-OH (**81**) and iodobenzene in the presence of Cs_2CO_3 and CuI. The formation of Ph-L-Phe-OH (**L22**) is shown at Scheme 4.26.



Scheme 4.26: Formation of Ph-L-Phe-OH (L22).

Two equivalents of Ph-L-Phe-OH (**L22**) were first deprotonated by reacting with *n*-BuLi at r.t. for 0.5 h and then reacted with $TiCl_4$ at r.t. for 1 h to form a chiral titanium complex. This complex was then applied to the DA reaction. Similarly, with the FMOC-L-Phe-OH (**L5**), white solid was formed after $TiCl_4$ was added to the deprotonated Ph-L-Phe-OH and only traces amount of the product was obtained from this reaction (entry 70, Table 4.6), possibly due to the low solubility of this chiral titanium complex in toluene.

The chiral ligand Bn_2-L-Phe-OH (**L23**) was prepared *via* C-N coupling reaction between L-Phe-OH (**81)** and benzyl chloride in the presence of K_2CO_3 and NaOH. The reaction scheme for the preparation of Bn_2-L-Phe-OH (**L23**) is depicted in Scheme 4.27.

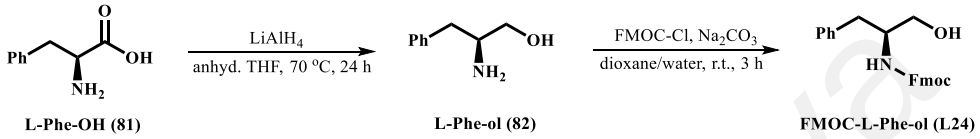


Scheme 4.27: Formation of Bn_2-L-Phe-OH (L23).

Two equivalents of Bn_2-L-Phe-OH (**L23**) were first deprotonated by three different bases (reacted with *n*-BuLi at r.t. for 0.5 h or reacted with NaOH or $NaHCO_3$ at r.t. for 17 h) and subsequently reacted with $TiCl_4$ at r.t. for 1 or 2 h to form chiral titanium complexes. The chiral titanium complexes were then applied to the DA reaction. While Bn_2-L-Phe-OH (**L23**) showed good solubility in toluene, its chiral titanium complex does not show the same feature. The low solubility of the chiral titanium complexes in toluene possibly led to all the reactions giving either no or low yields (entries 71-73, Table 4.6). Unlike with FMOC-L-Phe-OH **(L5)** (entry 53, Table 4.6), these reactions also did not

show any significant enantioselectivity. Presumably, the bulkiness of the benzyl group was insufficient to enable better enantioselectivity as compared to the FMOC group.

In subsequent reactions, the FMOC-L-Phe-ol (**L24**) was used as the chiral ligand which was synthesised by reducing L-Phe-OH (**81**) with $LiAH_4$ followed by protection with FMOC-Cl as shown in Scheme 4.28.



L-Phe-OH (81) L-Phe-ol (82) FMOC-L-Phe-ol (L24)

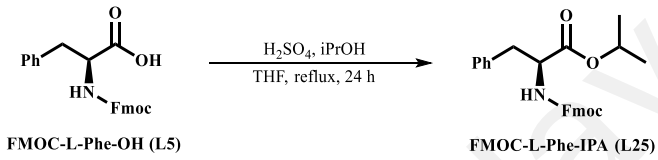
Scheme 4.28: Formation of FMOC-L-Phe-ol (L24).

Attempts to deprotonate the FMOC-L-Phe-ol (**L24**) with NaOH or $NaHCO_3$ were unsuccessful. Hence, FMOC-L-Phe-ol (**L24**) was used directly to complex with $TiCl_4$. The DA reactions with different ratios between $TiCl_4$ and FMOC-L-Phe-ol (**L24**) were carried out (entires 74-77, Table 4.6). The yield for the DA reaction with the 1:1 ratio (Ligand:Lewis acid) (entry 74, Table 4.6) was high at 75% but decreased when the amount of ligand **L24** used was increased to 2 equivalents (4%) (entry 76, Table 4.6). The great difference of DA yields in the two reactions (entry 74 & 76, Table 4.6) indicated two different chiral titanium complexes were formed. Unfortunately, neither of the complexes could bring any significant ee value to the DA product.

In addition, different complexation conditions for the complex can produce different enantioselectivities in DA reaction. In the reaction entry 75, Table 4.6, $TiCl_4$ was reacted with 2 equivalents of FMOC-L-Phe-ol (**L24**) at r.t. for 4 h before subjected to the DA reaction, while the complexation condition for reaction entry 76, Table 4.6 was 3 h at 80°C. Complex of reaction entry 75, Table 4.6 gave slightly better enantioselectivity in the DA reaction than that of reaction entry 76, Table 4.6 (-7% ee value for reaction entry 75, Table 4.6 & 0% ee value for reaction entry 76, Table 4.6). The difference in

enantioselectivities for these two complexes may be due to the complexes having different structural formulas.

The NH group chiral ligand, FMOC-L-Phe-IPA (**L25**) was synthesised by esterification reaction between the FMOC-L-Phe-OH (**L5**) and propan-2-ol in the presence of H_2SO_4. The reaction scheme for producing FMOC-L-Phe-IPA (**L25**) is shown in Scheme 4.29.



FMOC-L-Phe-OH (L5) FMOC-L-Phe-IPA (L25)

Scheme 4.29: Formation of FMOC-L-Phe-IPA (L25).

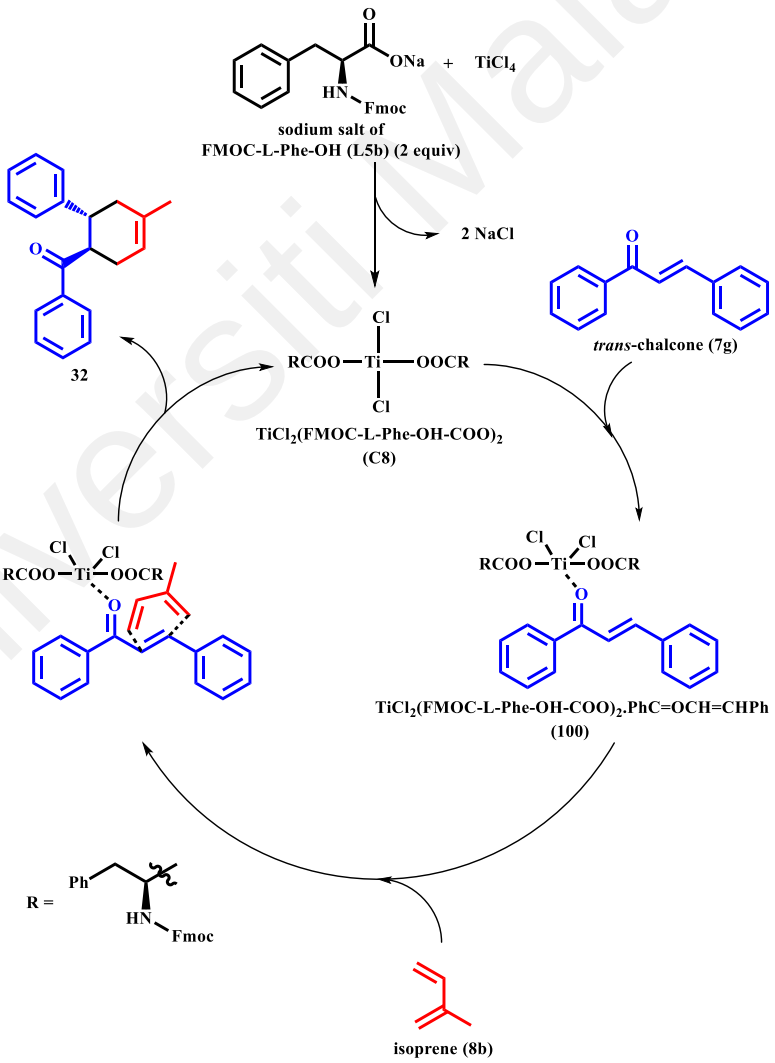
FMOC-L-Phe-IPA (**L25**) was reacted with $TiCl_4$ in ratios of 1:1 and 2:1 (Ligand:Lewis acid) and applied to DA reaction. Although different ratios of FMOC-L-IPA and $TiCl_4$ were used, the formed complexes gave similar yields and low ee values for the DA product [82% DA yield and 0% ee value for 1 equivalent FMOC-L-Phe-IPA (**L25**) used (entry 78, Table 4.6) & 73% DA yield and -3% ee value for 2 equivalents FMOC-L-Phe-IPA (**L25**) used (entry 79, Table 4.6)]. This may be due to no chiral titanium complexes being formed in the reactions. The complexation of FMOC-L-Phe-IPA **(L25)** with the Ti atom through N atom or other coordination atoms seemed to fail in these reactions. In addition, the complexation also was unsuccessful albeit at a longer reaction time (entry 80, Table 4.6) (In reaction entry 79, Table 4.6, complexation time of 2 equivalents FMOC-L-Phe-IPA (**L25**) with $TiCl_4$ was 3 h, while the complexation time in reaction entry 80, Table 4.6 was 17 h. The DA yield and ee value for reaction entry 79, Table 4.6 was 73% and -3%, while 86% and 0% for reaction entry 80, Table 4.6. The catalysts in the reactions produced similar DA yields and ee values, indicating that the catalysts in both reactions had the same molecular structure which is $TiCl_4$).

Since the use of single FMOC-L-amino acid with titanium-based Lewis acid failed to induce significant yield and enantioselectivity, three other different combinations comprising two different types of chiral ligands were complexed to $TiCl_4$ and applied to the DA reaction (entries 81-83, Table 4.6). The chiral titanium complex formed by complexing $TiCl_4$, *R*-BINOL **(L1**) and FMOC-L-Phe-OH (**L5**) gave 70% yield in the DA reaction (entry 81, Table 4.6), but the yield was decreased to 18% when FMOC-L-Phe-OH (**L5**) was replaced with sodium salt of FMOC-L-Phe-OH (**L5b**) (entry 82, Table 4.6). Although two different chiral titanium complexes were formed in the reactions, both complexes gave low ee values for the DA product, 2% and 9%, respectively (entries 81 & 82, Table 4.6).

The combination of *R*-BINOL **(L1)** and FMOC-L-Phe-ol (**L24)** ligands on titanium gave moderate yield of 53% with enantioselectivity up to 12% in the DA reaction (entry 83, Table 4.6). This result showed that a chiral titanium complex was formed and able to give some enantioselectivity in the DA reaction.

The study of the enantioselective Diels-Alder reaction between *trans*-chalcone (**7g**) and isoprene (**8b**) was stopped at this point. Based on the above results, several findings can be obtained. In this study, chiral titanium complexes were found to exhibit better reactivity and selectivity for the DA reaction compared to chiral aluminium complexes. Furthermore, the reactivity trend of the chiral complexes in the DA reaction depends on the quantity of chiral ligands attached to metal core. The greater the number of chiral ligands attached to the metal core, the lower the reactivity of the chiral complexes in DA reaction (entries 20 & 22; 33 & 34; 40-42; 52 & 53, Table 4.6). In contrast to reactivity, the selectivity trend of the chiral complexes in the DA reaction was not obtained due to fewer successful examples.

Among of the chiral complexes in this study, only the titanium complexed with 2 equivalents of FMOC-L-Phe-OH (**L5)** (**C8**) gave some ee value (entry 53, Table 4.6). The mechanism of the DA reaction catalysed by chiral complex **C8** was proposed, as shown in Scheme 4.30. Two equivalents of sodium salt of FMOC-L-Phe-OH (**L5b**) and $TiCl_4$ first formed a chiral titanium complex **C8** with loss of two NaCl molecules. Then, the oxygen of *trans*-chalcone (**7g)** coordinated with the complex **C8**, forming titanium complex, $TiCl_2$(FMOC-L-Phe-OH-COO)$_2$.PhC=OCH=CHPh (**100**). This coordination could promote the DA reaction with isoprene (**8b**) to form the adduct **32**. Finally, a desorption step turned over the catalytic cycle and released the cycloadduct **32**.



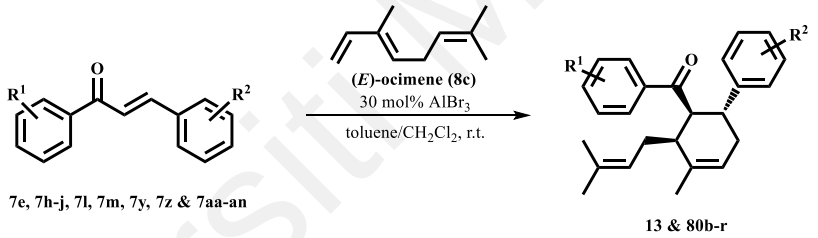
Scheme 4.30: Proposed mechanism of Diels-Alder reaction between *trans*-chalcone (7g) and isoprene (8b) catalysed by $TiCl_2$(FMOC-L-Phe-OH-COO)$_2$ (C8).

4.4. Application of the Developed Lewis Acid Catalyst and Chiral Lewis Acid Complex for the Approach of Synthesis of Selected Natural Products or their Derivatives

4.4.1 Synthesis of (±)-Panduratin A Derivatives 13 & 80b-r

Using the optimised conditions for the DA reaction obtained earlier (entry 27, Table 4.1), the approach to synthesise a series of (±)-panduratin A derivatives was attempted with 22 different types of chalcones **7e**, **7h-j**, **7l**, **7m**, **7y**, **7z** & **7aa-an** as dienophiles to react with (*E*)-ocimene (**8c**) as diene. Eighteen (±)-panduratin A derivatives **13** & **80b-r** were successfully synthesised with low to good yields under this condition tabulated in Table 4.7.

Table 4.7: Synthesis of (±)-panduratin A derivatives 13 & 80b-r[a].



7e, 7h-j, 7l, 7m, 7y, 7z & 7aa-an

13 & 80b-r

Entry	R^1	R^2	Chalcones	Time	Product	Yield (%)[b]
1[c,e]	2′-OH	H	**7l**	24	-	-
2[d,e]	2′-OCH_3	H	**7h**	24	-	-
3	2′-Cl	H	**7y**	24	**80b**	17
4	3′-Cl	H	**7z**	3	**80c**	74
5[c,e]	3′-OH	H	**7aa**	24	**-**	-
6[e]	3′-OCH_3	H	**7i**	6	**80d**	52
7	4′-Cl	H	**7ab**	3	**80e**	70
8	4′-Br	H	**7ac**	3	**80f**	56
9	4′-CH_3	H	**7j**	3	**80g**	62
10[c]	4′-OH	H	**7m**	24	**-**	-
11	4′-OCH_3	H	**7e**	24	**13**	17
12	H	3-NO_2	**7ad**	3	**80h**	64
13	H	4-Br	**7ae**	3	**80i**	62
14	H	4-Cl	**7af**	3	**80j**	69
15	H	4-CH_3	**7ag**	3	**80k**	44
16	H	4-OCH_3	**7ah**	24	**80l**	17
17[e]	H	4-NO_2	**7ai**	3	**80m**	71
18	4′-OCH_3	4-Br	**7aj**	24	**80n**	22
19	4′-OCH_3	4-CH_3	**7ak**	24	**80o**	10

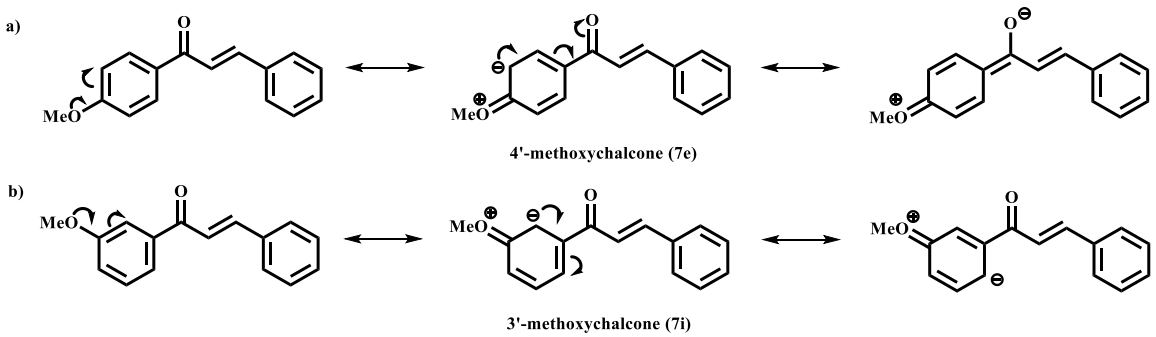
Table 4.7, continued. Synthesis of (±)-panduratin A derivatives 13 & 80b-r[a].

Entry	R^1	R^2	Chalcones	Time	Product	Yield (%)[b]
20	4′-OCH_3	4-NO_2	**7al**	24	**80p**	17
21	4′-Cl	4-OCH_3	**7am**	24	**80q**	11
22	4′-CH_3	4-OCH_3	**7an**	24	**80r**	9

[a] Reaction conditions: **7e, 7h-j, 7l, 7m, 7y, 7z** & **7aa-an** (0.5 mmol), **8c** (2.5 mmol), $AlBr_3$ (1.0 M) in CH_2Br_2 (30 mol%), r.t., anhyd. toluene (1.0 mL). [b] Isolated yield for the *endo*-isomer. A 95:5 diastereoselective ratio was determined from the ^1H NMR of the crude product. [c] No conversion was observed, starting material recovered. [d] Demethylation occurred. [e]Anhyd. CH_2Cl_2 was used as solvent.

Trans-chalcones derived from acetophenones featuring halogens (**7z**, **7ab** & **7ac**) or electron-donating substituents (**7i** & **7j**) in the aromatic ring R^1 gave the corresponding DA adducts **80c-g** in moderate to good yields (entries 4 & 6-9, Table 4.7). Electron-donating substituents (OCH_3 and CH_3) at the 3′- and 4′-positions of chalcones (**7i** & **7j**) underwent an efficient DA reaction with (*E*)-ocimene (**8c**) to give DA adducts of **80d** and **80g** in 52% and 62% yield, respectively (entries 6 & 9, Table 4.7). Similarly, a halogen substituent at the 3′- and 4′- positions of chalcones (**7z**, **7ab** & **7ac**) afforded the DA adducts, in 74%, 70% and 56% yield for **80c**, **80e** and **80f**, respectively (entries 4, 7 & 8, Table 4.7).

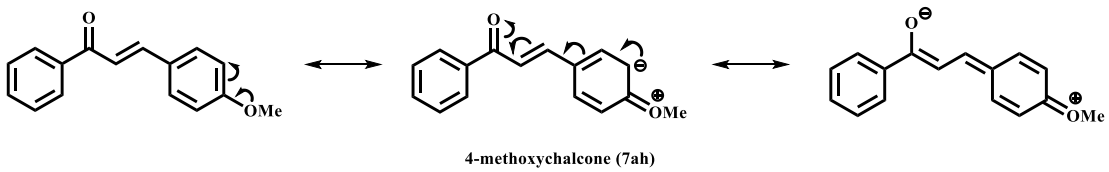
An electron-donating methoxy substituent at the 4′- position of chalcone (**7e**), however, led to a significant reduction in the yield of the desired DA adduct **13** (17%) (entry 11, Table 4.7). This is most likely due to the resonance effect of the chalcone **7e** (Scheme 4.31a). The resonance effect affects the double bond of the carbonyl group in 4′-methoxychalcone (**7e**), thereby weakening the electron-withdrawing ability of the carbonyl group (Pauling, 1960). The carbonyl group has a lower electron-withdrawing ability, making the dienophile **7e** less reactive. In addition, the resonance effect does not affect the carbonyl group in 3′-methoxychalcone (**7i)** (Scheme 4.31b), thus, the DA yield of 3′-methoxychalcone (**7i**) is higher than that of 4′-methoxychalcone (**7e**).



Scheme 4.31: Resonance effects of a) 4′-methoxychalcone (7e) and b) 3′-methoxychalcone (7i).

A lower yield was also observed with a chloro group at the 2′-position of the chalcone (**7y**; 17% yield), which may be due to a steric effect with the substituent being at this position of the ring (entry 3, Table 4.7). The desired product could not be detected when 2′-methoxychalcone (**7h**) was used in the DA reaction because demethylation was found to occur for 2′-methoxychalcone (**7h**) (entry 2, Table 4.7). No conversion was observed in the case of 2′-, 3′- and 4′-hydroxychalcones (**7l**, **7m** & **7aa**) (entries 1, 5 & 10, Table 4.7). This could be attributed to poor activation of these chalcone dienophiles **7l**, **7m** & **7aa** by the Lewis acid that were attributed to their electron-rich nature. The lack of reactivity of 2′-, 3′- and 4′-hydroxychalcones (**7l**, **7m** & **7aa**) has been well discussed by Corbett & Weavers (2008) and Porco′s group (Cong et al., 2008).

The reaction was also general with regards to the substituent R^2 of the *trans*-chalcone. As shown in Table 4.7, nitro (**7ad**, **7ai**), methyl (**7ag**), and halogen (**7ae**, **7af**) substituents at R^2 position of the chalcone dienophiles were able to give the corresponding DA adducts **80h-k & 80m** in moderate to good yields (entries 12-15 & 17, Table 4.7). However, lower yield was observed with 4-methoxy substituent (**7ah**) (entries 16, Table 4.7), presumably due to the resonance effect affecting the C=O and C=C bonds in 4-methoxychalcone (**7ah**) which then affecting the DA yield (Scheme 4.32).



Scheme 4.32: Resonance effect of 4-methoxychalcone (7ah).

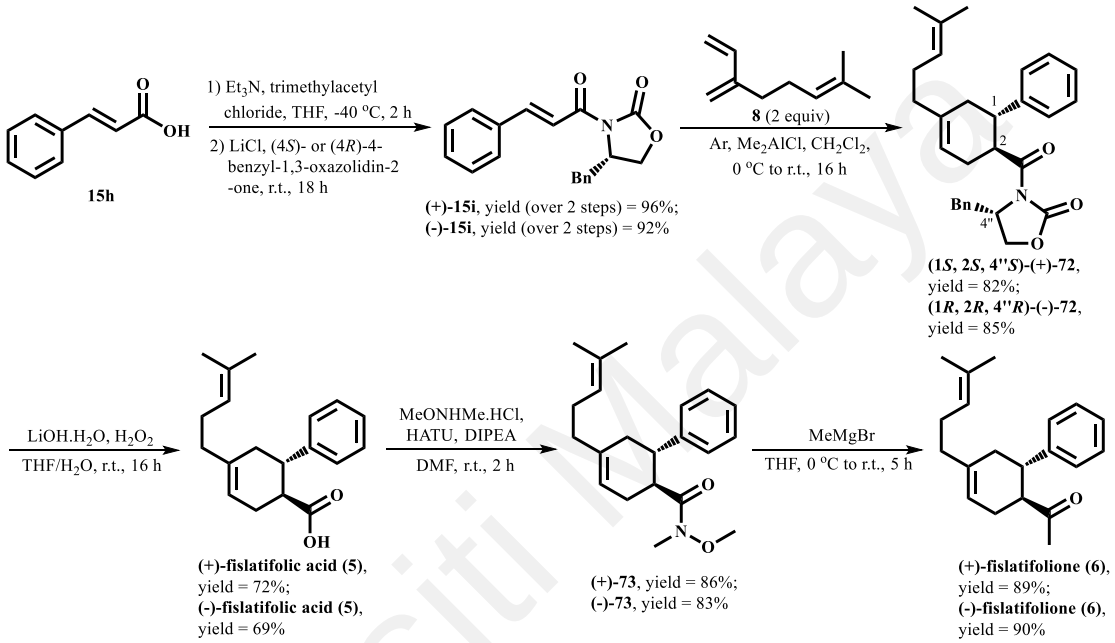
Attempts to improve the yields of 4′-methoxy or 4-methoxy DA adducts (**80n-r**) by leveraging on the efficiency of 4-Br, 4-CH_3, 4-NO_2, 4′-Cl and 4′-CH_3 groups (**7aj-an**) in the dienophile, however, were unsuccessful (entries 18-22, Table 4.7).

4.4.2 Synthesis of Natural Products, Fislatifolione (6), Isofislatifolione (6a), Fislatifolic Acid (5), Panduratin H (3) and Panduratin I (3a)

The natural products, fislatifolione (**6**), isofislatifolione (**6a**), fislatifolic acid (**5**), panduratin H (**3**) and panduratin I (**3a**) have a wide range of promising biological activities. However, the natural products are present in very small amounts in the natural sources (5 mg fislatifolione and 2 mg isofislatifolione were obtained from 917 g air-dried bark of *Fissistigma latifolium*), making large-scale extraction impractical. Therefore, it is necessary to develop synthetic methods to obtain large quantities of natural products for in-depth biological testing. The natural products can be envisioned to be formed *via* DA reactions between cinnamoyl dienophiles and terpene dienes. Fislatifolione (**6**) and its regioisomer, isofislatifolione (**6a**) and fislatifolic acid (**5**) and its unnatural regioisomer, isofislatifolic acid (**5a**) can be prepared by a DA reaction between a terpene diene, myrcene (**8**) with either the cinnamoyl dienophiles, *trans*-4-phenylbut-3-en-2-one (**15j**) and *trans*-cinnamic acid (**15h**), respectively. Panduratin H **(3)** and its regioisomer, panduratin I (**3a**) can be synthesised through DA reaction between methyl *trans*-cinnamate (**15**) and *(E)*-ocimene (**8c**).

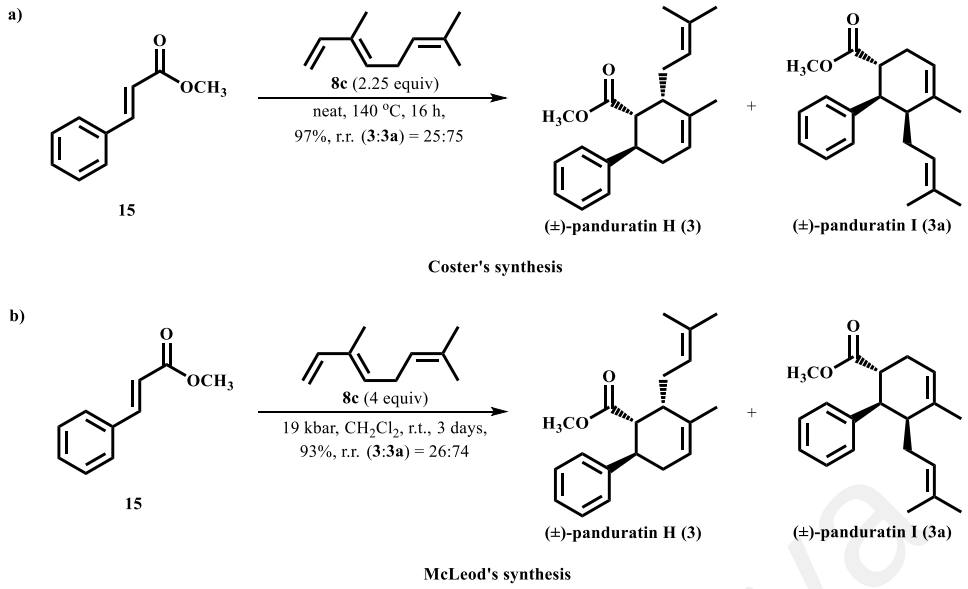
The literature has just a few studies on the synthesis of the natural products. For fislatifolione (**6**) and fislatifolic acid (**5**), the only report is the asymmetric total synthesis

of fislatifolione (**6**) and fislatifolic acid (**5**) in which Evan's oxazolidinone chiral auxiliary was used to induce the enantioselectivity of the DA reaction (Tiamas et al., 2018). The limitation of this synthetic method is that the natural products were not formed directly after the DA reaction. The chiral auxiliary must be removed after the DA reaction to obtain the desired natural products (Scheme 4.33).



Scheme 4.33: Roussi's synthesis of (+)- and (-)-fislatifolic acid (5) and fislatifolione (6).

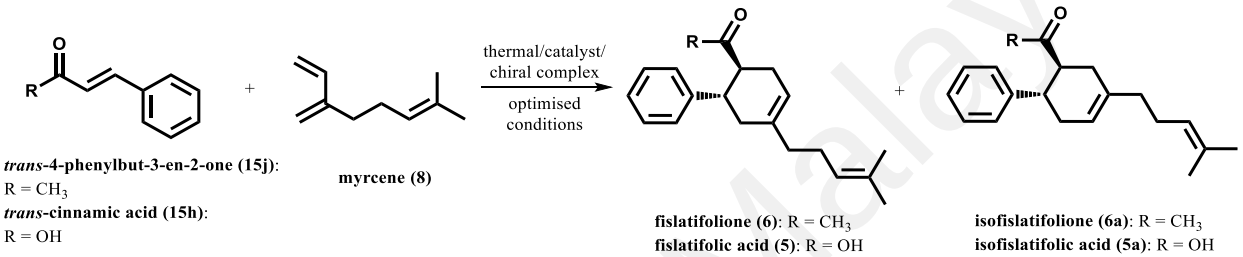
Furthermore, the literature syntheses of panduratins H (**3**) and I (**3a**) are limited to thermal and high-pressure methods (Pigott et al., 2014; Pasfield et al., 2013). Low regioselectivity and no enantioselectivity are the limitations of both methods (Scheme 4.34).



Scheme 4.34: a) Coster's and b) McLeod's syntheses of (±)-panduratins H (3) and I (3a).

Due to the limitations of the above methods, in this study, fislatifolione (**6**), isofislatifolione (**6a**), fislatifolic acid (**5**), isofislatifolic acid (**5a**), panduratin **H** (**3**) and panduratin **I** (**3a**) were tried to be synthesised through other methods such as thermal, catalyst and chiral complex methods, which are tabulated in Tables 4.8 & 4.10.

Table 4.8: Synthesis of fislatifolione (6), isofislatifolione (6a), fislatifolic acid (5) and isofislatifolic acid (5a) under thermal, catalyst and chiral complex methods[a].



***trans*-4-phenylbut-3-en-2-one (15j)**: R = CH_3
***trans*-cinnamic acid (15h)**: R = OH

myrcene (8)

fislatifolione (6): R = CH_3
fislatifolic acid (5): R = OH

isofislatifolione (6a): R = CH_3
isofislatifolic acid (5a): R = OH

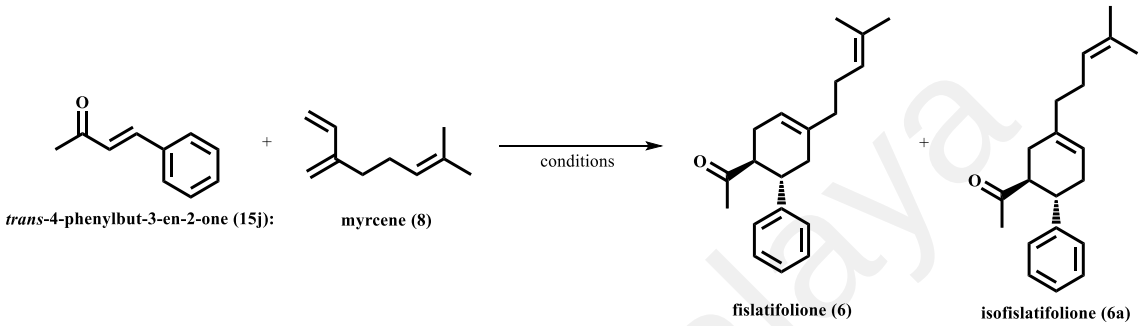
Entry	Dienophile	Lewis acid (LA)	Ligand	Ratio (LA: Ligand)	Base	LA loading (equiv)	Solvent	Solvent amount (mL)	Temp.	Time (h)	Yield (5/6+5a/6a) (%)[b]	5/6 (%)[c]	ee (%)[d]	5a/6a (%)[c]	ee (%)[e]
1	**15j**	-	-	-	-	-	toluene	0.4	150	24	39	67	-	33	-
2	**15j**	$AlBr_3$	-	-	-	0.3	toluene	0.4	r.t.	2	70	91	-	9	-
3	**15j**	$TiCl_4$	-	-	-	0.5	toluene	0.4	r.t.	0.5	71	95	-	5	-
4	**15j**	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	24	-	-	-	-	-
5	**15j**	$TiCl_4$	*R*-BINOL (**L1**)	1:1	*n*-BuLi	1	toluene	1.6	r.t.	24	65	87	0	13	-[f]
6	**15h**	-	-	-	-	-	toluene	0.4	150	24	35	64	-	36	-
7	**15h**	$AlBr_3$	-	-	-	0.3	CH_2Cl_2	0.4	r.t.	24	-	-	-	-	-
8	**15h**	$TiCl_4$	-	-	-	0.5	CH_2Cl_2	0.4	r.t.	24	-	-	-	-	-
9	**15h**	$TiCl_4$	-	-	-	1	CH_2Cl_2	0.4	r.t.	24	-	-	-	-	-
10	**15h**	$TiCl_4$	-	-	-	2	CH_2Cl_2	0.4	r.t.	24	-	-	-	-	-
11	**15h**	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	toluene/ CH_2Cl_2	1.6	r.t.	24	-	-	-	-	-
12	**15h**	$TiCl_4$	*R*-BINOL (**L1**)	1:1	*n*-BuLi	1	toluene/ CH_2Cl_2	1.6	r.t.	24	-	-	-	-	-

Table 4.8, continued. Synthesis of fislatifolione (6), isofislatifolione (6a), fislatifolic acid (5) and isofislatifolic acid (5a) under thermal, catalyst and chiral complex methods[a].

En-try	Dieno-phile	Lewis acid (LA)	Ligand	Ratio (LA: Ligand)	Base	LA loading (equiv)	Solvent	Solvent amount (mL)	Temp.	Time (h)	Yield (5/6+5a/ 6a) (%)[b]	5/6 (%)[c]	ee (%)[d]	5a/ 6a (%)[c]	ee (%)[e]
13	**15h**	$TiCl_4$	*R*-BINOL (**L1**)	1:1	*n*-BuLi	2	toluene/ CH_2Cl_2	1.6	r.t.	24	-	-	-	-	-

[a] Reaction conditions: **15j** & **15h** (0.2 mmol), **8** (1.0 mmol). [b] Isolated yield for mixture of **5**/**6** and **5a**/**6a**. [c] Determined from the ^{1}H NMR of crude product. [d] ee value for **5**/**6**. [e] ee value for **5a**/**6a**. [f] Not determined due to less adduct obtained.

The thermal-induced DA reaction between *trans*-4-phenylbut-3-en-2-one (**15j**) and myrcene (**8**) was carried out at 150 ^{o}C for 24 h to furnish the fislatifolione (**6**) and its regioisomer, isofislatifolione (**6a**) in 39% yield with ratio of 67:33 (entry 1, Table 4.8) shown in Scheme 4.35. Chromatography separation afforded pure regioisomers **6** and **6a** that conformed to the reported literature data (Geny et al., 2017).

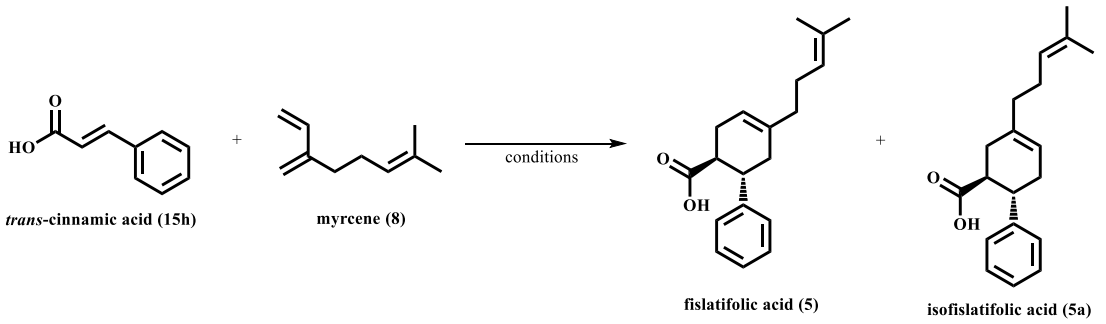


Scheme 4.35: Synthesis of fislatifolione (6) and its regioisomer, isofislatifolione (6a).

Using 0.3 equivalent of $AlBr_3$ as the catalyst in the DA reaction gave the corresponding DA products, **6** and **6a** in 70% yield with the ratio of 91:9 of the fislatifolione (**6**) and isofislatifolione (**6a**) (entry 2, Table 4.8). The improvement of regioselectivity from thermal to catalyst method can be explained by FMO theory. The regioselectivity is determined by the orbital coefficients of the atoms forming the σ-bonds (the two end atoms of diene and two atoms of dienophile). The greater the difference between the orbital coefficients of the two end atoms of diene and two atoms of dienophile, which form the two σ-bonds, the more regioselective the cycloaddition. Lewis acid-catalysed cycloadditions of dienophiles, such as α,β-unsaturated carbonyl compounds are generally highly regioselective because the oxygen complexation increases the difference of orbital coefficients of the atoms of alkene moiety (Fringuelli & Taticchi, 2002). A similar result was obtained when 0.5 equivalent of $TiCl_4$ was used as catalyst in the DA reaction (entry 3, Table 4.8). This catalyst afforded fislatifolione (**6**) and isofislatifolione (**6a**) in 71% yield with an improved ratio of 95:5.

Chiral complex was also applied to the DA reaction between *trans*-4-phenylbut-3-en-2-one (**15j**) and myrcene (**8**). First, the previously developed chiral complex **C8** (entry 53, Table 4.6), formed by reacting 1 equivalent of $TiCl_4$ with 2 equivalents of FMOC-L-Phe-OH (**L5)** in the presence of $NaHCO_3$ was applied in the DA reaction (entry 4, Table 4.8). Unfortunately, this chiral complex **C8** did not yield any product. This may be due to the chiral titanium complex **C8** not being reactive enough to induce the DA reaction between *trans*-4-phenylbut-3-en-2-one (**15j**) and myrcene (**8**). Subsequently, the more reactive chiral complex **C3** (as observed in earlier study; entry 20, Table 4.6), formed by reacting 1 equivalent of $TiCl_4$ with 1 equivalent of *R*-BINOL (**L1**) in the presence of *n*-BuLi was applied in the DA reaction (entry 5, Table 4.8). Unfortunately, the chiral complex **C3** also gave high DA yield and excellent regioselectivity, but no enantioselectivity. Compared with *trans*-chalcone (**7g**), chiral complex **C3** did not produce enantioselectivity to the DA product when *trans*-4-phenylbut-3-en-2-one (**15j**) was used as the dienophile. This may be due to the chiral *R*-BINOL ligand in chiral complex **C3** can form a π-π stacking interaction with the phenyl ring adjacent to the carbonyl group in *trans*-chalcone (**7g**), which shields the α-face of the dienophile and dicatetes the stereofacial approach of the diene from the less hindered β-face (Li et al., 2016).

The DA reaction between *trans*-cinnamic acid (**15h**) and myrcene (**8**) was carried out at 150 °C for 24 h to afford the fislatifolic acid (**5**) and its unnatural regioisomer, isofislatifolic acid (**5a**) in 35% yield with a ratio of 64:36 (entry 6, Table 4.8) (Scheme 4.36). Spectroscopic data for fislatifolic acid (**5**) agreed with that reported in the literature (Geny et al., 2017). However, isofislatifolic acid (**5a**) is a compound that has never been reported.



Scheme 4.36: Synthesis of fislatifolic acid (5) and its unnatural regioisomer, isofislatifolic acid (5a).

The structure of isofislatifolic acid (**5a**) was established from its spectral data, making use of COSY, HMQC and HMBC experiments in combination with ^{1}H and ^{13}C NMR spectroscopic data (Figure 4.6). The ^{1}H- and ^{13}C-NMR spectra of isofislatifolic acid (**5a**) in Table 4.9 displayed signals due to two aliphatic methines [δ_H 2.98 (H-1), 2.87 (H-2); δ_C 42.2, 46.0], four allylic methylenes [δ_H 2.28-2.40 (H_2-3), 2.19-2.25, 2.28-2.40 (H_2-6), 2.00-2.04 (H_2-7), 2.08-2.14 (H_2-8); δ_C 26.3, 32.1, 33.5, 37.3], two olefinic methines [δ_H 5.49 (H-5), 5.10 (H-9); δ_C 120.2, 123.9], two vinyl methyls [δ_H 1.61 (H_3-11), 1.70 (H_3-12); δ_C 17.7, 25.7], one phenyl ring [δ_H 7.17-7.21 (H-2′, 4′, 6′), 7.25-7.30 (H-3′, 5′); δ_C 126.5, 127.4, 128.4, 143.9], two olefinic quaternary carbons (δ_C 131.8, 135.6) and one carboxylic acid carbonyl carbon (δ_C 179.7). These NMR data were similar to those of isofislatifolione (**6a**), but with a hydroxycarbonyl group at C-2 in isofislatifolic acid (**5a**), instead of an acetyl group in isofislatifolione (**6a**). In the HMBC spectrum of isofislatifolic acid (**5a**) (Figure 4.7), correlations from H-1 (δ_H 2.98) to C-2 (δ_C 46.0), C-6 (δ_C 33.5), C-1′ (δ_C 143.9) and C-2′/6′ (δ_C 127.4) suggested the attachment of the phenyl group at C-1 of the cyclohexene moiety, whereas correlations from H-2 (δ_H 2.87) to C-1 (δ_C 42.2), C-3 (δ_C 32.1) and C-7′ (δ_C 179.7) connected the hydroxycarbonyl group at C-2. In addition, HMBC correlations between H-7 (δ_H 2.00-2.04) and C-3 (δ_C 32.1), C-4 (δ_C 135.6), C-5 (δ_C 120.2), C-8 (δ_C 26.3) and C-9 (δ_C 123.9) indicated that the prenyl chain is attached at C-4. For the stereochemistry of C-1 and C-2, since *trans*-cinnamic acid (**15h**)

was used in this DA reaction, so, a *trans*-diaxial relationship of the vicinal protons H-1 and H-2 was established.

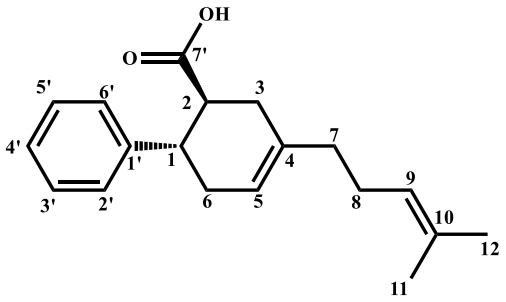


Figure 4.6: The structure of isofislatifolic acid (5a).

Table 4.9: ^{1}H and ^{13}C NMR data of isofislatifolic acid (5a).

Position	^{1}H NMR	^{13}C NMR
1	2.98 (td, *J* = 10.6, 5.6 Hz)	42.2
2	2.87 (td, *J* = 10.8, 5.6Hz)	46.0
3	2.28-2.40 (m)	32.1
4		135.6
5	5.49 (br s)	120.2
6	2.19-2.25 (m), 2.28-2.40 (m)	33.5
7	2.00-2.04 (m)	37.3
8	2.08-2.14 (m)	26.3
9	5.10 (t, *J* = 6.8 Hz)	123.9
10		131.8
11	1.61 (s)	17.7
12	1.70 (s)	25.7
1′		143.9
2′, 6′	7.17-7.21 (m)	127.4
3′, 5′	7.25-7.30 (m)	128.4
4′	7.17-7.21 (m)	126.5
7′		179.7

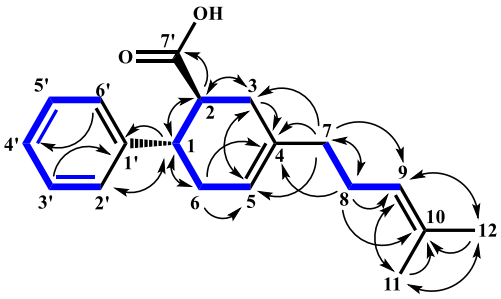
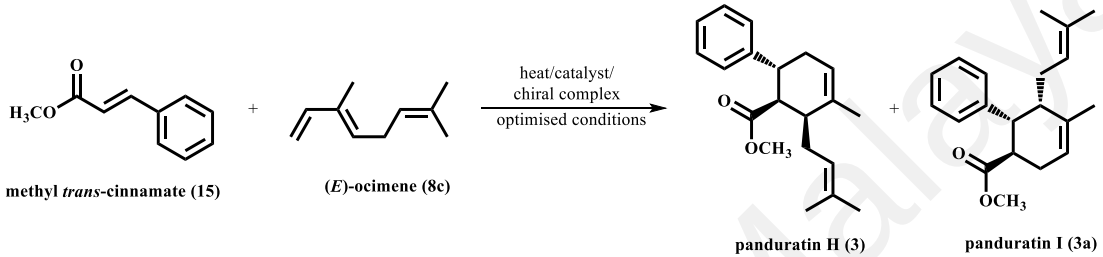


Figure 4.7: Selected COSY (blue & bold) and HMBC (arrows) correlations of isofislatifolic acid (5a).

For catalyst-induced DA reactions between cinnamic acid with myrcene, no adduct was observed when 0.3 equivalent $AlBr_3$ used as catalyst (entry 7, Table 4.8). A similar result was observed when 0.5 equivalent $TiCl_4$ was used as catalyst (entry 8, Table 4.8). No adduct was observed even though the amount of catalyst was increased to 2 equivalents (entries 9 & 10, Table 4.8). This may be due to the low reactivity of *trans*-cinnamic acid (**15h**), and myrcene (**8**) underwent polymerisation, rather than a DA reaction.

For the chiral complex-induced DA reactions, the chiral complex **C8** (entry 53, Table 4.6) was applied to the DA reaction (entry 11, Table 4.8). Like in the reaction of *trans*-4-phenylbut-3-en-2-one (**15j**), no product was observed in the reaction. Once again, the more reactive chiral complex **C3** (entry 20, Table 4.6) was used in the reaction. Unlike in the reaction with *trans*-4-phenylbut-3-en-2-one (**15j**), no conversion was observed when either 1 or 2 equivalents of the chiral titanium complex **C3** were used (entries 12-13, Table 4.8). This seems to indicate that *trans*-cinnamic acid (**15h**) is much more unreactive than *trans*-4-phenylbut-3-en-2-one (**15j**) in the DA reaction.

Table 4.10: Synthesis of panduratins H (3) and I (3a) under thermal, catalyst and chiral complex methods[a].

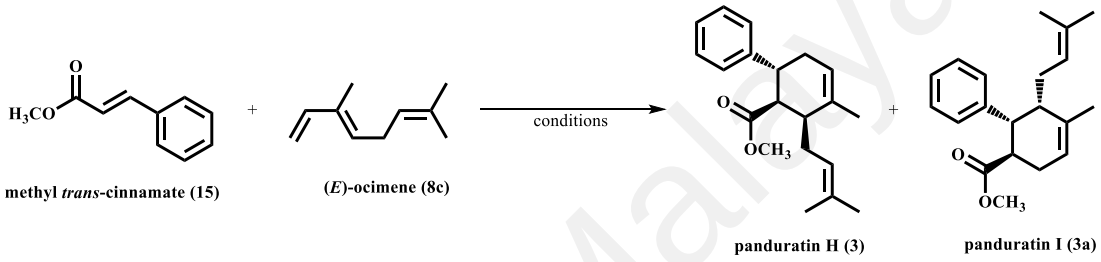


methyl *trans*-cinnamate (15) + (*E*)-ocimene (8c) → panduratin H (3) + panduratin I (3a)

Entry	Lewis acid (LA)	Ligand	Ratio (LA: Ligand)	Base	LA loading (equiv)	Solvent	Solvent amount (mL)	Temp.	Time (h)	Yield (3+3a) (%)[b]	3 (%)[c]	ee (%)[d]	3a (%)[c]	ee (%)[e]
1	-	-	-	-	-	toluene	0.4	150	24	28	23	-	77	-
2	$AlBr_3$	-	1:0	-	0.3	toluene	0.4	r.t.	24	-	-	-	-	-
3	$TiCl_4$	-	1:0	-	0.5	toluene	0.4	r.t.	24	-	-	-	-	-
4	$TiCl_4$	-	1:0	-	1	toluene	0.4	r.t.	24	-	-	-	-	-
5	$TiCl_4$	FMOC-L-Phe-OH (**L5**)	1:2	$NaHCO_3$	1	toluene	1.6	r.t.	24	-	-	-	-	-
6	$TiCl_4$	*R*-BINOL (**L1**)	1:1	*n*-BuLi	2	toluene	1.6	r.t.	24	-	-	-	-	-

[a] Reaction conditions: **15** (0.2 mmol), **8c** (1.0 mmol). [b] Isolated yield for mixture of **3** and **3a**. [c] Determined from the ^{1}H NMR of crude product. [d] ee value for **3**. [e] ee value for **3a**.

The DA reaction between methyl *trans*-cinnamate (**15**) and (*E*)-ocimene (**8c**) was carried out at 150 ^{o}C for 24 h to afford the panduratins H (**3**) and I (**3a**) in 28% yield with ratio of 23:77 (entry 1, Table 4.10) (Scheme 4.37). The spectroscopic data for panduratin H (**3**) and I (**3a**) agreed with that reported in the literature (Win et al., 2008). The selectivity of panduratins H **(3**) and I (**3a**) for this DA reaction (23:77) is comparable to that observed by McLeod's (Pasfield et al., 2013) and Coster's groups (Pigott et al., 2014) for this reaction under high-pressure (26: 74) and thermal conditions (25:75).



Scheme 4.37: Synthesis of panduratin H (3) and its regioisomer, panduratin I (3a).

Like with fislatifolic acid (**5**), no adduct was observed when 0.3 equivalent $AlBr_3$ was used as the catalyst (entry 2, Table 4.10). A similar result was also observed when 0.5 equivalent $TiCl_4$ was used as the catalyst (entry 3, Table 4.10). Increasing the amount of $TiCl_4$ from 0.5 equivalent to 1.0 equivalent did not affect the result either (entry 4, Table 4.10). This may be attributed to the low reactivity of methyl *trans*-cinnamate (**15**), and (*E*)-ocimene (**8c**) polymerising, rather than undergoing DA reaction.

In addition, attempts to synthesise enantiopure panduratins H (**3**) and I (**3a**) by using 2 types of developed chiral titanium complexes **C3** (entry 53, Table 4.6) & **C8** (entry 20, Table 4.6) were unsuccessful (entries 5 & 6, Table 4.10). No product was formed in the DA reactions. This seems to indicate that *trans*-methyl cinnamate (**15**), similar to *trans*-cinnamic acid (**15h**), is less reactive in the DA reactions compared to *trans*-4-phenylbutan-3-en-2-one (**15j**).

According to the above results, the natural products, fislatifolione (**6**), isofislatifolione (**6a**), fislatifolic acid (**5**), panduratin H (**3**) and panduratin I (**3a**) were found to be synthesised through thermal method. However, the thermal method has two disadvantages which are long reaction time and low regioselectivity. Less than 50% product yields were obtained after the reactions were carried out at 150 ^{o}C for 24 h (entries 1 & 6, Table 4.8 & entry 1, Table 4.10). The thermal-induced DA reactions also gave poor regioselectivity. Fortunately, these limitations can be addressed through catalysis. The Lewis acid-catalysed DA reactions between *trans*-4-phenylbut-3-en-2-one (**15j**) and myrcene (**8**) gave the fislatifolione (**6**) and its regioisomer, isofislatifolione (**6a**) in ratios of 91:9 or 95:5 (entries 2 & 3, Table 4.8) compared to ratio 67:33 (entry 1, Table 4.8) from thermal DA reaction. Unfortunately, catalyst method is only available for *trans*-4-phenylbut-3-en-2-one (**15j**) (entries 2 &3, Table 4.8). When other dienophiles such as *trans*-cinnamic acid (**15h**) and methyl *trans*-cinnamate (**15**) were used (entries 7-10, Table 4.8 & entries 2-4, Table 4.10), diene polymerisation was occurred, rather than productive DA reaction. For chiral complex-catalysed DA reaction study, both developed chiral complexes **C3** & **C8** gave disappointing results. The chiral titanium complex **C8** was unreactive to induce the DA reactions between *trans*-4-phenylbut-3-en-2-one (**15j**), *trans*-cinnamic acid (**15h**) and methyl *trans*-cinnamate (**15**) with myrcene (**8**) and (*E*)-ocimene (**8c**) (entries 4 & 11, Table 4.8 & entry 5, Table 4.10). Although the chiral titanium complex **C3** gave high DA yield and excellent regioselectivity when applied to DA reaction between *trans*-4-phenylbut-3-en-2-one (**15j**) with myrcene (**8**) (entry 5, Table 4.8). Unfortunately, no ee value for the DA product was observed. In addition, the chiral complex **C3** did not gave any DA product when *trans*-cinnamic acid (**15h**) and methyl *trans*-cinnamate (**15**) were used as dienophiles (entries 12 &13, Table 4.8 & entry 6, Table 4.10). Since the developed chiral complexes **C3** & **C8** could not produce significant yields and enantioselectivities in the synthesis of the natural products,

fislatifolione (**6**), isofislatifolione (**6a**), fislatifolic acid (**5**), panduratin H (**3**) and panduratin I (**3a**), a new chiral complex should be developed in future if the enantiopure natural products are to be synthesised.

CHAPTER 5: CONCLUSION

An efficient synthesis *via* DA reaction of cinnamoyl dienophile, *trans*-chalcone (**7g**) with terpene diene, (*E*)-ocimene (**8c**) has been successfully developed. The DA reaction mediated by $AlBr_3$ afforded the corresponding product **80** in high yield (72%) and with excellent regio- (100:0) and diastereoselectivities (95:5). The effectiveness of the $AlBr_3$ towards DA reactions between various dienophiles **7g**, **15**, **15c** & **15j** and dienes **8** & **8a-c** were investigated. The acyclic dienes such as isoprene (**8b**), 2,3-dimethylbutadiene (**8a**) and myrcene (**8**) underwent DA reaction with *trans*-chalcone (**7g**), affording the corresponding adducts **32**, **39** & **47** in relatively good yields (73-82%) and with excellent regioselectivities (90:10), whereas the dienophiles such as *trans*-cinnamaldehyde (**15c**), methyl *trans*-cinnamate (**15**) and *trans*-4-phenylbut-3-en-2-one (**15j**) did not give any of the desired DA adducts **3**, **18** & **84** when reacted with (*E*)-ocimene (**8c**). A chiral titanium complex with 2 equivalents of FMOC-L-Phe-OH (**L5**) (**C8**) afforded significant enantioselectivity (61% ee) in the study of asymmetric DA reaction of *trans*-chalcone (**7g**) and isoprene (**8b**) but unfortunately the yield was low (21%). Several methods have been used to increase the yield of the DA reaction for the chiral titanium complex **C8** but were unsuccessful.

Synthesis of a series of (±)-panduratin A derivatives were also attempted with 22 different types of chalcones **7e**, **7h-j**, **7l**, **7m**, **7y**, **7z** & **7aa-an** used as dienophiles to react with (*E*)-ocimene (**8c**) as diene by using $AlBr_3$ as the catalyst. Eighteen (±)-panduratin A derivatives **13** & **80b-r** were successfully synthesised with 9-71% yields. The natural products, fislatifolione (**6**), isofislatifolione (**6a**), fislatifolic acid (**5**), panduratin H (**3**) and panduratin I (**3a**) were synthesised through thermal, catalyst and chiral complex methods. The thermal-induced DA reaction between *trans*-4-phenylbut-3-en-2-one (**15j**) and myrcene (**8**) gave the fislatifolione (**6**) and its regioisomer, isofislatifolione (**6a**) in

moderate yield (39%) and with moderate regioselectivity (67:33). However, when the Lewis acids, $AlBr_3$ and $TiCl_4$ were used as catalysts, the DA reactions gave fislatifolione (**6**) and isofislatifolione (**6a**) in good yields (70 & 71%) and with excellent regioselectivities (91:1 to 95:5). For enantioselective study, the chiral complex formed by the reaction of 1 equivalent of $TiCl_4$ with 2 equivalents of FMOC-L-Phe-OH (**L5**) in the presence of $NaHCO_3$ (**C8**) did not give any DA adducts **6** & **6a**. However, for the chiral complex formed by reacting 1 equivalent of $TiCl_4$ with 1 equivalent of *R*-BINOL (**L1**) in the presence of *n*-BuLi (**C3**), fislatifolione (**6**) and isofislatifolione (**6a**) were obtained in good yield (65%) and with excellent regioselectivity (87:13), but no enantioselectivity was observed. For fislatifolic acid (**5**), isofislatifolic acid (**5a**) and panduratins H (**3**) and I (**3a**), the thermal-induced DA reactions afforded the corresponding adducts **3**, **3a**, **5** & **5a** in moderate yields (28-35%) and with moderate regioselectivities (64:36 to 77:23). However, when using Lewis acid catalysts ($AlBr_3$ & $TiCl_4$) and chiral titanium complexes **C3** & **C8**, no adducts of **3**, **3a**, **5** & **5a** were detected.

In summary, $AlBr_3$ is a good catalyst for Diels-Alder reactions between cinnamoyl dienophiles and terpene dienes, especially when non-2′-hydroxychalcones are used as dienophile. Furthermore, the developed chiral complex **C3** & **C8** are not suitable for the enantioselective Diels-Alder reactions between cinnamoyl dienophiles and terpene dienes. Therefore, the work of screening chiral ligands must be continued in future to obtain a suitable chiral complex for the enantioselective Diels-Alder reaction.

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