Aluminium triflate-mediated organic synthesis

by

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Litany against fear

I must not fear.
Fear is the mind-killer.
Fear is the little-death that brings total obliteration.
I will face my fear.
I will permit it to pass over me and through me.
And when it has gone past I will turn the inner eye to see its path.
Where the fear has gone there will be nothing.
Only I will remain.

Bene Gesserit Litany Against Fear - From Frank Herbert's Dune

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Anzani and Eduan, you were there from the start, always.

My Mom, Sister and Ouma for having the patience and trust to let me do as I please.

Carlé for exposing me to a world full of ideas, experiences and love.

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The Creator for providing the raw materials.

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Synopsis

The work described in this thesis was directed at advancing the applications of $Al(OTf)_3$, a metal triflate, in organic synthesis. Lewis acids play an important role in catalysis and catalyse reactions with high selectivities, unique reactivities under mild conditions. Metal triflates have become the Lewis acids of choice for acid catalysed organic transformations. A detailed literature study of metal triflates provided numerous examples of their use in organic transformations.

$Al(OTf)_3$ has been widely neglected as a Lewis acid which is contrasting to the attention the other metal triflates have received. Previous work in our laboratories had established $Al(OTf)_3$ as an effective Lewis acid catalyst for the ring-opening of epoxides with simple alcohols and amines.

The alcoholysis of epoxides provides a ready access to β-alkoxy alcohols. Whilst this reaction has been shown to occur with $Al(OTf)_3$ as a catalyst, the established protocol calls for the use of the nucleophilic alcohol in an excess amount. Whilst this proves no problem when simple alcohols are employed as nucleophiles in the ring-opening reaction, it is a problem when more complex and expensive alcoholic nucleophiles are utilised. A modified procedure utilising $Al(OTf)_3$ as a catalyst was developed which tolerates the use of only 1 equivalent of the nucleophilic alcohol for the ring opening reaction. The desymmetrisation of a *meso*-epoxide with chiral alcoholic nucleophiles was also investigated and the outcome of the diastereoselectivity of the reaction reported.

The aminolysis of epoxides has been established utilising $Al(OTf)_3$ as the Lewis acid catalyst. However, this has only been demonstrated for the ring opening of simple epoxides with simple amines. Piperazine derived β-amino alcohols with known biological activity were chosen as substrates with which to test the $Al(OTf)_3$ catalysed aminolysis of epoxides in the synthesis of more complex β-amino alcohols. The various starting epoxides and amine nucleophiles were synthesised. During which a new approach towards the synthesis of *N*-glycidyl amines was developed utilising a two step approach with the first step being

catalysed by $Al(OTf)_3$. It was also found that the optimal method for forming the β-amino alcohol bond was one in which the glycidyl motif was placed on the less basic heteroatom and ring opened by the more nucleophilic piperazine amine. It was also demonstrated that these reactions could be scaled up and the $Al(OTf)_3$ recovered and reused without significant loss in catalytic activity.

During the ring-opening of *meso*-epoxides by chiral alcohols it was found that $Al(OTf)_3$ could promote the nucleophilic substitution of pro-electrophilic/"activated" alcohols. This type of transformation is of particular importance in green chemistry due to the formation of the benign water molecule as compared to the salts usually formed during the nucleophilic substitution of alcohols. Whilst there is a fair amount of literature on the Lewis acid catalysed nucleophilic substitution of these types of "activated" alcohols, there hasn't been a single report on the use of $Al(OTf)_3$ as a catalyst for this type of reaction. The nucleophilic substitution of these "activated" alcohols was found to be effectively catalysed by $Al(OTf)_3$. Oxygen, carbon, sulfur and nitrogen nucleophiles were successfully employed in this reaction. This methodology was then extended to the intramolecular cyclisation of a chalcone type "activated" alcohol with a nucleophilic site present on the molecule. Oxygen and nitrogen nucleophiles were employed in this regard and furnished the corresponding 2*H*-chromenes and 1,2-dihydroquinolines in high yields.

Abbreviations

Å	angstrom
Ac	acetyl
Ar	aryl
Bmim	1-butyl-3-methylimidazolium
Bn	benzyl
°C	degrees Celsius
COSY	correlation spectroscopy
DEPT	distortionless enhancement by polarisation
DCE	dichloroethane
DCM	dichloromethane
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EIMS	electron ionisation mass spectroscopy
ESIMS	electrospray ionisation mass spectroscopy
eq	equivalents
Et	ethyl
EWG	electron withdrawing group
FID	flame ionization detector
GC	gas chromatography
h	hour

Hex	hexyl
HSQC	heteronuclear single-quantum correlation
i-Pr	*iso*-propyl
IR	infrared
LA	Lewis acid
Me	methyl
min	minute
m/m	mass to mass
MOM	methoxymethyl
Mp	melting point
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate (triflate)
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
RE	rare earth
rt	room temperature
t-Bu	*tert*-butyl
TBAB	tetra-*n*-butlyammonium bromide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl

TEA	triethylamine
TFOH	triflic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethyl-ethane-1,2-diamine
TMS	trimethylsilyl
Tosyl	toluenesulfonyl
Tr	triphenyl methyl (trityl)
Triflate	trifluoromethanesulfonate (the contraction ‘triflate’ is used throughout this thesis)
Trityl	triphenyl methyl
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

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Contributions

Aspects of the work covered in this manuscript have been published or presented both locally (South Africa) and internationally.

Research Papers

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Williams, D. B. G.; Cullen, A.; Fourie, A.; Henning, H.; Lawton, M.; Mommsen, W.; Nangu, P.; Parker, J.; Renison, A.; *Green Chem.* **2010**, *12*, 1919-1921.

Oral presentations at the conferences

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CATSA, Johannesburg, South Africa (November 2011)

Chapter 1

Metal triflates as Lewis acids-A literature overview

1.1 Introduction to Lewis acids

Metal triflates are emerging as prominent Lewis acid catalysts in organic transformations. These metal triflates are favoured above the traditional Lewis acids due to their increased activity and stability to moisture and air. This review will serve to illustrate their use in general organic transformations. Specifically the ring-opening of epoxides as well as the nucleophilic substitution of "activated" alcohols will be reported.

1.1.1 Acid/base definitions

Acids and bases play an important role in organic chemistry. They catalyse or promote a wide array of organic transformations.[1] There have been numerous definitions put forward in the history of chemistry as to what type of compound constitutes an acid or a base. The Arrhenius definition states that a species which dissolves in water and increases the concentration of hydrogen ions, H^+ (aq), is an acid. Conversely a base is one that will dissolve in water and increase the hydroxide ion concentration, OH^- (aq).[2] Brønsted and Lowry independently defined an acid as a proton donor and a base as a proton acceptor.[3] Shortly after this definition, Lewis proposed his definition of acids and bases, which is now one of the most widely recognised definitions due to its simplicity and applicability.[3] Lewis defined an acid as an electron pair acceptor and a base as an electron pair donor.[4]

Coordination chemists realised that certain metal ions (acids) displayed an affinity for certain non-metal ligands (bases).[3] This phenomenon can be explained by Pearson's[5] hard-soft acid-base theory. Hard acids are defined as small non-polarisable species carrying a large positive charge whereas soft acids are defined as large polarisable species carrying a diffuse positive charge.[5] Although this hard-soft acid-base theory can explain the stability of certain acid-base interactions it should be noted that relative acid/base strengths should also be taken into account. For example a strong, soft base can displace a weak, hard base from a hard acid.[3]An example of this type of displacement is when RS^- displaces H_2O from the hard acid H^+. This is an example of a kinetically stable complex being more prevalent than a thermodynamically stable complex.

Lewis acids have found wide application in organic synthesis as catalysts. This is because these catalysts allow mild reaction conditions and often show unique reactivities, and facilitate high selectivity for the production of the desired substance.[6] Traditional Lewis acids include $AlCl_3$, BF_3, $TiCl_4$ and $SnCl_4$. These acids suffer from moisture sensitivity with complete deactivation or decomposition occurring with even the smallest amounts of water in the reaction mixture. They are also often used in super-stoichiometric amounts with no possibility of recovery and reuse in subsequent reactions.[7]

1.1.2 Metal triflates in organic synthesis

1.1.2.1 Introduction to metal triflates

The first report of a metal triflate that was water compatible, lanthanum triflate ($Ln(OTf)_3$), was published in 1991.[8] (Throughout this text, the word 'triflate' refers to the trifluoromethane sulfonic anion. This is a convenient contraction of the much longer full name of the conjugate base of trifluoromethane sulfonic acid, and is commonly used in manuscripts on the subject.) After this, metal triflates become more widely used in organic chemistry, with a review article being written in 2002 by Kobayashi[7] listing over 400 references dealing with the use of metal triflates. Metal triflates, unlike their traditional Lewis acid counterparts, can be used in catalytic amounts, recovered and reused without significant loss in activity and also show stability to the presence of water or to other protic media in the reaction mixture.[7] It is these features that make them interesting candidates for the promotion of organic transformations. Rare earth metal triflates represent by far the most well-studied metal triflates in the literature. There are, however, other examples of metal triflates used such as indium and aluminium triflate.

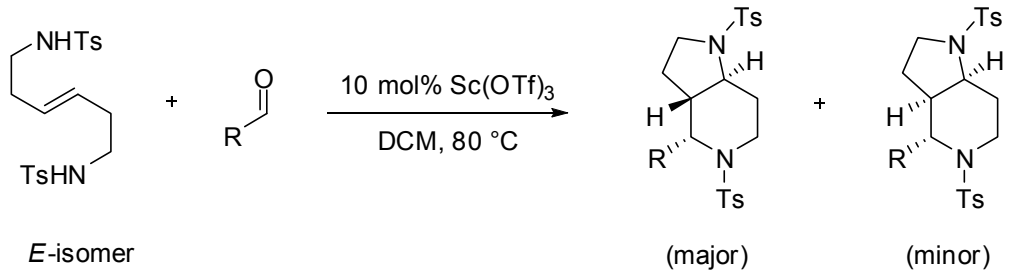
1.1.2.2 Rare earth metal triflates

The main rare earth metal triflates used in organic synthesis are $Ln(OTf)_3$, $Sc(OTf)_3$ and $Y(OTf)_3$. These Lewis acids have found application in carbon-carbon bond formation reactions, carbon-heteroatom bond formation reactions, oxidation-reduction reactions, rearrangements as well as protection-deprotection reactions.[7] They can be formed by heating the corresponding metal oxide or chloride in the presence of aqueous trifluoromethanesulfonic acid (TfOH).[8] These metal triflates then contain water within their molecular structure which can be removed at elevated temperatures under vacuum to obtain the anhydrous metal triflate.

1.1.2.2.1 Scandium triflate

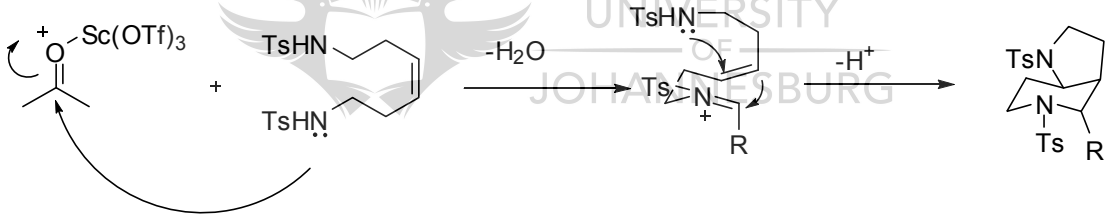
The aza-Prins cyclisation of a bis-homoallylic amide with an aldehyde was reported by Reddy and co-workers in 2010.[10a] Scandium triflate was used to catalyse the intramolecular

aza-Prins cyclisation of hex-3-ene-1,6-ditosylamide with various aldehydes (Scheme 1.1) to give the corresponding diaza-bicycles.



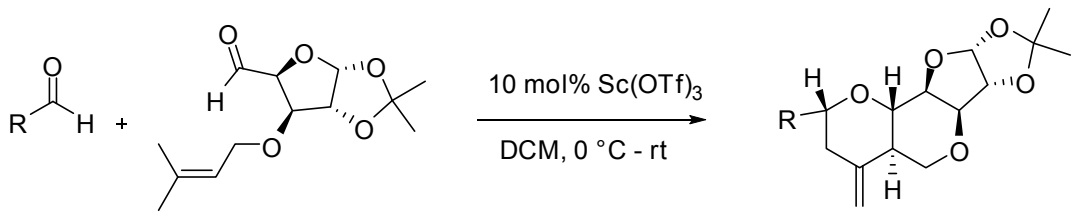
Scheme 1.1 : The aza-Prins cyclisation of a bis-homoallylic amide with an aldehyde.

Scandium triflate was found to be superior to lanthanum and indium triflates in catalysing this reaction. A proposed mechanism involves the formation of a *N*-sulfonyl iminium ion from the aldehyde and homoallylic tosylamine. The *N*-sulfonyl iminium ion undergoes cyclisation with subsequent trapping of the resultant carbocation by the *N*-tosylamine group to give the diaza product (Scheme 1.2).



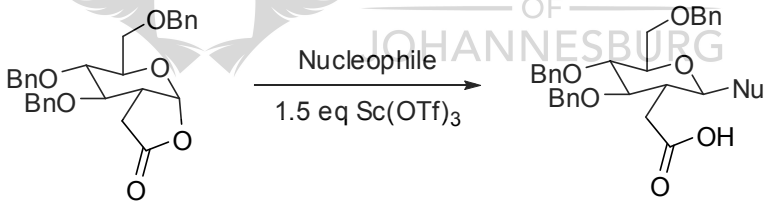
Scheme 1.2 : Proposed mechanism for the aza-Prins cyclisation.

The same group then went on to report a $Sc(OTf)_3$-catalysed sugar based tandem ene-Prins cyclisation.[10b] In this report an aldehyde and an olefin-tethered sugar aldehyde were reacted to give the sugar annulated pyranopyran in good yields and high selectivities (Scheme 1.3), in two consecutive Prins cyclisation reactions. These types of tandem reactions that construct fused rings in a single pot in multi-step sequences have the advantage of having high selectivity, efficiency and atom economy whilst being performed in a one-pot operation.[10b] In the present instance, the reaction presumably proceeds via an initial Prins reaction of the alkene onto the sugar aldehyde, followed by reaction of the cyclic alcohol with the aldehyde to form an oxy-carbenium species, which undergoes the second Prins cyclisation to produce the tricyclic product.



Scheme 1.3 : ene-Prins cyclisation of a prenyl tethered sugar aldehyde with benzaldehydes.

The nucleophilic ring-opening of bicyclic carbohydrate 1,2-lactones (Scheme 1.4) was realised utilising $Sc(OTf)_3$ as a Lewis acid. In this instance $Sc(OTf)_3$ was required in super-stoichiometric amounts but remained superior to other Lewis acids tested in equivalent amounts (Table 1.1).[10c] This procedure enables the introduction of a range of different substituent's at the anomeric position to afford a wide variety of functionalised carbohydrates. The results from Table 1.1 indicate that other Lewis acids failed to give the desired product leading only to decomposition of the starting sugar derivative. This is a good example of the high selectivities that can be obtained with metal triflates as opposed to other traditional Lewis acids.



Scheme 1.4 : Ring-opening of the carbohydrate 1,2-lactone with a nucleophile in the presence of $Sc(OTf)_3$.

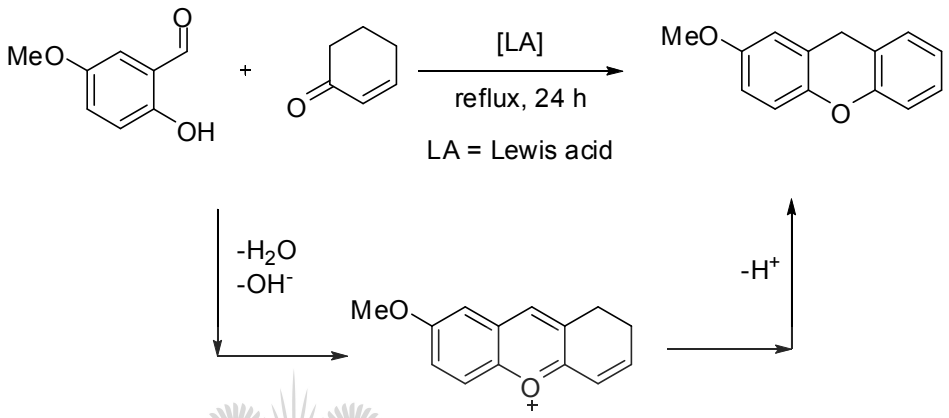
Table 1.1 : Comparison of Lewis acids for the ring-opening of carbohydrate 1,2-lactone.

Entry	Lewis acid	Solvent	Result[a]
a	TMSOTf	DCM	A
b	$SnCl_4$	DCM	B
c	$SnCl_4$	CH_3CN	B
d	$TiCl_4$	DCM	C
e	$TiCl_4$	CH_3CN	C
f	$BF_3{\cdot}OEt_2$	DCM	C
g	$Sc(OTf)_3$	THF	B
h	$Sc(OTf)_3$	CH_3CN	A
i	$Sc(OTf)_3$	DCM	90%[b]

[a]A : no conversion. B : cleavage of *O*-benzyl protecting group; C : decomposition of carbohydrate. [b]Yield of analytically pure product isolated by column chromatography.

The condensation of salicylaldehydes with cyclohexenones or tetralones to give the corresponding xanthenes (Scheme 1.5) has been catalysed by $Sc(OTf)_3$.[10d] This reaction is thought to proceed via an intermediate benzopyrilium salt formed by the acid catalysed condensation of the salicylaldehyde and cyclohexanone, a subsequent sigmatropic hydrogen shift would give the desired product (Scheme 1.5). The authors listed the occurrence of an intense colour during the reaction course as evidence for formation of the intermediate benzopyrilium salts. Other Lewis acids were also investigated (Table 1.2) and the yields found to be inferior to $Sc(OTf)_3$. In the absence of a catalyst no reaction was observed (Table 1.2, entry 1) and in the presence of a Brønsted acid (Table 1.2, entry 10) substrate decomposition was observed. The best yields were obtained by performing the reaction with a slight excess of the salicylaldehyde (Table 1.2, entry 11). It was also found that the reaction could be performed under microwave conditions (Table 1.2, entry 12) with the reaction being complete in 30 minutes as opposed to 24 hours required for a heated oil bath. Here, the yield was very high, as is often the case in microwave-assisted reactions. The presence of air and water was found to have no effect on the reaction yields indicating the stability of this catalyst and tolerance of the reaction to these entities. It was established that the reaction catalysed by $Sc(OTf)_3$ could be performed even in the presence of 10 vol% water. In further

reactions, the authors actively removed the two equivalents of water generated in the reaction by means of a Dean-Stark trap, in an attempt to investigate if removal of water would influence the outcome of the reaction. In this instance, the yield did not improve. Interestingly, the addition of molecular sieves actually resulted in a lower conversion, with only 6% product being isolated. Overall, the work demonstrates the ability of the $Sc(OTf)_3$ to function even when there is a relatively large amount of water present in the reaction mixture, where traditional Lewis acids like $ZnCl_2$ require the removal of the water formed in order to be effective in this reaction.[10e]



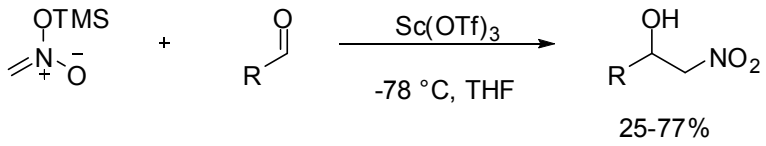
Scheme 1.5 : Lewis acid catalysed condensation between salicylaldehydes and cyclohex-2-enone.

Table 1.2 : Optimisation of reaction conditions for the condensation of salicylaldehyde and cyclohex-2-enone.[a]

Entry	Salicylaldehyde : cyclohex-2-enone	Lewis acid	Mol% catalyst	Yield (%)[b]
1	1 : 1	-	-	0
2	1 : 1	Zn_2Cl	20	50
3	1 : 1	$Zn(OTf)_3$	20	23
4	1 : 1	$Yb(OTf)_3$	20	40
5	1 : 1	$Y(OTf)_3$	20	22
6	1 : 1	$Er(OTf)_3$	20	42
7	1 : 1	$Sm(OTf)_3$	20	23
8	1 : 1	$Cu(OTf)_3$	20	23
9	1 : 1	$Sc(OTf)_3$	15	55
10	1 : 1	TfOH	20	9
11	1.1 : 1	$Sc(OTf)_3$	5	63
12[c]	1.1 : 1	$Sc(OTf)_3$	5	82

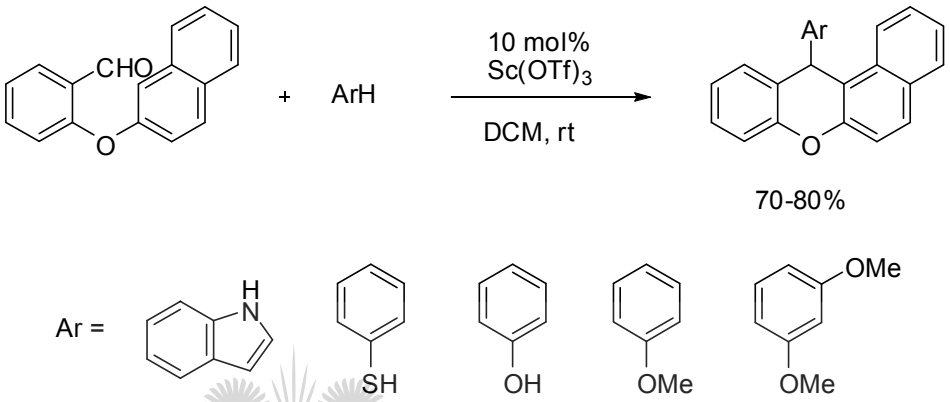
[a] Reaction conditions: 4 mL chlorobenzene per 1 mmol substrate. [b] Isolated yield. [c] Microwave heating at 180 °C for 30 minutes.

The Henry reaction is a carbon-carbon bond forming reaction between a nitronate and an aldehyde or ketone to generate the β-nitroalcohol.[10f] One of the major drawbacks of this reaction is the retro Henry reaction which leads to low reaction yields. This can be overcome by the use of a large excess of the nitronate or the use of a silyl nitronate which traps the Henry product preventing further reaction. Often, this reaction requires an anhydrous fluoride source in order to initiate the reaction.[10f] This fluoride source has to be prepared and is not commercially available. $Sc(OTf)_3$ has been reported to catalyse this reaction to give the corresponding Henry reaction products in low to good yields without the need of an anhydrous fluoride source (Scheme 1.6).[10f]



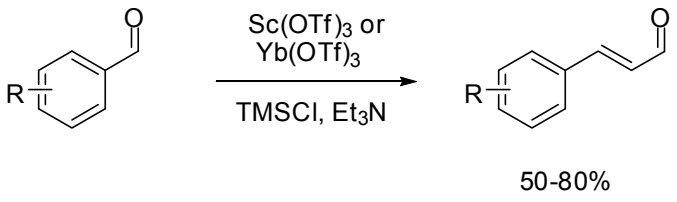
Scheme 1.6 : $Sc(OTf)_3$ catalysed Henry reaction.

The one-pot domino approach towards the synthesis of unsymmetrical 9-substituted xanthene derivatives catalysed by $Sc(OTf)_3$[10g] presents an attractive multi-bond forming reaction (Scheme 1.7). These types of multi-bond forming reactions are useful due to their high atom economy and reduced number of synthetic steps. The traditional synthesis of these xanthenes requires harsh reaction conditions, stoichiometric amounts of reaction promoters and the use of moisture sensitive catalysts. The authors found that by using $Sc(OTf)_3$ as the catalyst these limitations could be overcome.[10g]

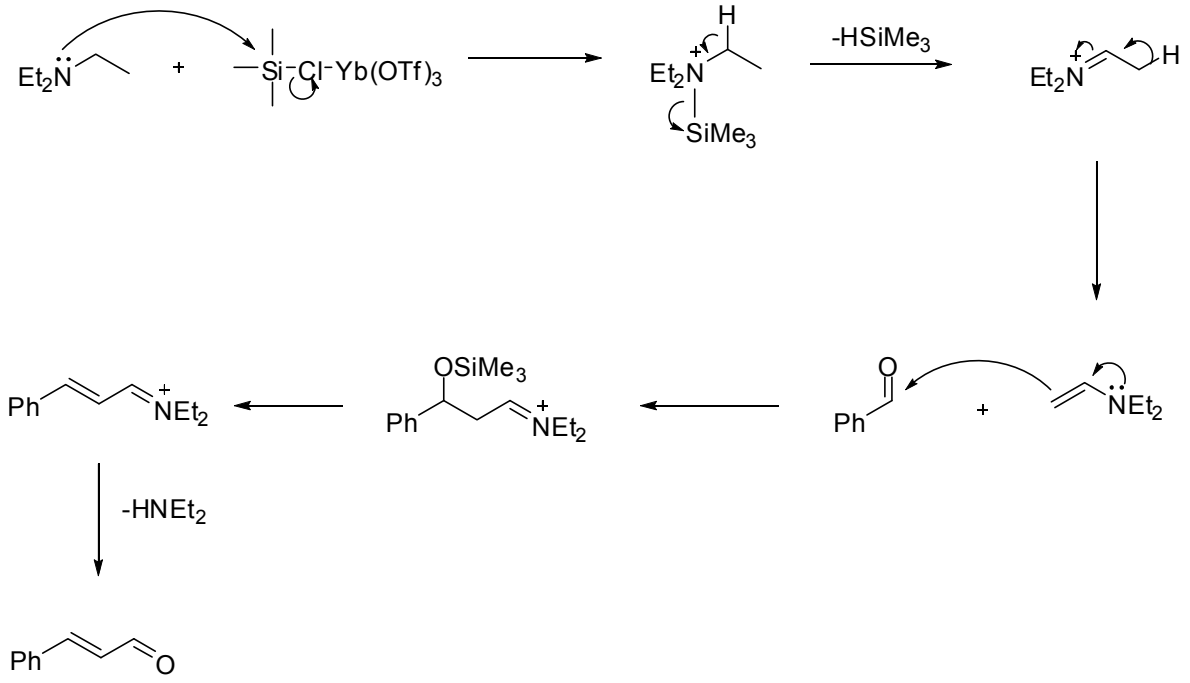


Scheme 1.7 : Tandem synthesis of unsymmetrical 9-aryl/heteroaryl xanthenes catalysed by $Sc(OTf)_3$.

It has been found that $Sc(OTf)_3$ as well as $Yb(OTf)_3$ can be used for the synthesis of α,β-unsaturated aldehydes from the corresponding benzaldehydes.[10h] This occurs through the activation of triethylamine (TEA) by the metal triflate and chlorotrimethylsilane to form the diethylvinylamine. This activated TEA then reacts with the benzaldehyde to form the two carbon extended aldehyde (Scheme 1.8). However this procedure required the use of a stoichiometric amount of the Lewis acid.

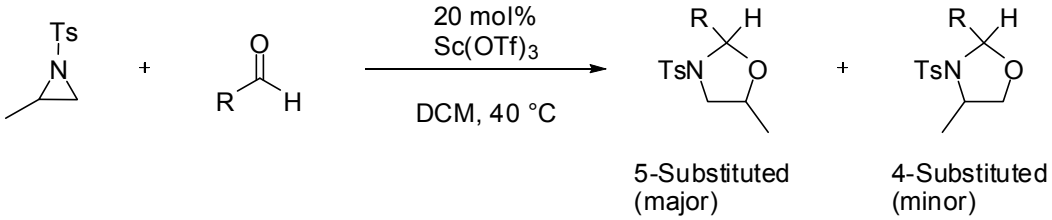


Scheme 1.8 : $Sc(OTf)_3$ or $Yb(OTf)_3$ mediated synthesis of α,β-unsaturated aldehydes from the corresponding benzaldehydes.



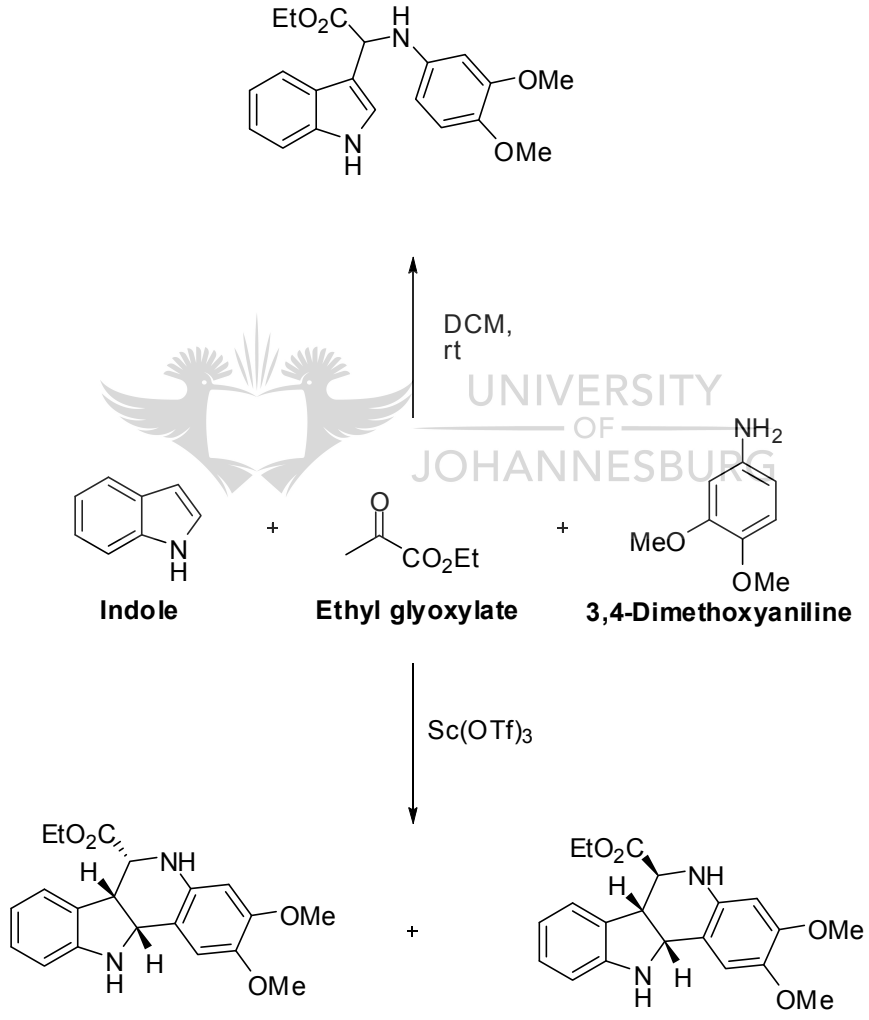
Scheme 1.9 : Proposed mechanism for the synthesis of α,β-unsaturated aldehydes from the corresponding benzaldehydes via reaction with diethylvinylamine.

5-Alkyl-1,3-oxazolidines could be obtained in excellent yields with high regioselectivity from the condensation of 2-alkyl-*N*-tosylaziridine with a variety of aldehydes and ketones (Scheme 1.10).[10i] This cycloaddition of an azidirine onto a carbonyl group was successfully catalysed by 20 mol% $Sc(OTf)_3$. The 5-alkyl-1,3-oxaxolidine products derived from aldehydes were obtained in yields in the excess of 80% with reaction times that where generally under 1 hour. Reaction times in excess of 2 hours were required for the products derived from ketones, quite a bit longer than that required for the aldehyde substrates. This presumably reflects the reduced electrophilicity of ketones compared to aldehydes. Despite this increased reaction time, high yields were still realised.



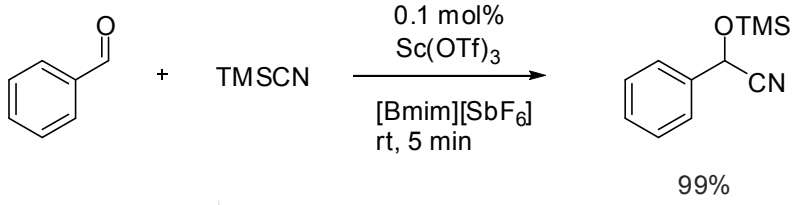
Scheme 1.10 : $Sc(OTf)_3$ catalysed condensation of the azidirine with an aldehyde.

Unique reactivities of substrates can be realised in the presence of metal triflates. This is illustrated in the multi-component reaction of indole, ethyl glyoxylate and 3,4-dimethoxyaniline (Scheme 1.11).[10j] In the absence of $Sc(OTf)_3$ the expected acetates are obtained. However, when $Sc(OTf)_3$ is introduced to the reaction, the aza-Diels-Alder adducts are obtained (Scheme 1.11). This results from the ethyl-2-(arylimino)acetates (azomethynes formed from the initial reaction of ethylglyoxylate and 3,4-dimethoxyaniline) behaving as heterodienes with indole as the dienophile. The acetate that normally forms in this reaction was found not to rearrange to the aza-Diels-Alder adducts when it was subjected to $Sc(OTf)_3$. The reaction thus follows a completely different pathway in the presence of $Sc(OTf)_3$.[10j]



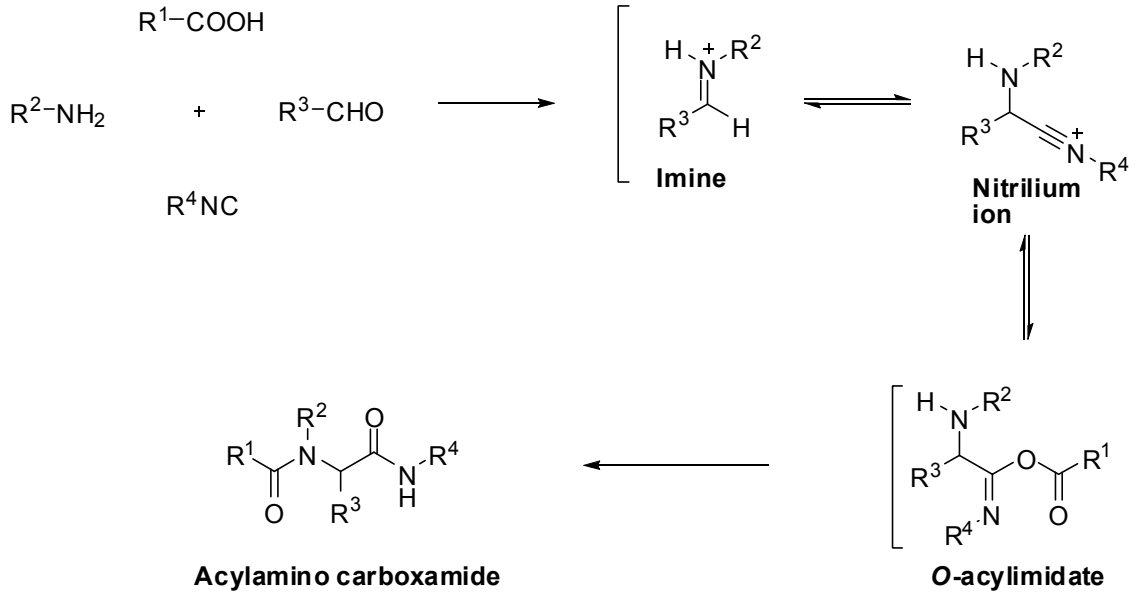
Scheme 1.11 : Multi-component reaction between indole, ethyl glyoxylate and 3,4-dimethoxyaniline in the presence and absence of $Sc(OTf)_3$.

Ionic liquids are attracting considerable attention as vehicles for metal catalyst immobilisation. In doing this, the recovery and reuse of the metal catalyst as well as of the ionic liquid is possible.[10k] The development of recyclable catalytic systems is of particular interest in green chemistry applications. The catalytic activity of $Sc(OTf)_3$ has been found to increase dramatically in some ionic liquids (e.g. $[Bmim][SbF_6]$) for the cyanosilylations of benzaldehydes (Scheme 1.12).[10k] This is presumably due to the anionic exchange between $Sc(OTf)_3$ and $[Bmim][SbF_6]$ to give a Lewis acid catalyst with increased acidic character when compared to $Sc(OTf)_3$ alone. In the absence of an ionic liquid, that is to say in DCM, the reaction gave only 7% yield, illustrating the importance of the combination of metal triflate and ionic liquid. This system was found to be recyclable for up to 10 cycles without significant loss of catalytic activity.



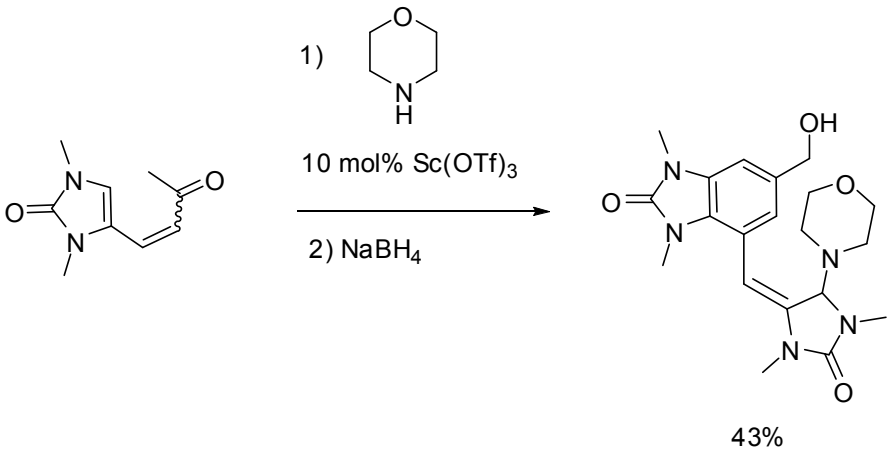
Scheme 1.12 : $Sc(OTf)_3$/$[Bmim][SbF_6]$ catalysed cyanosilylation of benzaldehydes.

The Ugi four component coupling reaction is another example of a multi-component reaction that can be promoted by $Sc(OTf)_3$.[10l] This reaction takes place between an isocyanide, an amine, a carboxylic acid and a ketone or aldehyde (Scheme 1.13). These components condense to give an α-acylamino carboxamide. The first step involves the condensation of the carbonyl with the amine to give the imine. It is believed that the Lewis acid protonates this intermediate imine thus activating it towards attack from the isocyanide to give the nitrilium ion. The carboxylate anion then adds to this nitrilium ion to form the *O*-acylimidate which then rearranges to the more stable α-acylamino carboxamide.[10l] 10 Mol% $Sc(OTf)_3$ or $Yb(OTf)_3$ were found to catalyse this reaction to give yields in the range of 50–70% in only 15 hours. In the absence of these catalysts, virtually no reaction product was observed.



Scheme 1.13 : The Ugi four component reaction to give the α-acylamino carboxamide.

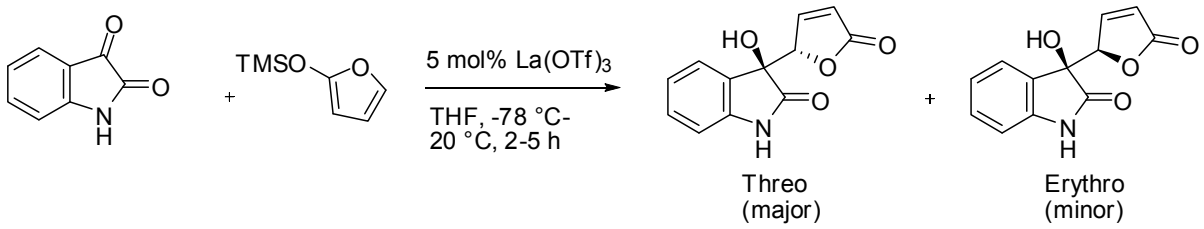
A novel AA'B, 2:1 coupling of imidazolone or benzofuran substituted enals with morpholine, promoted by $Sc(OTf)_3$/morpholine in a dual metal/amine catalysed reaction, has been reported (Scheme 1.14).[10m] This is consistent with the formal inverse electron demand Diels-Alder cycloaddition, which proceeds in a stepwise manner via a domino Michael-Mannich annulation process. This process involves activation of the iminium ion of the diene.



Scheme 1.14 : $Sc(OTf)_3$/morpholine promoted coupling of an imidazolone enal with a morpholine.

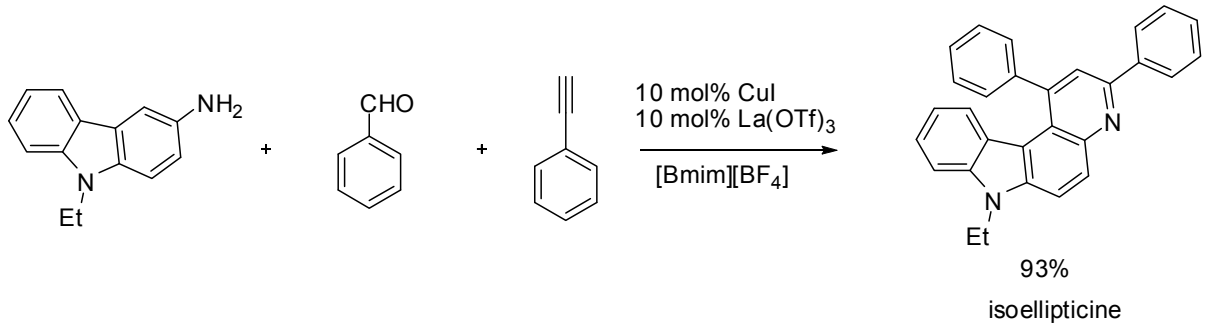
1.1.2.2.2 Lanthanum triflate

The vinylogous Mukaiyama aldol reaction of 2-(trimethylsiloxy)furan and various (*N*-alkyl)isatins proceeds diastereoselectively in the presence of 5 mol% $La(OTf)_3$ (Scheme 1.15).[11a] It is believed that the $La(OTf)_3$ chelates with the carbonyl groups of isatin activating them towards attack from the 2-(trimethylsiloxy)furan to give the corresponding 3-hydroxy-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one in a high yield (80-90%) and high diastereoselectivity (*threo*:*erythro*, 93:7).[11a]



Scheme 1.15 : Vinylagous Mukaiyama aldol reaction between an isatin and 2-(trimethylsiloxy)furan catalysed by $La(OTf)_3$.

Ellipticine and its analogues have found application as anticancer agents.[11b] The synthesis of isomeric ellipticine derivatives is reported via the tandem CuI/$La(OTf)_3$ catalysed reaction in the ionic liquid [Bmim][BF_4].[11b] This involved the reaction between an amine, an aldehyde and a terminal alkyne (Scheme 1.16), in a reaction which formally (but perhaps not mechanistically) involves a cycloaddition reaction to generate the ring structure.



Scheme 1.16 : CuI/$La(OTf)_3$ catalysed synthesis of isoellipticine.

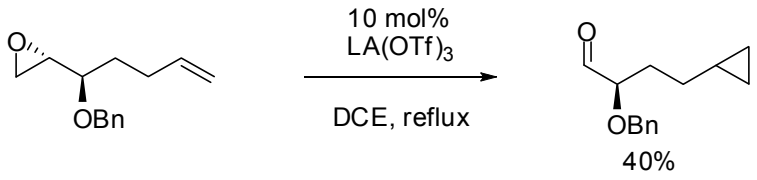
Initial experiments performed for the synthesis of isoellipticine utilised $BF_3{\cdot}OEt_2$ as the Lewis acid, but only yielded the imine and not the desired product (Table 1.3, entry 1).

Through the addition of CuI at 10 mol% it was possible to see activation of the triple bond towards attack onto the imine to give the desired product in a moderate yield (Table 1.3, entry 2). Various other Lewis acids were investigated (Table 1.3, entries 2-10). It was found that the rare earth metal triflates gave the best yield. Although $Sc(OTf)_3$ and $Yb(OTf)_3$ gave yields similar to $La(OTf)_3$ the authors decided on the use of $La(OTf)_3$ due to its lower price compared to the other two rare earth metal triflates. The use of other copper salts was also investigated (Table 1.3, entries 10-13). CuI was found to be the best copper salt for this reaction. It was also found that the reaction yield increased when performed in the ionic liquid [Bmim][BF_4] (Table 1.3, entry 17) as opposed to reactions performed in conventional organic solvents (Table 1.3, entries 13-15). The reaction could be performed in the absence of $La(OTf)_3$ (Table 1.3, entries 19-20). However, the presence of a CuI catalyst was found to be critical for this reaction to proceed to the desired product. The $La(OTf)_3$ in all likelihood serves to catalyse the initial imine formation step whilst the CuI serves to activate the terminal alkyne.

Table 1.3 : Comparison of Lewis acids used for the synthesis of isoellipticine.

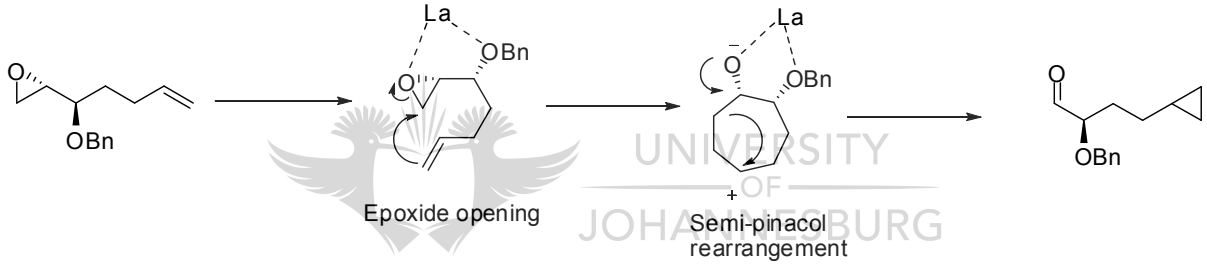
Entry	Catalyst	Time (h)	Yield (%)
1	$BF_3{\cdot}OEt_2$ (20 mol%)	24	-
2	CuI/ $BF_3{\cdot}OEt_2$ (20 mol%)	24	40
3	CuI/CF_3COOH (20 mol%)	24	42
4	$CuI/InCl_3$ (20 mol%)	12	70
5	$CuI/In(OTf)_3$ (10 mol%)	12	75
6	CuI/AgOTf(10 mol%)	12	52
7	$CuI/Cu(OTf)_2$ (10 mol%)	12	72
8	$CuI/Sc(OTf)_3$ (10 mol%)	8	83
9	$CuI/Yb(OTf)_3$ (10 mol%)	8	82
10	$CuI/La(OTf)_3$ (10 mol%)	8	85
11	$CuBr/La(OTf)_3$ (10 mol%)	10	62
12	$CuCl/La(OTf)_3$ (10 mol%)	12	51
13	$CuI/La(OTf)_3$ (10 mol%)/THF	8	72
14	$CuI/La(OTf)_3$ (10 mol%)/Toluene	8	75
15	$CuI/La(OTf)_3$ (10 mol%)/DMSO	8	73
16	$CuI/La(OTf)_3$ (10 mol%)/[Bmim][Cl]	6	88
17	$CuI/La(OTf)_3$ (10 mol%)/[Bmim][BF_4]	4	93
18	$CuI/La(OTf)_3$ (10 mol%)/[Bmim][PF_6]	4	90
19	CuI (10 mol%)/[Bmim][BF_4]	6	60
20	CuI (30 mol%)/[Bmim][BF_4]	6	62

During an attempted alcoholysis reaction of an epoxide catalysed by $La(OTf)_3$, Hardee and co workers discovered that a cyclopropyl aldehyde was forming (Scheme 1.17).[11c] This product arises due to a methylene-transfer cyclopropanation reaction. Other Lewis acids such as $Mg(OTf)_2$, $Zn(OTf)_2$, $Al(OTf)_3$ and $Bi(OTf)_3$ were found to give low yields for this reaction (<10%). Other rare earth metal triflate catalysts such as $Yb(OTf)_3$ and $Eu(OTf)_3$ gave slightly better yields (20%). The best yields (72%) were obtained using $La(OTf)_3$ in conjunction with 2,6-lutidine as a base and $LiClO_4$ as an additive. The stereospecificity of the reaction was maintained with *trans* or *cis* olefins giving *trans* or *cis*-cyclopropanes, respectively.



Scheme 1.17 : $La(OTf)_3$ catalysed internal methylene transfer on an epoxide to give the cyclopropyl aldehyde.

A mechanism for this reaction has been proposed (Scheme 1.18).[11c] This involves the chelation of a lanthanum ion to the alkoxy epoxide, activating it towards internal nucleophilic attack by the alkene moiety. A semipinacol-type collapse results in the intermediate carbocation which rearranges to the cyclopropyl aldehyde. The authors found internal olefins to more readily undergo methylene transfer than terminal olefins which further supports this mechanism.[11c]



Scheme 1.18 : Proposed mechanism for the cyclopropanation of an epoxide via an internal methylene transfer.

The catalytic asymmetric ring-opening of *meso*-azidirines with a malonate nucleophile provides access to cyclic γ-amino acids. Zu and co-workers[11d] were the first to report this in an asymmetric catalytic form, which involved the use of a 1:1:1 mixture of La(O-*i*Pr)$_3$/Yb(OTf)$_3$/Schiff base. Through the use of this mixture it was envisioned to create a dinuclear Schiff base complex from the corresponding Brønsted basic rare earth metal alkoxide and Lewis acidic rare earth metal triflate as shown in Figure 1.1. This Schiff base complex was then found to enantioselectively ring-open *meso*-azidirines to give chiral cyclic and acyclic γ-amino esters in high yields (63-99%) and high enantioselectivities (97-99.5% ee) (Scheme 1.19).[11d]

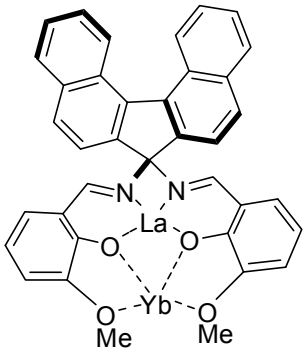
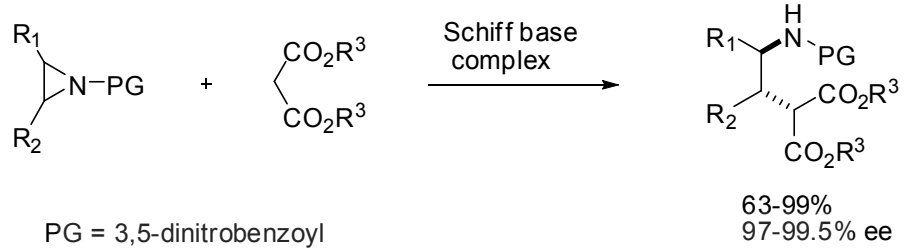
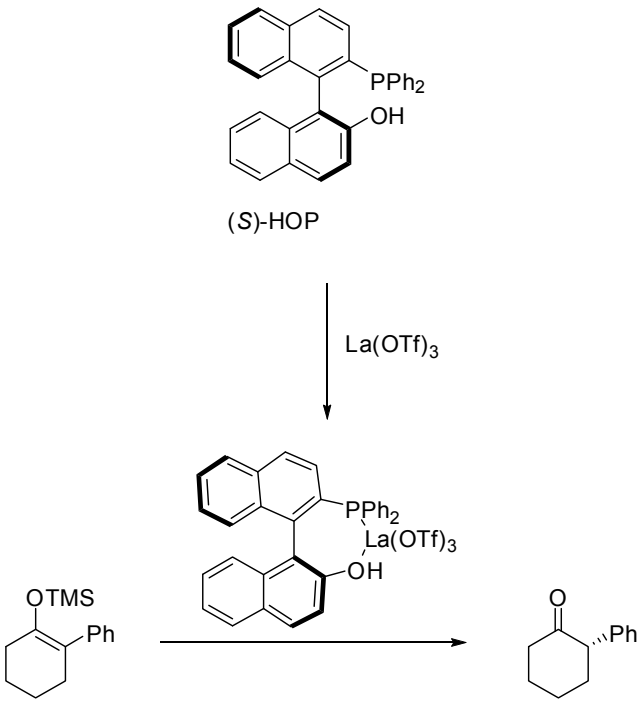


Figure 1.1 : Dinuclear Schiff base complex for the enantioselective ring-opening of *meso*-azidirines.



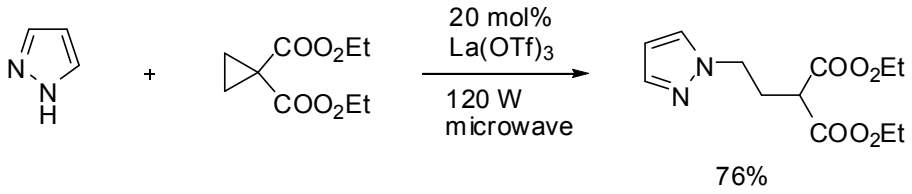
Scheme 1.19 : Enantioselective ring-opening of *meso*-azidirines to give the γ-amino esters using the dinuclear Schiff base complex in Figure 1.1.

$La(OTf)_3$ has been reported for the use as the Lewis acid component of a Lewis acid assisted chiral Brønsted acid catalyst for the asymmetric protonation of the silyl enol ethers of 2-substituted cyclic ketones (Scheme 1.20).[11e] The idea of utilising a chiral Brønsted acid in conjunction with a strong Lewis acid is receiving more attention in organic synthesis. The low acidic catalytic activity of chiral Brønsted acids is increased by complexation to the strong Lewis acid. The chiral Lewis assisted Brønsted acid was generated from (*S*)-2-hydroxy-2'-diphenylphosphino-1,1'-binaphthyl ((*S*)-HOP) and $La(OTf)_3$.[11e] It was found that this catalyst could be used in as little as 5 mol% to give moderate yields and moderate ee's (70%).



Scheme 1.20 : $La(OTf)_3$ promoted acidity of (*S*)-HOP for the enantioselective protonation of a silyl enol ether of a 2-substituted cyclic ketone.

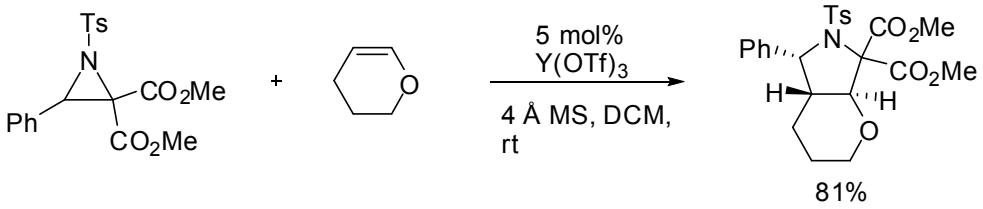
$La(OTf)_3$ has been used as a Lewis acid under microwave irradiation for the homo-conjugate addition of nitrogen heteroatomics to 1,1-cyclopropanedicarboxylates (Scheme 1.21).[11f] This transformation is usually very difficult due to the low nucleophilic nature of the *N*-heteroatomic nucleophile. In the absence of $La(OTf)_3$ there was no observable reaction. However, with 20 mol% $La(OTf)_3$ it was possible to realise yields as high as 76% in only 10 minutes.



Scheme 1.21 : Homo-conjugate addition of pyrazole with 1,1-cyclopropanedicarboxylate under microwave irradiation.

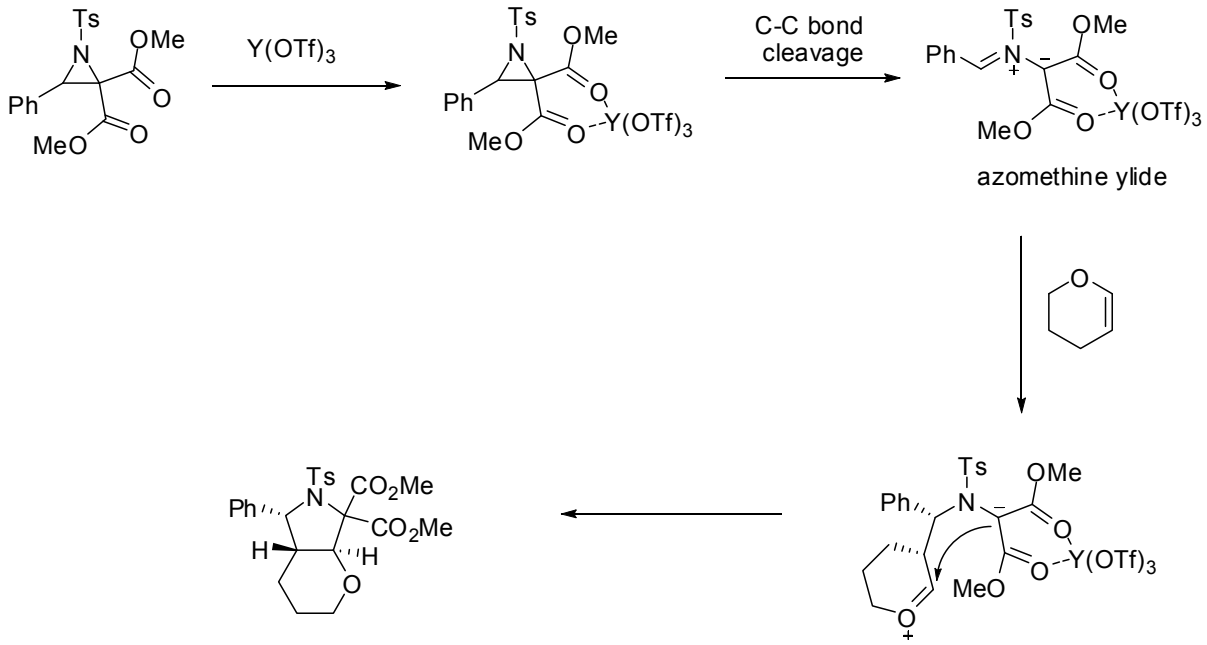
1.1.2.2.3 Yttrium triflate

$Y(OTf)_3$ has been used as a carbon-carbon bond cleaving agent for *N*-aryl azidirines to give the azomethine ylide. This ylide can then undergo a [3+2]-type cycloaddition reaction with a 3,4-dihydro-2*H*-pyran to give the corresponding *trans*-bicyclic pyrrolidine in a high yield (Scheme 1.22).[12a] It was found that this methodology could be applied to a range of substituted azidirines whilst still maintaining high yields.



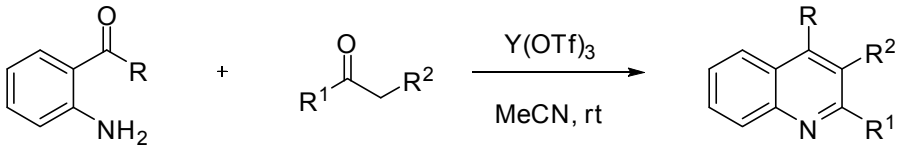
Scheme 1.22 : $Y(OTf)_3$ C-C bond cleavage of an azidirine and subsequent [3+2] dipolar cycloaddition with an electron rich olefin to give the pyrrolidine.

A stepwise reaction pathway has been postulated rather than a concerted cycloaddition mechanism, which would normally yield a *cis*-ring fused product (Scheme 1.23).[12a] This involves the coordination of $Y(OTf)_3$ to the dicarboxylate which aids in the C-C bond heterolysis to give the azomethine ylide. A diastereoselective addition of 3,4-dihydro-2*H*-pyran gives the zwitterionic intermediate. This intermediate then diastereoselectively cyclises to give the *trans*-bicyclic product (Scheme 1.23).



Scheme 1.23 : Proposed mechanism for the C-C bond heterolysis of an *N*-tosylazidirine with an electron rich olefin to give the substituted pyrrolidine.

$Y(OTf)_3$ has been found to catalyse the condensation of 2-aminoaryl ketones with α-methylene ketones to give the substituted quinolines (Scheme 1.24).[12b] This Friedlander condensation reaction can be performed under milder reaction conditions when compared to the conventional synthesis of quinolines.[12b] It was possible to vary the amino ketone as well as α-methylene ketone whilst still maintaining high reaction yields (70-90%). It was noted that of the Lewis acids tested only $Sc(OTf)_3$ gave similar yields to $Y(OTf)_3$, but $Y(OTf)_3$ was chosen due to its low cost in comparison to $Sc(OTf)_3$.



Scheme 1.24 : $Y(OTf)_3$ catalysed condensation of 2-aminoaryl ketones with α-methyl ketones to give the quinoline.

1.1.2.3 Group III metal triflates

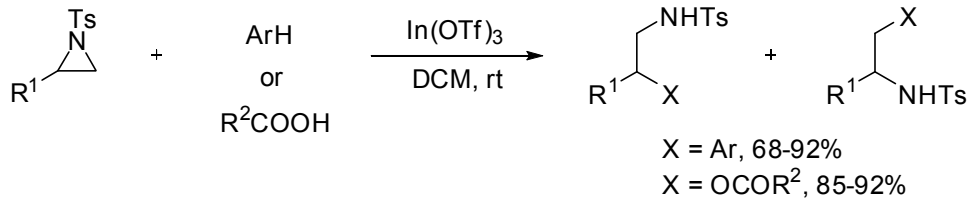
1.1.2.3.1 Indium triflate

After the rare earth metal triflates, the group III metal triflates are the most widely used metal triflates in organic synthesis. This is reinforced by large numbers of literature reports for these types of metal triflates. Indium triflate has been reported for the formation of acetals and thioacetals through the 1) conversion of carbonyl compound into 1,3-oxathiolanes,[13a] 2) the *trans*-thioacetalisation of oxyacetals into thioacetals[13b] and 3) the tetrahydropyranylation of alcohols.[13c] It has been reported as a catalyst for aromatic electrophilic substitution reactions, particularly acetylation of electron-rich aromatics[13d] as well as the Friedel-Crafts alkenylation of arenes using terminal and internal alkynes to give the 1,1-diarylalkenes.[13e] The aryl and alkyl sulfonation of aromatic systems has also been found to proceed in the presence of 5-10 mol% $In(OTf)_3$.[13f] Electrophilic aromatic nitration has also been performed with $In(OTf)_3$ as the catalyst.[13g]

$In(OTf)_3$ has found application as a catalyst for the coupling of carbonyl compounds to alkynes. This yielded the α,β-unsaturated ketone but required the use of a Ru co-catalyst.[13h] 1,3-Dicarbonyls have been shown to couple to terminal alkynes in the presence of $In(OTf)_3$.[13i] The dual activation of a soft nucleophile (alkyne) as well as a hard electrophile (carbonyl) has been reported through the use of *i*-$PrNEt_2$ with an In(III) salt.[13j]

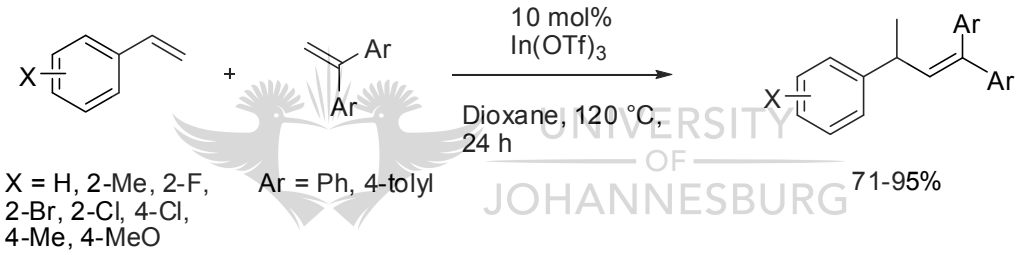
$In(OTf)_3$ has been established as a highly effective catalyst for the Diels-Alder reaction, specifically for the imino Diels-Alder reaction between Danishefsky's diene and various imines to furnish the corresponding *N*-heterocyclic compounds.[13k] It has also catalysed the intramolecular [4+2] Diels-Alder reaction of suitably ester-tethered compounds to furnish the cyclo-adducts in perfect *endo*-selectivity.[13l]

The *C*-arylation of azidirines to give the β-arylamine has been reported to be catalysed by $In(OTf)_3$ (Scheme 1.25).[13m] This $In(OTf)_3$ catalysed ring-opening has also been reported with carboxylic acids to give the corresponding β-amino acetates (Scheme 1.25).[13n]



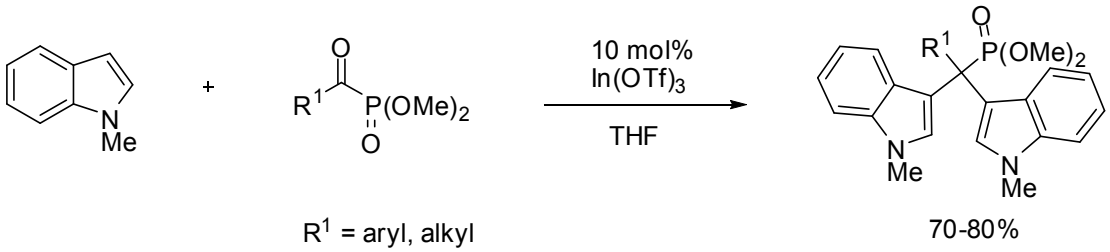
Scheme 1.25 : $In(OTf)_3$ catalysed ring-opening of azidirines with aryl and carboxylic nucleophiles.

More recently (2011), $In(OTf)_3$ has been reported for the head-to-tail dimerisation of vinylarenes with 1,1-diarylethenes (Scheme 1.26).[14a] This provides a direct access to longer chain alkenes from inexpensive alkenes. This dimerisation involves the generation of a benzylic carbocation which is then attacked by an alkene nucleophile to give the heterodimerisation product. This procedure allows for selective heterodimerisation of alkenes without the use of transition metal catalysts.



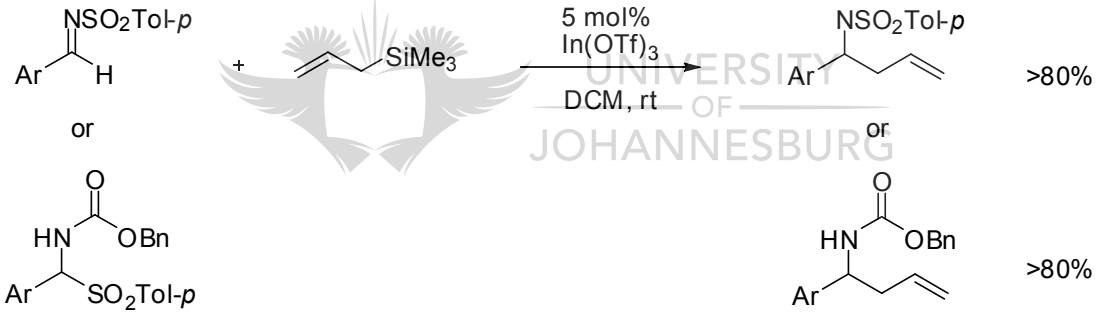
Scheme 1.26 : Head-to-tail dimerisation of vinylarenes with 1,1-diarylethenes catalysed by $In(OTf)_3$.

The synthesis of bis(indolyl)methane phosphonates has been reported to be catalysed by 10 mol% $In(OTf)_3$ to give the desired products in yields in excess of 70%.[14b] This involves the reaction of an *N*-methylindole with an alkyl or aryl phosphonate to give the bis(indolyl)methane phosphonate (Scheme 1.27). Amongst the Lewis acids investigated $BiCl_3$, $Bi(OTf)_3$, $Cu(OTf)_2$, $InCl_3$, $InBr_3$, InI_3, YCl_3, $Y(OTf)_3$, $Sc(OTf)_3$) $In(OTf)_3$ was found to give the best results.



Scheme 1.27 : $In(OTf)_3$ catalysed coupling of *N*-methylindoles and a phosphonate to give the bis(indolyl)methane phosphonate.

Homoallylic amines are useful building blocks in organic chemistry[14c] and have been synthesised from the corresponding *N*-sulfonyl amidines or *N*-alkoxycarbonylamino-*p*-tolylsulfones through the $In(OTf)_3$ catalysed allylation with allyltrimethylsilane (Scheme 1.28).[14c] In the case of the reactions of the *N*-alkoxycarbonylamino-*p*-tolylsulfones, it is believed that the reaction proceeds through an activated *N*-acyliminium species. $In(OTf)_3$ is involved in the generation and activation of this species.[14c]



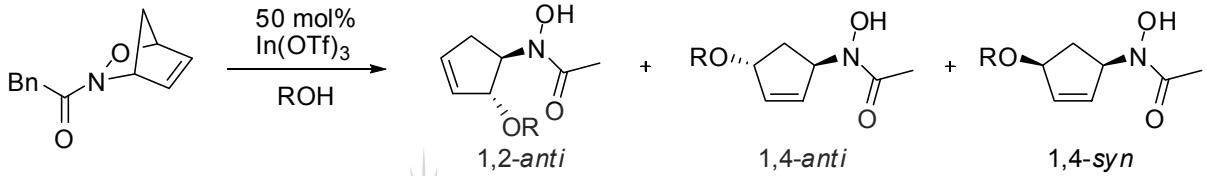
Scheme 1.28 : $In(OTf)_3$ catalysed synthesis of homoallylic amines.

The acetonide protecting group is an important protecting group in protection/de-protection strategies. Numerous conditions have been reported for the de-protection of acetonides which include Lewis acid catalysed strategies.[14d] However, many of these strategies have only been successful in the deprotection of terminal acetals.[14d] The deprotection of internal acetonides often requires harsher reaction conditions which leads to decomposition of acid sensitive substrates. A method has been developed that utilises $In(OTf)_3$ in the presence of water in an organic solvent (acetonitrile) under mild microwave conditions for the de-protection of internal and terminal acetonides.[14d] It was also found that a terminal acetonide could be de-protected in the presence of an internal acetonide through meticulous control of the reaction

temperature and reaction time. This de-protection procedure yielded the corresponding diol in near quantitative yield (>97%).[14d]

Natural products form a large portion of the drugs currently in clinical use. The selective derivatisation of the products allows for structure activity relationships to be established. It is important for these derivatisation methods to be mild and chemoselective as well as high yielding. $In(OTf)_3$ has been used in conjunction with *N*-iodosuccinimide for the iodination of arene-containing natural products.[14e] These iodinated natural products could also be used in cross coupling reactions to allow further derivatisation.

The nucleophilic ring-opening reaction of acylnitroso-Diels-Alder adducts has been reported to proceed in the presence of $In(OTf)_3$ with alcoholic solvents to yield the monocyclic *anti*-1,2-,*anti*-1,4- and *syn*-1,4-hydroxamic acids in good yields (Scheme 1.29).[14f-h]

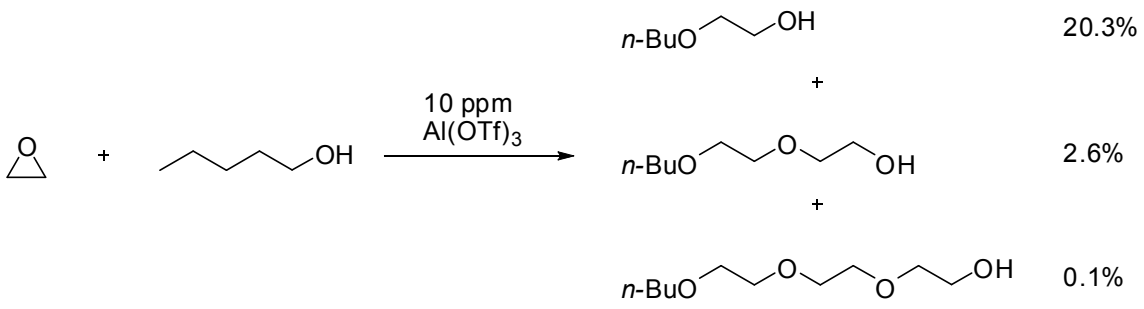


R = OMe, 63%, 7:86:7
R = *i*-Pr, 63%, 8:76:15
R = *t*-Bu, 61%, 7:73:20

Scheme 1.29 : $In(OTf)_3$ catalysed ring-opening of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene to give the monocyclic hydroxamic acid.

1.1.2.3.2.2 Aluminium triflate

Aluminium triflate was first prepared for the ring-opening of epoxides in 1985 by Falgoux *et al*.[15] The preparation of this Lewis acid was accomplished by reacting triflic acid with aluminium powder. The $Al(OTf)_3$ was isolated by filtering off the excess aluminium powder, evaporation and drying of the aqueous filtrate yielded the $Al(OTf)_3$ as a fine white powder. The catalytic activity of $Al(OTf)_3$ was then tested for the ring-opening of ethylene oxide with *n*-butanol to give the monoethylene-, diethylene and triethylenglycolmonobutylethers (Scheme 1.30).



Scheme 1.30 : $Al(OTf)_3$ catalysed ring-opening of ethylene oxide to give the monobutylethers.

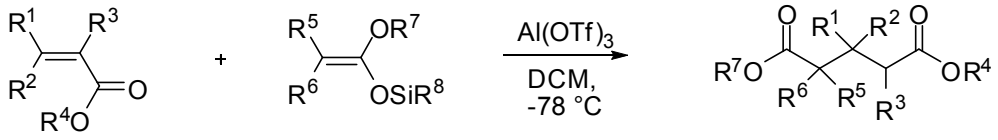
It was found that $Al(OTf)_3$ had a superior catalytic activity when compared to other catalysts known to catalyse this reaction, such as CH_3COOK, $Mg(ClO_4)_2$, $Zn(ClO_4)_2$ and $Zn(OTf)_2$ (Table 1.4). $Al(OTf)_3$ gave high activity whilst maintaining selectivity in low catalyst concentrations (Table 1.4, entry 1). Although comparable activity was attainable with potassium acetate (Table 1.4, entries 2-4), the selectivity was not as high as for the $Al(OTf)_3$ catalysed reactions. $Mg(ClO_4)_2$ and $Zn(ClO_4)_2$ gave good activity and increased selectivity (Table 1.4, entries 5-8). However, the amount of catalyst required was significantly higher than for $Al(OTf)_3$.

Table 1.4 : Catalyst comparison for the ring-opening of ethylene oxide by *n*-butanol.

Entry	Catalyst	Catalyst concentration (ppm)	Conversion rate of ethylene oxide[a]	Yield (Content of monobutyl ether by weight)			Selectivity[b]
				Monoethylene	Diethylene	Triethylene	
1	$Al(OTf)_3$	10	1.00	20.3	2.6	0.1	7.8
2	CH_3COOK	50	0.93	16.3	4.3	-	3.8
3	CH_3COOK	100	1.00	16.6	4.6	-	3.6
4	CH_3COOK	300	1.00	15.3	4.3	3.5	3.5
5	$Mg(ClO_4)_2$	100	0.78	17.0	1.4	-	12.1
6	$Mg(ClO_4)_2$	300	0.98	23.4	1.8	-	13.0
7	$Zn(ClO_4)_2$	100	0.67	16.3	1.1	-	14.8
8	$Zn(ClO_4)_2$	300	1.00	22.5	2.5	0.1	9.0
9	$Zn(OTf)_3$	50	1.00	7.8	2.5	-	7.1

[a]Conversion rate standardised to conversion rate obtained with $Al(OTf)_3$ [b]Selectivty : ratio of monethylene product to diethylene product.

The Michael reaction of *O*-silylated ketene acetals with α,β-unsaturated esters to give the corresponding glutarates has been reported to proceed in the presence of a catalytic amount of $Al(OTf)_3$ (Scheme 1.31).[16] The authors generated the $Al(OTf)_3$ *in situ* by the reaction of triflic acid with Me_3Al at -78 °C.



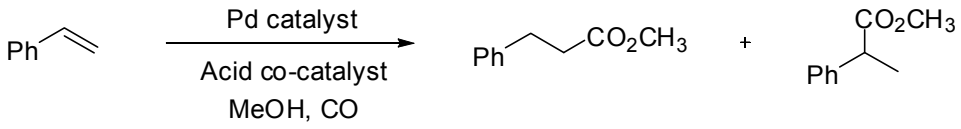
Scheme 1.31 : $Al(OTf)_3$ catalysed Michael reaction of *O*-silylated ketene acetals with α,β-unsaturated esters.

The preparation of $Al(OTf)_3$ from $AlCl_3$ and triflic acid was reported by Olah *et al*.[17] This catalyst was then used in the Friedel-Crafts alkylation and acetylation of benzene and toluene with various alkyl bromides and acetyl chlorides. Moderate yields were obtained for this reaction. However, the authors found $B(OTf)_3$ and $Ga(OTf)_3$ to be more effective catalysts.[17] This same group later found that $Al(OTf)_3$ could be used as a catalyst for the polymerisation of tetrahydrofuran.[18]

$Al(OTf)_3$ was reported for the epoxidation of cyclohexane with idosylbenzene.[19] The reactivity of $Al(OTf)_3$ was found to be close to that of $Fe(OTf)_3$, which had been previously been studied for epoxidation. The ring expansion of 3-hydroxy-3-propargylisoindolin-1-ones has also been effected by $Al(OTf)_3$.[20] The aldol reaction has also been reported to proceed with $Al(OTf)_3$ as the Lewis acid catalyst.[21]

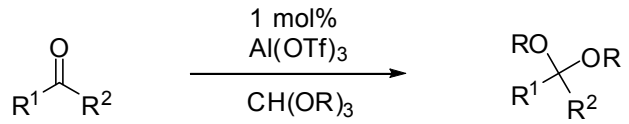
After these initial investigations into $Al(OTf)_3$ as a Lewis acid catalyst there were no further reports on its use as a Lewis acid in organic synthesis until 2005 when it was reported for the alcoholysis[22a] and aminolysis[22b] of epoxides. The alcoholysis was performed on styrene oxide, cyclohexane oxide and various glycidyl ethers with simple alcohols such as ethanol, methanol and *iso*-propanol. Only ppm levels of $Al(OTf)_3$ were required to catalyse this reaction to give yields in the range of 70-90%.[22a] The same group reported the aminolysis of these epoxides with various aromatic and aliphatic amines,[22b] although in the case of the amines the catalyst loadings required were in the range of 1-5 mol%. This was attributed to the basic nature of the amines leading to significant deactivation of the $Al(OTf)_3$ catalyst.

The methoxycarbonylation of vinyl aromatic compounds to give the ester requires the use of an acidic co-catalyst in addition to a Pd catalyst in the presence of carbon monoxide and a suitable alcohol (Scheme 1.32). Traditionally this acidic co-catalyst has been a Brønsted acid.[23] Williams *et al.*[23] reported $Al(OTf)_3$ to be a superior acid co-catalyst for this reaction giving higher activity and selectivity than for the more traditional Brønsted acid co-catalysts. This was the first report of a Lewis acid co-catalyst for the methoxycarbonylation of styrene.



Scheme 1.32 : Pd/acid catalysed methoxycarbonylation of an alkene to give the linear and branched ester.

The acetalisation of carbonyl compounds is an important protection strategy. $Al(OTf)_3$ has been reported to effect this acetalisation in high yields and short reaction times.[24] It was found that the acetalisation reaction could be performed with 1.5 molar equivalents of an orthoester to give the corresponding acetal (Scheme 1.33). This reaction could be performed under solvent free conditions which significantly improves the environmental impact, as reaction solvents are quite often environmentally unfriendly.[24]

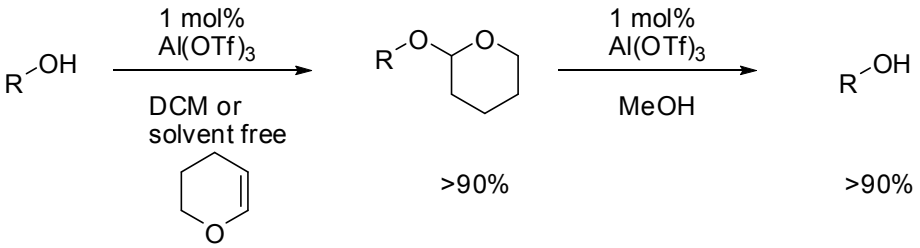


R^1 = aryl, alkyl
R^2 = alkyl, H
R = Me, Et

Scheme 1.33 : Acetalisation of carbonyls with an orthoester catalysed by $Al(OTf)_3$.

The acetylation of alcohols, phenols and thiophenols was reported to proceed under solvent free conditions with acetic anhydride in the presence of 0.1 mol% $Al(OTf)_3$.[25] The corresponding acetylated products were obtained in very high yields (>90%) in short reaction times.

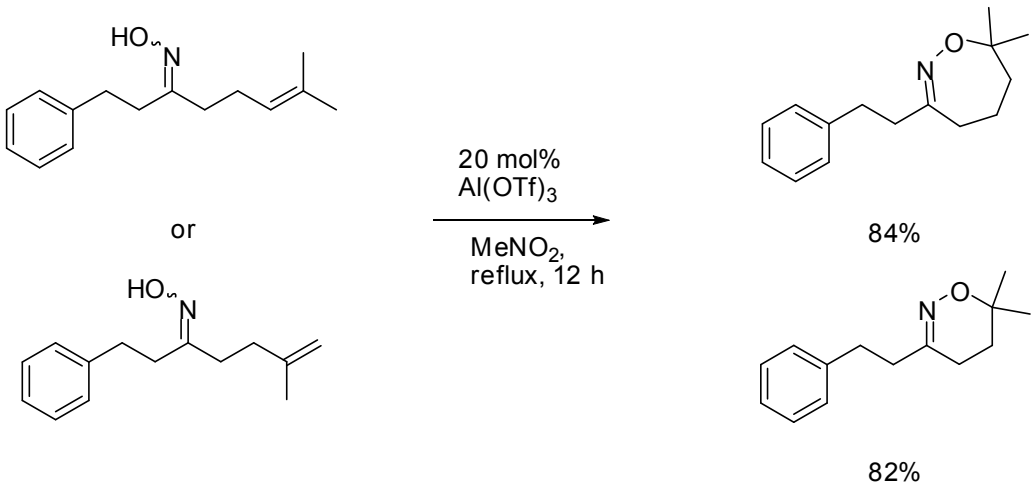
The tetrahydropyranylation of alcohols under solvent free conditions with $Al(OTf)_3$ as the catalyst was reported (Scheme 1.34).[26a] This gave the tetrahydropyran protected alcohols in good yields. In addition to this the tetrahydrofuranylation of alcohols with $Al(OTf)_3$ was also reported by a different group.[26b] This report also established a deprotection procedure for the tetrahydropyran and tetrahydrofuran protected alcohols utilising $Al(OTf)_3$ in methanol (Scheme 1.34).[26b] The conversion of alcohols, phenols and α-hydroxyphosponates to the corresponding *O*-silylated products has also been catalysed by $Al(OTf)_3$. This is achieved through the use of hexamethyldisilane as the silylating agent.[27]



Scheme 1.34 : Tetrahydropyranylation of an alcohol and subsequent deprotection catalysed by $Al(OTf)_3$.

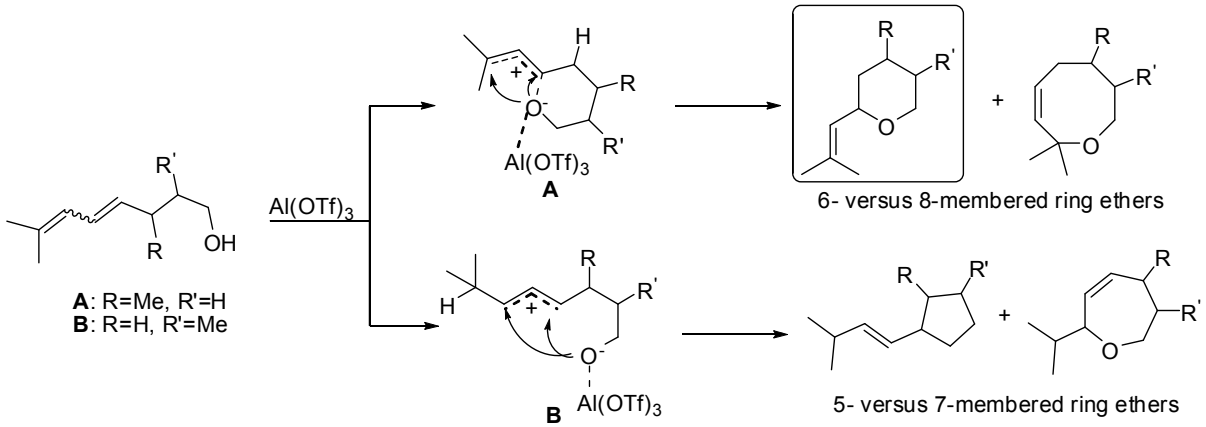
The esterification of acetic acid with *n*-propanol and ethanol has been reported to proceed with catalyst concentrations in the range of 5 ppm $Al(OTf)_3$.[28]

The cycloisomerisation of oximes bearing non-activated olefin moieties to give the 5-, 6- and 7-membered heterocyclic rings bearing an oxygen and nitrogen heteroatom has been reported to occur in the presence of $Al(OTf)_3$ (Scheme 1.35).[29] The cycloisomer is the product of the Markovnikov addition to the double bond. Compared to other acids such as $Sn(OTf)_4$, $Fe(OTf)_3$, $Cu(OTf)_2$ and TfOH, $Al(OTf)_3$ was found to give the best results. The other acids tested gave the ketone product which results from the hydrolysis of the starting oxime.



Scheme 1.35 : $Al(OTf)_3$ catalysed cycloisomerisation of oximes to give the corresponding 6- and 7-membered oxygen and nitrogen containing heterocycles.

The cycloisomerisation of unsaturated alcohols to the corresponding cyclic ethers has been effected with $Al(OTf)_3$.[30a] These cyclisations gave regioselectively the 6-membered products as opposed to the possible 5-, 7- or 8-membered products (Scheme 1.36). Theoretical calculations[30b] indicate the initial coordination of Al^{3+} to the hydroxyl group which increases the acidity of the hydroxyl proton. This proton then adds to the diene to generate the intermediate allylic carbocationic species A or B (Scheme 1.36). Intermediate A is more stable than B due to higher electron donation though the geminal dimethyl groups on the allylic carbocation species. Cyclisation to give the 6-membered ring is favoured above cyclisation to give the 8-memebered ring.[30b] This methodology could be extended to a range of substituted unsaturated alcohols to give the 6-membered products in high yields.[30a]

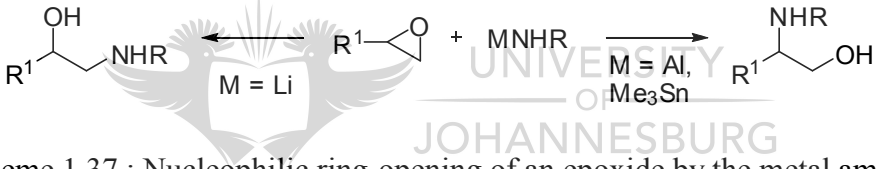


Scheme 1.36 : Mechanistic considerations for the cyclic of unsaturated alcohols.

1.2 Ring-opening reactions

1.2.1 Aminolysis of epoxides

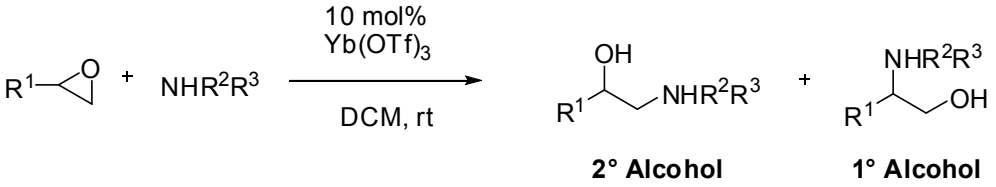
Epoxides are widely used in organic synthesis due to their ease of formation and their reactivity with nucleophiles to give the *trans*-1,2-difunctionalised system.[31] The nucleophilic ring-opening of epoxides by alcohols, thiols and amines is a well-studied topic.[31,32,33] These ring-opened products have found use in medical applications.[34,35] The ring-opening of epoxides by amines is limited by the relatively low nucleophilicity of amines which often requires elevated reaction temperatures in order to obtain satisfactory reaction yields.[33,36] Metal amides have been used to overcome this problem; this entails the generation of a suitable metal amide from the nucleophilic amine and a metal. Basic reagents such as lithium amides provide nucleophilic attack at the less hindered carbon whilst more acidic amides such as aluminium and trimethylstannane amides provide nucleophilic attack at the more hindered carbon (Scheme 1.37).[33] Although this yields the ring-opened product in satisfactory yields this method requires the stoichiometric use of the metal to generate metal amide.[33]



Scheme 1.37 : Nucleophilic ring-opening of an epoxide by the metal amide.

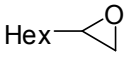
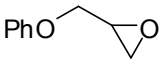
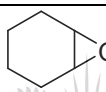
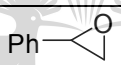
In 1994 the first reports of the use of rare earth metal triflates as catalysts for the ring-opening of epoxides by amines occurred.[33,37] Two independent groups reported that $Yb(OTf)_3$ successfully catalysed these ring-opening reactions (Scheme 1.38). The use of $Yb(i\text{-}PrO)_3$, $Yb(NBn_2)_3$, $Yb(CN)_3$, YbF_3 failed to yield any ring-opened product whilst $YbCl_3$ gave moderate yields of the ring-opened product.[33] This established the importance of the triflate counterion for an active ring-opening catalyst. In order for this reaction to proceed to high yields it was also found that anhydrous non-polar solvents were required (Table 1.5). The use of more polar solvents such as MeCN or the presence of water in the reaction solvent gave lower reaction yields.[37] The secondary alcohol was the predominant ring-opened product during these reactions (Table 1.5). THF could also be used as a reaction solvent. However, this required elevated reaction temperatures in order to obtain satisfactory yields.[33] This is due to coordination of the THF to the $Yb(OTf)_3$ which leads to catalyst deactivation.

However, better selectivities were reported for the reactions performed in THF than reactions performed in DCM which often gave erratic mixtures of reaction products.[33]



Scheme 1.38 : Aminolysis of epoxides catalysed by $Yb(OTf)_3$.

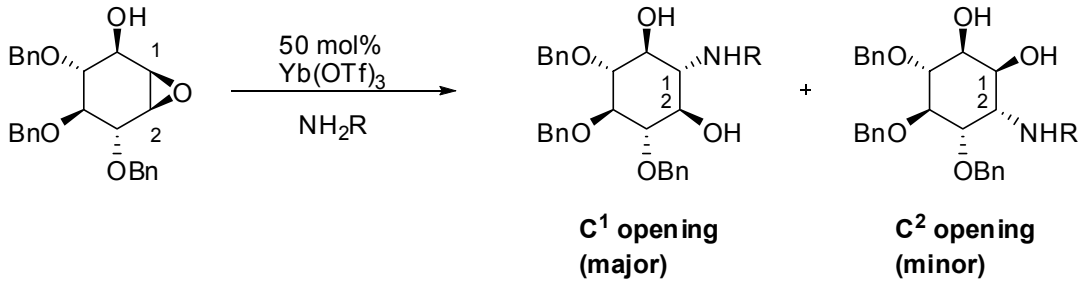
Table 1.5 : Aminolysis of epoxides catalysed by $Yb(OTf)_3$.

Entry	Epoxide	Amine	Yield (%)	2°/1°
1		$HNEt_2$	97	99/1
2		$HNEt_2$	100	99/1
3		H_2N^tBu	97	-
4		H_2N^tBu	97	90/10

The use of $Cu(OTf)_2$ and $Sn(OTf)_2$ as Lewis acid catalysts for the ring-opening of epoxides with aromatic amines has been reported.[38] These two metal triflates gave moderate yields for the ring-opening reaction utilising deactivated aromatic amines such as *p*-nitroaniline. It was found that $Sn(OTf)_2$ was a slightly more active catalyst than $Cu(OTf)_2$ and also that this reaction could be performed in diethyl ether, MeCN, DCM and THF with the highest yields being obtained from the use of diethyl ether. The biggest shortcoming of these two metal triflates was their inability to catalyse the ring-opening reaction in the presence of aliphatic amines, which is in contrast to the lanthanide triflates.[33] It was postulated that the increased basic nature of the aliphatic amines favoured the formation of a complex between the metal triflate and the amine which deactivated the metal triflate as a catalyst for the ring-opening reaction.[38]

$Yb(OTf)_3$ was found to be an effective catalyst for the aminolysis and azidolysis of cyclitol epoxides.[39] This ring-opening proceeded via a chelation-controlled mechanism with the

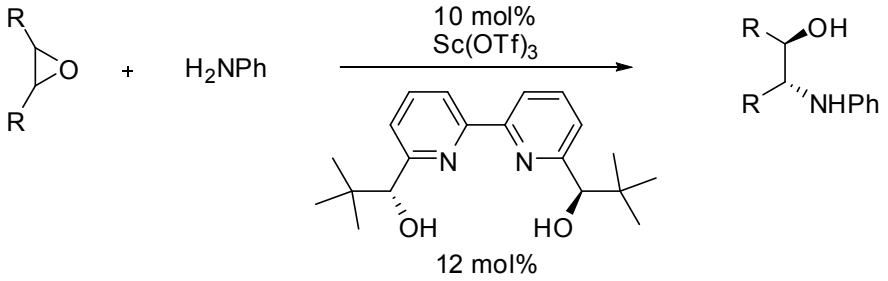
presence of a free OH group on the cyclitol providing a point of chelation for the $Yb(OTf)_3$ to give regioselectively the C^1 product (Scheme 1.39).



Scheme 1.39 : $Yb(OTf)_3$ catalysed aminolysis of a cyclitol epoxide to give the C^1 ring-opened product.

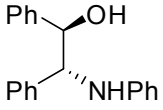
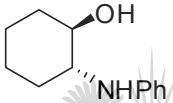
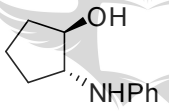
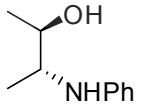
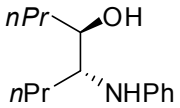
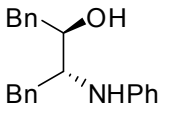
These previous examples of metal triflate catalysed ring-opening reactions of epoxides required the use of anhydrous reaction solvents. The use of $Bi(OTf)_3$ under aqueous conditions for the aminolysis of epoxides was thus an important development in terms of catalyst stability towards water.[40] These reactions could be conducted with only 10 mol% $Bi(OTf)_3$ and less reactive aromatic amines such as *p*-trifluoromethylaniline gave moderate yields. Since it is in principle possible for the metal triflate to hydrolyse to TfOH in the presence of water, the question as to whether or not TfOH was responsible for the catalytic activity was also addressed. Reactions were performed with the equivalent amount of triflic acid giving significantly decreased yields as compared to the reaction performed with $Bi(OTf)_3$. This illustrated the importance of the Lewis acid in this reaction as opposed to a Brønsted acid and provided a measure of evidence that it is unlikely that the TfOH formed in the reaction mixture is responsible for the catalytic activity.

The enantioselective ring-opening of *meso*-epoxides was performed in the presence of 10 mol% $Sc(OTf)_3$ and 12 mol% of a chiral bipyridine ligand (Scheme 1.40).[41] Initial investigations found that the reaction could be catalysed with only 10 mol% $Sc(OTf)_3$ and gave high yields and enantioselectivities (Table 1.6, entry 1). Other rare earth metal triflates were investigated. However, $Sc(OTf)_3$ gave the highest yields and enantioselectivities. It was found that *meso*-epoxides bearing aliphatic side chains gave lower enantioselectivities compared to epoxides bearing an aromatic group (Table 1.6).



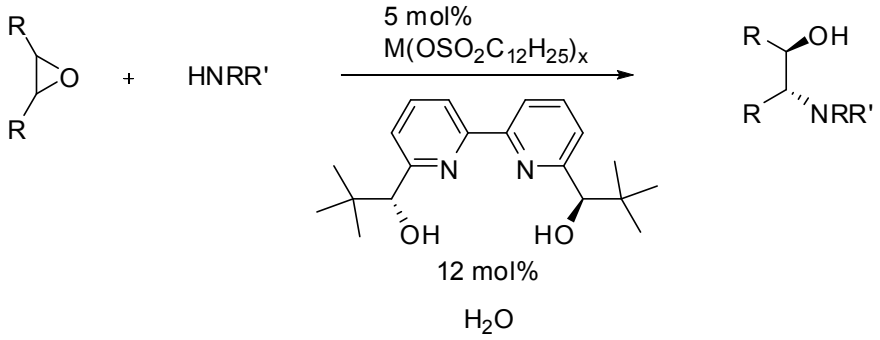
Scheme 1.40 : Enantioselective aminolysis of a *meso*-epoxide in the presence of $Sc(OTf)_3$ and a chiral bipyridine ligand.

Table 1.6 : Selected yields for the enantioselective aminolysis of *meso*-epoxides with $Sc(OTf)_3$ and a chiral bipyridine ligand.

Entry	Product	Temperature (°C)	Yield (%)	ee(%)
1		rt	95	93
2		-20	96	54
3		-20	89	41
4		0	92	60
5		rt	74	74
6		0	49	44

A similar aminolysis of *meso*-epoxides was reported to proceed in water in the presence of a Zn(II) or Cu(II) surfactant type catalyst utilising the same bipyridine ligand as previously mentioned (Scheme 1.41).[42] This system provided higher enantioselectivities than previously reported systems.[41] The reaction was found to proceed quicker in water than in DCM which can be ascribed to concentration effects due to the formation of reactive micelles or micro-droplet aggregations of the reagents and catalyst. It was also found that the opposite

enantiomer could be obtained by simply using Sc(III) as the active metal centre as opposed to Cu(II) or Zn(II).



Scheme 1.41 : Enantioselective aminolysis of *meso*-epoxides with a metal surfactant type Lewis acid and a chiral bipyridine ligand in water.

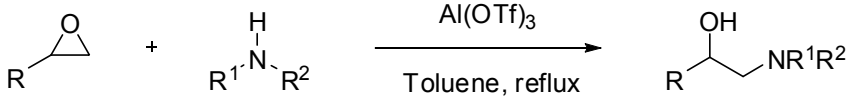
Table 1.7 : Selected yields and enantioselectivities for the aminolysis of *meso*-epoxides catalysed by a metal surfactant Lewis acid and a chiral bipyridine ligand.

Entry	**R**	**NHRR'**	**Metal**	**Yield (%)**	**ee (%)**
1	Ph	Aniline	Zn	97	92
2	Ph	2-Trifluoromethylaniline	Zn	100	92
3	Ph	1-Naphthylamine	Zn	55	95
4	Ph	*N*-Methylaniline	Zn	56	95
5	Ph	2-Methoxyaniline	Zn	43	91
6	3-MePh	Aniline	Zn	95	93
7	4-MePh	Aniline	Zn	82	93
8	4-BrPh	Aniline	Zn	44	90
9	Me	Aniline	Zn	80	54
10	Me	2-Naphthylamine	Zn	100	67
11	$-(CH_2)_4-$	Aniline	Zn	94	66
12	$-(CH_2)_4-$	2-Naphthylamine	Zn	77	79
13	Ph	Aniline	Cu	82	80
14	Ph	2-Trifluoromethylaniline	Cu	100	78
15	Ph	1-Naphthylamine	Cu	56	75
16	Ph	*N*-Methoxyaniline	Cu	88	91
17	Ph	2-Methoxyaniline	Cu	44	70
18	4-MePh	*N*-Methylaniline	Cu	78	90
19	4-BrPh	*N*-Methylaniline	Cu	72	92

In a move away from the metal triflates, an Fe containing montmorillonite clay, Fe-MCM-41 has been reported to effect the aminolysis of epoxides under solvent-free conditions.[43] This catalyst could catalyse the aminolysis of various epoxides with a range of aromatic and aliphatic amines at room temperature. The recycling of the heterogeneous catalyst was demonstrated for up to six reaction cycles.

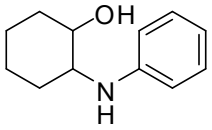
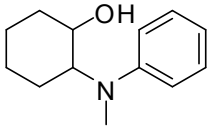
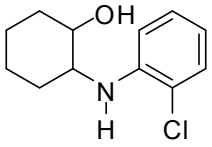
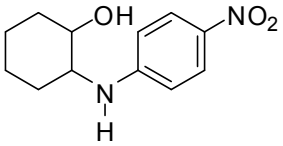
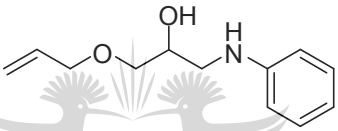
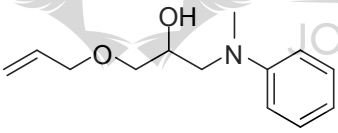
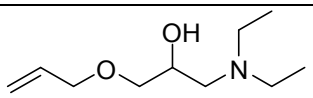
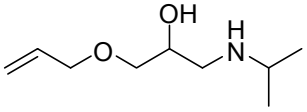
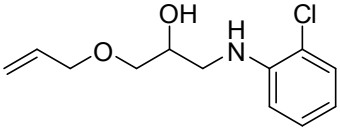
As has been previously mentioned, the aminolysis of epoxides requires the use of elevated temperatures in the absence of a suitable catalyst. It has been reported, however, that this reaction can be performed in the absence of a Lewis acid catalyst at moderate (55 °C) reaction temperatures through the use of microwave irradiation.[53] This reaction was performed in water and was complete in less than an hour.

$Al(OTf)_3$ has been reported for the aminolysis of epoxides.[22b] For this reaction it was found that only 5 mol% of the $Al(OTf)_3$ catalyst was required to realise good yields. It was also found that a non-polar reaction solvent such as toluene gave the best yields as opposed to more polar reaction solvents. This is due to more polar reaction solvents coordinating the $Al(OTf)_3$ thus, reducing its Lewis acidity, which decreases its catalytic activity. The recovery and reuse of $Al(OTf)_3$ was facilitated through the aqueous extraction of the reaction mixture followed by subsequent drying at reduced pressure and elevated temperatures. The reaction yielded the secondary alcohol as the main reaction product (Scheme 1.42). Aromatic amines could be successfully employed in the ring-opening of various epoxides (Table 1.8). The ring-opening by aliphatic amines required increased amounts of catalyst and furnished the ring-opened products in low to moderate yields (Table 1.8). Deactivated amines such as *p*-nitroaniline could be employed as nucleophiles albeit with slightly higher amounts of $Al(OTf)_3$ (Table 1.8).



Scheme 1.42 : $Al(OTf)_3$ catalysed aminolysis of epoxides.

Table 1.8 : Selected yields for the aminolysis of epoxides catalysed by $Al(OTf)_3$.

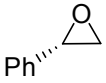
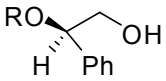
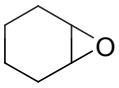
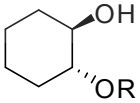
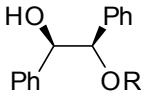
Entry	Product	Mol% $Al(OTf)_3$	Yield (%)
1		1	82
2		1	87
3		2	80
4		5	52
5		1	90
6		2	93
7		2	80
8		1	33
9		2	88

Other Lewis acids reported to be active towards the ring-opening of epoxides include $Ti(O^iPr)_4$,[45] $TaCl_5$,[46] Bi salts,[47] $ZrCl_4$,[48] $Sm(OTf)_3$,[49] $CoCl_2$,[50] $CuBF_4$,[51] $ZnCl_2$[52] and $Sc(OTf)_3$.[53]

1.2.2 Alcoholysis of epoxides

The alcoholysis of epoxides has been reported to proceed with 0.2 mol% $Yb(OTf)_3$ with the alcohol being used in excess (2 equivalents) and serving as both the nucleophile and the reaction solvent.[54] The ring-opened products were obtained in high yields with good regioselectivities (Table 1.9).

Table 1.9 : $Yb(OTf)_3$ catalysed alcoholysis of epoxides.

Entry	Epoxide	ROH	Product	Yield (%)
1		Me		95
2		Et		98
3		Et		0[a]
4		*n*-Pr		98
5		*i*-Pr		98
6		*n*-Bu		96
7		*i*-Bu		98
8		*t*-Bu		98
9		*c*-C_6H_{11}		89
10		Allyl		75
11		Propargyl		76
12		Me		91
13		Et		95
14		Me		80

[a] 0 mol% catalyst used.

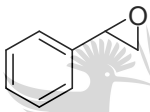
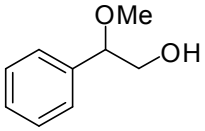
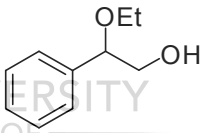
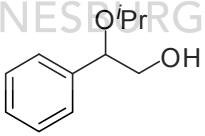
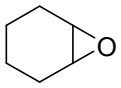
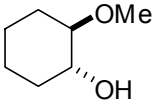
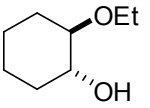
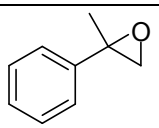
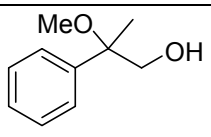
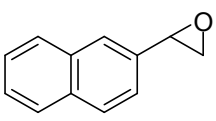
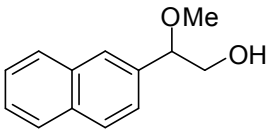
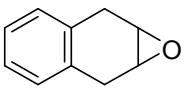
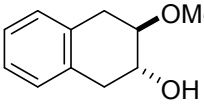
$Ce(OTf)_3$ was also found to be an effective catalyst for the alcoholysis of epoxides.[55] Similar yields and regioselectivities were obtained as for the $Yb(OTf)_3$ catalysed ring-opening. It was possible to use this catalyst in 0.01 mol%. However, once again it was necessary to use the alcohol in excess as the reaction solvent and nucleophile. It was found that this catalyst was effective for the ring-opening reaction in the presence of water.

The rare earth metal triflates have also been screened as catalysts for the alcoholysis of epoxides.[56] IR-thermography screening established that $Sc(OTf)_3$ gave the most pronounced

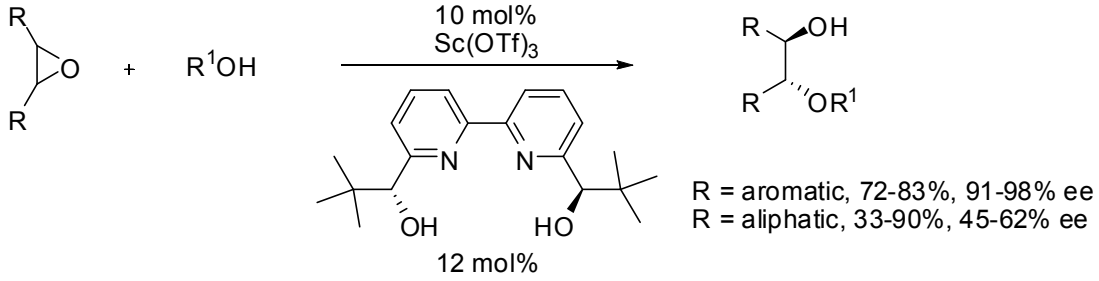
initial temperature exotherm. This was an indication of the high catalytic activity of $Sc(OTf)_3$ compared to the other rare earth metal triflates screened for the alcoholysis of epoxides.

A mesoporous aluminosilicate with a Si to Al ratio of 14 has been reported for the alcoholysis of epoxides to the corresponding β-alkoxyalcohols.[57] The authors found that plain silicate material displayed no catalytic activity whatsoever. This indicates the necessity of the Lewis acidic component of the aluminosilicate rather than the Brønsted acidic component. This procedure required the use of 40 % m/m of the alumina silicate and could be performed at room temperature to give the ring-opened products in good yields (Table 1.10). It was once again necessary to use the alcohol in a vast excess.

Table 1.10 : Yields for the mesoporous aluminosilicate catalysed alcoholysis of epoxides.

Entry	Epoxide	Time (h)	Product	Yield (%)
1		1.5		95
2		2.5		86
3		3.5		52
4		1		69
5		1		96
6		3		97
7		4.5		90
8		1		99

The enantioselective alcoholysis of *meso*-epoxides has been found to occur in the presence of $Sc(OTf)_3$ and a chiral bipyridine ligand (Scheme 1.43).[58] This same system has been reported for the enantioselective aminolysis of *meso*-epoxides.[41] Of the metal triflates screened it was found that $Sc(OTf)_3$ gave the highest yields and enantioselectivities. Whilst high yields were obtained for the alcoholysis of aromatic and aliphatic derived *meso*-epoxides, high enantioselectivities were only realised for the aromatic derived *meso*-epoxides.



Scheme 1.43 : The $Sc(OTf)_3$ bipyridine catalysed enantioselective alcoholysis of *meso*-epoxides.

$Al(OTf)_3$ has been used to good effect for the alcoholysis of epoxides.[22a] For the ring-opening of styrene oxide and cyclohexene oxide it was found that only 0.002 mol% of the $Al(OTf)_3$ was required to obtain high reaction yields (Table 1.11). The reaction of styrene oxide with ethanol (Table 1.11, entry 2) was repeated with triflic acid as the acid and after 24 hours it was found that only 4% of the product had formed. It was concluded that although triflic acid could potentially form through the hydrolysis of $Al(OTf)_3$ it was the presence of the Lewis acidic Al^{3+} that was responsible for the catalytic activity observed. Various glycidyl ethers were also examined as epoxide substrates for the ring-opening reaction (Table 1.11, entries 15-20). It was found that these epoxides required substantially more $Al(OTf)_3$ (0.02 mol%) for reactivity to be seen.

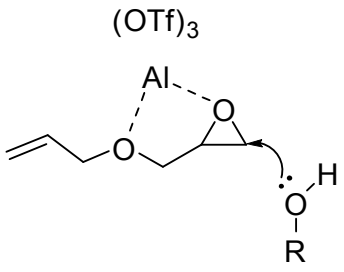
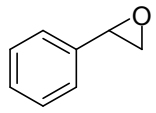
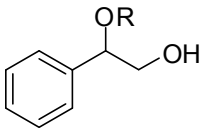
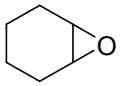
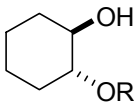
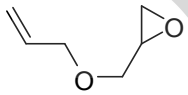
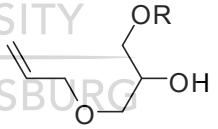
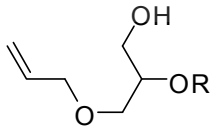
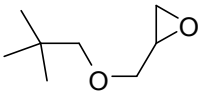
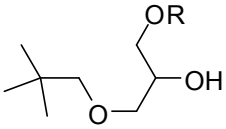
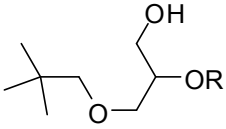
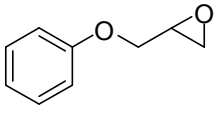
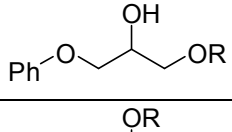
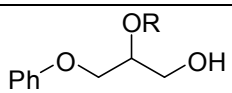


Figure 1.2 : Intermediate 5-membered chelate structure.

It was postulated that a 5-membered chelate structure was forming between the Al^{3+} catalyst and the glycidyl ether (Figure 1.2), with electron-donation from the etheric oxygen onto the aluminium leading to significant catalyst deactivation. The ring-opening of glycidyl ethers yielded a mixture of primary and secondary alcohol products (Table 1.11, entries 15-20). The secondary alcohol was the major product which can be ascribed to the formation of this intermediate chelate structure leading to steric effects playing a more important role than electronic effects.

Table 1.11 : Yields for the $Al(OTf)_3$ catalysed alcoholysis of epoxides.

Entry	Epoxide	ROH	mol% $Al(OTf)_3$	Product	Yield (%)
1		MeOH	0.002		98
2		EtOH	0.002		95
3		*n*-PrOH	0.002		97
4		*i*-PrOH	0.002		92
5		*n*-BuOH	0.002		97
6		2-BuOH	0.004		85
7		*t*-BuOH	0.004		81
8		MeOH	0.002		86
9		EtOH	0.002		83
10		*n*-PrOH	0.002		88
11		*i*-PrOH	0.003		62
12		*n*-BuOH	0.002		89
13		2-BuOH	0.002		45
14		*t*-BuOH	0.01		18
15		EtOH	0.02		69
16					19
17		EtOH	0.02		63
18					21
19		EtOH	0.02		60
20					26

1.3 Nucleophilic substitution of "activated" alcohols

1.3.1 Introduction

The ACS Green chemistry initiative and global pharmaceutical industries developed the ACS GCI Pharmaceutical Roundtable to promote the integration of Green chemistry principles into the pharmaceutical industry.[59] One of the key research areas listed was the activation of hydroxyl groups for nucleophilic substitution. This would give water as the only by-product but, remains a challenge due to the poor leaving ability of the hydroxyl group.[59,60] The direct activation of benzylic, allylic and propargylic alcohols has received considerable attention in the last few years.[60] Due to the structure of these alcohols they are prime candidates to undergo S_N1 type substitution reactions.[1]

The use of carbocations in organic synthesis has come a long way since the pioneering work done by Olah.[61a,b] These carbocationic species are highly reactive and react to the diffusion limit. It is thus possible for a nucleophile to intercept the carbocation and allow for reaction to take place.[62]

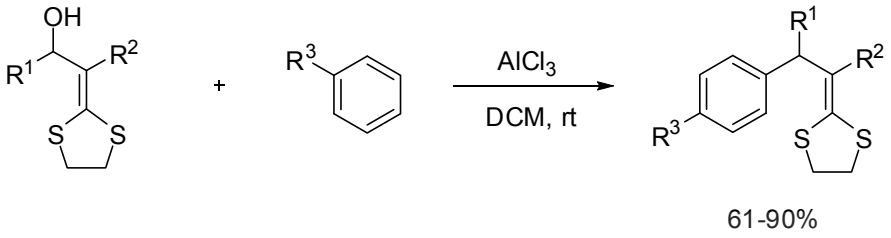
Mayr has introduced electrophilicity parameters that allow for the quantitative description of reactions between electrophiles (carbocations, metal-π-complexes and diazonium ions) and nucleophiles.[63a,b,c] It was demonstrated that the rate of these reactions can be described by one parameter for electrophiles (*E*) and two parameters for nucleophiles (*s* and *N*). The electrophilic parameter for many diarylcarbenium electrophiles has already been determined[63b] with *s* being the nucleophile-specific parameter and *N* the nucleophilicity parameter.

$$logk_{(20\,^{\circ}C)} = s(N + E)$$

Through the use of this scale of reactivity it is possible to predict the reactivity of several S_N1 type reactions between carbocations and nucleophiles. Although this description is quite accurate in most cases it doesn't take steric effects into account as is the case with the bulky trityl cation.[64] Another important factor to consider in these reactions is the use of a suitable solvent whose nucleophilic character does not out compete the nucleophilic character of the nucleophile.[65] The occurrence of electron donating groups on the benzylic rings of the carbocationic intermediate increases the stability of these species.[66] The electrophilic parameters of allylic carbocations have also been reported.[67]

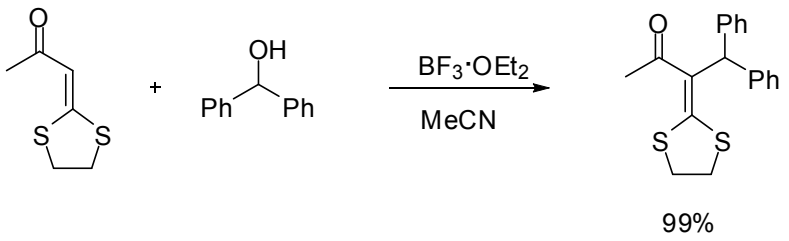
1.3.2 Reactions of "activated" alcohols promoted by stoichiometric amounts of acid

There are many reports on the stoichiometric use of Lewis or Brønsted acids for the generation of carbocations from "activated" alcohols.[60] The use of $AlCl_3$ for the promotion of the carbon-carbon bond formation between α-hydroxyketene-*S*,*S*-acetals and various arenes has been reported.[68] This involves the nucleophilic substitution of the hydroxyl group on the α-hydroxyketene-*S*,*S*-acetals (Scheme 1.44). H_2SO_4 was also tested for this reaction and gave no reaction whereas other Lewis acids ($BF_3{\cdot}OEt_2$, $FeCl_3$) gave lower yields when compared to $AlCl_3$.



Scheme 1.44 : $AlCl_3$ promoted nucleophilic substitution of α-hydroxyketene-*S*,*S*-acetals with substituted arenes.

The same group reported the carbon-carbon coupling reaction of α-EWG ketene-*S*,*S*-acetals with various alcohols promoted by $BF_3{\cdot}OEt_2$ (Scheme 1.45).[69] Although other Lewis acids were tested for this reaction ($AlCl_3$, $FeCl_3$) they required significantly longer reaction times to realise the same yields. It was also found that a Brønsted acid (H_2SO_4) could promote this reaction albeit with substantially longer reaction times.



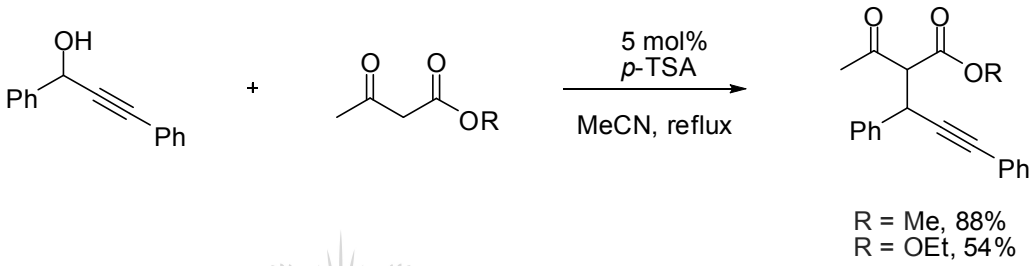
Scheme 1.45 : Nucleophilic substitution of benzhydrol with an α-EWG ketene-*S*,*S*-acetal.

1.3.3 Reactions of "activated" alcohols promoted by catalytic amounts of acid

Although there are other examples[60] of nucleophilic substitutions of "activated" alcohols promoted by stoichiometric amounts of an acid it is more desirable to have a catalytic system in terms of the overall green impact of the reaction.[59]

1.3.3.1 Brønsted acid catalysed reactions

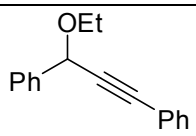
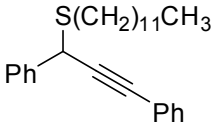
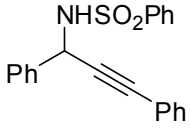
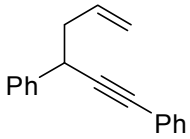
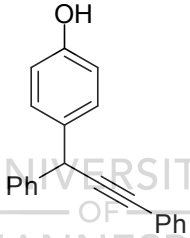
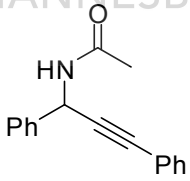
The nucleophilic substitution of propargylic alcohols by 1,3-dicarbonyl compounds has been found to proceed in the presence of 5 mol% *p*-toluenesulfonic acid (Scheme 1.46).[70] It was possible to utilise propargylic alcohols bearing an aromatic or heteroatomic group at the propargylic position.



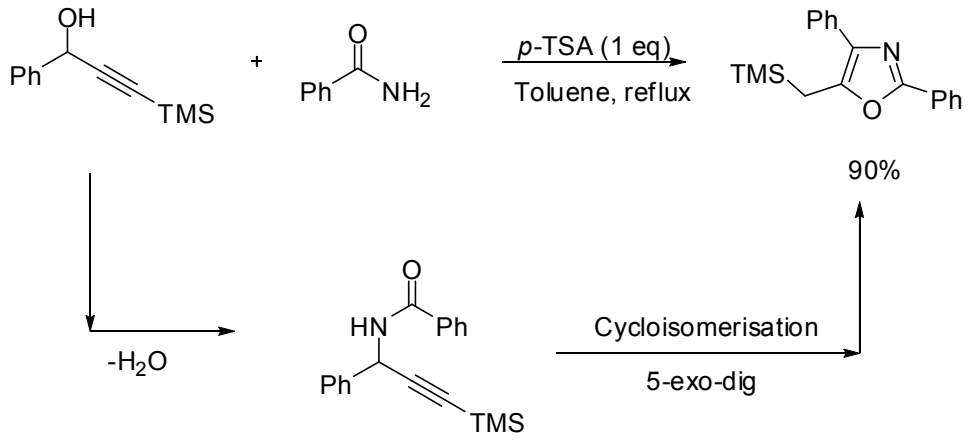
Scheme 1.46 : *p*-Toluenesulfonic acid catalysed substitution of a propargylic alcohol with a 1,3-dicarbonyl substrate.

The nucleophilic substitution of these propargylic alcohols could also be performed with oxygen, sulfur, sulfonamide, allyl and arene nucleophiles (Table 1.12).[71] This substrate could also be reacted with acetonitrile to give the corresponding amide (Table 1.12, entry 6). This reaction is known as a Ritter reaction and required the use of a more acidic catalyst which came in the form of 2,4-dinitrobenzenesulfonic acid.[72]

Table 1.12 : Yields for the nucleophilic substitution of the propargylic alcohol in Scheme 1.46 with various nucleophiles catalysed by *p*-toluenesulfonic acid.

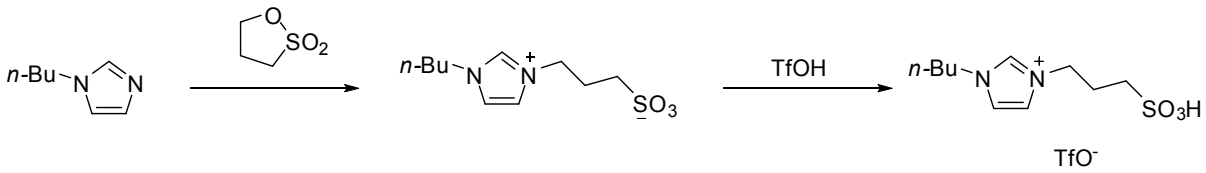
Entry	Nucleophile	Product	Yield (%)
1	EtOH		80
2	$CH_3(CH_2)_{11}SH$		80
3	$PhSO_2NH_2$		67
4	Allyltrimethylsilane		80
5	Phenol		66
6	MeCN		85

The propargylation/cycloisomerisation tandem reaction of propargylic alcohols and amides has been reported to proceed in the presence of *p*-toluenesulfonic acid (*p*-TSA) to give the corresponding oxazole (Scheme 1.47).[73] The use of a catalytic amount of *p*-TSA gave substantially lower yields. Lewis acids such as $Cu(OTf)_3$ and $BiCl_3$ were also tested and although they gave yields lower than the reaction with one molar equivalent of *p*-TSA their yields were superior to those obtained with a catalytic amount of *p*-TSA.

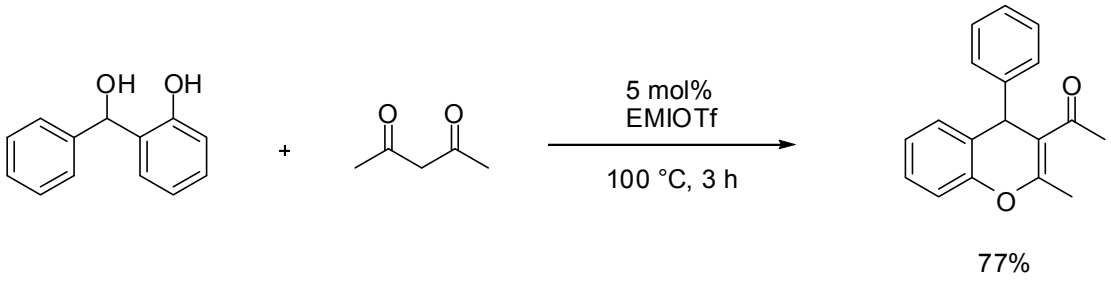


Scheme 1.47 : Propargylation/cycloisomerisation of a propargyl alcohol and an amide to give the oxazole.

The development of a recyclable Brønsted acid catalyst came in the form of a Brønsted acidic ionic liquid bearing a triflate counterion.[74] This ionic liquid was formed by the reaction of 1-butylimidazole with 1,3-propanesultone which was subsequently reacted with triflic acid to give the [*N*-ethyl-*N*-methylimidazolium][triflate] (EMIOTf) (Scheme 1.48). This ionic liquid could be used in 5 mol% loadings to effect the nucleophilic substitution of benzylic, allylic and propargylic alcohols. It was also used for the one-pot synthesis of 4*H*-chromenes (Scheme 1.49). The use of this Brønsted acidic ionic liquid eliminated the need for a reaction solvent. It was found that this catalyst could be recovered and reused for up to three reaction cycles.

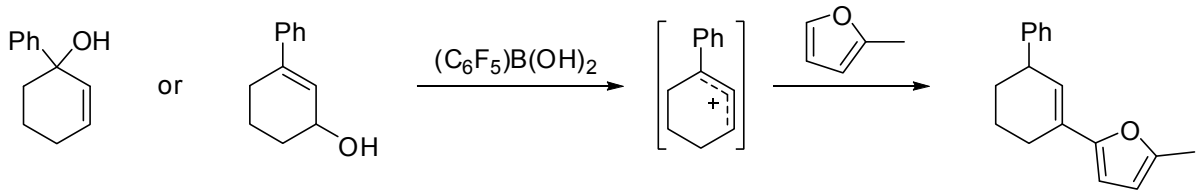


Scheme 1.48 : Preparation of the EMIOTf ionic liquid.



Scheme 1.49 : One-pot synthesis of a substituted 4*H*-chromene from the corresponding alcohol and 1,3-dicarbonyl reagent.

Pentafluorophenylboronic acid was found to catalyse a regioselective coupling of allylic alcohols with a range of electron-rich aromatics and heteroaromatics.[75a] This required only 5 mol% of the catalyst and could be performed at room temperature. It was interesting to note that the main regioisomer formed during the reaction would suggest an S_N2' reaction mechanism instead of an S_N1 mechanism. However, a mechanistic study on two regioisomeric alcohols would suggest the formation of an intermediate allylic carbocation (Scheme 1.50). This acid could be used to catalyse the Friedel-Crafts arylation of benzylic alcohols using phenols, indoles and methoxy substituted benzenes, giving the Friedel-Crafts products in yields in excess of 75% after heating under reflux in dichloroethane for 16 hours.[75b]



Scheme 1.50 : Mechanistic study on the nucleophilic substitution of allylic alcohols catalysed by pentafluorophenylboronic acid.

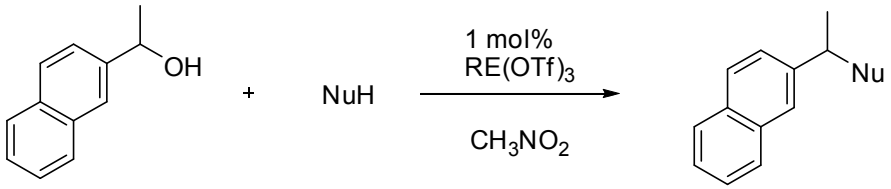
A surfactant type Brønsted acid catalyst has been developed in the form of a calyx[6]arene sulfonic acid bearing a pendant aliphatic side chain (C_8H_{17}).[76] The reaction of *trans*-1,3-diphenyl-2-propen-1-ol with various indoles and electron rich aromatics was found to proceed to give high yields in moderate reaction times. This reaction could be performed in water. The catalytic system could be recycled by simply extracting the reactants and product

out of the aqueous reaction mixture with an organic solvent thereby leaving the calyx[6]arene Brønsted acid in the aqueous phase. Fresh reactants could be added to the aqueous catalyst containing phase and the reaction repeated.

1.3.3.2 Lewis acid catalysed reactions

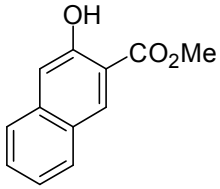
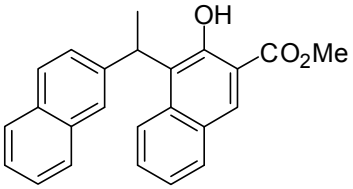
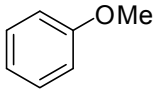
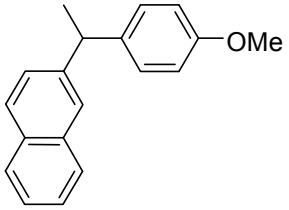
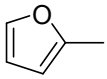
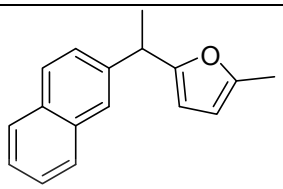
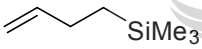
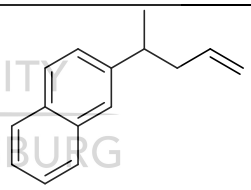
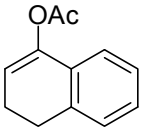
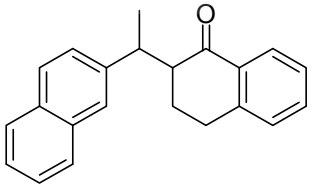
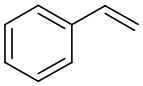
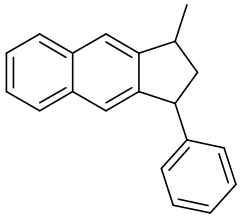
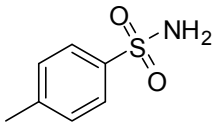
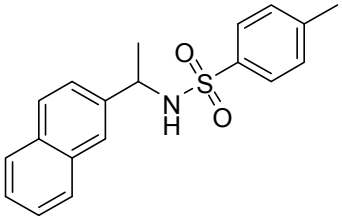
1.3.3.2.1 Rare earth metal triflates

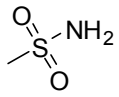
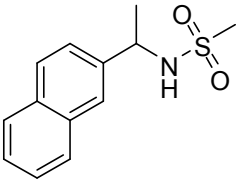
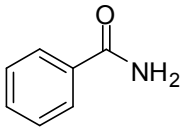
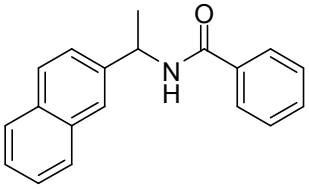
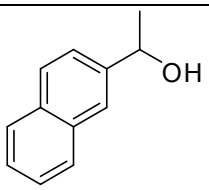
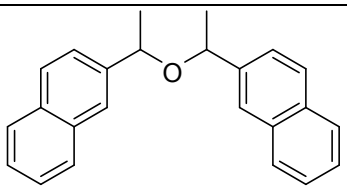
The first report on the use of a rare earth metal triflate for the nucleophilic substitution of secondary benzyl alcohols occurred in 2003 by Ishii.[77] Of the initial acids investigated for this reaction $La(OTf)_3$ was found to be superior to $BF_3 \cdot OEt_2$ which was required in a stoichiometric amount to realise reactivity. Further investigation into the use of other rare earth triflates revealed that $Hf(OTf)_4$ was the most active catalyst. The catalytic activity of the metal triflates investigated increases in the following order $La(OTf)_3 < Yb(OTf)_3 <$ TfOH $< Sc(OTf)_3 < Hf(OTf)_4$. It was found that TfOH could also catalyse these reactions. A range of nucleophiles were tested for reactivity, including carbon (aromatics, olefins and enol acetates), nitrogen (amides), and oxygen (alcohols) bearing systems (Table 1.13). The formation of the symmetrical ether, derived from the "activated" alcohol, during these reactions was also detected (Table 1.13, entry 10). Interestingly it was found that these reactions could be performed utilising the symmetrical ether as the starting material instead of the starting alcohol. This is due to a reversible equilibrium between the symmetrical ether and the alcohol which proceeds in the presence of water. Indeed the realisation of high yields of the symmetrical ether product was promoted by the azeotropic removal of water from the reaction mixture.



Scheme 1.51 : Nucleophilic substitution of a secondary benzylic alcohol catalysed by a rare earth metal triflate.

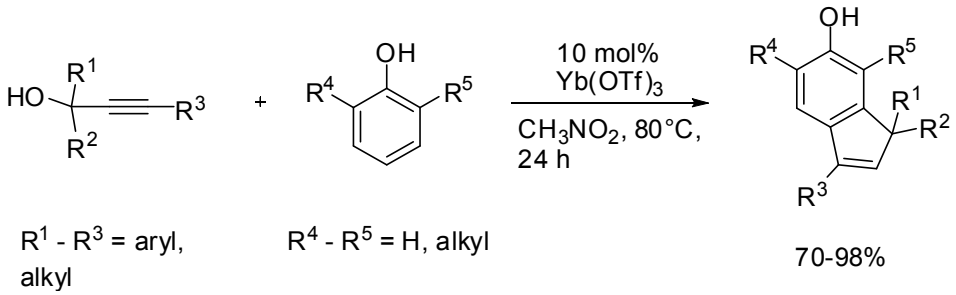
Table 1.13 : Yields for the nucleophilic substitution of a secondary benzylic alcohol by various nucleophiles.

Entry	Nucleophile	Triflate	Temperature (°C)	Time (h)	Product	Yield (%)
1		$La(OTf)_3$	100	0.33		96
2		$La(OTf)_3$	100	1		96[a]
3		$La(OTf)_3$	60	1		74
4		$La(OTf)_3$	100	1		54
5		$La(OTf)_3$	100	0.33		95
6		$La(OTf)_3$	100	0.66		88
7		$Yb(OTf)_3$	70	24		89

8		$Yb(OTf)_3$	70	24		88
9		$Hf(OTf)_3$	50	50		69
10		$La(OTf)_3$	100	1		81

[a] Mixture of the *ortho*/*para* substituted products.

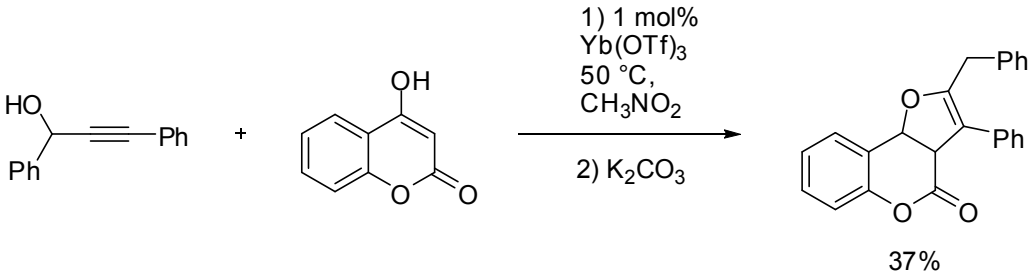
Indenols have been successfully prepared by the tandem Friedel-Crafts alkylation/hydroarylation of propargylic alcohols with phenols catalysed by $Yb(OTf)_3$.[78] The intermediate Friedel-Crafts alkylation product was isolated by performing the reaction at room temperature. When this product was subjected to reflux conditions with the $Yb(OTf)_3$ catalyst the hydroarylation product was obtained thus demonstrating the alkylation/hydroarylation mechanism.



Scheme 1.52 : Tandem alkylation/hydroarylation of propargylic alcohols with phenols catalysed by $Yb(OTf)_3$.

$Yb(OTf)_3$ has also been employed in the selective propargylation or allylation of 1,3-dicarbonyl compounds, this reaction realises the reaction of 4-hydroxycoumarins at the 3 position.[79] The selective application of this reaction at the key step yields the multi-

substituted furocoumarin in a one pot procedure. The $Sc(OTf)_3$ catalysed substitution of phenylsulfonyl and phenylselanyl propargyl alcohols has also been reported.[80] This included reaction with arene, heteroarene, enol silyl and allyl silane derivatives to give the substituted products in high yields.



Scheme 1.53 : One pot synthesis of a substituted furocoumarin from the propargylation of 4-hydroxycoumarin catalysed by $Yb(OTf)_3$.

1.3.3.2.2 Group III metal triflates and other Group III derivatives

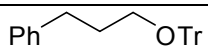
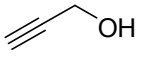
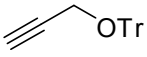
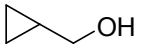
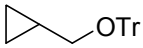
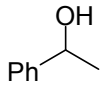
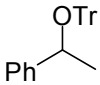
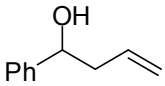
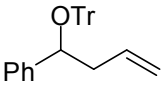
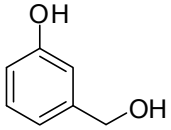
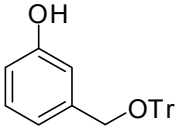
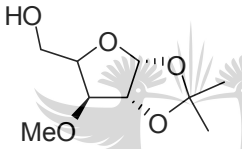
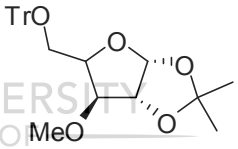
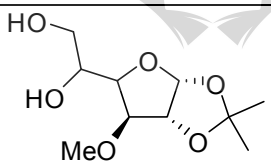
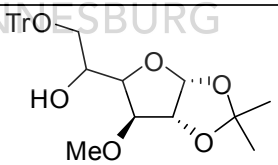
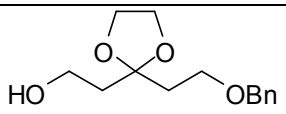
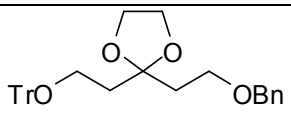
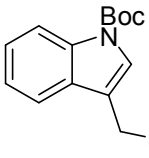
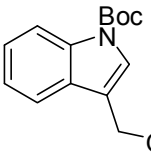
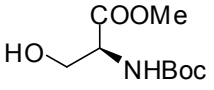
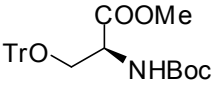
1.3.3.2.2.1 Boron

The preparation of α-aryl nitriles from the corresponding α-aryl alcohols catalysed by 3 mol% $B(C_6F_5)_3$ has been reported and although this is not a metal triflate the results are still relevant to the present literature study due to the Lewis acidic nature of this species.[81] This occurs through the nucleophilic attack of a cyanide source, $(CH_3)_3SiCN$ (TMSCN), onto the α-aryl alcohol derived carbocation. The use of α-aryl thiols in the generation of the α-aryl nitriles was also reported. Lower yields were obtained for these thiol substrates even with higher catalyst loadings and longer reaction times. In addition to this the generation of H_2S is less attractive than the generation of H_2O as the reaction by-product.

The tritylation of alcohols is a recognised protection procedure for alcohols. It was found that $B(C_6F_5)_3$ could promote the tritylation of various alcohols through the nucleophilic substitution of the hydroxyl group of triphenylmethanol.[82] This reaction was found to proceed at room temperature in DCM to afford the trityl ethers in good yields (Table 1.14). Due to the S_N1 nature of the reaction it was possible to tritylate selectively a primary alcohol in the presence of a secondary alcohol (Table 1.14, entry 8). Tritylation was found to also occur in the presence of other protecting groups (OTHP, OTBDMS, OTBDPS, OMOM, OPMB, OBn,

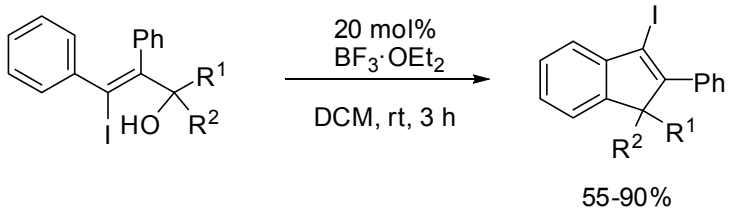
OTr, OTs) without de-protection of these groups. A de-protection procedure of the trityl ethers formed could not be established with $B(C_6F_5)_3$.

Table 1.14 : $B(C_6F_5)_3$ catalysed tritylation of primary alcohols.

Entry	Substrate	Time (h)	Product	Yield (%)
1		3		92
2		3.5		87
3		4		93
4		8		48
5		8		56
6		4.5		88
7		4		90
8		3.5		90
9		4		94
10		4		87
11		3.5		95

$BF_3 \cdot OEt_2$ was found to catalyse the cyclisation of iodinated allylic alcohols to provide the 3-iodo-1*H*-indene derivatives in good yields (Scheme 1.54).[83] Although this reaction could be promoted by stoichiometric amounts of concentrated sulphuric acid, only 20 mol% $BF_3 \cdot OEt_2$ was required to realise high reaction yields in as little as 3 hours. The 3-iodo-1*H*-indene

derivatives could be used in subsequent Suzuki cross coupling reactions with boronic acids to furnish the multiaryl substituted indenes.



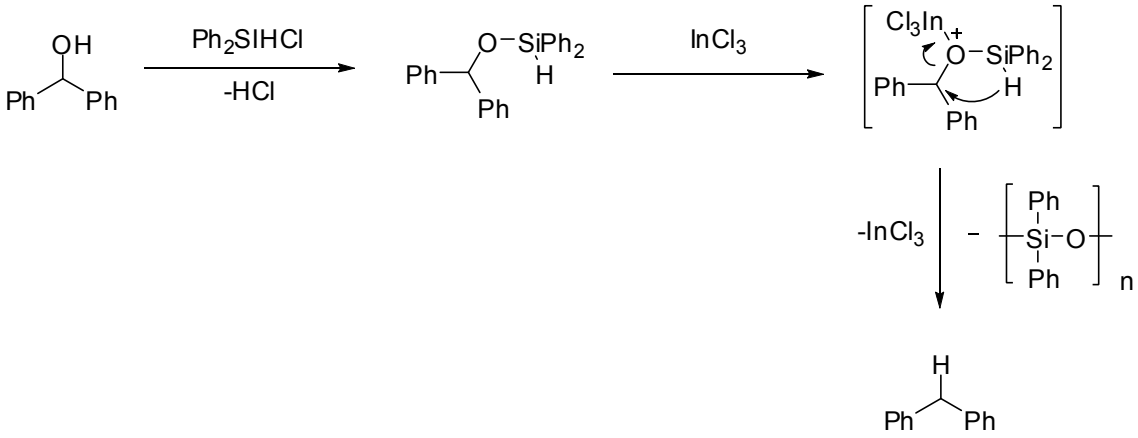
Scheme 1.54 : $BF_3 \cdot OEt_2$ catalysed cyclisation of iodinated allylic alcohols.

1.3.3.2.2.2 Indium

The $InCl_3$ catalysed nucleophilic substitution of allylic and benzylic alcohols was reported by Baba *et al.* in 2006.[84] These alcohols were found to react with 1,3-diesters, keto esters and diketones as well as indoles to give the substitution products in high yields. This catalyst was found to be superior to other Lewis acids ($AlCl_3$, $GaCl_3$, $BF_3 \cdot OEt_2$ and $Sc(OTf)_3$) when used in toluene at 80 °C. The formation of a symmetrical ether derived from the starting alcohol was also detected in the reaction. A mechanistic study once again revealed that the nucleophilic substitution with the carbon nucleophiles could be performed from the corresponding symmetrical ether as easily as from the starting allylic or benzylic alcohol. Other indium salts were evaluated ($In(OAc)_3$, $In(OH)_3$, $In(acac)_3$ and $InBr_3$) and $InBr_3$ was found to give comparable yields to $InCl_3$ whereas the other salts showed no activity whatsoever.

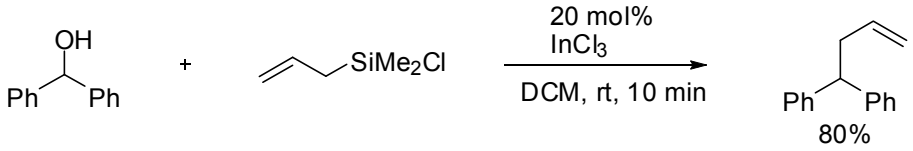
The direct reduction of secondary and tertiary alcohols utilising chlorodiphenylsilane as a hydride source proceeds in the presence of a catalytic amount of $InCl_3$.[85] This system was effective in the selective reduction of benzylic, secondary and tertiary alcohols. A secondary alcohol could be reduced in the presence of a primary alcohol although workup with *n*-Bu_4NF was required to obtain the de-silylated primary alcohol. Groups (esters, halides or nitro groups) that are usually sensitive to traditional reduction methods such as $LiAlH_4$ were found to be stable to the $InCl_3/(Ph)_2SiHCl$ system which reduced only the alcohol. The reaction mechanism was elucidated by NMR studies during the reaction course (Scheme 1.55). It is believed that the hydrodiphenylsilyl ether is initially formed, since this intermediate was detected via NMR spectroscopy. Complexation of the $InCl_3$ to the oxygen atom generates the oxonium complex with de-silylation occurring by donation of the hydrogen onto the

electrophilic carbon atom. $AlCl_3$ and $BF_3 \cdot OEt_2$ were also tested for this reaction and gave no reduced product. It was postulated that the low affinity of indium for oxygen as compared to boron or aluminium is what makes it possible for this reduction to occur in a catalytic manner.



Scheme 1.55 : Mechanism for the $InCl_3/Ph_2SiHCl$ reduction of an alcohol.

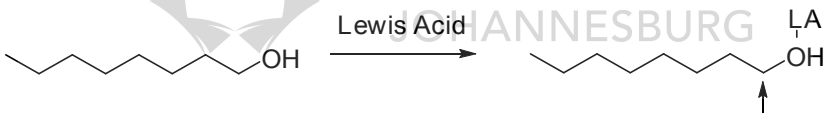
This methodology was then extended by the same group to the substitution of hydroxyl groups by allyl-, propargyl- and alkynyl silanes.[86] Once again $AlCl_3$ and $BF_3 \cdot OEt_2$ were evaluated for catalytic activity and were found to have none. $Sc(OTf)_3$ showed some activity and the allylated product was obtained in a 13% yield. An investigation into the reaction mechanism was done by means of NMR spectroscopy and interestingly none of the silyl ether product was detected. Instead the symmetrical ether and allylated product were seen. This is in contrast to the previously mentioned reduction of alcohols which proceeds through an intermediate silyl ether. It was thus possible that this reaction mechanism was following a different but presently unknown pathway. It was nevertheless possible that the reaction indeed proceeds via the silyl ether but that its lifetime and concentration are not conducive to detection by NMR spectroscopy. This methodology was successfully extended to a range of benzylic alcohols utilising allyl-, propargyl- and alkynylsilanes with high reaction yields being realised in short reaction times.



Scheme 1.56 : Allylation of benzhydrol by allylchlorodimethylsilane catalysed by $InCl_3$.

An improvement on this system was later reported through the use of Me_3SiBr as an additive.[87] This allowed the use of only 5 mol% $InCl_3$ and 10 mol% Me_3SiBr. A shift in the ^{13}C NMR spectrum for the α-carbon of 1-octanol was used as a probe for the relative acidic strength of the $InCl_3$, the Me_3SiBr and a mixture of the two (Table 1.15). This confirmed the formation of a Lewis acid complex between $InCl_3$ and Me_3SiBr leading to a more active catalyst. Using these new data a revised mechanism was proposed whereby the benzylic alcohol forms an intermediate carbocation which then reacts with the allytrimethylsilane to give the allylated product. It remains unclear if the same applies to the reactions employing $InCl_3$/allylchlorodimethylsilane.

Table 1.15 : Effects of Lewis acids on the ^{13}C NMR chemical shifts (δ) of the α-carbon of 1-octanol.



Entry	Lewis acid	δ(^{13}C)/ppm	Δδ(^{13}C)/ppm
1	none	62.7	0
2	Me_3SiCl	62.8	+0.1
3	Me_3SiBr	64.0	+1.3
4	$InCl_3$	65.2	+2.5
5	$InBr_3$	65.2	+2.5
6	$InCl_3$ + Me_3SiCl	66.0	+3.3
7	$InCl_3$ + Me_3SiBr	66.3	+3.6
8	$InBr_3$ + Me_3SiCl	67.4	+4.7
9	$InBr_3$ + Me_3SiBr	70.2	+7.5

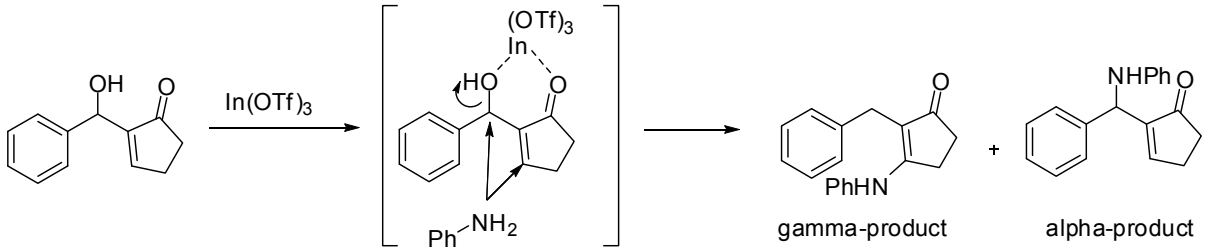
It was found by Baba *et al.* that the addition of benzil (PhCOCOPh) to the reaction of 1-phenyl-2-propanol with $HSiPh_2Cl$ catalysed by $InCl_3$ gave the corresponding chloride instead

of the expected reduction product.[88] Initially, a yield of 47% 2-chloro-1-phenylpropane was obtained, however by using $HSiMe_2Cl$ this was increased to 68%. In the absence of $InCl_3$ no reaction was observed. The use of a α-ketoester or an α-alkoxyalkane in place of the benzil did not yield the desired product in comparable yields. It was noted that benzil was recovered unchanged after the reaction.

The reaction of propargylic alcohols with various heteroatomic aromatic compounds has been catalysed by $InBr_3$.[89] The cyanation of benzylic alcohols with TMSCN could be achieved in 5-30 minutes under the catalysis of $InBr_3$ in catalytic amounts as little as 5-10 mol%.[90]

Allylindium reagents have been generated from indium metal and an allyl bromide. These allylindium reagents have been successfully used in the nucleophilic substitution of tertiary propargylic alcohols.[91] The allylindium reagents were found to be far easier to prepare and handle than the corresponding organometallics prepared from magnesium or zinc metal. This methodology could not be extended to the nucleophilic substitution of secondary alcohols.

$In(OTf)_3$ has been found to be an active catalyst for the α-regioselective *N*-nucleophilic substitution of Baylis-Hilman adducts.[92] The reaction of these Baylis-Hilman adducts with aromatic amines saw the rearrangement of the γ-product to the more thermodynamically stable α-product (Scheme 1.57). $Zn(OTf)_2$, $Sc(OTf)_3$ and AgOTf were tested as acid catalysts but gave marginally lower yields for this reaction.

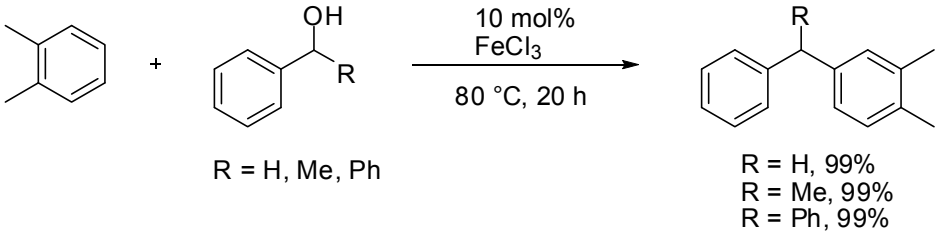


Scheme 1.57 : *N*-nucleophilic substitution of a Baylis-Hilman adduct catalysed by $In(OTf)_3$.

1.3.3.2.3 Iron

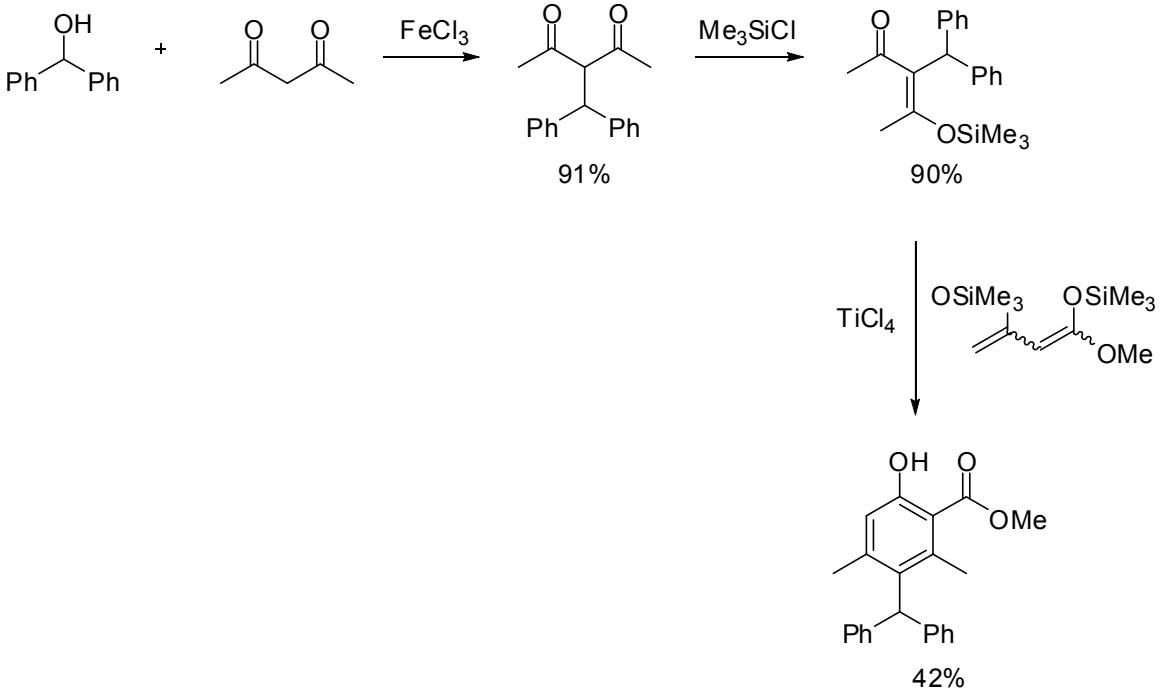
The first report of iron as a catalyst for the nucleophilic substitution of "activated" alcohols occurred in 2005 by Beller *et al*.[93] Initial work had focused on finding a catalyst that could promote the arylation of benzyl carboxylates and of the various metals screened (Co, Cu, Zn, Mn, and Fe) iron in the form of $FeCl_3$ was found to be the most active. Further investigations

revealed that this Friedel-Crafts alkylation reaction between aryl carboxylates and *ortho*-xylene was tolerant of a range of functional groups including CHO, CO_2R, I, Br, Cl, F, OH, and OMe. It was then noted that benzyl alcohols could be utilised instead of benzyl carboxylates, the obvious advantage being the generation of water as the reaction by-product as opposed to a carboxylic acid.



Scheme 1.58 : Arylation of benzylic alcohols catalysed by $FeCl_3$.

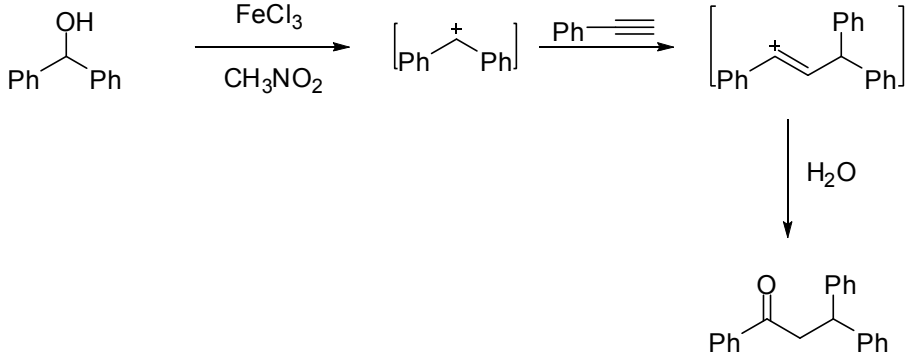
Beller *et al.*[94a] as well as Jana *et al.*[94b] went on to report the use of $FeCl_3$ as a catalyst for the nucleophilic substitution benzylic alcohols by 1,3-dicarbonyl compounds. This reaction was reported to proceed at room temperature which was a significant improvement in terms of finding milder reaction conditions at which to perform these nucleophilic substitution reactions. An application of this methodology saw the use of the nucleophilic substitution products as precursors for the synthesis of functionalised triarylmethanes.[95] This $FeCl_3$ catalysed benzylation/[3+3] cyclocondensation strategy involved the benzylation of acetylacetone to give the 3-(diarylmethyl)pentane-2,4-dione, which underwent a [3+3] cyclisation with 1,3-bis(trimethylsiloxy)-1,3-diene to give the triarylmethane (Scheme 1.59). These highly functionalised triarylmethanes are not readily available via other preparation methods.



Scheme 1.59 : $FeCl_3$ catalysed benzylation/[3+3] cyclocondensation to give functionalised triaryl compounds.

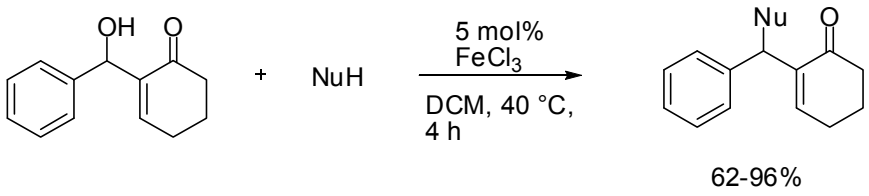
The nucleophilic substitution of propargylic alcohols was found to proceed in the presence of only 5 mol% $FeCl_3$ with carbon nucleophiles, heteroatom type nucleophiles such as allyl trimethylsilane, alcohols, aromatic compounds, thiols and amides.[96] This catalyst was both air and moisture tolerant. Various other benzylic and allylic alcohols were found to react with primary amides such as benzamide, sulfonamide, acetamide and acrylamide to give the corresponding secondary amides in moderate to high yields.[97] Indoles were also reported as nucleophiles for these substrates.[98]

The addition of terminal alkynes to benzylic alcohols catalysed by $FeCl_3$ provides a direct and simple method for obtaining substituted aryl ketones under mild reaction conditions.[99] A proposed mechanism (Scheme 1.60) involves the generation of an alkenyl cation after the attack of the terminal alkyne onto the benzylic carbocation. Nucleophilic attack of water onto this alkenyl cation and subsequent deprotonation and tautomerisation furnishes the ketone.



Scheme 1.60 : Proposed mechanism for the formation of the aryl ketones via nucleophilic attack of a terminal alkyne onto a benzylic carbocation.

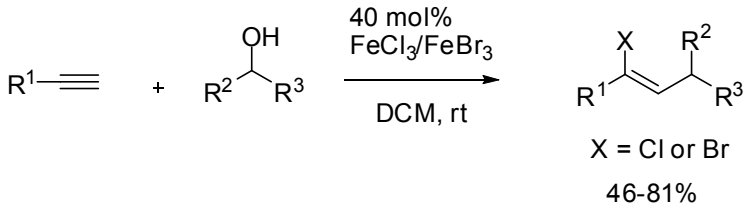
The Ritter reaction was also found to be catalysed by $FeCl_3$ to give the corresponding amide via the nucleophilic substitution of benzylic alcohols.[100] The intramolecular Friedel-Crafts cyclisation of aryl-substituted allylic alcohols to yield the indene derivatives was also reported to occur in the presence of $FeCl_3$.[101] Morita-Baylis-Hilman adducts are receiving increasing attention for nucleophilic substitution reactions due to their versatility as building blocks in organic synthesis.[102] The α-substitution of these adducts could be successfully performed with a catalytic amount of $FeCl_3$.[102] The nucleophiles used included alcohols, arenes, 1,3-dicarbonyls and thiols and the α-substituted products were obtained in moderate to excellent yields (Scheme 1.61). This same reaction was also reported by another group.[103]



Scheme 1.61 : $FeCl_3$ catalysed nucleophilic α-substitution of Morita-Baylis-Hilman adducts by various nucleophiles.

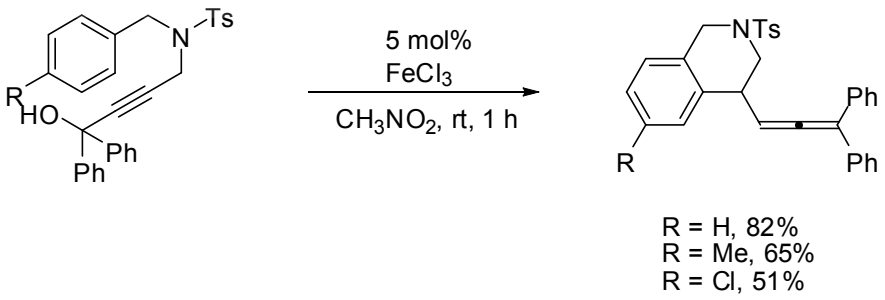
The novel one-pot reaction of alkynes with various "activated" alcohols catalysed by 40 mol% $FeCl_3$ or $FeBr_3$ in dichloromethane was reported to give the corresponding alkenyl halide in moderate yields (Scheme 1.62).[104] The synthesis of substituted aryl ketones from benzylic alcohols and terminal alkynes has been mentioned.[99] The main difference observed in reactivity stems from the use of DCM as the reaction solvent as opposed to nitroethane. In the previously mentioned mechanism the intermediate alkenyl cation is quenched with a

molecule of water to give the corresponding ketone. However, when the reaction is performed in DCM there is not a significant amount of water present due to the low miscibility of water and DCM, and accordingly the alkenyl cation reacts with a halide of the iron complex to give the alkenyl halide.



Scheme 1.62 : $FeCl_3/FeBr_3$ catalysed conversion of "activated" alcohols into the corresponding alkenyl halides.

The synthesis of dihydro- and tetrahydroisoquinolines was reported in an $FeCl_3$ catalysed intramolecular allenylation/cyclisation of benzylamino substituted propargylic alcohols (Scheme 1.63).[105] The other Lewis acids investigated ($Yb(OTf)_3$, $ZnCl_2$) gave similar yields but required longer reaction times. $InCl_3$ was found to give similar yields in comparable reaction times. This reaction was found to not occur in the presence of a Brønsted acid (TsOH).

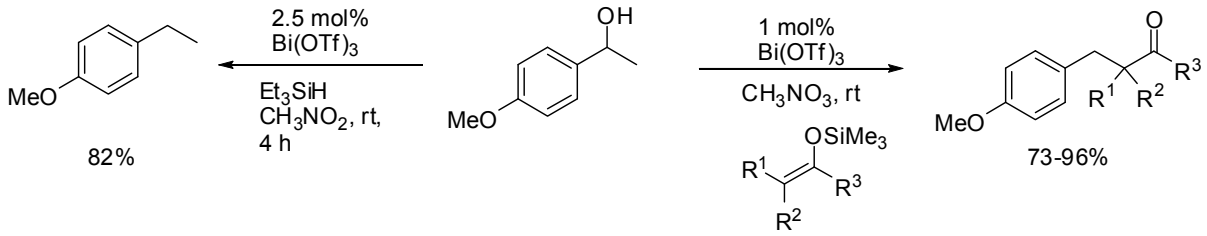


Scheme 1.63 : $FeCl_3$ catalysed intramolecularallenylation/cyclisation of benzylamino substituted propargylic alcohols.

1.3.3.2.4 Bismuth

$Bi(OTf)_3$ has been utilised as a catalyst for the direct alkylation of silyl enol ethers with *para*-methoxybenzylic alcohols to afford the α-benzylated carbonyl compounds in high yields (Scheme 1.64).[106] It was found that the same reaction could be performed utilising the *para*-

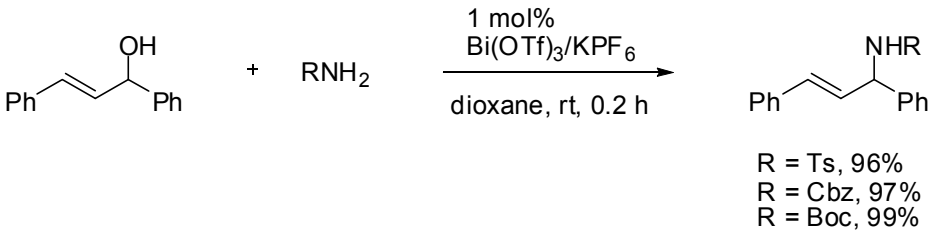
methoxybenzyl acetate to afford the α-benzylated carbonyl compound in yields comparable to the use of *para*-methoxybenzyl alcohols as starting materials. The catalytic reduction of these benzylic alcohols could also be performed with triethylsilane as the hydride source to give the reduced compound in a high yield (Scheme 1.64).



Scheme 1.64 : $Bi(OTf)_3$ catalysed nucleophilic substitution of *para*-methoxybenzyl alcohol with silyl enol ethers as well as the catalytic reduction with triethylsilane.

$BiCl_3$ has been reported to catalyse the nucleophilic substitution of propargylic alcohols by allyl trimethylsilane, alcohols, aromatics, thiols and amides.[107] This required the use of 10 mol% $BiCl_3$ in acetonitrile and gave the substituted products in moderate to high yields. It was also noted that amines (aniline, piperidine) could not be utilised as nucleophiles for these reactions.

Shibasaki and Matsunaga have reported the substitution of the hydroxyl group of allylic and propargylic alcohols with amides in the presence of $Bi(OTf)_3/KPF_6$ in as little as 1 mol%.[108] It was found that $BiCl_3$ could promote these reactions as well as $Bi(OTf)_3$ but that the highest yields were obtained through the use of $Bi(OTf)_3$ with KPF_6 as an additive. It must be noted that KPF_6 alone did not promote this reaction at all. The scope of the amides utilised for this reaction was quite diverse with carbamates, oxazolidinones and unsaturated amides functioning as suitable nucleophiles (Scheme 1.65).



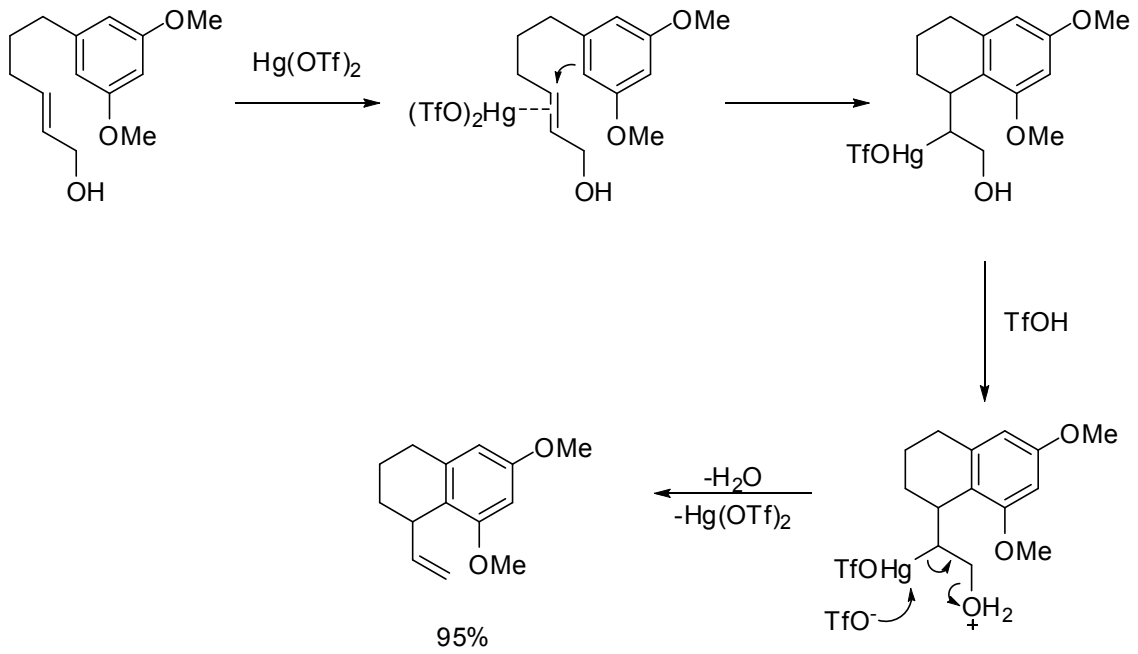
Scheme 1.65 : $Bi(OTf)_3/KPF_6$ catalysed nucleophilic substitution of an allylic alcohol with a deactivated amine.

1.3.3.2.5 Other metals

The deoxygenative deallylation of propargylic alcohols with allylsilanes has been catalysed by 10 mol% $Cu(BF_4)_2$ in acetonitrile to afford the corresponding 1,5-enynes in high yields.[109] $Cu(BF_4)_2$ was found to be more active than $Cu(OTf)_2$, $Cu(acac)_2$ and $Cu(ClO_4)_2$. However, similar catalytic activity was observed when $Sc(OTf)_3$ was used. $CuBr_2$ has also been used in the nucleophilic substitution of propargylic alcohols by other alcohols, thiols and carbon nucleophiles.[110]

Primary benzylic alcohols have been successfully aminated with sulfonamides to give the corresponding amides in high yields.[111] This reaction was catalysed by 10 mol% AgOTf in nitromethane under reflux. These primary benzylic alcohols do not undergo nucleophilic substitution as readily as secondary and tertiary benzylic alcohols and for this reason this catalytic system is of particular interest. Prolonged reaction times (8 hours) were required to realise high yields. $Cu(OTf)_2$, $Sc(OTf)_3$ and $Bi(OTf)_3$ were found to have similar catalytic activity.

The $Hg(OTf)_2$ catalysed cyclisation of allylic alcohols to give the corresponding arylene has been reported.[112] A mechanism has been proposed (Scheme 1.66). It is believed that initial complexation of the $Hg(OTf)_2$ to the double bond activates it towards nucleophilic attack from the aromatic ring in a Friedel-Crafts type cyclisation. Protonation of the hydroxyl group by *in situ* generated triflic acid leads to the oxonium cation which gives the corresponding arylene through elimination of water as well as $Hg(OTf)_2$ through demercuration. This reaction was limited to methoxy- and indole-substituted benzene rings.

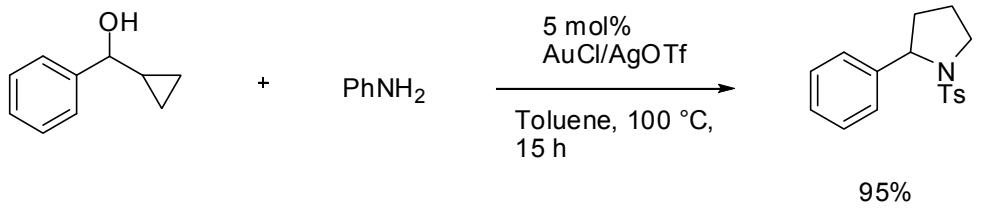


Scheme 1.66 : Proposed mechanism for the $Hg(OTf)_2$ catalysed cyclisation of an allyl alcohol to give the corresponding arylene.

Ruthenium complexes ($\eta 5$-C_5Me_5*$RuCl(\eta_2SMe)_2$) have found application in the nucleophilic substitution of propargylic alcohols.[113] Anilines, alcohols, thiols and phosphane oxides have been reported as nucleophiles for this Ru promoted reaction.[114] The use of a catalytic amount of added NH_4BF_4 was, however, required for these reactions to proceed smoothly. Acetones and diketones were also found to be suitable nucleophiles, as were silylenol ethers.[115,116] Indoles and arenes could be employed as activated carbon nucleophiles.[117] The triethylsilane reduction of propargylic alcohols was also found to occur in the presence of these ruthenium complexes.[118] The nucleophilic substitution of allylic alcohols with various nucleophiles has also been reported.[119] This reaction requires the presence of a catalytic amount of camphorsulfonic acid to realise acceptable yields.

Au(III) salts have been found to catalyse the nucleophilic substitution of propargylic alcohols.[120] $NaAuCl_4 \cdot 2H_2O$ could be used in as little as 5 mol% to see the nucleophilic substitution with allylsilanes, alcohols, furans, dimethoxybenzenes and thiols. Au(I) salts were found to have lower catalytic activity whilst $PtCl_2$ and $PdCl_2(PhCN)$ showed no catalytic activity whatsoever. Allylstannanes could undergo an intramolecular coupling with allylic alcohols through the use of a gold complex.[121] The preparation of unsymmetrical benzyl ethers from the corresponding benzyl alcohol and nucleophilic alcohol was also

reported.[122] In this reaction the nucleophilic alcohol was used as the reaction solvent in order to ensure the formation of the unsymmetrical ether. A Au(I) salt could be used as a catalyst in the presence of a AgOTf co-catalyst for tandem amination/ring expansion of substituted cyclopropyl methanols with a sulphonamide (Scheme 1.67).[123]



Scheme 1.67 : AuCl/AgOTf catalysed tandem amination/ring expansion of substituted cyclopropyl methanols.

Molecular iodine can function as a moderate Lewis acid and has received attention in organic transformations.[124a-d] The C3-alkylation of 4-hydroxycoumarins with benzylic, benzhydrilic, allylic and propargylic alcohols has been effected with 10 mol% molecular iodine.[125] This gave the 3-alkylated-4-hydroxycoumarins in yields of 65-97%. The alkylation of sulfonamides and carbamates with allylic alcohols has been reported with I_2 as the Lewis acid catalyst.[126] Propargylic alcohols have shown reactivity for nucleophilic displacement reactions with carbon and oxygen nucleophiles which could be catalysed by 5 mol% I_2 in CH_3NO_2 to give yields in the range of 85-95%.[127] By using molecular iodine in conjunction with hypophosphorus acid it was possible to reduce a range of benzhydrilic alcohols to the corresponding diphenylmethanes.[128] The authors postulated that hydrogen iodide was being generated under the reaction conditions to catalyse the formation of benzylic carbocations which then react with the hydride provided by the hypophosphoric acid.

1.4 Conclusions

Metal triflates have found widespread applications in organic transformations as Lewis acid substitutes for the traditional Brønsted and Lewis acids. They display comparable and in most cases superior results in terms of yield and selectivity. They can also be utilised in catalytic amounts as opposed to the stoichiometric amounts of traditional acids required. These metal triflates can also be recovered and recycled without significant loss in activity. They are also

remarkably stable to water with the traditional Lewis acids showing no activity in the presence of water.

The ring-opening of epoxides by alcohols and amines has been well studied and found to be promoted by a wide array of metal triflates, with $Al(OTf)_3$ also being reported as a catalyst. These reports are, however, limited to the use of super stoichiometric amounts of alcohols as well as the use of rather simple amines. The application of $Al(OTf)_3$ as a Lewis acid for the aminolysis of epoxides for the synthesis of more complicated and biologically active molecules has not been reported. This application played a significant role in this study.

The nucleophilic substitution of "activated" alcohols has become a widely studied topic with catalysis being promoted by a wide range of Lewis acids. These Lewis acids are not limited to metal triflates alone. It was quite surprising to find no mention whatsoever of $Al(OTf)_3$ for these types of reactions in the literature, and the present study also aimed to address this aspect.

1.5 Aims of the present study

Given the omissions in the literature noted immediately above, it was one of the aims of the present study to investigate the ring-opening of epoxides with various alcohols but where the amount of alcohol is reduced to approximately stoichiometric levels. Given the preponderance in the literature for the use of large excesses of nucleophilic alcohols, in many cases being used as the reaction medium, it was thought that the ability to reduce the amount of alcohol employed for the reaction would improve the overall efficiency of the reaction to render it more compliant with the concepts of green chemistry.

A second aim of the study was to employ more complex amines in the ring-opening of epoxides, given that to date most of the amines used in this transformation have been relatively simple systems. It was envisaged that the successful application of more complex amines would allow the chemistry to be translated in the synthesis of quite complicated molecular systems such as piperazine derivatives, which are known to be physiologically active.

Finally, it was intended to pursue the use of $Al(OTf)_3$ for the displacement of the hydroxyl group in "activated" alcohols using various nucleophiles. Here, various nucleophiles would be employed and the reaction would be applied to the synthesis of ring systems such as chromenes in intramolecular systems.

1.6 References

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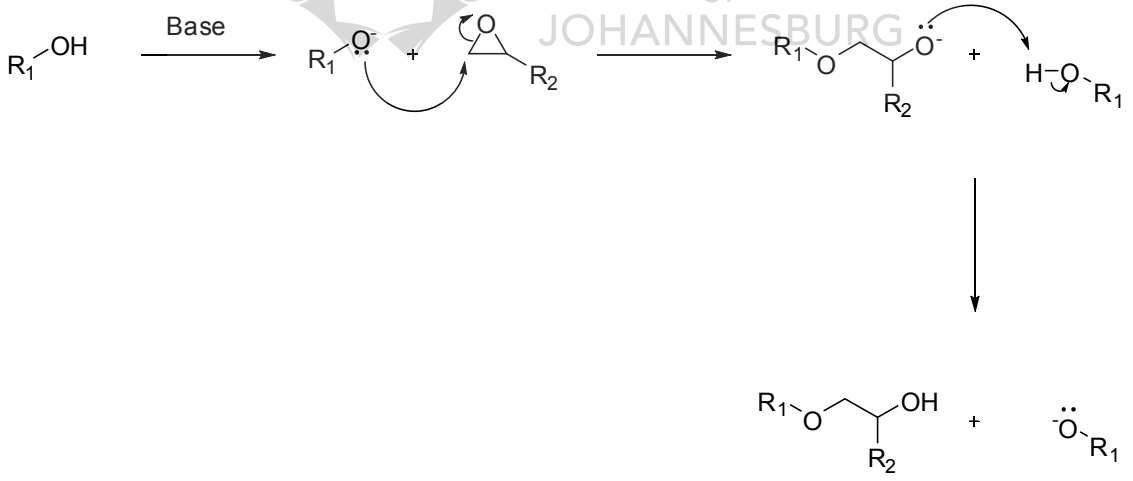
Chapter 2

Aluminium triflate : A Lewis acid catalyst for the alcoholysis of epoxides

2.1 Introduction

Epoxides are important starting materials for organic synthesis, where they serve as a source of β-alkoxy alcohols via the alcoholysis of epoxides as well as of β-amino alcohols via the aminolysis of epoxides.[1] The three membered ring structure of epoxides is, by its nature, strained. This renders them very reactive towards nucleophiles.[2] The ring strain is released via a ring-opening reaction, for example during a nucleophilic attack on the ring.[1]

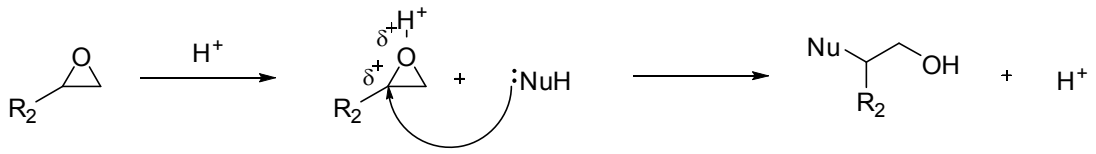
The ring-opening of epoxides can be promoted in two ways. The first is through a base-catalysed reaction (Scheme 2.1) proceeding via an S_N2 type mechanism. The requirement for this type of chemistry is that the nucleophile is also a strong base such as an alkoxide or hydroxide ion.[2] The S_N2 type mechanism is characterised by attack of the nucleophile at the less hindered carbon of the epoxide ring, as is usually anticipated, because S_N2 reactions favour substrates that are not sterically hindered.[2]



Scheme 2.1 : Base catalysed ring-opening of an epoxide.

In the second instance an acid can be used to catalyse the reaction. In this case the ring-opening resembles an S_N1 type mechanism and is often referred to as a borderline S_N2 reaction (Scheme 2.2).[3] The intermediate state of a borderline S_N2 reaction resembles

the carbocationic intermediate species of an S_N1 reaction and nucleophilic attack tends to occur on the more hindered carbon bearing the most positive charge.



Scheme 2.2 : Acid catalysed ring-opening of an epoxide.

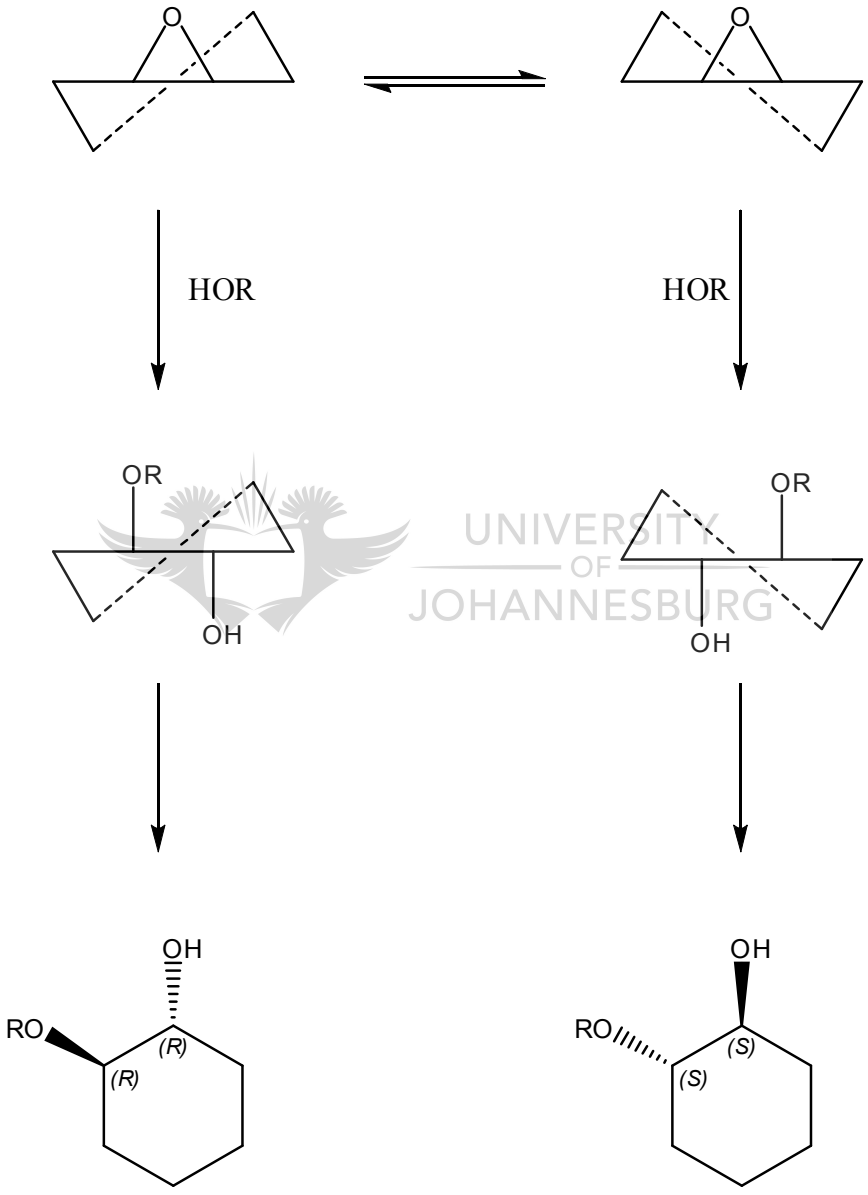
Previous work has established $Al(OTf)_3$ as a catalyst for the ring-opening of epoxides with alcohol nucleophiles.[4] This work provided an effective protocol for the alcoholysis of various epoxides with simple alcohols, whereby the epoxide is ring-opened in the presence of 6 equivalents of the alcohol.

The desymmetrisation of achiral or *meso*-epoxides provides a useful way of obtaining enantiopure compounds.[5] These epoxides are derived from alkenes such as cyclohexene that provide homotopic faces for epoxidation. Epoxides derived from alkenes that are not symmetrically substituted, i.e. with heterotopic faces, can be obtained in the racemic or non-racemic forms.[6]

Desymmetrisation of achiral epoxides can be done by enantioselective deprotonation or by enantioselective addition, the former being base-promoted and the latter acid-catalysed. Of particular interest is the enantioselective addition which can be promoted by an acid catalyst. These reactions require the presence of a chiral ligand[7] or the use of a chiral Lewis acid catalyst.[8]

The use of a chiral alcoholic nucleophile for the desymmetrisation of *meso*-epoxides has not yet been investigated. The chirality already present on the alcohol would remain fixed during the ring-opening reaction to give diastereomeric products, depending on the configuration of the chiral centres of the ring-opened epoxide (Scheme 2.3). Due to rapid ring flip of the cyclohexene oxide (Scheme 2.3) there exist two states of cyclohexene oxide that can be ring-opened, if one form is preferred for ring-opening above the other, then significant diastereoselectivity could be imparted on the reaction. It was thought that complexation of the chiral alcohol to the active $Al(OTf)_3$ catalyst would generate an *in situ* chiral catalyst that might diastereoselectively ring-open the

cyclohexene oxide. Given the cost of chiral alcohols, the idea would be expensive to execute if a large excess of the alcohol is required for a successful reaction. As a consequence, conditions were first sought with which to reduce the excess of alcohol normally present during such transformations. It should be recalled at this juncture that the usual approach had been to use the alcohol in a 6 molar equivalents excess.

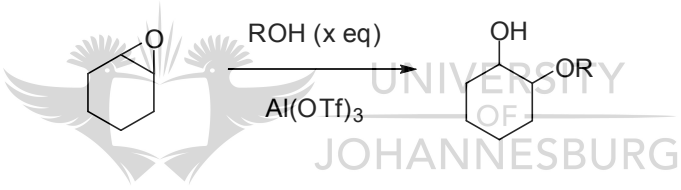


Scheme 2.3 : Desymmetrisation of cyclohexene oxide with a chiral alcohol.

2.2 Ring-opening of cyclohexene oxide

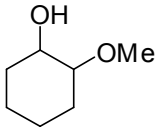
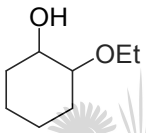
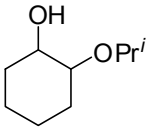
2.2.1 Reduction in equivalents of alcohol required for the ring-opening of cyclohexene oxide

Previous work that reported the use of $Al(OTf)_3$ for the alcoholysis of epoxides required the use of 6 equivalents of alcohol in order to maintain high reaction yields.[4] This protocol is suitable for the use of simple alcohols that are cheap and readily available. However, when more complex alcohols are used, i.e. chiral alcohols, the use of 6 equivalents of the alcohol is not desirable. It was necessary to investigate whether the molar equivalents of alcohol required for this reaction could be reduced whilst maintaining the high yields previously reported. For this purpose simple alcohols (methanol, ethanol, *iso*-propanol) were used to ring-open cyclohexene oxide (Scheme 2.4) with 0.002 mol% $Al(OTf)_3$ catalyst under reflux for 1 hour. The amount of alcohol used in the reaction was systematically reduced from 6 equivalents to 2 equivalents to 1 equivalent. The results are summarised in Table 2.1.



Scheme 2.4 : Ring-opening of cyclohexene oxide with simple alcohols.

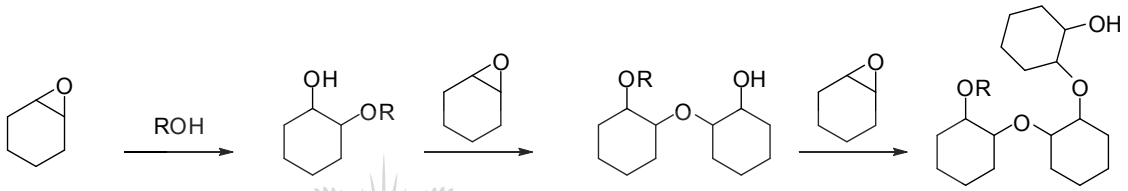
Table 2.1 : Reactions yields (%)[a] for alcoholysis of cyclohexene oxide with reduced equivalents of alcohol.

Entry	Compound	Yield (%) with 6 eq alcohol	Yield (%) with 2 eq alcohol	Yield (%) with 1 eq alcohol
1	 **2.1**	85 (79)[b]	59	23
2	 **2.2**	86 (86)[b]	63	32
3	 **2.3**	80 (76)[b]	60	20

[a]Yields determined by GC-FID. [b]Yields in parenthesis refer to isolated yields.

As the molar excess of alcohol is reduced from 6 to 1, there is a decrease in the reaction yield (Table 2.1).This is not surprising considering that the reaction follows a borderline S_N2 mechanism in which the reaction rate is directly proportional to the concentration of the two reacting species, namely cyclohexene oxide and the desired alcohol.[2] A reduction in the alcohol concentration would thus lead to a reduction in the reaction rate and also a decrease in the reaction yield. It was interesting to note that there was

complete consumption of the cyclohexene oxide after 1 hour for the reactions where only 1 equivalent of alcohol was used. This would imply that another, competing, reaction is taking place. Previous work had established the formation of an oligomeric species when styrene oxide was ring-opened with simple alcohols.[4] It is thus entirely possible that a similar phenomenon was occurring for the ring-opening of cyclohexene oxide. This occurs when the alcohol that forms after the first ring-opening reaction reacts with another molecule of cyclohexene oxide (Scheme 2.5) to give the dimer. This dimer could then react with another molecule of cyclohexene oxide to give the oligomer. The reduction of the equivalents of alcohol thus did not reduce the reactivity of the cyclohexene oxide but instead reduced the rate of the desired ring-opening reaction. This means that the unwanted side-reaction, to form the oligomer, could now compete with the desired ring-opening reaction.



Scheme 2.5 : Formation of oligomeric cyclohexene oxide species.

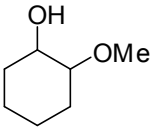
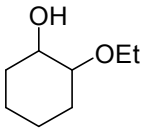
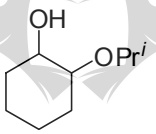
The effects of catalyst concentration, reaction time and reaction temperature were then investigated in order to ascertain if it would be possible to minimise the side-reaction by varying these parameters. The use of 2 equivalents of alcohol was chosen as the benchmark reaction in order to clearly see a decrease or increase in yield as previous reactions with 2 equivalents of alcohol gave yields in the range of 50% (Table 2.1), which is a sensitive probe towards both increases and decreases in yield given its mid-range.

A decrease in the amount of $Al(OTf)_3$ from 0.002 mol% to 0.001 mol% (Table 2.2, entries 2, 5, and 9) had no significant effect on the yield, whereas an increase from 0.002 mol% to 0.02 mol% $Al(OTf)_3$ led to a significant decrease in the yield (Table 2.2, entries 1, 6, and 10). This decrease is due to an increase in overall reactivity leading to an increased side-reaction rate and thus more by-product.

It was then decided to slow the reaction down by cooling the reaction mixture to 0 °C. It was hoped that this would lead to a significant distinction between the rates of the desired reaction and side-reaction. This was, however, not the case (Table 2.2, entries 3, 7, and 11). It was interesting to note that the reaction could be performed at lower reaction temperatures, which indicated that the use of higher temperatures (reflux conditions) were not necessary and could in fact actually be detrimental to the reaction yield. Further reactions were then performed at room temperature.

Finally it was decided to attempt to differentiate the reaction rates of the desired and side-reaction by slowly adding the epoxide to a solution of $Al(OTf)_3$ and 2 equivalents of the desired alcohol. This would mimic previous reaction conditions where the alcohol was present in excess relative to the epoxide. This change gave a marked increase (10-20%) in yields (Table 2.2, entries 4, 8 and 12). The higher concentration of starting alcohol (also, higher ratio of alcohol to substrate) imposed by these reaction conditions ensures that the reaction rate for the formation of the desired product is significantly higher than the reaction rate for the formation of the oligomer. The improved alcohol/substrate ratio enhances the selectivity of the reaction.

Table 2.2 : Effects of catalyst loading, temperature and epoxide addition.

Entry	Compound	Mol% $Al(OTf)_3$	Temperature (°C)	Yield (%)[a]
1	 **2.1**	0.02	reflux	8
2		0.001	reflux	60
3		0.002	0	73
4		0.002	room temp	77[b]
5	 **2.2**	0.02	reflux	11
6		0.001	reflux	65
7		0.002	0	64
8		0.002	room temp	82[b]
9	 **2.3**	0.02	reflux	12
10		0.001	reflux	44
11		0.002	0	30
12		0.002	room temp	71[b]

[a]Yields determined by GC-FID, reactions carried out with 2 equivalents of alcohol and run for 1 hour. [b]Epoxide added slowly over the course of the reaction.

This slow addition method was then applied to the ring-opening of cyclohexene oxide with 1 equivalent of alcohol. Previous reactions with only 1 equivalent had given the desired reaction product in low yields (Table 2.1) of 20-30%. With this modified protocol it is possible to obtain yields comparable to those seen when 6 equivalents of alcohol were utilised. Figure 2.1 summarises the effect of the slow addition methodology upon the reaction yield.

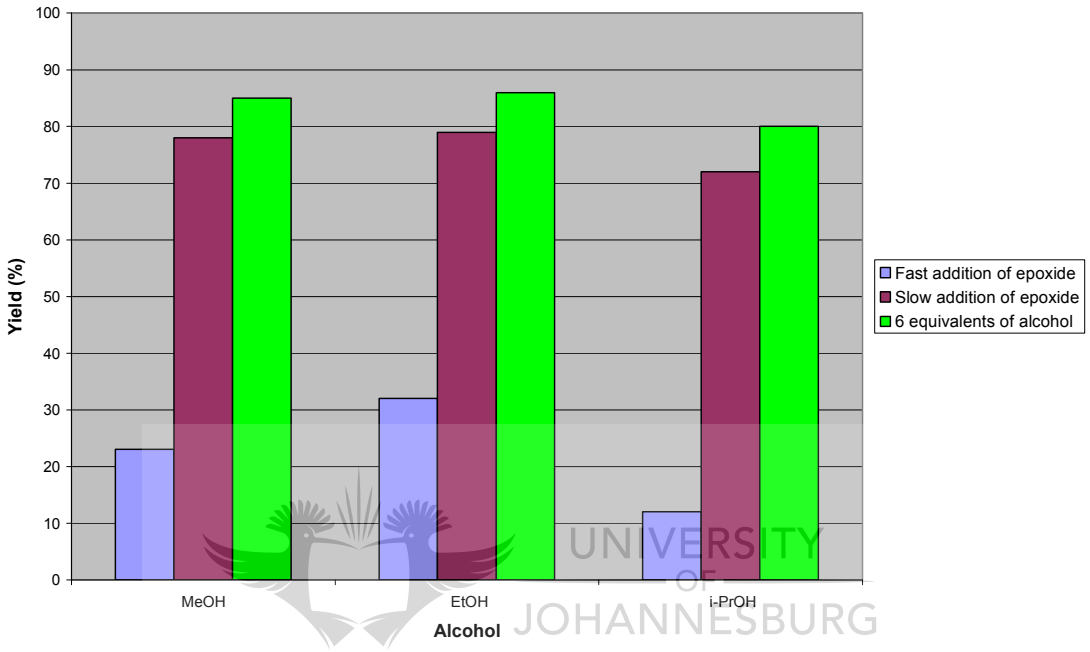
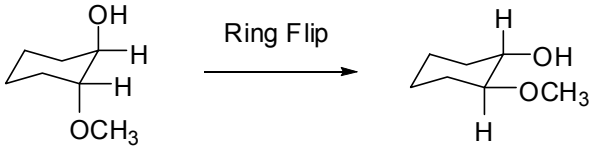


Figure 2.1 : Comparison of slow and fast epoxide addition on the reaction of cyclohexene oxide with 1 equivalent of the respective alcohol.

2.2.2 Stereochemistry of the ring-opened products of cyclohexene oxide

Using NMR spectroscopy it was possible to determine the stereochemistry of the ring-opened products (**2.1**-**2.3**) of cyclohexene oxide. Six membered cyclic rings typically adopt conformations whereby the sterically most demanding groups occupy the equatorial positions. (Exceptions to this rule occur, for example, where the anomeric effect causes large but electronegative groups to occupy axial positions). This conformation is more stable than when these groups occupy the axial positions due to a minimisation of 1,3-diaxial interactions. The vicinal coupling constants for the protons of these positions are a diagnostic tool with which to assign the arrangement of these sterically demanding groups.[9] 1,2-*Trans*-diaxial arrangements of protons show coupling

constants in the order of 10 Hertz whilst 1,2-*cis*-axial/equatorial arrangements display significantly smaller coupling constants. The Fürst-Plattner rule[10] indicates that ring-opened epoxides give the *trans*-diaxial glycol ether as the intermediate product with the hydrogen atoms being placed in the equatorial positions (Scheme 2.6). This *trans*-diaxial glycol ether can ring-flip to the more stable conformation thus placing the hydrogen atoms of interest in the 1,2-*trans*-diaxial arrangement (Scheme 2.6).



Scheme 2.6 : *Trans*-diaxial immediate product **2.1** of the ring-opening of cyclohexene oxide.

A coupling constant for the protons of the *trans* product is expected to be in the range of 9-11 Hz (Figure 2.2). Table 2.3 lists the coupling constants (*J*) for H1 and H2 (Figure 2.2) of the ring-opened products of cyclohexene oxide. It can be seen from the coupling constants (Table 2.3) that the substituents are arranged in a *trans* manner.

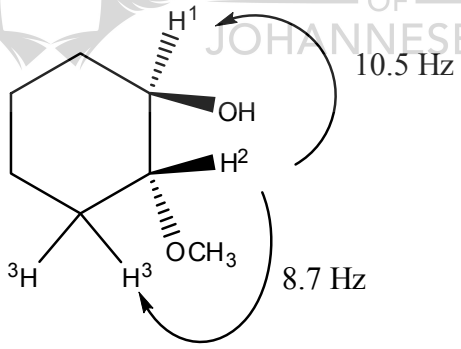
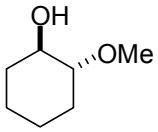
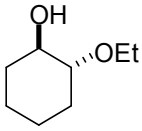
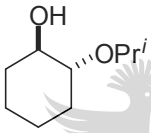


Figure 2.2 : Expected coupling constants for the *trans*-diaxial arrangement.

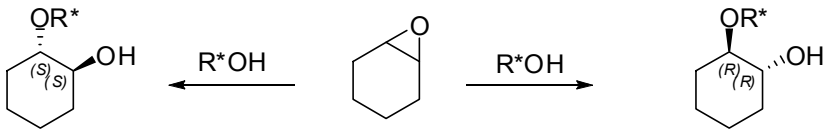
Table 2.3 : Coupling constants for products **2.1**-**2.3**.

Entry	Compound	Signal multiplicity (H^1)	*J* (Hz) H^2-H^1	*J* (Hz) H^2-H^3ax	*J* (Hz) H^2-H^3eq
1	 **2.1**	ddd	10.7	8.5	4.2
2	 **2.2**	ddd	10.4	8.5	4.4
3	 **2.3**	ddd	10.5	8.7	4.3

2.2.3 Ring-opening of cyclohexene oxide with chiral alcohols

It had been demonstrated that the ring-opening of cyclohexene oxide could be performed with only 1 equivalent of alcohol and not 6 equivalents, and that acceptable yields may be secured when adding the epoxide slowly to a solution of the alcohol. It was then decided to perform the ring-opening of cyclohexene oxide with chiral alcoholic nucleophiles in order to determine the diastereoselectivity of this reaction between a *meso*-epoxide and a chiral alcohol (Scheme 2.7). It was thought that a chiral alcohol might impart significant diastereoselectivity during the ring-opening reaction through association with the $Al(OTf)_3$ catalyst during the ring-opening step. This reaction would yield a diastereomeric mixture of products. This is due to the chirality on the alcohol remaining fixed whilst the chirality on the epoxide derived ring can vary. (Scheme 2.7). The underlying rationale is in the proposed binding of the alcohol to the

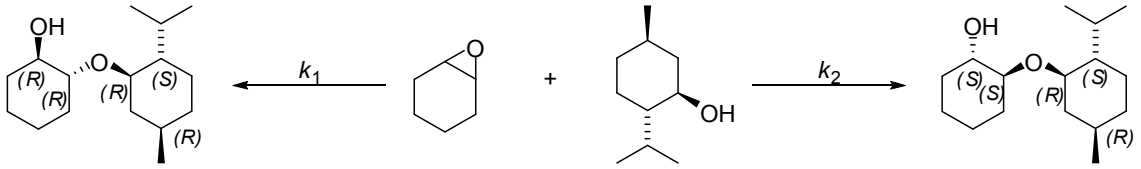
Al centre and that this binding may be maintained throughout the course of the reaction, including binding to the epoxide. Previous work in our laboratories[11] have shown that solutions of $Al(OTf)_3$ in MeOH are substantially acidic, caused by a putative MeOH-$Al(OTf)_3$ complex which leads to Lewis-assisted Brønsted acidity. Furthermore, a theoretical study by Duñach and co-workers,[12] used to help to explain experimental observations, indicates that $Al(OTf)_3$ binds quite strongly to alcohols and causes significant Brønsted acidity as a consequence. So in the present instance, it was hoped that the chiral alcohol would be retained as a ligand riding on the Al centre and in so doing generate a chiral Lewis acid catalyst for the epoxide ring-opening reaction.



Scheme 2.7 : Desymmetrisation of cyclohexene oxide to give the respective diastereomers.

2.2.3.1 Desymmetrisation of cyclohexene oxide with *l*-menthol

The first desymmetrisation of cyclohexene oxide attempted was performed using *l*-menthol as the chiral alcohol (Scheme 2.8). In previous reactions the alcohol served both as a reactant and a solvent with the reactions being performed at room temperature. Due to *l*-menthol being a solid with a melting point of 36 °C, toluene was used as a reaction solvent. Toluene has been established previously as the optimal solvent in which to perform the $Al(OTf)_3$ catalysed ring-opening of epoxides.[4] The effect of temperature on the diastereoselectivity of the ring-opening reaction was examined by first performing the ring-opening reactions at 100 °C and then performing them at 0 °C (Table 2.4).



2.4 **2.4**

Scheme 2.8 : Desymmetrisation of cyclohexene oxide with *l*-menthol to give **2.4**.

Table 2.4 : Results for the desymmetrisation of cyclohexene oxide with *l*-menthol.

Entry	Mol% $Al(OTf)_3$	Temperature (°C)	Time (h)	Yield (%)[a]	Diastereoselectivity[b]
1[c]	1	100	5	16	1:1.94
2[c]	5	100	5	35	1:1.62
3	1	100	5	17	1:1.82
4	5	100	5	38	1:2.89
5	1	0	20	45	1:2.36
6	10	0	20	64	1:1.97
7[d]	5	40	5	64	1:2.01

[a]Isolated yield of inseparable diastereomers. [b]Diastereoselectivity determined by GC-FID. [c]Epoxide added slowly over the reaction duration. [d]Reaction performed under solventless conditions.

Initial reactions (Table 2.4, entries 1 and 2) utilised the slow addition of cyclohexene oxide as had been previously established (Section 2.2.1). However, this was found to have no effect on the yield of the reaction, as reactions performed where all the epoxide was added at once at the start of the reaction (Table 2.4, entries 3 and 4) gave similar results compared to the slow addition methodology. This indicates a low reaction rate, a concept which was reinforced by the presence of unconsumed cyclohexene oxide at the end of the reaction, as well as the low yields even over longer reaction times (5 hours). The diastereoselectivity was determined by GC-FID (Figure 2.3) with the two diastereomers separating at around 12 minutes retention time. This determination was possible due to the diastereomers interacting differently with the solid phase of the GC-column.

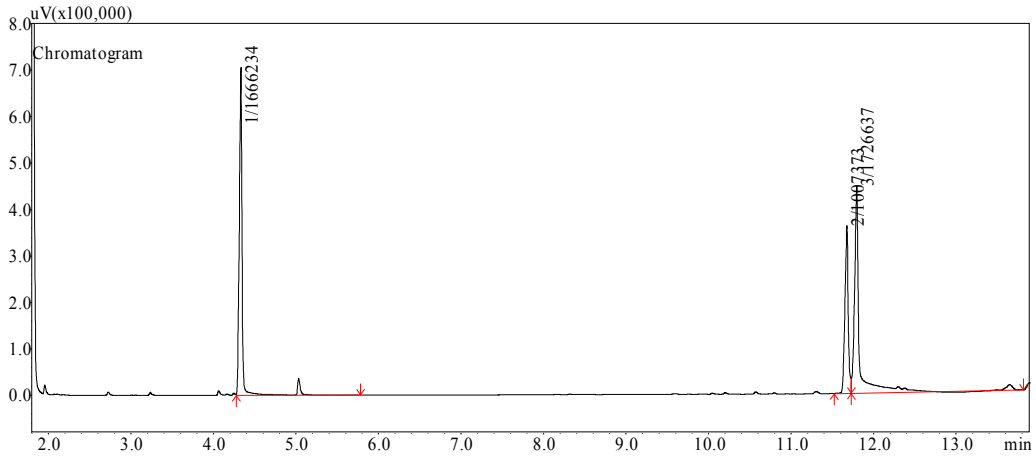


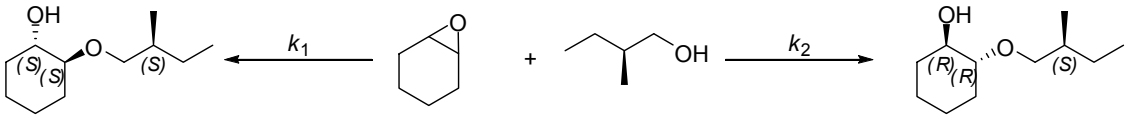
Figure 2.3 : GC-FID chromatogram of ring-opening of cyclohexene oxide with *l*-menthol.

It was hoped that a reduction in the reaction temperature might allow sufficient differentiation between the reaction rates k_1 and k_2 (Scheme 2.8) so that one diastereomer might be favoured above the other thus leading to some measure of diastereoselectivity. Reducing the reaction temperature to 0 °C had no effect on the diastereoselectivity of the reaction (Table 2.4, entries 4 and 5), but longer reaction times (20 hours) were required to realise acceptable yields. These results suggested that the temperature reduction would not have any effect on the diastereoselectivity (at least not when an appreciable rate of reaction is sought). In addition to this any further reductions in reaction temperature would require significant extension of the reaction time to observe any appreciable yield. It was decided not to pursue any further reduction of reaction temperature.

It was nevertheless possible to realise high reaction yields in moderate reaction times (Table 2.4, entry 7) by the omission of solvent from these reactions. For this the reaction was performed at 40 °C, since the melting point of *l*-menthol is 36 °C. This allowed *l*-menthol to behave as the reaction solvent as well as a reactant and in doing so a dramatic increase in the reaction yield was observed. Apart from enhanced reaction rate due to the elevated temperature, the improvement in yield is presumably also due to the increased concentration of the reactants caused by a reduction in the overall volume of the reaction mixture.

2.3.2.2 Desymmetrisation of cyclohexene oxide with (*S*)-2-methyl-1-butanol

(*S*)-2-Methyl-1-butanol was then investigated as the chiral alcohol with which to ring-open cyclohexene oxide (Scheme 2.9). Although there is no chirality on the OH-bearing carbon atom it was hoped that the chirality at the carbon adjacent to the alcoholic carbon might impart some diastereoselectivity. (*S*)-2-Methyl-1-butanol presents significantly less steric bulk than *l*-menthol so at least the reaction rates were hoped to be better than that of *l*-menthol.



2.5 **2.5**

Scheme 2.9 : Desymmetrisation of cyclohexene oxide with (*S*)-2-methyl-1-butanol to give **2.5**.

The protocol with which the epoxide is added to the reaction mixture was once again found to have little effect on the reaction yields. In order to investigate the diastereoselectivity achievable, a standard set of conditions was used whereby the reaction was run for 1 hour at the specified temperature and catalyst concentration. These reactions were thus not optimised for yield. The use of toluene as a reaction solvent was necessary in order to properly dilute the reaction mixture as the absence thereof led to the formation viscous syrup presumably due to oligomer formation as has been previously mentioned.

Table 2.5 : Results for the desymmetrisation of cyclohexene oxide with (*S*)-2-methyl-1-butanol.

Entry	Mol% $Al(OTf)_3$	Temperature (°C)	Yield (%)[a]	Diastereoselectivity[b]
1	0.5	100	53	1:1.06
2	1	100	48	1:1.20
3	0.5	80	47	1:1.03
4	1	80	48	1:1.05
5	0.5	room temp	23	1:1.17
6	1	room temp	31	1:1.07
7	0.5	0	12	1:1.16
8	1	0	32	1:1.20

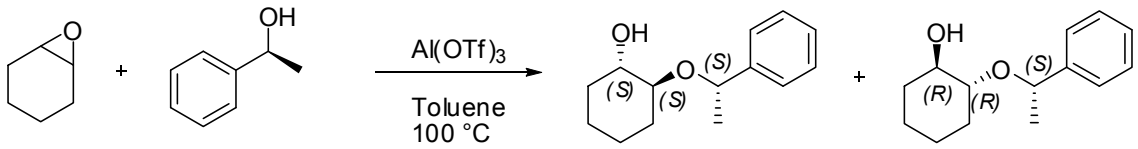
[a]Isolated yield of inseparable diastereomers. [b]Diastereoselectivity determined by ^{1}H NMR spectroscopy.

The separation of the diastereomers (Scheme 2.9) was insufficient on the GC-FID chromatogram to allow for determination of diastereoselectivity. No attempts were made to modify the GC-FID program in order to obtain better resolution since the ^{1}H NMR spectrum showed significant splitting of the diastereomeric protons, thereby allowing diastereoselectivities to be determined with ease. This was observed as individual doublet of doublets signals for the C<u>H</u>OCH_2 protons on the cyclohexane ring into signals at 2.95 and 2.91 ppm respectively. It was thus possible to measure the diastereoselectivity of the reaction by ^{1}H NMR spectroscopy. This was not the case for **2.4** due to significant overlap of signals in the ^{1}H NMR spectrum attributed to the large number of aliphatic protons present on the molecule. A decrease in reaction temperature and/or catalyst loading had little to no effect on the diasteroselectivity of the reaction. A further reduction in reaction temperature was not attempted due to the sluggish nature of

the reaction at low temperatures. It is clear from Table 2.5 that there was essentially no diastereoselectivity manifesting in these reactions.

2.2.3.3 Desymmetrisation of cyclohexene oxide with (*S*)-1-phenylethanol

(*S*)-1-Phenylethanol was then investigated as the chiral alcohol with which to ring-open cyclohexene oxide (Scheme 2.10). With chirality directly on the alcoholic carbon as well as significant steric bulk it was hoped that improved diastereoselectivity would be observed.

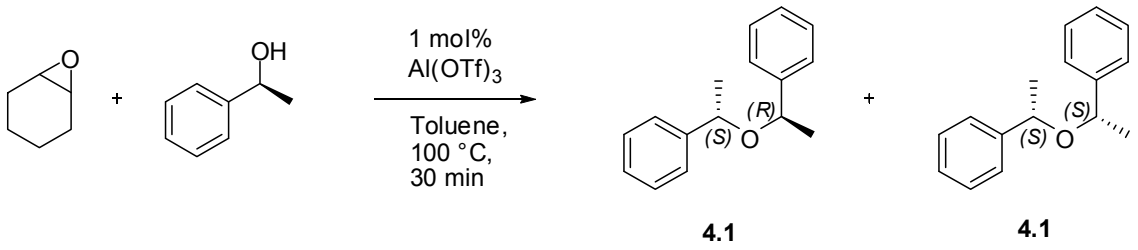


2.6 **2.6**

1:1

Scheme 2.10 : Desymmetrisation of cyclohexene oxide with (*S*)-1-phenylethanol.

Initial reactions at 100 °C in toluene did not yield the desired ring-opened product. Instead a diastereomeric mixture of a symmetrically substituted ether was found (Scheme 2.11). The yield of this ether was virtually quantitative. The details of this reaction will be further discussed in Chapter 4. Reduction of the reaction temperature in an attempt to suppress the ether formation and favour the ring-opened product was futile, with the only product formed being the symmetrical (but diastereomeric) ether **4.1**. Of the alcohols employed, it was thought that *l*-menthol would produce the most favourable results, given its bulky nature. This was indeed the case. However, the diastereoselectivities obtained were modest at best. It was thus decided to not pursue this reaction any further as no positive results in terms of diastereoselectivity during the ring-opening reaction were expected.

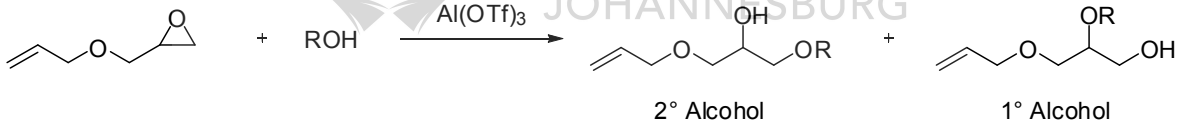


Scheme 2.11 : Unexpected side reaction to give the symmetrically substituted ether **4.1**.

2.3 Ring-opening of allyl glycidyl ether

2.3.1 Reduction in equivalents of alcohol required for the ring-opening of allyl glycidyl ether

The $Al(OTf)_3$ catalysed ring-opening of allyl glycidyl ether with 6 equivalents of ethanol has been reported.[4] Following the results obtained for the ring-opening of cyclohexene oxide with simple alcohols (Section 2.2.1), it was decided to test whether the ring-opening of allyl glycidyl ether could be performed using reduced molar equivalents of a simple alcohol (Scheme 2.12).



Scheme 2.12 : Ring-opening of allyl glycidyl ether with an alcohol to give primary and secondary alcohols.

Unlike cyclohexene oxide, allyl glycidyl ether has two distinctly different positions on the epoxide ring where nucleophilic attack can occur (the internal more sterically hindered and the less sterically hindered external carbon atoms) to give two distinct products. The reaction was expected to give a regioisomeric mixture (Scheme 2.12) of products which is in accordance with expectations.[3] It was anticipated that the primary alcohol would be the dominant product in this reaction. This is due to the reaction following a borderline S_N2 reaction pathway whereby the more substituted internal carbon would be more electrophilic than the terminal less substituted carbon (due to substantial carbocation character) and thus more susceptible towards nucleophilic

attack.[3] However, this was not the case as the secondary alcohol, where attack occurred on the less substituted carbon atom, was the dominant regioisomer. This was confirmed via 2-D NMR experiments. Similar observations have been reported with $Al(OTf)_3$ catalysed ring-openings of glycidyl ethers.[4]

This can be explained by the formation of a chelate structure between the $Al(OTf)_3$ and the glycidyl ether (Figure 2.4). By forming this type of structure, the $Al(OTf)_3$ has a reduced ability to withdraw electrons from the epoxide oxygen due to electron donation from the ether oxygen of the allyl glycidyl ether. This, in turn, would lead to less electron withdrawal from the α-carbons of the epoxide ring, specifically the internal carbon atom. The nett effect would be that steric effects would play a more dominant role during the ring-opening reaction as opposed to electronic effects. The less substituted carbon atom would then being the preferred position for nucleophilic attack.

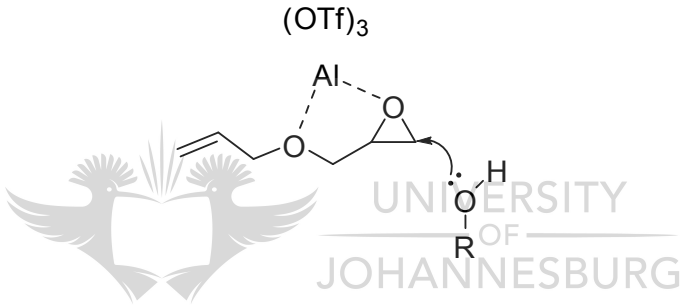
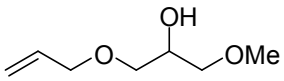
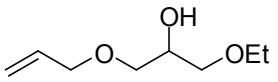
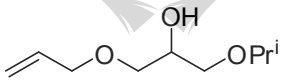


Figure 2.4 : Intermediate chelate structure.

The reduction in the equivalents of alcohol for this reaction was investigated. Three different alcohols were used, namely methanol, ethanol and *iso*-propanol with reactions being run under reflux for 1 hour. It was possible to reduce the equivalents of alcohol required from 6 to 1 without a significant drop in reaction yield and without the use of a modified reaction protocol (Table 2.6). Unlike cyclohexene oxide, the allyl glycidyl ether is considerably less active given its predilection towards chelation, giving rise to the intermediate chelate structure formed between the $Al(OTf)_3$ and the glycidyl ether (Figure 2.4). This means that the side-reaction which was occurring for the cyclohexene oxide was not occurring to the same extent for the allyl glycidyl ether, leading to more selective reactions.

Table 2.6 : Reduction in the equivalents of alcohol for the ring-opening of allyl glycidyl ether.

Entry	Product	Mol% $Al(OTf)_3$	Equivalents alcohol	Yield (%)[a]	Ratio of 1°:2° alcohol[b]
1	 **2.7**	0.02	6	80 (81)[c]	1:3.5
2		0.02	2	86	1:3.6
3		0.02	1	89	1:3.2
4	 **2.8**	0.02	6	85 (87)[c]	1:3.7
5		0.02	2	90	1:3.5
6		0.02	1	80	1:3.7
7	 **2.8**	0.02	6	82 (74)[c]	1:4.1
8		0.02	2	90	1:4.3
9		0.02	1	85	1:4.1

[a]Yield determined by GC-FID. [b]Regioisomeric ratio determined by GC-FID. [c]Yields in parenthesis refer to isolated yields.

2.4 Conclusions

It was possible to reduce the molar equivalents of alcohol required for the ring-opening of cyclohexene oxide with simple alcohols from 6 equivalents to only 1 equivalent. The use of a modified protocol whereby the cyclohexene oxide is added slowly to the $Al(OTf)_3$ catalyst dissolved in the nucleophilic alcohol was required. This protocol suppressed the side reaction (oligomerisation of the cyclohexene oxide) by enhancing

the rate of the desired reaction due to control over the concentration of the nucleophilic alcohol.

The attempted desymmetrisation of cyclohexene oxide with *l*-menthol and (*S*)-methyl-1-butanol did not show significant diastereoselectivity. These reactions also required increased amounts of catalyst as well as prolonged reaction times. This unreactivity of these nucleophiles is due to their inherent sterically bulky nature. The use of chiral alcohols for the diastereoselective ring-opening of cyclohexene oxide catalysed by $Al(OTf)_3$ does not seem to be a viable method of obtaining enantiopure β-alkoxy alcohols. Perhaps unreactive but chelating ligands would generate active chiral Lewis acid catalysts which would provide better results by virtue of their inherent chirality. The present work shows that if the chiral alcohols binds to the Al centre, the complex so formed is not a good catalyst for the desymmetrisation of epoxides and that more discriminating catalysts should be sought.

The desymmetrisation of cyclohexene oxide with (*S*)-1-phenylethanol yielded interesting results. The bulky nature of the (*S*)-1-phenylethanol prevents it from functioning as a particularly good nucleophile for the ring-opening of epoxides. Considering the electronic nature of this alcohol the symmetrical ether formation is not such an unexpected reaction. This secondary benzylic alcohol is a prime candidate for carbocation formation due to stabilisation of the benzylic position thus generating an electrophile for an S_N1 type reaction. The use of $Al(OTf)_3$ as a Lewis acid catalyst for the formation of stabilised benzylic carbocations was thus stumbled upon by pure chance and the investigation thereof will be discussed in a later section (Chapter 4).

The reduction in the molar equivalents of alcohol required for the ring-opening of allyl glycidyl ether was successfully established. The ring-opening of glycidyl ethers with only 1 molar equivalent of alcohol was possible due to the lower reactivity of this substrate. This lowered reactivity can be ascribed to the formation of an intermediate chelate structure with the $Al(OTf)_3$ catalyst.

2.5 References

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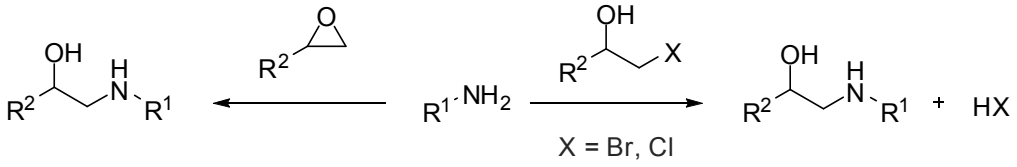
Chapter 3

Synthesis of piperazine derived β-amino alcohols via the aluminium triflate mediated ring-opening of epoxides

3.1 Introduction

1,2-Amino alcohols (β-amino alcohols) represent an important class of organic molecules. They have found application in medicinal chemistry,[1] organic synthesis in general and particularly in asymmetric synthesis as chiral ligands and auxillaries.[2] These molecules are usually prepared by reacting an epoxide at elevated temperatures in the presence of an excess of an amine (Scheme 3.1).[3] Alternatively, a halohydrin can be reacted with an amine in the presence of a stoichiometric amount of a base (Scheme 3.1).[4a-d]



Scheme 3.1 : Formation of β-amino alcohol from an amine and an epoxide or halohydrin.

The apparent disadvantage of this method is the generation of undesired hydrohalous acid, which has to be neutralised with an equimolar amount of base, generating significant amounts of salts in the process, which then have to be dealt with. This generation of unwanted by-products is undesirable from a green chemistry perspective.[5] From a simple atom efficiency point of view, the use of an epoxide as the starting material presents a more favourable approach to these β-amino alcohols.

Piperazine based β-amino alcohols are known for their biological activity.[4-8] They find applications as positive inotropic agents, increasing myocardial contractility in the treatment of cardiac disorders such as congestive heart failure.[5-9] Examples include Carsatrin[5] and DPI201-1067 (Figure 3.1, **1** and **2**). A notable β-amino alcohol is propranolol (Figure 3.1, **3**), which was one of the first non-selective β-blockers developed finding widespread use in the treatment of hypertension. β-Amino alcohols have also found applications as Ca^{2+} antagonists[4a-d] and dopamine uptake inhibitors.[4a-d] The quinoline based β-amino alcohols bearing the piperazine motif (Figure 3.1, **4**) have even found application in the reversal of

multidrug resistance in drug resistant cancer cell lines[8] and have shown activity four times higher than Verapamil, a calcium channel blocking drug that is known to reverse multidrug resistance in cancerous cells.[8]

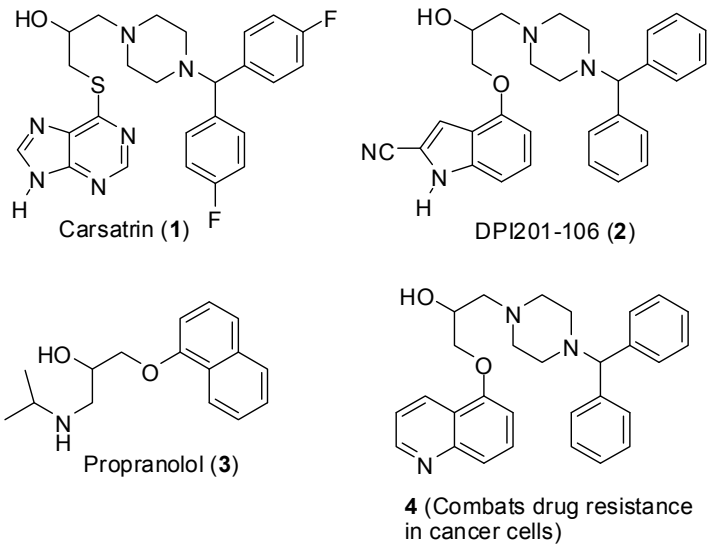


Figure 3.1 : Biologically active piperazine-based compounds.

It was clear from the literature[4-8] that the important structural features for activity in these piperazine derived β-amino alcohols was a piperazine subunit linked to a diphenylmethyl group on one end and a heteroatomic β-amino alcohol bearing a heteroatomic sulfur, oxygen or nitrogen on the other end (Figure 3.2).

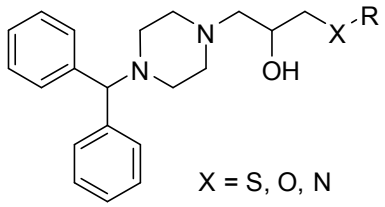
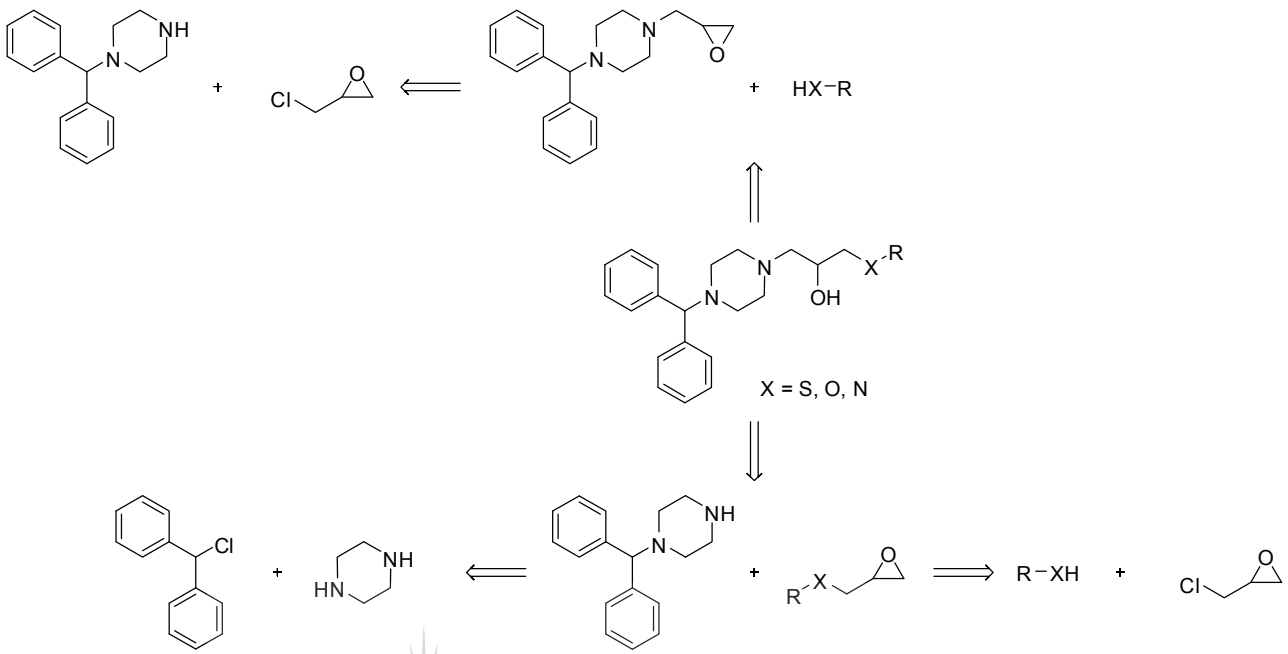


Figure 3.2 : Key structural features for activity in piperazine derived β-amino alcohols.

In most cases the synthesis of these piperazine derived β-amino alcohols involves the reaction of a chlorohydrin with an amine in the presence of stoichiometric amounts of base. Alternatively an epoxide is ring-opened by the amine at elevated temperatures.[4a-d,5-8] Scheme

3.2 shows a retrosynthetic analysis of the target piperazine derived β-amino alcohols from the corresponding nucleophiles and epoxides.



Scheme 3.2 : Retrosynthetic analysis of the piperazine derived β-amino alcohols.

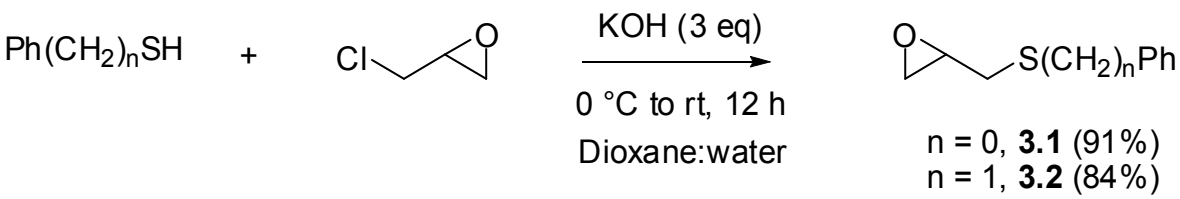
There have been no reports on the synthesis of these types of β-amino alcohols utilising a Lewis acid for the catalysis of the ring-opening step. $Al(OTf)_3$ has been reported as an efficient Lewis acid catalyst for the ring-opening of epoxides by various alcohols as well as by aliphatic and aromatic amines.[9] In these reports the aminolysis reaction was found to be regioselective for nucleophilic attack at the less hindered carbon atom of the epoxide ring, a feature of S_N2-type reaction mechanisms as opposed to a borderline S_N2-type mechanism which may favour attack at the more hindered internal epoxide carbon.[9] Recycling of the $Al(OTf)_3$ was also accomplished by simple extraction of the catalyst with water once the reaction had been completed, and subsequent removal of the water under reduced pressure and elevated temperatures. The catalyst was found to retain its activity through three cycles. Other Lewis acids reported to be active towards the ring-opening of epoxides include $Ti(O^iPr)_4$,[10] $TaCl_5$,[11] Bi salts,[12] $ZrCl_4$,[13] $Sm(OTf)_3$,[14] $CoCl_2$,[15] $CuBF_4$,[16] $ZnCl_2$[17] and $Sc(OTf)_3$.[5]

It was clear that Lewis acids could be used as catalysts for the aminolysis of epoxides. The question to be asked was whether a Lewis acid, $Al(OTf)_3$ specifically, could be used for the synthesis of the more complex piperazine derived β-amino alcohols. This also raised the question of where to place the glycidyl motif for the ring-opening reaction, i.e. which approach depicted in Scheme 3.2 would be the better to use to obtain the β-amino alcohol product. For this it was necessary to synthesise the epoxide as well as amine substrates required for the ring-opening reactions to be tested.

3.2 Synthesis of epoxide substrates

3.2.1 Synthesis of *S*-glycidyl ethers

The *S*-glycidyl epoxides were prepared according to a literature procedure[18] (Scheme 3.3) to give the desired *S*-glycidyl ethers **3.1** and **3.2** in high yields. The presence of a base ensures that the acidic thiol is deprotonated to give the nucleophilic thiolate anion which is a good nucleophile[19] and reacts readily with the epichlorohydrin at the terminal epoxide carbon atom to give an intermediate halohydrin. The terminal carbon group of the epoxide ring is more accessible and electrophilic than the internal carbon atom, thereby favouring attack at the terminal position during an S_N2 reaction. This halohydrin is then dehydrohalogenated by the excess aqueous base to give the epoxide product.



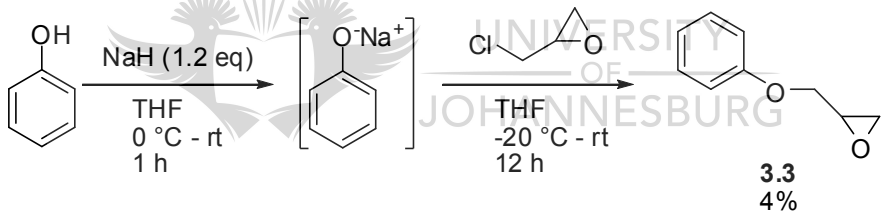
Scheme 3.3 : Synthesis of *S*-glycidyl ethers.

3.2.2 Synthesis of *O*-glycidyl ethers

The biphasic system that was used for the synthesis of *S*-glycidyl ethers (Scheme 3.3) was applied to the synthesis of *O*-glycidyl ethers from the corresponding aromatic alcohols. This approach failed to yield any *O*-glycidyl ether in appreciable yields. For the *S*-glycidyl ether synthesis the thiol can function as a suitable nucleophile without being deprotonated.[20] In the

case of phenol, in order for it to function as an effective nucleophile deprotonation is required. However, deprotonation generates the phenolate anion which, while partnered by a Na^+ counterion exists primarily in the aqueous phase and is unable to act as a nucleophile onto the epichlorohydrin which is in the organic phase. This difference in reactivity can also be explained by the highly nucleophilic nature of sulfur as opposed to the oxygen atom, which is due to the high-energy nonbonding lone pairs ($3sp^3$) of the sulfur atom as opposed to those for oxygen ($2sp^3$).[19] So although the thiolate and phenolate anions could form in the reactions, respectively, and exist in the aqueous phase thus precluding them from reaction with the epichlorohydrin, the main difference observed in reactivity is probably due to the increased nucleophilicity of thiols above phenols in their neutral forms in the organic phase.[20]

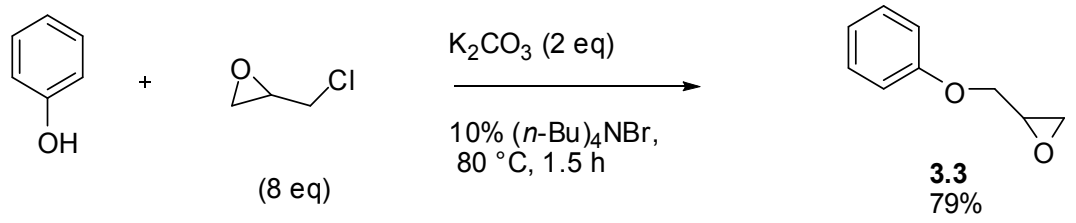
Phenol was then reacted with sodium hydride in THF to obtain sodium phenolate which was then reacted with epichlorohydrin in THF (Scheme 3.4). This gave the desired *O*-glycidyl ether **3.3** in a meagre 4% yield. This low yield is likely due to the low solubility of the sodium phenolate in THF, as evidenced by the formation of a precipitate upon addition of NaH to the solution of phenol in THF.



Scheme 3.4 : Deprotonation of phenol and subsequent reaction with epichlorohydrin.

In an attempt to overcome this solubility issue of the phenolate anion, phenol was heated in acetonitrile with epichlorohydrin for 12 hours in the presence of K_2CO_3 thus rendering the entire liquid system mono-phasic. An improved yield of 37% of the desired glycidyl ether **3.1** was obtained by this method. This relatively low yield is probably due to the low nucleophilicity of phenol, as already discussed.

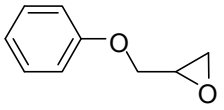
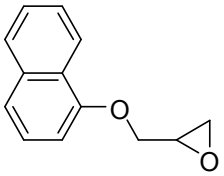
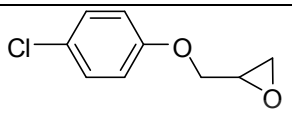
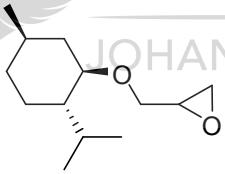
It was then decided to employ a phase transfer catalyst for this reaction, and a literature procedure was found[21] whereby the desired aromatic alcohol is heated in eight equivalents of epichlorohydrin with K_2CO_3 and a catalytic amount of tetra-*n*-butyl ammonium bromide (Scheme 3.5). This afforded the desired *O*-glycidyl ether **3.3** in a high yield (79%).



Scheme 3.5 : Phase transfer catalyst promoted synthesis of *O*-glycidyl ethers.

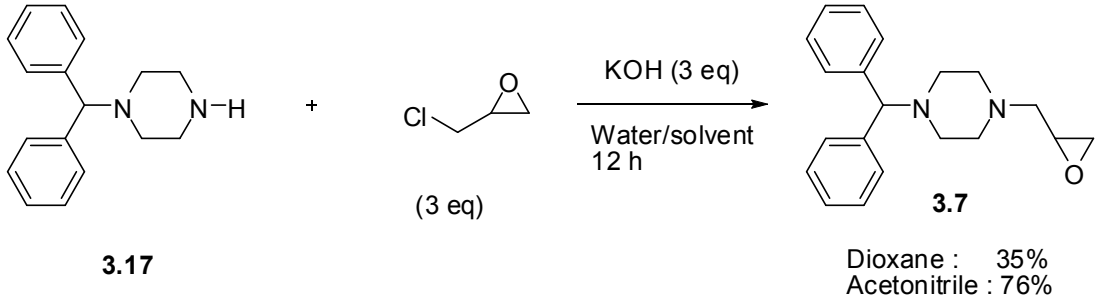
This methodology was applied to other aromatic alcohols to give the desired *O*-glycidyl ethers in acceptable yields (Table 3.1, entries 1-3). However, upon application to the sterically hindered aliphatic alcohol *l*-menthol, a very low yield of only 18% was obtained (Table 3.1, entry 4). This is presumably due to the ability of aromatic alcohols to more easily exist in their anionic form due to stabilisation provided by the phenyl ring (giving a more acidic system),[19] which is not the case for aliphatic alcohols, and secondly the steric bulk of the *l*-menthol which decreases its reactivity.

Table 3.1 : Yields for *O*-glycidyl ethers via phase transfer catalysis

Entry	Structure	Yield (%)
1	 **3.3**	79
2	 **3.4**	63
3	 **3.5**	73
4	 **3.6**	18

3.2.3 Synthesis of *N*-glycidyl ethers

3.2.3.1 Synthesis of *N*-glycidyl amines via base promoted methodology



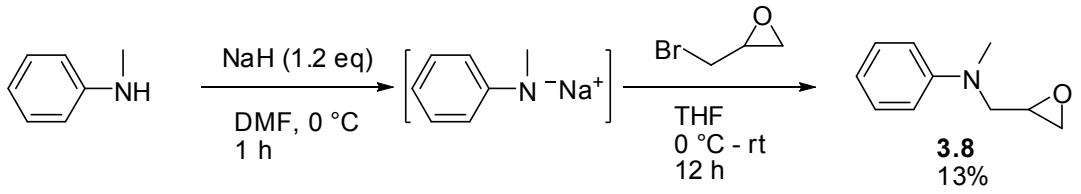
Scheme 3.6 : Synthesis of *N*-glycidyl amine **3.7** from piperazine **3.17**.

The methodology employed for the synthesis of *S*-glycidyl ethers (Scheme 3.3), namely the biphasic dioxane/water system with excess base and epichlorohydrin was investigated for the synthesis of *N*-glycidyl amine **3.7** from the diphenylmethylpiperazine amine **3.17** and its *N*-glycidyl amine **3.7** was obtained in a 35% yield (Scheme 3.6). An aliphatic secondary amine is considered basic and will not easily deprotonate like aromatic thiols or aromatic alcohols.[22] This reaction of the amine with epichlorohydrin is thus likely not to proceed via a deprotonation step. The amine functions as a nucleophile due to its free electron pair, which is readily available for binding.[19] By changing the reaction solvent from dioxane to the more polar acetonitrile, the S_N2 reaction between the amine and the epichlorohydrin is promoted and it was possible to realise a 76% yield.[22] The presence of the base in this reaction merely serves to neutralise the acid formed during the reaction.

The acetonitrile/water system employed for the synthesis of *N*-glycidyl amine **3.7** was tested for an aromatic amine namely, *N*-methyl aniline. This reaction failed to yield the desired product **3.8** in an appreciable yield after 12 hours. A literature method[23] reported the deprotonation of *N*-methyl aniline with sodium hydride in DMF followed by the subsequent reaction with epibromohydrin (Scheme 3.7), which in the present instance gave the desired *N*-glycidyl amine **3.8** in a low 13% yield. Unreacted amine was recovered from the reaction mixture.

The methodology utilised for the synthesis of the *O*-glycidyl ethers (Scheme 3.5) was also tested, but yielded a mixture of reaction products with quaternisation of the amine being the

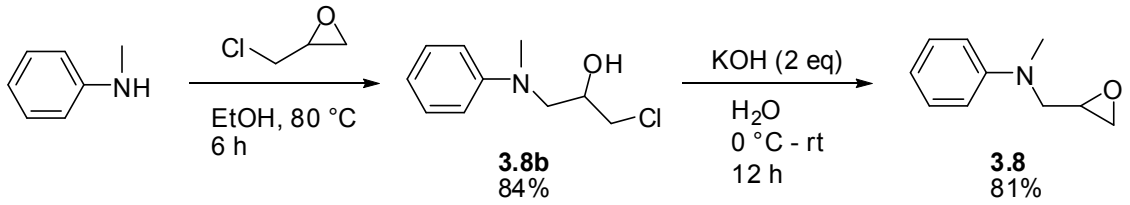
dominant side-reaction. This quaternisation is due to the increased reactivity of the amine after it undergoes alkylation[19] as extra alkyl groups lead to additional electron density on the nitrogen atom, thus leading to increased nucleophilicity of the nitrogen. It was clear from these results that a base-promoted approach to the aromatic *N*-glycidyl amines continued to fail to yield acceptable yields of the desired *N*-glycidyl ether and a different approach was required.



Scheme 3.7 : Deprotonation of *N*-methyl aniline and subsequent reaction with epibromohydrin.

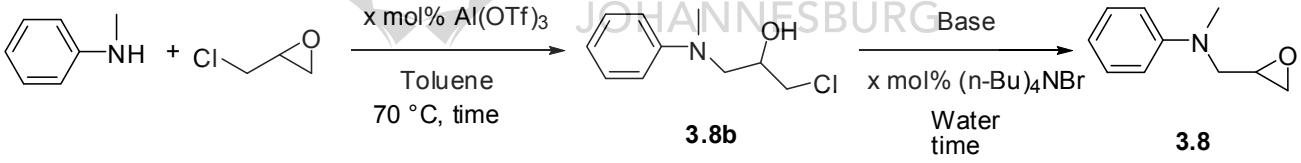
3.2.3.2 Synthesis of *N*-glycidyl amines via acid catalysis methodology

Amines are able to function as nucleophiles without being deprotonated, including reactions in which epoxides are used as the electrophile. It was decided to react the *N*-methyl aniline with the epichlorohydrin in a polar solvent at elevated temperatures in order to obtain the ring-opened product. This ring-opened product could then be dehydrohalogenated to give the desired *N*-glycidyl amines. Application of this method gave the desired *N*-glycidyl amine **3.8** in high yield (Scheme 3.8). It was possible to isolate the intermediate halohydrin **3.8b** although it was not stable for extended periods of time. The dehydrohalogenation of halohydrins is a well-known route to epoxides.[20] During dehydrohalogenation the intermediate halohydrin is deprotonated on the hydroxyl group which then attacks the carbon atom to which the chloride is attached in an internal S_N2 reaction.[20] Halohydrin **3.8b** could readily be dehydrohalogenated under basic conditions to give *N*-glycidyl amine **3.8** in a high yield (Scheme 3.8).



Scheme 3.8 : Two step approach for the synthesis of *N*-glycidyl amine **3.8**.

The biggest drawback of this approach was the long reaction times required for the two steps to be performed. Previous work[9a] had established $Al(OTf)_3$ as a catalyst for the ring-opening of epoxides with amines. It was thus a logical conclusion to apply this catalyst for the ring-opening of epichlorohydrin with *N*-methyl aniline (Scheme 3.9). In addition, the use of a phase transfer catalyst for the dehydrohalogenation step was also investigated (Scheme 3.9). In a literature search, no reference was found to the synthesis of *N*-glycidyl amines via this two-step approach utilising both a Lewis acid and a phase transfer catalyst, respectively, for the two steps. The results are summarised in Table 3.2.



Scheme 3.9 : Catalysed synthesis of *N*-glycidyl amine **3.8**.

Table 3.2 : Investigation into catalysis for *N*-glycidyl amine **3.8** formation.

Entry	Mol% $Al(OTf)_3$	Time for first step (h)	Yield of Halohydrin (%)	Base used	Mol% TBAB	Time for second step	Yield *N*-glycidyl ether (%)
1	0	6	84	KOH(aq)	0	12	81
2	5	0.5	96	KOH(aq)	0	12	95
3	5	0.5	97	K_2CO_3 (solid)	10	12	50
4	5	0.5	[a]	KOH(aq)	10	2.5	98
5	5	0.5	[a]	KOH(aq)	0	2.5	77
6	5	0.5	[a]	none	0	24	2
7	0.5	30	60	KOH(aq)	10	2.5	55

[a]Reaction complete by TLC.

The use of just 5 mol% $Al(OTf)_3$ (Table 3.2, entry 2) reduced the reaction time for the first step from 6 hours to a mere 30 minutes, and using toluene as solvent according to previous work,[9a] which had shown toluene to be a superior solvent for the $Al(OTf)_3$ mediated epoxide ring-opening reactions. The subsequent dehydrohalogenation yielded the desired *N*-glycidyl amine in an excellent yield of 95%. The intermediate halohydrin was isolated in a high yield of 96% to show that is was in fact the $Al(OTf)_3$ promoting the reaction and not the aqueous potassium hydroxide, which served as a dehydrohalogenation agent.

Investigation into the use of solid K_2CO_3 with 10 mol% TBAB as the phase transfer catalyst with which to generate the dehydrohalogenation agent (Table 3.2, entry 3) led to a decreased yield of 50% of **3.8**, with unreacted halohydrin from the first step of the reaction being recovered.

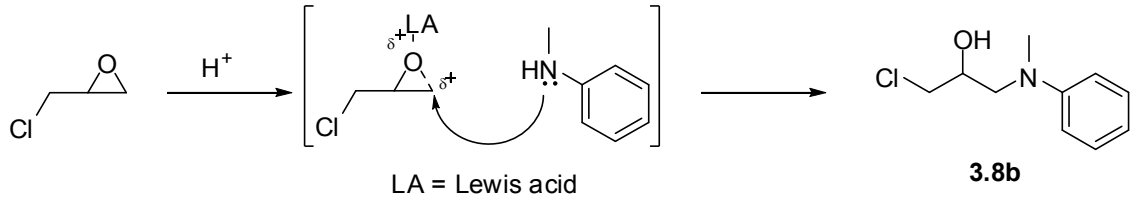
Aqueous potassium hydroxide with 10% TBAB was then investigated as the dehydrohalogenation agent (Table 3.2, entry 4) and found to be effective, giving **3.8** in a 98% yield in only 2.5 hours. Under the same conditions but in the absence of TBAB (Table 3.2,

entry 5) **3.8** was obtained in only 77% during the same time frame, thus indicating the importance of the use of a phase transfer catalyst for the dehydrohalogenation step. It was important to ensure that the stirring of the reaction was occurring at a high rate to favour the formation of a mixture with very fine droplets thus increasing the overall surface area between the two phases present in the reaction mixture. This ensured that the phase transfer catalyst was adequately dispersed throughout the reaction mixture.

In the absence of any base and where heat only was used, that is to say, after the first step was complete the reaction mixture was heated up to its reflux temperature for 24 hours (Table 3.2, entry 6), only 2% of **3.8** was obtained. This was done in order to assess the possible role of $Al(OTf)_3$ as a dehydrohalogenation catalyst. Finally, the use of reduced amounts of $Al(OTf)_3$ were investigated (Table 3.2, entry 7) and although it was found to catalyse the first step of the reaction, the rate was much lower than with 5 mol% $Al(OTf)_3$. This could possibly be overcome with prolonged reaction times but this aspect was not pursued.

It must be stressed that the dehydrohalogenation step could be performed without any workup or purification after the ring-opening step. The aqueous base containing the phase transfer catalyst and base could simply be added to the reaction mixture once ring-opening had been completed. Presumably, the aqueous base neutralises the $Al(OTf)_3$.

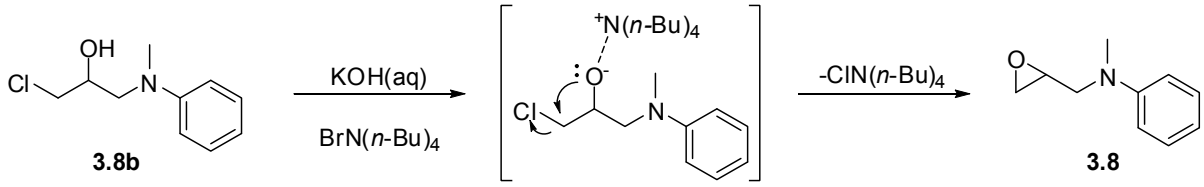
In the first step (Scheme 3.10) of this process the Lewis acid serves to activate the epoxide ring to nucleophilic attack (Chapter 2).



Scheme 3.10 : Acid activation of epichlorohydrin towards nucleophilic attack by *N*-methyl aniline.

In the second step (Scheme 3.11), the dehydrohalogenation, the hydroxyl group of the halohydrin is deprotonated at the interface with the basic aqueous solution, the quaternary

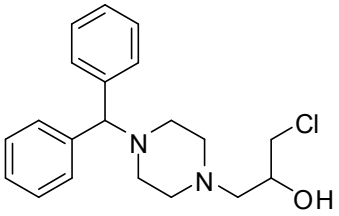
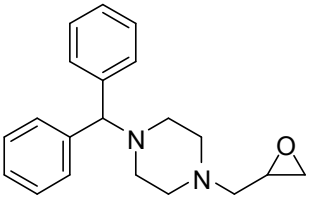
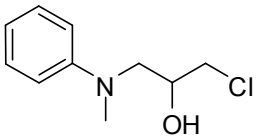
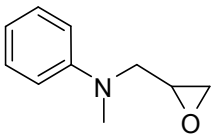
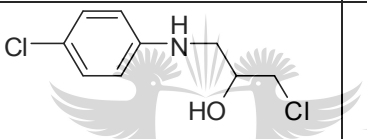
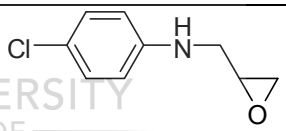
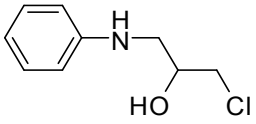
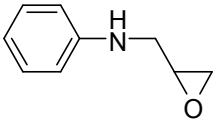
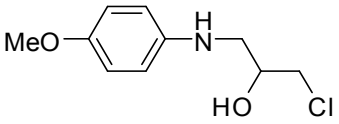
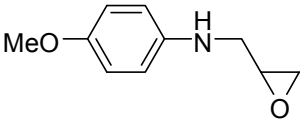
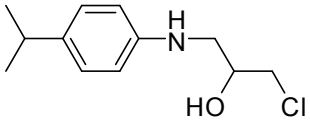
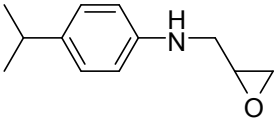
ammonium cation then complexes the hydroxyl anion thus solubilising it in the organic phase. The deprotonated halohydrin then undergoes an internal S_N2 reaction with the deprotonated hydroxyl group attacking the β-carbon thereby displacing the chloride to give the desired epoxide.



Scheme 3.11 : Dehydrohalogenation of **3.8b** promoted by the quaternary ammonium salt to give **3.8**.

This $Al(OTf)_3$-mediated two-step methodology was then extended to other aromatic amines as well as a previously prepared diphenylmethylpiperazine amine **3.17** (Table 3.3). In all cases moderate to excellent yields were realised. The reaction using diphenylmethylpiperazine amine **3.17** also provided a good yield of the desired product (Table 3.3, entry 1), albeit slightly lower than that achieved with the previous based promoted method (Scheme 3.6). However, the overall reaction time allowed for the acid catalysed route, 3 hours, is significantly shorter than for the base promoted route (12 hours). Although excellent yields were obtained when *N*-methyl aniline was used (Table 3.3, entry 2), lower yields were obtained when other aromatic amines were utilised (Table 3.3, entries 3-6). This is despite the complete consumption of these amines in the reaction. This can be ascribed to the formation of the di-substituted product, where the amine has attacked two molecules of epichlorohydrin. This cannot occur for *N*-methyl aniline without formation of the ammonium derivative (which is presumably not favoured under the present conditions since this compound was not detected in any instance), presumably accounting for the high yield. The use of reduced amounts of $Al(OTf)_3$ catalyst for the aromatic amines (Table 3.3, entries 3-6) was possible due to the reduced basicity of the amines. This reduced basicity is due to electron withdrawal from the nitrogen atom by the substituted aromatic ring, and would cause less competition for the Al centre by the N atom than in the presence of more highly basic analogues.[20]

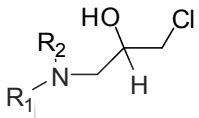
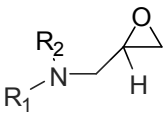
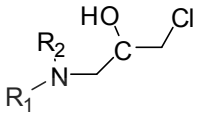
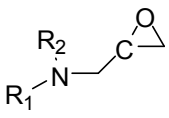
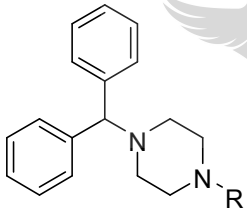
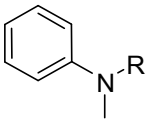
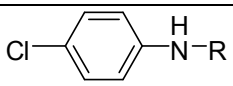
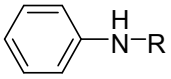
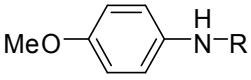
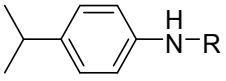
Table 3.3 : Yields for the halohydrins and *N*-glycidyl amines.

Entry	Mol% $Al(OTf)_3$	Halohydrin	Yield (%)	*N*-glycidyl amine	Yield for ring-closing (%)
1	5	 **3.7b**	70	 **3.7**	68
2	5	 **3.8b**	99	 **3.8**	99
3	0.5	 **3.9b**	74	 **3.9**	67
4	1	 **3.10b**	75	 **3.10**	65
5	1	 **3.11b**	63	 **3.11**	61
6	1	 **3.12b**	79	 **3.12**	60

3.2.3.3 NMR spectroscopic characteristics of the *N*-halohydrins and *N*-glycidyl amines

The R_f values for the halohydrins (**3.7b**-**3.12b**) and *N*-glycidyl amines (**3.7**-**3.12**) were very similar. It was only through isolation of the compounds and comparison of the respective ^{1}H and ^{13}C NMR spectra that halohydrin formation was confirmed. The key NMR shifts are summarised in Table 3.4. Here, an upfield shift for the internal proton of the glycidyl moiety after ring closure had occurred was diagnostic for the formation of the epoxide. This was also the case for the corresponding signal in the ^{13}C NMR spectrum of the compound. The upfield shift is due to less deshielding due to the formation of the strained epoxide ring.

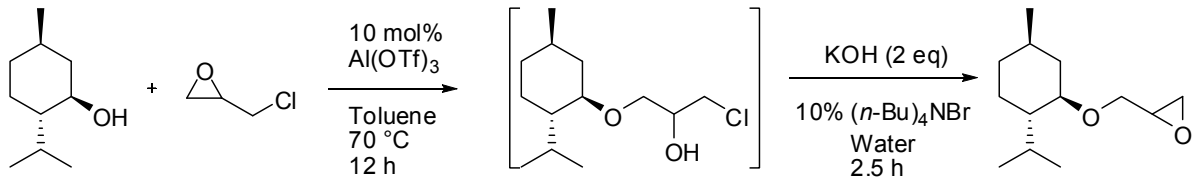
Table 3.4 : NMR data for halohydrins and *N*-glycidyl amines.

Entry	Amine	**^{1}H NMR Chemical Shift (δ) and Multiplicity**		**^{13}C NMR chemical shift (δ)**	
					
1		3.85-3.77 (m)	3.09-3.03 (m)	66.4	50.1
2		4.15-4.11 (m)	3.17-3.12 (m)	68.8	50.4
3		4.07-3.99 (m)	3.20-3.15 (m)	69.7	50.8
4		4.09-4.01 (m)	3.24-3.18 (m)	69.7	50.9
5		4.07-4.00 (m)	3.21-3.11 (m)	69.6	51.1
6		4.09-4.02 (m)	3.24-3.28 (m)	69.7	51.0

3.2.3.5 Application of the $Al(OTf)_3$-catalysed two-step methodology to the synthesis of the *l*-menthol derived *O*-glycidyl ether

With this two-step acid-catalysed methodology in hand, it was decided to revisit the synthesis of *O*-glycidyl ether **3.6**. It should be recalled that the previously employed base-promoted methodology (Scheme 3.5) gave product **3.6** in a modest 18% yield (Table 3.1, entry 4). This low yield was presumably due to the lower acidity of the aliphatic alcohol which would resist deprotonation to a large extent under the reaction conditions. It is known that aromatic alcohols are better able to stabilise an anion than aliphatic alcohols (4.4.1), which favours anion formation in phenols.[19] It was thus thought to use the aliphatic alcohol, *l*-menthol, as a nucleophile without deprotonation under acidic catalysis conditions (Scheme 3.12). Aromatic alcohols are weak nucleophiles unless they are deprotonated, due to electron withdrawal by the phenyl ring.[20] Because of this fact aromatic alcohols do not respond well to the acid catalysed ring-opening of epoxides.

Using this methodology it was possible to obtain *O*-glycidyl ether **3.6** in a 40% yield over two steps. No isolation of the intermediate halohydrin was done, but the reaction for the halohydrin was monitored via TLC and when it was deemed that no further reaction between the alcohol and halohydrin was occurring, the dehydrohalogenation step was performed as before. The low yield compared to the *N*-glycidyl amines is presumably due to the unreactive nature of *l*-menthol as a nucleophile owing to its steric bulk. Nevertheless, the increase in the yield from 18% to 40% is a significant improvement.



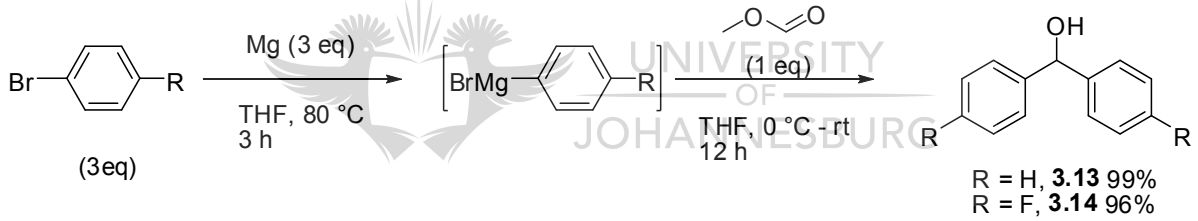
3.6
40%

Scheme 3.12 : Application of the two step acid catalysed methodology to *l*-menthol to give *O*-glycidyl ether **3.6**.

3.3 Synthesis of diphenylmethylpiperazine based amines

3.3.1 Synthesis of the diphenylmethanols

The Grignard reaction is a well-known reaction for the formation of C-C bonds.[25a] A Grignard reagent can be formed by the reaction of an aryl halide with magnesium.[25b] The aryl halide is converted into the magnesium bromide salt which forms a carbon nucleophile.[22] This nucleophilic Grignard reagent can react with a carbonyl electrophile to give the corresponding alcohol.[20] For the synthesis of diphenylmethanols **3.13** and **3.14**, the corresponding aryl bromides were reacted with magnesium metal in THF to give the Grignard reagent (Scheme 3.13). These Grignard reagents, present in a three molar equivalent excess, were reacted with methyl formate to give the corresponding diphenylmethanol in high yield (Scheme 3.13). In an ideal reaction, two equivalents of the Grignard reagent react with one equivalent of the methyl formate. The use of excess Grignard reagent ensured that no mono-substitution occurred, which would have yielded the corresponding benzaldehyde, possibly affording mixtures of products.



Scheme 3.13 : Grignard reaction of bromobenzene derivatives to give diphenylmethanols **3.13** and **3.14**.

The ^{1}H NMR spectrum of **3.14** revealed a coupling between the aromatic protons and the fluorine atom on the aromatic ring giving a doublet of doublets multiplicity at 7.29 ppm and triplet at 7.00 ppm. This coupling occurs due to the ½ spin number of the ^{19}F nucleus.[26] The ^{13}C NMR spectrum of **3.14** also revealed coupling between the aromatic carbons and the fluorine nucleus. The coupling constants are listed in Table 3.5. The *ipso*-carbon, to which fluorine is attached, displays the largest coupling constant (Table 3.5, entry 1, J = 244 Hz) whilst the *para*-carbon furthest from the fluorine displays the smallest (Table 3.5, entry 2, J = 3 Hz). The *ortho*-carbon groups (Table 3.5, entry 4, J = 21 Hz), which are closer to the fluorine atom than the *meta*-carbon atoms (Table 3.5, entry 3, J = 8 Hz) display the larger

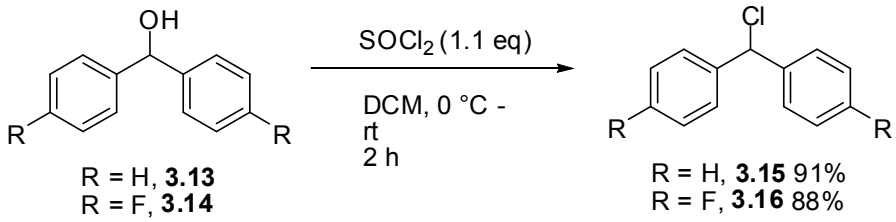
coupling constant of the two. All of the fluorine-containing compounds generated in this part of the study displayed this sort of trend in their ^{1}H and ^{13}C NMR spectra.

Table 3.5 : ^{13}C chemical shifts and coupling constants for **3.14**.

Entry	Carbon	^{13}C Chemical Shift (δ)	Carbon coupling constant with ^{19}F (Hz)
1	C-*ipso*	162.2	244
2	C-*para*	139.3	3
3	C-*meta*	128.1	8
4	C-*ortho*	115.3	21

3.3.2 Synthesis of the diphenylmethylchlorides

Thionyl chloride is a well-known reagent for the conversion of alcohols into chlorides.[27] Reaction of the diphenylmethanols with thionylchloride in DCM gave the corresponding chlorides in high yields (Scheme 3.14). These chlorides were considerably less polar than the corresponding alcohols on TLC. The shift of the ^{1}H NMR signal for the benzylic protons of **3.15** from 5.82 ppm to 6.18 ppm indicated that the alcohol had been converted into the chloride.

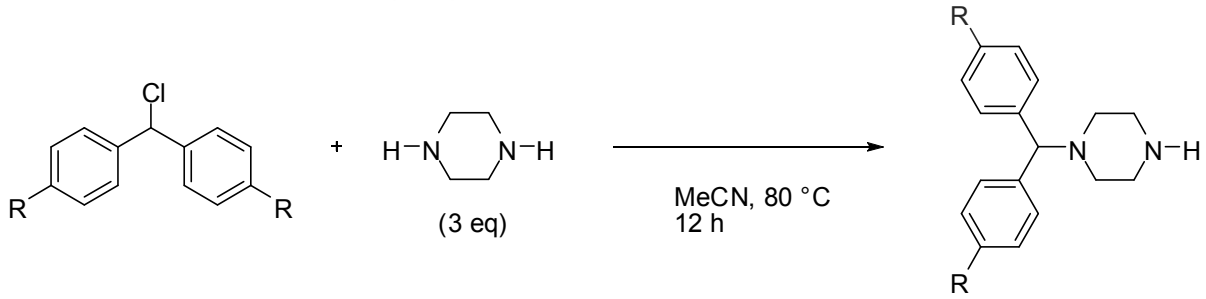


Scheme 3.14 : Conversion of diphenylmethanols **3.13** and **3.14** to the corresponding chlorides **3.15** and **3.16**.

3.3.3 Synthesis of the diphenylmethylpiperazine amines

The diphenylmethylchlorides **3.15** and **3.16** were then reacted with three equivalents of piperazine in acetonitrile to give the corresponding diphenylmethylpiperazines **3.17** and **3.18** in good yields (Scheme 3.15). A polar solvent such as acetonitrile promotes nucleophilic substitution reactions better than a less polar one, such as toluene.[21] This was also reflected in the reaction, when toluene was first used as reaction solvent as there was no significant reaction between the chloride and the amine.

Three equivalents of the piperazine amine were used for the reaction for two purposes. The first was to ensure that mono-substitution of the piperazine amine occurred. The second was to neutralise the HCl acid that forms during the reaction. The diphenylmethylchloride was completely consumed during these reactions, despite which only 70% of the diphenylmethylpiperazine product **3.17** was isolated. This is due to the di-substitution reaction in which one molecule of piperazine reacts with two diphenylmethylchlorides to give the di-substituted product. ^{1}H NMR spectroscopy showed a shift in the benzylic proton for **3.17** from 6.18 ppm for the chloride to 4.22 ppm for the amine. This shift upfield is due to the diminished electron withdrawal from the benzylic carbon caused by the amine compared to the chloride, leading to less deshielding of this benzylic proton.

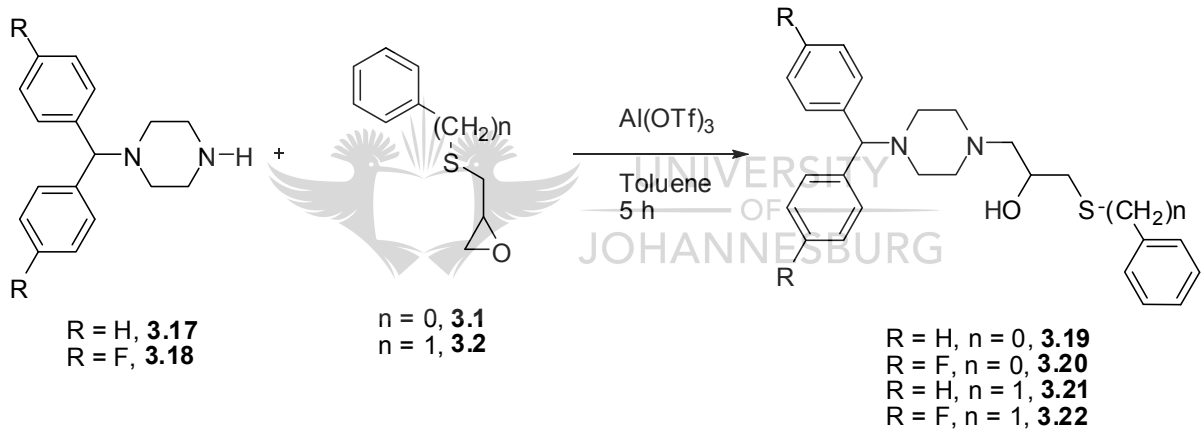


Scheme 3.15 : Synthesis of diphenylmethylpiperazines **3.17** and **3.18** from the corresponding chlorides.

3.4 $Al(OTf)_3$-mediated ring-opening of epoxides to give piperazine-derived β-amino alcohols

3.4.1 Initial optimisation reactions

Initial optimisation reactions were performed on the *S*-glycidyl ethers **3.1** and **3.2** with the two diphenylmethylpiperazine amines **3.17** and **3.18** (Scheme 3.16). Previous work had established the need to use 1 to 5 mol% $Al(OTf)_3$ for the ring-opening of epoxides with simple amine nucleophiles.[9a] This is due to a competition for complexation of the $Al(OTf)_3$ between the amine and the epoxide, which necessitated higher levels of catalyst to be present.[9a] It was necessary to investigate the effect of using more complex epoxides and amine nucleophiles on the amount of $Al(OTf)_3$ required to perform these ring-opening reactions. Towards this end the reaction temperature as well as the amount of $Al(OTf)_3$ used were varied in order to determine the optimal conditions for these reactions. The results are summarised in Table 3.6 and Table 3.7.

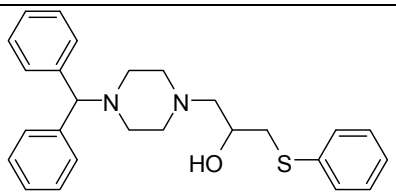
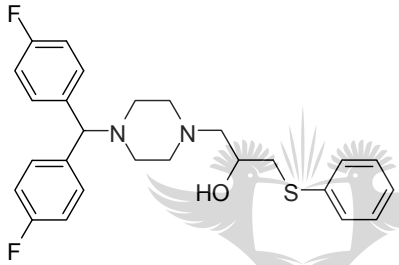
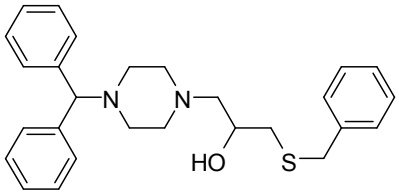
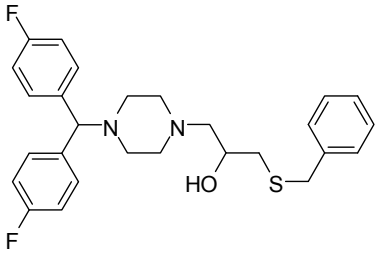


Scheme 3.16 : Optimisation of the ring-opening of *S*-glycidyl ethers **3.1** and **3.2** with diphenylmethylpiperazine amines **3.17** and **3.18**.

The ring-opening reaction was initially performed at 100 °C for 5 hours (Table 3.6) and high yields were obtained with the use of 5 mol% catalyst (Table 3.6, entries 1-4). Interestingly, the base line reaction, where 0 mol% catalyst was used, also gave significant yields (Table 3.6, entries 1-4). These results were not surprising considering that the conventional way in which to ring-open an epoxide is to heat it in the presence of the desired nucleophile.[3] In order to demonstrate the catalytic ability of $Al(OTf)_3$, the reaction temperature was lowered

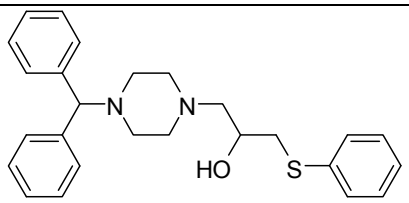
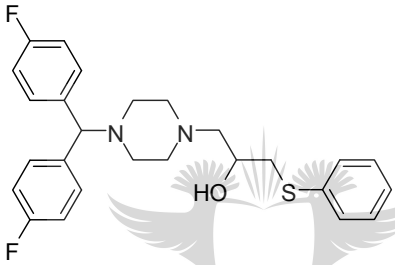
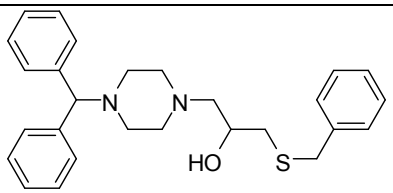
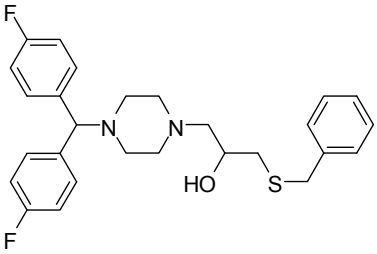
to 70 °C and the catalyst concentration varied, the results of which are summarised in Table 3.7.

Table 3.6 : Ring-opening reactions of **3.**1 and **3.2** performed at 100 °C for 5 hours at various catalyst loadings with **3.17** and **3.18**.

Entry	**Compound**	**Yield (%) with 0 mol% $Al(OTf)_3$**	**Yield (%) with 5 mol% $Al(OTf)_3$**
1	 **3.19**	41	74
2	 **3.20**	24	84
3	 **3.21**	42	85
4	 **3.22**	23	67

A drop in reaction temperature from 100 °C to 70 °C, led to a decrease in the base line reaction (Table 3.7). The catalytic effect of $Al(OTf)_3$ could now clearly be seen. With the addition of 5 mol% $Al(OTf)_3$ to the reaction the yield increased significantly, from less than 10% to approximately 50% (Table 3.7). An increase in the catalyst loading to 10 mol% gave a further increase in yield to about 80% (Table 3.7). Although 10 mol% is a significant amount of catalyst it should be taken into account that the ring-opening reaction does not proceed appreciably at 70 °C without $Al(OTf)_3$. The only way in which to perform these ring-opening reactions without a catalyst would be to increase the reaction temperature, which may pose a problem for heat sensitive substrates.

Table 3.7 : Ring-opening reactions of **3.1** and **3.2** performed at 70 °C for 5 hours at various catalyst loadings with **3.17** and **3.18**.

Entry	Compound	Yield (%) with 0 mol% $Al(OTf)_3$	Yield (%) with 5 mol% $Al(OTf)_3$	Yield (%) with 10 mol% $Al(OTf)_3$
1	 **3.19**	3	46	82
2	 **3.20**	8	45	75
3	 **3.21**	13	60	86
4	 **3.22**	9	55	66

The ring-opening of **3.1** with **3.17** to form compound **3.19** (Scheme 3.16) was used to probe the effect of prolonged reaction times as well as the omission of solvent on the reaction yield; the results are summarised in Table 3.8.

Table 3.8 : Effect of prolonged reaction time and solvent free conditions on the yield of **3.19**.

Entry	**Mol % $Al(OTf)_3$**	**Time (h)**	**Yield (%)**
1	10	5	82
2	10	10	70
3	5	5	46
4[a]	5	5	34

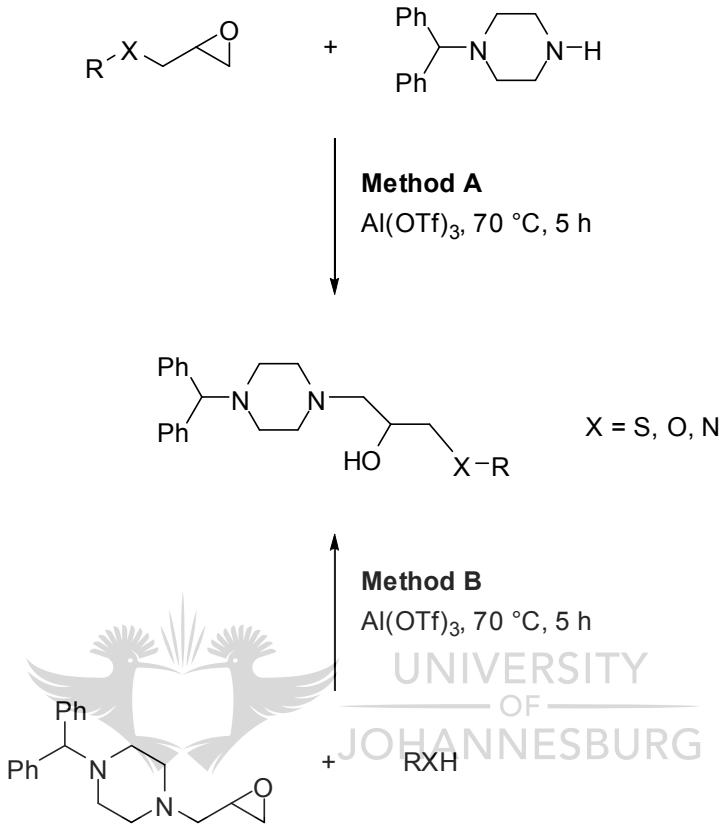
[a]Solvent free conditions.

An extension of the reaction time from 5 hours (Table 3.8, entry 1) to 10 hours (Table 3.8, entry 2) did not increase the yield of the reaction. It is thought that prolonged exposure to the acidic conditions could possibly lead to a degradation of the reaction product, evidenced by a darkening of the reaction mixture from light yellow to dark brown upon more extended heating. Performing the reaction under solvent free conditions yielded erratic irreproducible results (Table 3.8, entry 4), primarily being due to difficulty experienced in stirring the reaction mixture. On heating of the reagents under solvent free conditions a viscous oil is formed which could not always be stirred properly and would sometimes solidify. Constant attention to the reaction was required in order to ensure the stirring was proceeding optimally. These few results indicated that the conditions employed for Table 3.8, entry 1, were optimal within the bounds of the conditions varied.

3.4.2 Method evaluation for the formation of the β-amino alcohol

Retrosynthetic analysis of the target piperazine derived β-amino alcohols provides two positions where the β-amino alcohol bond disconnection could occur (Scheme 3.2). Therefore, two different approaches were investigated for the formation of the β-amino alcohol bond (Scheme 3.17). In the first approach (Scheme 3.17, method A) the glycidyl

moiety was placed on the heteroatom (S, O, N) atom and the resultant epoxide ring-opened by a piperazine amine. In the second approach (Scheme 3.17, method B) the glycidyl moiety was placed on the nitrogen atom of the piperazine amine and the resultant epoxide ring-opened by a heteroatomic (S, O, N) nucleophile. The results are summarised in Table 3.9.



Scheme 3.17 : Approaches taken for the formation of the β-amino alcohol.

Inspection of the comparative results detailed in Table 3.9 reveals that the use of a piperazine-based amine to ring-open a heteroatom glycidyl ether (Method A) is the favoured method for the preparation of the target piperazine derived β-amino alcohols. The improved activity of the catalyst under these conditions may be rationalised by invoking the formation of a deactivated metal-glycidyl epoxide chelate species (Figure 3.3). It has been proposed that for the ring-opening of glycidyl ethers, the $Al(OTf)_3$ catalyst complexes the oxygen atom of the epoxide as well as the heteroatom of the gycidyl ether (Figure 3.3).[9] The positive charge that is transferred to the α-carbon of the epoxide via acid complexation is diminished by chelation of the heteroatom of the glycidyl ether to the aluminium catalyst. This is due to electron-donation from the heteroatom onto the aluminium catalyst. This effect would be

more pronounced with glycidyl ethers bearing a more basic, electron-donating heteroatom functionality.

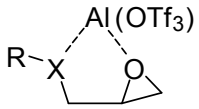


Figure 3.3 : Proposed metal chelate structure of aluminium catalyst and heteroatom glycidyl ether.

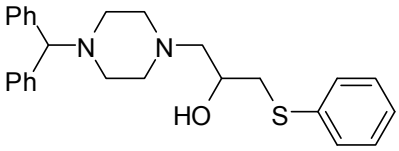
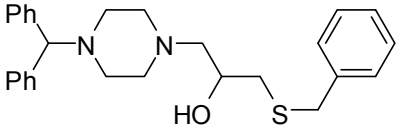
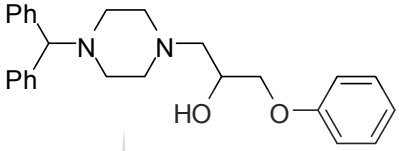
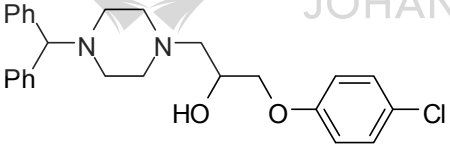
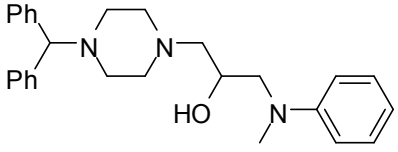
When the heteroatom is a sulfur atom (Table 3.9, entries 1-4) better yields are obtained by using the *S*-glycidyl ethers (Table 3.9, entries 1 and 3) as opposed to the *N*-glycidyl amines (Table 3.9, entries 2 and 4). This can be explained with Pearson's hard-soft acid-base theory[28] which states that hard acids prefer to complex hard bases and soft acids prefer to complex soft bases. Sulfur, being a soft Lewis base,[28] will tend to complex less strongly with the Al^{3+} catalyst, as a glycidyl ether, compared to the hard Lewis base, nitrogen, in the *N*-glycidyl amines.[28] The decreased level of binding of the sulfur atom will lead to less deactivation of the intermediate chelate structure and thus increased activity. In contrast, significantly stronger complexation and thus electron donation from the nitrogen of the *N*-glycidyl amine will lead to decreased activity of the intermediate chelate structure towards nucleophilic attack.

The difference in outcome is more pronounced when the *O*-glycidyl ethers are compared to the *N*-glycidyl ethers (Table 3.9, entries 5-8) and it became clear that method A was superior to method B. Although oxygen is considered a hard Lewis base[28] it is still not as basic as nitrogen and thus deactivation of the intermediate chelate structure is not as pronounced as for the *N*-glycidyl amines (Table 3.9, entries 6 and 8) and favourable yields were obtained with the *O*-glycidyl ethers (Table 3.9, entries 5 and 7). The absence of any reaction for ring-opening of the *N*-glycidyl amines with phenols can mainly be ascribed to the low nucleophilicity of the aromatic oxygen nucleophiles utilised for the reaction (Table 3.9, entries 6 and 8), which becomes determinative with the more poorly activated epoxide.

The difference in the two methods employed to obtain the desired β-amino alcohols was somewhat less pronounced when *N*-glycidyl amines and nitrogen nucleophiles were used (Table 3.9, entries 9 and 10). The difference in yields that was observed could be explained

by the difference in basicity of the two *N*-glycidyl amines. Aromatic amines are considered less basic than aliphatic ones.[19] This is due to electron withdrawal from the nitrogen atom by the phenyl ring.[19] This would mean that an intermediate *N*-glycidyl amine chelate structure bearing an aromatic amine (Table 3.9, entry 9) would be slightly less deactivated than one bearing an aliphatic amine (Table 3.9, entry 10), thus accounting for the difference in yields observed (Table 3.9, entries 9 and 10). Also, an aliphatic amine is considerably more nucleophilic than an aromatic analogue[20] and thus the most favourable combination would be one in which the amine that is least basic is used as the *N*-glycidyl amine substrate whilst the amine that is most nucleophilic is used as the nucleophile for the ring-opening reaction. This logic also holds true for the previous examples. It is thus best to use the glycidyl ether that will show the least deactivation in the intermediate state in combination with the heteroatom nucleophile that will show the best nucleophilicity.

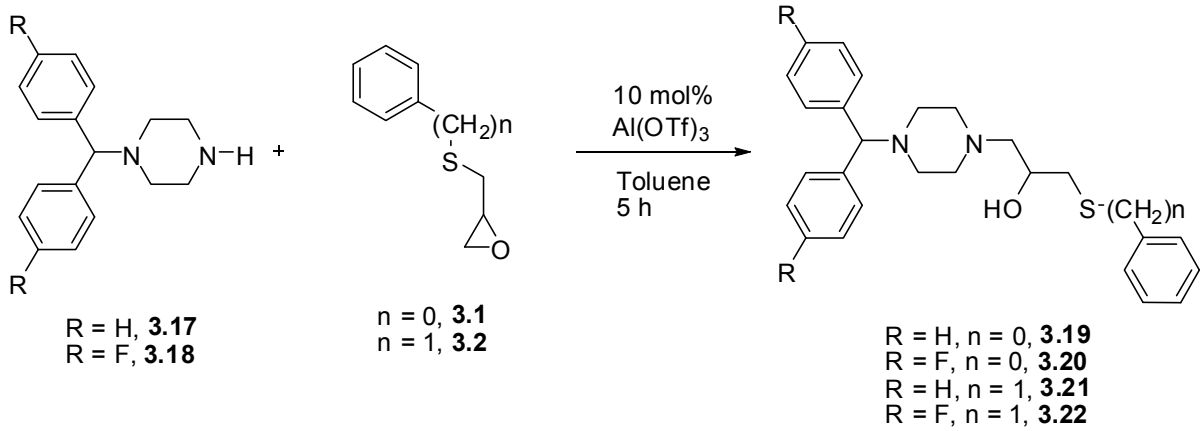
Table 3.9 : Comparison of methods A and B for obtaining β-amino alcohols.

Entry	Product	Method	Yield (%)
1[a]		A	82
2[a]	**3.19**	B	48
3[a]		A	86
4[a]	**3.21**	B	30
5[b]		A	73
6[b]	**3.23**	B	0
7[b]		A	85
8[b]	**3.24**	B	0
9[b]		A	78
10[b]	**3.25**	B	33

[a]10mol% $Al(OTf)_3$ catalyst. [b]5mol% $Al(OTf)_3$ catalyst.

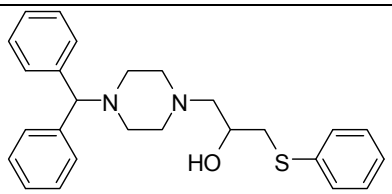
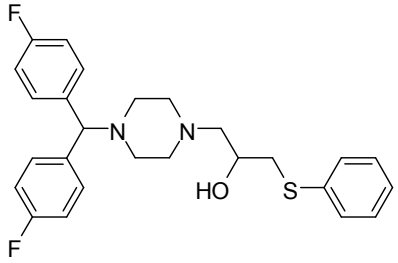
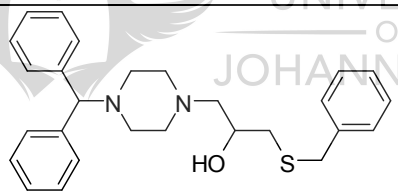
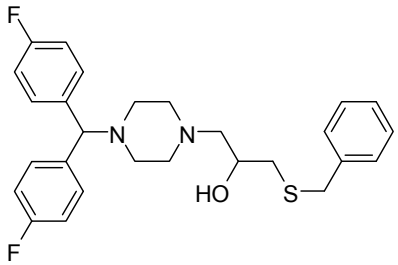
3.4.3 Synthesis of piperazine derived β-amino alcohols bearing a sulfur heteroatom

The optimal method for obtaining piperazine derived β-amino alcohols via the ring-opening of an epoxide had been determined (Sections 3.4.1 and 3.4.2). *S*-glycidyl ethers **3.1** and **3.2** were reacted with piperzine amines **3.17** and **3.18** (Scheme 3.18) in toluene with 10 mol% $Al(OTf)_3$. High yields were obtained for this reaction in only 5 hours (Table 3.10).



Scheme 3.18 : Synthesis of piperazine derived β-amino alcohols bearing a sulfur heteroatom.

Table 3.10 : Results for the synthesis of piperazine derived β-amino alcohols bearing a sulfur heteroatom.

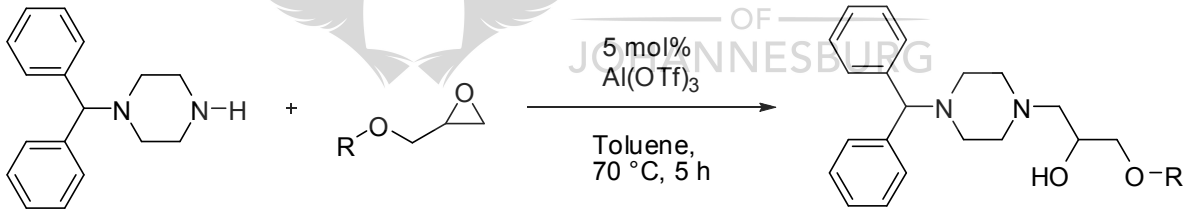
Entry	Compound	Yield (%)
1	 **3.19**	82
2	 **3.20**	75
3	 **3.21**	86
4	 **3.22**	66

The ^{13}C NMR spectrum showed a shift in the position of the signal for the terminal carbon of the epoxide of **3.1** from 47.4 ppm to 53.5 ppm for the ring-opened product, with considerable

line broadening occurring due to the adjacent nitrogen atom of the diphenylmethylpiperazine. The occurrence of this broadened ^{13}C NMR signal at 53.5 ppm was characteristic for all the ring-opened products.

3.4.4 Synthesis of piperazine-derived β-amino alcohols bearing an oxygen heteroatom

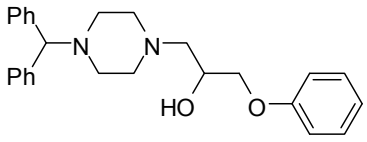
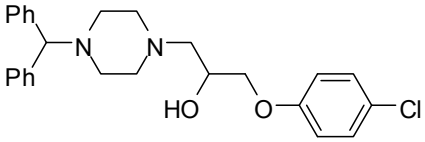
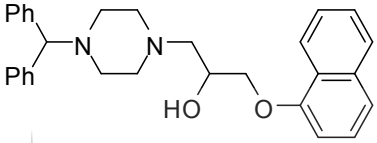
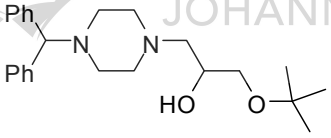
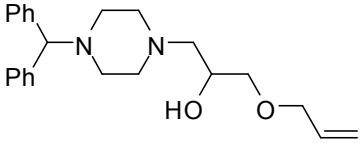
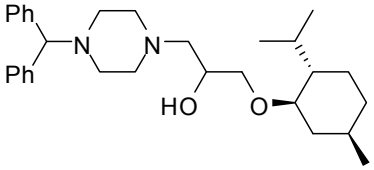
The optimal method previously established for the synthesis of oxygen-based β-amino alcohols (Table 3.9) was applied to the synthesis of piperazine derived β-amino alcohols bearing an oxygen heteroatom. The required *O*-glycidyl ether was ring-opened by piperazine amine **3.17** (Scheme 3.19). The *O*-glycidyl ethers were either first synthesised (Table 3.11, entries 1-3 and 6) as determined in Section 3.2.2 or used as is from a commercial source (Table 3.11, entries 4 and 5). For these reactions only 5 mol% of $Al(OTf)_3$ was required to obtain high yields within 5 hours at 70 °C (Table 3.11). Aromatic *O*-glycidyl ethers (Table 3.11, entries 1-3) as well as aliphatic *O*-glycidyl (Table 3.11) ethers could be used with good results. The structure of the moiety attached to the *O*-glycidyl ether was found to have little effect on the reaction yield.



3.17

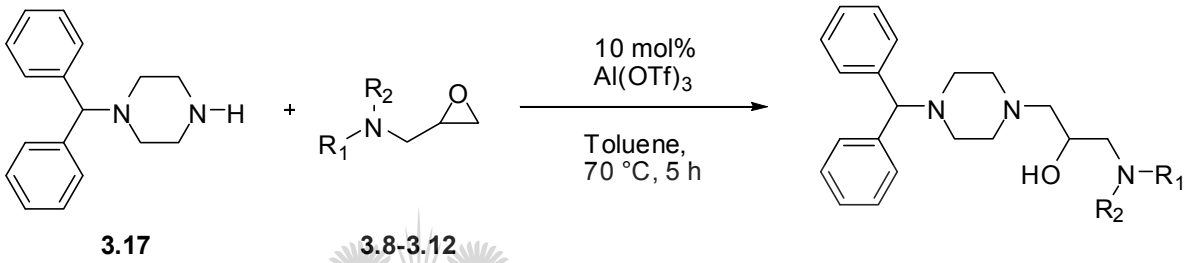
Scheme 3.19 : Synthesis of piperazine derived β-amino alcohols bearing an oxygen heteroatom.

Table 3.11 : Yields for piperazine derived β-amino alcohols bearing an oxygen heteroatom.

Entry	Compound	Yield (%)
1	 **3.23**	73
2	 **3.24**	85
3	 **3.26**	85
4	 **3.27**	88
5	 **3.28**	79
6	 **3.29**	72

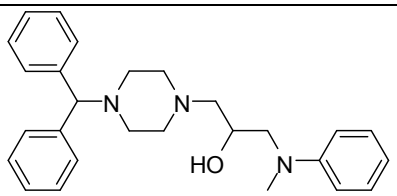
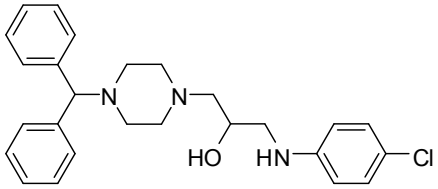
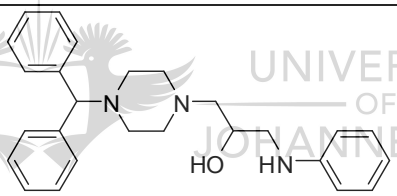
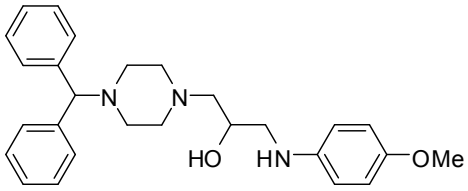
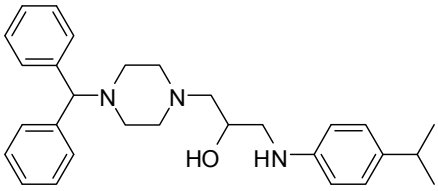
3.4.5 Synthesis of piperazine derived β-amino alcohols bearing a nitrogen heteroatom

It had been established the optimal method with which to form the piperazine-derived β-amino alcohols bearing a nitrogen heteroatom was to place the glycidyl motif on the aromatic nitrogen that was the less basic (Section 3.4.2). The *N*-glycidyl amines synthesised in Table 3.3 were then ring-opened with diphenylmethylpiperazine **3.17** in the presence of 10 mol% $Al(OTf)_3$ (Scheme 3.20). The piperazine-derived β-amino alcohols bearing a nitrogen heteroatom were obtained in high yields after only 5 hours of reaction time (Table 3.12). The aromatic substituent on the heteroatomic nitrogen atom could be varied in whilst still maintaining good yields for the reaction conditions.



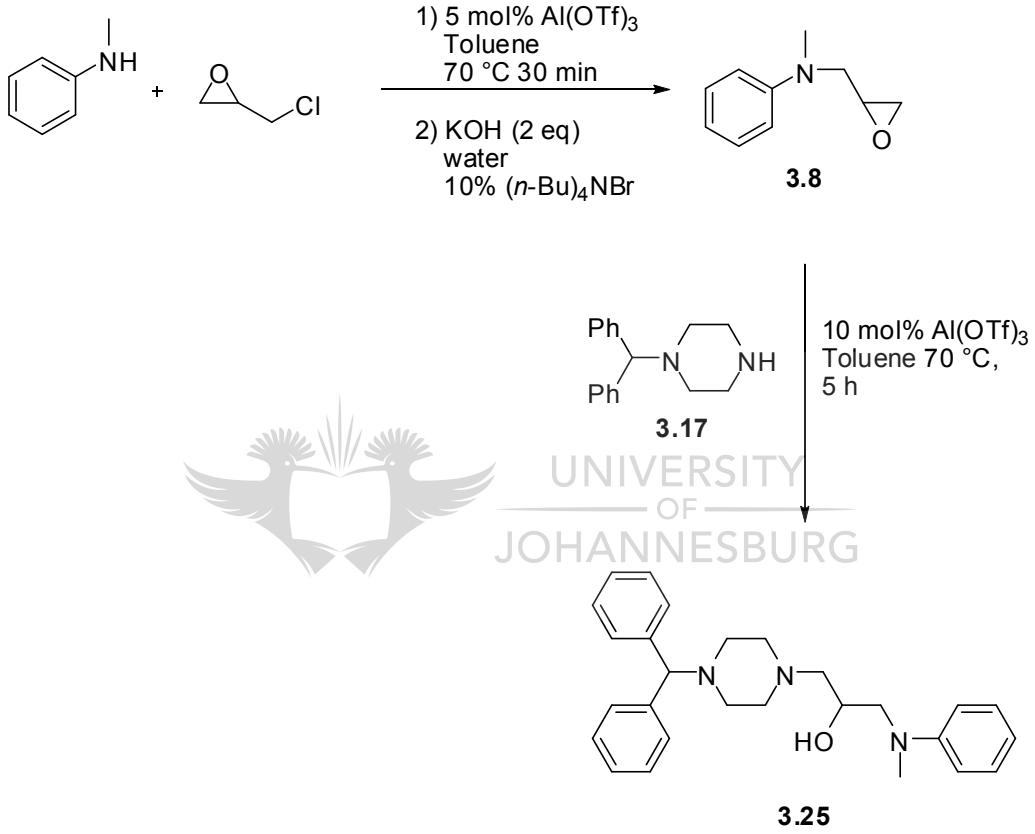
Scheme 3.20 : Synthesis of piperazine-derived β-amino alcohols bearing a nitrogen heteroatom.

Table 3.12 : Results for the synthesis of piperazine derived β-amino alcohols bearing a nitrogen heteroatom.

Entry	Compound	Yield (%)
1	 **3.25**	78
2	 **3.30**	86
3	 **3.31**	88
4	 **3.32**	81
5	 **3.33**	67

3.4.6 Scale up and recycling reactions

Up to this point the general scale on which reactions were performed was a 0.2 g scale. It was decided to demonstrate the applicability of the $Al(OTf)_3$ catalysed ring-opening reaction on a larger scale (10 g) (Scheme 3.21). This entailed the use of $Al(OTf)_3$ for the two step synthesis of an *N*-glycidyl amine as well as the subsequent ring-opening by diphenylmethylpiperazine **3.17**. The recyclability of the $Al(OTf)_3$ was also tested for these two reaction steps. The results are summarised in Table 3.13.



Scheme 3.21 : Scale up of the synthesis of *N*-glycidyl amine **3.8** and the subsequent ring-opening reaction to give **3.25**.

Table 3.13 : Results for scale up reactions for the synthesis of the *N*-glycidyl amine **3.8** and subsequent ring-opening reaction to give **3.25**.

Scale (g)	Yield Epoxide (%)[a]				Yield β-amino alcohol (%)[a]			
	1st run	2nd run	3rd run	Average	1st run	2nd run	3rd run	Average
0.2	99	99	98	99	82	76	77	78
2	96	84	73	84	82	69	86	80
10	80	76	77	78	76	83	84	81

[a]Average yield of three reactions with recycled catalyst; yield is for first two steps.

For the scale up of the *N*-glycidyl amine, *N*-methyl aniline was chosen as a substrate because of the ease of isolation of the products through vacuum distillation. On a 0.2 g scale the main method of isolation for the *N*-glycidyl amine was silica flash chromatography. Upon moving to a 2 g and a 10 g scale bulb-to-bulb vacuum distillation was utilised which significantly simplified isolation. There was a drop in yield from virtually quantitative yield to 78% (Table 3.13), which may be explained by the polymerisation of the *N*-glycidyl amine during the heating step of the distillation which was witnessed through the formation of a discoloured solid in the original bulb during the bulb-to-bulb distillation.

A major drawback in the scale up was the synthesis of the diphenylmethylpiperazine amine **3.17**, mainly due to the polar nature of this amine making isolation on a polar flash silica column very difficult. Previous preparations had only dealt with the isolation of approximately 2 g of **3.17**, but scale up would require 10 g of the amine. During scale up a significant problem was encountered due to the formation of the hydrochloride salt of the mono-substituted piperazine. This problem was solved by suspending the crude reaction mixture in THF after the reaction solvent, acetonitrile, had been removed under reduced pressure. The hydrochloride salt was neutralised by the addition of aqueous KOH. This formed a biphasic system with the mono and di-substituted products being in the organic THF layer. Normally THF and water are miscible and would form a monophasic system. However, due to the high concentration of salts in the aqueous layer which were formed by the neutralisation step, a biphasic mixture was formed and separation was possible. The free piperazine has limited solubility in water and could be removed by aqueous extraction of the organic phase. In order to separate the mono and di-substituted (*N*,*N*') products, the THF was removed under reduced pressure and the mixture of mono and di-substituted products was suspended in hexane. Fortunately there was a significant difference in solubility of the mono

and di-substituted products in hexane, with the di-substituted product being less soluble than the mono-substituted product. It was thus possible to crystallise the di-substituted product out of hexane at room temperature whereas the mono-substituted product remained in solution at that temperature and required the hexane to be cooled to 0 °C before crystallisation occurred. It was thus possible to scale the synthesis of the piperazine based amine to a 10 g scale and still maintain yields in excess of 80% without the need of utilising silica chromatography for the purification of the diphenylmethylpiperazine amine **3.17**.

The scale up reaction for the β-amino alcohol proceeded well up to the 10 g scale (Scheme 3.21). It was not possible to isolate **3.25** by vacuum distillation due to the high boiling point of **3.25**, with decomposition occurring before the boiling point had been reached even under reduced pressures. For this reason flash silica chromatography was used.

The recycling of the catalyst was effected by simply extracting the reaction mixture with water after the elapsed reaction time. This aqueous phase was then back extracted with DCM to ensure no amine was present in the water phase. The aqueous phase containing the $Al(OTf)_3$ was then dried by heating to 100 °C while passing a constant stream of dried nitrogen gas through the flask. Alternatively the drying could be performed by heating the aqueous phase under reduced pressures. The former method required significantly less time than the latter method. After the drying step a glassy residue was left in the reaction flask. In order to ensure dissolution of the recycled $Al(OTf)_3$, the reaction flask was first charged with toluene and the desired amine and heated to 70 °C for an hour prior to the addition of the *N*-glycidyl amine. In this manner it was possible to recycle the $Al(OTf)_3$, for the synthesis of the *N*-glycidyl amines as well as the ring-opening reaction for three cycles without significant loss in catalytic activity (Table 3.13).

3.5 Conclusions

The synthesis of the starting diphenylmethylpiperazine amines was accomplished in only 3 steps in good overall yield. The synthesis of the *S*- and *O*-glycidyl ethers was also accomplished in high yields utilising base promoted methodologies. A new two-step methodology for the synthesis of *N*-glycidyl amines using $Al(OTf)_3$ was pursued due to the failure of the base promoted methodology to provide acceptable yields of product. This approach shows a significant improvement over base-promoted methods in terms of product selectivity and overall reaction times.

The optimal method for forming the β-amino alcohol bond through the ring-opening of an epoxide has been established. This method entailed the placement of a glycidyl moiety on the less reactive/less basic heteroatom followed by the $Al(OTf)_3$ catalysed ring-opening by the more nucleophilic diphenylmethylpiperazine amine. This methodology was successfully extended to a range of β-amino alcohols bearing a sulfur, nitrogen or oxygen heteroatomic functionalities.

The scale up of a particular reaction sequence was also demonstrated up to the 10 g scale indicating the synthetic utility of this $Al(OTf)_3$ catalysed methodology. It was also found that the $Al(OTf)_3$ catalyst could be successfully recovered and reused without significant loss in overall activity for up to three reaction cycles.

3.6 References

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Chapter 4

The nucleophilic substitution of "activated" alcohols using aluminium triflate as a Lewis acid catalyst

4.1 Introduction

Alcohols are widespread throughout nature and have many uses in industrial, pharmaceutical and biological applications.[1] Nucleophilic substitution reactions are one of the most common and versatile reactions in organic chemistry.[1] The ability of a functional group to act as a leaving group is directly related to the pK_a of the conjugate acid (Table 4.1): the lower the pK_a value the better the leaving group.[2] Thus the best leaving groups are usually the weakest bases in their anionic form.[3] It is for this reason that the alcohol group, which would form the relatively basic hydroxide anion, is not a good leaving group. Alcohols usually have to be converted into suitable leaving groups before they can be used in nucleophilic substitution reactions.[2]

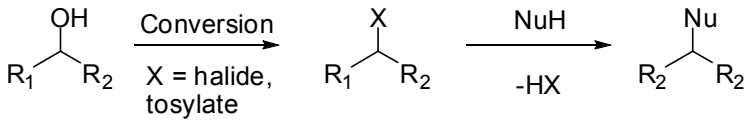
Table 4.1 : pKa values of conjugate acids of various leaving groups.[7]

Leaving group	Conjugate acid	pK_a of conjugate acid
^-OH	H_2O	16
Br^-	HBr	-9
I^-	HI	-10
^-OTs	HOTs	-2.8
^-OTf	HOTf	-15
H_2O	H_3O^+	-1.7

Halides are often used as leaving groups in organic synthesis.[3] The low pK_a of the conjugate acids of halides (Table 4.1) indicates their ability to function as good leaving groups. Alcohols present a more convenient, readily available starting material for nucleophilic substitution reactions; however, they require conversion into suitable leaving groups before they can be utilised. The most common conversion performed on alcohols is to the corresponding sulfonic ester.[2] The *p*-toluenesulfonate group is a far better leaving group than a halide[4a] even more so the trifluoromethanesulfonate group.[4b] This is due to their increased ability to stabilise the negative charge that develops upon the heterolytic bond cleavage that occurs during the nucleophilic substitution reaction.[3] The unavoidable consequence of

utilising these halides or sulfonic esters in nucleophilic substitution reactions is the generation of the conjugate acid of the leaving anion (Scheme 4.1). This conjugate acid usually has to be neutralised in order for the reaction to proceed.

The selection of a starting material is an important step in any synthesis, whilst reactivity is an important factor to consider it is ever more increasingly becoming important to consider the environmental impact of the synthesis.[5] From simply this point of view, the use of halides or sulfonic esters, despite their good reactivity, do not prove favourable starting materials for nucleophilic substitution reactions from an atom efficiency and environmental soundness perspective, due to the generation of these undesired by-products.

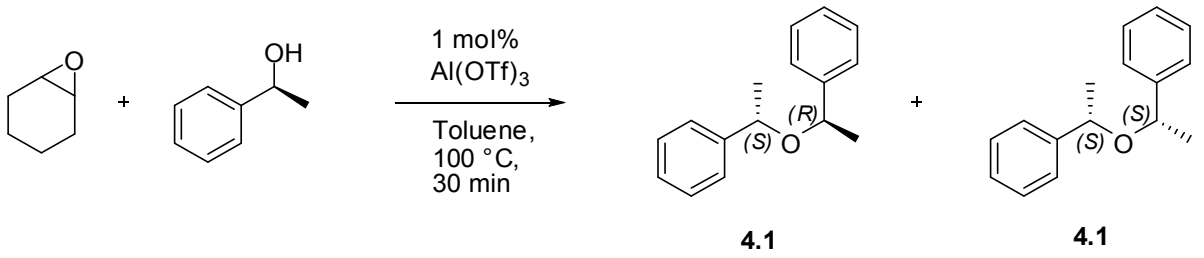


Scheme 4.1 : Conversion and subsequent nucleophilic displacement of an alcohol group.

Although hydroxyl groups are weak leaving groups they can function as leaving groups when they become protonated.[3] This occurs in the presence of a strong acid. This protonation of a hydroxyl group generates the ROH_2^+ species, which upon O-C bond cleavage generates water as the leaving group. The conjugate acid of water is the hydronium ion, with a pK_a of -1.7 (Table 4.1), this low pK_a being a good indication of its ability to function as a leaving group. These types of nucleophilic reactions, in which the leaving group has to be protonated in order to come off, are designated S_N1cA or S_N2cA reactions.[3] The cA in these designations indicates conjugate acid because substitution occurs on the conjugate acid of the substrate.[3] From a green chemistry perspective the use of alcohols directly in nucleophilic substitution reactions is favourable, since the by-product, water, is benign from an environmental aspect. This activation of alcohols towards nucleophilic substitution has been noted as one of the key areas of green chemistry research by the ACS Green Chemistry Institute.[6]

4.2 The reaction of (*S*)-1-phenylethanol

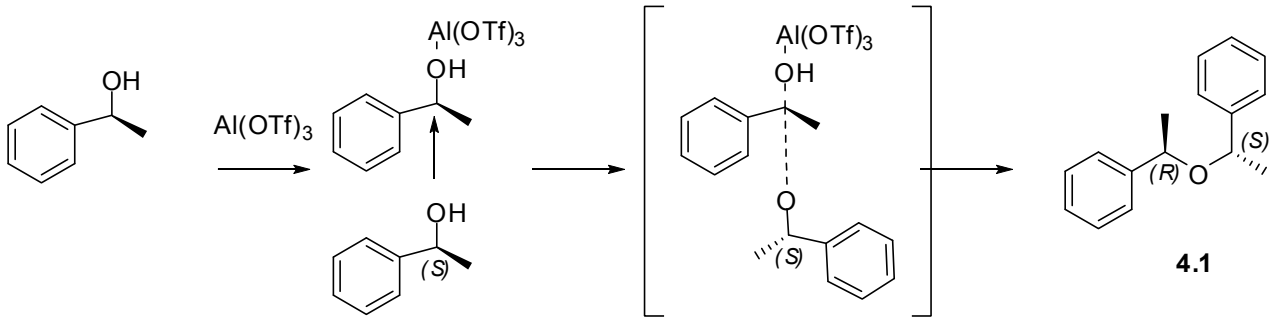
During previous work done (Chapter 2), (*S*)-1-phenylethanol was used as a chiral alcohol to ring open a *meso*-epoxide. However, upon reaction an unanticipated side reaction occurred to yield the symmetrically substituted ether derivative of (*S*)-1-phenylethanol (Scheme 4.2). This demonstrated the possible application of $Al(OTf)_3$ as a catalyst for the nucleophilic substitution of alcohols. The question then was whether this could be extended to other alcohols.



Scheme 4.2 : Unexpected side reaction of (*S*)-1-phenylethanol.

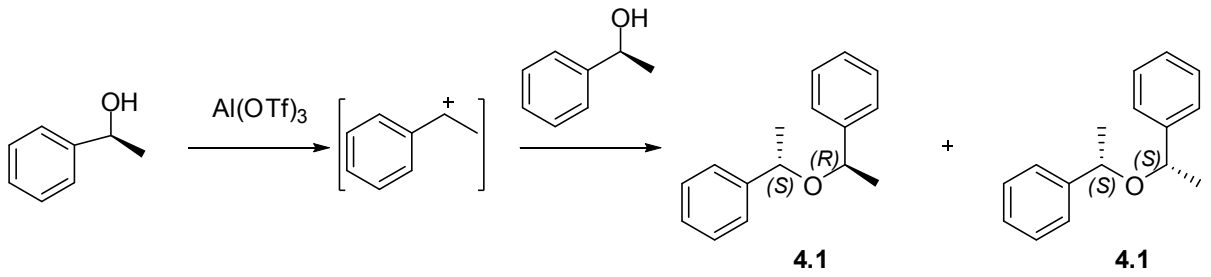
Upon inspection of the ^{1}H NMR spectrum of the product obtained from this reaction, a split in the benzylic and methyl protons was observed as well as a doubling up of all the signals in the ^{13}C NMR spectrum, which implied the presence of diastereomers.

If the reaction were following an S_N2cA type mechanism, a single enantiomer, namely the (*S*,*R*) would be expected. This due to the inversion of stereochemistry at the reactive alcohol with retention of stereochemistry at the nucleophilic alcohol (Scheme 4.3).



Scheme 4.3 : S_N2cA type mechanism for symmetrical ether formation.

The presence of diastereomers, however, suggests an S_N1cA type mechanism (Scheme 4.4) whereby an intermediate carbocation is formed, thus losing any chirality present on the benzylic position. This intermediate planar carbocation can be attacked from either side (i.e. the *re* face or the *si* face) to yield the (*R*) or (*S*) product. The products of this reaction would be reasonably evenly distributed between the (*S*,*R*) and (*S*,*S*) diastereomers, as was found to be the case, as anticipated from the work performed earlier in this study, when making use of chiral alcohols in the attempted desymmetrisation of *meso*-epoxides.



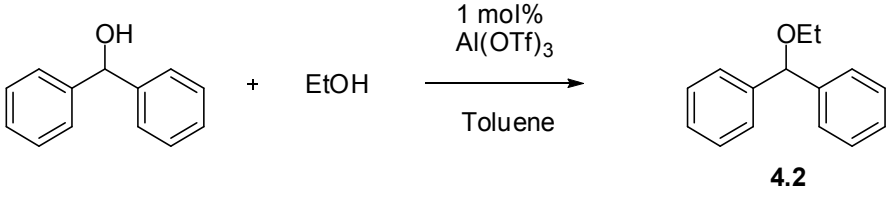
Scheme 4.4 : S_N1cA type mechanism for the symmetrical ether formation.

4.3 Optimisation experiments

It was clear that $Al(OTf)_3$ could be used as a catalyst for the nucleophilic substitution of "activated" alcohols. Further investigations were then performed to determine the optimal conditions for this reaction. For these investigations benzhydrol was used as the "activated" alcohol instead of (*S*)-1-phenylethanol.

4.3.1 Temperature study

The effect of temperature was then examined to determine not only the optimal temperature but also the lowest temperature at which this reaction could be performed. Benzhydrol was reacted with ethanol (1 eq) in toluene with 1 mol% $Al(OTf)_3$ at various temperatures (Scheme 4.5) to give ether **4.2**.



Scheme 4.5 : Temperature study on the reaction between benzhydrol and ethanol.

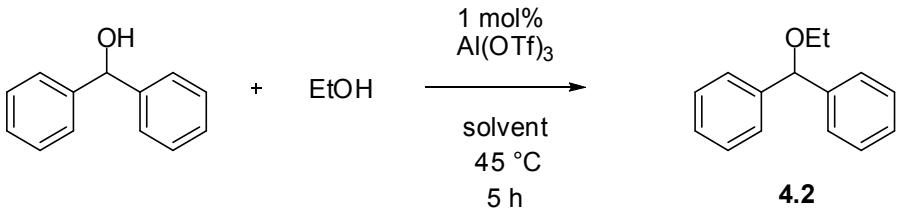
A decrease in reaction temperature led to a decrease in reaction yields and an increase in reaction times (Table 4.2). The fact that the reaction proceeds at lower temperatures is important when the use of temperature sensitive nucleophiles is required or anticipated.

Table 4.2 : Effect of temperature on the reaction between benzhydrol and ethanol.

Entry	Temperature (°C)	Time (h)	Yield (%)
1	100	0.5	98
2	80	1	89
3	60	5	82
4	40	72	84
5	Room temp	648	50

4.3.2 Solvent study

A solvent study was then conducted on the reaction between benzhydrol and ethanol with 1 mol% $Al(OTf)_3$ and various solvents (Scheme 4.6). The reaction was run for 5 hours at 45 °C after which the reaction mixture was neutralised with saturated aqueous sodium bicarbonate and the reaction yield determined by isolating ether **4.2**. This would make it possible to see the influence of the reaction solvent on the product yield.



Scheme 4.6 : Solvent study on the reaction between benzhydrol and ethanol.

The rate of S_N1 reactions is greatly increased in polar protic solvents.[2] This is due to the ability of the solvent to solvate the cations and anions formed during S_N1 reactions.[3] The dielectric constant of a solvent is directly related to its ability to separate two opposite

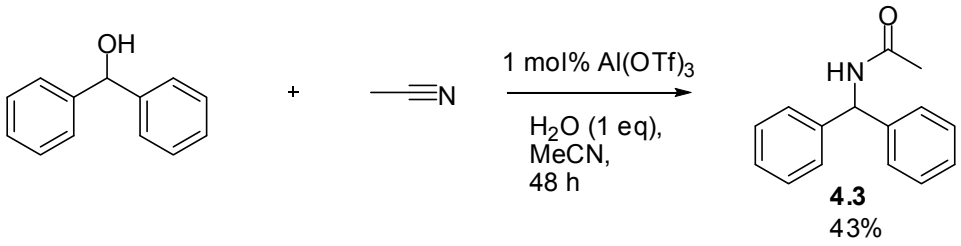
charges and serves as a rough indication of its polarity, where low dielectric constants indicate low polarity solvents and higher dielectric constants indicate high polarity solvents.[2] One of the Hughes-Ingold rules[7] for solvent effects states that if the transition state, in this case a carbocation, is capable of greater solvation than the reagent, then an increase in reaction rate can be brought about through the use of a more polar sovent.[7] A solvent with a low dielectric constant (non-polar) such as toluene (Table 4.3, entry 1) does not solvate the charged intermediate as readily as a solvent with a higher dielectric constant (polar) such as acetonitrile (Table 4.3, entry 2).

An important observation when using acetonitrile is that in the absence of a suitably active nucleophile it was found that the acetonitrile could react with the formed carbocation in a so called Ritter[8] reaction to give the corresponding amide **4.3** (Scheme 4.7). For this reason it was important to note that while nitroethane (Table 4.3, entry 4) did not provide as high yields as acetonitrile (Table 4.3, entry 2), it did not react with the formed carbocation and was thus the solvent of choice for these reactions. Nitrobenzene is also considered a polar solvent and the reaction was indeed tested in this solvent. TLC analysis revealed that the reaction did proceed, but due to the difficulty of separating the reaction products from nitrobenzene it was decided that this was not a suitable reaction solvent.

Table 4.3 : Solvent study for the reaction between benzhydrol and ethanol.

Entry	**Solvent**	**Dielectric constant of the solvent**[7]	**Yield (%)**[a]
1	Toluene	2.4	10
2	Acetonitrile	37.5	79
3	Nitrobenzene	34.8	[b]
4	Nitroethane	19.7	49
5	Dichloromethane	8.9	29

[a]Isolated yields. [b]Reaction not worked up.



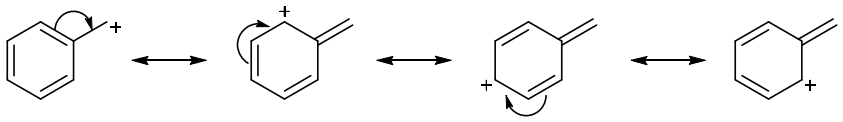
Scheme 4.7 : Ritter type reaction of benzhydrol with acetonitrile to give amide **4.3**.

4.4 Reaction scope

The optimal reaction conditions between benzhydrol and ethanol had been established. It was now important to establish if other nucleophiles could be used for this reaction and also to investigate if it was possible to use more complex "activated" alcohols.

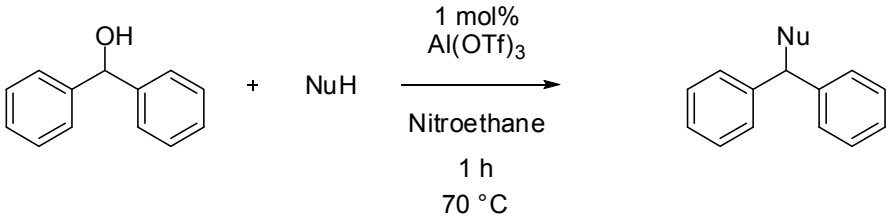
4.4.1 Reactions with benzhydrol as the "activated" alcohol

Reactions that follow an S_N1 type mechanism involve the generation of an intermediate carbocation.[2] Benzylic carbocations are stabilised by the delocalisation of the positive charge onto the phenyl ring (Scheme 4.8).[9] It is important to note that although the charge is delocalised onto the phenylic ring, nucleophilic attack occurs exclusively at the side chain carbon. In the case of a dibenzylic system such as benzhydrol, this delocalisation is more pronounced thus making it a very reactive substrate following exclusively an S_N1 type mechanism.



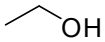
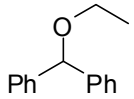
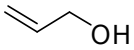
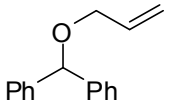
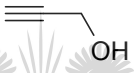
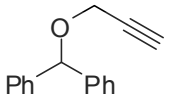
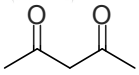
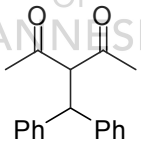
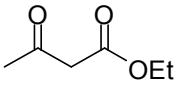
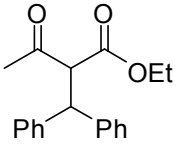
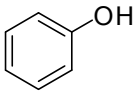
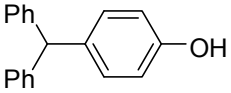
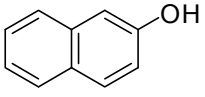
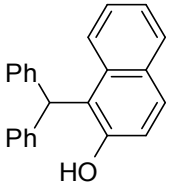
Scheme 4.8 : Delocalisation of the positive charge of a carbocation onto the benzylic ring.

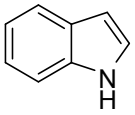
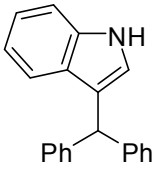
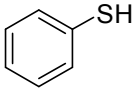
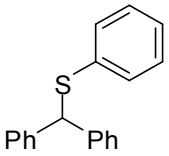
Benzhydrol was reacted with a range of nucleophiles (Scheme 4.9) and the results summarised in Table 4.4.



Scheme 4.9 : Nucleophilic substitution of benzhydrol.

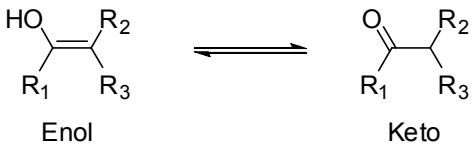
Table 4.4 : Results for the nucleophilic substitution of benzhydrol.

Entry	Nucleophile	Product	Yield (%)
1		 **4.2**	98
2		 **4.4**	94
3		 **4.5**	99
4		 **4.6**	96
5		 **4.7**	80
6		 **4.8**	64
7		 **4.9**	98

8		 **4.10**	80
9		 **4.11**	98

Reaction of benzhydrol with simple alcohols (ethanol, allyl alcohol and propargyl alcohol) yielded the desired unsymmetrical ethers in high yields (Table 4.4, entries 1-3). It is possible that these simple alcohols could also complex to $Al(OTf)_3$ because of their hard Lewis base character, which is in line with Pearson's hard-soft acid-base theory.[10] However, benzhydrol is able to compete with these simple alcohols for Al^{3+} complexation to a significant extent and thus activation of the hydroxyl group of benzhydrol can occur. This is evident by the fact that the reaction does proceed in the presence of these simple alcohols. The ^1H NMR spectrum of ether **4.2** displayed a shift in the position of the benzylic proton from δ 5.82 ppm in the alcohol to δ 5.40 ppm in the ether. This upfield shift is due to electron donation from the etheric oxygen onto the benzylic carbon.

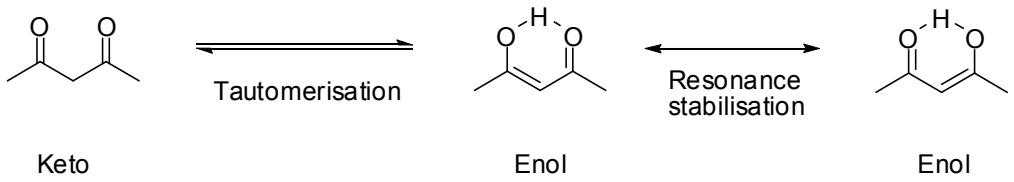
Carbonyl compounds are able to undergo a constitutional isomerism known as tautomerism.[2] The two forms of the tautomers can be interconverted in the presence of an acid or base and are known as the keto and enol form respectively and exist in a state of equilibrium (Scheme 4.10). The keto form is more stable than the enol form in simple systems, and accordingly monocarbonyl compounds exist primarily in the keto form.[3]



Scheme 4.10 : Keto-enol tautomerism of a carbonyl compound.

In β-dicarbonyl compounds, there are two carbonyl groups separated by a CH_2 group. The amount of enol form present is much higher than for monocarbonyl compounds. This is due

to resonance stabilisation through conjugated double bonds and hydrogen bonding (Scheme 4.11) to form a six membered intermediate structure.[2] It is through this ready enolisation of β-dicarbonyls that they are able to act as carbon nucleophiles at the α-carbon.



Scheme 4.11 : Tautomerism and resonance stabilisation of a β-dicarbonyl.

Two β-dicarbonyl compounds, acetyl acetone (Table 4.4, entry 4) and ethyl acetoacetate (Table 4.4, entry 5) were used as nucleophiles in the nucleophilic substitution reaction of benzhydrol. Both of these nucleophiles reacted readily with the diphenyl carbocation to give the alkylated product in high yield (Table 4.4, entries 3 and 4).

Phenols were examined as nucleophiles. The acidity of an aromatic alcohol is considerably higher than that of an aliphatic analogue, which is primarily due to the increased electronegativity of an sp^2 carbon (aromatic alcohols) as opposed to an sp^3 carbon (aliphatic alcohols).[9] This increased acidity would ensure that the phenolic hydroxyl group would not compete with the hydroxyl of the benzhydrol to the same extent that an aliphatic hydroxyl group would. The carbocation formation would then occur readily and despite the low nucleophilicity of the phenolic oxygen it could react with the carbocation in the absence of any other nucleophile. It was thus with some surprise that the phenols used in the reaction with benzhydrol (Table 4.4, entries 6 and 7) did not yield the expected ethers but gave instead the *C*-alkylated product. This *C*-alkylation arises from electrophilic aromatic substitution on the phenylic ring of the phenol.

The reaction with phenol to give product **4.8** showed complete consumption of the benzhydrol with only a moderate yield of 64% (Table 4.4, entry 6). This can be explained by multiple alkylations on a single phenol molecule, although no attempts were made to isolate these multiple alkylated products. Product **4.8** was identified as the *para*-substituted isomer due to the appearance of two doublets at δ 7.02 and δ 6.77 ppm, respectively, each corresponding to two protons.

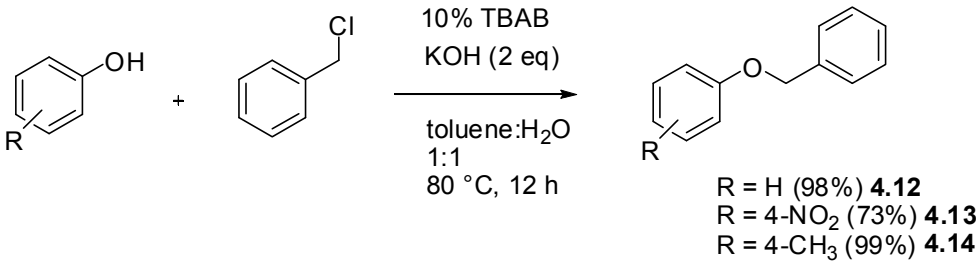
2-Naphthol gave exclusively alkylation in the 1 position on the aromatic ring to give product **4.9** (Table 4.4, entry 7). This substitution can be explained by activation of the *ortho*-position from the hydroxyl group and adjacent benzene ring. The ^{1}H NMR spectrum showed doublets occurring at δ 7.89 and δ 7.25 ppm with mutual coupling and are representative of protons in positions 3 and 4 of the naphthyl ring, thereby indicating substitution at the 1 position. Coupling of these two doublets was established through ^{1}H NMR decoupling experiments. If substitution had occurred at the 3 position one would anticipate the presence of two singlets in the spectrum as opposed to the two doublets seen.

It is known that the indole can act as a nucleophile, with electrophilic attack frequently occurring at the 3 position on the ring.[9] When reacted with benzhydrol it was found that the *C*-alkylated product was obtained in high a high yield (Table 4.4, entry 8). No *N*-alkylation was detected.

The reaction of benzhydrol with thiophenol yielded the *S*-alkylated product **4.11** in a high yield (Table 4.4, entry 9). It was interesting to observe that no *C*-alkylation had occurred as was the case for phenol. This was confirmed by the absence of the SH peak in the ^{1}H NMR spectrum. More concrete evidence was also obtained from the ^{13}C NMR spectrum of the product which displayed signals consistent with a symmetrical *S*-phenyl ring. The explanation for this observation is given in Section 4.4.1.1.

4.4.1.1 <u>*C*-alkylation as opposed to *O*-alkylation in phenols</u>

The *C*-alkylation of the aromatic alcohols (Table 4.4, entries 6 and 7) was a somewhat unexpected outcome and a question as to whether this reaction proceeded through an intermediate *O*-alkylation product arose. Despite numerous attempts, no *O*-alkylation product could be isolated from the reaction. It was thus necessary to synthesise them through base-promoted methodology. Three phenols (phenol, 4-nitrophenol and 4-methylphenol) were reacted with benzyl chloride under basic biphasic conditions in the presence of the biphasic catalyst tetra-*n*-butyl ammonium bromide (Scheme 4.12) to give the corresponding phenol derived benzylic ethers, **4.12** (phenol), **4.13** (4-nitrophenol) and **4.14** (4-methylphenol) in good yields. The ^{1}H NMR spectra of these three ethers displayed a shift in the position of the benzylic singlet from about δ 4.6 ppm for benzyl chloride to approximately δ 5.1 ppm (Table 4.5), this being indicative of the nucleophilic substitution of the chloride by an alcohol.

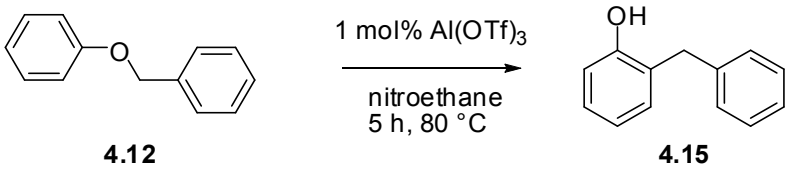


Scheme 4.12 : Base promoted synthesis of phenolic benzyl ethers.

Table 4.5 : Chemical shifts for the benzylic protons for the phenol derived benzyl ethers.

Product	Benzylic protons (δ/ppm)
4.12	5.14
4.13	5.15
4.14	5.05

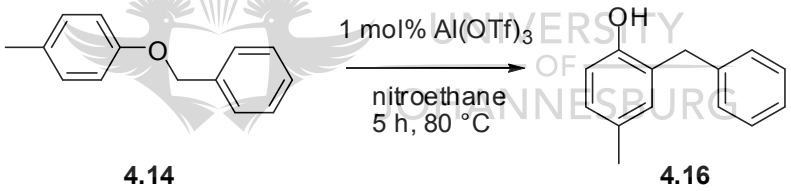
The phenol derived benzylic ethers were subjected to reaction in the presence of 1mol% $Al(OTf)_3$ in nitroethane for 5 hours at 80 °C in an attempt to observe the rearrangement of the *O*-alkylated ethers to the *C*-alkylated products. In the case of the rearrangement of ether **4.12** (Scheme 4.13), the *ortho*-alkylated product was obtained exclusively after 5 hours. The structure of this product was confirmed by the appearance of a signal consistent with an aromatic hydroxyl group at δ 4.71 ppm, which disappeared with the addition of D_2O, as well as a shift in the resonances of the benzylic protons from δ 5.14 to δ 4.00 ppm. The *ortho*-substitution was confirmed via HSQC and COSY NMR techniques with the appearance of an overlapping doublet and triplet at 7.13 ppm as well as a triplet and doublet at δ 6.89 and δ 6.78 ppm, respectively. If *para*-substitution had occurred there would have been two doublets in the ^{1}H NMR spectrum of the product, accounting for the four protons on the phenolic ring. This *ortho*-substitution is in contrast to the reaction of benzhydrol with phenol (Table 4.4, entry 6) which yields exclusively the *para*-alkylated product. In the case of benzhydrol the steric bulk of the diphenyl carbocation could be preventing attack at the *ortho*-position and thus only attack at the *para*-position is observed. This steric bulk is markedly absent in the case of the benzylic carbocation generated from **4.12** and thus attack can occur at the *ortho*-position of the phenolic ring.



4.12 **4.15**

Scheme 4.13 : $Al(OTf)_3$ catalysed rearrangement of phenol derived ether **4.12**.

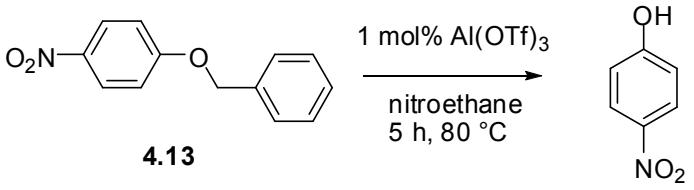
In the case of the ether **4.14** it is only the *ortho*-position that is susceptible towards electrophilic attack as the *para*-position is blocked by a methyl group. Accordingly this ether rearranged quantitatively to the *ortho*-*C*-alkylated product **4.16** with 1 mol% $Al(OTf)_3$ in nitroethane after 5 hours at 80 °C (Scheme 4.14). The shift in the benzylic protons from δ 5.05 to δ 3.96 ppm as well as the appearance of the hydroxyl proton at δ 4.59 ppm confirmed that the rearrangement had taken place. The appearance of an overlapping singlet and doublet, which represent two protons that corresponded to two different carbon atoms (HSQC NMR) at δ 6.92 ppm as well as a doublet at δ 6.67 ppm confirm this *ortho*-substitution.



4.14 **4.16**

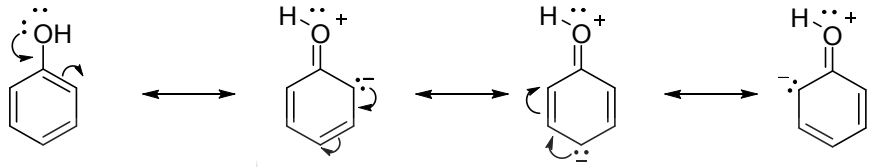
Scheme 4.14 : $Al(OTf)_3$ catalysed rearrangement of *para*-cresol derived ether **4.14**.

Rearrangement of the nitro ether **4.13** yielded exclusively the unprotected nitro-phenol (Scheme 4.15). This is presumably due to the deactivation of the phenol as a nucleophile via the highly electron withdrawing nitro group present on the benzene ring. It is important to note that the unprotected phenol was recovered quantitatively. This result would suggest that cleavage of the benzylic ether is possible with $Al(OTf)_3$ and that the 4-nitrophenol is simply too deactivated to function as a suitable nucleophile to re-attack the carbocation.



Scheme 4.15 : $Al(OTf)_3$ catalysed rearrangement of 4-nitrophenol derived ether **4.13**.

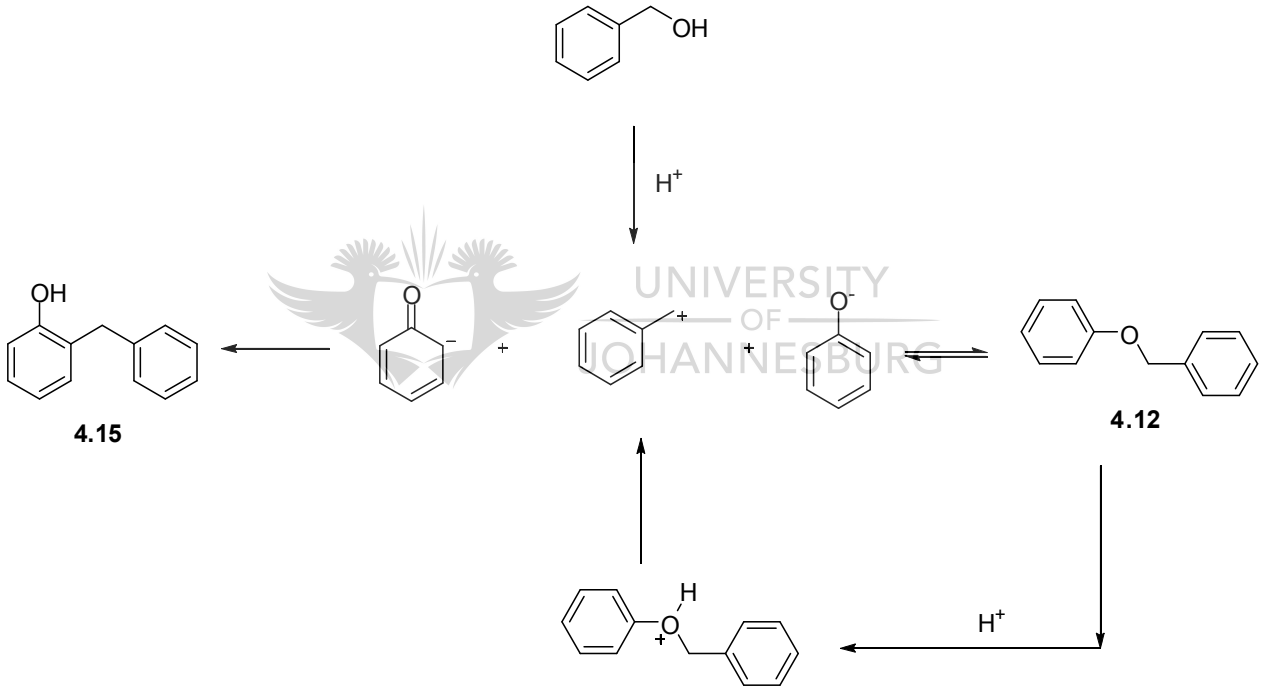
Phenol can undergo resonance stabilisation (Scheme 4.16).[2] These resonances allow for the *ortho*- and *para*-position on the phenolic ring to be activated towards electrophilic attack and would explain why *para*- or *ortho*-alkylation are observed for phenol and 2-naphthol, respectively. The build-up of charge at these positions also helps to explain why rearrangement of ethers **4.12** and **4.14** gives the *ortho*-products.



Scheme 4.16 : Theoretical resonance structures of phenol.

Scheme 4.17 proposes an explanation for the observed *C*-alkylation above *O*-alkylation. Although *O*-alkylation of the intermediate carbocation may occur, it would appear that in the presence of a strong Lewis acid such as $Al(OTf)_3$ it is possible to break this O-C bond via protonation/Al-activation of the oxygen atom. This observation is confirmed by the quantitative recovery of 4-nitrophenol from ether **4.13.** This O-C bond cleavage would regenerate the intermediate carbocation, which can then be electrophilically attacked by one of the activated positions on the benzene ring, be it the *ortho*- or *para*-position. The *C*-alkylated product is impervious towards further reactions catalysed by the strong Lewis acid and does not revert to the intermediate carbocation and the phenol, respectively. The fact that rearrangement does not occur with the thioether product **4.11** obtained from the reaction of benzhydrol with thiophenol (Table 4.4, entry 9) supports this theory of the protonation/Al-activation of the benzylic ether. The sulfur atom of a thioether is classified as a soft Lewis base, according to Pearson's hard-soft-acid-base theory.[10] Thus protonation or complexation between the sulfur and the Al^{3+} species would not readily occur or be stable and the thiolate anion would not be activated as a leaving group. It is probably for this reason that *S*-

alkylation is observed as the only product of the reaction between benzhydrol and thiophenol. It is however important to note that there was no evidence observed for the formation of phenol-*O*-benzhydrol during the nucleophilic substitution of benzhydrol with phenol (Table 4.4, entry 6) and it is entirely possible that the reaction could be proceeding through *C*-alkylation only. This is reinforced by the observation of *para*-alkylation as the predominant product during nucleophilic substitution of benzhydrol (Table 4.4, entry 6). Whereas *ortho*-alkylation was observed for the rearrangement of phenolic benzyl ethers (Scheme 4.13 and 4.14). This *ortho*-selectivity is presumably due to the reactive nature of the intermediate carbocation coupled with the proximity of the nucleophilic *ortho*-site. The intermediate does not have time to react with the distil *para*-position which would entail salvation of the separated ions.



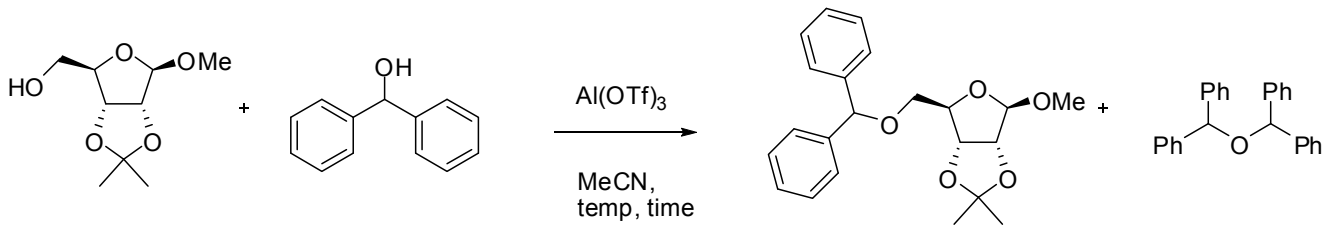
Scheme 4.17 : Proposed mechanism for the rearrangement of phenol derived benzyl ethers.

4.4.1.2 Reaction of benzhydrol with more complex alcohols

4.4.1.2.1 Reaction with a protected ribose

The benzylic protection of alcohols is a common protection methodology.[11] It was thought to establish a protocol whereby a benzylic alcohol is utilised as the source of the benzyl group as opposed to a benzyl halide. Benzhydrol was chosen as the "activated" alcohol on which to

test this protocol due to its increased reactivity as compared to benzyl alcohol. Initial reactions were done with benzhydrol and the protected ribose **4.17** (Scheme 4.18) in order to establish the viability of the use of benzhydrol as the source of the benzylic protection. The results are summarised in Table 4.6.



4.17 **4.18** **4.19**

Scheme 4.18 : Reaction of benzhydrol with protected ribose **4.17**.

Table 4.6 : Results for the reaction between benzhydrol and the protected ribose **4.17**.

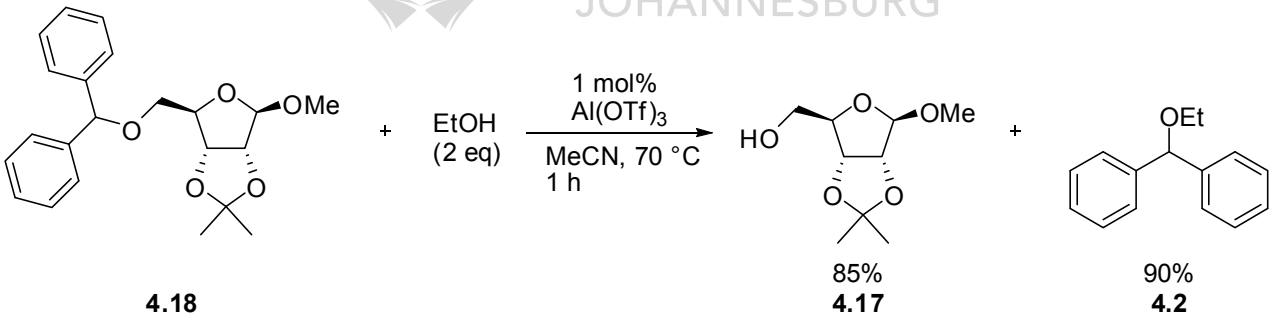
Entry	**Mol% $Al(OTf)_3$**	**Temperature (°C)**	**Time (h)**	**Product Yield (%)**	**By-product Yield (%)**
1	1	70	30	25	18
2[a]	1	70	30	13	10
3	1	40	1	33	18
4	1	room temp	2	18	9
5	0.5	40	1	31	16

[a]Benzhydrol dissolved in acetonitrile and added slowly to the reaction mixture.

The initial reaction between benzhydrol and the protected ribose (Table 4.6, entry 1) gave only 25% yield of the desired product **4.18**. An interesting observation was the complete consumption of the benzhydrol, which manifested itself through the formation of the symmetrical benzhydrol derived ether **4.19**. In an attempt to mitigate this symmetrical ether formation the reaction temperature was lowered (Table 4.6, entries 3 and 4). This had little effect on the distribution of the reaction products. A reduction in catalyst loading (Table 4.6,

entry 5) also had no effect on the product distribution. It was then thought that by adding the benzhydrol slowly to the reaction mixture (Table 4.6, entry 2) of the protected ribose **4.17** and $Al(OTf)_3$ a favourable ratio of protected ribose to benzhydrol could be maintained and higher yields could be obtained. This also had little effect on the reaction yield and only served to decrease the overall yield of the reaction. These results indicated an equilibrium between the benzhydrol protected ribose and the symmetrical ether.

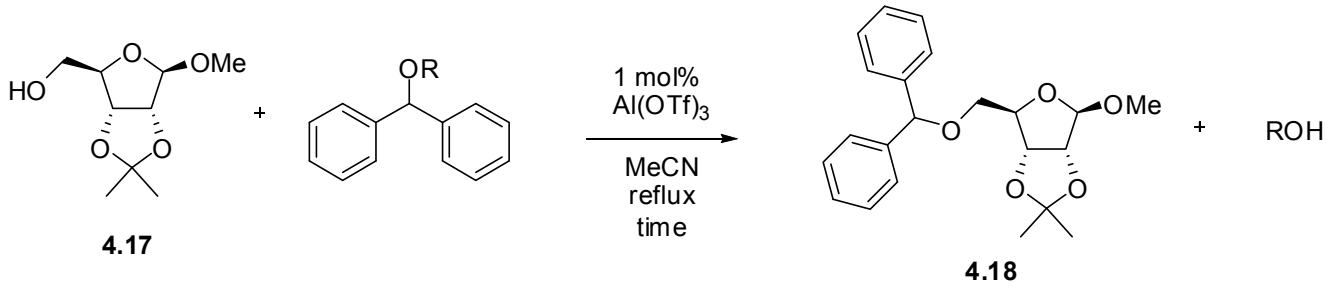
In order to confirm the reversibility of this reaction, the benzhydrol protected ribose **4.18** was subjected to similar conditions as its formation. However, 2 equivalents of ethanol were introduced as a source of a nucleophilic alcohol (Scheme 4.19). Ethanol would serve as a nucleophile to de-benzylate the ribose and result in the formation of the ethanol derived benzylic ether **4.2**. This reaction yielded the unsymmetrical ethanol derived ether **4.2** in a 90% yield with the ribose derivative **4.17** being recovered in 85% yield. This showed that the reaction to form the benzhydrol protected ribose was indeed reversible and in order to realise high yields a means would have to be found of forcing the equilibrium towards the benzhydrol protected ribose. This also once again showed the ability of $Al(OTf)_3$ to activate benzylic ethers as leaving groups. This also demonstrated the use of $Al(OTf)_3$ as a suitable catalyst for the de-benzylation of these types of ethers.



4.18 **4.17** **4.2**

Scheme 4.19 : Alcoholysis of the benzhydrol protected ribose **4.18** to **4.17**.

This discovery of reversibility in the ether formation reaction then prompted the use of benzylic substituted ethers as starting materials for the protection of the ribose derivative **4.17**. It was thought that if the alcohol produced from the reaction were of suitable volatility it could be removed by distillation thereby driving the reaction equilibrium towards the benzhydrol protected ribose derivative **4.18** (Scheme 4.20). This removal was accomplished by distillation with the use of a Dean-Stark apparatus.



4.17 **4.18**

Scheme 4.20 : Reaction of protected ribose derivative with various benzylic ethers.

Table 4.7 : Results for the reaction of the protected ribose derivative and various benzylic ethers.

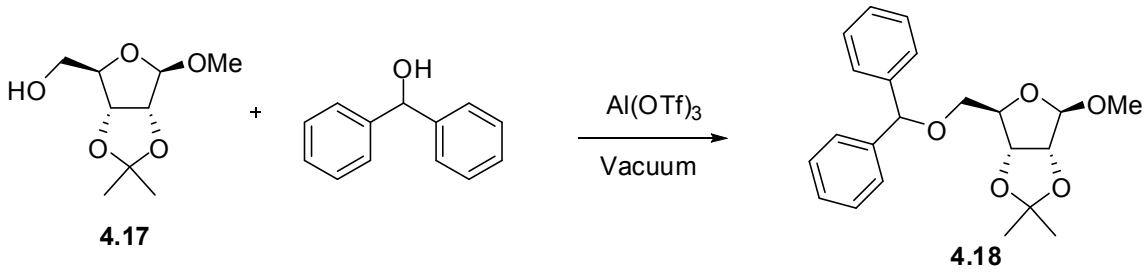
Entry	R	Time (h)	Product Yield (%)	Recovered Starting ether Yield (%)
1	Me	1	37	46
2	Et	1	34	42
3	$CH(Ph)_2$	1	21	70
4[a]	$CH(Ph)_2$	1	11	-

[a]5 equivalents of the ether used.

Reaction of the methyl ether derivative (Table 4.7, entry 1) gave a yield of 37%. This showed that in principle a benzylic ether could be reacted with a nucleophilic alcohol to give a new ether and alcohol. However, the starting ether was recovered indicating the reaction had not gone to completion, longer reaction times led only to the consumption of the starting ether with no increase in reaction yield. A similar result was obtained for the ethyl derivative (Table 4.7, entry 2). The use of the benzhydrol derived symmetrically substituted ether (Table 4.7, entry 3) gave a lower yield with a higher recovery of starting ether, this presumably due to the fact that the formed alcohol, benzhydrol, is not volatile and will thus not be lost during distillation. The use of a large excess of the symmetrical benzhydrol derived ether (Table 4.7, entry 4) was hoped would push the equilibrium towards the benzhydrol protected ribose but

instead only lowered the reaction yield. This is presumably due to an increase in the amount of etheric oxygens deactivating the $Al(OTf)_3$ catalyst.

The next progression was to perform the reaction of benzhydrol with the protected ribose **4.17** in solvent free conditions under a vacuum (Scheme 4.21). The reasoning behind this was that the water generated in the reaction would be removed by the vacuum and the reaction would thus be driven to completion.



Scheme 4.21 : Reaction of protected ribose with benzhydrol under vacuum conditions.

The initial reaction temperature of 70 °C gave a moderate yield of 50% after 1 hour (Table 4.8, entry 1). Longer reaction times gave decreased yields (Table 4.8, entry 2), which is likely due to degradation of the product under the acidic conditions of the reaction. A decrease in reaction temperature to 40 °C gave lower yields after 2 hours (Table 4.8, entry 3) compared to reactions at 70 °C for one hour. However, the reaction product did not decompose to the same extent and the reaction could be run for longer and gave increased reaction yields (Table 4.8, entries 4 and 5). Increasing the catalyst loading to 10 mol% (Table 4.8, entries 6 and 7) gave a decrease in reaction time. It was noted that increasing the reaction time from 2 hours to 5 hours for 10 mol% $Al(OTf)_3$ (Table 4.8, entries 6 and 7) had no effect on the yield thus suggesting the reaction had reached its limit.

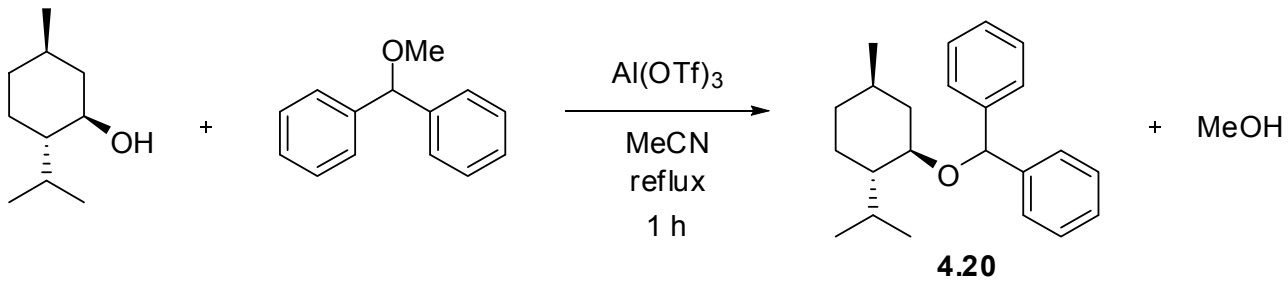
Table 4.8 : Results for the reaction of protected ribose with benzhydrol under vacuum conditions.

Entry	Mol% $Al(OTf)_3$	Time (h)	Temperature (°C)	Conversion (%)[a]
1	1	1	70	50
2	1	5	70	36
3	1	2	40	26
4	1	6	40	47
5	1	20	40	68
6	10	2	40	72
7	10	5	40	72

[a]Conversion determined via ^{1}H NMR.

4.4.1.2.2 Reaction with *l*-menthol

This benzylic ether formation was then tested on *l*-menthol, a secondary hindered alcohol. *l*-Menthol represents an alcohol slightly less complex than a protected carbohydrate (Scheme 4.22) but is more hindered a nucleophile.



4.20

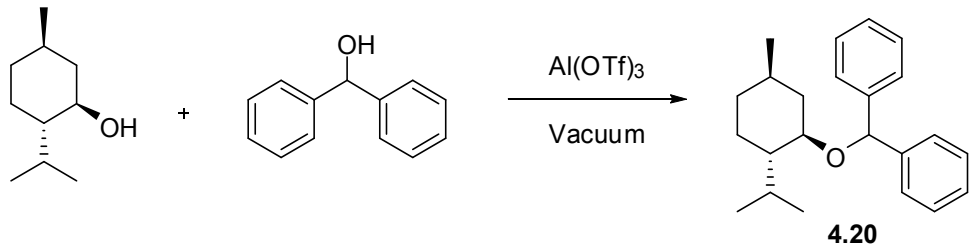
Scheme 4.22 : Reaction of *l*-menthol with benzhydrol derived ether.

Table 4.9 : Results for the reaction of *l*-menthol with benzhydrol derived methyl ether.

Entry	Mol% Catalyst	Yield (%)
1[a,b]	1	46
2[b]	1	49
3[b]	5	48
4[c]	1	79
5[c,d]	1	1

[a]Benzhydrol used as starting material. [b]MeCN added throughout reaction period. [c]MeCN added in one portion at start of reaction period. [d]No distillation.

Reaction of *l*-menthol with benzhydrol yielded the unsymmetrical ether in a 46% yield (Table 4.9, entry 1). The use of the methyl ether derivative of benzhydrol as the source of the benzylic carbocation (Table 4.9, entry 2) did not show a significant improvement in yields. The use of 5 mol% $Al(OTf)_3$ also had no effect on the reaction yield (Table 4.9, entry 3). It was then noted that throughout the reaction involving the distillation of acetonitrile insufficient acetonitrile was present in the reaction flask to maintain reflux conditions and new solvent had to be added throughout the course of the reaction thus leading to significant amounts of time when the reaction mixture was not at its reflux temperature. It was then thought to add the required amount of acetonitrile (that was on average consumed by these reactions) in one portion at the start of the reaction. This move would significantly dilute the reaction but allow for continuous heating at reflux temperature. This led to a notable increase in yield (Table 4.9, from 48% to 79%, entry 4). A reaction performed without distillation, i.e. in a sealed reaction vessel with ordinary reflux conditions gave a low 1% yield of product (Table 4.9, entry 5), indicating the importance of the removal of the formed methanol in order to drive the reaction to completion.



4.20

Scheme 4.23 : Reaction of *l*-menthol with benzhydrol under vacuum conditions.

The reaction between *l*-menthol and benzhydrol was then performed in solvent free conditions under vacuum (Scheme 4.23) as was previously done with the protected ribose molecule. Similar results were obtained (Table 4.10) and after 48 hours it was possible to obtain a 85% conversion of the alcohol into the ether.

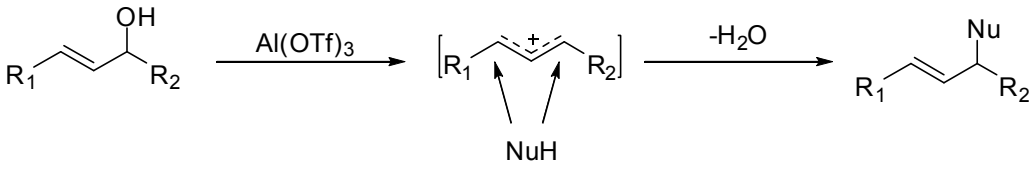
Table 4.10 : Results for the reaction of *l*-menthol with benzhydrol under vacuum conditions.

Entry	**Mol% $Al(OTf)_3$**	**Time (h)**	**Temperature (°C)**	**Conversion (%)[a]**
1	1	2	40	4
2	1	6	40	17
3	1	48	40	85

[a]Conversion determined via ^{1}H NMR.

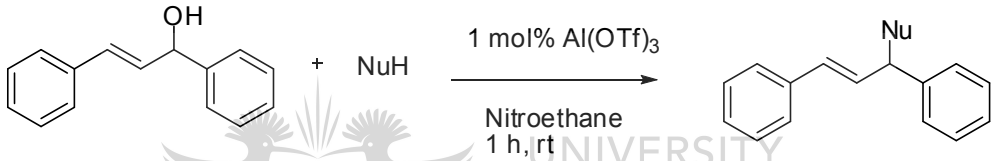
4.4.2 Reactions with *trans*-1,3-diphenylprop-2-en-1-ol as the "activated" alcohol

The nucleophilic substitution of benzhydrol had been reasonably thoroughly investigated with a range of nucleophiles. It was then thought to increase the complexity of the "activated" alcohol. As has been previously mentioned (Section 4.4.1), carbocations can be stabilised through delocalisation of the positive charge onto phenyl rings. They can also be stabilised by conjugation with π or lone pair electrons.[9] The lone pair electrons become delocalised over the three atoms of the allyl-carbocation (Scheme 4.24) with empty orbitals on the ends of the allyl-carbocation. Nucleophilic attack occurs at positions 1 and 3 of the allyl-carcocation.[9] The position of nucleophilic attack is very difficult to control.[3]



Scheme 4.24 : Delocalised carbocation derived from *trans*-1,3-diphenylprop-2-en-1-ol.

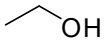
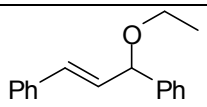
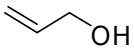
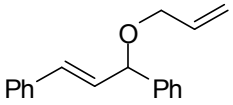
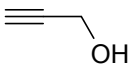
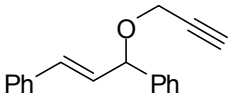
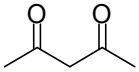
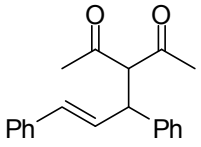
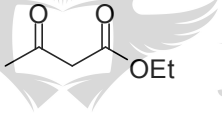
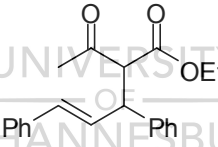
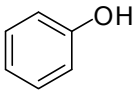
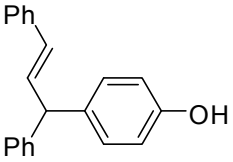
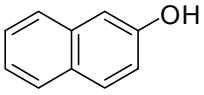
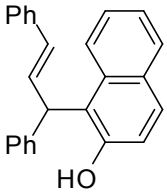
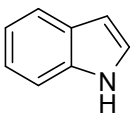
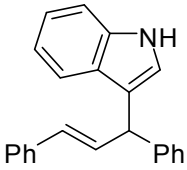
Trans-1,3-Diphenylprop-2-en-1-ol was used as the "activated" alcohol (Scheme 4.25). With its allylic system and 1,3-diphenyl substitution it presented a significantly more active alcohol in terms of carbocation formation. This activity was reflected by the fact that these reactions could all be performed at room temperature and not 80 °C, which was the case for benzhydrol. Although nucleophilic attack could occur at the 1 or 3 position of the allylic carbocation, the products would be the same due to the symmetrical nature of this particular allylic-carbocation.

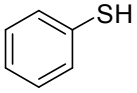
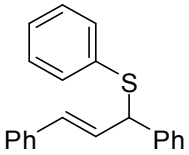


Scheme 4.25 : Nucleophilic substitution of *trans*-1,3-diphenylprop-2-en-1-ol.

The nucleophilic substitution of *trans*-1,3-diphenylprop-2-en-1-ol gave similar results (Table 4.11) to the ones obtained for benzhydrol (Table 4.4). The reaction with simple alcohols (Table 4.11, entries 1-3) gave the corresponding ethers **4.21**, **4.22** and **4.23** in high yields.

Table 4.11 : Results for the nucleophilic substitution of *trans*-1,3-diphenylprop-2-en-1-ol.

Entry	Nucleophile	Product	Yield (%)
1		 **4.21**	85
2		 **4.22**	84
3		 **4.23**	96
4		 **4.24**	98
5		 **4.25**	98
6		 **4.26**	52
7		 **4.27**	72
8		 **4.28**	77

9		 **4.29**	86

β-Dicarbonyl compounds could be successfully employed as nucleophiles (Table 4.11, entries 4 and 5). The loss of symmetry in product **4.24** manifested itself through the non-equivalence of the two acyl CH_3 groups. This resulted in two singlet resonances at δ 2.24 and δ 1.92 ppm, as opposed to a single singlet representing 6 protons as was the case for the symmetrical **4.6**. The introduction of the prochiral ethylacetoacetate into *trans*-1,3-diphenylprop-2-en-1-ol to give product **4.25** led to a 1:1 mixture of diastereomeric products.

Once again *C*-alkylation of phenols was observed above *O*-alkylation (Table 4.11, entries 6 and 7) confirmed by the appearance of aromatic hydroxyl peaks at δ 4.74 ppm for **4.26** and at δ 5.52 ppm for **4.27**. Phenol gave exclusively the *para*-isomer, as confirmed by the two doublets at δ 7.08 and δ 6.77 ppm representing two protons each, and 2-naphthol gave substitution in the 1 position which was confirmed in the same way as done for **4.9**.

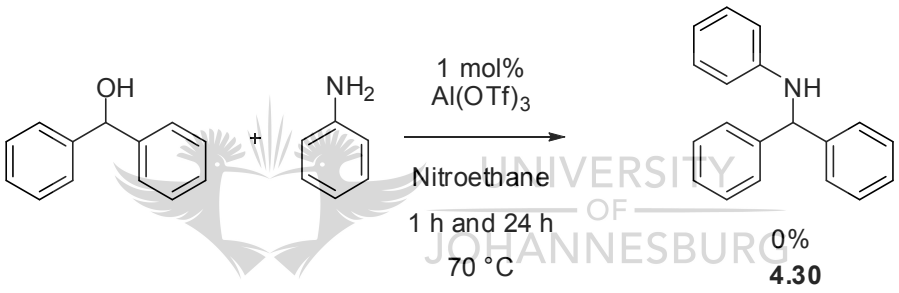
The reaction with indole gave product **4.28** in a high yield (Table 4.11, entry 8). Reaction with thiophenol yielded the *S*-alkylated product **4.28** in high yield (Table 4.11, entry 9). The use of *trans*-1,3-diphenylprop-2-en-1-ol showed that "activated" alcohols with more structural diversity could be employed.

4.4.3 Nitrogen nucleophiles

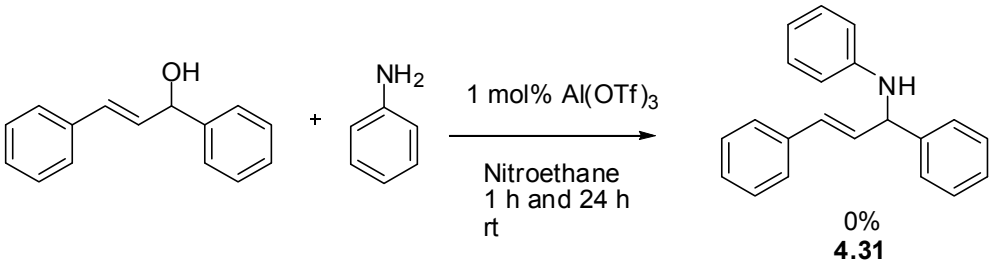
Up until this point none of the nucleophiles examined for the nucleophilic substitution reactions had been significantly basic. The carbon-nitrogen bond is prominent in organic chemistry.[2] Previous work (Chapter 3) established that aromatic and aliphatic nitrogen nucleophiles could be used in the ring opening of epoxides, in an S_N2 type reaction, catalysed by the Lewis acid $Al(OTf)_3$. It was hoped that these nucleophiles could also be used in the nucleophilic substitution of "activated" alcohols in an S_N1 type reaction.

Aniline was chosen as the test amine to be used, as aniline is considerably less basic than aliphatic amines and would have more chance of yielding a successful reaction. This lowered

basicity can be explained by the electron withdrawing effect of the phenyl ring connected to the amine: sp^2 carbons are significantly more electronegative than sp^3 carbons.[2] Additionally, conjugation of the lone pair with the ring would also render the N atom less basic. Aniline was reacted with benzhydrol (Scheme 4.26) and *trans*-1,3-diphenylprop-2-en-1-ol (Scheme 4.27), respectively. In both cases there was no observed reaction after 1 hour, which, considering previous results, was rather disappointing, and the two starting materials were recovered quantitatively. Increasing the reaction time to 24 hours still did not yield any product. This result may not be surprising considering the reaction follows a S_N1cA mechanism which requires that the alcohol be protonated or otherwise activated before it can act as a leaving group.[3] With aniline being a fairly good base, this intermediate protonation/activation step would be rendered more difficult and the alcohol group can thus not be activated to leave. It was thus clear that aniline would have to be deactivated as a base in order for this reaction to have any chance of success.



Scheme 4.26 : Reaction of benzhydrol with aniline.

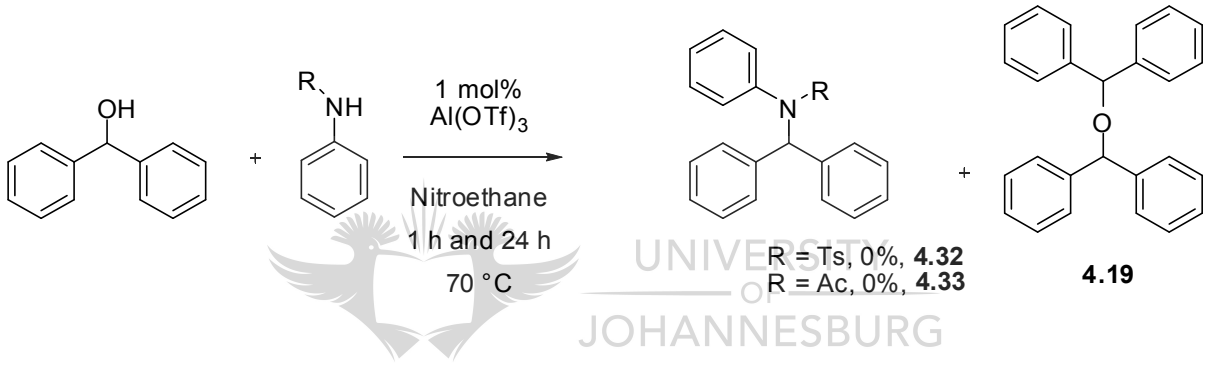


Scheme 4.27 : Reaction of *trans*-1,3-diphenylprop-2-en-1-ol with aniline.

In order to achieve this deactivation of aniline it was decided to use it in the tosylated and acetylated forms. Tosylation of aniline leads to the nitrogen becoming acidic,[12] due to electron withdrawal by the sulfonate group from the nitrogen atom.[9] Acylation leads to a

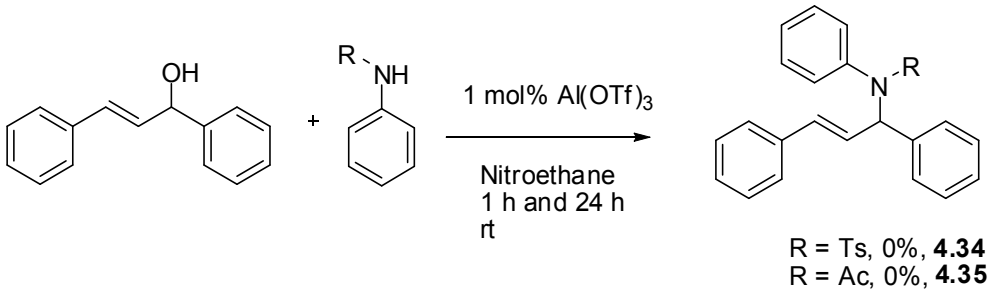
significant decrease in the basicity of the amines which occurs due to the conjugation of the free electrons of the amine onto the carbonyl group attached to the amine.[3]

These deactivated anilines were reacted with benzhydrol (Scheme 4.28) and *trans*-1,3-diphenylprop-2-en-1-ol (Scheme 4.29), respectively. The reaction of benzhydrol with tosylated aniline (Scheme 4.28) did not give the desired carbon-nitrogen bond formation. Instead it was found that the starting alcohol was completely consumed within 1 hour to give the corresponding symmetrical ether. A similar result was obtained for the reaction of benzhydrol with acetanilide. It was thought that leaving the reaction for 24 hours might lead to the desired carbon-nitrogen bond formation through the reversal of the carbon-oxygen bond formation and the subsequent carbon-nitrogen bond formation. This was attempted without success.



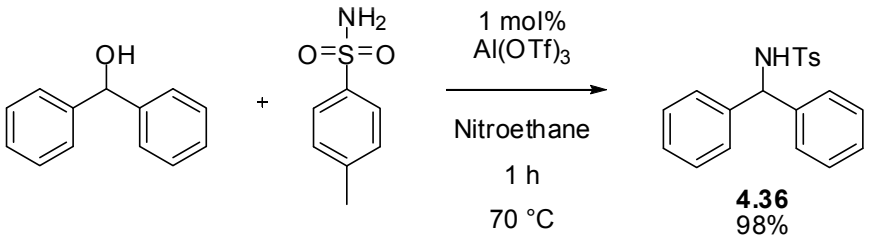
Scheme 4.28 : Reaction of benzhydrol with tosylated and acetylated aniline.

Similar results were obtained for the reaction of *trans*-1,3-diphenylprop-2-en-1-ol with the tosylated aniline and acetanilide (Scheme 4.29). The main difference was that instead of obtaining the symmetrical ether, as in the case of the reaction with benzhydrol, the initial alcohol is consumed to form a mixture of unidentifiable products with the starting amine being retrieved quantitatively. This degradation of the "activated" alcohol is probably due to the highly reactive nature of substrate coupled to its bifunctional nature which would lead to a variety of products.

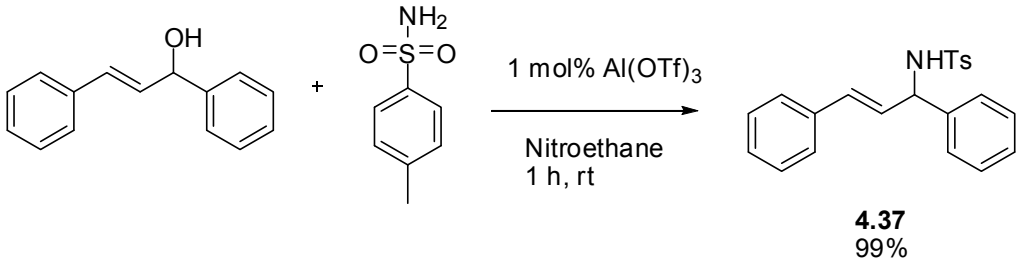


Scheme 4.29 : Reaction of *trans*-1,3-diphenylprop-2-en-1-ol with tosylated and acetylated aniline.

It was apparent that the deactivation of aniline was successful and allowed the $Al(OTf)_3$ to continue to be an effective catalyst for the nucleophilic substitution of alcohols through the generation of an intermediate carbocation. A less hindered nitrogen nucleophile that was still deactivated was then examined in the form of *p*-toluenesulfonyl amine for the nucleophilic substitution of benzhydrol and *trans*-1,3-diphenylprop-2-en-1-ol (Scheme 4.30, Scheme 4.31). This gave the desired nucleophilic substitution reaction with the corresponding amides **4.36** and **4.37** both being obtained in high yields. It was thus apparent that the steric bulk present on acetanilide prevents their reaction with the intermediate carbocations whereas the sterically un-cumbered tosyl amine reacts smoothly.



Scheme 4.30 : Reaction of benzhydrol with tosyl amine.

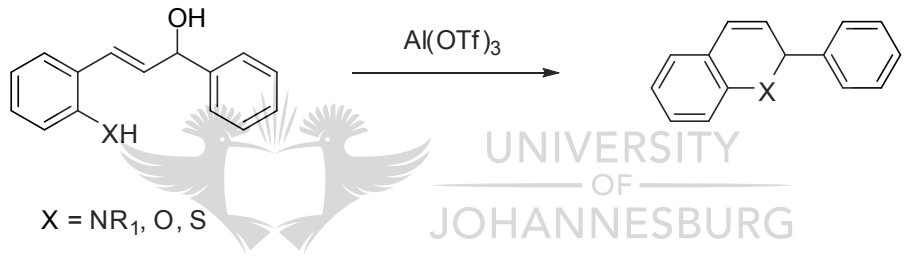


Scheme 4.31 : Reaction of *trans*-1,3-diphenylprop-2-en-1-ol with tosyl amine.

4.5 $Al(OTf)_3$ catalysed intramolecular cyclisation of "activated" alcohols

4.5.1 Introduction

The $Al(OTf)_3$ catalysed nucleophilic substitution of "activated" alcohols by various nucleophiles had been established as part of this study. It was then decided to apply this methodology to the intramolecular cyclisation of an "activated" alcohol with a nucleophile to give the corresponding cyclic product (Scheme 4.32). An oxygen nucleophile would yield the *2H*-chromene, a nitrogen nucleophile would yield the 1,2-dihydroquinoline and a sulfur nucleophile would yield the 2*H*-thiochromene. In order for this $Al(OTf)_3$ mediated cyclisation to be tested, the "activated" alcohols would have to synthesised from suitable starting materials. The retrosynthetic analysis as well as synthesis are discussed elsewhere in this chapter.



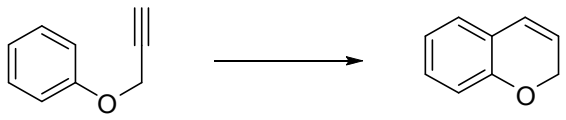
Scheme 4.32 : Envisioned cyclisation of an "activated" alcohol by a suitable internal nucleophile to give the corresponding cyclic structure.

4.5.1.1 2*H*-Chromenes

The 2*H*-chrmomene motif is an important component that is found in a wide array of natural products.[14a] This sub-structure is found in a range of biologically active molecules that are active as anti-HIV,[14b,c,d] antitumour,[14e] antibacterial[14f,g] and fungicidal[14h] agents. They have also been reported as powerful antioxidants having activity higher than α-tocopherol.[14i]They have also been used as photochromic agents.[14j]

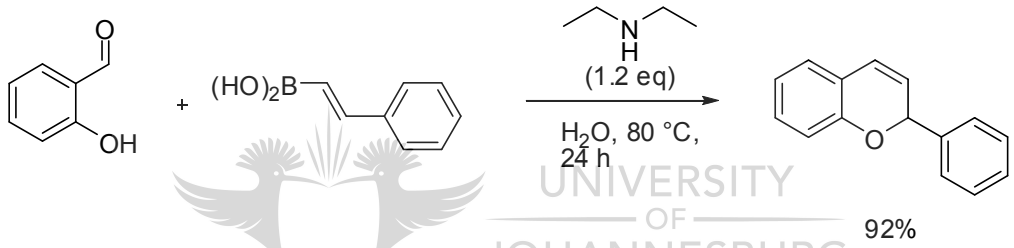
There has been a significant drive towards the synthesis of this 2*H*-chromene core.[14a] However, most methodologies involve the use of stoichiometric amounts of reagents, low yields and limited substrate availability.[14k] Catalytic methods involving the hydroarylation of terminal alkynes is one approach for obtaining 2*H*-chromenes (Scheme 4.33) and can be

promoted by Pt,[15a] Pd,[15b] Au[15c] and Fe[14k] catalysts. They can also be synthesised via a ring closing metathesis promoted by Ru.[15d] In most cases, the catalyst is not recoverable.



Scheme 4.33 : Hydroarylation of a terminal alkyne to give the 2*H*-chromene motif.

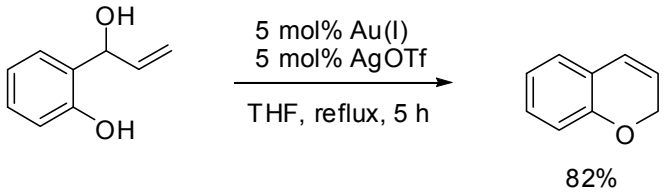
The Petasis-borono-Mannich reaction has been reported for the synthesis of the 2*H*-chromene motif.[15d,e] This reaction was performed in water utilising a suitable salicylaldehyde and boronic acid and is promoted by an secondary amine (Scheme 4.34). This methodology required long reaction times and the use of stoichiometric amounts of a secondary amine base.



Scheme 4.34 : Petasis-borono-Mannich reaction to give 2-phenyl-2*H*-chromene.

The acid-catalysed cyclisation of a diol derived from the reductive opening of a 2,3-benzofuran has been reported.[15f] This procedure required the use of super-stoichiometric amounts of phosphoric acid at reflux conditions. A Lewis acid, $ZnCl_2$, was also investigated for this cyclisation. However, a stoichiometric amount of this acid was required for acceptable yields to be realised.

The Au(I)-catalysed dehydrative *endo*-cyclisation of *ortho*-(1-hydroxyallyl)-phenols to give the corresponding 2*H*-chromes has been reported (Scheme 4.35).[15g] This required the use of AgOTf as a co-catalyst. The authors reported the failure of other Lewis acids in this type of cyclisation. These included $BF_3{\cdot}OEt_2$, $Zn(OTf)_2$, $InBr_3$, $Yb(OTf)_3$, $FeCl_3$ and $Pd(OAc)_2$.



Scheme 4.35 : Au(I) catalysed cyclisation of a salicylaldehyde derived diol.

It was clear that a number of methods had been developed for the synthesis of 2*H*-chromenes. Notably a few methods utilised the acid catalysed cyclisation of a diol. However, no reports were found that successfully employed a metal triflate Lewis acid catalyst, specifically $Al(OTf)_3$.

4.5.1.2 1,2-Dihydroquinolines

1,2-Dihydroquinolines are an important class of building blocks in organic synthesis and are used for the synthesis of more complex tetrahydroquinolines with these molecules often showing biological activity.[14a16a,b]

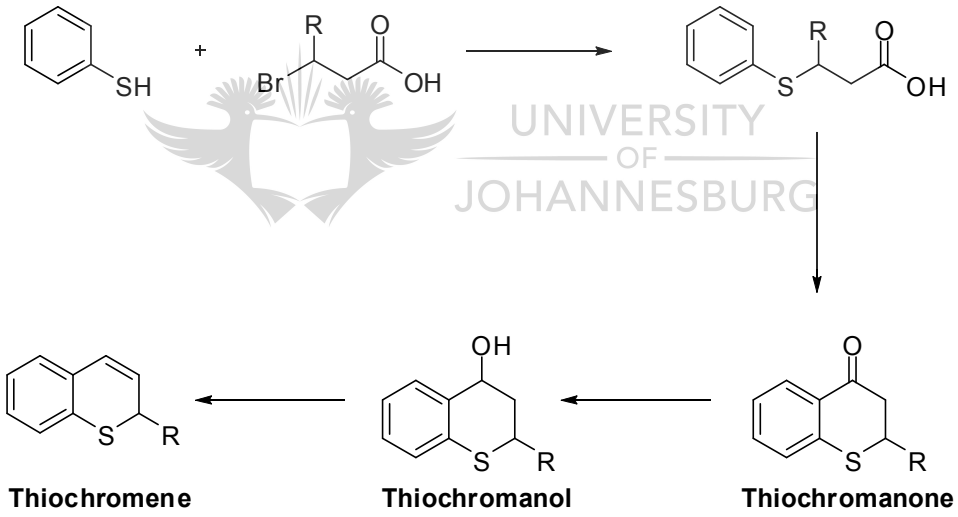
The synthesis of quinolines from the corresponding alcohol has been reported via the Friedländer reaction,[17a,b] the aza-Wacker oxidative cyclisation,[17c] or the Cu/Pd catalysed cyclodehydration of 1-(2-aminoaryl)-2-yn-1-ols.[17d] The required 1,2-dihydroquinolines can then be obtained via the reduction of a quinoline to the 1,2-dihydroquinoline. The synthesis of 1,2-dihydroquinolines from the corresponding alcohols is limited to only three reports. The first involves a thermolytic electrocyclisation of *N*-methyl-2-hydroxyalkylanilines at elevated temperatures.[18a] The second revolves around an intramolecular cyclisation of *ortho*-(1-hydroxy-2-alkenyl)phenyl isocyanides at 0 °C with $BF_3{\cdot}OEt_2$ as the catalyst.[18b] Both of these methods suffer from low reaction yields. $AuCl_3/AgSbF_6$ was the first catalytic system reported for the cyclisation of an "activated" alcohol with a tosylated amine to give the corresponding 1,2-dihydroquinoline.[18c] The authors screened other Lewis acids (AuCl, $Yb(OTf)_3$, $Cu(OTf)_2$, $InCl_3$, $FeCl_3{\cdot}6H_2O$ and $BF_3{\cdot}OEt_2$) for this cyclisation and found that they gave low reaction yields in the range of 7-18%. When Brønsted acids were employed (*p*-TsOH, TfOH and HCl) a varied mixture of inseparable products was formed, none of which were identifiable via ^1H NMR spectroscopy. This methodology required the use of 5 mol% $AuCl_3$ with 15 mol% of the $AgSbF_6$ co-catalyst. In the present context, it was thought that

$Al(OTf)_3$ might be better at promoting this ring closing reaction to give the 1,2-dihydroquinoline, since it is a significantly harder Lewis acid.

4.5.1.3 2*H*-Thiochromenes

Thiochromenes are the sulfur analogues of chromenes. They have found application as reversible inhibitors of the human steroid sulfatase enzyme in the treatment of androgen and estrogen dependent disorders,[19a] as dopamine receptor binders for the treatment of Parkinson's disease[19b] and they have also shown antifungal activity.[19c]

The synthesis of thiochromenes involves the reaction of a thiophenol with a β-bromopropionic acid to give the corresponding propionic acid. This propionic acid is then converted into the corresponding thiochromanone which is reduced to the thiochromanol. This thiochromanol can then be reduced to the thiochromene (Scheme 4.36).[20a-f]



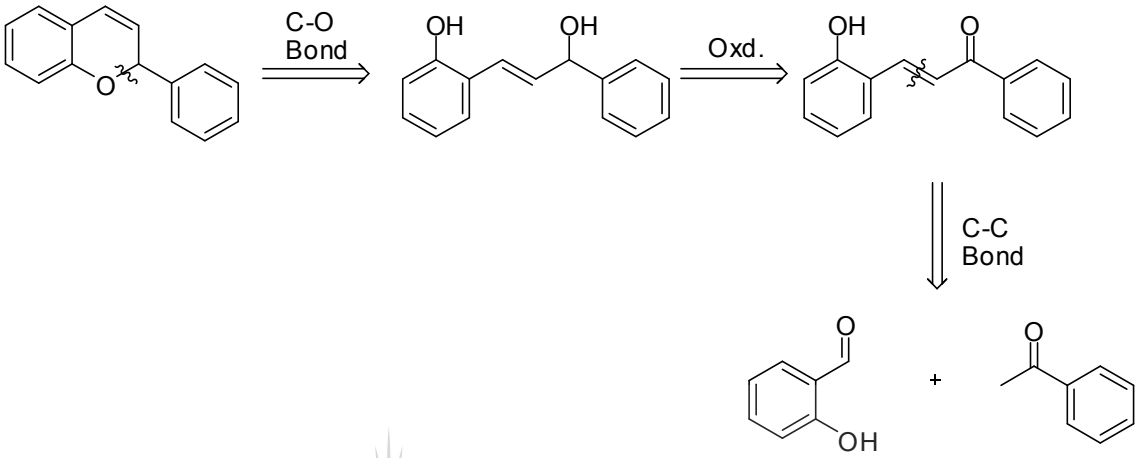
Scheme 4.36 : Literature synthesis of 2-substituted thiochromenes.[20a-f]

The reported synthetic route to thiochromene involves multiple steps and harsh reaction conditions with toxic reagents.[20a-f] The cyclisation of an "activated" alcohol with an internal sulfur nucleophile to give the corresponding thiochromene has not been reported. It was thus of interest to test $Al(OTf)_3$ as a catalyst for this reaction, since this would provide a new synthetic route towards thiochromenes.

4.5.2 Intramolecular cyclisation utilising an oxygen nucleophile

4.5.2.1 Retrosynthetic analysis for the target 2-phenyl-2*H*-chromene

The retrosynthetic analysis of 2-phenyl-2*H*-chromene (Scheme 4.37) involved a C-O bond disconnection to the "activated" alcohol. This "activated" alcohol could be obtained by the reduction of the corresponding 2-hydroxychalcone. A C-C bond-forming reaction between salicylaldehyde and acetophenone could be utilised to form the desired 2-hydroxychalcone.

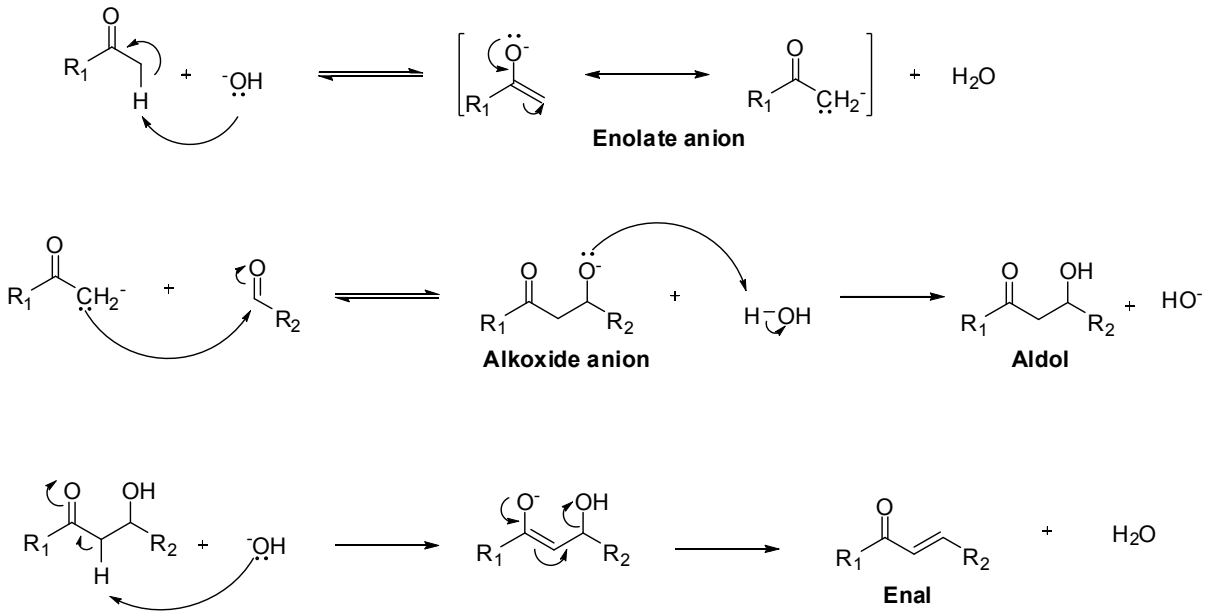


Scheme 4.37 : Retrosynthetic analysis for the formation of the "activated" alcohol to be used for the synthesis of 2-phenyl-2*H*-chromene.

4.5.2.2 2-Hydroxychalcone synthesis

It was envisioned to obtain the required 2-hydroxychalcone from the aldol condensation between salicylaldehyde and acetophenone (Scheme 4.37). Aldol reactions are important in organic synthesis when two molecules need to be linked via a C-C bond.[2] An aldol reaction involves the addition from the carbon of a ketone or aldehyde to the carbon of another ketone or aldehyde.[3] These reactions can be acid- or base-catalysed, with the base-catalysed route being the preferred approach. If the α-hydrogen atom of the aldol reaction product is suitably acidic, dehydration can occur to form the corresponding enal and this is referred to as an aldol condensation reaction.[2] When an aldehyde is reacted with a ketone the reaction is called a Claisen-Schmidt reaction and this usually requires that the aldehyde does not have an α-hydrogen atom present in order to secure product selectivity.[3] This reaction proceeds via the deprotonation of the α-hydrogen of the ketone to give the enolate anion (Scheme 4.38). This nucleophilic enolate anion then attacks the electrophilic aldehyde carbon to give the alkoxide

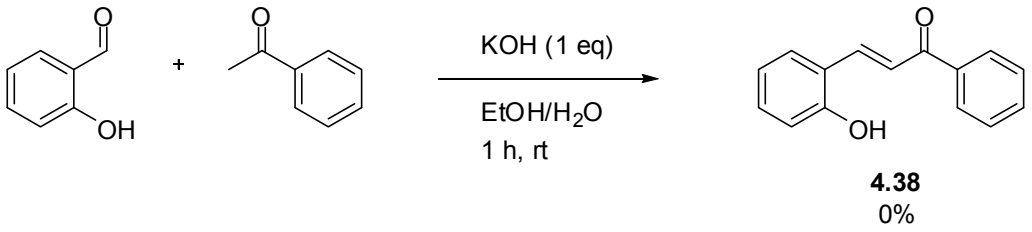
anion which can then abstract a proton from water to give the aldol product (Scheme 4.38). If the α-hydrogen is sufficiently acidic or the reaction medium is heated the corresponding enal/α,β-unsaturated ketone will form by the loss of water (Scheme 4.38).



Scheme 4.38 : Claisen-Schmidt condensation between an aldehyde and a ketone.

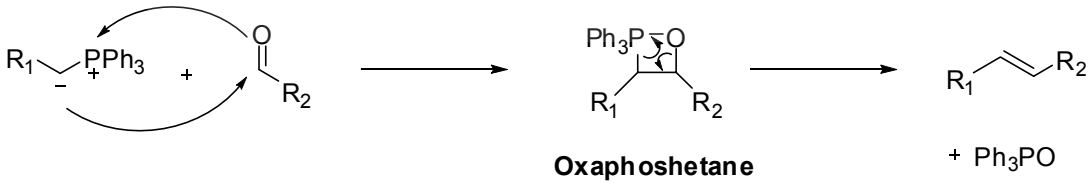
With this Claisen-Schmidt reaction in mind, salicyladehyde was reacted with acetophenone in the presence of potassium hydroxide with the hopes of obtaining 2-hydroxychalcone **4.38**. This reaction failed to yield the desired 2-hydroxychalcone. Heating of the reaction mixture did not improve the reaction yield, neither did the addition of an excess of base. Deprotonation of the acetophenone in dry THF utilising 1.2 equivalents of sodium hydride, to give the enolate anion, with addition of the enolate anion to salicylaldehyde in THF also failed to give any appreciable yield of **4.38**. The failure of this reaction can possibly be attributed to two factors. Firstly the salicylaldehyde possesses an acidic phenolic group which would presumably react with the enolate anion in an acid-base reaction to give the phenolate anion and the starting ketone. It was hoped that the addition of excess amounts of base would fully deprotonate the phenolic alcohol and then also deprotonate the ketone to an extent to see reactivity towards the aldol reaction. However, this was not the case and no product was observed. Secondly, the salicylaldehyde, with its electron-donating alcohol/alkoxide group, presents a poor electrophile for the nucleophilic enolate anion to attack. So if any enolate anion were present in the reaction it would not have a suitably reactive electrophile partner. Possible ways to circumvent this would be the protection of the phenolic alcohol and

subsequent Claisen-Schmidt reaction. This was not investigated; instead it was thought to form the α,β-unsaturated ketone via a Wittig reaction.



Scheme 4.39 : Attempted Claisen-Schmidt condensation of salicylaldehyde with acetophenone to give 2-hydroxychalcone.

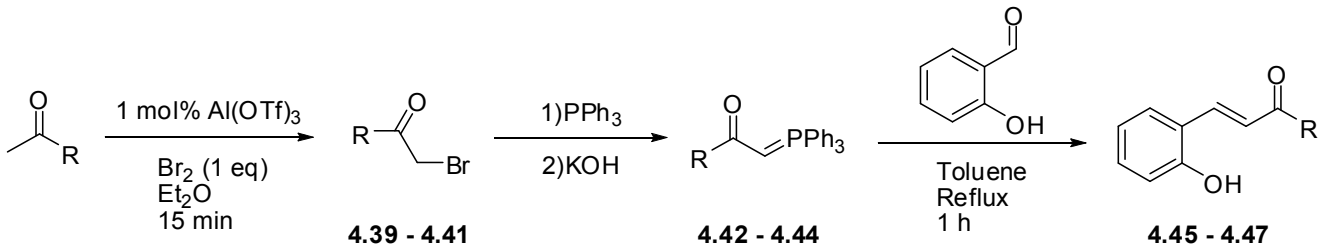
The Wittig reaction is an important reaction for obtaining alkenes and is performed between an aldehyde or ketone and a phosphorus ylide.[9,21] This reaction involves the nucleophilic attack of a phosphorous ylide onto a carbonyl group to form the intermediate oxaphosphetane. This oxaphosphetane undergoes elimination to give the alkene and the phosphine oxide (Scheme 4.40). The formation of the oxygen-phosphorus bond to give the phosphine oxide is a thermodynamically favoured process and drives the reaction to completion.[3]



Scheme 4.40 : The Wittig reaction.

The phosphorous ylide was synthesised from acetophenone in three steps (Scheme 4.41). This involved the initial bromination of the corresponding acetophenones. $AlCl_3$ used in super stoichiometric amounts has been reported to promote this type of reaction. However, the report noted that extended reaction times led to a degradation of the reaction product resulting in low yields.[22] 1 mol% $Al(OTf)_3$ was used instead of $AlCl_3$ and was found to catalyse the reaction without the degradation of reaction products and gave the desired α-brominated products in high yields (Table 4.12). This bromination proceeds via the acid catalysed enolation of the ketone which is then attacked by the electrophilic bromine molecule to yield

the α-brominated product.[9] The acid catalyst ensures that bromination occurs regioselectively due to the increased nucleophilicity of the formed enol above the benzene ring. The acid catalysed approach is also selective for mono-bromination. This selectivity for mono-bromination is not the case when a base promoted reaction is performed.[9]



Scheme 4.41 : Synthesis of the phosphorous ylide and subsequent reaction with salicylaldehyde to give the corresponding 2-hydroxychalcone.

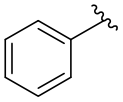
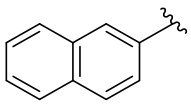
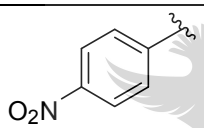
These brominated products were reacted with triphenyl phosphine to give the phosphorus ylide salt which was deprotonated with an aqueous potassium hydroxide methanol mixture to give the corresponding phosphorous ylide in a high yield (Table 4.12). These phosphorous ylides are classified as stabilized phosophorous ylides due to the carbonyl groups present. These carbonyl groups withdraw electron density from the α-carbon of the phosphorous ylide thus stabilising the negative charge of the phosphorous ylide.

The Wittig reaction of the phosphorous ylide with salicylaldehyde (Scheme 4.41) gave 2-hydroxychalcones **4.45** and **4.46** in high yields (Table 4.12, entries 1 and 2). The reaction of the 4-nitroacetophenone derived phosphorous ylide gave a low yield for the Wittig reaction to form **4.47** (Table 4.12, entry 3). This is because of the decreased nucleophilicity of the phosphorous ylide due to electron withdrawal effects of the *para*-nitro group. Longer reaction times and increased reaction temperatures did not give significant improvement in the reaction yield of the Wittig reaction.

The ^{1}H NMR spectrum for **4.45** revealed a coupling constant (*J*) of 16.0 Hz for the respective doublet signals of the protons of the double bond. This indicates a *trans* configuration across the double bond indicative of the *E* alkene. The coupling constant for protons that have a *trans* configuration across the double bond are in the range of 12-18 Hz, whilst those for protons in the *cis* configuration are about 6-12 Hz.[13] This *trans* configuration is expected due

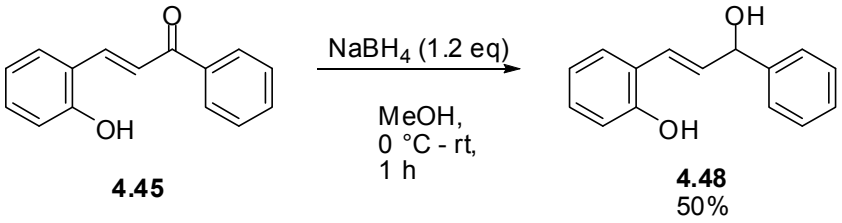
to the use of a stabilised Wittig reagent which gives the *E*-isomer as the reaction product. The opposite would be true for the use of an unstabilised Wittig reagent.[9]

Table 4.12 : Yields for the bromination, phosphorous ylide formation and subsequent Wittig reactions of various acetophenones.

Entry	R	Bromination Yield (%)	Wittig Ylide Yield (%)	Wittig Reaction Yield (%)	Overall Yield (%) of 2-hydroxychalcone
1		94 (**4.39**)	99 (**4.42**)	98 (**4.45**)	73
2		98 (**4.40**)	98 (**4.43**)	66 (**4.46**)	45
3		99 (**4.41**)	78 (**4.44**)	13 (**4.47**)	8

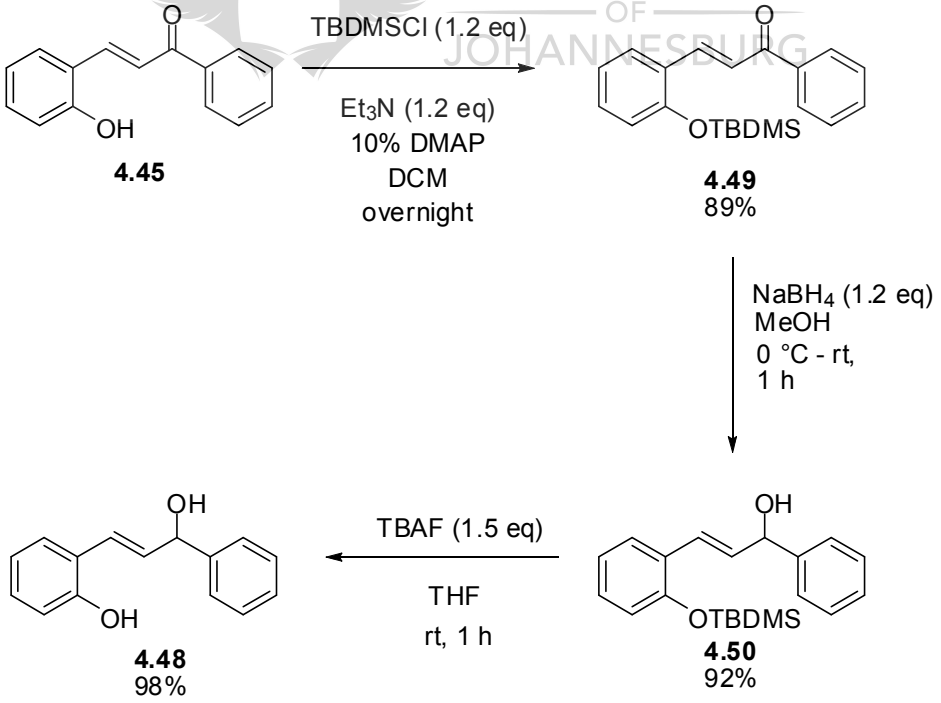
4.4.2.3 Reduction of the 2-hydroxychalcone substrates to give the corresponding diols

Initial reductions of 2-hydroxychalcone **4.45** were carried out with 1.2 equivalents of sodium borohydride in methanol. This gave only 50% of the desired diol with numerous by-products being detected on the TLC plate of the crude reaction mixture (Scheme 4.42). It was noted that with the addition of sodium borohydride a vigorous reaction was observed and a colour change from clear to orange was observed. The reduction of the ketone of a chalcone substrate with sodium borohydride is a well-known procedure and usually gives very high yields of the alcohol.[23] It was not expected to obtain such low yields for the reduction of the 2-hydroxychalcone which only had an extra hydroxyl group when compared to chalcone. It was clear that the aromatic hydroxyl group was having a significant influence on this reaction.



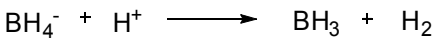
Scheme 4.42 : Reduction of 2-hydroxycahlcone **4.45** to give **4.48**.

In order to demonstrate the influence that the aromatic hydroxyl group of 2-hydroxychalcone **4.45** was having on the sodium borohydride reduction, the hydroxyl group of 2-hydroxychalcone **4.45** was silylated to form the silylether **4.49**. Reaction of **4.45** with TBDMSCl in the presence of triethylamine and 10 mol% DMAP (Scheme 4.43) gave silylether **4.49** in a high yield. This silylether could then be reduced with 1.2 equivalents of sodium borohydride in an excellent yield (Scheme 4.43) which is in stark contrast to the previous reduction of 2-hydroxychalcone **4.45**. Subsequent deprotection of the silylether with tetra-*n*-butyl ammonium fluoride gave the corresponding diol in near-quantitative yield (Scheme 4.43). The overall yield for the three steps to obtain the desired diol **4.48** was 80%.



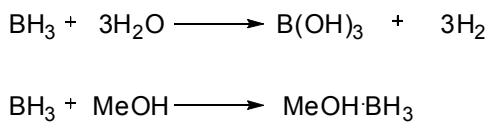
Scheme 4.43 : TBDMS protection of 2-hydroxychalcone **4.45** and the subsequent reduction and deprotection to give diol **4.48**.

It was now clear that the aromatic hydroxyl group was to blame for the low yields obtained for the sodium borohydride reduction of 2-hydroxychalcone **4.45**. It is known that sodium borohydride decomposes in the presence of an acid.[23] In fact, Schlesinger *et al.* utilised various organic acids to decompose sodium borohydride in order to generate hydrogen gas *in situ* during hydrogenation reactions.[24] They found that elevated temperatures also enhanced the decomposition of sodium borohydride to hydrogen gas. This occurs due to the reaction of the borohydride anion with an acidic proton, to release hydrogen gas and borane (Scheme 4.44). Aromatic hydroxyl groups are considered acidic, and it is thus entirely possible that the acidic proton of the aromatic hydroxyl group could be promoting the decomposition of the borohydride before the hydride attack on the ketone could occur. This case is not helped by the fact that the reaction is exothermic and generates heat which would contribute to the decomposition of the borohydride.



Scheme 4.44 : Acid promoted decomposition of the borohydride anion.

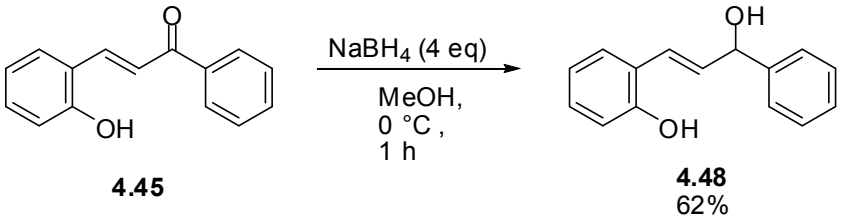
The borane generated can then further be hydrolysed by water to give boric acid and three additional molecules of hydrogen gas are released (Scheme 4.45). Alternatively, the borane could form a Lewis acid/base pair with the methanol which is known to occur (Scheme 4.45).[25]



Scheme 4.45 : Hydrolysis of borane and the formation of the Lewis acid/base pair with methanol.

If decomposition of sodium borohydride by the aromatic hydroxyl group present on 2-hydroxychalcone **4.45** was to blame, then it was possible that an excess of the reductant may solve the problem, and it was decided to simply add 4 molar equivalents of sodium borohydride and also to perform the reaction at 0 °C whilst adding **4.45** very slowly to the reaction mixture (Scheme 4.46). This was done in an attempt to limit the generation of heat during this reaction. This led to a slight increase of the yield from 50% to 62%. While not

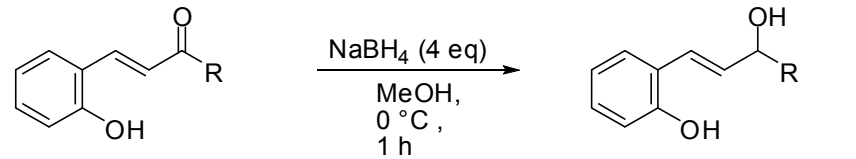
entirely comparable to the protection route, this improvement would allow sufficient product to be formed to allow the crux of the research to be investigated.



4.45 **4.48** 62%

Scheme 4.46 : Reduction of 2-hydroxychalcone **4.45** with 4 equivalents of sodium borohydride to give diol **4.48**.

2-Hydroxychalcones **4.46** and **4.47** were then reduced with 4 molar equivalents of sodium borohydride in methanol to give the corresponding diols **4.51** and **4.52** (Scheme 4.47). The reduction of the 2-naphthyl derived hydroxychalcone **4.44** gave only 52% of the desired diol **4.51**. Once again the decomposition of sodium borohydride was thought to be the main reason for the low yield. The reduction of the 4-nitrophenyl derived hydroxychalcone **4.47** gave the desired diol **4.52** in a good yield of 79%. This is can be explained by the increased electrophilicity of the ketone of the 2-hydroxychalcone **4.47** due to the electron withdrawal effect of the 4-nitrophenyl ring. This increased electrophilicity allows the ketone to compete with the aromatic hydroxyl group for the borohydride anion. No reduction of the nitro group to the amine was detected.



R = 2-naphthyl, **4.46**
R = 4-$NO_2C_6H_4$, **4.47**

R = 2-naphthyl, **4.51**, 52%
R = 4-$NO_2C_6H_4$, **4.52**, 79%

Scheme 4.47 : Reduction of 2-hydroxychalcones **4.46** and **4.47** with 4 equivalents of sodium borohydride to give diols **4.51** and **4.52**.

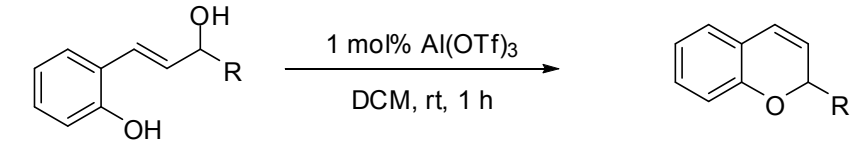
^{1}H NMR spectroscopy of these diols (**4.48**, **4.51** and **4.52**) was performed in deuterated DMSO due to their low solubility in chloroform. The coupling constant of approximately 16

Hz for the double bond protons revealed retention of the *trans* configuration of the double bond.

4.5.2.4 $Al(OTf)_3$-catalysed cyclisation of the "activated" alcohol with an oxygen nucleophile

The first attempts at cyclisation of diol **4.48** were performed in nitroethane with 1 mol% $Al(OTf)_3$. This was due to previous work in the present study showing nitroethane to be the solvent of choice for the nucleophilic substitution of these "activated" alcohols (Section 4.3.2). Upon addition of **4.45** to the $Al(OTf)_3$ containing nitroethane solution a deep purple colour was observed. This colour observation is probably due to the formation of the delocalised carbocationic intermediate. After just 30 minutes all of the starting diol **4.48** had been consumed; however, there was a diverse mixture of reaction products, probably due to the high reactivity of the intermediate carbocation. It was clear that the reactivity had to be tamed. To achieve this, the reaction solvent was changed from nitroethane to DCM. Although markedly lower yields for the nucleophilic substitution of "activated" alcohols were obtained in DCM (Section 4.3.2) there was still reactivity in this solvent.

The intramolecular cyclisation of **4.48** in DCM with 1 mol% $Al(OTf)_3$ was complete within 1 hour at room temperature (Scheme 4.48) and gave the 2-phenyl-2*H*-chromene **4.53** in a high yield. No purple colour formation was detected during this reaction, which is probably a mark of the slower formation of the intermediate carbocation in this solvent. It was rather fortuitous to find that DCM did not dissolve diol **4.48** particularly well: it was noted that only after 30 minutes had passed had all of the diol dissolved into the reaction mixture. This served to ensure that the concentration of diol **4.48** (and there from a carbocationic derivative intermediate) was always low in the reaction medium thus ensuring intramolecular cyclisation as opposed to intermolecular nucleophilic substitution.



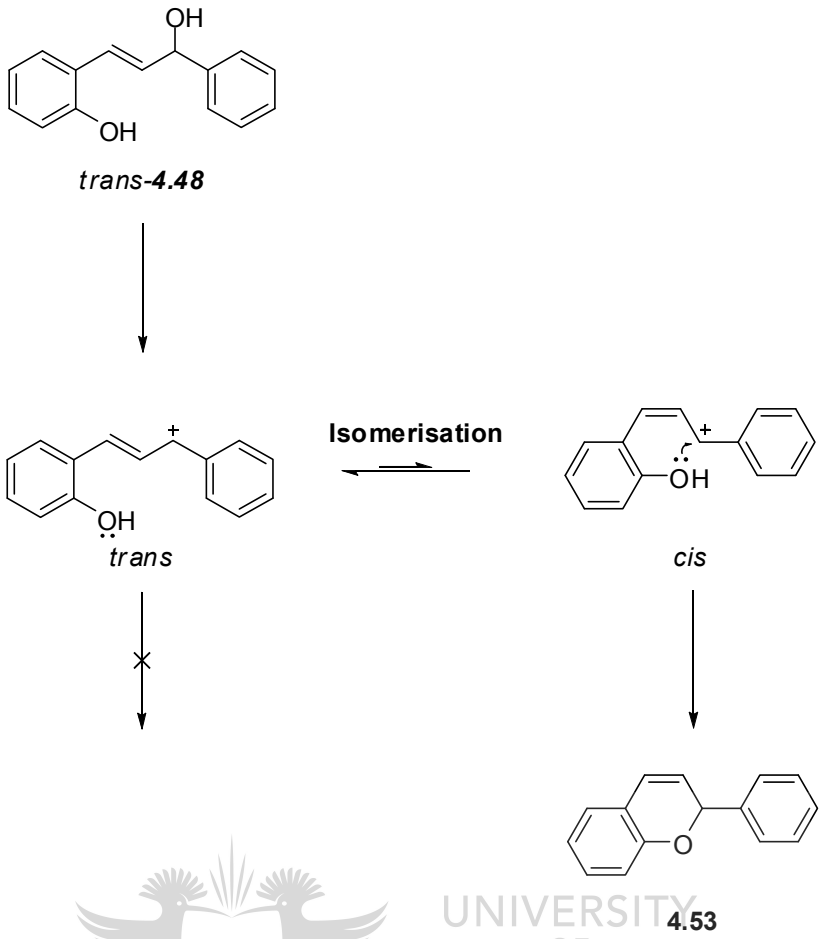
R = Ph, **4.48**
R = 2-naphthyl, **4.51**
R = 4-nitrophenyl, **4.52**

R = Ph, **4.53**, 84%
R = 2-naphthyl, **4.54**, 54%
R = 4-nitrophenyl, **4.55**, 47%

Scheme 4.48 : $Al(OTf)_3$-catalysed cyclisation of diols **4.48**, **4.51** and **4.52** to give the corresponding 2*H*-chromenes **4.53**, **4.54** and **4.55**.

This methodology was extended to diols **4.51** and **4.52** (Scheme 4.48) and found to give the desired 2*H*-chromenes in a moderate yield. This decrease in reaction yield is possibly due to a competing Friedel-Crafts alkylation of the activated phenylic rings to give the corresponding indenes. This is due to activation of the *ortho*-positions towards electrophilic attack of the 2-naphthyl and 4-nitrophenyl rings. Although no attempt was made to isolate these by-products. The use of allylic carbocations in the synthesis of these types of indenes has been reported.[26ab]

Although the starting diol **4.48** had a *trans* double bond configuration the ^{1}H NMR spectrum of **4.53** shows a coupling constant (*J*) for the double bond of 9.9 Hz which indicates a cyclic alkene with a *cis* double bond configuration, as would normally be anticipated for six-membered rings.[13] This implies that nucleophilic attack occurs on the *cis* configured allylic-carbocation (Scheme 4.49). This isomerisation from a *trans* configuration to a *cis* one is required as the *trans* configuration places the allylic-carbocation out of reach for the nucleophilic hydroxyl group. Isomerisation of alkenes is known to be promoted by strong acids.[9] $Al(OTf)_3$ serves as the strong Lewis acid which brings about isomerisation of the alkene during this reaction.

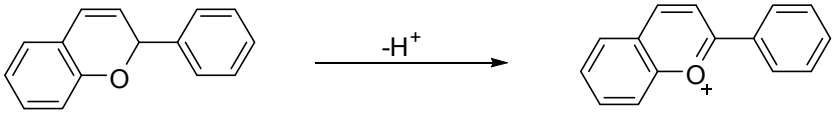


Scheme 4.49 : *trans/cis* Isomerisation of **4.48** and the subsequent cyclisation reaction of the *cis* configuration.

A comparison between the hydroarylation of terminal alkynes[14k,15a,b,c] or the metathesis of alkenes[15d] and the $Al(OTf)_3$-promoted cyclisation reveals that although good yields can be obtained via the other methods, the catalysts are costly and considerably more toxic than $Al(OTf)_3$. Additionally, a comparison to the Petasis-borono-Mannich methodology,[15d,e] which generates boronic acid as a by-product, reveals that the $Al(OTf)_3$ methodology is greener with water being the by-product of the cyclisation. Although other acids have been reported for this cyclisation, they are required in stoichiometric amounts at elevated temperatures[15f] whilst $Al(OTf)_3$ can be used at room temperature in as little as 1 mol%. Traditional Lewis acids have been reported not to catalyse this reaction.[15g] However, a catalytic mixture of Au(I)/AgOTf 5 mol%/15 mol% has been reported[15g] for this reaction, but it is still more expensive and complex than $Al(OTf)_3$ which requires only 1 mol%. Furthermore, $Al(OTf)_3$

has been demonstrated to be recyclable by simple recovery methods which include aqueous extraction and drying under vacuum.[28]

The EI mass spectrum for **4.53** gave an intense signal for a mass of 207. This peak is due to the formation of the flavylium cation and is due to the deprotonation of the benzylic proton and subsequent formation of the oxonium ion which is stabilised due to formation of an aromatic ring (Scheme 4.50). The EI-HRMS for this peak also confirms the formation of the flavylium cation.



4.53 **Flavylium cation**

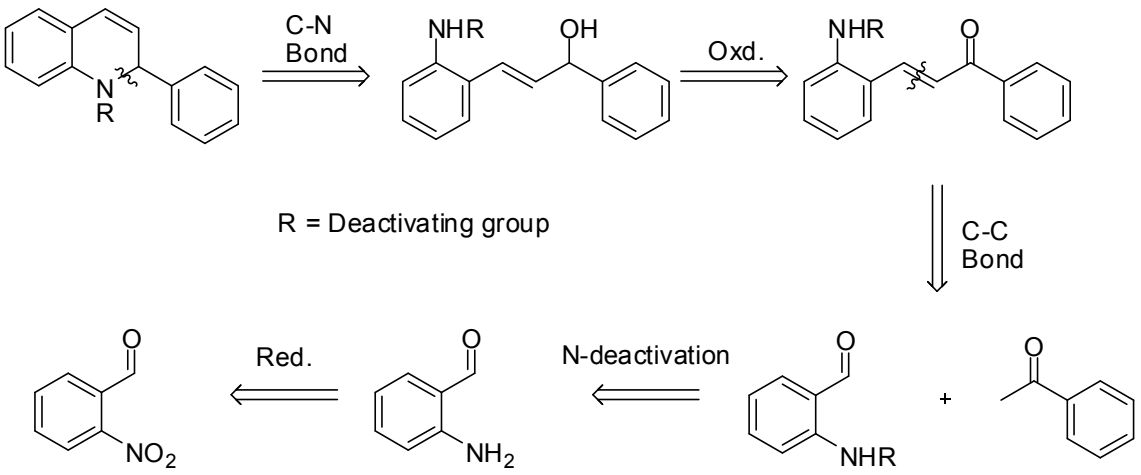
Scheme 4.50 : Flavylium cation formation from **4.53** as observed in the EIMS of **4.53**.

4.5.3 Intramolecular cyclisation utilising a nitrogen nucleophile

4.5.3.1 Retrosynthetic analysis for 2-phenyl-1,2-dihydroquinoline

The retrosynthetic analysis (Scheme 4.51) for 2-phenyl-1,2-dihydroquinoline involved a C-O bond cleavage to the "activated" chalcone type alcohol which could be obtained via the reduction of a suitable 2-aminochalcone. This 2-aminochalcone could be formed via the C-C bond forming reaction between a suitable 2-aminobenzaldehyde and the corresponding acetophenone. The suitable 2-aminobenzaldehyde could be obtained from the corresponding 2-nitrobenzaldehyde.

Previous work in the present study (Section 4.3) had established that in the presence of a free amine group such as aniline, no nucleophilic substitution of the "activated" alcohol occurred due to deactivation of the $Al(OTf)_3$. Deactivation of the amine through tosylation or acetylation allowed for carbocation formation. However, only a sterically un-encumbered primary sulfonamide was able to react under these conditions. Deactivation of the amine group on the 2-aminochalcone was presumed to thus be necessary to see reactivity of the alcohol towards nucleophilic attack, even given the intramolecular nature of the proposed transformation. It was hoped that the proximity of the deactivated amine in relation to the intermediate carbocation would lead to reactivity towards nucleophilic substitution by the amine despite previous work suggesting potential problems.

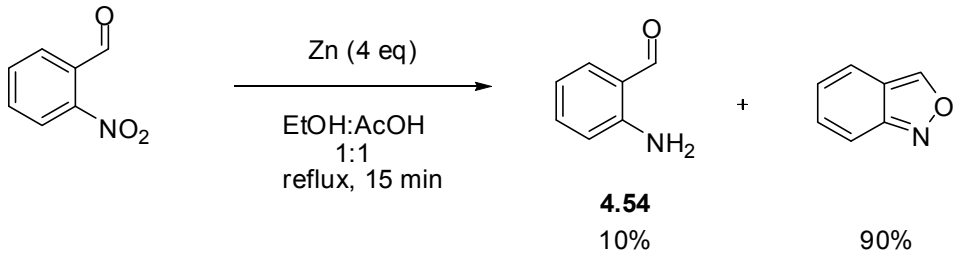


Scheme 4.51 : Retrosynthetic analysis for the "activated" alcohol to be used for the synthesis of the 1,2-dihydroquinoline.

4.5.3.2 Reduction of 2-nitrobenzaldehyde and the amine group deactivation

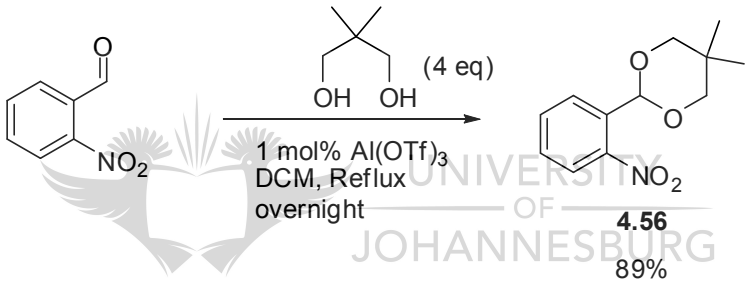
2-Nitrobenzaldehyde was chosen as the starting material for the synthesis of the 2-aminochalcone derived alcohol. This was because of the ready availability of 2-nitrobenzaldehyde, which presented a nitrogen atom in the desired 2-position on the phenyl ring. It was hoped that the desired 2-aminobenzaldehyde could be obtained via a selective reduction of the nitro group to the amine.

One of the most widely utilised methods for the reduction of aromatic nitro groups is the use of Zn(0) metal with an acid.[3] 2-Nitrobenzaldehyde was reacted with zinc metal in an acidic ethanol acetic acid mixture (Scheme 4.52). This gave the desired amino benzaldehyde in only a 10% yield with the rest of the product being insufficiently reduced and being present in the form of the benzo[c]isoxazole product shown in Scheme 4.52. This by-product was identified via comparison of the ^{1}H NMR spectrum with literature precedent.[27a] The 2-aminobenzaldehyde was found to be inseparable from the benzo[c]isoxazole. The acetic acid used in the reduction step was replaced by ammonium formate which has been reported for use with zinc for the reduction of aromatic nitro groups.[27b] This methodology failed to yield the desired 2-aminobenzaldehyde in appreciable yield giving similar results to the acetic acid-promoted reduction. It was noted that the reaction was very exothermic, generating significant amounts of heat.



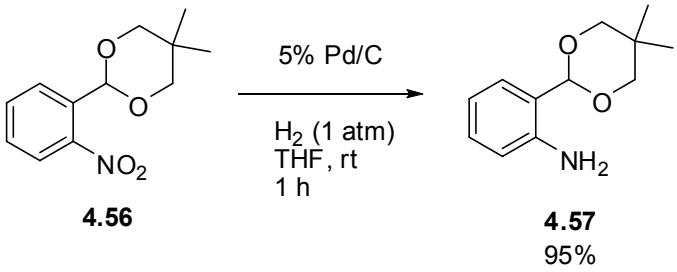
Scheme 4.52 : Zn reduction of 2-nitrobenzaldehyde.

In an attempt to preclude the intervention of the aldehydre group in the desired reactions, it was protected as the cyclic acetal by reaction with 2,2-dimethylpropane-1,3-diol (Scheme 4.53) to give **4.56**. $Al(OTf)_3$ has been reported[28] to catalyse the cyclic acetal formation reaction from the corresponding diol and aldehyde and was found to give the desired acetal in a high yield (Scheme 4.53).



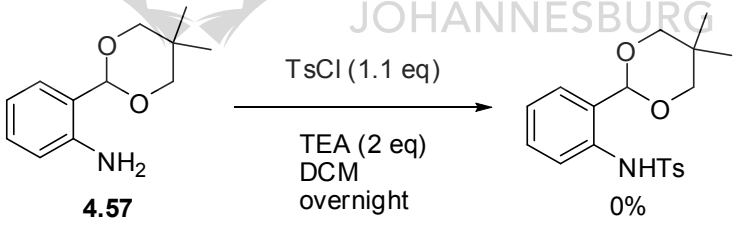
Scheme 4.53 : $Al(OTf)_3$ catalysed cyclic acetal protection of 2-nitrobenzaldehyde.

The cyclic acetal protected **4.56** was then subjected to reduction via the zinc/acetic acid reduction conditions. This gave a mixture of reaction products with no appreciable yield of the desired amine. This may be due to the removal of the acetal group by the acidic conditions present in the reaction mixture. It was thought that neutral reaction conditions were required to facilitate the reduction of the nitro-group without promoting subsequent reactions with the aldehyde functionality. For this reason, palladium on carbon under a hydrogen atmosphere was chosen for the next attempted reduction reaction. The reduction of cyclic acetal **4.56** to the corresponding amine has been reported.[29] This reaction gave the desired amine **4.57** in a high yield (Scheme 4.54).



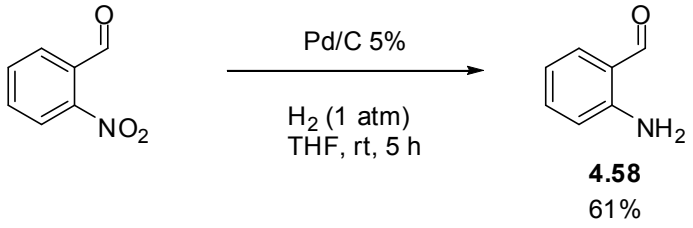
Scheme 4.54 : Pd/C promoted reduction of cyclic acetal **4.56** to **4.57.**

Now that the reduction of the nitro-group to the corresponding amine had been achieved it was thought to tosylate the amine so as to deactivate it before deprotection of the cyclic acetal was performed. Tosylation of an amine results in the formation of a sulfonamide, in which electron withdrawal from the amine by the sulfonyl group occurs to the extent that the amine actually becomes mildly acidic.[3] This would ensure the stability of the 2-aminobezaldehyde adduct as the deactivated amine would not be able to react with the aldehyde functionality. Reaction of amine **4.57** with tosylchloride in the presence of a base (Scheme 4.55) failed to yield the tosylated product, perhaps due to the steric bulk of the cyclic acetal group which prevents the tosylation step.



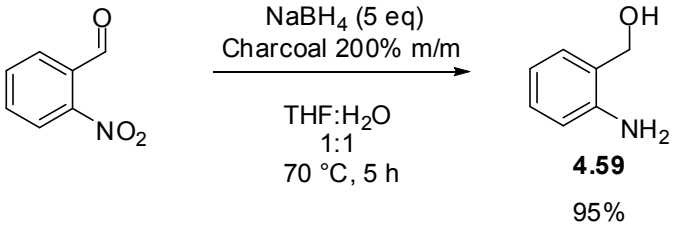
Scheme 4.55 : Tosylation of amine **4.57**.

Following the failure of the tosylation of amine **4.57** it was decided to investigate the selective reduction of 2-nitrobenzaldehyde directly via the Pd/C hydrogen system (Scheme 4.56). This gave the desired 2-aminobenzaldehyde **4.58** in a 61% yield. This reaction was initially performed on a 200 mg scale. Upon scale up to the 2 g scale the reaction yield dropped drastically giving only 10% of the desired amine **4.58**. This is presumably due to reaction of the amine functionality with the aldehyde functionality. In addition to this the 2-aminobenzaldehyde **4.58** was found to not be particularly stable. So although it was possible to obtain 2-aminobenzaldehyde it was thought that stability would be an issue in subsequent reactions.



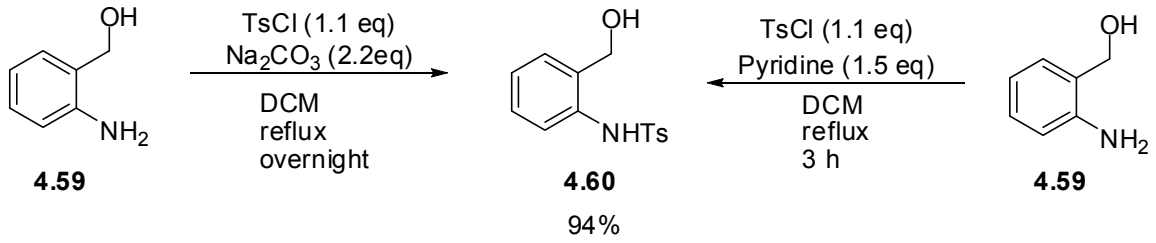
Scheme 4.56 : Pd/C promoted reduction of 2-nitrobenzaldehyde to 2-aminobenzaldehyde **4.58**.

From these preliminary investigations it was apparent that it was not favourable to have the amine and the aldehyde functionality present on the molecule at the same time. It was thus thought to fully reduce 2-nitrobenzaldehyde to the corresponding amino alcohol. This would make it possible to deactivate the amine before reintroduction of the aldehyde functionality. The reduction of 2-nitrobenzaldehyde to 2-aminobenzyl alcohol has been reported.[30a] This was accomplished via the $NaBH_4$/charcoal reduction in a H_2O/THF mixture to give the *ortho*-aminobenzyl alcohol in a high yield (Scheme 4.57). It is known that $NaBH_4$ can be used to reduce aldehydes to the corresponding alcohols, but this reagent will not normally reduce an aromatic nitro group to the corresponding amine.[30a] There has been a review for the use of sodium borohydride in conjunction with metal halides or salts for the reduction of aromatic nitro-groups.[30b] It is also known that Pd/C with $NaBH_4$ can be used.[30c] The work by Zeynizadeh *et al.* reported the use of carbon in the form of activated charcoal to promote the reduction of aromatic nitro-groups with $NaBH_4$, without other promoters being present[30a] It must be noted that this reaction required the presence of H_2O in order to proceed. The authors suggested that the addition of water to the reaction facilitated the slow release of hydrogen gas throughout the reaction period. The carbonyl reduction proceeds via the hydride attack whilst the nitro reduction presumably proceeds via a reaction with hydrogen that is slowly released throughout the course of the reaction.



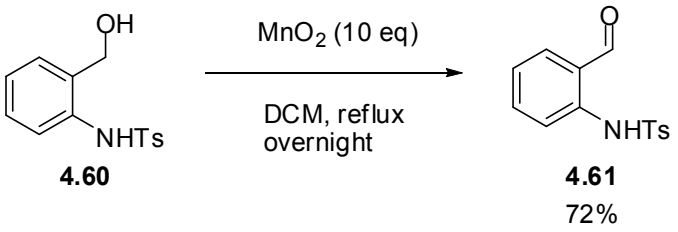
Scheme 4.57 : $NaBH_4$/charcoal reduction of 2-nitrobenzaldehyde to give amino benzylalcohol **4.59**.

2-Aminobenzyl alcohol **4.59** could be tosylated without difficulty to provide **4.59** (Scheme 4.58). This could be accomplished via the use of Na_2CO_3 as the base or alternatively via the literature reported use of pyridine as the base.[31] Isolation of **4.60** was simplified by the acidic nature of the amine which made it possible to remove the parent amine **4.59** via an acid extraction whilst **4.60** could be isolated via a base extraction and subsequent neutralisation reaction. This made it straightforward to synthesise **4.60** on a relatively large scale (2 g).



Scheme 4.58 : Tosylation of 2-aminobelzylacohol **4.59**.

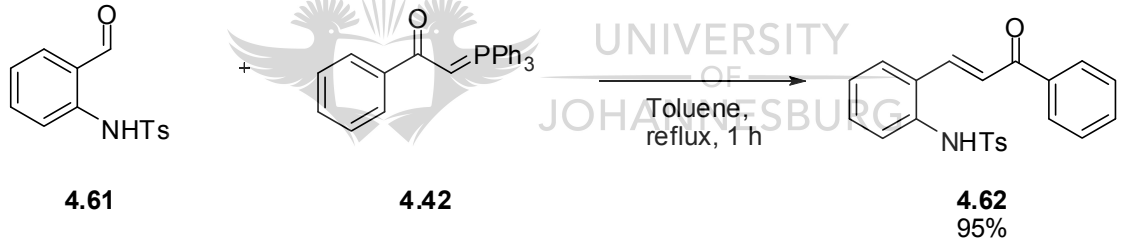
Manganese dioxide has been reported as an oxidant for the oxidation of allylic and benzylic alcohols to the corresponding aldehydes.[32a] Initial oxidation of **4.60** with 4 molar equivalents of MnO_2 gave low yields. This oxidising agent is known for its erratic yield of oxidised product which is often due to the preparation method of the MnO_2.[32a] The MnO_2 was then activated via a literature procedure[32b] which entailed washing the MnO_2 with nitric acid, then water then 1% aqueous sodium bicarbonate and then water again. The MnO_2 was then dried to a constant weight at 120 °C. The reaction was repeated with 4 molar equivalents of the oxidant and the yield was only slightly higher. Oxidation was taking place, just not to the extent that was desired. The molar equivalents of MnO_2 was then increased to 10 and the reaction repeated and aldehyde **4.61** was obtained in a high yield (Scheme 4.59). This 2-tosylamino-benzaldehyde **4.61** was found to be stable, unlike 2-aminobenzaldehyde **4.58**. The MnO_2 oxidation, although lengthy and requiring 10 equivalents of the oxidant, is significantly less complicated than other oxidation methods such as the Swern or Jones oxidation. High yields were obtainable via this method and so additional oxidation methods were not investigated.



Scheme 4.59 : Oxidation of alcohol **4.60** to aldehyde **4.61**.

4.5.3.3 2-Tosylaminochalcone synthesis

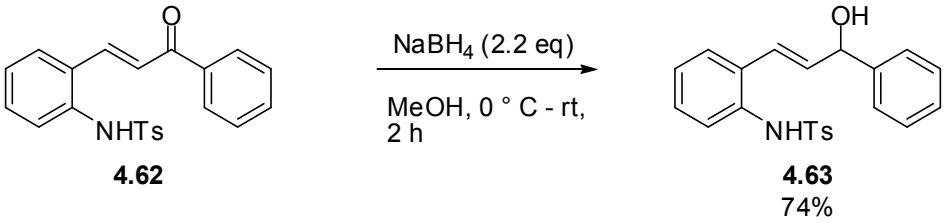
Previous syntheses of the 2-hydroxychalcones (Section 4.4.2.2) via the Wittig reaction of salicylaldehyde with the corresponding Wittig ylide were successful. It was decided to perform a similar Wittig reaction on the 2-tosylaminobenzaldehyde **4.61** (Scheme 4.60). This gave the desired 2-tosylaminochalcone in a high yield. The ^{1}H NMR spectrum of this product once again revealed the *trans*-configuration of the double bond with a coupling constant (*J*) of 15.6 Hz.



Scheme 4.60 : 2-Tosylaminochalcone synthesis from the corresponding aldehyde **4.61** and Wittig ylide **4.42**.

4.5.3.4 2-Tosylaminochalcone reduction

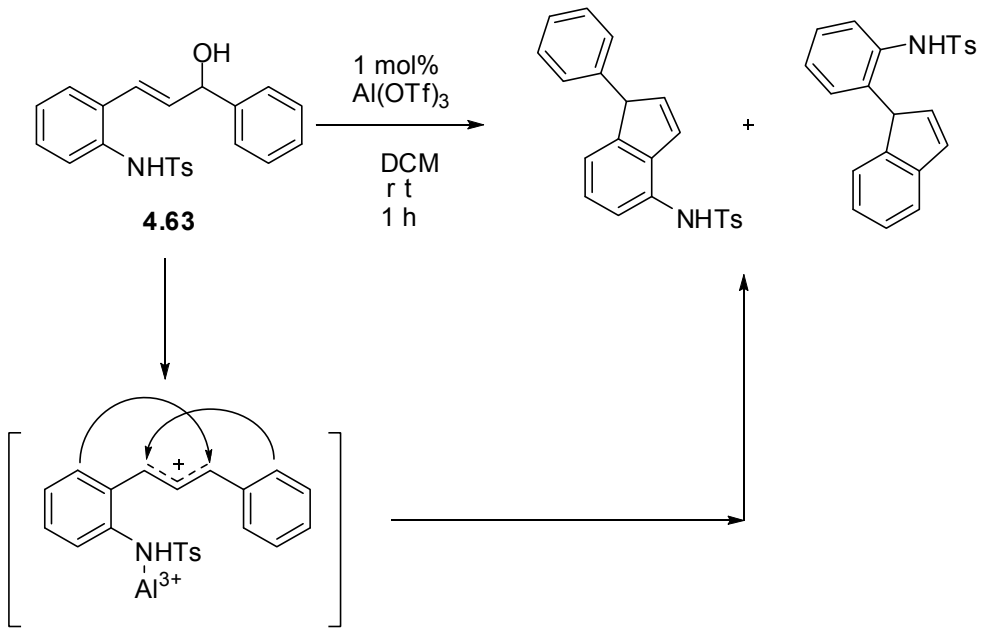
The initial reduction of 2-tosylaminochalcone **4.62** was performed with only 1.2 equivalents of $NaBH_4$ for 1 hour and gave a moderate yield of 52%. The tosylated amine is slightly acidic and it was once again thought that degradation of the $NaBH_4$ was occurring which was the case for the reduction of the 2-hydroxychalcones. In order to overcome this degradation 1.2 equivalents of $NaBH_4$ initially used was increased to 2.2 equivalents, which were added in two separate portions 1 hour apart (Scheme 4.61). This mitigated the degradation of $NaBH_4$ significantly and gave the desired "activated" alcohol in a good yield.



Scheme 4.61 : $NaBH_4$ reduction of 2-tosylaminochalcone **4.62** to give the "activated" alcohol **4.63**.

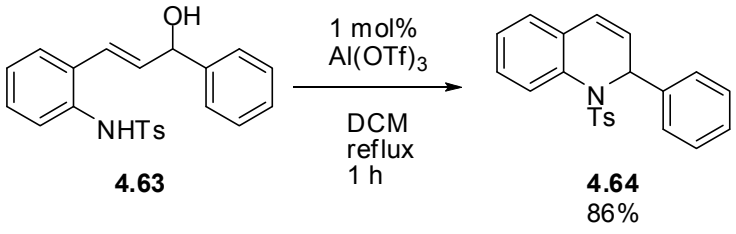
4.5.2.4 Cyclisation of the "activated" alcohol with a nitrogen nucleophile

The cyclisation of the 2-hydroxychalcone derived alcohols could be performed at room temperature utilising only 1 mol% $Al(OTf)_3$ (Scheme 4.48). This methodology was applied to the tosylamino derivative **4.63** (Scheme 4.62). However, after 1 hour of reaction time complete consumption of the starting alcohol **4.63** was observed, but with the formation of a complex mixture of reaction products with no appreciable yield of the desired product. This suggested that the intermediate carbocation was indeed forming but it was not reacting with the deactivated amine functionality. In the absence of a suitable nucleophile the carbocation could possibly be reacting with the *ortho*-positions of the aromatic rings in a Friedel-Crafts type alkylation reaction to give the indene derivatives. Once again no attempt was made to isolate these reaction products. As has been mentioned this type of reaction for allylic-carbocations has been reported.[26a,b] This simply reflects the reactive nature of these carbocations.



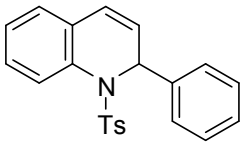
Scheme 4.62 : Proposed $Al(OTf)_3$ catalysed cyclisation of **4.63** to the possible indene derivatives.

In an attempt to overcome the unreactivity of the tosylamine group the reaction was repeated, counterintuitively, at an increased reaction temperature (Scheme 4.63). This gave the desired 1,2-dihydroquinoline **4.64** in a high yield. The non-reactivity of the tosylamine at lower temperatures could possibly be explained by the complexation of the tosylamine to an Al^{3+} cation (Scheme 4.62). This would withdraw significant electron density from the nitrogen of the amine rendering it unreactive as a nucleophile. At elevated temperatures it would be possible for this complex to have a significant equilibrium with the uncomplexed tosyl amine, which was sufficiently nucleophilic to attack the intermediate carbocation.

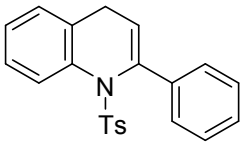


Scheme 4.63 : $Al(OTf)_3$ catalysed cyclisation of **4.63** to the corresponding 1,2-dihydroquinoline **4.64**.

The structure of 2-phenyl-1,2-dihydroquinoline **4.64** was confirmed by 2-D NMR experiments. It was possible for the reaction to form one of two products, which could possibly also interconvert via an isomerisation process (Scheme 4.64). This 1,4-dihydroquinoline product would show CH_2 signals on a DEPT NMR analysis. However, the absence of any CH_2 signals indicated that the product was in fact the 1,2-dihydroquinoline that had formed and not the 1,4-dihydroquinoline.



4.64



1,4-dihydroquinoline

Scheme 4.64 : Potential isomerisation of 1,2-dihydroquinoline **4.64** to the 1,4-dihydroquinoline.

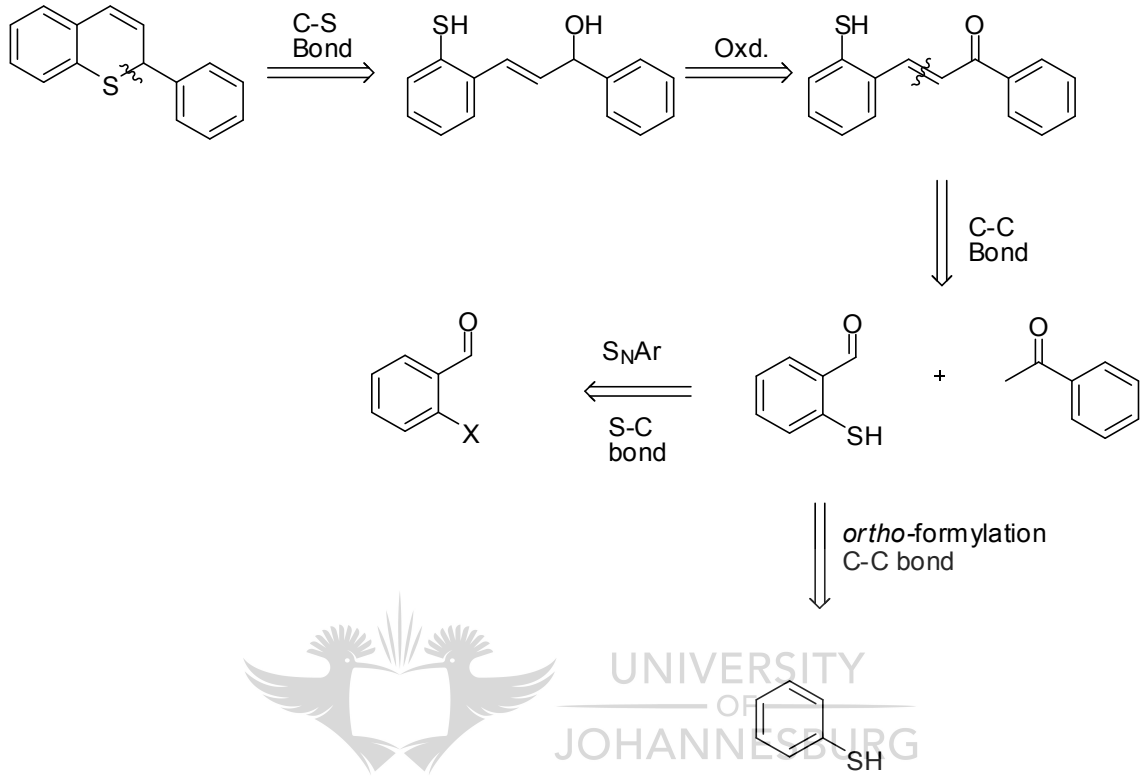
The thermolytic electrocyclisation of *N*-methyl-2-hydroxyalkylanilines[18a] and the intramolecular cyclisation of *ortho*-(1-hydroxy-2-alkenyl)phenyl isocyanides with $BF_3{\cdot}OEt_2$[18b] gave lower yields for 1,2-dihydroquinolines when compared to the $Al(OTf)_3$ methodology. Although there has been a report of a Lewis acidic $AuCl_3/AgSbF_6$ system[18c] being useful for the cyclisation of alcohols with tosylamines, in terms of catalyst loading and cost it is inferior to the $Al(OTf)_3$ catalysed system. Notably this report also mentioned the failure of traditional Lewis acids for this reaction.[18c]

4.5.4 Intramolecular cyclisation utilising a sulfur nucleophile

4.5.4.1 Retrosynthetic analysis for 2-phenyl-2*H*-thiochromene

The retrosynthetic analysis of 2-phenyl-2*H*-thiochromene (Scheme 4.65) entails a C-S bond disconnection to give the "activated" chalcone type alcohol which could be obtained from the corresponding 2-mercaptochalcone. This 2-mercaptochalcone could be disconnected through a C-C bond disconnection to acetophenone and 2-mercaptobenzaldehyde. The 2-mercaptobenzaldehyde could possibly be obtained from an S_NAr reaction of a suitable 2-substituted benzaldehyde. Alternatively, *ortho*-formylation of thiophenol could yield the desired 2-mercaptobenzaldehyde. Previous results for the nucleophilic substitution of

"activated" alcohols with a thiol nucleophile gave good results (Sections 4.4.1 and 4.4.2). It was anticipated that if the "activated" chalcone type alcohol bearing the thiol group could be synthesised there would not be an issue with $Al(OTf)_3$ catalysed cyclisation to the corresponding 2*H*-thiochromene.



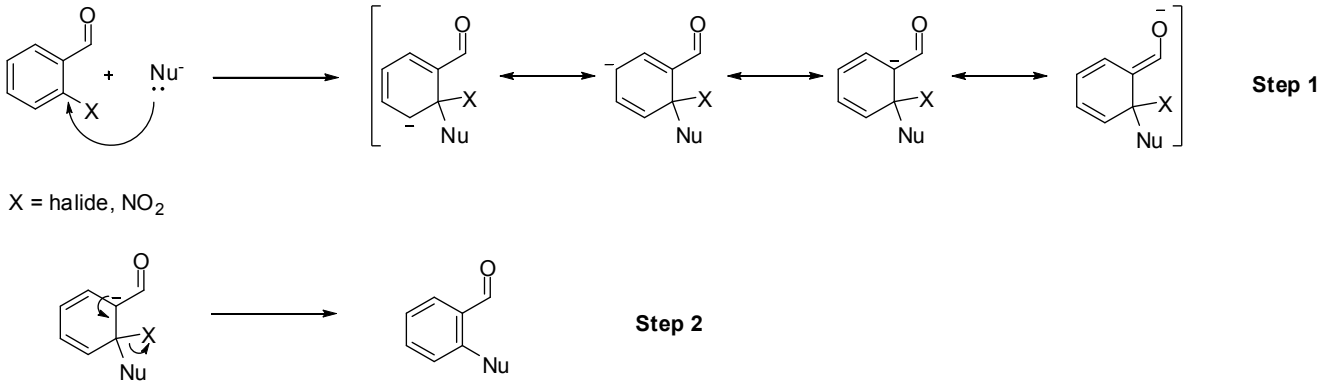
Scheme 4.65 : Retrosynthetic analysis for the formation of the "activated" alcohol to be used for the synthesis of 2-phenyl-2*H*-thiochromene.

4.5.4.2 Synthesis of 2-mercaptobenzaldehyde

4.5.4.2.1 Synthesis of 2-mercaptobenzaldehyde via S_NAr chemistry

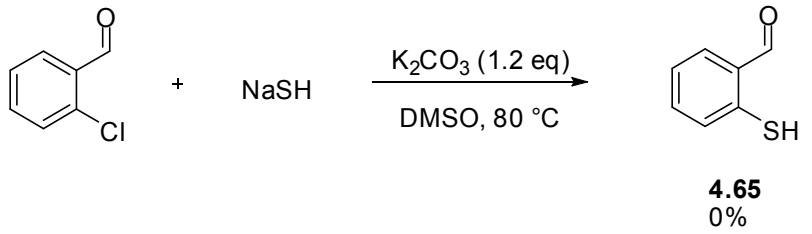
2-Chlorobenzaldehyde was chosen as a substrate on which to perform S_NAr chemistry with a thiol nucleophile. An *ortho*-substituted benzaldehyde with an electron withdrawing group in the *ortho*-position is a good candidate for an S_NAr reaction due to the stability imparted during the intermediate reaction steps (Scheme 4.66).[3] The first step involves the attack of the nucleophile onto the *ortho*-position to give the ring carbanion. This carbanion is stabilised through resonance, and the carbonyl group with its electron withdrawing nature is of particular help in this regard (Scheme 4.66). The first step of this reaction is the rate determining step, not least of which because of the loss of aromaticity.[3] It is important to note

that the leaving group ability is different when compared to aliphatic nucleophilic substitution. The approximate order of leaving group ability is as follows F >NO_2> OTs >SOPh>Cl, Br, I > N_3> NR_3^+>OAr, OR, SR, NH_2.[33] From this evaluation it would have been best to utilise 2-fluorobenzaldehyde for this reaction. However, 2-nitrobenzaldehyde and 2-chlorobenzaldehyde were readily available. Initial reactions with 2-nitrobenzaldehyde were not successful and it was decided to continue with 2-chlorobenzaldehyde.



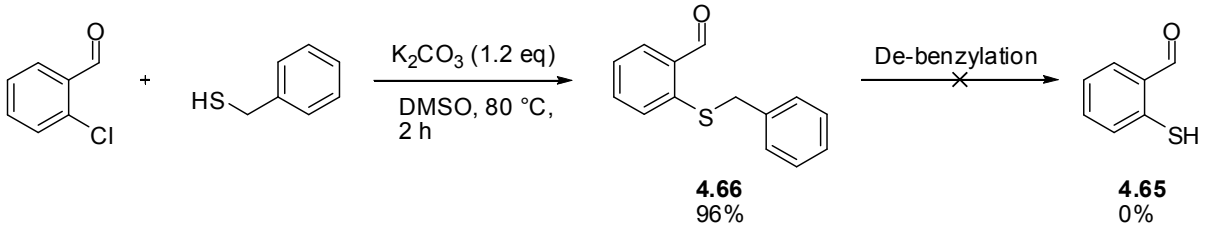
Scheme 4.66 : S_NAr mechanism for *ortho*-substituted benzaldehydes

Sodium sulfhydride (NaSH) can be used as a nucleophile in nucleophilic substitution reactions.[3] The nucleophilic aromatic substitution of 2-chlorobenzaldehyde by sodium sulfhydride was attempted (Scheme 4.67) in DMSO. This failed to give the desired 2-mercaptobenzaldehyde. It was initially thought the sodium sulfhydride was not dissolving in the reaction mixture and 10 mol% TBAB was added to the reaction mixture as a phase transfer catalyst. However, this did not lead to the desired nucleophilic aromatic substitution reaction. It was noted that the addition of the sodium sulfhydride to the reaction mixture gave an intense yellow colour. The sodium sulfhydride was thought to be decomposing before it could react as a nucleophile. No attempts were made to investigate this further in order to counteract this degradation.



Scheme 4.67 : Nucleophilic aromatic substitution of 2-chlorobenzaldehyde by sodium sulfhydride.

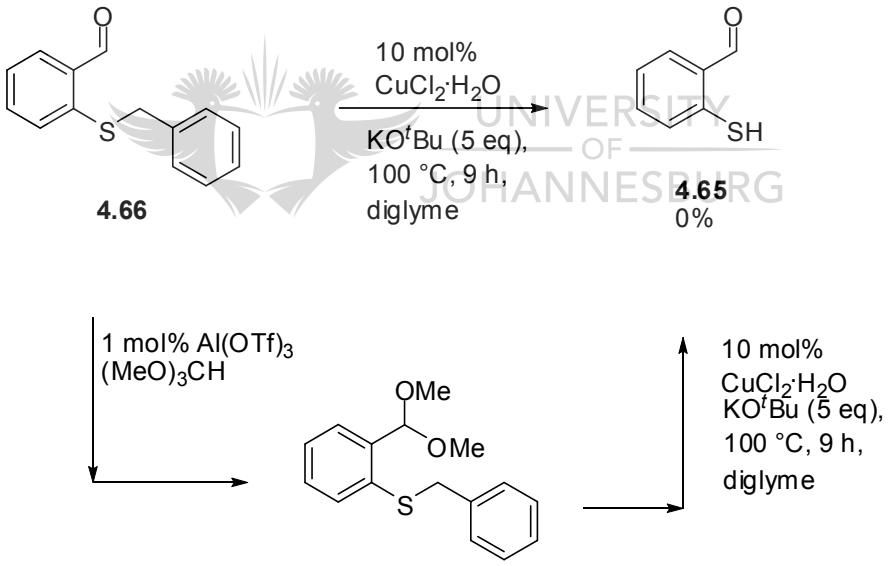
The nucleophilic aromatic substitution of 2-chlorobenzaldehyde by benzylmercaptan in DMSO gave **4.65** in a high yield (Scheme 4.68). The reasoning behind this approach was to introduce a sulfur functionality that was attached to a group that could be removed later in the synthesis to yield the desired 2-mercaptobenzaldehyde or 2-mercaptochalcone. This organosulfur nucleophile (benzylmercaptan) functioned well in the nucleophilic aromatic substitution reaction where the sodium sulfhydride nucleophile had failed. This type of approach to obtaining 2-mercaptobenzaldehyde has been previously reported.[34] However, the reported approach utilised 2-nitrobenzaldehyde for the nucleophilic aromatic substitution step, the product of which was subsequently debenzylated to give the corresponding 2-mercaptobenzaldehyde.



Scheme 4.68 : Nucleophilic aromatic substitution of 2-chlorobenzaldehyde by benzylmercaptan and subsequent de-benzylation to 2-mercaptobenzaldehyde.

The de-benzylation of benzylthioethers has been performed with Na in NH_3,[35a] Li in NH_3/THF[35b] as well as Na in boiling ethyl alcohol.[35c] These procedures seemed to be too harsh for the aldehyde functionality and a milder approach was investigated for the de-benzylation of **4.66**. This entailed the reaction of the thioether in the presence of excess KO^{t}Bu with the soft Lewis acid, $CuCl_2 \cdot 2H_2O$.[35d] This procedure reported the de-benzylation

of benzyl(phenyl)sulfane to the corresponding thiophenol in 62% yield in 9 hours at 115 °C. This methodology was applied to **4.66** (Scheme 4.69) but did not give the desired 2-mercaptobenzaldehyde **4.65** in any appreciable yield. It was noted that the starting thioether **4.66** was completely consumed during the reaction to give a mixture of reaction products. It was then thought to protect the carbonyl functionality as the corresponding acetal. This was done by an $Al(OTf)_3$ catalysed reaction between **4.66** and excess trimethylorthoformate.[28] The intermediate acetal was not isolated but complete conversion to the acetal was confirmed via ^1H NMR spectroscopy. The de-benzylation procedure was repeated and an acidic workup was incorporated into the procedure to hydrolyse the acetal (Scheme 4.69). This did not yield the 2-mercaptobenzaldehyde at all, although complete consumption of the starting **4.66** was noted. It was thus apparent that the combination of a (masked) carbonyl and thiol functionality on the aromatic ring was leading to an unstable product. Indeed it has been reported that these type of thiols are unstable and rigorous purification often results in further decomposition.[36a,b]



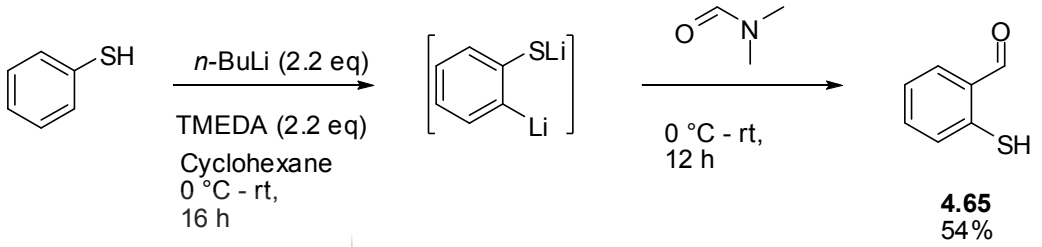
Scheme 4.69 : Attempted de-benzylation of **4.66** to give 2-mercaptobenzaldehyde **4.65**.

4.5.4.2.2 Synthesis of 2-mercaptobenzaldehyde via *ortho*-formylation of thiophenol

A different approach was needed for the formation of the desired 2-mercaptobenzaldehyde. The reduction of 2-mercaptobenzoic acid and subsequent oxidation to the desired 2-mercaptobenzaldehyde has been reported.[36a,c] This route was considered, however, upon investigation of the methods for making 2-mercaptobenzoic acid, the *ortho*-lithiation of

thiophenol and subsequent trapping of the carbon nucleophile with CO_2 to give the corresponding 2-mercaptobenzoic acid was found.[37a] Further investigation revealed a procedure whereby the intermediate lithiated thiophenol is trapped with DMF to give the *ortho*-formylated thiophenol.[37b]

Thiophenol was *ortho*-lithiated with 2.2 equivalents of *n*-BuLi in the presence of TMEDA, this *ortho*-lithiated thiophenol was then quenched with excess DMF to give 2-mercaptobenzaldehyde in a moderate yield (Scheme 4.70). It was important for the *ortho*-lithiation to be performed in cyclohexane with 2.2 equivalents of TMEDA. As this non-polar unreactive solvent favours coordination of the lithium cations, already coordinated to the TMEDA, to the benzenethiolate anionic sulfur to give the *ortho*-di-lithiated species.[37a]

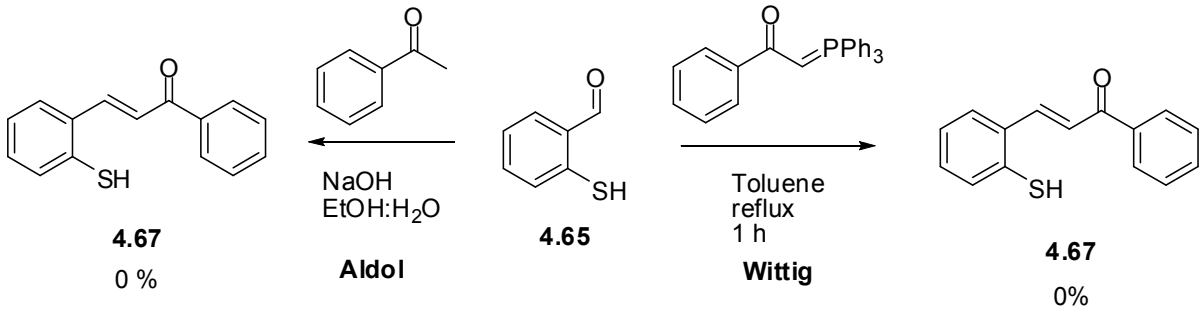


Scheme 4.70 : *ortho*-Lithiation of thiophenol and subsequent reaction with DMF to give 2-mercaptobenzaldehyde **4.65**.

4.5.4.3.2 2-Mercaptochalcone synthesis

Now that 2-mercaptobenzaldehyde **4.65** had been obtained the synthesis of 2-mercaptochalcone **4.67** was attempted. Initially a Wittig reaction was performed (Scheme 4.71) as this had been successful previously in the synthesis of the 2-hydroxychalcones. However this failed to give the desired 2-mercaptochalcone. As has been mentioned 2-mercaptobenzaldehyde is not a stable molecule.[36a,c] Decomposition was in all likelihood occurring at the elevated temperatures required for the Wittig reaction. This could possibly have been overcome by performing the reaction at lower temperatures for longer reaction times. An Aldol condensation was then attempted between 2-mercaptobenzaldehyde **4.65** and acetophenone (Scheme 4.71). This reaction failed to yield the desired 2-mercaptochalcone **4.67**. It was thought that the reaction was failing for similar reasons as noted for the Aldol condensation between salicylaldehyde and acetophenone (Section 4.4.2.2). Although a more thorough investigation into the synthesis of 2-mercaptochalcone could have been performed

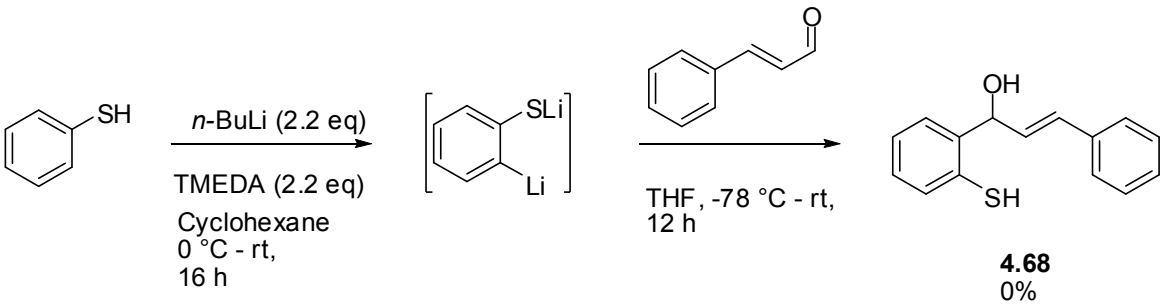
it was thought that the inherent instability of this system would prove problematic in terms of isolation and subsequent reactions. This route to obtaining the 2*H*-thiochromenes was thus abandoned due to the inherent instability of a molecule containing both a thiol and carbonyl functionality.



Scheme 4.71 : Attempted Aldol and Wittig reaction of **4.65** in an attempt to synthesise 2-mercaptochalcone **4.67**.

4.5.4.4 Attempted reaction of *ortho*-lithiated thiophenol with cinnamaldehyde to give the "activated" 2'-mercaptochalcone derived alcohol

A completely different approach was then taken. The *ortho*-lithiation of thiophenol had been accomplished. It was decided to react the *ortho*-lithiated thiophenol with cinnamaldehyde. This failed to give the corresponding alcohol **4.68** (Scheme 4.72). In the previous quenching of the *ortho*-lithiated thiophenol with DMF, it was possible to add the DMF neat to the reaction mixture at 0 °C. However, in the case of cinnamaldehyde this addition method proved problematic. This is due to the low solubility of cinnamaldehyde in cyclohexane which causes the cinnamaldehyde to freeze to the sides of the reaction vessel and thus not react with the lithiated thiophenol. In an attempt to overcome this cinnamaldehyde was first dissolved in THF and then added to the *ortho*-lithiated thiophenol. This addition of the electrophile was performed at -78 °C in order to limit side-reactions. This process also failed to yield the desired alcohol **4.68** in any yield. It was noted that thiophenol was completely consumed during these reactions and not detected in the crude reaction mixture. However, the *trans*-cinnamaldehyde was recovered in near quantitative yields. The limited solubility of the *trans*-cinnamaldehyde in the required cyclohexane reaction solvent was thought to be the main reason for the failure of this reaction.

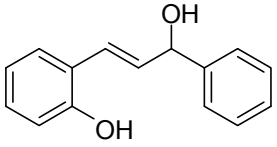
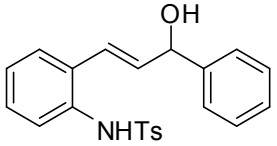


Scheme 4.72 : Attempted *ortho*-lithiation of thiophenol and subsequent reaction with cinnamaldehyde to give the 2'-mercaptochalcone derived "activated" alcohol **4.68**.

4.5.5 Comparison of the yields for the cyclised products starting from the starting aldehydes

The overall yields for the cyclised products from the corresponding aldehyde were then compared and the results summarised in Table 4.13.

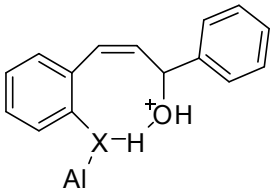
Table 4.13 : Comparison of yield for the cyclised products starting from the corresponding aldehydes.

Entry	"Activated" alcohol	Steps from the corresponding aldehyde	Yield (%) for the alcohol from the aldehyde	$Al(OTf)_3$ cyclisation Yield (%)	Overall Yield (%) after cyclisation
1	 **4.48**	2	61	84	51
2	 **4.62**	2	70	86	60

The cyclisation of **4.48** could be performed at room temperature for 1 hour whilst the cyclisation of **4.62** required higher reaction temperatures and longer reaction times. This can possibly be explained by the complexation of the $Al(OTf)_3$ to the heteroatomic atom on the chalcone structure to give an Lewis assisted Brønsted acid (Figure 4.1). Complexation of the

$Al(OTf)_3$ to the heteroatom would increase the acidity of the hydrogen attached to the heteroatom. This hydrogen with its increased acidity would protonate the "activated" alcohol thus generating the required leaving group ($-OH_2^+$) to form the carbocationic intermediate.

For the 2-hydroxychalcone structure **4.48** this complexation would be strong due to the favourable hard/hard Lewis acid/base complex formation between $Al(OTf)_3$ and the aromatic hydroxyl group.[10] Although nitrogen is also considered a hard Lewis base and complexation to the hard $Al(OTf)_3$ acid should occur readily, the acid base pair that would form between the tosylamine of **4.62** and $Al(OTf)_3$ would not be as acidic due to the increased basic nature of the amine compared to the aromatic hydroxyl group of 2-hydroxychalcone **4.48**. This is seen by the increased reaction temperature required for the cyclisation of **4.62**.



X = O, NTs

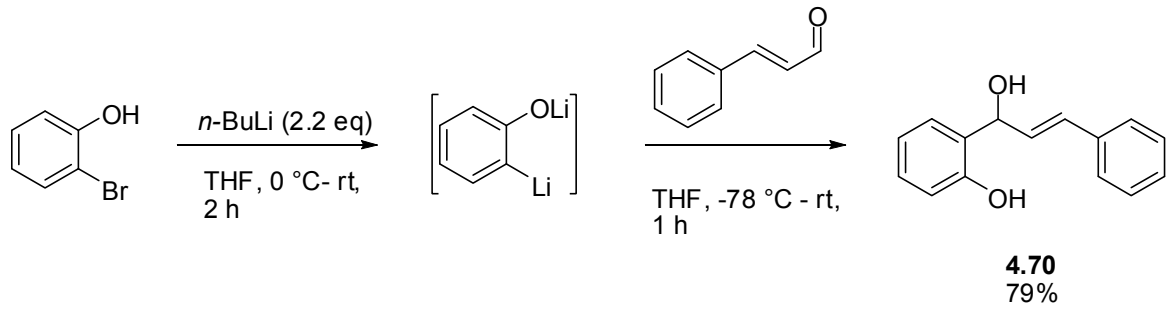
Figure 4.1 : Possible Lewis assisted Brønsted acidic intermediate.

4.5.6 Intramolecular cyclisation utilising an oxygen nucleophile revisited

4.5.6.1 Synthesis of 2'-hydroxychalcone utilising the *ortho*-lithiation of a phenol

The question had been raised as to the position of the leaving hydroxyl group on the allylic moiety during the attempts to synthesise the precursor 2-mercaptochalcone. It was decided to revisit the cyclisation of an "activated" alcohol with an oxygen nucleophile with the leaving hydroxyl group in the wrong position.

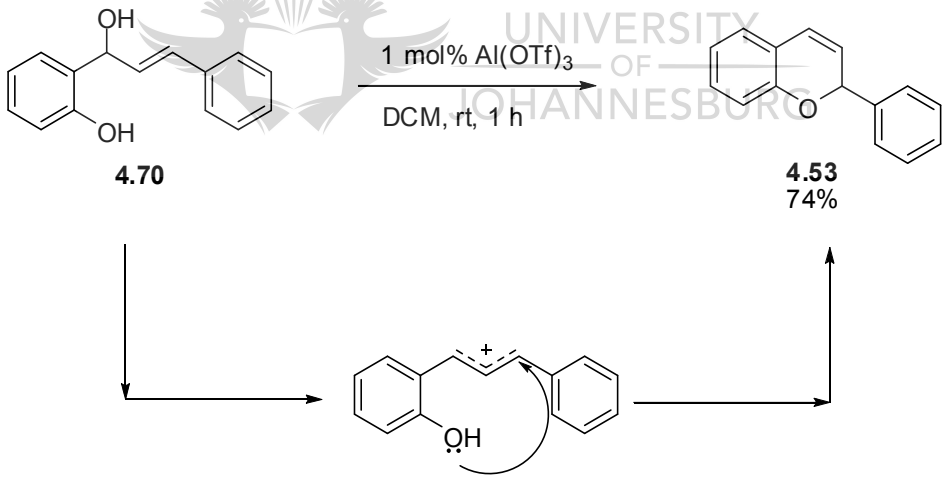
The 2'-hydroxychalcone type alcohol was synthesised in a high yield from 2-bromophenol via halogen lithium exchange and subsequent reaction with *trans*-cinnamaldehyde (Scheme 4.74). It was possible to obtain the desired 2'-hydroxychalcone in only one step from the corresponding 2-bromophenol (Scheme 4.74). The one step yield of 79% is a significant improvement over the two step, Wittig reaction/$NaBH_4$ reduction, yield of 61% (Table 4.13).



Scheme 4.73 : Lithiation of 2-bromphenol and subsequent reaction with cinnamaldehyde to give the 2'-hydroxychalcone type alcohol **4.70**.

4.5.6.2 Al(OTf)$_3$ catalysed cyclisation of 2'-hydroxychalcone type "activated" alcohol

The 2'-hydroxychalcone alcohol **4.70** was then subjected to the same reaction conditions utilised for the cyclisation of 2-hydroxychalcone alcohol **4.48** (Scheme 4.75). This gave the desired 2-phenyl-2*H*-chromene **4.53** in a high yield, this illustrating that formation of the delocalised carbocation favours cyclisation to give the six membered ring (Scheme 4.75).



Scheme 4.74 : Formation of the delocalised allylic carbocation of **4.65** to give **4.66**.

The cyclisation yield of **4.70** of 74% is slightly lower than the previous cyclisation of **4.48** of 84%. However the overall yield of **4.53** via this route (58%) is higher than the previous route (Table 4.13, entry 1, 51%). In addition to the increased overall yield there is one less reaction step to be performed via this route.

4.6 Conclusions

The initial observation that $Al(OTf)_3$ can promote the S_N1cA type substitution of (*S*)-1-phenyl ethanol to give the symmetrical ether was an unexpected discovery. Upon further investigation of this reaction it was found that the optimal solvent in which to perform these reactions is a polar one such as nitroethane. The reaction temperature can be varied according to the temperature limitations of the reactants.

It was possible to react "activated" alcohols such as benzhydrol and *trans*-1,3-diphenylprop-2-en-1-ol with oxygen carbon and sulfur nucleophiles. These reactions furnished the substituted products in high yields and short reaction times. The Friedel-Crafts *C*-alkylation of aromatic alcohols can be ascribed to the reversibility of the *O*-alkylated product as compared to the non-reversibility of the *C*-alkylated product. This rearrangement was demonstrated with phenolic derived benzyl ethers which rearranged to the corresponding *C*-alkylation products. The reaction of benzhydrol with more complex alcohols was found to be highly problematic due to the reversible nature of the formed O-C bond.

$Al(OTf)_3$ was found to successfully catalyse the internal nucleophilic substitution of chalcone derived "activated" alcohols with oxygen and nitrogen nucleophiles to furnish the corresponding 2*H*-chromenes and 1,2-dihydroquinolines respectively. These cyclised products were obtained in high yields. This synthetic procedure for obtaining these cyclised products presents a significant improvement on literature methods. The extension of the cyclisation methodology to sulfur nucleophiles has yet to be established. This is due to the difficulty experienced in obtaining a suitable substrate with which to demonstrate this cyclisation step.

It was also found that the position of the leaving hydroxyl group on the allylic moiety has little influence on the outcome of the reaction as cyclisation to the favoured six membered ring occurs regardless of the position of the leaving hydroxyl group.

4.7 Final Conclusions

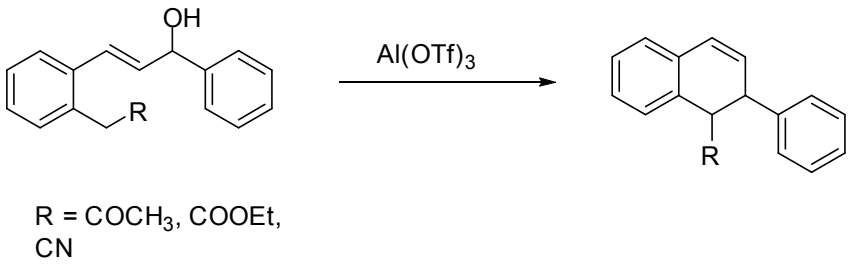
This study has shown the usefulness of $Al(OTf)_3$ as a Lewis acid catalyst in selected organic transformations, in particular the ring-opening of epoxides and nucleophilic substitution of "activated" alcohols.

It was found that the alcoholysis of epoxides could be performed with only 1 equivalent of the nucleophilic alcohol, which is a significant improvement over previous methods that utilised the nucleophilic alcohol in 6 equivalents. The $Al(OTf)_3$ catalysed desymmetrisation of *meso*-epoxides with chiral alcohol showed no significant diastereoselectivity. Future work could revolve around investigations of a chiral Al^{3+} type catalyst for the ring-opening of epoxides. This catalyst would bear unreactive but chelating ligands to generate the chiral Lewis acid catalyst.

The $Al(OTf)_3$ catalysed aminolysis of epoxides was successfully applied to the synthesis of piperazine derived β-amino alcohols with known biological activity. A range of piperazine derived β-amino alcohols bearing different heteroatomic functionalities was synthesised utilising this methodology. The optimal method for the formation of the key β-amino alcohol bond was also determined and reaction scale up as well as catalyst recycling were demonstrated. An important output from this work was the development of a two-step methodology for the synthesis of *N*-glycidyl amines starting from the parent amine and epichlorohydrin. With the key C-N bond formation between the amine and epichlorohydrin effectively being catalysed by $Al(OTf)_3$.

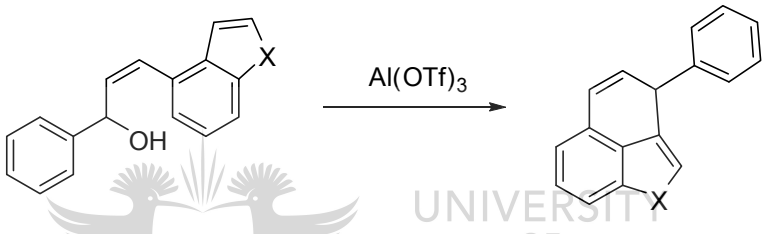
$Al(OTf)_3$ was found to be an effective catalyst for the nucleophilic substitution of "activated" alcohols. Alcohol, carbon and sulfur nucleophiles could be utilised with these "activated" alcohols. Nitrogen nucleophiles were however limited to deactivated sterically unhindered sulfonamides. This nucleophilic substitution of hydroxyl groups is an improvement in terms of the overall environmental impact of this reaction with the traditional conversion of the hydroxyl group into a suitable leaving group being mitigated. It was possible to apply this methodology to the synthesis of 2*H*-chromenes and 1,2-dihydroquinnoline from the corresponding "activated" alcohols. It was found that the position of the leaving hydroxyl group on the allylic moiety has little outcome on the reaction product. This simplifies the requirements of the synthesis of the "activated" alcohol. Future work in this area would no doubt involve the expansion of the scope of the intramolecular cyclisation of an "activated" alcohol with a nucleophilic site already present on the molecule. In this regard the cyclisation

utilising a sulfur nucleophile has yet to be demonstrated. Carbon nucleophiles could also be investigated (Scheme 4.75).



Scheme 4.75 : Possible cyclisation of an "activated" alcohol with a carbon nucleophile.

An investigation into the cyclisation of indole, benzofuran and benzo[*b*]thiophene type molecules could also be performed (Scheme 4.76).



Scheme 4.76 : Possible cyclisation of an indole, benzofuran or benzo[*b*]thiophene type "activated" alcohol.

4.8 References

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Chapter 5

Experimental data

5.1 Standard experimental techniques

5.1.1 Chromatography

Thin-layer chromatography (TLC) was conducted on Merck GF_{254} pre-coated silica gel aluminium backed plates (0.25 mm layer). Various solvent mixtures were used for the elution of the chromatograms with a mixture of hexane and EtOAc usually being the eluent of choice. Compounds were visualised by either their fluorescence under UV light (254 nm) or by spraying the TLC plate with vanillin/H_2SO_4 solution and then heating it with a heat gun.

Flash column chromatography (FCC) refers to column chromatography performed under nitrogen pressure (*ca.* 50 kPa). The columns were packed with Merck Kieselgel 60 (230-400 mesh) and eluted with the appropriate solvent mixture.

5.1.2 Anhydrous solvents and reagents

Tetrahydrofuran (THF), diethyl ether and *toluene* were heated respectively under reflux over sodium under N_2 with benzophenone as the indicator until a dark blue colour persisted. These were distilled prior to use. *Dichloromethane* was heated over CaH_2 under N_2 with subsequent distillation. Solvents were also purified using a MBraun MB-SPS-800 (solvent purification system), that uses filter columns flushed with nitrogen to purify solvents and to remove moisture. *Ethyl acetate* was distilled from K_2CO_3 using a Vigreux distillation column. *Hexanes* were distilled prior to use.

5.2 Spectroscopic methods

5.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were recorded using a Varian Gemini 2000, 300 MHz and a Bruker Ultrashield 400 MHz spectrometer in $CDCl_3$ unless otherwise indicated. The ^1H NMR data are listed in the order : chemical shift (δ, reported in ppm and referenced to the residual solvent peak of $CDCl_3$ [δ = 7.24 ppm] or in the case of aromatic compounds to TMS [δ = 0.00ppm]), the

multiplicity (s = singlet, d = doublet, q = quartet, br s = broad singlet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublets of doublets, ddt = doublet of doublets of triplets, p = pentet, sx = sextet, sp = septet), the number of integrated protons, the coupling constant *J* expressed in Hz, and finally the specific hydrogen allocation. Spin decoupling assisted with the determination of the coupling constants and hydrogen allocation. ^{13}C NMR data are listed in the order : chemical shift (δ, reported in ppm and referenced to the residual solvent peak of $CDCl_3$ [δ = 77.0 ppm]) and the specific carbon atom allocation. In most cases HSQC, HMBC, and COSY spectroscopy were used to assist in allocation of the spectra.

5.2.2 Mass spectroscopy (m/z)

Mass spectrometry was performed on Thermo Double Focussing Sector high resolution mass spectrometer. Ionisation techniques include EIMS and ESIMS.

5.2.3 Infrared Spectroscopy (IR)

A Tensor 27 spectrophotometer was used to record IR spectra using an ATR fitting. The data are listed with the characteristic peaks indicated in wavenumber (cm^{-1}).

5.3 Melting points

Melting points were determined using a Gallenkamp oil immersion apparatus and are uncorrected.

5.4 Chemical methods

5.4.1 Aluminium triflate : A Lewis acid catalyst for the alcoholysis of epoxides

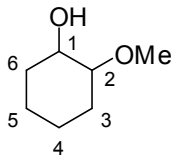
5.4.1.1 General procedure for the alcoholysis of cyclohexene oxide with 6 molar equivalents of alcohol

The alcohol (6 eq) and the required amount of $Al(OTf)_3$ were added to a flask. To this was added cyclohexene oxide (2 mL, 19.7 mmol). The reaction mixture was heated to reflux for 1 hour. After this the reaction mixture was passed over a short silica filter column to remove the $Al(OTf)_3$ and analysed using GC-FID. The excess alcohol was removed from the remainder of the solution under reduced pressure and the product purified via bulb-to-bulb vacuum distillation on a Kugel Rohr vacuum apparatus for characterisation purposes. Alternatively the product was isolated via flash silica column chromatography.

5.4.1.2 Modified procedure for the ring-opening of cyclohexene oxide with 1 equivalent of alcohol

The reaction flask was charged with the required alcohol (1 eq) and $Al(OTf)_3$. To this was added the cyclohexene oxide (2 mL, 19.7 mmol) slowly over the course of 1 hour whilst the mixture was stirred at room temperature. After the addition of cyclohexene oxide had been completed the reaction was worked up in the same way as for the reactions performed with 6 equivalents of alcohol.

2-Methoxycyclohexanol (2.1)[1]



Catalyst : 0.002 mol% $Al(OTf)_3$

Yield : 79 %, clear oil

Distillation : 90 °C, 0.8 mm Hg.

^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 3.38-3.29 (m, 1H, C<u>H</u>OH), 3.32 (s, 3H, OC<u>H</u>$_3$), 3.01 (br s, 1H, O<u>H</u>), 2.86 (ddd, 1H, *J* = 10.7, 8.5 and 4.2 Hz, C*H*OCH$_3$), 2.05-1.92 (m,

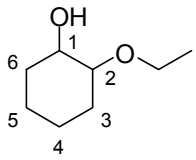
1H, H_{3A}), 1.93-1.84 (m, 1H, H_{6A}), 1.68-1.56 (m, 2H, H_{4A}, H_{5A}), 1.21-1.10 (m, 3H, H_{3B}, H_{4B}, H_{5B}), 1.05-0.98 (m, 1H, H_{6B})

^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 84.9 (C2), 73.5 (C1), 56.2 (O<u>C</u>H_3), 32.0 (C3), 28.2 (C6), 24.0 (C1), 23.8 (C5)

IR : ν_{max} (ATR) 2933, 2862, 1452, 1190, 1094, 995, 845, 504, 447, 435 cm^{-1}

EIMS (*m/z*): 131 (M + 1, 20%), 113 (M + 1 –OH, 15%), 98 (25%), 84 (M + 1 – OH, OCH_3, 35%), 71 (100%)

2-Ethoxycyclohexanol (2.2)[1]



Catalyst : 0.002 mol% $Al(OTf)_3$

Yield : 87 %, clear oil

Distillation : 100 °C, 0.9 mm Hg

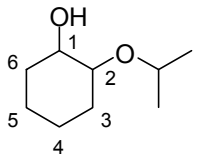
^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 3.57 (dq, 1H, *J* = 9.3 and 7.0 Hz, OC<u>H_{2A}</u>CH_3), 3.29 (dq, 1H, *J* = 9.3 and 7.0 Hz, OC<u>H_{2B}</u>CH_3), 3.31-3.23 (m, 1H, C<u>H</u>OH), 2.89 (ddd, 1H, *J* = 10.4, 8.5 and 4.4 Hz, C*H*OCH_2CH_3), 2.46 (br s, 1H, O<u>H</u>), 1.83 – 1.97 (m, 2H, H_{3A}, H_{6A}), 1.60-1.55 (m, 2H, H_{4A}, H_{5A}), 1.18-0.97 (m, 4H, H3B, H4B, H5B, H6B), 1.08 (t, 3H, *J* = 7.1 Hz, OCH_2C<u>H_3</u>)

^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 83.2 (C2), 73.3 (C1), 63.8 (O<u>C</u>H_2CH_3), 31.9 (C3 or C6), 29.0 (C3 or C6), 24.0 (C4 or C5), 23.7 (C4 or C5), 15.4 (OCH_2<u>C</u>H_3)

IR : ν_{max} (ATR) 2931, 2861, 1450, 1376, 1077, 1027, 888, 840, 495, 474, 449 cm^{-1}

EIMS (*m/z*): 145 (M + 1, 20%), 127 (M + 1 – OH, 100%), 85 (M + 1 – OH, OCH_2CH_3), 81 (35%)

2-Isopropoxycyclohexanol (2.3)[1]



Catalyst : 0.002 mol% $Al(OTf)_3$

Yield : 66 %, clear oil

Distillation : 100 °C, 1 mm Hg

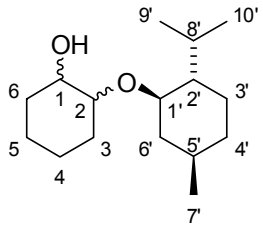
^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 3.70 (sp, 1H, J = 6.0 Hz, C<u>H</u>$(CH_3)_2$), 3.29-3.37 (m, 1H, C<u>H</u>OH), 3.03 (ddd, 1H, J = 10.5, 8.7 and 4.3 Hz, C<u>H</u>OCH$(CH_3)_2$), 2.59 (br s, 1H, O<u>H</u>), 2.00-1.93 (m, 2H, H_{3A}, H_{6A}), 1.69-1.63 (m, 2H, H_{4A}, H_{5A}), 1.26-1.06 (m, 4H, H_{3B}, H_{4B}, H_{5B}, H_{6B}), 1.14 (d, 3H, J = 6.0 Hz, C<u>H</u>$_3$), 1.12 (d, 3H, J = 6.0 Hz, C<u>H</u>$_3$)

^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 81.3 (C2), 73.7 (C1), 69.5 (<u>C</u>H$(CH_3)_2$), 31.9 (C3 or C6), 30.3 (C3 or C6), 24.3 (C4 or C5), 24.0 (C4 or C5), 23.7 (<u>C</u>H$_3$), 22.2 (<u>C</u>H$_3$)

IR : ν_{max} (ATR) 2931, 2863 1451, 1375, 1077, 1027, 889, 840, 495, 474, 450 cm^{-1}

EIMS (*m/z*): 159 (M + 1, 95%), 143 (M + 1 – OH, 100%)

2-(2-Isopropyl-5-methylcyclohexyloxy)cyclohexanol (2.4)



Catalyst : 5 mol% $Al(OTf)_3$

Yield : 64 %, clear oil, diastereomeric mixture

TLC : 0.53 (4:1 Hexane:EtOAc)

^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 3.37-3.30 (m, 1H, H_1), 3.21-3.05 (m, 2H, H_2, $H_{1'}$), 2.24-2.08 (m, 1H, $H_{8'}$), 1.96-1.95 (m, 3H, $H_{2'}$, $H_{3'A}$, H_{6A}), 1.62-1.56 (m, 5H, H_{3A}, H_{5A}, $H_{5'}$, $H_{6'A}$), 1.31-1.08 (m, 8H, $H_{1'A}$, $H_{3'B}$, $H_{4'A}$, H_{6B}, H_{3B}, H_{4B}, H_{5B}), 0.86-0.80 (m, 6H, $CH(C\underline{H}_3)_2$), 0.75 (d, 3H, J = 6.9 Hz, $C\underline{H}_3$), **0.70 (d, 3H, J = 6.6 Hz, $C\underline{H}_3$)** (data in bold here and throughout the rest of the chapter represent the NMR signals for the other diastereomers)

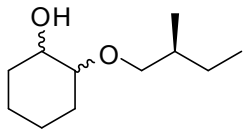
^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 83.2 (C2), 79.8 (C1'), **78.9 (C2)**, **75.3 (C1')**, 74.5 (C1), **73.5 (C1)**, 49.0 (C2'), **48.2 (C2')**, 43.4 (C8'), **41.1 (C8')**, 34.5 (C4'), **34.3 (C4')**, 32.1 (C5'), **32.0 (C5')**, 31.8 (C3), **31.6 (C3)**, 31.5 (C6'), **29.6 (C6')**, 25.1 ($\underline{C}H(CH_3)_2$), **24.9 (($\underline{C}H(CH_3)_2$)**, 24.4 (C5), **24.3 (C5)**, 23.9 (C4), **23.8 (C4)**, 23.1 (C3'), **22.8 (C3')**, 22.3 ($CH(\underline{C}H_3)(CH_3)$), **22.2 ($CH(\underline{C}H_3)(CH_3)$)**, 21.3 ($CH(\underline{C}H_3)(CH_3)$), **21.1 ($CH(\underline{C}H_3)(CH_3)$)**, 15.9 ($\underline{C}H_3$), **15.6 ($\underline{C}H_3$)**

IR : ν_{max} (ATR) 2927, 2863, 1450, 1081, 844, 492, 454, 439 cm^{-1}

EIMS (*m/z*): 245 (M, 5%), 169 (60%), 138 (100%), 116 (M – $C_{10}H_{20}$, 70%), 95 (60%), 83 (90%)

EIMS/ESI HRMS: M^+ Calcd for $C_{16}H_{30}O_2$, 254.2246; found, 254.2247

2-(2-Methylbutoxy)cyclohexanol (2.5)



Catalyst : 1 mol% $Al(OTf)_3$

Yield : 47 %, clear oil, diastereomeric mixture

Distillation : 110 °C, 0.4 mm Hg

^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 3.46-3.32 (m, 2H, CHO$\underline{H}$, O$C\underline{H}_{2A}$), 3.16 (dd, 1H, J = 9.0 and 6.0 Hz, O$C\underline{H}_{2B}$), **3.07 (dd, 1H, J = 9.0 and 6.6 Hz, O$C\underline{H}_{2B}$)**, 2.95 (dd, 1H, J = 7.2 and 3.3 Hz, $C\underline{H}OCH_2$), **2.91 (dd, 1H, J = 7.5 and 3.0 Hz $C\underline{H}OCH_2$)**, 2.70 (br s, 1H, O$\underline{H}$), 2.03-1.91 (m, 2H, H_{3A}, H_{6A}), 1.64-1.52 (m,

3H, H4A, H5A, C<u>H</u>(CH_2CH_3)(CH_3)), 1.47-1.29 (m, 2H, C<u>H_2</u>CH_3), 1.24-0.99 (m, 6H, H_{3B}, H_{4B}, H_{5B}, H_{6B}, **CH_2CH_3**), 0.86-0.81 (m, 6H, CH(CH_2C<u>H_3</u>)(C<u>H_3</u>))

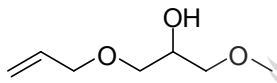
^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 83.7 (C2), **83.6 (C2)**, 73.9 (C1), 73.8 (O<u>C</u>H_2), 35.3 (<u>C</u>H(CH_2CH_3)(CH_3)), **35.2 (<u>C</u>H(CH_2CH_3)(CH_3))**, 31.8 (C3 or C6), 28.9 (C3 or C6), 26.2 (CH(<u>C</u>H_2CH_3)(CH_3)), **26.1 (CH(<u>C</u>H_2CH_3)(CH_3))**, 24.2 (C4 or C5), 23.9 (C4 or C5), 16.6 (CH_3), 11.2 (CH_3)

IR : ν_{max} (ATR) 2932, 1732, 1452, 1084, 499, 414, 424 cm^{-1}

EIMS (*m/z*): 186 (M, 10%), 99 (90%), 96 (60%), 82 (50%), 81 (100%), 71 (40%), 70 (50%)

EIMS/ESI HRMS: M^+ Calcd for $C_{11}H_{22}O_2$, 186.1620; found, 186.1626

1-(Allyloxy)-3-methoxypropan-2-ol (2.7)[2]



Catalyst : 0.02 mol% $Al(OTf)_3$

Yield : 81 %, clear oil

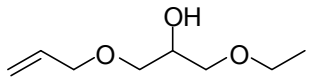
Distillation : 85 °C, 0.5 mm Hg

^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 5.81 (ddt, 1H, *J* = 19.2, 10.5 and 5.7 Hz, H_2C=C<u>H</u>), 5.19 (dq, 1H, *J* = 19.2 and 1.5 Hz, <u>H_{2A}</u>C=CH), 5.10 (dq, 1H, *J* = 10.5 and 1.5 Hz, <u>H_{2B}</u>C=CH), 3.93 (dt, 2H, *J* = 5.7 and 1.5 Hz, H_2C=CHC<u>H_2</u>O), 3.89-3.85 (m, 1H, C<u>H</u>OH), 3.47-3.32 (m, 4H, OC<u>H_2</u>CHOH), C<u>H_2</u>OCH_3), 3.29 (s, 3H, OCH_3), 2.92 (br s, 1H, O<u>H</u>)

^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 134.3 (H_2C=<u>C</u>H), 117.0 (H_2<u>C</u>=CH), 73.8 (H_2C=CH<u>C</u>H_2O), 72.1 (O<u>C</u>H_2CHOH or <u>C</u>H_2O<u>C</u>$H_2$$CH_3$), 71.2 (O<u>C</u>$H_2$CHOH or <u>C</u>$H_2$O<u>C</u>$H_2$$CH_3$), 69.2 (<u>C</u>HOH), 59.0 (O<u>C</u>H_3)

IR : ν_{max} (ATR) 2882, 1726, 1080, 491, 481, 457, 420 cm^{-1}

1-(Allyloxy)-3-ethoxypropan-2-ol (2.8)[2]



Catalyst : 0.02 mol% $Al(OTf)_3$

Yield : 87 %, clear oil

Distillation : 90 °C, 0.5 mm Hg

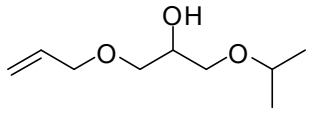
^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 6.02 (ddt, 1H, *J* = 17.3, 10.2 and 5.6 Hz, H_2C=C<u>H</u>), 5.39 (dq, 1H, *J* = 17.3 and 1.5 Hz, <u>H_{2A}</u>C=CH), 5.31 (dq, 1H, *J* = 10.2 and 1.5 Hz, <u>H_{2B}</u>C=CH), 4.12 (dt, 2H, *J* = 5.6 and 1.5 Hz, H_2C=CHC<u>H_2</u>O), 4.05 – 4.09 (m, 1H, C<u>H</u>OH), 3.68-3.54 (m, 6H, OC<u>H_2</u>CHOH), C<u>H_2</u>OCH_2CH_3, CH_2OC<u>H_2</u>CH_3), 3.01 (br s, 1H, O<u>H</u>), 1.32 (t, 3H, *J* = 7.0 Hz, OCH_2C<u>H_3</u>)

^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 134.4 (H_2C=<u>C</u>H), 117.2 (H_2<u>C</u>=CH), 72.3 (H_2C=CH<u>C</u>H_2O), 71.6 (O<u>C</u>H_2CHOH or <u>C</u>H_2OCH_2CH_3), 71.3 (O<u>C</u>H_2CHOH or <u>C</u>H_2OCH_2CH_3), 69.4 (<u>C</u>HOH), 66.8 (O<u>C</u>H_2CH_3), 15.0 (OCH_2<u>C</u>H_3)

IR : ν_{max} (ATR) 2868, 1727, 927, 529, 438, 427 cm^{-1}

EIMS (*m/z*) : 161 (M + 1, 40%), 103 (M + 1 – $CH_2OCH_2CH_3$, 35%), 87 (M + 1 – CH2OCH2CH3, OH, 45%), 71 (35%), 59 (100%)

1-(Allyloxy)-3-isopropoxypropan-2-ol (2.9)[2]



Catalyst : 0.02 mol% $Al(OTf)_3$

Yield : 74 %, clear oil

Distillation : 90 °C, 0.5 mm Hg

^{1}H nmr : (300 MHz, $CDCl_3$) δ_H 5.87 (ddt, 1H, *J* = 17.1, 10.2 and 5.7 Hz, H_2C=C<u>H</u>), 5.24 (dq, 1H, *J* = 17.1 and 1.5 Hz, <u>H_{2A}</u>C=CH), 5.15 (dq, 1H, *J* = 10.2 and 1.5

Hz, $\underline{H_{2B}}C=CH$), 3.99 (dt, 2H, *J* = 5.7 and 1.5 Hz, $H_2C=CHC\underline{H_2}O$), 3.88 – 3.90 (m, 1H, C<u>H</u>OH), 3.67-3.40 (m, 5H, $OC\underline{H_2}CHOH$), $C\underline{H_2}OCH(CH_3)_2$, $CH_2OC\underline{H}(CH_3)_2$), 3.18 (br s, 1H, O<u>H</u>), 1.13 (d, 6H, *J* = 6.0 Hz, $OCH(C\underline{H_3})_2$)

^{13}C nmr : (75 MHz, $CDCl_3$) δ_C 134.4 ($H_2C=\underline{C}H$), 117.0 ($H_2\underline{C}=CH$), 72.1 ($H_2C=CH\underline{C}H_2O$), 72.1 ($O\underline{C}H_2CHOH$ or $\underline{C}H_2OCH_2CH_3$), 71.2 ($O\underline{C}H_2CHOH$ or $\underline{C}H_2OCH_2CH_3$), 69.5 (<u>C</u>HOH), 69.1 ($O\underline{C}H(CH_3)_2$)

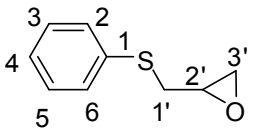
IR : ν_{max} (ATR) 2972, 1727, 1077, 923, 482, 463, 440 cm^{-1}

5.4.2 <u>Synthesis of piperazine-derived β-amino alcohols via the aluminium triflate mediated ring-opening of epoxides</u>

5.4.2.1 <u>Typical procedure for the preparation of *S*-glycidyl ethers</u>

Potassium hydroxide (1.68 g, 30 mmol) and epichlorohydrin (2.34 mL, 30 mmol) were dissolved in a 1:1 mixture of water and dioxane (5 mL:5 mL) and cooled to 0 °C. Benzyl mercaptan (1.17 mL, 10 mmol) was added to this solution. The mixture was allowed to warm to room temperature and stirred for 12 hours under nitrogen. The reaction mixture was extracted with DCM (3 x 10 mL), and the combined organic layers washed with water (2 x 10 mL) and then dried with magnesium sulfate. The excess organic solvent wash then removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

2-Phenylsulfanylmethyl-oxirane (3.1)[3]



Yield: 92%, clear oil

TLC: 0.63 (20:3 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.41 (d, 2H, *J* = 7.2 Hz, H3, H5), 7.28 (t, 2H, *J* = 7.1 Hz, H2, H6), 7.21 (d, 1H, *J* = 7.2 Hz, H4), 3.18-3.11 (m, 2H, $SCH_2C\underline{H}OCH_2$,

$SC\underline{H_{2A}}CHOCH_2$), 2.92 (dd, 1H, *J* = 15.2 and 7.4 Hz, $SC\underline{H_{2B}}CHOCH_2$), 2.74 (t, 1H, J = 4.4 Hz, $SCH_2CHOC\underline{H_{2A'}}$), 2.49 (dd, 1H, *J* = 4.8 and 2.4 Hz, $SCH_2CHOC\underline{H_{2B'}}$)

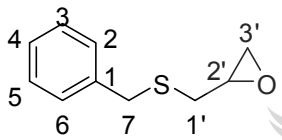
^{13}C NMR: ($CDCl_3$) δ_C : 135.2 (C1), 130.2 (C3, C5), 128.9 (C4), 126.7 (C2, C6), 50.9 (C2'), 47.3 (C3'), 36.6 (C1')

IR: ν_{max} (ATR) 3055, 2993, 2920, 1584, 1480, 922, 828, 690 cm^{-1}

EIMS (*m/z*): 166(M, 35%), 123(M-CHOCH2, 45%), 110 (M-CH2CHOCH2, 100%), 109(40%)

EIMS/ESI HRMS: M^+ Calcd for $C_9H_{10}OS$, 166.0452; found, 166.0445

2-Benzylsulfanylmethyl-oxirane (3.2)[3]



Yield: 84%, clear oil

TLC: 0.46 (20:2 Hexane: EtOAc)

^{1}H NMR: ($CDCl_3$) δ_H : 7.34-7.21 (m, 5H, $\underline{H}$-aromatic), 3.79 (s, 2H, $PhC\underline{H_2}S$), 3.09-3.03 (m, 1H, $SCH_2C\underline{H}OCH_2$), 2.74 (t, 1H, *J* = 4.4 Hz, $SCH_2CHOC\underline{H_{2A'}}$), 2.64-2.47 (m, 3H $SC\underline{H_{2A}}CHOCH_2$, $SC\underline{H_{2B}}CHOCH_2$, $SCH_2CHOC\underline{H_{2B'}}$)

^{13}C NMR: ($CDCl_3$) δ_C : 138.0 (C1), 128.9 (C3, C5), 128.5 (C4), 127.1 (C2, C6), 51.7 (C2'), 46.7 (C3'), 36.4 (C7), 33.2 (C1')

IR: ν_{max} (ATR) 3028, 2916, 1494, 1454, 922, 841, 699 cm^{-1}

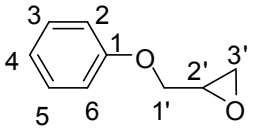
EIMS (*m/z*): 180(M, 20%), 123 (M-CH_2CHOCH_2, 30%), 122 (90%), 106 (80%), 105(100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{10}H_{12}OS$, 180.0609; found, 180.0601

5.4.2.2 Typical procedure for the preparation of *O*-glycidyl ethers

To a mixture of phenol (0.94 g, 10 mmol) and epichlorohydrin (6.26 mL, 80 mmol) was added K_2CO_3 (2.76 g, 20 mmol) and $(n\text{-}Bu)_4NBr$ (0.322 g , 1 mmol). The resulting mixture was stirred at 80 °C for 1.5 hours. The reaction mixture was then diluted with water (10 mL) and extracted with DCM (3 x 10 mL), and the combined organic layers washed with water (2 x 10 mL) and then dried with magnesium sulfate. The excess organic solvent wash then removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

2-Phenoxymethyl-oxirane (3.3)[4]



Yield: 79%, clear oil

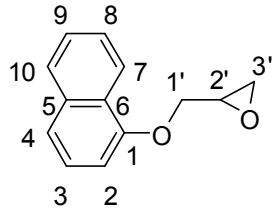
TLC: 0.70 (10:1 Toluene:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.29 (d, 2H, J = 7.6 Hz, H3, H5), 6.99-6.90 (m, 3H, H2, H4, H6), 4.20 (dd, 1H, J = 11.1 and 3.3 Hz, $OCH_{2A}CHOCH_2$), 3.94 (dd, 1H, J = 11.3 and 5.6 Hz, $OCH_{2B}CHOCH_2$), 3.36-3.33 (m, 1H, OCH_2CHOCH_2), 2.88 (t, 1H, J = 4.5 Hz, $OCH_2CHOCH_{2A'}$), 2.74 (dd, 1H, J = 4.7 and 2.6 Hz, $OCH_2CHOCH_{2B'}$)

^{13}C NMR: (75MHz, $CDCl_3$) δ_C : 158.4 (C1), 129.4 (C3, C5), 121.1 (C4), 114.5 (C2, C6), 68.5 (C1'), 50.0 (C2'), 44.6 (C3')

IR: ν_{max} (ATR) 3033, 3010, 2926, 1599, 1493, 1240, 1038, 814, 691 cm^{-1}

2-(Naphthalen-1-yloxymethyl)-oxirane (3.4)[4]



Yield: 63%, yellow oil

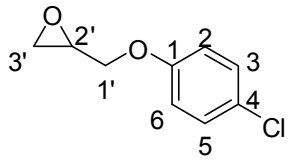
TLC: 0.62 (20:1 Toluene:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 8.30-8.27 (m, 1H, H10), 7.80-7.77 (m, 1H, H9), 7.51-7.32 (m, 3H, H3, H4, H7, H8), 6.80 (d, 1H , J = 7.5 Hz, H2), 4.39 (dd, 1H, J = 11.1 and 3.3 Hz, $OCH_{2A}CHOCH_2$), 4.14 (dd, 1H, J = 11.3 and 5.6 Hz, $OCH_{2B}CHOCH_2$), 3.51-3.56 (m, 1H, OCH_2CHOCH_2), 2.96 (t, J = 4.5Hz, $OCH_2CHOCH_{2A'}$), 2.84 (dd, 1H, J = 5.1 and 2.7 Hz, $OCH_2CHOCH_{2B'}$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 154.2 (C1), 134.5 (C5), 127.4 (C10), 126.5 (C9), 125.7 (C3), 125.6 (C6), 125.3 (C8), 122.0 (C7), 120.8 (C4), 105.0 (C2), 68.9 (C1'), 50.2 (C2'), 44.7 (C3')

IR: ν_{max} (ATR) 3054, 2926, 1579, 1397, 1270, 1240, 1100, 792, 796, 729 cm^{-1}.

2-(4-Chloro-phenoxymethyl)-oxirane (3.5)[4]



Yield: 73%, yellow oil

TLC: 0.42 (10:1 Toluene:EtOAc)

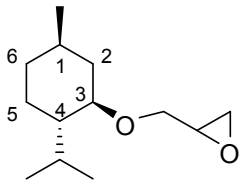
^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.21 (d, 2H, J = 9.0 Hz, H3, H5) 6.83 (d, 2H, J = 9.3 Hz, H2, H6), 4.19 (dd, 1H, J = 11.1 and 3.0 Hz, $OCH_{2A}CHOCH_2$), 3.89 (dd, 1H, J = 11.1 and 5.7 Hz, $OCH_{2B}CHOCH_2$), 3.34-3.29 (m, 1H,

$OCH_2C\underline{H}OCH_2$), 2.88 (t, 1H, *J* = 4.5Hz, $OCH_2CHOC\underline{H_{2A'}}$), 2.72 (dd, 1H, *J* = 5.0 and 2.9 Hz, $OCH_2CHOC\underline{H_{2B'}}$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 157.0 (C1), 129.3 (C3, C5), 126.0 (C4), 115.9 (C2, C6), 69.0 (C1'), 49.9 (C2'), 44.5 (C3')

IR: ν_{max} (ATR) 2928, 1491, 1240, 909, 823, 755, 731 cm^{-1}

2-(2-Isopropyl-5-methyl-cyclohexyloxymethyl)-oxirane (3.6)



Yield: 18%, yellow oil, diastereomeric mixture

TLC: 0.48 (10:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 3.76 (dd, 1H, *J* = 11.3 and 3.2 Hz, $OC\underline{H_{2A}}CHOCH_2$), 3.56 (dd, 1H, *J* = 10.1 and 2.6 Hz, H3), **3.51 (dd, 1H, H3, *J* = 10.1 and 3.8 Hz)**, **3.33 (dd, 1H, *J* = 11.3 and 5.9 Hz, $OC\underline{H_{2A}}CHOCH_2$)**, 3.15-3.00 (m, 2H, $OC\underline{H_{2B}}CHOCH_2$, $OCH_2C\underline{H}OCH_2$), 2.75 (dd, 1H, *J* = 9.1 and 4.6 Hz, $OCH_2CHOC\underline{H_{2A'}}$), 2.57 (dd, 1H, *J* = 4.5 and 2.1 Hz, $OCH_2CHOC\underline{H_{2B'}}$), **2.55 (dd, 1H, *J* = 4.5 and 2.1 Hz, $OCH_2CHOC\underline{H_{2B'}}$)**, 2.26-2.12 (m, 1H, H8), 2.09-2.01 (m, 1H, $H2_A$), 1.64-1.55 (2H, $H5_A$, $H6_A$), 1.39-1.16 (2H, H1, H4), 0.88 (d, 3H, *J* = 6.0 Hz, H9), 0.86 (d, 3H, *J* = 6.9 Hz, H10), 0.77 (d, 3H, *J* = 5.1 Hz, H7), 0.74 **(d, 3H, *J* = 5.1 Hz, H7)**, 1.02-0.74 (m, 3H, $H2_B$, $H5_B$, $H6_B$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 80.1 (C3), **79.6 (C3)**, 69.6 (C1'), **69.1 (C1')**, 51.2 (C4), **51.1 (C4)**, 48.2 (C2), 44.7 (C2'), **44.4 (C2')**, 40.5 (C3'), **40.2 (C3')**, 34.5 (C6), 31.52 (C1), **31.45 (C1)**, 25.6 (C8), 23.4 (C5), **23.3 (C5)**, 22.3 (C7), 20.89 (C9), **20.88 (C9)**, 16.27 (C10), **16.22 (C10)**

IR: ν_{max} (ATR) 2955, 2922, 2869, 1090, 910 cm^{-1}

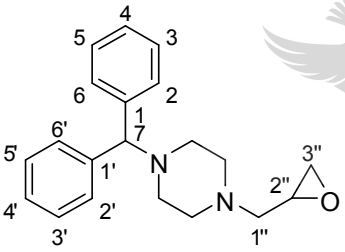
ESIMS (*m/z*): 213 ($[M+H]^+$, 21), 199 (95), 177 (100), 169 (40), 147 (25), 139 (30), 121 (65), 111 (45), 89 (90)

EIMS/ESI HRMS: $[M+H]^+$ Calcd for $C_{13}H_{25}O_2$, 213.1855; found, 213.1849

5.4.2.3 Typical procedure for the preparation of *N*-glycidyl ethers

To a mixture of $Al(OTf)_3$ (0.024 g, 50 μmol) and the required amine (1 mmol) in toluene (5 mL) was added epichlorohydrin (0.081 mL, 1 mmol). The reaction mixture was then stirred at 70 °C for 30 minutes. The mixture was then cooled to room temperature and KOH (0.112 g, 20 mmol), (*n*-Bu)NBr (0.032 g, 100 μmol) and water (5 mL) were added. The mixture was then stirred for 2.5 hours at room temperature. The reaction mixture was then extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and then dried with magnesium sulfate. The excess organic solvent wash then removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

1-Benzhydryl-4-oxiranylmethyl-piperazine (3.7)[5]



Yield: 68%, white solid

Mp: 97-102 °C

TLC: 0.51 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.39 (d, 4H, *J* = 6.9 Hz, H3, H3', H5, H5'), 7.24 (t, 4H, J = 7.4 Hz, H2, H2', H6, H6'), 7.14 (t, 2H, *J* = 7.2 Hz, H4, H4'), 4.21 (s, 1H, H7), 3.09-3.03 (m, 1H, H2''), 2.73 (t, 1H, *J* = 4.5 Hz, H3''$_{A'}$), 2.69 (dd, 1H, *J* = 13.2 and 3.6 Hz, H3''$_{B'}$), 2.61-2.44 (m, 8H, N((C$\underline{H}_2$)$_2$)$_2$N), 2.45 (dd, 1H, *J* = 4.8 and 2.7 Hz, H1''$_A$), 2.30 (dd, 1H, *J* = 13.2 and 6.6 Hz, H1''$_B$)

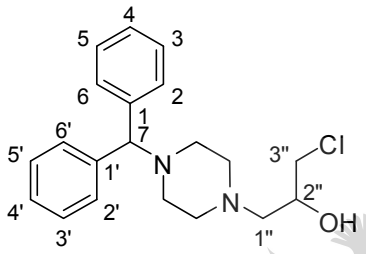
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.6 (C1, C1'), 128.4 (C3, C3', C5, C5'), 127.8 (C2, C2', C6, C6'), 126.8 (C4, C4'), 76.1 (C7), 60.9 (C1''), 53.8 ((CHN($\underline{C}H_2)_2$), 51.7 (($\underline{C}H_2)_2$NH), 50.1 (C2''), 45.0 (C3'')

IR: ν_{max} (ATR) 2955, 2805, 1451, 1136, 1008, 917, 852, 844, 759, 742, 704, 694 cm^{-1}

ESIMS (*m/z*): 309 ($[M+H]^+$, 65%), 168 (10%), 167 ($[PhCH]^+$, 100%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{20}H_{25}ON_2$, 309.1967; found, 309.1966

1-(4-Benzhydryl-piperazin-1-yl)-3-chloro-propan-2-ol(3a-chlorohydrin) (3.7b)



Yield: 66%, yellow solid.

Mp: 119-124 °C

TLC: 0.56 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.32 (d, 4H, *J* = 6.9 Hz, H3, H3', H5, H5'7.18 (t, 4H, *J* = 7.3 Hz, H2, H2', H6, H6'), 7.08 (d, 2H, *J* = 7.0 Hz, H4, H4'), 4.14 (s, 1H, H7), 3.85-3.77 (m, 1H, H2''), 3.48 (dd, 1H, *J* = 10.4 and 4.1Hz, H3''$_A$), 3.42 (dd, 1H, *J* = 10.4 and 4.7 Hz, H3''$_B$), 2.57-2.55 (m, 2H, H1''), 2.39-2.37 (m, 8H, N(($\underline{C}H_2)_2)_2$N)

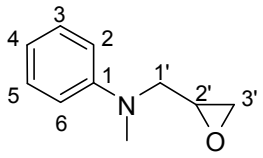
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.5 (C1, C1'), 128.4 (C3, C3', C5, C5'), 127.8 (C2, C2', C6, C6'), 126.9 (C4, C4'), 76.0 (C7), 66.4 (C2''), 60.8 (C1''), 53.5 ((CHN($\underline{C}H_2)_2$), 51.8 (($\underline{C}H_2)_2$NH), 47.1 (C3'')

IR: ν_{max} (ATR) 3270, 3010, 2982, 2807, 2797, 1450, 1307, 1086, 1006, 873, 758, 706, 595 cm^{-1}

ESIMS (*m/z*): 345 ($[M+H]^+$, 65%), 310 (20%), 309 (100%), 167 ($[Ph_2CH]^+$, 35%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{20}H_{26}ON_2Cl$, 345.1734; found, 345.1747

Methyl-oxiranylmethyl-phenyl-amine (3.8)[6]



Yield: 95%, yellow oil

TLC: 0.58 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.24 (d, 2H, J = 7.9 Hz, H3, H5), 6.78-6.71 (m, 3H, H2, H6), 3.64 (dd, 1H, J = 15.5 and 3.2 Hz, $NCH_{2A}CHOCH_2$), 3.39 (dd, 1H, J = 15.6 and 4.8 Hz, $NCH_{2B}CHOCH_2$), 3.12-3.17 (m, 1H, NCH_2CHOCH_2), 2.99 (s, 3H, NCH_3), 2.78 (t, 1H, J = 4.4 Hz, $NCH_2CHOCH_{2A'}$), 2.56 (dd, 1H, J = 5.1 and 2.7 Hz, $NCH_2CHOCH_{2B'}$)

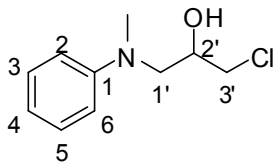
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 149.4 (C1), 129.1 (C3, C5), 116.7 (C4), 112.0 (C2, C6), 54.1 (C1'), 50.4 (C2'), 44.9 (C4'), 38.9 (C3')

IR: ν_{max} (ATR) 3015, 2981, 2920, 1599, 1505, 692 cm^{-1}

ESIMS (*m/z*): 164 ($[M+H]^+$, 100%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{10}H_{14}ON$, 164.1075; found, 164.1031

1-Chloro-3-(methyl-phenyl-amino)-propan-2-ol(3b-chlorohydrin) (3.8b)[7]



Yield: 99%, yellow oil

TLC: 0.43 (4:1 Hexane:EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.29 (t, 2H, J = 8.2 Hz, H3, H5), 6.84-6.78 (m, 3H, H2, H4, H6), 4.15-4.11 (m, 1H, $NCH_2C\underline{H}OHCH_2Cl$), 3.69 (dd, 1H, J = 11.4 and 4.2 Hz, $NCH_2CHOHC\underline{H}_{2A}Cl$), 3.59 (dd, 1H, J = 11.3 and 5.3 Hz, $NCH_2CHOHC\underline{H}_{2B}Cl$), 3.45 (d, 1H, J = 6.6 Hz, $NC\underline{H}_2CHOHCH_2Cl$), 3.00 (s, 1H, $NC\underline{H}_3$), 2.47 (d, 1H, J = 4.2 Hz, O$\underline{H}$)

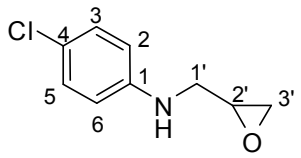
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 149.4 (C1), 129.2 (C3, C5), 117.2 (C4), 112.7 (C2, C6), 68.9 (C2'), 56.3 (C1'), 47.6 (C4'), 39.4 (C3')

IR: ν_{max} (ATR) 3420, 2980, 2853, 2720, 1599, 1505, 1364, 1082, 991, 747, 692 cm^{-1}

ESIMS (*m/z*): 200 ($[M+H]^+$, 100%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{10}H_{15}ONCl$, 200.0842; found, 200.0838

(4-Chloro-phenyl)-oxiranylmethyl-amine (3.9)[8]



Yield: 67%, yellow Solid

Mp: 106-110 °C

TLC: 0.32 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.11 (d, 2H, J = 8.7 Hz, H-aromatic), 6.54 (d, 2H, J = 8.7 Hz, H-aromatic), 3.86 (bs, 1H, NH), 3.52-3.49 (m, 1H, $NC\underline{H}_{2A}CHOCH_2$), 3.20-3.15 (m, 2H, $NC\underline{H}_{2B}CHOCH_2$, $NCH_2C\underline{H}OCH_2$), 2.80 (t, 1H, J = 4.5Hz, $NCH_2CHOC\underline{H}_{2A'}$), 2.66 (dd, 1H, J = 4.5 and 2.4Hz, $NCH_2CHOC\underline{H}_{2B'}$)

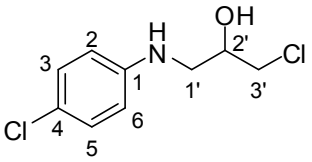
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 146.4 (C1), 129.0 (C3, C5), 122.3 (C4), 114.0 (C2, C6), 50.8 (C2'), 45.2 (C1'), 45.0 (C3')

IR: ν_{max} (ATR) 3380, 2978, 1596, 1496, 1356, 1233, 1177, 1097, 806, 645 cm^{-1}

ESIMS (*m/z*): 184 ([M+H]$^+$, 5%), 177 (20%), 139 (45%), 111 (15%), 103 (15%), 102 (100%), 89 (30%)

EIMS/ESI HRMS: [M+H]$^+$ Calcd for $C_9H_{11}ON^{35}Cl$, 184.0529; found, 184.0463; [M+H]$^+$ Calcd for $C_9H_{11}ON^{37}Cl$, 186.0500; found, 186.0477

1-Chloro-3-(4-chloro-phenylamino)-propan-2-ol (3.9b)[9]



Yield: 74%, yellow solid

Mp: 56-60 °C

TLC: 0.30 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.11 (d, 2H, *J* = 8.7 Hz, H-aromatic), 6.55 (d, 2H, *J* = 8.4 Hz, H-aromatic), 4.07-3.99 (m, 1H, $NCH_2\underline{C}HOHCH_2Cl$), 3.65 (dd, 1H, *J* = 11.1 and 4.5 Hz, $NCH_2CHOHC\underline{H_{2A}}Cl$), 3.58 (dd, 1H, *J* = 11.4 and 6.0 Hz, $NCH_2CHOHC\underline{H_{2B}}Cl$), 3.31 (dd, 1H, *J* = 13.2 and 3.9 Hz, $NC\underline{H_{2A}}CHOHCH_2Cl$), 3.24 (bs, 1H, N<u>H</u>), 3.16 (dd, 1H, *J* = 13.2 and 7.2 Hz, $NC\underline{H_{2B}}CHOHCH_2Cl$)

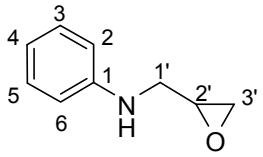
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 146.3 (C1), 129.1 (C3, C5), 122.7 (C4), 114.3 (C2, C6), 69.7 (C2'), 47.5 (C1'), 47.1 (C3')

IR: ν_{max} (ATR) 3338, 3482, 2989, 2865, 1596, 1495, 1238, 1086, 817, 742, 663 cm^{-1}

ESIMS (*m/z*): 220 ([M+H]$^+$, 100%), 199 (10%), 102 (5%)

EIMS/ESI HRMS: [M+H]$^+$ Calcd for $C_9H_{12}ON^{35}Cl_2$, 220.0296; found, 220.0284; [M+H]$^+$ Calcd for $C_9H_{12}ON^{35}Cl^{37}Cl$, 222.0266; found, 222.0340; [M+H]$^+$ Calcd for $C_9H_{12}ONCl_2$, 223.0300; found, 223.0308

Oxiranylmethyl-phenyl-amine (3.10)[10]



Yield: 65%, yellow solid.

Mp: 115-120 °C

TLC: 0.41 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.20 (d, 2H, *J* = 7.8 Hz, H*3,* H5), 6.75 (d, 1H, *J* = 7.4Hz, H4), 6.65 (d, 2H, *J* = 7.5 Hz, *H2,* H6), 3.92 (bs, 1H, NH), 3.55-3.49 (m, 1H, $NC\underline{H_{2A}}CHOCH_2$), 3.24-3.18 (m, 2H, $NC\underline{H_{2B}}CHOCH_2$, $NCH_2C\underline{H}OCH_2$), 2.81 (t, 1H, *J* = 4.4 Hz, $NCH_2CHOC\underline{H_{2A'}}$), 2.67 (dd, 1H, *J* = 2.4 and 5.1 Hz, $NCH_2CHOC\underline{H_{2B'}}$)

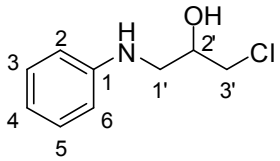
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 147.7 (C1), 129.2 (C3, C5), 117.7 (C4), 112.8 (C2, C6), 50.9 (C2'), 45.2 (C1'), 45.0 (C3')

IR: ν_{max} (ATR) 3370, 2870, 1598, 1503, 1345, 1232, 1035, 992, 745, 692 cm^{-1}

ESIMS (*m/z*): 150 ($[M+H]^+$, 25%), 146 (10%), 120 (100%), 106 (25%), 102 (15%), 89 (20%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_9H_{12}O_1N_1$, 150.0919; found, 150.0918

1-Chloro-3-phenylamino-propan-2-ol (3.10b)[11]



Yield: 75%, yellow oil

TLC: 0.23 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.20 (t, 2H, *J* = 7.9 Hz, H3, H5), 6.76 (t, 1H, *J* = 7.3 Hz, H4), 6.66 (d, 2H, *J* = 7.8 Hz, H*2, H6*), 4.09-4.01 (m, 1H, $NCH_2C\underline{H}OHCH_2Cl$), 3.66 (dd, 1H, *J* = 11.4 and 4.8 Hz,$NCH_2CHOHC\underline{H_{2A}}Cl$), 3.60 (dd, 1H, *J* = 11.3 and 5.9 Hz, $NCH_2CHOHC\underline{H_{2B}}Cl$), 3.36 (dd, 1H, *J* = 13.2 and 4.5 Hz, $NC\underline{H_{2A'}}CHOHCH_2Cl$), 3.20 (dd, 1H, *J* = 13.2 and 7.5 Hz, $NC\underline{H_{2B'}}CHOHCH_2Cl$)

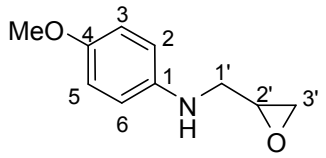
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 147.5 (C1), 129.3 (C3, C5), 118.3 (C4), 113.4 (C2, C6), 69.7 (C2'), 47.6 (C1'), 47.1 (C3')

IR: ν_{max} (ATR) 3384, 2989, 1602, 1504, 1259, 1071, 749, 692 cm^{-1}

ESIMS (*m/z*): 186 ($[M+H]^+$, 100%), 170 (10%), 168 (50%), 132 (25%), 119 (10%), 106 (10%)

EIMS/ESI HRMS: M^+ + H Calcd for $C_9H_{13}O_1N_1{}^{35}Cl_1$, 186.0686; found, 186.0672, M^+ + H Calcd for $C_9H_{13}O_1N_1{}^{37}Cl_1$, 188.0656; found, 188.0653

(4-Methoxy-phenyl)-oxiranylmethyl-amine (3.11)



Yield: 61%, yellow solid.

Mp: 50-54 °C

TLC: 0.62 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 6.77 (d, 2H, *J* = 9.0 Hz, H3*,* H5), 6.60 (d, 2H, *J* = 9.0 Hz, H2*,* H6), 3.73 (s, 3H, $OC\underline{H_3}$), 3.63 (br s, 1H, NH), 3.48 (br d, 1H, *J* = 10.8 Hz, $NC\underline{H_{2A}}CHOCH_2$), 3.21-3.11 (m, 2H, $NC\underline{H_{2B}}CHOCH_2$, $NCH_2C\underline{H}OCH_2$), 2.80 (dd, 1H, *J* = 4.95 and 4.05 Hz, $NCH_2CHOC\underline{H_{2A'}}$), 2.68 (dd, 1H, *J* = 4.95 and 2.55 Hz, $NCH_2CHOC\underline{H_{2B'}}$)

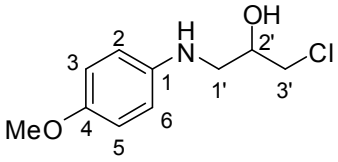
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 152.4 (C1), 141.9 (C4), 114.9 (C3, C5), 114.3 (C2, C6), 55.7 ($O\underline{C}H_3$), 51.1 (C2'), 46.1 (C1'), 45.4 (C3')

IR: ν_{max} (ATR) 3417, 2942, 2788, 1599, 1509, 1450, 1236, 1151, 1006, 907 cm^{-1}

ESIMS (*m/z*): 180 ($[M+H]^+$,5%), 176 (10%), 162 (25%), 151 (10%), 150 (100%), 134 (10%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{10}H_{14}O_2N_1$, 180.1025; found, 180.1039

1-Chloro-3-(4-methoxy-phenylamino)-propan-2-ol (3.11b)[11]



Yield: 63%, yellow oil

TLC: 0.56 (1:1 Hexane:EtOAc)

^1H NMR: (300 MHz, $CDCl_3$) δ_H : 6.70 (d, 2H, *J* = 9.0 Hz, H3, H5), 6.60 (d, 2H, *J* = 9.0 Hz, H2, H6), 4.07 – 4.00 (m, 1H, H2'), 3.73 (s, 3H, OMe), 3.66 (dd, *J* = 11.3 and 4.7 Hz, $NCH_2CHOHCH_{2A'}Cl$), 3.61 (dd, 1H, *J* = 11.3 and 6.2 Hz, $NCH_2CHOHCH_{2B'}Cl$), 3.31 (dd, 1H, *J* = 13.1 and 4.1 Hz $NCH_{2A'}CHOHCH_2Cl$), 3,15 (dd, 1H, *J* = 13.1 and 7.4 Hz, $NCH_{2B'}CHOHCH_2Cl$), 3.07 (bs, 1H, NH)

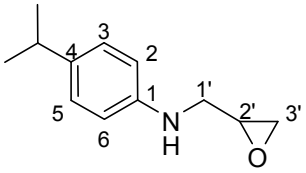
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 152.6 (C1), 141.7 (C4), 116.5 (C3, C5), 114.8 (C2, C6), 69.7 (C2'), 55.7 ($PhOCH_3$), 48.2 (C1'), 47.6 (C3')

IR: ν_{max} (ATR) 3320, 2950, 2783, 1510, 1234, 1032, 820, 749 cm^{-1}

ESIMS (*m/z*): 216 ($[M+H]^+$, 60%), 198 (25%), 162 (15%), 136 (40%), 124 (100%), 123 (20%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{10}H_{15}O_2N_1Cl_1$, 216..0791; found, 216.0792

(4-Isopropyl-phenyl)-oxiranylmethyl-amine (3.12)



Yield: 60%, yellow oil

TLC: 0.35 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.06 (d, 2H, *J* = 8.7, Hz H3, H5), 6.60 (d, 2H, *J* = 8.7 Hz, H2, H6), 3.78 (br s, 1H, N<u>H</u>), 3.51 (dd, 1H, *J* = 15.5 and 4.7 Hz, NC<u>H$_{2A}$</u>CHOCH$_2$), 3.24-3.18 (m, 2H, NC<u>H$_{2B}$</u>CHOCH$_2$, NCH$_2$C<u>H</u>OCH$_2$), 2.81(dd, 1H, *J* = 5.4 and 3.9 Hz, NCH$_2$CHOC<u>H$_{2A'}$</u>), 2.81 (h, 1H, *J* =6.6 Hz, (CH$_3$)$_2$C<u>H</u>), 2.69 (dd, 1H, *J* = 5.1and 2.4 Hz, NCH$_2$CHOC<u>H$_{2B'}$</u>), 1.21 (d, 6H, *J* = 7.2 Hz, (C<u>H$_3$</u>)$_2$CH)

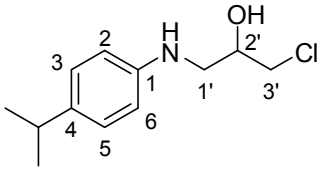
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 145.8 (C1), 138.4 (C4), 127.1 (C3, C5), 113.0 (C2, C6), 51.0 (C2'), 45.4 (C1'), 45.3 (C3'), 33.1 ((CH$_3$)$_2$<u>C</u>H), 24.2 (<u>C</u>H$_3$)$_2$CH)

IR: ν_{max} (ATR) 3305, 2957, 1614, 1518, 1361, 1196 cm^{-1}

ESIMS (*m/z*): 192 ([M+H]$^+$, 5%), 167 (30%), 149 (65%), 138 (100%), 117 (25%), 110 (15%)

EIMS/ESI HRMS: M$^+$ + H Calcd for $C_{12}H_{18}O_1N_1$, 192.1388; found, 192.1385

1-Chloro-3-(4-isopropyl-phenylamino)-propan-2-ol (3.12 b)



Yield: 79%, yellow oil

TLC: 0.31 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.07 (d, 2H, *J* = 8.4 Hz, H3, H5), 6.52 (d, 2H, *J* = 8.4 Hz, H2, H6), 4.09-4.02 (m, 1H, NCH$_2$C<u>H</u>OHCH$_2$Cl), 3.67 (dd, 1H, *J* = 11.4

and 4.5 Hz, $NCH_2CHOHC\underline{H}_{2A}Cl$), 3.50 (dd, 1H, *J* = 11.4 and 6.0 Hz, $NCH_2CHOHC\underline{H}_{2B}Cl$), 3.35 (dd, 1H, *J* = 13.4 and 4.4 Hz, $NC\underline{H}_{2A'}CHOHCH_2Cl$), 3.20 (dd, 1H, *J* = 13.2 and 7.2 Hz, $NC\underline{H}_{2B'}CHOHCH_2Cl$), 2.81 (h, 1H, *J* = 6.9 Hz, $(CH_3)_2C\underline{H}$), 1.21 (d, 6H, *J* = 7.2 Hz, $(C\underline{H}_3)_2CH$)

C^{13} NMR: (75 MHz, $CDCl_3$) δ_C : 145.6 (C1), 138.9 (C4), 127.2 (C3, C5), 113.4 (C2, C6), 69.8 (C2'), 47.6 (C1'), 47.4 (C3'), 33.1 ($(CH_3)_2\underline{C}H$), 24.2 ($\underline{C}H_3)_2CH$)

IR: ν_{max} (ATR) 3389, 2957, 1615, 1518, 1256, 1084 cm^{-1}

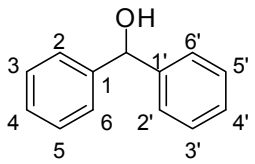
ESIMS (*m/z*): 228 ($[M+H]^+$, 100%), 210 (25%), 186 (30%), 168 (35%), 148 (25%), 136 (40%), 132 (20%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{12}H_{19}O_1N_1Cl_1$, 228.1155; found, 228.1151

5.4.2.4 Synthesis of the diphenylmethanols

To a suspension of magnesium (0.365 g, 15 mmol) in THF (5 mL), the required bromobenzene (15 mmol) dissolved in THF (5 mL) was added slowly at room temperature. The mixture was then heated to 80 °C for 3 h. In a separate flask, methyl formate (0.31 mL, 5 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. To this mixture was added the preformed Grignard reagent in a dropwise manner. The reaction was then allowed to warm to room temperature and stirred overnight. The reaction was then quenched with saturated ammonium chloride (5 mL) and then extracted with DCM (3 x 5 mL).The combined organic layers washed with water (2 x 5 mL) and then dried with magnesium sulfate. The excess organic solvent wash then removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

Diphenyl-methanol (3.13)



Yield: 99%, white solid

Mp: 65-69 °C

TLC: 0.50 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.38-7.22 (m, 10H, H-aromatic), 5.82 (d, 1H, J = 3.6 Hz, $Ph_2C\underline{H}OH$), 2.20 (d, 1H, J = 3.6 Hz, $Ph_2CHO\underline{H}$)

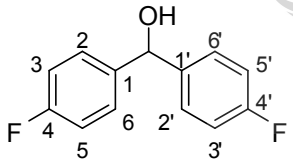
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 143.8 (C1, C1'), 128.5 (C3, C3', C5, C5'), 127.6 (C4, C4'), 126.5 (C2, C2', C6, C6'), 76.2 ($PH_2\underline{C}HOH$)

IR: ν_{max} (ATR) 3279, 1016, 739, 698 cm^{-1}

EIMS (*m/z*): 184 (M, 15%), 167 (M – OH, 30%), 105 (M – C_6H_5 , 100 %)

EIMS/ESI HRMS: M^+ Calcd for $C_{13}H_{12}O_1$, 184.0888; found, 184.0882

Bis-(4-fluoro-phenyl)-methanol (3.14)



Yield: 96%, white solid

Mp: 43-46 °C

TLC: 0.60 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.29 (dd, 4H, J = 8.5 and 5.5 Hz, H2, H2', H6, H6'), 7.00 (t, 4H, J = 8.7 Hz, H3, H3', H5, H5'), 5.76 (d, 1H, J = 2.7 Hz, 4-F-$PH_2C\underline{H}OH$), 2.41 (d, 1H, J = 3.0 Hz, $(4\text{-F-Ph})_2CHO\underline{H}$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 162.2 (d, J = 244.4 Hz, C4, C4'), 139.3 (d, J = 3.2 Hz, C1, C1'), 128.1 (d, J = 8.0 Hz, C2, C2', C6, C6'), 115.3 (d, J = 21.4 Hz, C3, C3', C5, C5'), 74.8 ($(4\text{-F-PH})_2\underline{C}HOH$)

IR: ν_{max} 3260, 1507, 1219, 822 (ATR) cm^{-1}

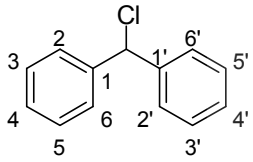
EIMS (*m/z*): 220 (M, 10%), 203 (M – OH, 15%), 201(M – F, 20%), 183 (M – 2F, 20%), 123 (M – C_6H_4F, 100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{13}H_{10}O_1F_2$, 220.0700; found, 220.0696

5.4.2.5 Preparation of the diphenylmethylchlorides

3.13 (1.844 g, 10 mmol) was dissolved in DCM (5 mL) and cooled down to 0 °C. To this mixture was added thionyl chloride (0.88 mL, 12 mmol) in a dropwise manner. The resultant mixture stirred for 2 hours at 0 °C. The reaction was then quenched with Na_2CO_3(aq) (5 mL) and then extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and then dried with magnesium sulfate. The excess organic solvent wash then removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

1-(Chloro-diphenyl)-methine (3.15)



Yield: 91%, clear oil

TLC: 0.79 (4:1 Hexane:EtOAc)

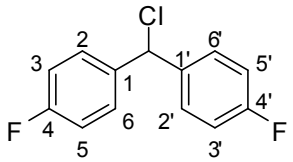
^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.49-7.30 (m, 10H, H-aromatic), 6.18 (s, 1H, $Ph_2C\underline{H}Cl$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 141.0 (C1, C1'), 128.5 (C3, C3'), 128.0 (C4, C4'), 127.7 (C2, C2', C6, C6'), 64.2 ($PH_2\underline{C}HCl$)

IR: ν_{max} (ATR) 1494, 1450, 694 cm^{-1}

EIMS/ESI HRMS: M^+ Calcd for $C_{13}H_{11}Cl_1$, 202.0549 found, 202.0547

1-(Chloro-bis-(4-flouro-phenyl))-methine (3.16)



Yield: 88%, clear oil

TLC: 0.80 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.23 (dd, 4H, *J* = 8.5 and 5.2 Hz, H2, H2', H6, H6'), 6.89 (t, 4H, *J* = 8.7 Hz, H3, H3', H5, H5'), 5.97 (d, 1H, *J* = 2.7 Hz, 4-F-$PH_2C\underline{H}Cl$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 162.3 (d, *J* = 246.4 Hz, C4, C4'), 136.7 (d, *J* = 3.5 Hz, C1, C1'), 129.4 (d, J = 8.5 Hz, C2, C2', C6, C6'), 115.5 (d, *J* = 21.5 Hz, C3, C3', C5, C5'), 62.7 ((4-F-$PH)_2\underline{C}HCl$)

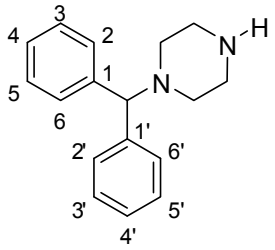
IR: ν_{max} (ATR) 1603, 1221, 832, 557 cm^{-1}

EIMS/ESI HRMS: M^+ Calcd for $C_{13}H_9Cl_1F_2$, 238.0361; found, 238.0356

5.4.2.6 Preparation of the diphenylmethylpiperazines

Piperazine (2.584 g, 30 mmol) was dissolved in acetonitrile (5 mL) and heated to 80 °C. **3.15** (2.029 g, 10 mmol) was dissolved in acetonitrile (5 mL) and slowly added to the heated piperazine mixture. The mixture was then allowed to stir overnight at 80 °C. The acetonitrile was then removed under reduced pressure and the resulting residue suspended between 1 M NaOH (5 mL) and DCM (5 mL). The DCM layer was removed and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic layers washed with water (2 x 5 mL) and then dried with magnesium sulfate. The excess organic solvent wash then removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

1-Benzhydrylpiperazine (3.17)



Yield: 70%, white solid

Mp: 55-60 °C

TLC: 0.53 (9:1 DCM:MeOH)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.43 (d, 4H, *J* = 7.5 Hz, H3, H3', H5, H5'), 7.27 (t, 2H, *J* = 7.7 Hz, H4, H4'), 7.18 (d, 4H, *J* = 8.7 Hz, H2, H2', H6, H6'), 4.13 (s, 1H, $Ph_2C\underline{H}N$), 2.81 (t, 4H, *J* = 4.95, $CHN(C\underline{H_2})_2$), 2.29 (bs, 4H, $(C\underline{H_2})_2NH$), 2.18 (bs, 1H, $N\underline{H}$)

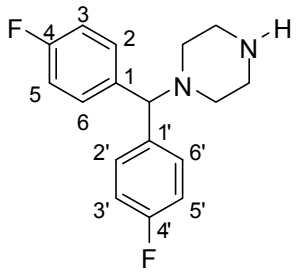
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.7 (C1, C1'), 128.4 (C3, C3', C5, C5'), 128.0 (C4, C4'), 126.9 (C2, C2', C6, C6'), 76.6 ($PH_2\underline{C}HN$), 53.4 ($CHN(\underline{C}H_2)_2$), 46.4 ($(\underline{C}H_2)_2NH$)

IR: ν_{max} (ATR) 3282, 3.026, 2951, 2917, 2812, 1451, 859, 746, 706, 695 cm^{-1}

EIMS (*m/z*): 252 (M, 10%), 207 (35%), 168 (35%), 167 (M – NC_4H_8NH, 100%), 165 (70%), 152 (35%)

EIMS/ESI HRMS: M^+ Calcd for $C_{17}H_{20}N_2$, 252.1626; found, 252.1614

1-[Bis-(4-fluoro-phenyl)-methyl]-piperazine (3.18)



Yield: 74%, white solid

Mp: 80-84 °C

TLC: 0.47 (9:1 DCM:MeOH)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.30 (dd, 4H, *J* = 8.7 and 5.7 Hz, H2, H2', H6, H6'), 6.92 (t, 4H, *J* = 8.7 Hz, H3, H3', H5, H5'), 4.18 (s, 1H, (4-F-Ph)$_2$C<u>H</u>N), 2.86 (t, 4H, *J* = 4.8 Hz, CHN(C<u>H$_2$</u>)$_2$), 2.77 (bs, 1H, N<u>H</u>), 2.32 (bs, 4H, (C<u>H$_2$</u>)$_2$NH)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 161.7 (d, *J* = 243.8 Hz, C4, C4'), 138.0 (d, *J* = 3.2 Hz, C1, C1'), 129.2 (d, *J* = 7.7 Hz, C2, C2', C6, C6'), 115.3 (d, *J* = 21.1 Hz, C3, C3', C5, C5'), 74.8 ((4-F-PH)$_2$<u>C</u>HN), 52.7 (CHN(<u>C</u>H$_2$)$_2$), 46.0 ((<u>C</u>H$_2$)$_2$NH)

IR: ν_{max} (ATR) 2816, 1505, 836, 820 cm^{-1}

EIMS (*m/z*): 288 (M, 5%), 243 (25%), 204 (25%), 203 (M – NC_4H_8NH, 100%), 201 (50%), 183 (55%)

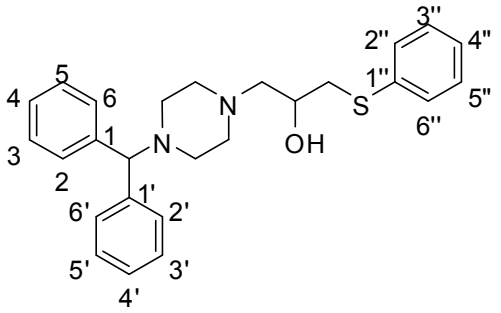
EIMS/ESI HRMS: M^+ Calcd for $C_{17}H_{18}N_2F_2$, 288.1438; found, 288.1432

5.4.2.7 <u>Typical procedure for the aminolysis of epoxides</u>

To a mixture of the epoxide (0.792 mmol) and $Al(OTf)_3$ (0.038 g, 0.079 mmol) in toluene (2 mL) was added **3.17** (0.151 g, 0.792 mmol). The reaction mixture was allowed to stir at 70 °C for 5 hours. The reaction was then quenched with aqueous sodium bicarbonate (5 mL). The reaction mixture was then extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and then dried with magnesium sulfate. The excess

organic solvent wash then removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

1-(4-Benzhydryl-piperazin-1-yl)-3-phenylsulfanyl-propan-2-ol (3.19)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 82%, white solid

Mp: 115-118 °C

TLC: 0.42 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.37 (t, 6H, J = 8.5 Hz, H3, H3', H3'', H5, H5', H5''), 7.24 (t, 6H, J = 7.3 Hz, H2, H2', H2'', H6, H6', H6''), 7.15 (t, 3H, J = 7.7 Hz, H4, H4', H4''), 4.19 (s, 1H, $Ph_2C\underline{H}N$), 3.86-3.78 (m, 1H, $NCH_2C\underline{H}OHCH_2S$), 3.04 (dd, 1H, J = 13.5 and 6.3 Hz, $NCH_2CHOHC\underline{H_{2A}}S$), 2.96 (dd, 1H, J = 13.4 Hz and 5.9 Hz, $NCH_2CHOHC\underline{H_{2B}}S$), 2.63-2.56 (m, 2H, $NC\underline{H_2}CHOHCH_2S$), 2.52-2.30 (m 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

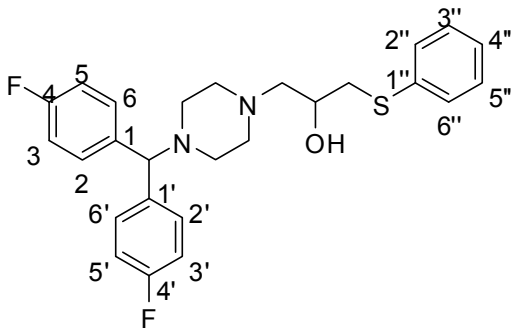
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.6 (C1, C1'), 136.2 (C1''), 129.4 (C3, C3', C5, C5'), 128.9 (C3'', C5''), 128.5 (C2, C2', C6, C6'), 127.9 (C2'', C6''), 126.9 (C4,C4'), 126.1 (C4''), 76.1 ($PH_2\underline{C}HN$), 65.6 ($NCH_2\underline{C}HOHCH_2S$), 62.7 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.5 ($N\underline{C}H_2CHOHCH_2S$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 38.7 ($NCH_2CHOH\underline{C}H_2S$)

IR: ν_{max} (ATR) 3449, 3027, 2946, 2877, 2801, 2756, 1450, 1287, 1151, 1006, 852, 704 cm^{-1}

EIMS (*m/z*): 418 ([M]$^+$, 10%), 341 (2%), 309 (5%), 266 (60%), 251 (10%), 168 (65%), 167 ([Ph_2CH]$^+$ 100%), 152 (65%), 125 (60%), 110 (50%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{26}H_{31}O_1N_2S_1$, 419.2157; found, 419.2150

1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-3-phenylsulfanyl-propan-2-ol (3.20)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 75%, yellow oil

TLC: 0.42 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.36-7.12 (m, 9H, H2, H2', H2'', H3'', H4'', H5'', H6, H6', H6''), 6.94 (t, 4H, *J* = 8.7 Hz, H3, H3', H5, H5), 4.17 (s, (4-F-Ph)$_2$C<u>H</u>N), 3.86-3.77 (m, 1H, NCH$_2$C<u>H</u>OHCH$_2$S), 3.04 (dd, 1H, *J* = 13.5 and 6.3 Hz, NCH$_2$CHOHC<u>H$_{2A}$</u>S), 2.96 (dd, 1H, *J* = 13.4 Hz and 5.9 Hz, NCH$_2$CHOHC<u>H$_{2B}$</u>S), 2.60-2.58 (m, 2H, NC<u>H$_2$</u>CHOHCH$_2$S), 2.41 – 2.33 (m, 8H, (4-F-Ph)$_2$CHN(C<u>H$_2$</u>C<u>H$_2$</u>)$_2$NCH$_2$)

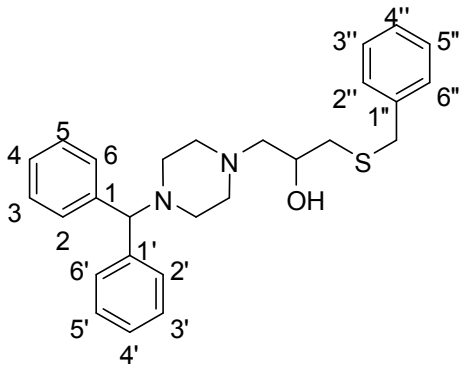
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 161.8 (d, *J* = 244.2 Hz, C4, C4'), 137.1 (d, J = 144.9, C1, C1'), 129.2 (d, *J* = 1.1 Hz, C2, C2', C6, C6'), 129.1 (C3'', C5''), 129.12 (C4''), 128.9 (C2'', C6''), 126. 2 (C1'') 115.4 (d, J = 21.1 Hz, C3, C3', C5, C5'), 74.41 (((4-F-PH)$_2$<u>C</u>HN), 65.6 (NCH$_2$<u>C</u>HOHCH$_2$S), 62.7((4-F-Ph)$_2$CHN(CH$_2$<u>C</u>H$_2$)$_2$NCH$_2$), 53.4 (N<u>C</u>H$_2$CHOHCH$_2$S), 51.7 (((4-F-Ph)$_2$CHN(<u>C</u>H$_2$CH$_2$)$_2$NCH$_2$), 38.7 (NCH$_2$CHOH<u>C</u>H$_2$S)

IR: ν_{max} (ATR) 3415, 2934, 2813, 1504, 1220, 1152, 1006, 825, 738, 690 cm^{-1}

EIMS (*m/z*): 454 ([M]$^+$, 5%), 302 (15%), 301 (45%), 204 (35%), 203 ([4-F-Ph)$_2$CH]$^+$ 100%), 183 (45%)

EIMS/ESI HRMS: M^+ Calcd for $C_{26}H_{28}O_1N_2F_2S_1$, 454.1890; found, 454.1883

1-(4-Benzhydryl-piperazin-1-yl)-3-benzylsulfanyl-propan-2-ol (3.21)



Catalyst: 10 mol% Al(OTf)$_3$

Yield: 86%, white solid

Mp: 95-98 °C

TLC: 0.42 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.39 (d, 4H, J = 7.3 Hz), 7.30-7.22 (m, 9H), 7.16 (t, 2H, J = 7.3 Hz), 4.20 (s, 1H, $Ph_2C\underline{H}N$), 3.75 (s, 2H, $SC\underline{H_2}Ph$), 3.80-3.69 (m, 1H, $NCH_2C\underline{H}OHCH_2S$), 2.62-2.52 (m, 2H, $NC\underline{H_2}CHOHCH_2S$), 2.49 (d, 2H, J = 6.6 Hz, $NCH_2CHOHC\underline{H_2}S$), 2.45-2.62 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

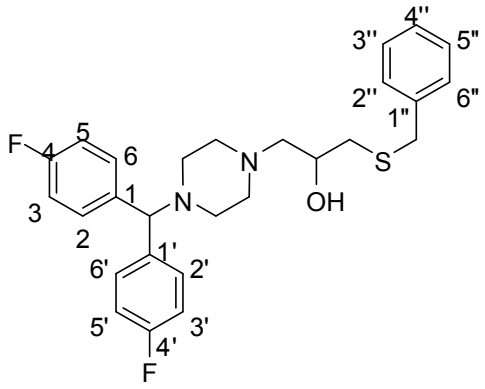
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.7 (C1, C1'), 138.4 (C1''), 129.0 (C3, C3', C5, C5'), 128.5 (C3'', C5''), 127.9 (C2, C2', C6, C6'), 127.9 (C2'', C6''), 127.0 (C4,C4'), 126.9 (C4''), 76.2 ($PH_2\underline{C}HN$), 66.1 ($NCH_2\underline{C}HOHCH_2S$), 62.8 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.4 ($N\underline{C}H_2CHOHCH_2S$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 37.0 ($NCH_2CHOHCH_2S\underline{C}H_2$), 35.9 ($NCH_2CHOH\underline{C}H_2SCH_2$)

IR: ν_{max} (ATR) 3444, 3025, 2954, 2806, 1491, 1450, 1295, 1150, 1093, 1008 cm^{-1}

EIMS (*m/z*): 432 ([M]$^+$, 5%), 341 (5%), 309 (4%), 266 (15%), 265 (43%), 168 (39%), 167 ([Ph_2CH]$^+$ 100%), 152 (35%), 125 (30%)

EIMS/ESI HRMS: $[M+H]^+$Calcd for $C_{27}H_{31}ON_2F_2S$, 469.2125; found, 469.2127

1-Benzylsulfanyl-3-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-propan-2-ol (3.22)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 66%, yellow oil

Mp: 110-114 °C

TLC: 0.42 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.34-7.20 (m, 9H, H-aromatic), 6.95 (t, 4H, *J* = 8.55, H3, H3', H5, H5'), 4.18 (s, 1H, $(4\text{-F-Ph})_2C\underline{H}N$), 3.75 (s, 2H, $SC\underline{H_2}Ph$), 3.79-3.69 (m, 1H, $NCH_2C\underline{H}OHCH_2S$), 2.59-2.57 (m, 2H, $NC\underline{H_2}CHOHCH_2S$), 2.49 (d, 2H, *J* = 6.0 Hz, $NCH_2CHOHC\underline{H_2}S$), 2.37-2.31 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

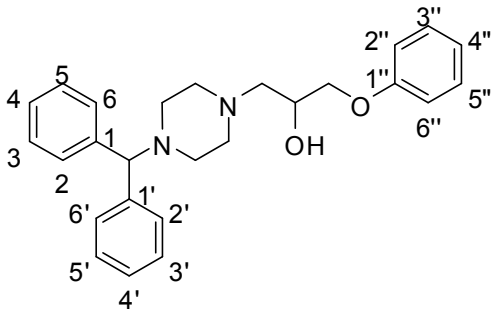
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 161.7 (d, *J* = 243.9 Hz, C4, C4'), 138.2 (d, *J* = 18.2, C1, C1'), 129.2 (d, *J* = 7.7 Hz, C2, C2', C6, C6'), 128.9 (C3'', C4'', C5''), 128.4 (C2'', C6''), 127.0 (C1''), 115.4 (d, *J* = 21.1 Hz, C3, C3', C5, C5'), 74.4 ($PH_2\underline{C}HN$), 66.1 ($NCH_2\underline{C}HOHCH_2S$), 62.7 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.3 ($N\underline{C}H_2CHOHCH_2S$), 51.4 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 37.0 ($NCH_2CHOHCH_2S\underline{C}H_2$), 35.9 ($NCH_2CHOH\underline{C}H_2SCH_2$)

IR: ν_{max} (ATR) 3457, 2938, 2811, 1603, 1221, 1152, 1006, 825 cm^{-1}

ESIMS (*m/z*): 469 ([M+H]$^+$, 100%), 289 (20%)

EIMS/ESI HRMS: M^+ - H Calcd for $C_{27}H_{29}O_1N_2F_2S_1$, 467.1969; found, 467.1935

1-(4-Benzhydryl-piperazin-1-yl)-3-phenoxy-propan-2-ol (3.23)[12]



Catalyst: 5 mol% $Al(OTf)_3$

Yield: 73%, yellow solid

Mp: 106-112 °C

TLC: 0.57 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.25 (d, 4H, *J* = 7.2 Hz, H3, H3', H5, H5'), 7.11 (t, 6H, *J* = 7.5 Hz, H2, H2', H4, H4', H6, H6'), 7.01 (t, 2H, *J* = 7.2 Hz, H3'', H5''), 6.80-6.74 (m, 3H, H2'', H4'', H6''), 4.07 (s, 1H, $Ph_2C\underline{H}N$), 3.95-3.87 (m, 1H, $NCH_2C\underline{H}OHCH_2O$), 3.80 (d, *J* = 5.1 Hz, $NCH_2CHOHC\underline{H_2}O$), 2.54-2.52 (m, 2H, $NC\underline{H_2}CHOHCH_2O$), 2.45-2.29 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

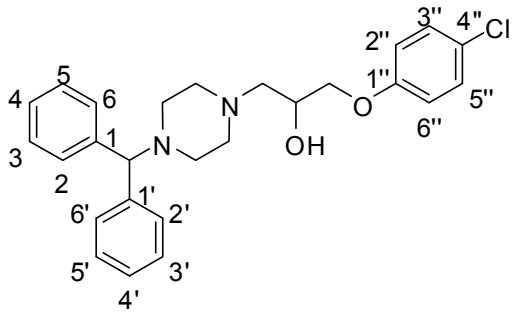
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 158.7 (C1''), 142.7 (C1), 142.6 (C1'), 129.4 (C3'', C5''), 128.5 (C3, C3', C5, C5'), 127.9 (C2, C6), 127.9 (C2', C6'), 126.9 (C4, C4'), 120.9 (C4''), 114.5 (C2'', C6''), 76.2 ($PH_2\underline{C}HN$), 70.2 ($NCH_2CHOH\underline{C}H_2O$), 65.4 ($NCH_2\underline{C}HOHCH_2O$), 60.4 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.5 ($N\underline{C}H_2CHOHCH_2O$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$)

IR: ν_{max} (ATR) 3543, 3041, 2944, 2891, 2843, 2812, 1599, 1491, 1251, 1003, 753, 735 cm^{-1}

ESIMS (*m/z*): 403 ([M+H]$^+$, 100%), 167 ([Ph_2CH]$^+$, 25%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{26}H_{31}O_2N_2$, 403.2386; found, 403.2380

1-(4-Benzhydryl-piperazin-1-yl)-3-(4-chloro-phenoxy)-propan-2-ol (3.24)



Catalyst: 5 mol% $Al(OTf)_3$

Yield: 85%, yellow solid

Mp: 154-160 °C

TLC: 0.59 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.41 (d, 4H, *J* = 7.2 Hz, H3, H3', H5, H5'), 7.29-7.15 (m, 8H, H2, H2', H3'', H4, H4', H5'', H6, H6'), 6.83 (d, 3H, *J* = 9.0 Hz, H2'', H4'', H6''), 4.23 (s, 1H, Ph_2CHN), 4.05-4.02 (m, 1H, $NCH_2CHOHCH_2O$), 3.92 (d, *J* = 4.8 Hz, $NCH_2CHOHCH_2O$), 2.69-2.67 (m, 2H, $NCH_2CHOHCH_2O$), 2.59-2.45 (m, 8H, $Ph_2CHN(CH_2CH_2)_2NCH_2$)

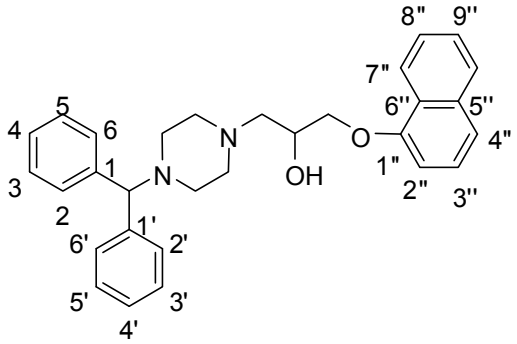
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 157.4 (C1''), 142.6 (C1), 142.6 (C1'), 129.3 (C3'', C5''), 128.5 (C3, C3', C5, C5'), 127.9 (C2, C6), 127.9 (C2', C6'), 126.9 (C4, C4'), 125.79 (C4''), 115.8 (C2'', C6''), 76.1 (PH_2CHN), 70.6 ($NCH_2CHOHCH_2O$), 65.3 ($NCH_2CHOHCH_2O$), 60.3 ($Ph_2CHN(CH_2CH_2)_2NCH_2$), 53.5 ($NCH_2CHOHCH_2O$), 51.9 ($Ph_2CHN(CH_2CH_2)_2NCH_2$)

IR: ν_{max} (ATR) 3427, 2945, 2811, 2361, 1494, 1452, 1251, 999, 705 cm^{-1}.

ESIMS (*m/z*): 437 ([M+H]$^+$, 100%), 429 (30%), 167 ([Ph_2CH]$^+$, 20%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{26}H_{30}O_2N_2Cl_1$, 437.1996; found, 437.2003

1-(4-Benzhydryl-piperazin-1-yl)-3-(naphthalen-1-yloxy)-propan-2-ol (3.26)[12]



Catalyst: 5 mol% $Al(OTf)_3$

Yield: 88%, orange solid

Mp: 104-108 °C

TLC: 0.62 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 8.16-8.13 (m, 1H, H10''), 7.68-7.65 (m, 1H, H9''), 7.36-7.03 (m, 14H, H-aromatic), 6.68 (d, 1H, J = 7.2 Hz, H2''), 4.12 (s, 1H, $Ph_2C\underline{H}N$), 4.13-3.95 (m, 3H, $NCH_2C\underline{H}OHCH_2O$, $NCH_2CHOHC\underline{H_2}O$), 2.60-2.50 (m, 2H, $NC\underline{H_2}CHOHCH_2O$), 2.42-2.24 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

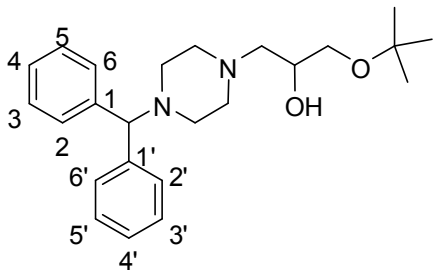
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 154.4 (C1''), 142.6 (C1), 142.6 (C1'), 134.4 (C5''), 128.4 (C3, C3', C5, C5'), 127.8 (C10''), 127.4 (C2, C2', C6, C6'), 126.9 (C4, C4'), 126.3 (C9''), 125.8 (C3''), 125.6 (C6''), 125.1 (C8''), 121.9 (C7''), 120.5 (C4''), 104.8 (C2), 76.1 ($PH_2\underline{C}HN$), 70.5 ($NCH_2CHOH\underline{C}H_2O$), 65.5 ($NCH_2\underline{C}HOHCH_2O$), 60.8 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.6 ($N\underline{C}H_2CHOHCH_2O$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$)

IR: ν_{max} (ATR) 3487, 3015, 3009, 2811, 1580, 149, 1397, 1274, 1102, 1007, 758, 704 cm^{-1}

ESIMS (*m/z*): 453 ($[M+H]^+$, 100%), 242 (30%), 167 ($[Ph_2CH]^+$, 20%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{30}H_{33}O_2N_2$, 453.2542; found, 453.2532

1-(4-Benzhydryl-piperazin-1-yl)-3-tert-butoxy-propan-2-ol (3.27)



Catalyst: 5 mol% $Al(OTf)_3$

Yield: 88%, white solid

Mp: 98-101 °C

TLC: 0.29 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.41 (d, 4H, J = 7.2 Hz, H2, H2', H6, H6') 7.26 (t, 4H, J = 7.3 Hz, H3, H3', H5, H5'), 7.16 (t, 2H, J = 7.4 Hz, H4, H4'), 4.22 (s, 1H, $Ph_2C\underline{H}N$), 3.82-3.78 (m, 1H, $NCH_2C\underline{H}OHCH_2O$), 3.35 (d, J = 5.1 Hz, $NCH_2CHOHC\underline{H}_2O$), 2.65-2.63 (m, 2H, $NC\underline{H}_2CHOHCH_2O$), 2.47-2.38 (m, 8H, $Ph_2CHN(C\underline{H}_2C\underline{H}_2)_2NCH_2$), 1.19 (s, 12H, $OC(C\underline{H}_3)_3$)

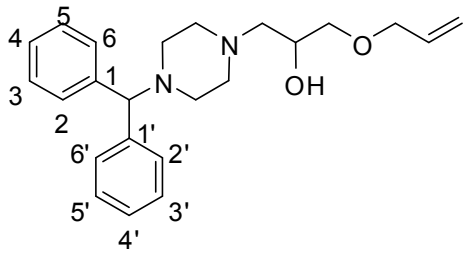
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.7 (C1), 142.7 (C1'), 128.4 (C3, C3', C5, C5'), 127.8 (C2, C2', C6, C6'), 126.8 (C4, C4'), 76.2 ($PH_2\underline{C}HN$), 72.9 ($O\underline{C}(CH_3)_3$), 66.4 ($NCH_2CHOH\underline{C}H_2O$), 64.5 ($NCH_2\underline{C}HOHCH_2O$), 60.9 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.5 ($N\underline{C}H_2CHOHCH_2O$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 27.4 ($OC(\underline{C}H_3)_3$)

IR: ν_{max} (ATR) 3486, 2969, 2801, 2784, 1452, 1194, 1156, 1104, 1008, 895, 848, 696 cm^{-1}

ESIMS (*m/z*): 383 ($[M+H]^+$, 100%), 167 ($[Ph_2CH]^+$, 40%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{24}H_{35}O_2N_2$, 383.2699; found, 383.2659

1-Allyloxy-3-(4-benzhydryl-piperazin-1-yl)-propan-2-ol (3.28)



Catalyst: 5 mol% $Al(OTf)_3$

Yield: 79%, yellow oil

TLC: 0.23 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.49 (d, 4H, *J* = 6.9 Hz, H2, H2', H6, H6'), 7.26 (t, 4H, *J* = 7.4 Hz, H3, H3', H5, H5'), 7.16 (t, 2H, *J* = 7.2 Hz, H4, H4'), 5.90 (ddt, 1H, *J* = 17.4, 10.7 and 5.2 Hz, $OCH_2C\underline{H}CH_2$), 5.26 (dq, 1H, *J* = 17.2 and 1.6 Hz, $OCH_2CHC\underline{H}_{2A}$), 5.17 (dq, 1H, *J* = 10.7 and 1.6 Hz, $OCH_2CHC\underline{H}_{2B}$), 4.22 (s, 1H, $PH_2C\underline{H}N$), 4.02 (dt, 2H, *J* = 5.6 and 1.6 Hz, $OC\underline{H}_2CHCH_2$), 3.91-3.83 (m, 1H, $NCH_2C\underline{H}OHCH_2O$), 3.47 (dd, 1H, *J* = 10.1 and 4.9 Hz, $NCH_2CHOHC\underline{H}_{2A}O$), 3.41 (dd, 1H, *J* = 9.8 and 4.9 Hz, $NCH_2CHOHC\underline{H}_{2B}O$), 3.32 (s, 1H, O<u>H</u>), 2.68-2.62 (m, 2H, $NC\underline{H}_2CHOHCH_2O$), 2.56-2.35 (m, 8H, $Ph_2CHN(C\underline{H}_2C\underline{H}_2)_2NCH_2$)

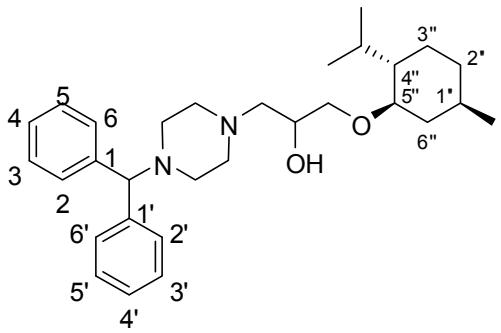
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.6 (C1), 142.6 (C1'), 134.5 ($OCH_2\underline{C}HCH_2$), 128.4 (C2, C2', C6, C6'), 127.8 (C3, C3', C5, C5'), 126.8 (C4, C4'), 117.1 ($OCH_2CH\underline{C}H_2$), 76.6 ($PH_2\underline{C}HN$), 72.5 ($O\underline{C}H_2CHCH_2$), 72.3 ($NCH_2CHOH\underline{C}H_2O$), 65.9 ($NCH_2\underline{C}HOHCH_2O$), 60.4 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.4 ($N\underline{C}H_2CHOHCH_2O$), 51.8 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$)

IR: ν_{max} (ATR) 3472, 2810, 1451, 1138, 1006, 705 cm^{-1}

ESIMS (*m/z*): 367 ($[M+H]^+$, 100%), 167 ($[Ph_2CH]^+$, 30%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{23}H_{31}O_2N_2$, 367.2386; found, 367.2387

1-(4-Benzhydryl-piperazin-1-yl)-3-(2-isopropyl-5-methyl-cyclohexyloxy)-propan-2-ol (3.29)



Catalyst: 5 mol% $Al(OTf)_3$

Yield: 72%, yellow oil, diastereomeric mixture

TLC: 0.30 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.39 (d, 4H, *J* = 7.2 Hz, H3, H3', H5, H5'), 7.25 (t, 4H, *J* = 7.5 Hz, H2, H2', H6, H6'), 7.15 (d, 2H, *J* = 2.35 Hz, H4, H4'), 4.19 (s, 1H, $PH_2C\underline{H}N$), 3.84-3.76 (m, 1H, $NCH_2C\underline{H}OHCH_2O$), 3.64-3.56 (m, 1H, $NCH_2CHOHC\underline{H}_{2A}O$), 3.26 (dd, 1H, *J* = 9.8 and 5.6 Hz, $NCH_2CHOHC\underline{H}_{2B}O$), 3.02 (td, 1H , *J* = 10.7 and 4.1 Hz, H3''), 2.63 (br s, 2H, $NC\underline{H}_2CHOHCH_2O$), 2.63-2.35 (m, 8H, $Ph_2CHN(C\underline{H}_2C\underline{H}_2)_2NCH_2$), 2.16 (sp d, 1H, *J* = 7.1 and 2.7 Hz, H8''), 2.06 (br d, 1H, *J* = 12.3 Hz, $H2''_{A'}$), 1.64-1.55 (m, 2H, $H5''_{A'}$, $H6''_{A'}$), 1.38-1.18 (m, 2H, H1'', H4''), 0.89 (d, 3H, *J* = 7.2 Hz, H9''), 0.86 (d, 3H, *J* = 7.5 Hz, H10''), 0.74 (d, 3H, *J* = 6.6 Hz, H7''), 1.01-0.73 (m, 3H, $H2''_{B'}$, $H6''_{B'}$, $H5''_{B'}$)

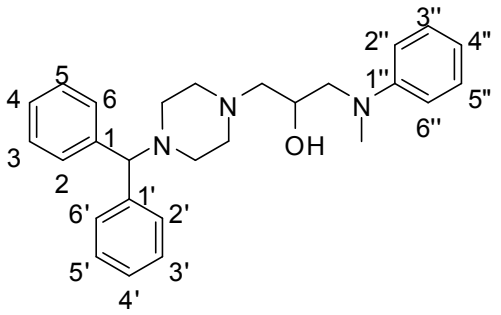
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.7 (C1, C1'), 128.4 (C2, C2', C6, C6'), 127.9 (C3, C3', C5, C5'), 126.9 (C4, C4'), 79.8 (C3''), 76.2 ($PH_2\underline{C}HN$), 71.1 ($NCH_2CHOH\underline{C}H_2O$), **70.9 ($NCH_2CHOH\underline{C}H_2O$)**, 66.3 ($NCH_2\underline{C}HOHCH_2O$), **66.3 ($NCH_2\underline{C}HOHCH_2O$)**, 61.0 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), **60.7 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$)**, 53.5 ($N\underline{C}H_2CHOHCH_2O$), 52.0 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 48.14 (C5''), 48.10 (C6''), 40.2 (C2''), 34.5 (C6''), 31.5 (C1''), 25.61 (C8''), **25.56 (C8'')**, 23.3 (C5''), 22.3 (C7''), 20.9 (C9''), 16.2 (C10'')

IR: ν_{max} (ATR) 2921, 1451, 1111, 1007, 908, 730, 704 cm^{-1}

EIMS (*m/z*): 465 ([M+H]$^+$, 100%), 167 ([Ph_2CH]$^+$, 15%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{30}H_{45}O_2N_2$, 465.3481; found, 465.3491

1-(4-Benzhydryl-piperazin-1-yl)-3-(methyl-phenyl-amino)-propan-2-ol (3.25)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 78%, yellow solid

Mp: 70-78 °C

TLC: 0.23 (2:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.45 (d, 4H, *J* = 8.3 Hz, H-aromatic), 7.33-7.18 (m, 8H, H-aromatic), 6.77 (t, 2H, *J* = 8.3 Hz, H-aromatic), 6.75 (t, 1H, *J* = 7.5 Hz, H- aromatic), 4.24 (s, 1H, $PH_2C\underline{H}N$), 4.05 – 3.97 (m, 1H, $NCH_2C\underline{H}OHCH_2NCH_3$), 3.38 (d, 2H, *J* = 5.7 Hz, $NCH_2CHOHC\underline{H_2}NCH_3$), 3.02 (s, 3H, NCH_3), 2.70-2.62 (m, 2H, $NC\underline{H_2}CHOHCH_2NCH_3$), 2.47-2.37 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

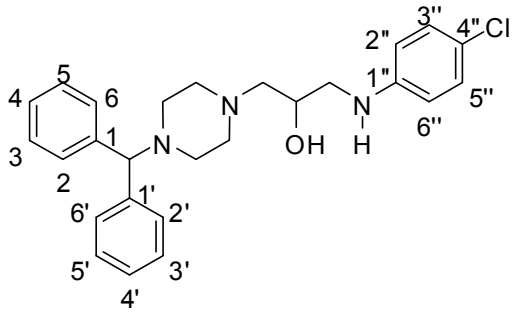
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 149.7 (C1''), 142.6 (C1, C1'), 129.1 (C3, C3', C5, C5'), 128.4 (C3'', C5''), 127.8 (C4. C4'), 126.8 (C4''), 116.4 (C2'', C6''), 112.3 (C2, C2', C6, C6'), 76.1 ($PH_2\underline{C}HN$), 65.3 ($NCH_2\underline{C}HOHCH_2NCH_3$), 61.9 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 57.3 ($NCH_2CHOH\underline{C}H_2NCH_3$), 53.5 ($N\underline{C}H_2CHOHCH_2NCH_3$), 52.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 39.5 ($N\underline{C}H_3$)

IR: ν_{max} (ATR) 3421, 2933, 2813, 1599, 1506, 1449, 1138, 1076, 1006 cm^{-1}.

ESIMS (*m/z*): 416 ([M+H]$^+$, 100%), 167 ([Ph_2CH]$^+$, 20%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{27}H_{34}O_1N_3$, 416.2702; found, 416.2692

1-(4-Benzhydryl-piperazin-1-yl)-3-(4-chloro-phenylamino)-propan-2-ol (3.30)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 86%, yellow solid

Mp: 144-150 °C

TLC: 0.30 (4:1 Hexane:EtOAc to 9:1 DCM:MeOH)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.33 (d, 4H, J = 7.3 Hz, H-aromatic), 7.17 (t, 4H, J = 7.3 Hz, H-aromatic), 7.10 (t, 2H, J = 7.3 Hz, H-aromatic), 7.02 (d, 2H, J = 8.7 Hz, H-aromatic), 6.46 (d, 2H, J = 8.7 Hz, H-aromatic), 4.15 (s, 1H, $PH_2C\underline{H}N$), 4.06 (br s, 1H, N$\underline{H}$), 3.88-3.80 (m, 1H, $NCH_2C\underline{H}OHCH_2NH$), 3.13 (dd, 1H, J = 12.2 and 3.5 Hz, $NCH_2CHOHC\underline{H_{2A}}NH$), 2.91 (dd, 1H, J = 12.5 and 6.2 Hz, $NCH_2CHOHC\underline{H_{2B}}NH$), 2.64-2.56 (m, 2H, $NC\underline{H_2}CHOHC\underline{H_2}NH$), 2.46-2.27 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

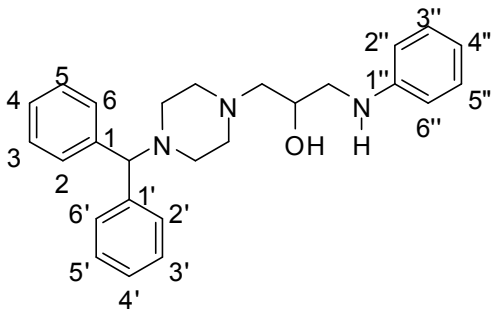
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 147.0 (C1''), 142.6 (C1, C1'), 129.0 (C2'', C2''), 128.5 (C2, C2', C6, C6'), 127.9 (C3, C3', C5, C5'), 127.0 (C3'', C5''), 122.1 (C4''), 114.1 (C4, C4'), 76.1 ($PH_2\underline{C}HN$), 65.0 ($NCH_2\underline{C}HOHCH_2NH$), 61.3 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.5 ($N\underline{C}H_2CHOHCH_2NH$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 47.7 ($NCH_2CHOH\underline{C}H_2NH$)

IR: ν_{max} (ATR) 3407, 2932, 2811, 1598, 1451, 1104, 1004, 813, 748, 705 cm^{-1}

ESIMS (*m/z*): 436 ([M+H]$^+$, 100%), 420 (35%), 417 (25%), 364 (30%), 296 (30%), 291 (20%), 167 ([Ph_2CH]$^+$, 25%)

EIMS/ESI HRMS: M^+ + H Calcd for $C_{26}H_{31}O_1N_3{}^{35}Cl_1$, 436.2156; found, 436.2153, M^+ + H Calcd for $C_{26}H_{31}O_1N_3{}^{37}Cl_1$, 438.2126; found, 438.2118

1-(4-Benzhydryl-piperazin-1-yl)-3-phenylamino-propan-2-ol (3.31)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 88%, yellow solid

Mp: 132-135 °C

TLC: 0.46 (1:2 Hexane:EtOAc to 9:1 DCM:MeOH)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.32 (d, 4H, J = 7.2 Hz, H3, H3', H5, H5'), 7.22-7.17 (m, 4H, H2, H2', H6, H6'), 7.13-7.07 (m, 4H, H4, H4', H3'', H5''), 6.65-6.53 (m, 3H, H2'', H6'', H4''), 4.15 (s, 1H, $PH_2C\underline{H}N$), 4.04 (bs, 1H, $N\underline{H}$), 3.90 – 3.82 (m, 1H, $NCH_2C\underline{H}OHCH_2NH$), 3.18 (d, 1H, J = 12.0 Hz, $NCH_2CHOHC\underline{H}_{2A}NH$), 2.96 (dd, 1H, J = 11.9 and 5.9 Hz, $NCH_2CHOHC\underline{H}_{2B}NH$), 2.64-2.57 (m, 2H, $NC\underline{H}_2CHOHCH_2NH$), 2.48-2.29 (m, 8H, $Ph_2CHN(C\underline{H}_2C\underline{H}_2)_2NCH_2$)

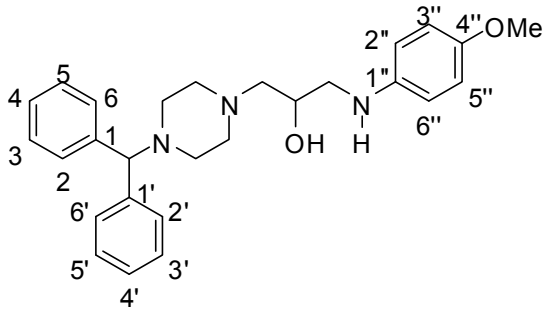
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 148.4 (C1''), 142.6 (C1, C1'), 128.2 (C2'', C6''), 128.5 (C2, C2', C6, C6'), 127.9 (C3, C3', C5, C5'), 126.9 (C3'', C5''), 117.6 (C4''), 113.1 (C4, C4'), 76.1 ($PH_2\underline{C}HN$), 65.1 ($NCH_2\underline{C}HOHCH_2NH$), 61.4 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.5 ($N\underline{C}H_2CHOHCH_2NH$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 47.6 ($NCH_2CHOH\underline{C}H_2NH$)

IR: ν_{max} (ATR) 3420, 3010, 2980, 2804, 1602, 1507, 1308, 1102, 1001, 749, 706 cm^{-1}

ESIMS (*m/z*): 402 ($[M+H]^+$, 100%), 167 ($[Ph_2CH]^+$, 35%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{26}H_{32}O_1N_3$, 402.2545; found, 402.2547

1-(4-Benzhydryl-piperazin-1-yl)-3-(4-methoxy-phenylamino)-propan-2-ol (3.32)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 81%, yellow solid

Mp: 120-125 °C

TLC: 0.32 (2:1 Hexane:EtOAc to 9:1 DCM:MeOH)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.42 (d, 4H, *J* = 7.1 Hz, H3, H3', H5, H5'), 7.27 (t, 4H, *J* = 7.1 Hz, H2, H2', H6, H6'), 7.21-7.15 (t, 2H, *J* = 7.1 Hz, H4, H4'), 6.79 (d, 2H, *J* = 8.7 Hz, H2'', H6''), 6.63 (d, 2H, *J* = 8.7 Hz, H3'', H5''), 4.22 (s, 1H, $PH_2C\underline{H}N$), 3.97-3.89 (m, 1H, $NCH_2C\underline{H}OHCH_2NH$), 3.75 (s, 3H, $PhOCH_3$), 3.20 (dd, 1H, *J* = 12.2 and 3.8 Hz, $NCH_2CHOHC\underline{H_{2A}}NH$), 2.98 (dd, 1H, *J* = 12.3 and 6.3 Hz, $NCH_2CHOHC\underline{H_{2B}}NH$), 2.67-2.56 (m, 2H, $NC\underline{H_2}CHOHCH_2NH$), 2.53-2.35 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

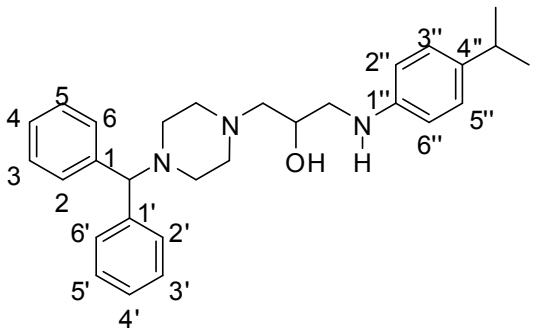
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 152.1 (C1''), 142.6 (C1,C1'), 142.5 (C4''), 128.4 (C2, C2', C6, C6'), 127.8 (C3'', C5''), 126.9 (C4, C4'), 114.7 (C2'', C6''), 114.4 (C3'', C5''), 76.1 ($PH_2\underline{C}HN$), 65.1 ($NCH_2\underline{C}HOHCH_2NH$), 61.4 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 55.7 ($PhO\underline{C}H_3$), 53.4 ($N\underline{C}H_2CHOHCH_2NH$), 51.9 ($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 48.6 ($NCH_2CHOH\underline{C}H_2NH$)

IR: ν_{max} (ATR) 3391, 2937, 2812, 1511, 1451, 1234, 1037, 1006, 818, 747, 705 cm^{-1}

ESIMS (*m/z*): 432 ($[M+H]^+$, 100%), 167 ($[Ph_2CH]^+$, 40%)

EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{27}H_{34}O_2N_3$, 432.2651; found, 432.2654

1-(4-Benzhydryl-piperazin-1-yl)-3-(4-isopropyl-phenylamino)-propan-2-ol (3.33)



Catalyst: 10 mol% $Al(OTf)_3$

Yield: 67%, yellow oil

TLC: 0.41 (1:1 Hexane:EtOAc to 9:1 DCM:MeOH)

^1H NMR: (300 MHz, $CDCl_3$) δ_H : δ_H 7.46 (d, 4H, *J* = 7.4 Hz, H3, H3', H5, H5'), 7.31 (t, 4H, *J* = 7.4 Hz, H2, H2', H6, H6'), 7.06 (t, 2H, *J* = 7.4 Hz, , H4, H4'), 6.95 (d, 2H, *J* = 8.4 Hz, H2'', H6''), 6.48 (d, 2H, *J* = 8.4 Hz, H3'', H5''), 4.12 (s, 1H, $PH_2C\underline{H}N$), 3.87-3.79 (m, 1H, $NCH_2C\underline{H}OHCH_2NH$), 3.13 (dd, 1H, *J* = 12.4, 3.6 Hz, $NCH_2CHOHC\underline{H_{2A}}NH$), 2.92 (dd, 1H, *J* = 12.4, 6.5 Hz, $NCH_2CHOHC\underline{H_{2B}}NH$), 2.71 (sp, 1H, *J* = 6.9 Hz, $(CH_3)_2C\underline{H}$), 2.60–2.50 (m, 2H, $NC\underline{H_2}CHOHCH_2NH$), 2.45-2.25 (m, 8H, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$), 1.11 (d, 6H, *J* = 6.9 Hz, $Ph_2CHN(C\underline{H_2}C\underline{H_2})_2NCH_2$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 146.3 (C1''), 142.6 (C1, C1'), 138.1 (C4''), 128.5 (C2, C2', C6, C6'), 127.8 (C3'', C5''), 127.0 (C2'', C6''), 126.9 (C4, C4'), 113.1 (C3'', C5''), 76.1 ($PH_2\underline{C}HN$), 65.1 ($NCH_2\underline{C}HOHCH_2NH$), 61.4 ($Ph_2CHN(CH_2\underline{C}H_2)_2NCH_2$), 53.4 ($N\underline{C}H_2CHOHCH_2NH$), 51.9

($Ph_2CHN(\underline{C}H_2CH_2)_2NCH_2$), 47.9 ($NCH_2CHOH\underline{C}H_2NH$), 33.1 ($(CH_3)_2\underline{C}H$), 24.2 ($\underline{C}H_3)_2CH$)

IR: ν_{max} (ATR) 3411, 2963, 2797, 1615, 1519, 1451, 1138 cm^{-1}

ESIMS (*m/z*): 444 ($[M+H]^+$, 100%), 167 ($[Ph_2CH]^+$, 10%)

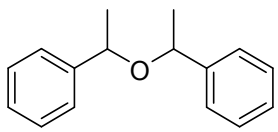
EIMS/ESI HRMS: $M^+ + H$ Calcd for $C_{29}H_{38}O_1N_3$, 444.3015; found, 444.3007

5.4.3 The nucleophilic substitution of "activated" alcohols using aluminium triflate as a Lewis acid catalyst

5.4.3.1 General procedure for the $Al(OTf)_3$ catalysed nucleophilic substitution of benzhydrol

To a mixture of benzhydrol (0.2 g, 1.09 mmol) and $Al(OTf)_3$ (0.005 g, 1 mol%) in nitroethane (2 mL) was added 1 equivalent of the appropriate nucleophile. The mixture was stirred for 1 hour at 70 °C. The reaction was then quenched with the addition of saturated aqueous sodium bicarbonate (5 mL). The reaction mixture was extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

1,1'-Oxybis(ethane-1,1-diyl)dibenzene (4.1)[13]



Yield: 99%, clear oil, diastereomeric mixture

TLC: 0.89 (4:1 Hexane:EtOAc)

^1H NMR: (400 MHz, $CDCl_3$) δ_H : 7.30-7.12 (m, 10H, H-aromatic), 4.45 (q, 2H, J = 6.6 Hz, ($PhC\underline{H}CH_3)_2O$), **4.17 (q, 2H, J = 6.6 Hz, ($PhC\underline{H}CH_3)_2O$)**, 1.39 (d, 6H, J = 6.6 Hz, ($PhCHC\underline{H_3})_2O$), 1.31 **(d, 6H, J = 6.6 Hz, ($PhCHC\underline{H_3})_2O$)**

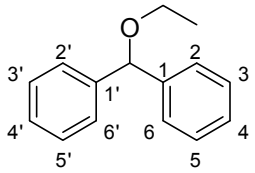
^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 144.2 (*ipso*), **144.1 (*ipso*)**, 128.4 (*meta*), **128.2 (*meta*)**, 127.3 (*para*), **127.1 (*para*)**, 126.3 (*ortho*), **126.2 (*ortho*)**, 74.6 ($(PhCHCH_3)_2O$, **74.4 ($(PhCHCH_3)_2O$)**, 24.7 ($(PhCHCH_3)_2O$), **23.0 ($(PhCHCH_3)_2O$)**

IR: ν_{max} (ATR) 3027, 2973, 2927, 1492, 1450, 1281, 1086, 759, 697, 425 cm^{-1}

EIMS (*m/z*): 105 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{16}H_{18}O$, 226.1358; found, 226.1335

(Ethoxymethylene)dibenzene (4.2)[14]



Yield: 98%, clear oil

TLC: 0.86 (4:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 7.40 (d, 4H, *J* = 7.2 Hz, H2, H2', H6, H6'), 7.35 (t, 4H, *J* = 7.2 Hz, H3, H3', H5, H5'), 7.30-7.25 (m, 2H, H4, H4'), 5.40 (s, 1H, $Ph_2CHOCH_2CH_3$), 3.56 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 1.31 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3)

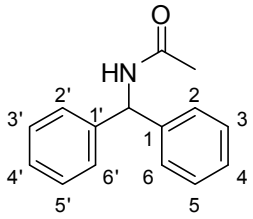
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.5 (C1, C1'), 128.3 (C3, C3', C5, C5'), 127.2 (C4, C4'), 126.9 (C1, C1', C6, C6'), 83.4 ($Ph_2CHOCH_2CH_3$), 64.4 ($Ph_2CHOCH_2CH_3$), 15.2 ($Ph_2CHOCH_2CH_3$)

IR: ν_{max} (ATR) 3027, 2974, 2866, 1493, 1452, 1093, 1072, 739, 696, 414 cm^{-1}

EIMS (*m/z*): 212 (M, 20%), 168 (20%), 167 (30%), 166 (20%), 136 (M – C_6H_5, 20%), 105 (20%)

EIMS/ESI HRMS: M^+ Calcd for $C_{15}H_{16}O$, 212.1201; found, 212.1188

_N_-Benzhydrylacetamide (4.3)[15]



Yield: 43%, White solid

Mp: 137-142 °C

TLC: 0.38 (1:1 Hexane:EtOAc)

H^1 NMR: (300 MHz, $CDCl_3$) δ_H : 7.30-7.19 (m, 10H, H-aromatic), 6.38 (br s, 1H, N<u>H</u>), 6.21 (d, 1H, J = 8.1 Hz, $Ph_2C\underline{H}$), 1.98 (s, 3H, $COC\underline{H_3}$)

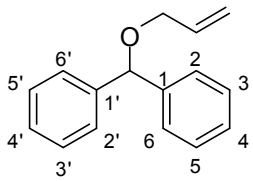
C^{13} NMR: (75 MHz, $CDCl_3$) δ_C : 169.2 (<u>C</u>=O), 141.5 (C1, C1'), 128.6 (C3, C3', C5, C5'), 127.4 (C2, C2', C6, C6', C4, C4'), 56.9 ($Ph_2\underline{C}H$), 23.2 ($CO\underline{C}H_3$)

IR: ν_{max} (ATR) 3254, 2160, 2030, 1643, 1541, 1288, 696, 551, 447 cm^{-1}

EIMS (*m/z*): 225 (M, 100%), 182 ($C_{13}H_{14}$, 60%), 165 (50%), 106 (40%), 104 (40%)

EIMS/ESI HRMS: M^+ Calcd for $C_{15}H_{15}NO$, 225.1154; found, 225.1134

(Allyloxymethylene)dibenzene (4.4)[16]



Yield: 94%, clear oil

TLC: 0.89 (4:1 Hexane:EtOAc)

H^1 NMR: (300 MHz, $CDCl_3$) δ_H : 7.34-7.22 (m, 10H, H – aromatic), 5.98 (ddt, 1H, J = 17.3, 10.4 and 5.7 Hz, $OCH_2C\underline{H}CH_2$), 5.43 (s, 1H, $Ph_2C\underline{H}$), 5.31 (dq, 1H, J =

17.3 and 1.8 Hz, $OCH_2CHC\underline{H}_{2A}$), 5.20 (dq, 1H, *J* = 10.4 and 1.6 Hz, $OCH_2CHC\underline{H}_{2B}$), 4.02 (dt, 2H, *J* = 5.7 and 1.5 Hz, $OC\underline{H}_2CHCH_2$)

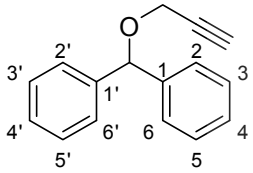
C^{13} NMR: (75 MHz, $CDCl_3$) δ_C : 142.2 (C1, C1'), 134.8 ($OCH_2\underline{C}HCH_2$), 128.4 (C3, C3', C5, C5'), 127.4 (C4, C4'), 127.0 (C2, C2', C6, C6'), 116.9 ($OCH_2C\underline{C}H_2$), 82.6 ($Ph_2\underline{C}H$), 69.7 ($O\underline{C}H_2CHCH_2$)

IR: ν_{max} (ATR) 3028, 1725, 1658, 1449, 1276, 1027, 919, 696, 638, 464 cm^{-1}

EIMS (*m/z*): 224 (M, 10%), 182 ($C_{13}H_{14}$, 80%), 168 ($C_{13}H_{12}$, 80%), 167 (100%), 165 (90%), 152 (70%), 147 (70%), 105 (90%)

EIMS/ESI HRMS: M^+ Calcd for $C_{16}H_{16}O$, 224.1201; found, 224.1197

(Prop-2-ynyloxy)methylene)dibenzene (4.5)[17]



Yield: 99%, clear oil

TLC: 0.78 (4:1 Hexane:EtOAc)

H^1 NMR: (300 MHz, $CDCl_3$) δ_H : 7.51 (d, 4H, *J* = 7.6 Hz, H2, H2', H6, H6'), 7.45 (t, 4H, *J* = 7.4 Hz, H3, H3', H5, H5'), 7.37 (t, 2H, *J* = 7.2 Hz, H4, H4'), 5.82 (s, 1H, $Ph_2C\underline{H}$), 4.28 (d, 2H, *J* = 2.4 Hz, $OC\underline{H}_2CCH$), 2.56 (t, 1H, *J* = 2.0 Hz, $OCH_2CC\underline{H}$)

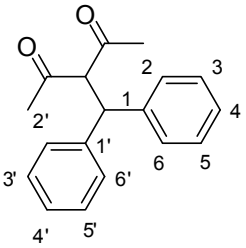
C^{13} NMR: (75 MHz, $CDCl_3$) δ_C : 141.1 (C1, C1'), 128.3 (C3, C3', C5, C5'), 127.6 (C4, C4'), 127.1 (C2, C2', C6, C6'), 81.5 ($PH_2\underline{C}H$), 79.6 ($OCH_2\underline{C}CH$), 74.6 ($OCH_2C\underline{C}H$), 55.6($O\underline{C}H_2CCH$)

IR: ν_{max} (ATR) 3288, 3028, 2855, 1493, 1452, 1259, 1065, 1026, 740, 696, 578, 468 cm^{-1}

EIMS (*m/z*): 222 (m, 10%), 182 ($C_{13}H_{14}$, 60%), 168 ($C_{13}H_{12}$, 30%) 167 (90%), 166 (80%), 152 (50%), 145 (90%), 115 (30%), 105 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{16}H_{14}O$, 222.1045; found, 222.1028

3-Benzhydrylpentane-2,4-dione (4.6)[13]



Yield: 96%, white solid

Mp: 111-113 °C

TLC: 0.33 (8:1 Hexane:EtOAc)

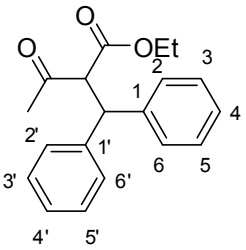
^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 7.27 (d, 4H, *J* = 7.2 Hz, H2, H2', H6, H6'), 7.24 (t, 4H, *J* = 7.6 Hz, H3, H3', H5, H5'), 7.14 (t, 2H, *J* = 6.8 Hz, H4, H4'), 4.89 (d, 1H, *J* = 12.4 Hz, $Ph_2C\underline{H}$), 4.71 (d, 1H, *J* = 12.4 Hz, $Ph_2CHC\underline{H}(COCH_3)_2$), 1.98 (s, 6H, $COC\underline{H}_3$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 202.7 ($\underline{C}OCH_3$), 141.1 (C1, C1), 128.7 (C3, C3', C5, C5'), 127.6 (C4, C4'), 126.8 (C2, C2', C6, C6'), 74.2 ($Ph_2\underline{C}H$), 51.0 ($Ph_2CH\underline{C}H(COCH_3)_2$), 29.5 ($CO\underline{C}H_3$)

IR: ν_{max} (ATR) 2160, 2031, 1692, 1355, 1183, 1153, 756, 699, 539, 510, 416 cm^{-1}

EIMS (*m/z*): 266 (M, 5%), 223 (M – $COCH_3$, 50%), 167 (M – $C(COCH_3)_2$, 45%), 165 (50%)

Ethyl-2-benzhydryl-3-oxobutanoate (4.7)[13]



Yield: 80%, white solid

Mp: 84-86 °C

TLC: 0.35 (4:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 7.28-7.21 (m, 8H, H2, H2', H3, H3', H5, H5', H6, H6'), 7.14-7.16 (m, 2H, H4, H4'), 4.99 (d, 1H, J = 12.0 Hz, $Ph_2C\underline{H}$), 4.27 (d, 1H, J = 12.0 Hz, $Ph_2CHC\underline{H}(COCH_3)(COOCH_2CH_3)$), 3.96 (q, 2H, J = 6.8 Hz, $Ph_2CHCH(COCH_3)(COOC\underline{H}_2CH_3)$), 2.08 (s, 3H, $Ph_2CHCH(COC\underline{H}_3)(COOCH_2CH_3)$), 0.98 (t, 3H, J = 7.0 Hz, $Ph_2CHCH(COCH_3)(COOCH_2C\underline{H}_3)$)

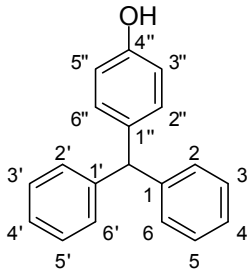
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 201.8 ($\underline{C}OCH_3$), 167.7 ($\underline{C}OOCH_2CH_3$), 141.4 (C1, C1'), 128.7 (C3, C3', C5, C5'), 127.7 (C4, C4'), 126.9 (C2, C2', C6, C6'), 65.2 ($Ph_2\underline{C}H$), 61.5 ($O\underline{C}H_2CH_3$), 50.9 ($Ph_2CH\underline{C}H(COCH_3)(COOCH_2CH_3)$), 30.0 ($CO\underline{C}H_3$), 13.8 ($OCH_2\underline{C}H_3$)

IR: ν_{max} (ATR) 2159, 2028, 1736, 1361, 1144, 700, 495, 445 cm^{-1}

EIMS (*m/z*): 278 (85%), 253 (M – $COCH_3$, 25%), 207 (100%), 205 (55%), 178 (50%), 167 (60%), 165 (65%), 152 (35%)

EIMS/ESI HRMS: M^+ Calcd for$C_{19}H_{20}O_3$, 296.1412; found, 296.1395

4-Benzhydrylphenol (4.8)[18,19]



Yield: 64%, yellow solid

Mp: 105-108 °C

TLC: 0.23 (8:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 7.33 (t, 4H, *J* = 7.4 Hz, H3, H3', H5, H5'), 7.26 (t, 2H, *J* = 7.2 Hz, H4, H4'), 7.17 (d, 4H, *J* = 7.2 Hz, H2, H2', H6, H6'), 7.02 (d, 2H, *J* = 8.4 Hz, H2'', H6''), 6.77 (d, 2H, *J* = 8.8 Hz, H3'' H5''), 5.54 (s, 1H, $Ph_2C\underline{H}$)

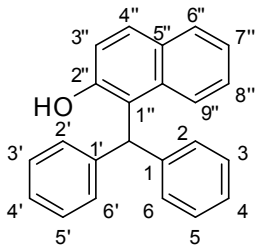
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 153.7 (C4''), 144.1 (C1, C1'), 136.2 (C1''), 130.5 (C2'', C6''), 129.3 (C3, C3', C5, C5'), 128.2 (C2, C2', C6, C6'), 126.2 (C4, C4'), 115.1 (C2'', C6''), 55.9 ($Ph_2\underline{C}H$)

IR: ν_{max} (ATR) 2160, 2031, 1510, 1450, 1237, 698, 565, 446 cm^{-1}

EIMS (*m/z*): 260 (M, 100%), 259 (35%), 229 (25%), 183 (M – C_6H_5, 80%), 181 (35%), 165 (60%), 152 (30%)

EIMS/ESI HRMS: M^+ Calcd for $C_{19}H_{16}O$, 260.1201; found, 260.1193

1-Benzhydrylnaphthalen-2-ol (4.9)[17,19]



Yield: 98%, white foam

TLC: 0.44 (8:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 8.20 (d, 1H, *J* = 8.8 Hz, H9''), 7.94 (d, 1H, *J* = 8.0 Hz, H6''), 7.89 (d, 1H, *J* = 8.8 Hz, H4''), 7.56 (t, 1H, *J* = 7.4 Hz, H8''), 7.35-7.49 (m, 11 H, H1, H1', H2, H2', H3, H3', H4, H4', H5, H5', H6, H6', H7''), 7.25 (d, 1H, *J* = 9.2 Hz, H3''), 6.63 (s, 1H, O<u>H</u>), 5.44 (s, 1H, Ph_2C<u>H</u>)

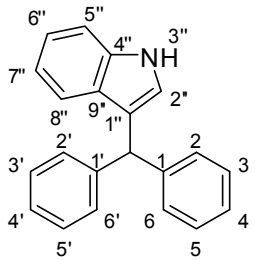
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 152.7 (C2''), 141.6 (C1, C1'), 133.3 (*Ar*), 129.6 (*Ar*), 129.0 (*Ar)*, 128.9 (*Ar*), 128.7 (*Ar*), 128.2 (*Ar*), 127.1 (*Ar*), 126.7 (*Ar*), 125.2 (*Ar*), 123.1 (*Ar*), 122.8 (*Ar*), 120.2 (*Ar*), 119.7 (*Ar*), 48.4 (Ph_2<u>C</u>H)

IR: ν_{max} (ATR) 3498, 2160, 2031, 1598, 1465, 1202, 815, 745, 700, 508 cm^{-1}

EIMS (*m/z*): 310 (M, 100%), 307 (70%), 233 (M – C_6H_5, 20%), 231 (90%), 215 (30%), 202 (35%), 167 (M – $C_{10}H_7OH$, 60%), 165 (45%)

EIMS/ESI HRMS: M^+ Calcd for $C_{23}H_{18}O$, 310.1358; found, 310.1348

3-Benzhydryl-1*H*-indole (4.10)[17,19]



Yield: 80%, white solid

Mp: 113-115 °C

TLC: 0.39 (8:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 7.79 (s, 1H, N<u>H</u>), 7.25-7.36 (m, 12H, H-Aromatic), 7.22 (t, 1H, *J* = 7.6 Hz, H7''), 7.05 (t, 1H, *J* = 7.4 Hz, H6''), 6.55 (d, 1H, *J* = 1.6 Hz, H2''), 5.73 (s, 1H, Ph_2C<u>H</u>)

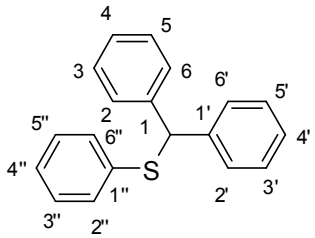
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 143.9 (C2, C2', C6, C6'), 136.6 (C4''), 129.0 (C3, C3', C5, C5'), 128.2 (C2, C2', C6, C6'), 126.9 (C9''), 126.2 (C4, C4'), 124.0 (C2''), 122.0 (C6''), 119.8 (C7''), 119.8 (C1''), 119.3 (C8''), 111.0 (C5''), 48.7 (Ph_2<u>C</u>H)

IR: ν_{max} (ATR) 3379, 2160, 2029, 1450, 746, 696, 504 cm^{-1}

EIMS (*m/z*): 283 (M, 90%), 282 (25%), 206 (M – C_6H_5, 100%), 204 (30%)

EIMS/ESI HRMS: M^+ Calcd for $C_{21}H_{17}N$, 283.1361; found, 283.1356

Benzhydryl(phenyl)sulfane (4.11)[17]



Yield: 98%, white solid

Mp: 76-80 °C

TLC: 0.55 (50:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.59-7.55 (m, 4H, H-Aromatic), 7.20-7.44 (m, 11-H, H-Aromatic), 5.71 (s, 1H, Ph_2C<u>H</u>)

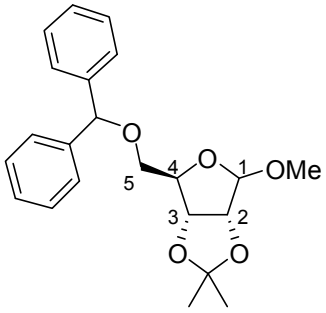
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 140.9 (C1, C1'), 136.1 (C1''), 130.4 (C2'', C6''), 128.6 (C3'', C5''), 128.4 (C2, C2', C6, C6'), 128.3 (C3, C3', C5, C5'), 127.1 (C4, C4'), 126.5 (C4''), 57.3 (Ph_2<u>C</u>H)

IR: ν_{max} (ATR) 2159, 2028, 14791024, 732, 694, 411 cm^{-1}

EIMS (*m/z*): 276 (M, 10%), 168 (20%), 167 (80%), 165 (60%), 152 (30%)

EIMS/ESI HRMS: M^+ Calcd for $C_{19}H_{16}S$, 276.0973; found, 283.1003

(3aR,4R,6aR)-4-(benzhydryloxymethyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole (4.18)



Yield: 72%, white solid

Mp: 75-79 °C

TLC: 0.43 (8:1 Hexane:EtOAc)

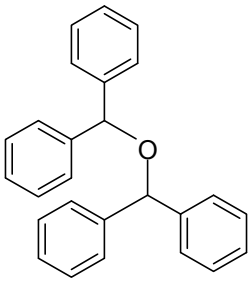
^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.41 (d, 4H, *J* = 7.5 Hz, H-*ortho*), 7.34 (t, 4H, *J* = 5.9 Hz, H-*meta*), 7.27 (d, 2H, *J* = 6.9 Hz, H-*para*), 5.41 (s, 1H, $Ph_2C\underline{H}$), 5.01 (s, 1H, H1), 4.76 (d, 1H, *J* = 5.9 Hz, H2), 4.61 (d, 1H, *J* = 5.9 Hz, H3), 4.51 (t, 1H, *J* = 6.9 Hz, H4), 3.47 – 3.60 (m, 2H, H5), 3.27 (s, 3H, OMe), 1.54 (s, 3H, $C\underline{H_3}$), 1.35 (s, 3H, $C\underline{H_3}$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 141.9 (*ipso*), 141.8 (*ipso*), 128.2 (*meta*), 127.3 (*para*), 127.3 (*para*), 126.8 (*ortho*), 126.8 (*ortho*), 112.1 ($\underline{C}(CH_3)_2$), 109.2 (C1), 85.2 (C3), 85.1 (C4), 82.1 ($Ph_2\underline{C}H$), 82.1 (C2), 69.8 (C5), 54.6 (OMe), 26.4 ($\underline{C}H_3$), 24.9 ($\underline{C}H_3$)

IR: ν_{max} (ATR) 2941, 2509, 2159, 2029, 1976, 1453, 1092, 1059, 1047, 873, 696, 449 cm^{-1}

EIMS (*m/z*): 323 (30%), 207 (20%), 183 (20%), 167 (100%)

Oxybis(methanetriyl)tetrabenzene (4.19)[16]



Yield: 99%, white solid

Mp: 105-108 °C

TLC: 0.76 (8:1 Hexane:EtOAc)

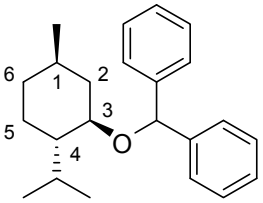
^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.44 (d, 4H, *J* = 7.5 Hz, H-*ortho*), 7.38 (t, 4H, *J* = 7.2 Hz, H-*meta*), 7.31 (t, 2H, *J* = 6.9 Hz, H-*para*), 5.49 (s, 2H, $Ph_2C\underline{H}$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 142.2 (*ipso*), 128.4 (*meta*), 127.4 (*para*), 127.2 (*ortho*), 80.0 ($Ph_2\underline{C}H$)

IR: ν_{max} (ATR) 2160, 2031,1493, 1446, 1051, 1027, 739, 699, 504 cm^{-1}

EIMS (*m/z*): 183 (30%), 168(70%), 167 (100%), 165 (60%), 152 (40%), 105 (40%), 77 (50%)

((2-Isopropyl-5-methylcyclohexyloxy)methylene)dibenzene (4.20)[20]



Yield: 85%, white solid

Mp: 68-70 °C

TLC: 0.74 (50:1 Hexane:EtOAc)

H^1 NMR: (300 MHz, $CDCl_3$) δ_H : 7.36-7.16 (m, 10H, H-aromatic), 3.12 (td, 1H, J = 10.5 and 4.3 Hz, H3), 2.35 (t, 1H, J = 6.9 Hz, C<u>H</u>$(CH_3)_2$), 2.16-2.12 (m, 1H, $H2_A$), 1.60-1.53 (m, 2H, $H5_A$, $H6_A$), 1.32-1.23 (m, 2H, H1, H4), 0.97-0.80 (m, 9H, $H2_B$, $H5_B$, $H6_B$, CH(C<u>H</u>$_3)_2$), 0.42 (d, 3H, J = 6.6 Hz, C<u>H</u>$_3$)

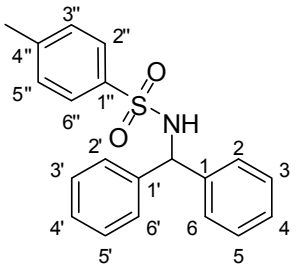
C^{13} NMR: (75 MHz, $CDCl_3$) δ_C : 143.8 (*ipso*), 142.5 (*ipso*), 128.2 (*meta*), 128.0 (*meta*), 127.9 (*ortho*), 127.4 (*para*), 126.8 (*para*), 126.6 (*ortho*), 79.8 (Ph_2<u>C</u>H), 75.7 (C3), 48.7 (C4), 40.3 (C2), 34.5 (C5), 31.4 (C1), 25.0 (<u>C</u>H$(CH_3)_2$), 22.8 (C6), 22.4 (CH(<u>C</u>H$_3$)(CH$_3$)), 21.3 (CH(CH$_3$)(<u>C</u>H$_3$)), 15.6 (<u>C</u>H$_3$)

IR: ν_{max} (ATR) 2941, 2159, 2031, 1453, 1044, 764, 737, 699, 613, 452 cm^{-1}

EIMS (*m/z*): 304 (20%), 180 (20%), 168 (80%), 167 (100%), 165 (80%), 152 (80%), 137 (70%)

EIMS/ESI HRMS: M^+ Calcd for $C_{23}H_{30}O$, 322.2297; found, 322.2299

_N_-benzhydryl-4-methylbenzenesulfonamide (4.36)[21]



Yield: 98%, white solid

Mp: 150-152 °C

TLC: 0.46 (4:1 Hexane:EtOAc)

H^1 NMR: (300 MHz, $CDCl_3$) δ_H : 7.55 (d, 2H, J = 7.8 Hz, H2'', H6''), 7.16-7.07 (m, 12 H, H-aromatic, H3'', H5''), 5.67 (d, 1H, J = 7.7 Hz, Ph_2C<u>H</u>), 5.57 (d, 1H, J = 7.7 Hz, N<u>H</u>), 2.34 (s, 3H, C<u>H</u>$_3$)

C^{13} NMR: (75 MHz, $CDCl_3$) δ_C : 143.0 (C1''), 140.5 (C1, C1'), 137.3 (C4''), 129.2 (C3'', C5''), 128.4 (C3, C3', C5, C5'), 127.4 (C2'', C6''), 127.3 (C2, C2', C6, C6'), 127.1 (C4, C4'), 61.2 (Ph<u>C</u>H), 21.4 (<u>C</u>H$_3$)

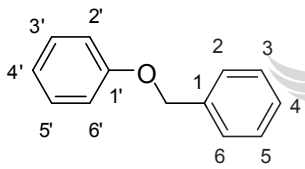
IR: ν_{max} (ATR) 3246, 2159, 2030, 1450, 1313, 1157, 1058, 698, 672, 406 cm^{-1}

EIMS (*m/z*): 218 (10%), 207 (30%), 182 (70%), 91 (100%)

5.4.3.2 Benzylation of phenols

To a solution of benzyl chloride (0.245 ml, 2.1 mmol) and TBAB (69 mg, 10 mol%) in toluene (2 mL) was added 1.5 equivalents of the phenol. KOH (0.238 g, 2.1 mmol) was dissolved in water (2 mL) and added to the reaction mixture. This mixture was heated to 80 °C for 12 hours. The reaction was diluted with DCM (10 mL) and washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

Benzyloxybenzene (4.12)[22]



Yield: 98%, white solid

Mp: 30-33 °C

TLC: 0.64 (20:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.37-7.55 (m, 8H, H-aromatic), 7.09 (d, 2H, J = 8.7 Hz, H2', H6'), 5.14 (s, 2H, PhC$\underline{H_2}$)

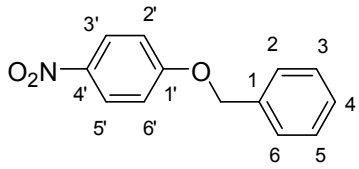
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 158.7 (C1'), 137.0 (C1), 129.4 (C3', C5'), 128.5 (C3, C5), 127.8 (C4), 127.4 (C2, C6), 120.9 (C4'), 114.8 (C2', C6'), 69.8 (Ph$\underline{C}H_2$)

IR: ν_{max} (ATR) 3036, 2907, 2159, 32031, 1584, 1490, 1455, 1376, 1237, 1169, 1011, 742, 689, 506 cm^{-1}

EIMS (*m/z*): 184 (M, 10%), 91 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{13}H_{12}O$, 184.0888; found, 184.0882

1-(Benzyloxy)-4-nitrobenzene (4.13)[23]



Yield: 73%, white solid

Mp: 100-102 °C

TLC: 0.45 (10:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 8.18 (d, 2H, *J* = 8.9 Hz, C3', C5'), 7.42-7.37 (m, 5H, H-aromatic), 7.01 (d, 2H, *J* = 8.9 Hz, H2', H6'), 5.15 (s, 3H, PhC<u>H</u>$_2$)

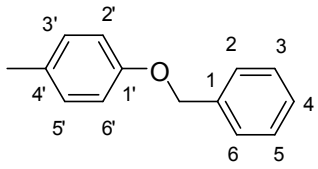
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 163.6 (C1'), 141.6 (C4'), 135.4 (C1), 128.7 (C3, C5), 128.4 (C4), 127.4 (C2, C6), 125.8 (C2', C5'), 114.8 (C2', C6'), 70.6 (Ph<u>C</u>H$_2$)

IR: ν_{max} (ATR) 2448, 2159, 2031, 1589, 1493, 1345, 1248, 1005, 841, 750, 701, 417 cm^{-1}

EIMS (*m/z*): 229 (M, 10%), 133 (20%), 117 (20%), 103 (20%), 91 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{13}H_{11}NO_3$, 229.0739; found, 229.0769

1-(Benzyloxy)-4-methylbenzene (4.14)[23]



Yield: 99%, white solid

Mp: 100-102 °C

TLC: 0.68 (10:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.45-7.32 (m, 5H, H-aromatic), 7.10 (d, 2H, *J* = 8.1 Hz, H3', H5'), 6.89 (d, 2H, *J* = 8.1 Hz, C2', C6'), 5.05 (s, 2H, PhC$\underline{H_2}$), 2.30 (s, 3H, C$\underline{H_3}$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 156.7 (C1'), 137.3 (C1), 130.1 (C4'), 129.9 (C3', C5'), 128.5 (C3, C5), 127.8 (C4), 127.4 (C2, C6), 114.7 (C2', C6'), 70.0 (PhC$\underline{H_2}$), 20.5 (C$\underline{H_3}$)

IR: ν_{max} (ATR) 2159, 1610, 1508, 1381, 1236, 1009, 807, 732, 694, 409 cm^{-1}

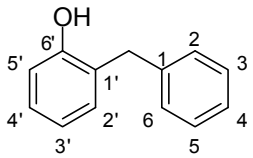
EIMS (*m/z*): 198 (M, 10%), 91 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{14}H_{14}O$, 198.1045; found, 198.1046

5.4.3.3 $\underline{Al(OTf)_3}$ catalysed rearrangement of phenol derived benzylic ethers

To a solution of nitroethane (2 mL) containing $Al(OTf)_3$ (0.005 g, 1 mol%) was added the required ether **4.12-4.14** (1.0 mmol). This mixture was heated to 80 °C for 5 hours. The reaction was then quenched with the addition of saturated aqueous sodium bicarbonate (5 mL). The reaction mixture was extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

2-Benzylphenol (4.15)[24a,b]



Yield: 98%, yellow oil

TLC: 0.52 (10:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.22-7.32 (m, 5H, H-aromatic), 7.15-7.11 (m, 2H, H2', H4'), 6.89 (t, 1H, *J* = 7.4 Hz, H3'), 6.78 (d, 1H, *J* = 7.5 Hz, H5'), 4.71 (br s, 1H, O<u>H</u>), 4.00 (s, 2H, PhC<u>H</u>$_2$)

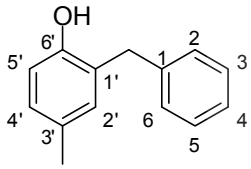
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 153.7 (C6'), 139.8 (C1), 131.0 (C2'), 128.7 (C3, C5), 128.6 (C2, C6), 127.8 (C4'), 126.9 (C1'), 126.3 (C4), 120.9 (C3'), 115.7 (C5'), 36.3 (Ph<u>C</u>H$_2$)

IR: ν_{max} (ATR) 3531, 3026, 1921, 2442, 2159, 2029, 1976, 1493, 1452, 1167, 1093, 752, 728, 696, 492 cm^{-1}

EIMS (*m/z*): 184 (M, 100%), 183 (50%), 165 (50%), 106 (50%)

EIMS/ESI HRMS: M^+ Calcd for $C_{13}H_{12}O$, 184.0888; found, 184.0779

2-Benzyl-4-methylphenol (4.16)[18]



Yield: 99%, clear oil

TLC: 0.53 (10:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.32-7.24 (m, 5H, H-aromatic), 6.93-6.91 (m, 2H, H2', H4'), 6.67 (d, 1H, *J* = 8.7 Hz, H5'), 4.59 (s, 1H, O<u>H</u>), 3.96 (s, 2H, PhC<u>H</u>$_2$), 2.26 (s, 3H, C<u>H</u>$_3$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 151.4 (C6'), 140.0 (C1), 131.5 (C2'), 130.1 (C3'), 128.6 (C2, C3, C5, C6), 128.1 (C4'), 126.7 (C1'), 126.3 (C4), 115.6 (C5'), 36.3 (Ph<u>C</u>H$_2$), 20.5 (<u>C</u>H$_3$)

IR: ν_{max} (ATR) 3529, 3026, 2921, 2521, 2159, 2030, 1494, 1452, 1185, 1101, 810, 696, 435 cm^{-1}

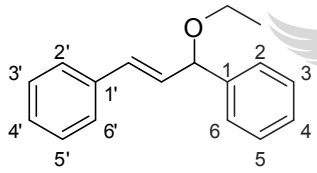
EIMS (*m/z*): 198 (M, 100%), 183 (30%), 165 (20%), 120 (50%)

EIMS/ESI HRMS: M^+ Calcd for $C_{14}H_{14}O$, 198.1045; found, 198.1051

5.4.3.4 General procedure for the $Al(OTf)_3$ catalysed nucleophilic substitution of *trans*-1,3-diphenylprop-2-en-1-ol

To a mixture of *trans*-1,3-diphenylprop-2-en-1-ol (0.231 g, 1.1 mmol) and $Al(OTf)_3$ (0.005 g, 1 mol%) in nitroethane (2 mL) was added 1 equivalent of the appropriate nucleophile. The mixture was left to stir for 1 hour at room temperature. The reaction was then quenched with the addition of saturated aqueous sodium bicarbonate (5 mL). The reaction mixture was extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

(3-Ethoxyprop-1-ene-1,3-diyl)dibenzene (4.21)[25]



Yield: 85%, clear oil

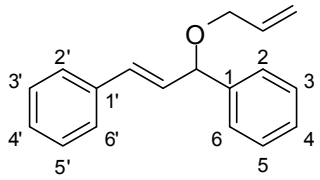
TLC: 0.51 (50:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.43-7.18 (m, 10H, H-aromatic), 6.61 (d, 1H, J = 15.9 Hz, PhC<u>H</u>=CH), 6.31 (dd, 1H, J = 16.1 and 7.0 Hz, PhCH=C<u>H</u>), 4.92 (d, 1H, J = 7.2 Hz, PhCH=CHC<u>H</u>Ph), 3.59 (dq, 1H, J = 9.1 and 7.0 Hz, OC<u>H_{2A}</u>CH_3), 3.49 (dq, 1H, J = 9.3 and 7.2 Hz, OC<u>H_{2B}</u>CH_3), 1.27 (t, 3H, J = 7.0 Hz, OCH_2C<u>H_3</u>)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 141.5 (C1), 136.6 (C1'), 131.1 (Ph<u>C</u>H=CH), 130.6 (PhCH=<u>C</u>H), 128.5 (C2, C2', C6, C6'), 127.6 (C4, C4'), 126.8 (C3, C5), 126.6 (C3', C5'), 82.5 (PhCH=CH<u>C</u>HPh), 64.0 (O<u>C</u>H_2CH_3), 15.3 (OCH_2<u>C</u>H_3)

IR: ν_{max} (ATR) 2159, 2030, 1720, 2602, 1450, 1214, 1097, 1017, 747, 696, 499 cm^{-1}

(3-(Allyloxy)prop-1-ene-1,3-diyl)dibenzene (4.22)[26]



Yield: 84%, clear oil

TLC: 0.52 (50:1 Hexane:EtOAc)

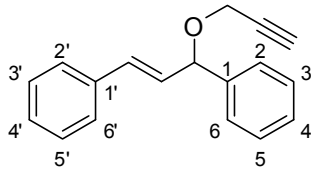
^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.49-7.24 (m, 10H, H-Aromatic), 6.68 (d, 1H, *J* = 16.2 Hz, PhC<u>H</u>=CH), 6.36 (dd, 1H, *J* = 15.8 Hz and 7.1 Hz, PhCH=C<u>H</u>), 6.03 (ddt, 1H, *J* = 17.2 and 9.9 Hz, $OCH_2CH=CH_2$), 5.38 (dq, 1H, *J* = 17.2 and 1.7 Hz, $OCH_2CH=C\underline{H}_{2A}$), 5.26 (dq, 1H, *J* = 9.9 and 5.2 Hz, $OCH_2CH=C\underline{H}_{2B}$), 5.04 (d, 1H, *J* = 7.2 Hz, PhCH=CHC<u>H</u>Ph), 4.10 (dt, 2H, *J* = 9.9 and 1.5 Hz, $OC\underline{H}_2CH=CH_2$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 141.1 (C1), 136.5 (C1'), 134.8 ($OCH_2\underline{C}H=CH_2$), 131.3 (Ph<u>C</u>H=CH), 130.2 (PhCH=<u>C</u>H), 128.5 (C2, C2', C6, C6'), 127.7 (C4), 127.6 (C4'), 126.8 (C3, C5), 126.5 (C3', C5'), 116.9 ($OCH_2CH=CH_2$), 81.7 (PhCH=CH<u>C</u>HPh), 69.2 ($OC\underline{H}_2CH=CH_2$)

IR: ν_{max} (ATR) 3030, 2159, 2029, 1719, 1450, 1269, 1025, 748, 696, 483 cm^{-1}

EIMS (*m/z*): 192 (100%), 191 (60%), 189 (30%), 165 (50%), 115 (40%), 105 (30%), 77 (40%)

(3-(Prop-2-ynyloxy)prop-1-ene-1,3-diyl)dibenzene (4.23)



Yield: 96%, clear oil

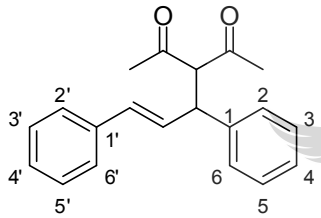
TLC: 0.33 (50:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.44-7.20 (m, 10H, H-aromatic), 6.66 (d, 1H, *J* = 15.9 Hz, PhC<u>H</u>=CH), 6.29 (d, 1H, *J* = 16.1 and 7.7 Hz, PhCH=C<u>H</u>), 5.20 (d, 1H, *J* = 7.2 Hz, PhCH=CHC<u>H</u>Ph), 4.24 (dd, 1H, *J* = 15.5 and 2.5 Hz, OC<u>H_{2A}</u>), 4.14 (dd, 1H, *J* = 15.6 and 2.4 Hz, OC<u>H_{2B}</u>), 2.45 (t, 1H, *J* = 1.9 Hz, OCH_2CC<u>H</u>)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 140.2 (C1), 136.4 (C1'), 132.4 (Ph<u>C</u>H=CH), 129.1 (PhCH=<u>C</u>H), 128.6 (C2,C2', C6, C6'), 127.9 (C4, C4'), 127.1 (C3, C5), 126.6 (C3', C5'), 80.9 (PhCH=CH<u>C</u>HPh), 79.8 (OCH_2<u>C</u>CH), 74.4 (OCH_2C<u>C</u>H), 55.3 (O<u>C</u>H_2CCH)

IR: ν_{max} (ATR) 3288, 3029, 2511, 2159, 2030, 1494, 1450, 1068, 1026, 967, 746, 695, 458 cm^{-1}

3-(1,3-Diphenylallyl)pentane-2,4-dione (4.24)[25]



Yield: 98% , white solid

Mp: 78-80 °C

TLC: 0.54 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.31-7.18 (m, 10H, H-Aromatic), 6.45 (d, 1H, *J* = 15.9 Hz, PhC<u>H</u>CH), 6.25 (dd, 1H, *J* = 5.4 and 2.1 Hz, PhCH=C<u>H</u>), 6.20 (dd, 1H, *J* = 5.5 and 2.2 Hz, PhCH=C<u>H</u>), 4.38-4.36 (m, 2H, PhCH=CHC<u>H</u>(Ph)C<u>H</u>$(COCH_3)_2$), 2.24 (s, 3H, CH(COC<u>H_3</u>)), 1.92 (s, 3H, CH(COC<u>H_3</u>))

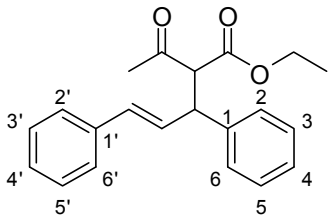
^{13} C NMR: (75 MHz, $CDCl_3$) δ_C : 202.4 (<u>C</u>OCH_3), 202.3 (<u>C</u>OCH_3), 139.9 (C1), 136.6 (C1'), 131.3 (Ph<u>C</u>H=CH), 129.1 (PhCH=<u>C</u>H), 128.7 (C2, C6), 128.3 (C2',C6'), 127.7 (C3, C5), 127.4 (C4'), 127.0 (C4), 126.1 (C3', C5'), 74.1 (<u>C</u>H$(COCH_3)$), 48.9 (<u>C</u>H(Ph)CH$(COCH_3)$), 29.8 (CO<u>C</u>H_3), 29.5 (CO<u>C</u>H_3)

IR: ν_{max} (ATR) 3026, 2918, 2439, 2160, 1976, 2721, 1359, 1138, 974, 693, 420 cm^{-1}

EIMS (*m/z*): 274 (M – H_2O, 40%), 249 (M – $COCH_3$, 80%), 232 (35%), 193 (M – $C(COCH_3)_2$, 65%), 191 (50%), 178 (45%), 115 (95%), 91 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{20}H_{20}O_2$, 292.1463; found, 292.1461

Ethyl 2-acetyl-3,5-diphenylpent-4-enoate (4.25)[25]



Yield: 98%, clear oil, diastereomeric mixture

TLC: 0.5 (8:1 Hexane:EtOAc)

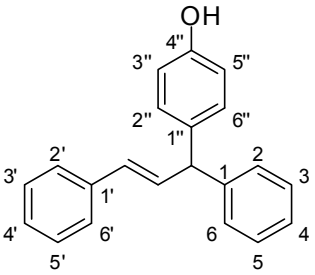
^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.48-7.33 (m, 10H, H-Aromatic), 6.61 (d, 1H, *J* = 11.1 Hz, PhC<u>H</u>=CH), **6.56 (d, 1H, *J* = 11.4 Hz, PhC<u>H</u>=CH)**, 6.44 (dd, 1H, *J* = 15.9 and 8.1 Hz, PhCH=C<u>H</u>), **6.38 (dd, 1H, *J* = 15.1 and 8.2 Hz, PhCH=C<u>H</u>)**, 4.43 (t, 1H, *J* = 9.8 Hz, PhCH=CHC<u>H</u>Ph), 4.36-4.20 (m, 3H, $OC\underline{H_2}CH_3$, $C\underline{H}(COOCH_2CH_3)(COCH_3)$), **4.08 (q, 2H, *J* = 6.9 Hz, $OC\underline{H_2}CH_3$)**, 2.44 (s, 3H, $COC\underline{H_3}$), **2.18 (s, 3H, $COC\underline{H_3}$)**, 1.35 (t, 3H, *J* = 8.1 Hz, OCH_2CH_3), **1.12 (t, 3H, *J* = 7.0 Hz, $OCH_2C\underline{H_3}$)**

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 201.6 ($\underline{C}OCH_3$), **201.4 ($\underline{C}OCH_3$)**, 167.8 ($\underline{C}OOCH_2CH_3$), **167.5 ($\underline{C}OOCH_2CH_3$)**, 140.3 (C1), **140.1 (C1)**, 136.7 (C1'), **136.6 (C1')**, 131.7 (Ph<u>C</u>H=CH), **131.4 (Ph<u>C</u>H=CH)**, 129.4 (PhCH=<u>C</u>H), **129.2 (PhCH=<u>C</u>H)**, 128.8 (C2', C6'), **128.6 (C2', C6')**, 128.4 (C3, C5), 127.9 (C3', C5'), **127.9 (C3', C5')**, 127.5 (C4), **127.5 (C4)**, 127.1 (C4'), **127.0 (C4')**, 126.3 (C2, C6), **126.2 (C2, C6)**, 65.4 ($\underline{C}H(COCH_3)(COOCH_2CH_3)$, **65.1 ($\underline{C}H(COCH_3)(COOCH_2CH_3)$)**, 61.5 ($OCH_2CH_3$), **61.3 ($OCH_2CH_3$)**, 48.9 (PhCH=CH<u>C</u>HPh), **48.7 (PhCH=CH<u>C</u>HPh)**, 30.0 ($CO\underline{C}H_3$), **29.8 ($CO\underline{C}H_3$)**, 14.1 (OCH_2CH_3), **13.7 (OCH_2CH_3)**

IR: ν_{max} (ATR) 3028, 2512, 2159, 2028, 1452, 1153, 965, 745, 685, 486 cm^{-1}

EIMS (*m/z*): 304 (M – H_2O, 95%), 279 (M – COCH3, 15%), 233 (50%), 193 (M – $C(OCH_3)(COOCH_2CH_3)$, 80%), 115 (95%), 91 (45%)

4-(1,3-Diphenylallyl)phenol (4.26)[25]



Yield: 52%, yellow oil

TLC: 0.44 (10:1 Toluene:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.37-7.16 (m, 10H, H-Aromatic), 7.08 (d, 2H, *J* = 8.1 Hz, H2'', H6''), 6.77 (d, 2H, *J* = 6.6 Hz, H3'', H5''), 6.63 (dd, 1H, *J* = 15.9 and 7.5 Hz, PhCH=C<u>H</u>), 6.31 (d, 1H, *J* = 16.1 Hz, PhC<u>H</u>=CH), 4.82 (d, 1H, *J* = 7.5 Hz, PhCH=CHC<u>H</u>Ph), 4.74 (s, 1H, O<u>H</u>)

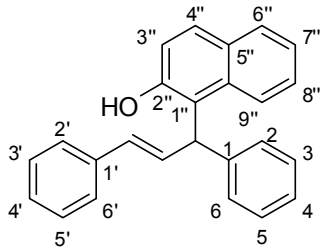
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 153.9 (C4''), 143.7 (C1), 137.3 (C1''), 135.8 (C1'), 132.8 (PhCH=<u>C</u>H), 131.1 (Ph<u>C</u>H=CH), 129.8 (C2'', C6''), 128.6 (C2, C6), 128.5 (C2', C6'), 128.4 (C3, C5), 127.3 (C4), 126.4 (C4'), 126.4 (C3', C5'), 115.3 (C3'', C5''), 53.3 PhCH=CH<u>C</u>HPh)

IR: ν_{max} (ATR) 3317, 3025, 2494, 2159, 2030, 1510, 1171, 744, 695, 475 cm^{-1}

EIMS (*m/z*): 286 (M, 50%), 209 (M – C_6H_5, 35%), 208 (100%), 207 (70%), 192 (70%), 165 (35%), 121 (90%), 105 (50%)

EIMS/ESI HRMS: M^+ Calcd for $C_{21}H_{18}O$, 286.1358; found, 286.1351

1-(1,3-Diphenylallyl)naphthalen-2-ol (4.27)[27]



Yield: 72%, yellow oil

TLC: 0.44 (8:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.98 (d, 1H, *J* = 8.7 Hz, H9''), 7.79 (d, 1H, *J* = 7.8 Hz, H6''), 7.73 (d, 1H, *J* = 8.7 Hz, H4''), 7.43 (t, 1H, *J* = 7.0 Hz, H8''), 7.20-7.38 (m, 11H, H7'', H-Aromatic), 7.10 (d, 1H, *J* = 8.7 Hz, H3''), 6.97 (dd, 1H, *J* = 6.6 and 1.2 Hz, PhCH=C<u>H</u>), **6.91 (dd, 1H, *J* = 7.1 and 1.0 Hz, PhCH=C<u>H</u>)**, 6.49 (d, 1H, *J* = 15.6 Hz, PhC<u>H</u>=CH), 5.87 (d, 1H, *J* = 6.6 Hz, PhCH=CHC<u>H</u>Ph), 5.52 (s, 1H, O<u>H</u>)

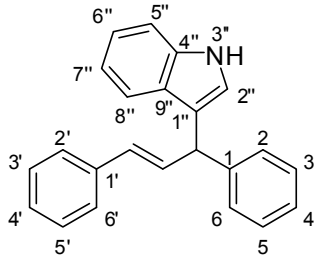
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 152.2 (C2''), 141.6 (C1'), 136.7 (C1), 133.1 (Ph<u>C</u>H=CH), **133.0 (Ph<u>C</u>H=CH)**, 130.0 (PhCH=<u>C</u>H), **129.7 (PhCH=<u>C</u>H)**, 129.3 (C4''), 128.9 (C2', C6'), 128.8 (C6''), 128.5 (C3, C5), 128.0 (C3', C5'), 127.6 (C7''), 126.8 (C4), 126.7 (C4'), 126.4 (C2, C6), 123.2 (C8''), 123.0 (C9''), 119.7 (C1''), 119.1 (C3''), 45.2 (PhCH=CH<u>C</u>HPh)

IR: ν_{max} (ATR) 2361, 2159, 2031, 1260, 813, 692, 489 cm^{-1}

EIMS (*m/z*): 336 (M, 50%), 334 (M – 2H, 90%), 260 (35%), 257 (90%), 245 (95%), 231 (95%), 215 (80%), 202 (60%), 115 (40%), 105 (40%)

EIMS/ESI HRMS: M^+ Calcd for $C_{25}H_{20}O$, 336.1514; found, 336.1499

3-(1,3-Diphenylallyl)-1*H*-indole (4.28)[25]



Yield: 77%, yellow oil

TLC: 0.36 (8:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.87 (s, 1H, N<u>H</u>), 7.53 (d, 1H, *J* = 8.1 Hz, H8''), 7.45-7.22 (m, 12H, H5'', H6'', H-Aromatic), 7.12 (t, 1H, *J* = 7.5 Hz, H7''), 6.88 (d, 1H, *J* = 2.3 Hz, H2''), 6.82 (dd, 1H, *J* = 15.7 and 7.4 Hz, PhCH=C<u>H</u>), 6.53 (d, 1H, *J* = 15.9 Hz, PhC<u>H</u>=CH), 5.20 (d, 1H, *J* = 7.2 Hz, PhCH=CHC<u>H</u>Ph)

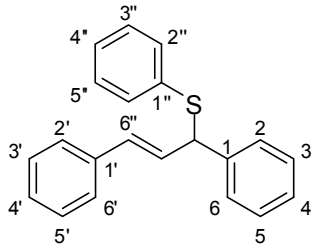
^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 143.3 (C1), 137.4 (C1'), 136.6 (C4''), 132.5 (PhCH=<u>C</u>H), 130.5 (Ph<u>C</u>H=CH), 128.4 (C2, C6), 128.4 (C2', C6'), 127.1 (C4), 126.7 (C4'), 126.3 (C3, C5), 126.3 (C43', C5'), 122.6 (C2''), 122.0 (C1''), 119.8 (C8''), 119.4 (C7''), 118.5 (C9''), 111.1 (C5''), 46.1 (PhCH=CH<u>C</u>HPh)

IR: ν_{max} (ATR) 3057, 2923, 2509, 2160, 1977, 1695, 1450, 742, 695, 511 cm^{-1}

EIMS (*m/z*): 309 (M, 5%), 208 (25%), 207 (35%), 149 (30%), 105 (35%), 77 (C_6H_5, 50%)

EIMS/ESI HRMS: M^+ Calcd for $C_{23}H_{19}N$, 309.1517; found, 309.1506

(1,3-Diphenylallyl)(phenyl)sulfane (4.29)[28]



Yield: 86%, white solid

Mp: 69-72 °C

TLC: 0.49 (50:1 Hexane:EtOAc)

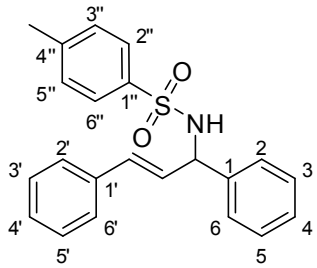
^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.56-7.27 (m, 10H, H-aromatic), 6.60 (dd, 1H, *J* = 15.5 and 8.2 Hz, PhCH=C<u>H</u>), 6.42 (d, 1H, *J* = 15.3 Hz, PhC<u>H</u>=CH), 5.06 (d, 1H, *J* = 8.1 Hz, PhCH=CHC<u>H</u>Ph)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 140.1 (C1), 136.6 (C1'), 134.8 (C1''), 133.0 (C2'', C6''), 131.4 (Ph<u>C</u>H=CH), 129.0 (PhCH=<u>C</u>H), 128.6, 128.4, 127.9, 127.5, 127.4, 126.4

IR: ν_{max} (ATR) 3060, 3027, 2509, 2160, 2030, 1478, 1438, 1025, 968, 739, 687, 487 cm^{-1}

EIMS/ESI HRMS: M^+ Calcd for $C_{21}H_{17}S$, 301.1051; found, 301.1059

(*E*)-*N*-(1,3-diphenylallyl)-4-methylbenzenesulfonamide (4.37)[25]



Yield: 99%, white solid

Mp: 130-132 °C

TLC: 0.43 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.67 (d, 2H, *J* = 8.1 Hz, H2'', H6''), 7.21-7.11 (m, 10H, H-aromatic), 7.10 (d, 2H, *J* = 8.1 Hz, H3'', H5''), 6.33 ((1H, *J* = 15.9 Hz, PhC<u>H</u>=CHCHPh), 6.07 (dd, 1H, *J* = 15.9 and 6.6 Hz, PhCH=C<u>H</u>CHPh), 5.58 (d, 1H, *J* = 7.5 Hz, N<u>H</u>), 5.11 (t, 1H, *J* = 7.0 Hz, PhCH=CHC<u>H</u>Ph), 2.28 (s, 3H, C<u>H</u>$_3$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 143.1 (C1), 139.6 (C1''), 137.7 (C4''), 136.0 (C1'), 131.9 (Ph<u>C</u>H=CHCHPh), 129.3 (C3'', C5''), 128.6 (C3, C5), 128.3 (C3', C5'), 128.1 (PhCH=<u>C</u>HCHPh), 127.7 (C4'), 127.6 (C4), 127.2 (C2', C6'), 127.0 (C2'', C6''), 126.4 (C2, C6), 59.7 (PhCH=CH<u>C</u>HPh), 21.3 (<u>C</u>H$_3$)

IR: ν_{max} (ATR) 3290, 3028, 2480, 2160, 1977, 1425, 1324, 1292, 1151, 966, 751, 667, 447 cm^{-1}

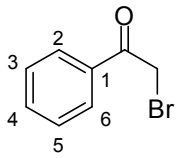
EIMS (*m/z*): 192 (70%), 191 (40%), 165 (20%), 91 (100%)

5.4.3.5 <u>Synthesis of 2*H*-chromenes</u>

5.4.3.5.1 <u>α-Bromination of acetophenone</u>

Acetophenone (1 g, 8.32 mmol) and $Al(OTf)_3$ (0.039 g, 82.3 μmol) were dissolved in Et_2O (5mL) in a two necked flask equipped with a reflux condenser. To this solution, bromine (0.42 mL, 8.32 mmol) was added by means of a dropping funnel so as to maintain a gentle reflux. Upon completion of the bromine addition the organic solvent was removed under reduced pressure, under a constant airstream. The resultant residue was washed with *n*-hexane (5 mL) and then water (5 X 10 mL). The white solid was then collected and dried under reduced pressure.

2-Bromo-1-phenylethanone (4.39)[29]



Yield: 94%, white solid

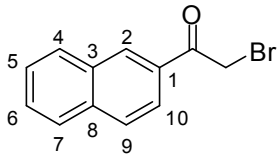
Mp: 42-45 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 7.97 (d, 2H, J = 8.0 Hz, H2, H6), 7.59 (t, 1H, J = 7.4 Hz, H4), 7.48 (t, 2H, J = 7.4 Hz, H3, H5), 4.44 (s, 2H, COC$\underline{H_2}$Br)

^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 191.3 ($\underline{C}$=O), 133.9 (C1), 129.7 (C4), 128.9 (C2, C6), 128.8 (C3, C5), 30.9 (CO$\underline{C}H_2$Br)

IR: ν_{max} (ATR) 3065, 3002, 1953, 1476, 2160, 2028, 1690, 1580, 1447, 1389, 1281, 1196, 991, 745, 685, 620, 504 cm^{-1}

2-Bromo-1-(naphthalen-2-yl)ethanone (4.40)[30]



Yield: 98%, white solid

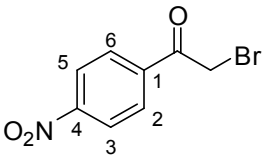
Mp: 79-81 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 8.49 (s, 1H, H2), 8.00 (d, 1H, J = 8.4 Hz, H4), 7.96 (d, 1H, J = 8.0 Hz, H7), 7.91-7.86 (m, 2H, H9, H10), 7.61 (t, 1H, J = 7.6 Hz, H6), 7.56 (t, 1H, J = 7.6 Hz, H5), 4.56 (s, 2H, COC$\underline{H_2}$Br)

^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 1919.2 ($\underline{C}$=O), 135.8 (C1), 132.2 (C3), 131.2 (C8), 130.9 (C2), 129.7 (C4), 129.0 (C6), 128.8 (C9), 127.8 (C5), 127.0 (C7), 124.1 (C10), 30.9 (COC$\underline{H_2}$Br)

IR: ν_{max} (ATR) 2442, 2159, 2026, 1976, 1689, 1384, 1158, 1029, 853, 810, 678, 514 cm^{-1}

2-Bromo-1-(4-nitrophenyl)ethanone (4.41)[30]



Yield: 99%, white solid

Mp: 91-93 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 8.31 (d, 2H, *J* = 8.4 Hz, H3, H5), 8.13 (d, 2H, *J* = 8.4 Hz, H2, H6), 4.45 (s, 2H, $C\underline{H_2}Br$)

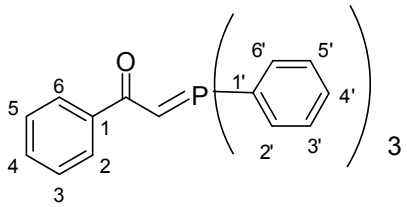
^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 189.9 ($\underline{C}$=O), 150.6 (C4), 138.3 (C1), 130.0 (C2, C6), 124.0 (C3, C5), 30.2 ($\underline{C}H_2Br$)

IR: ν_{max} (ATR) 3109, 2446, 2160, 2031, 1977, 1699, 1515, 1341, 1191, 998, 841, 744, 480 cm^{-1}

5.4.3.5.2 Formation of the Wittig ylide from the corresponding bromides

Triphenyl phosphine (1 g, 3.81 mmol) was dissolved in THF (5 mL). To this was added α bromo-acetophenone **4.39** (0.759 g, 3.81 mmol) in a portion wise manner. The mixture was stirred at room temperature overnight. The resultant white precipitate was collected via filtration and washed with *n*-hexane (5 X 5 mL) and the dried under reduced pressure. The dried white solid was dissolved in MeOH (20 mL), to this was added KOH (2.14 g, 38.12 mmol) dissolved in H_2O (20 mL) in a drop wise fashion. The mixture was allowed to stir at room temperature for 2 hours. The MeOH was removed under reduced pressure and the crude reaction mixture extracted with DCM (3 X 10 mL). The combined organic layers were washed with water (3 X 10 mL) and dried with magnesium sulfate. The organic solvent was removed under reduced pressure to afford the ylide which was further purified by re-crystallisation from hot ethanol.

1-Phenyl-2-(triphenylphosphoranylidene)-ethanone (4.42)[31]



Yield: 86%, white solid

Mp: 175-178 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 7.99-7.94 (m, 2H, H2, H6), 7.70 (dd, 6H, *J* = 12.2 and 7.8 Hz, H2', H6'), 7.55-7.52 (m, 3H, H3, H4, H5), 7.46-7.45 (m, 6H, H3', H5'), 7.40-7.30 (m, 3H, H4'), 4.41 (d, 1H, *J* = 24.4 Hz, COC<u>H</u>=PPh_3)

^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 184.7 (<u>C</u>=O), 141.1 (d, *J* = 13.0 Hz, C1'), 133.0 (d, *J* = 10.1 Hz, C2', C6'), 132.0 (*Ar*), 129.3 (*Ar*), 128.8 (d, *J* = 12.2 Hz, C3', C5'), 127.6 (*Ar*), 127.4 (*Ar*), 126.8 (*Ar*), 126.4 (*Ar*), 50.6 (d, *J* = 111.0 Hz, CO<u>C</u>H=PPh_3)

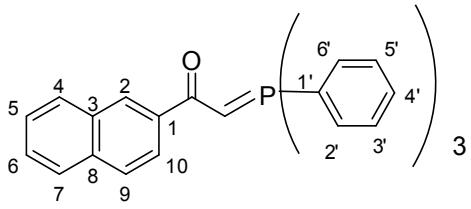
^{31}P NMR: (160 MHz, $CDCl_3$) δ_P : 16.96

IR: ν_{max} (ATR) 3049, 2505, 2160, 2028, 1976, 1587, 1513, 1436, 1385, 1104, 873, 747, 710, 689, 461 cm^{-1}

EIMS (*m/z*): 380 (M, 85%), 379 (100%), 303 (M – C_6H_5, 100%), 277 (M – C_6H_5CO, 60%), 202 (40%), 183 (70%)

EIMS/ESI HRMS: M^+ Calcd for $C_{26}H_{21}OP$, 380.1330; found 380.1314

1-(2-Naphthalenyl)-2-(triphenylphosphoranylidene)-ethanone (4.43)[32]



Yield: 65%, yellow solid

Mp: 176-179 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 8.50 (s, 1H, H2), 8.06 (d, *J* = 8.4 Hz, H9), 7.88-7.72 (m,8H, H-aromatic), 7.69-7.45 (m,12H, H-aromatic), 4.57 (d, 1H, *J* = 24.4 Hz, COC<u>H</u>=PPh_3)

^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 184.6 (<u>C</u>=O), 138.5 (d, *J* = 14.5 Hz, C1') 134.1, 133.2 (d, *J* = 10.1 Hz, C2', C6'), 133.0 (*Ar*), 132.1 (*Ar*), 128.9 (d, *J* = 12.3 Hz, C3', C5'), 127.4 (*Ar*), 127.1 (C9), 126.5 (*Ar*), 126.2 (*Ar*), 125.7 (*Ar*), 124.9 (C2), 51.6, (d, *J* = 111.0 Hz, CO<u>C</u>H=PPh_3)

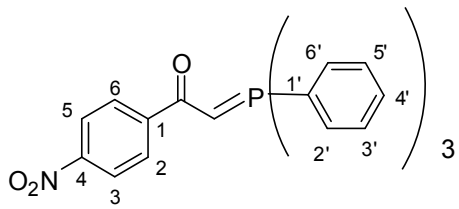
P^{31} NMR: (160 MHz, $CDCl_3$) δ_P : 17.02

IR: ν_{max} (ATR) 3050, 2504, 2159, 2028, 2977, 1520, 2435, 1395, 1105, 873, 757, 691, 435 cm^{-1}

EIMS (*m/z*): 430 (M, 95%), 429 (100%), 401 (25%), 303 (M – $C_{10}H_7$, 90%), 277 (65%), 183 (55%)

EIMS/ESI HRMS: M^+ Calcd for $C_30H_{23}OP$, 430.1487; found, 430.1484

1-(4-Nitrophenyl)-2-(triphenylphosphoranylidene)-ethanone (4.44)[32]



Yield: 62%, yellow solid

Mp: 151-152 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 8.16 (d, 2H, *J* = 11.6 Hz, H2, H6), 8.05 (d, 2H, *J* = 12.0 Hz, H3, H5), 7.72-7.65 (m, 6H, H2', H6'), 7.60-7.55 (m, 3H, H4'), 7.51-7.45 (m, 6H, H3', H5'), 4.49 (d, 1H, *J* = 30.4 Hz, COC<u>H</u>PPh_3).

^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 181.8 (<u>C</u>=O), 148.2 (C4), 147.1 (d, *J* = 15.0 Hz, C1'), 133.1 (d, *J* = 10.2 Hz, C2', C6'), 132.0 (*Ar*), 129.0 (d, *J* = 12.2 Hz, C3', C5'), 127.7(*Ar*), 126.6 (*Ar*), 125.6 (*Ar*), 123.1 (*Ar*), 53.7 (d, *J* = 109.0 Hz, CO<u>C</u>HPPh_3)

^{31}P NMR: (160 MHz, $CDCl_3$) δ_P : 17.02

IR: ν_{max} (ATR) 3065, 2442, 2159, 2031, 1976, 1525, 1436, 1407, 1339, 1103, 863, 715, 692, 512 cm^{-1}

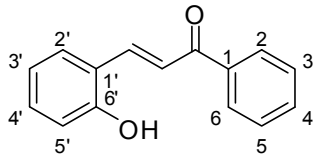
EIMS (*m/z*): 425 (M, 60%), 424 (100%), 303 (M – $C_6H_4NO_2$, 75%), 277 (65%), 183 (65%)

EIMS/ESI HRMS: M^+ Calcd for $C_{26}H_{20}O_3NP$, 425.1181; found, 425.1174

5.4.3.5.3 <u>Synthesis of 2-hydroxychalcones via the Wittig reaction</u>

4.42 (1 g, 2.62 mmol) was dissolved in toluene (10 mL) in a two necked flask equipped with a reflux condenser. To this was added salicylaldehyde (0.321 g, 2.63 mmol) dissolved in toluene (5 mL). The reaction mixture was stirred at reflux for 1 hour. The toluene was removed under reduced pressure and the resultant residue purified by flash silica column chromatography.

(*E*)-3-(2-Hydroxyphenyl)-1-phenylprop-2-en-1-one (4.45)[33]



Yield: 98%, yellow solid

Mp: 152-154 °C

TLC: 0.24 (4:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, $CDCl_3$) δ_H : 8.13 (d, 1H, *J* = 16.0 Hz, PhC<u>H</u>=CH), 8.02 (d, 2H, *J* = 7.6 Hz, H2,H6), 7.69 (d, 1H, *J* = 16.0 Hz, PhCH=C<u>H</u>), 7.59-7.47 (m, 4H, H2', H3, H4, H5), 7.26 (t, 1H, *J* = 8.0 Hz, H4'), 6.95 (t, 1H, *J* = 7.4 Hz, H3'), 6.90 (d, 1H, *J* = 8.4 Hz, H5'), 6.35 (br s, 1H, O<u>H</u>)

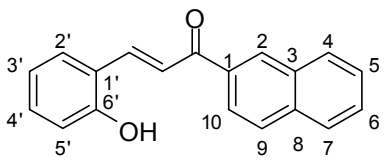
^{13}C NMR: (100 MHz, $CDCl_3$) δ_C : 191.8 (C=O), 155.7 (C6'), 140.8 (Ph<u>C</u>H=CH), 138.3 (C1), 132.7 (C2'), 131.8 (C4), 129.6 (C4'), 128.6 (C2, C3, C5, C6), 122.9 (C1'), 122.2 (PhCH=<u>C</u>H), 121.0 (C3'), 116.6 (C5')

IR: ν_{max} (ATR) 3185, 2504, 2159, 2028, 1976, 1638, 1560, 1455, 1344, 1229, 1022, 731, 513, 471 cm^{-1}

EIMS (*m/z*): 224 (M, 15%), 208 (35%), 207 (100%), 178 (55%), 147 (M – C_6H_5, 20%). 105 (25%), 77 (25%)

EIMS/ESI HRMS: M^+ Calcd for $C_{15}H_{12}O_2$, 224.0837; found, 224.0832

(*E*)-3-(2-hydroxyphenyl)-1-(naphthalen-2-yl)prop-2-en-1-one (4.46)



Yield: 66%, yellow solid

Mp: 156-159 °C

TLC: 0.48 (2:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, DMSO) δ_H : 10.17 (s, 1H, OH), 8.85 (s, 1H, H2), 8.11-7.92 (m, 5H, H-aromatic, PhCH=CH), 7.65 (t, 2H, *J* = 8.4 Hz, H5, H6), 7.28 (t, 1H, *J* = 7.6 Hz, H4'), 6.95 (d, 1H, *J* = 8.0 Hz, H5'), 6.80 (t, 1H, *J* = 7.6 Hz, H3')

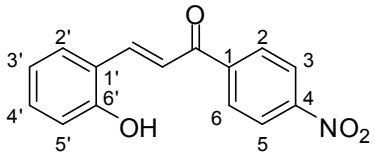
^{13}C NMR: (100 MHz, DMSO) δ_C : 189.15 (C=O), 157.2 (C6'), 139.3 (PhCH=CH), 135.2 (*Ar*), 134.9 (*Ar*), 132.3 (*Ar*), 132.1 (*Ar*), 130.1 (*Ar*), 129.6 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 128.4 (*Ar*), 127.7 (*Ar*), 126.9 (*Ar*), 124.2 (*Ar*), 121.4 (PhCH=CH), 120.8 (*Ar*), 119.4 (*Ar*), 116.2 (*Ar*)

IR: ν_{max} (ATR) 3184, 2522, 2159, 2030, 1976, 1645, 1585, 1458, 1333, 1187, 986, 826, 746, 586, 431 cm^{-1}

EIMS (*m/z*): 274 (M, 10%), 258 (M – O, 30%), 257 (M – OH, 100%), 228 (20%), 155 (15%), 127 (20%)

EIMS/ESI HRMS: M^+ Calcd for $C_{19}H_{14}O_2$, 274.0994; found, 274.0988

(*E*)-3-(2-hydroxyphenyl)-1-(4-nitrophenyl)-2-Propen-1-one (4.47)



Yield: 13%, yellow solid

Mp: 195-200 °C

TLC: 0.61 (2:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, DMSO) δ_H : 10.40 (s, 1H, OH), 8.34 (d, 2H, *J* = 8.4 Hz, H3, H5), 8.27 (d, 2H, *J* = 8.4 Hz, H2, H6), 8.07 (d, 1H, *J* = 15.6 Hz, PhCH=CH), 7.85 (d, 1H, *J* = 5.2 Hz, H2'), 7.83 (d, 1H, *J* = 15.6 Hz, PhCH=CH), 7.28 (t, 1H, *J* = 7.4 Hz, H4'), 6.96 (d, 1H, *J* = 8.0 Hz, H5'), 6.87 (t, 1H, *J* = 7.2 Hz, H3')

^{13}C NMR: (100 MHz, DMSO) δ_C : 188.6 (C=O), 157.6 (C6'), 149.6 (C4), 142.7 (C1), 141.1 (PhCH=CH), 132.5 (C2'), 129.6 (C2, C6), 128.9 (C2), 128.8 (C4'), 123.8 (C3, C5), 121.0 (C1'), 120.6 (PhCH=CH), 119.4 (C3'), 116.3 (C5')

IR: ν_{max} (ATR) 3462, 3333, 2447, 2160, 2029, 1976, 1673, 1651, 1572, 1518, 1339, 1214, 1033, 848, 755, 426 cm^{-1}

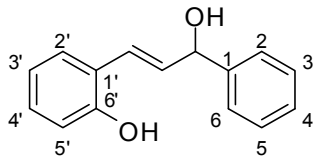
EIMS (*m/z*): 269 (M, 25%), 252 (95%), 206 (50%), 150 (40%), 147 (M – $C_6H_4NO_2$, 50%), 119 (45%)

EIMS/ESI HRMS: M^+ Calcd for $C_{15}H_{11}O_4N$, 269.0688; found, 269.0681

5.4.3.5.4 Sodium borohydride reduction of 2-hydroxychalcones

4.45 (1 g, 4.460 mmol) was dissolved in MeOH (10 mL) and cooled to 0 °C. To this mixture $NaBH_4$ (0.675 g, 17.838 mmol) was added in a portion wise fashion. The resultant mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with 1 M HCl (10 mL), extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

(*E*)-2-(3-hydroxy-3-phenylprop-1-enyl)phenol (4.48)[35]



Yield: 62%, white solid

Mp: 102-105 °C

TLC: 0.31 (2:1 Hexane:EtOAc)

^{1}H NMR: (400 MHz, DMSO) δ_H : 9.58 (s, 1H, PHOH), 7.39 (d, 2H, *J* = 7.2 Hz, H2, H6), 7.35-7.30 (m, 3H, H3, H5, H5'), 7.22 (t, 1H, *J* = 7.2 Hz, H4), 7.25 (t, 1H, *J* = 8.4 Hz, H3'), 6.83 (d, 1H, *J* = 16.0 Hz, PhCH=CH), 6.86-6.81 (m, 1H, H2'), 6.73 (t, 1H, *J* = 7.4 Hz, H4'), 6.53 (dd, 1H, *J* = 16.0 and 6.4 Hz, PhCH=CH), 5.55 (d, 1H, *J* = 4.4 Hz, PhCH=CHCOH), 5.22 (t, 1H, *J* = 5.6 Hz, PhCH=CHCHPh)

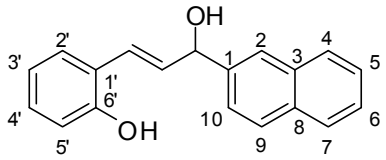
^{13}C NMR: (100 MHz, DMSO) δ_C : 154.7 (C6'), 144.8 (C1'), 133.0 (PhCH=CH), 128.2, (C3'), 128.1 (C3, C5), 126.7 (C5'), 126.6 (C4), 126.2 (C2, C6), 123.6 (C1'), 123.3 (PhCH=CH), 119.1 (C4'), 115.7 (C2'), 73.8 (PhCH=CHCHPh)

IR: ν_{max} (ATR) 2922, 2441, 2159, 2030, 1976, 1731, 1599, 1487, 1450, 1022, 751, 697, 414 cm^{-1}

EIMS (*m/z*): 223 (20%), 222 (45%), 221 (30%), 208 (M – H_2O, 70%), 207 (M-H_3O, 100%), 105 (95%), 77 (C_6H_5, 60%)

EIMS/ESI HRMS: M^+ Calcd for C15H14O2, 226.0994; found, 226.0981

(*E*)-2-(3-hydroxy-3-(naphthalen-2-yl)prop-1-enyl)phenol (4.51)



Yield: 52%, off white solid

Mp: 103-105 °C

TLC: 0.43 (3:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, DMSO) δ_H : 9.61 (s, 1H, PhOH), 7.91-7.87 (m, 4H, H2, H4, H7, H9), 7.56 (dd, 1H, *J* = 11.2 and 2.0 Hz, H10), 7.52-7.44 (m2H, H5, H6), 7.37 (dd, 1H, 10.4 and 2.0 Hz, H2'), 7.04 (dt, 1H, *J* = 14.1 and 4.8 Hz, H4'), 6.93 (d, 1H, *J* = 21.2 Hz, PhCH=CH), 6.84 (d, 1H, *J* = 11.2 Hz, H5'), 6.74 (t, 1H, *J* = 10.2 Hz, H3'), 6.44 (dd, 1H, 21.2 and 8.8 Hz, PhCH=CH), 5.72 (d, 1H, *J* = 5.6 Hz, PhCHOH), 5.41 (t, 1H, *J* = 6.8 Hz, PhCH=CHCHOHPh)

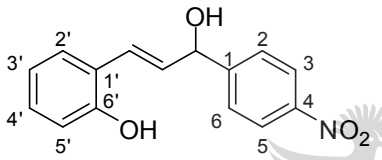
^{13}C NMR: (75 MHz, DMSO) δ_C : 154.7 (C6'), 142.3 (C1), 132.9 (C3), 132.8 (C8), 132.2 (PhCH=CH), 128.3 (C4'), 127.8 (C1'), 127.6 (*Ar*), 127.5 (*Ar*), 126.7 (C2'), 126.0 (C5), 125.6 (C6), 125.1 (C10), 124.2 (*Ar*), 123.9 (*Ar*), 123.4 (PhCH=CH), 119.1 (C5'), 115.7 (C3'), 73.9 (PhCH=CHCHOHPh)

IR: ν_{max} (ATR) 3343, 3051, 2556, 2159, 2030, 1976, 1453, 1246, 1089, 818, 753, 455 cm^{-1}

EIMS (*m/z*): 276 (M, 5%), 260 (100%), 258 (M – H_2O, 50%), 257 (M – H_3O, 40%), 154 (30%)

EIMS/ESI HRMS: M^+ Calcd for $C_{19}H_{16}O_2$, 276.1150; found, 276.1142

(*E*)-2-(3-hydroxy-3-(4-nitrophenyl)prop-1-enyl)phenol (4.52)



Yield: 79%, red solid

Mp: 139-142 °C.

TLC: 0.44 (2:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, DMSO) δ_H : 9.65 (s, 1H, PhOH), 8.21 (d, 2H, *J* = 11.6 Hz, H3, H5), 7.67 (d, 2H, *J* = 11.2 Hz, H2, H6), 7.35 (dd, 1H, *J* = 10.2 and 2.2 Hz, H2'), 7.05 (t, 1H, *J* = 9.2 Hz, H4'), 6.90 (d, 1H, *J* = 21.1 Hz, PhCH=CH), 6.82 (dd, 1H, *J* = 10.8 and 1.6 Hz, H5'), 6.73 (t, 1H, *J* = 10.6 Hz, H3'), 6.33 (dd, 1H, *J* = 21.1 and 9.0 Hz, PhCH=CHCHOH), 5.92 (d, 1H, *J* = 4.8 Hz, PhCHOH), 5.39 (d, 1H, *J* = 6.0 Hz, PhCHOH)

^{13}C NMR: (75 MHz, DMSO) δ_C : 154.8 (C6'), 152.6 (C1), 146.4 (C4), 131.7 (PhCH=CH), 128.6 (C4'), 127.2 (C2, C6), 126.9 (C2'), 124.9 (PhCH=CH), 123.5 (C3, C5), 123.0 (C1'), 119.2 (C3'), 115.7 (C5'), 73.1 (PhCHOH)

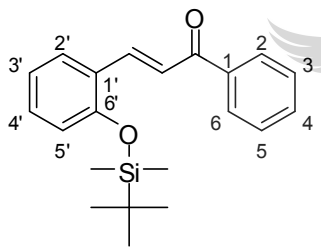
IR: ν_{max} (ATR) 2159, 2031, 1516, 1454, 1343, 855, 752, 699, 474 cm^{-1}

EIMS (*m/z*): 253 (50%), 252 (40%), 206 (30%), 178 (40%), 131 (100%)

5.4.3.5.5 TBDMS protection of the 2-hydroxychalcone **4.45**

2-Hydroxychalcone **4.45** (0.5 g, 2.23 mmol) was dissolved in DCM (10 mL). To this was added Et_3N (0.373 mL, 2.68 mmol) and DMAP (0.027 g, 0.22 mmol). The mixture was cooled to 0 °C and to this was added slowly TBDMSCl (0.403 g, 2.68 mmol). The reaction mixture was then allowed to warm to room temperature over the course of 1 hour. After which the reaction was quenched with 1M HCl (20 mL). The reaction mixture was extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

(*E*)-3-(2-(tert-butyldimethylsilyloxy)phenyl)-1-phenylprop-2-en-1-one (4.49)



Yield: 89%, clear oil

TLC: 0.57 (10:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 8.68 (d, 1H, *J* = 15.9 Hz, PhC<u>H</u>=CH), 8.50 (d, 2H, *J* = 7.2 Hz, H2, H6), 8.21 (dd, 1H, *J* = 7.7 and 1.7 Hz, H2'), 8.10-7.97 (m, 3H, H3, H4, H5), 7.96 (d, 1H, *J* = 15.9 Hz, PhCH=C<u>H</u>), 7.80 (t, 1H, *J* = 8.7 Hz, H4'), 7.52 (1H, 1H, *J* = 7.4 Hz, H3'), 7.39 (d, 1H, *J* = 8.1 Hz, H5'), 1.52 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.75 (s, 6H, $Si(C\underline{H}_3)_2C(CH_3)_3$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 191.2 (C=O), 155.1 (C6'), 140.5 (Ph<u>C</u>H=CH), 138.3 (C1), 132.3 (C2'), 131.5 (C4), 128.4 (C2, C3, C5, C6), 127.5 (C4'), 126.2 (C1'), 122.2 (PhCH=<u>C</u>H), 121.5 (C3'), 119.9 (C5'), 25.6 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), -4.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$)

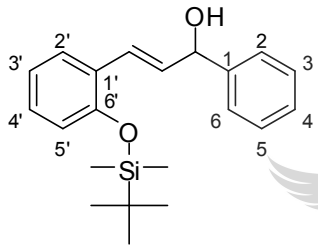
IR: ν_{max} (ATR) 2955, 2929, 2858, 1662, 1597, 1481, 1455, 1253, 1210, 1015, 915, 780, 755, 692, 512 cm^{-1}

EIMS (*m/z*): 281 (50%), 218 (30%), 207 (30%), 130 (20%), 105 (100%), 77 (50%), 69 (100%)

5.4.3.5.6 Sodium borohydride reduction of **4.49**

The sodium borohydride reduction of **4.49** was performed in the same manner as the reduction of **4.45** except only 1.2 equivalents of sodium borohydride was used.

(*E*)-3-(2-(tert-butyldimethylsilyloxy)phenyl)-1-phenylprop-2-en-1-ol (4.50)[34]



Yield: 92%, clear oil

TLC: 0.31 (10:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.49-7.29 (m, 6H, H2, H2', H3, H4, H5, H6), 7.14 (t, 1H, *J* = 7.8 Hz, H4'), 6.8 (d, 1H, *J* = 16.5 Hz, PhC<u>H</u>=CH), 6.93 (t, 1H, *J* = 6.9 Hz, H3'), 6.82 (dd, 1H, *J* = 8.1 and 0.9 Hz, H5'), 6.37 (dd, 1H, *J* = 16.5 and 6.4 Hz, PhCH=C<u>H</u>), 5.38 (d, 1H, *J* = 6.6 Hz, PhCH=CHC<u>H</u>Ph), 1.03 (s, 9H, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.22 (s, 6H, $Si(C\underline{H_3})_2C(CH_3)_3$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 153.0 (C6'), 142.9 (C1), 131.5 (Ph<u>C</u>H=CH), 128.6 (PhCH=<u>C</u>H), 128.5 (C3, C5), 127.9 (C4'), 127.6 (C4), 126.5 (C2'), 126.3 (C2, C6), 126.0 (C1'), 121.3 (C3'), 119.5 (C5'), 75.5 (PhCH=CH<u>C</u>HPh), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), -4.27 ($Si(\underline{C}H_3)_2C(CH_3)_3$)

IR: ν_{max} (ATR) 2955, 2929, 2857, 2492, 2159, 2030, 1976, 1598, 1484, 1452, 1251, 916, 836, 753, 429 cm^{-1}

EIMS/ESI HRMS: M^+ Calcd for $C_{21}H_{28}O_2Si$, 340.1859; found, 340.1808

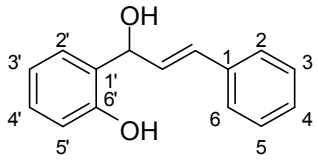
5.4.3.5.7 Silyl ether deprotection of **4.50**

4.50 (0.5 g, 1.47 mmol) was dissolved in THF (10 mL). To this was added *n*-TBAF (0.695 g, 2.21 mmol). The reaction mixture was allowed to stir for 1 hour at room temperature. After which the reaction mixture was diluted with ether (10 mL) and the organic layer washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography to give **4.48**.

5.4.3.5.8 Synthesis of 2'-hydroxychalcone **4.70**

To a flamed out two-necked reaction flask was added anhydrous THF (5 mL) and *n*-BuLi (2.31 mmol, 0.9 M).This mixture was cooled to 0 °C and to this was added 2-bromophenol (0.2 g, 1.16 mmol) dissolved in THF (2 mL). This mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then cooled to -78 °C and to it was added *trans*-cinnamaldehyde (0.146 ml, 1.16 mmol) dissolved in THF (5 mL). The reaction mixture was allowed to warm to 0 °C and stirred for 1 hour. The reaction was quenched by the addition of aqueous saturated NH_4Cl (10 mL). The reaction mixture was diluted with ether (10 mL) and the organic layer washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

(*E*)-2-(1-hydroxy-3-phenylallyl)phenol (4.70)



Yield: 79%, yellow oil

TLC: 0.37 (4:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, DMSO) δ_H : 9.43 (br s, 1H, PhOH), 7.38 (d, 2H, *J* = 7.2 Hz, H2, H6), 7.29 (t, 2H, *J* = 7.2 Hz, H3, H5), 7.20 (d, 1H, *J* = 7.2 Hz, H4), 7.22-7.17 (m, 1H, H2'), 7.06 (t, 1H, *J* = 7.5 Hz, H4'), 6.82-6.80 (m, 2H, H3', H5'), 6,59 (d, 1H, *J* = 16.1 Hz, PhCHOHCH=CHPh), 6.40 (dd, 1H, *J* = 16.1 and 5.0 Hz, PhCHOHCH=CHPh), 5.57 (d, 1H, *J* = 5.0 Hz, PhCHOHCH=CHPh)

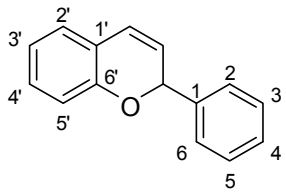
^{13}C NMR: (75 MHz, DMSO) δ_C : 153.9 (C6'), 136.9 (C1), 133.0 (PhCHOHCH=CHPh), 130.3 (C1'), 128.6 (C3, C5), 127.6 (PhCHOHCH=CHPh), 127.2 (C4), 126.8 (C2'), 126.2 (C2, C6), 119.0 (C3'), 115.0 (C5'), 67.5 (PhCHOHCH=CHPh)

IR: ν_{max} (ATR) 3028, 1732, 1603, 1485, 1452, 1226, 1202, 750, 696, 409 cm^{-1}

5.4.3.5.9 Cyclisation of "activated" diols

Al(OTf)$_3$ (0.004g, 8.840 µmol) was dissolved in DCM (10mL). To this **4.48** (0.2 g, 0.884 mmol) was added. The reaction mixture was allowed to stir at room temperature for 1 hour. The reaction was then quenched with aqueous sodium bicarbonate (5 mL) and extracted with DCM (3 x 5 mL) and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by column chromatography.

2-Phenyl-2*H*-chromene (4.53)[34, 35]



Yield: 99%, yellow oil

TLC: 0.55 (20:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.46 (dd, 2H, *J* = 7.9 and 1.7 Hz, H2, H6), 7.40-7.32 (m, 3H, H3, H4, H5), 7.11 (dt, 1H, *J* = 10.8 and 3.8 Hz, H5'), 7.02 (dd, 1H, *J* = 11.2 and 5.8 Hz, H5'), 6.86 (dt, 1H, *J* = 10.3 and 3.8 Hz, H4'), 6.79 (d, 1H, *J* = 8.1 Hz, H2'), 6.53 (dd, 1H, *J* = 9.9 and 2.0 Hz, PhC<u>H</u>=CHCHOPh), 5.92 (dd, 1H, *J* = 3.4 and 2.0 Hz, PhCH=CHC<u>H</u>OPh), 5.80 (dd, 1H, *J* = 9.9 and 3.4 Hz, PhCH=C<u>H</u>CHOPh)

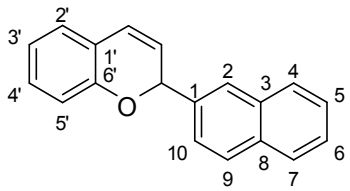
^{13}C NMR: (75 MHz, $CDCL_3$) δ_C : 153.1 (C6'), 140.8 (C1), 129.4 (C3'), 128.6 (C2, C6), 128.3 (C4), 127.0 (C3, C5), 126.6 (C5'), 124.8 (PhCH=<u>C</u>HCHOPh), 124.0 (Ph<u>C</u>H=CHCHOPh), 121.3 (C1'), 121.1 (C4'), 116.0 (C2'), 77.1 (PhCH=CH<u>C</u>HOPh)

IR: ν_{max} (ATR) 2921, 2442, 2159, 2029, 1976, 1449, 1259, 1014, 752, 697, 509 cm^{-1}

EIMS (*m/z*): 208 (M, 65%), 207 (M - H, 100%), 178 (30%), 131 (M – C_6H_5, 40%)

EIMS/ESI HRMS: M^+ Calcd for $C_{15}H_{12}O$, 208.0888; found, 208.0882

2-(Naphthalen-2-yl)-2*H*-chromene (4.54)



Yield: 47%, white solid

Mp: 88-90 °C

TLC: 0.62 (20:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.89-7.82 (m, 4H, H2, H4, H7, H9), 7.63 (dd, 1H, *J* = 11.2 and 2.4 Hz, H10), 7.53-7.47 (m, 2H, H5, H6), 7.15 (dt, 1H, *J* = 14.3 and 5.2 Hz, H4'), 7.06 (dd, 1H, *J* = 9.8 and 2.2 Hz, H5'), 6.90 (dt, 1H, *J* = 13.6 and 4.8 Hz, H3'), 6.85 (d, 1H, *J* = 10.4 Hz, H2'), 6.60 (dd, 1H, *J* = 9.9 and 1.6 Hz, PhC<u>H</u>=CHCHOPh), 6.11 (dd, 1H, *J* = 3.2 and 1.6 Hz, PhCH=CHC<u>H</u>OPh), 5.89 (dd, 1H, *J* = 9.9 and 3.2 Hz, PhCH=C<u>H</u>CHOPh)

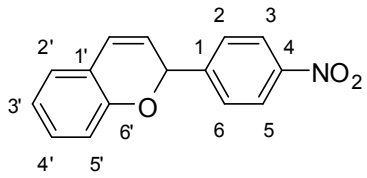
^{13}C NMR: (75 MHz, $CDCL_3$) δ_C : 153.2 (C6'), 138.0 (C1), 133.3 (C3), 133.2 (C8), 129.5 (C4'), 128.6 (C7), 128.2 (C9), 127.7 (C10), 126.6 (C5'), 126.2 (C2, C5), 126.0 (C6), 124.9 (C10), 124.7 (Ph<u>C</u>H=CHCHOPh), 124.2 (PhCH=<u>C</u>HCHOPh), 121.3 (C1'), 121.2 (C3'), 116.0 (C2'), 77.2 (PhCH=CHC<u>H</u>OPh)

IR: ν_{max} (ATR) 3054, 2159, 2031, 1601, 1483, 1230, 1108, 798, 740, 410 cm^{-1}

EIMS (*m/z*): 258 (M, 100%), 257 (M – H, 95%), 131 (M – $C_{10}H_7$, 25%)

EIMS/ESI HRMS: M^+ Calcd for $C_{19}H_{14}O$, 258.1045; found, 258.1040

2-(4-Nitrophenyl)-2*H*-chromene (4.55)[36]



Yield: 47%, yellow oil

TLC: 0.60 (20:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 8.20 (d, 2H, *J* = 11.6 Hz, H3, H5), 7.60 (d, 2H, *J* = 10.8 Hz, H3, H5), 7.13 (dt, 1H, *J* = 14.3 and 5.2 Hz, H4'), 7.01 (dd, 1H, *J* = 9.8 and 2.2 Hz, H5'), 6.88 (dt, 1H, *J* = 13.9 and 5.0 Hz, H3'), 6.81 (d, 1H, *J* = 10.8 Hz, H2'), 6.56 (dd, 1H, *J* = 13.0 and 2.0 Hz, PhC<u>H</u>=CHCHOPh), 5.99

(dd, 1H, *J* = 4.8 and 2.0 Hz, PhCH=CHCHOPh), 5.78 (dd, 1H, *J* = 13.0 and 4.8 Hz, PhCH=CHCHOPh)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 152.6 (C1), 147.9 (C4), 129.9 (C4'), 127.5 (C2, C6), 126.9 (C5'), 125.0 (PhCH=CHCHOPh), 123.9 (C3, C5), 123.3 (PhCH=CHCHOPh), 121.8 (C3'), 121.0 (C1'), 116.0 (C2'), 75.7 (PhCH=CHCHOPh)

IR: ν_{max} (ATR) 2923, 2156, 2030, 1605, 1518, 1344, 1012, 853, 753, 509 cm^{-1}

EIMS (*m/z*): 253 (M, 10%), 252 (M – H, 10%), 218 (20%), 207 (10%), 178 (10%), 130 (30%), 68 (100%)

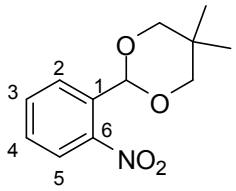
EIMS/ESI HRMS: M^+ Calcd for $C_{15}H_{11}NO_3$, 253.0739; found, 253.0708

5.4.3.6 Synthesis of 1,2-dihydroquinolines

5.4.3.6.1 Acetal protection of 2-nitrobenzaldehyde

2-Nitrobenzaldehyde (0.5 g, 3.31 mmol) and $Al(OTf)_3$ (1.6 mg, 33.1 μmol) were dissolved in DCM (10 mL). To this was added 2,2-dimethylpropane-1,3-diol (1.34 g, 13.24 mmol). The reaction mixture was then heated to reflux and stirred for 12 hours. The reaction was then quenched with aqueous sodium bicarbonate (10 mL) and extracted with DCM (3 x 10 mL) and the combined organic layers washed with water (2 x 10 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by column chromatography.

5,5-Dimethyl-2-(2-nitrophenyl)-1,3-dioxane (4.56)



Yield: 89%, yellow solid

Mp: 74-77 °C

TLC: 0.50 (8:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.90 (dd, 1H, *J* = 8.1 and 1.2 Hz, H5), 7.82 (dd, 1H, *J* = 8.2 and 1.4 Hz, H2), 7.60 (dt, 1H, *J* = 10.6 and 3.9 Hz, H3), 7.45 (dt, 1H, *J* = 10.8 and 3.9 Hz, H4), 5.97 (s, 1H, PhC<u>H</u>), 3.73 (d, 2H, *J* = 11.4 Hz, OC<u>H$_2$</u>), 3.66 (d, 2H, *J* = 10.5 Hz, OC<u>H$_2$</u>), 1.23 (s, 3H, C<u>H$_3$</u>), 0.77 (s, 3H, C<u>H$_3$</u>)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 132.7 (C3), 132.3 (C1), 129.4 (C4), 127.7 (C2), 124.0 (C5), 97.0 (Ph<u>C</u>H), 77.8 (O<u>C</u>H$_2$), 30.2 (<u>C</u>(CH$_3$)$_2$), 23.1 (<u>C</u>H$_3$), 21.6 (<u>C</u>H$_3$)

IR: ν_{max} (ATR) 2956, 2444, 2160, 2030, 1976, 1523, 1354, 1103, 1080, 788, 740, 477 cm^{-1}

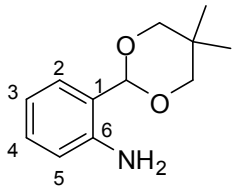
EIMS (*m/z*): 220 (80%), 207 (30%), 190 (40%), 152 (90%), 135 (90%), 135 (80%), 121 (70%), 104 (80%)

EIMS/ESI HRMS: M^+ Calcd for $C_{12}H_{15}NO_4$, 237.1001; found, 237.0993

5.4.3.6.2 <u>Pd/C promoted reduction of **4.56**</u>

10 % Pd/C (45.0 mg, 5 mol%) was suspended in THF (5 mL) in a two-necked reaction flask. The reaction flask was purged with N_2 gas. To this was then added **4.56** (0.2 g, 0.84 mmol). The N_2 gas was replaced by H_2 gas and the reaction mixture was stirred for 1 hour under 1 atm H_2. After which the Pd/C was filtered off and washed with ether (10 mL). The organic solvent was removed under reduced pressure and the residue purified by flash silica column chromatography.

2-(5,5-Dimethyl-1,3-dioxan-2-yl)aniline (4.57)



Yield: 95 %, yellow oil

TLC: 0.27 (8:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.28 (dd, 1H, *J* = 7.8 and 1.5 Hz, H2), 7.11 (dt, 1H, *J* = 10.8 and 3.7 Hz, H4), 6.73 (dt, 1H, *J* = 10.4 and 3.8 Hz, H3), 6.66 (dd, 1H, *J* = 8.1 and 1.2 Hz, H5), 5.38 (s, 1H, PhC<u>H</u>), 4.04 (br s, 2H, $PhNH_2$), 3.78 (d, 2H, *J* = 10.2 Hz, O<u>C</u>H_2), 3.65 (d, 2H, *J* = 10.8 Hz, O<u>C</u>H_2), 1.29 (s, 3H, <u>C</u>H_3), 0.79 (s, 3H, <u>C</u>H_3)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 144.7 (C6), 129.7 (C2), 127.6 (C4), 122.3 (C1), 118.0 (C3), 116.6 (C5), 102.3 (Ph<u>C</u>H), 77.7 (O<u>C</u>H_2), 30.2 (<u>C</u>$(CH_3)_2$), 23.3 (<u>C</u>H_3), 21.9 (<u>C</u>H_3)

IR: ν_{max} (ATR) 3289, 2956, 2159, 2029, 1476, 1391, 1031, 750, 420 cm^{-1}

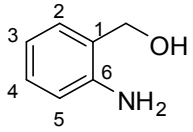
EIMS (*m/z*): 207 (M, 40%), 121 (40%), 93 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{12}H_{17}NO_2$, 207.1259; found, 207.1265

5.4.3.6.3 <u>$NaBH_4$ reduction of 2-nitrobenzaldehyde to 2-aminobenzylalcohol</u>

2-Nitrobenzaldehyde (0.2 g, 1.32 mmol) was dissolved in a 2:1 mixture of THF and H_2O (2 mL: 1 mL). To this was added activated charcoal (0.4 g, 200% m/m). The mixture was heated to 70 °C and stirred for 5 hours. To this was added over the course of 5 hours $NaBH_4$ (0.25 g, 6.60 mmol). After the elapsed reaction time the reaction mixture was filtered and the charcoal washed with ether (10 mL) and then EtOac (10 mL). The organic layer was separated from the aqueous layer and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

(2-Aminophenyl)methanol (4.59)[37a,b]



Yield: 74 %, yellow solid

Mp: 77-79 °C

TLC: 0.41 (1:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.11 (d, 1H, *J* = 10.7 and 3.8 Hz, H4), 7.01 (dd, 1H, *J* = 7.3 and 1.4 Hz, H2), 6.71 (dt, 1H, *J* = 10.2 and 3.7 Hz, H3), 6.66 (d, 1H, *J* = 8.1 Hz, H5), 4.57 (s, 2H, PhC<u>H</u>$_2$), 3.66 (br s, 2H, PhN<u>H</u>$_2$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 145.4 (C6), 129.2 (C2), 129.1 (C4), 125.1 (C1), 118.5 (C3), 116.2 (C5), 63.9 (Ph<u>C</u>H_2OH)

IR: ν_{max} (ATR) 3388, 2517, 2160, 2031, 1976, 1589, 1456, 1268, 1002, 745, 475 cm^{-1}

EIMS (*m/z*): 123 (M, 100%), 106 (30%), 105 (80%), 104 (100%), 94 (20%), 78 (50%)

EIMS/ESI HRMS: M^+ Calcd for C_7H_9NO, 123.0684; found, 123.0677

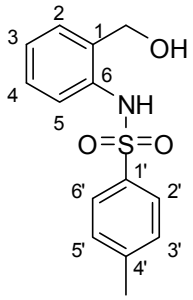
5.4.3.6.4 <u>Tosylation of 2-aminobenzylalcohol **4.59**</u>

2-Aminobenzylalcohol (0.2 g, 1.62 mmol) and Na_2CO_3 (0.19 g, 1.78 mmol) were dissolved in DCM (5 mL).To this was added tosylchloride (0.34 g, 1.78 mmol). The reaction mixture was then heated to reflux for 12 hours.

Alternatively 2-aminobenzylalcohol (0.2 g, 1.62 mmol) and pyridine (0.78 mL, 9.72 mmol) were dissolved in DCM (10 mL). To this was added tosylchloride (0.34 g, 1.78 mmol). The reaction mixture was then heated to reflux for 3 hours.

After the elapsed time the reaction mixture was diluted with DCM (10 mL) and washed with H_2O (10 mL) then 1 M HCl (10 mL). The organic layer was then extracted with 1 M NaOH (4 X 10 mL). The basic aqueous extractions were combined and cooled to 0 °C and then neutralised with concentrated HCl. The white precipitate was filtered off and dried under reduced pressure.

***N*-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (4.60)[38]**



Yield: 94 %, white solid

Mp: 134-136 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.88 (br s, 1H, PhN<u>H</u>Ts), 7.62 (d, 2H, *J* = 8.4 Hz, H2', H6'), 7.40 (d, 1H, *J* = 8.1 Hz, H2), 7.24 (t, 1H, *J* = 4.3 Hz, H4), 7.19 (d, 2H, *J* = 8.1 Hz, H3', H5'), 7.07-7.05 (m, 2H, H3, H5), 4.37 (s, 2H, PhC<u>H$_2$</u>OH), 2.36 (s, 3H, SO_2PhC<u>H$_3$</u>)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 143.8 (C1), 136.9 (C4'), 136.4 (C1'), 131.6 (C6), 129.6 (C3', C5'), 129.2 (C4), 129.0 (C3), 127.0 (C2', C6'), 125.3 (C5), 123.4 (C2), 63.9 (Ph<u>C</u>H$_2$OH), 21.5 (SO_2Ph<u>C</u>H$_3$)

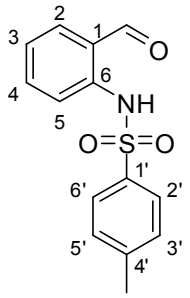
IR: ν_{max} (ATR) 3430, 2506, 2027, 1977, 1412, 1315, 1150, 1031, 928, 761, 547, 470 cm^{-1}

EIMS/ESI HRMS: M^+ Calcd for $C_{14}H_{16}NO_3S$, 278.0851; found, 278.0850

5.4.3.6.5 <u>Oxidation of benzylalcohol **4.60**</u>

Benzylalcohol **4.60** (0.2 g, 4.36 mmol) was dissolved in DCM (10 mL). To this was added MnO_2 (0.25 g, 17.4 mmol). The reaction was stirred at reflux for 12 hours. After the elapsed reaction time the MnO_2 was filtered of and the excess organic solvent removed under reduced pressure. The residue was purified by flash silica column chromatography.

***N*-(2-formylphenyl)-4-methylbenzenesulfonamide (4.61)**[39]



Yield: 72 %, yellow solid

Mp: 131-133 °C

TLC: 0.51 (2:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 10.8 (br s, 1H, N<u>H</u>Ts), 9.79 (s, 1H, PhC<u>H</u>O), 7.74 (d, 2H, *J* = 8.4 Hz, H2', H6'), 7.64 (d, 1H, *J* = 8.1 Hz, H2), 7.56 (dd, 1H, *J* = 7.7 and 1.4 Hz, H5), 7.47 (dt, 1H, *J* = 11.1 and 4.0 Hz, H3), 7.20 (d, 2H, *J* = 8.4 Hz, H3', H5'), 7.13 (dt, 1H, *J* = 10.3 and 3.7 Hz, H4), 2.33 (s, 3H, $SO_2PhC\underline{H_3}$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 195.0 (<u>C</u>=O), 144.2 (C6), 139.8 (C4'), 136.2 (C1'), 136.1 (C5), 135.7 (C3), 129.7 (C3', C5'), 127.2 (C2', C6'), 122.9 (C4), 121.7 (C1), 117.6 (C2), 21.4 ($SO_2Ph\underline{C}H_3$)

IR: ν_{max} (ATR) 3115, 2513, 2160, 2030, 1976, 1662, 1581, 1493, 1455, 1337, 1154, 929, 812, 758, 659, 543, 452 cm^{-1}

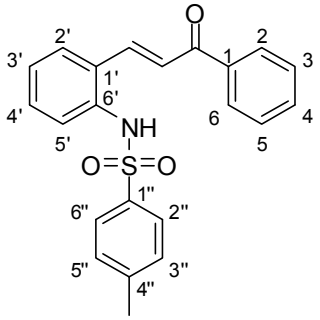
EIMS (*m/z*): 275 (M, 50%), 218 (20%), 120 (100%), 119 (40%)

EIMS/ESI HRMS: M^+ Calcd for $C_{14}H_{13}NO_3S$, 275.0616; found, 275.0568

5.4.3.6.6 <u>Synthesis of 2-tosylaminoxychalcone via the Wittig reaction</u>

4.42 (0.69 g, 1.82 mmol) was dissolved in toluene (10 mL) in a two necked flask equipped with a reflux condenser. To this was added **4.61** (0.5 g, 1.82 mmol) dissolved in toluene (5 mL). The reaction mixture was stirred at reflux for 1 hour. After the elapsed time the toluene was removed under reduced pressure and the resultant residue purified by flash silica column chromatography.

(*E*)-4-methyl-*N*-(2-(3-oxo-3-phenylprop-1-enyl)phenyl)benzenesulfonamide (4.62)[40]



Yield: 95 %, yellow solid

Mp: 170-173 °C

TLC: 0.46 (2:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.84 (d, 2H, *J* = 7.2 Hz, H2, H6), 7.59 (d, 1H, *J* = 15.6 Hz, PhC<u>H</u>=CH), 7.50-7.40 (m, 3H, H3, H4, H5), 7.44 (d, 2H, *J* = 8.4 Hz, H2'', H6''), 7.37 (d, 2H, *J* = 7.6 Hz, H3'', H5''), 7.28 (dt, 1H, *J* = 10.7 and 3.9 Hz, H3'), 7.14 – 7.19 (m, 2H, N<u>H</u>, H5'), 7.09 (d, 1H, *J* = 15.6 Hz, PhCH=C<u>H</u>), 7.00 (d, 2H, H1', H5'), 2.03 (s, 3H, C<u>H$_3$</u>)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 190.0 (<u>C</u>=O), 143.9 (C6), 139.0 (C4''), 137.6 (Ph<u>C</u>H=CH), 135.8 (C1''), 135.3 (C1), 133.1 (C4'), 131.1 (C2'), 130.9 (C1), 129.7 (C2, C6), 129.7 (C3'', C5''), 128.7 (C3, C5), 128.6 (C4), 127.7 (PhCH=<u>C</u>H), 127.2 (C2'', C6''), 127.2 (C3'), 124.3 (C5')

IR: ν_{max} (ATR) 3181, 2501, 2159, 2030, 1976, 1592, 1456, 1341, 1156, 1019, 755, 682, 450 cm^{-1}

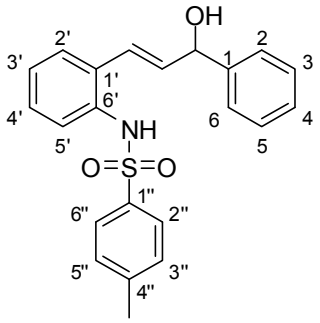
EIMS/ESI HRMS: M^+ Calcd for $C_{22}H_{20}NO_3S$, 378.1164; found, 378.1156

5.4.3.6.7 4 <u>Sodium borohydride reduction of 2-tosylaminochalcone</u>

2-Tosylaminochalcone **4.62** (0.2 g, 0.53 mmol) was dissolved in MeOH (5 mL) and cooled to 0 °C. To this mixture $NaBH_4$ (0.03 g, 0.80 mmol) was added in a portion wise fashion. The resultant mixture was allowed to warm to room temperature and stirred for 1 hour. The

reaction was quenched with 1 M HCl (10 mL), extracted with DCM (3 x 5 mL), and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

(*E*)-*N*-(2-(3-hydroxy-3-phenylprop-1-enyl)phenyl)-4-methylbenzenesulfonamide (4.63)[40]



Yield: 74 %, white solid

Mp: 143-145 °C

TLC: 0.34 (2:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, DMSO) δ_H : 9.69 (br s, 1H, NH), 7.54 (d, 2H, *J* = 8.1 Hz, H2'', H6''), 7.49 (d, 1H, *J* = 4.8 Hz, H5'), 7.35-7.25 (m, 5H, H2, H3, H4, H5, H6), 7.30 (d, 2H, *J* = 7.8Hz, H3'', H5''), 7.13-7.11 (m, 2H, H2', H3'), 6.93-6.92 (m, 1H, H4'), 6.82 (d, 1H, *J* = 15.9 Hz, PhCH=CHCHOHPh), 6.19 (dd, 1H, *J* = 15.9 and 6.6 Hz, PhCH=CHCHOHPh), 5.56 (d, 1H, *J* = 4.2 Hz, OH), 5.11 (t, 1H, *J* = 6.6 Hz, PhCH=CHCHOHPh), 2.33 (s, 3H, CH_3)

^{13}C NMR: (75 MHz, DMSO) δ_C : 144.4 (C6'), 143.0 (C1), 137.4 (C4''), 134.6 (PhCH=CHCHOHPh), 133.7 (C1''), 133.4 (C1'), 129.6 (C3'', C5''), 128.1 (C3, C5), 127.7 (C3'), 127.0 (C4'), 126.9 (C4), 126.7 (C2', C2'', C6''), 126.3 (C2, C6). 125.9 (C5'), 123.8 (PhCH=CHCHOHPh), 73.6 (PhCH=CHCHOHPh), 21.0 (CH_3)

IR: ν_{max} (ATR) 3266, 2488, 2159, 2028, 1976, 1486, 1394, 1326, 1155, 1090, 765, 671, 514 cm^{-1}

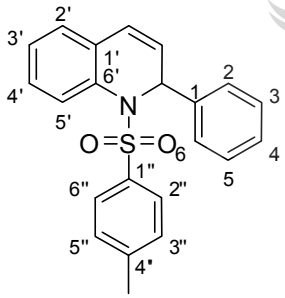
EIMS (*m/z*): 361 (10%), 284 (20%), 206 (90%), 205 (80%), 204 (60%), 155 (30%), 128 (60%), 101 (20%), 91 (100%), 77 (50%)

EIMS/ESI HRMS: M^+ Calcd for $C_{22}H_{21}NO_3S$, 379.1242; found, 379.1236

5.4.3.6.8 Cyclisation of **4.63**

$Al(OTf)_3$ (0.008g, 15.8 µmol) was dissolved in DCM (10mL). To this **4.63** (0.6 g, 1.58 mmol) was added. The reaction mixture was allowed to stir at reflux for 1 hour. The reaction was then quenched with aqueous sodium bicarbonate (5 mL) and extracted with DCM (3 x 5 mL) and the combined organic layers washed with water (2 x 5 mL) and dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

2-Phenyl-1-tosyl-1,2-dihydroquinoline (4.64)[40]



Yield: 86 %, white solid

Mp: 123-126 °C

TLC: 0.69 (2:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 7.65 (d, 1H, *J* = 7.8 Hz, H2'), 7.35-7.32 (m, 4H, H2, H6, H2'', H6''), 7.23-7.06 (m, 5H, H3, H4, H5, H3', H5'), 7.08 (d, 2H, *J* = 8.4 Hz, H3'', H5''), 6.96 (d, 1H, *J* = 7.5 Hz, H4'), 6.27 (d, 1H, *J* = 9.5 Hz, PhC<u>H</u>=CH), 6.03 (d, 1H, *J* = 5.9 Hz, NTsC<u>H</u>Ph), 5.88 (dd, 1H, *J* = 9.5 and 5.9 Hz, PhCH=C<u>H</u>), 2.33 (s, 3H, C<u>H</u>$_3$)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 143.4 (C1), 138.3 (C6'), 136.0 (C4''), 132.8 (C1''), 129.0 (C3'', C5''), 128.6 (C1'), 128.3 (C3, C5), 128.1 (C4'), 127.8 (C2'), 127.5 (C5'), 127.3 (C2, C6), 127.1 (C2'', C6''), 126.4 (C3'), 126.2 (PhCH=CH), 125.4 (PhCH=CH), 56.8 (NTsCHPh), 21.4 (CH_3)

IR: ν_{max} (ATR) 2160, 2031, 1451, 1334, 1154, 811, 775, 690, 655, 575, 471 cm^{-1}

EIMS (*m/z*): 361 (M, 20%), 206 (100%), 205 (40%)155 (30%), 128 (30%)

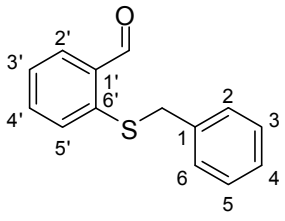
EIMS/ESI HRMS: M^+ Calcd for $C_{22}H_{19}NO_2S$, 361.1136; found, 361.1154

5.4.3.7 Synthesis of 2*H*-thiochromenes

5.4.3.7.1 S_NAr reaction of 2-chlorobenzaldehyde to synthesise **4.66**

2-Chlorobenzaldehyde (0.2 g, 1.42 mmol) was dissolved in DMSO (2 ml) and to this was added K_2CO_3 (0.236 g, 1.70 mmol). Benzylmercaptan (0.176 g, 1.42 mmmol) was added and the reaction mixture allowed to stir at 80 °C for 2 hours. The reaction mixture was diluted with DCM (10 mL) and washed with water (3 x 5 mL). The organic phase was dried with magnesium sulfate. The excess organic solvent was removed under reduced pressure and the resulting residue purified by flash silica column chromatography.

2-(Benzylthio)benzaldehyde (2.66)[41]



Yield: 96 %, white solid

Mp: 55-58 °C

TLC: 0.39 (8:1 Hexane:EtOAc)

^{1}H NMR: (300 MHz, $CDCl_3$) δ_H : 9.89 (s, 1H, CHO), 7.72 (d, 2H, *J* = 8.1 Hz, H2, H6), 7.37-7.24 (m, 7H, H-aromatic), 4.22 (s, 2H, SCH_2Ph)

^{13}C NMR: (75 MHz, $CDCl_3$) δ_C : 191.2 (CHO), 146.3 (C6'), 135.9 (C1), 133.4 (C1'), 130.0 (C2, C6), 128.7 (C2', C3', C4', C5'), 127.6 (C4), 126.8 (C3, C5)

IR: ν_{max} (ATR) 2819, 2719, 2525, 2159, 2031, 1976, 1692, 1583, 1215, 1170, 1092, 813, 698. 441 cm^{-1}

EIMS (*m/z*): 228 (M, 30%), 91 (100%)

EIMS/ESI HRMS: M^+ Calcd for $C_{14}H_{12}OS$, 228.0609; found, 228.0579

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