Synthesis of Chiral Homoallylic Alcohols and Phthalans

Through the Asymmetric Allylation of Carbonyl Compounds

By

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ABSTRACT

The implementation of chiral centres within biologically active compounds has been a perplexing yet motivational force in chemistry. This work presents the attempted formation of a concurrent or sequential tandem catalysed methodology of enantioselective nucleophilic addition and electrophilic cyclization. The 2'-arylalkynyl-aldehyde, ketone, and imine substrates used within were adeptly chosen with a dually activated structure; 1) for nucleophilic addition to the electrophilic substituents; and 2) for carbolphilic activation of the alkyne substituent to undergo cyclization. To accomplish the nucleophilic addition, two distinct allylation methodologies were pursued: (R)-BINOL catalysed-allylboration and (S)-BINAP·AgF catalysed-allylsilylation. BINAP catalysed enantioselective allylation of 2'-arylalkynyl-aldehydes, to form chiral homoallylic alcohols, was successful. Homoallylic alcohols were isolated with high enantio-purity (>80%), which then underwent sequential cyclization to form chiral allylic phthalans, in moderate yields. An application of this methodology towards the construction of biologically active compounds was included with the partial synthesis of the natural product and H. pylori inhibitor, (+)-Spirolaxine methyl ether.
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ABBREVIATIONS

BINOL- 1,1’-bi(2-naphthol)
BINAP- 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
3,3’-Br2-BINOL- 3,3’-dibromo-1,1’-bi(2-naphthol)
c. – concentration
C/c- clear and colourless
CTC – concurrent tandem catalysis
d.r. - diastereomeric ratio
DCM - dichloromethane
e.e. – enantiomeric excess
EtOAc – ethyl acetate
equiv.- equivalents
h- hours
MeOH - methanol
MS – mass spectrometry
NMR – nuclear magnetic resonance
Nu - nucleophile
ON- overnight
PCC- pyridinium chlorochromate
Ph - phenyl
PhCF3- a,a,a-trifluorotoluene
PhMe- toluene
PMP – para-methoxyphenyl
ppt - precipitate
rt- room temperature
STC – sequential tandem catalysis
TLC – thin layer chromatography
THF- tetrahydrofuran
p-Tolyl-BINAP - 2,2’-bis(p-tolyl-phosphino)-1,1’-binaphthyl
Ts – p-toluenesulfonyl
1. Introduction

The following introduction has been divided into sections based on the individual aspects of this thesis project. Each aspect is briefly discussed, with its literature precedent, and emphasis on its relevance to this project. The research within this thesis discusses the devisal of an atom-economic, concurrent or sequential tandem catalyzed methodology of enantioselective nucleophilic addition and electrophilic cyclization. This methodology was designed for the formation of biologically active compounds and their precursors.

1.1 Importance of Chirality in Natural Products and Medicinal Compounds

Biological systems are highly ordered, with complex metabolic pathways that have an innate discernment at the molecular level that is pertinent for the ability to function. Compound recognition of small molecules or natural products within such metabolic pathways is deemed relevant for cellular penetration, localization and metabolic stimulation or inhibition.

In the context of medicinal treatment, natural products are most commonly thought of as compounds derived from plants, microbes, or animals that are utilized as a major source for remedies. Natural products are also widely used in other industrial fields including herbicides, insecticides, and biopolymers.\(^1\) Within the context of this thesis, the use of the term natural products will focus on their application in the production of medicinal compounds.
Natural products have different physical properties and metabolic activation potentials based on their stereochemistry, whereby, a compound with the same atomic connectivity has varied atomic spatial arrangement (stereoisomers) and distinct cellular interaction. The relevance of atomic spatial arrangement in pharmaceutical compounds can be demonstrated by a compound’s ability to induce a positive, negative, or null effect on a cellular target. Thus, identification of the exact stereochemistry of a compound is a vital step prior to its clinical acceptance.

Previously enantiopure pharmaceuticals were considered irrelevant by *in vitro* methods. However, numerous examples have shown that the use of racemic compounds can be detrimental *in vivo*, causing cellular shutdown or induction of the wrong pathways that can ultimately lead to cell apoptosis, mutation, or metastasis. The progression of research in protein structure, function, and activity, has established that the stereochemistry of a molecule is one of the defining factors in protein recognition. This relates back to the 20 natural amino acids that comprise proteins and their predominant L-configuration. This thesis focuses on the application of stereoselective synthetic methodologies for the construction of biologically relevant compounds.

1.2 Synthetic Methods vs. Isolation from Biological Systems

Natural products have been directly employed as medicinal compounds or derivatized to more active compounds. Their significance as a source for pharmaceuticals has been noted, with almost half of the drugs in clinical use being of natural product origin. Isolation of compounds from their natural sources can be a
tenuous, expensive, wasteful, and time-consuming process. Some natural products are limited by their purification, and they cannot be isolated with 100% purity in a significant quantity for any application.

The main advantage of isolating natural products from their biological source is that they inherently possess the optimal geometry for activity. This, however, is not a trivial attribute that can be easily incorporated when using synthetic methods to construct the same compounds. This complexity in synthesis is one reason why the medicinal/natural product area in organic chemistry is expansive and continually progressing in the quantity and function of synthetic methodologies.

The manufacture of synthetic natural products and analogues can also be tenuous and time-consuming. The reduction in the waste and cost compared to product isolation from natural sources, make their chemical syntheses of greater benefit. Synthetic control over the construction of these compounds is also beneficial. Compounds can easily be derivatized in copious quantities and screened for greater activity and efficiency than their natural product counterparts. The development of methodologies that incorporate these points is exceptionally practical and advantageous. As the knowledge surrounding the chemical synthesis of biologically active compounds improves, it will reduce the overall time required for product development. The work presented herein was designed as a stereoselective methodology for the construction of potentially biologically active compounds.
1.3 Skeletal Structures of Some Common Natural Products

There are two prominent classes of natural products with biological activity: the aromatic polyketides and alkaloids; both categorized as heterocyclic compounds. Representatives of such compounds are the oxo-arenes: benzofuran and benzopyran with their iso-analogues; and the nitrogen-arenes: quinoline and indole with their iso-analogues (Figure 1).

These arenes are also commonly found as their hydrated equivalents in biologically active compounds. Thus the overall method development for heterocycle synthesis is highly valuable for pharmaceutical production.

![Figure 1](image)

**Figure 1.** Basic skeletal structure of polyketides (R = O) and alkaloids (R = N); benzopyran (n = 2), benzofuran (n = 1), quinoline (n =2) and indole (n = 1) are represented by structure 1 and their iso-analogues represented by structure 2.

The chemical construction of these natural product frameworks has been well documented in the literature, predominantly for quinolines and isoquinolines. However, one aspect that is difficult to incorporate within these syntheses is the implementation of a chiral centre. There are numerous achiral syntheses of isoquinolines that are recognized, frequently by name, such as the Bischler-Napieralski reaction, Pictet-Spengler isoquinoline synthesis, and the Pomeranz-Fritsch reaction (Scheme 1).

---

^1^4
The position labeled $C(1)$ in Scheme 1, is the designated site for the inclusion of a chiral center by the methodology presented within this thesis. Several chiral modifications have already been made for these isoquinoline syntheses, most commonly through the incorporation of chiral auxiliaries.

![Scheme 1](image)

**Scheme 1.** Established procedures for the synthesis of isoquinolines. **A.** Bischler-Napieralski reaction. **B.** Pictet-Spengler synthesis. **C.** Pomeranz-Fritsch reaction.

In the Bischler-Napieralski reaction, diastereoselective hydride reductions have been performed on substrates with N-appended chiral auxiliaries. Enantioselective reductions have also been accomplished through the use of chiral hydride agents, such as triacyloxy borohydrides. The Pictet-Spengler isoquinoline synthesis has established chiral centres at $C(1)$ during ring closure through the use of chiral auxiliaries on β-arylethynylamines or aldehydes. The Pomeranz-Fritsch reaction has been performed enantioselectively through the inclusion of chiral benzyl
alcohols with aminoacetaldehydes or chiral benzylamines. One of the limitations to chiral auxiliaries is that they require removal or modification to achieve the desired chiral dihydro-isoquinoline.

Development of a methodology that can catalytically establish a functionalized chiral C(1)-centre in the isoquinoline structure is highly advantageous. The incorporation of more reactive functionalities at the chiral centre also allows for further chemical transformation to generate more elaborate structures.

The prevalence of syntheses of benzofurans and benzopyrans is less than the nitrogen variants. This could be accounted for by the reduced stability of the oxygen heterocycles, mainly due to their inability to form a fully resonant structure, 3, and sensitivity to the formation of a fluctuating complex, 4. This complex 4 is prone to ring opening and ring closure, and not necessarily to form the same compound (Figure 2).

![Figure 2](image)

Figure 2. Schematic comparison of stable resonant quinoline vs. acid and base sensitive benzopyran.

A methodology that could generate both nitrogen and oxygen heterocycles depending on the substrate, with minimal procedural changes, would be highly beneficial. The works of Larock et al. were highly influential in this regard. Their
work has often employed electrophile-induced propargyllannulations of anilines 5, and aryl ethers 9, as well as iminoannulations 7, and carbonylannulations 11, with intramolecular alkynes to formulate quinolines, 6, dihydroisoquinolines, 8, 2H-1-benzopyrans, 10, and 1H-isobenzopyrans, 12, respectively. (Scheme 2).

![Scheme 2: Selected contributions of Larock et al. to the construction of alkaloids and polyketides.](image)

The objective of this thesis was to expand on these contributions, through enantioselective nucleophilic additions and electrophilic annulations. The enantioselective installment of a functionalized moiety, especially within the aromatic polyketide and alkaloid framework, is one of the more crucial aspects in the chemical synthesis of complex natural products and their derivatives. Therefore, the focus of this thesis encompasses the construction of natural product intermediates and the development of a conventional methodology that would provide the basic aromatic polyketide or alkaloid skeletal structure with a chiral centre at C(1) of the iso-analogues. The chiral centre would also provide a functionalized site that could be
further manipulated to expand the chemical structure after it is implemented through nucleophilic addition (Scheme 3).

\[
\begin{array}{c}
\text{A = O or N; B = H or Me; C = H, OMe, F; D = aryl, alkyl}
\end{array}
\]

**Scheme 3.** Nucleophilic addition and subsequent annulation on imino and carbonyl compounds to generate chiral hetero-aromatic frameworks.

1.4 Atom Economic Approach – Concurrent Tandem Catalysis and Domino Reactions

The atom economic approach within procedure development has proven to be of substantial benefit in the area of 'green' chemistry. This approach embodies the maximization and efficient use of raw materials with the minimization of waste.\(^{12}\) The term 'atom economy' broadly entails the minimization of atoms involved in a reaction to create a complex product.\(^{13}\) This is accomplished through the maximization of molecule turnover, cascade/domino reaction sequences, and tandem catalytic reactions in a concurrent or sequential manner.

To clarify, molecule turnover is maximized through catalysis. Cascade/domino reaction sequences couple individual reactions with the removal of the intermediate isolation step, in the formation of a lower energy species that is often difficult to obtain from a single process.\(^{14}\) Tandem catalytic reactions are multiple reactions combined into one synthetic operation; sequential tandem catalysis (STC) is
the combination of independent operations often requiring additional reagents or a change in reaction conditions after the first process is complete. Concurrent tandem catalysis (CTC) is the cooperative action of two or more catalytic cycles in a single reaction vessel without an additive or change in conditions.\textsuperscript{15}

**Figure 3** is an elemental representation of the tandem catalytic cycles.\textsuperscript{15} The CTC pathway follows the substrate (S) being subjected to catalyst-1 (C\textsuperscript{1}) and catalyst-2 (C\textsuperscript{2}) in one reaction vessel, upon which C\textsuperscript{1} will transform S into an intermediate (I) compound that C\textsuperscript{2} can then react with to form product (P). The STC pathway follows S interacting exclusively in the presence of C\textsuperscript{1} and when I is completely formed, C\textsuperscript{2} is added to the same reaction vessel to turn I into P.

![Diagram of tandem catalytic cycles](image)

**Figure 3.** Elemental representation of tandem catalytic cycles.

With this in mind, this project sought to design a reaction method involving a predetermined functionalized substrate that could undergo CTC or STC, to form natural product precursors in an atom-economic style (**Scheme 3**).

### 1.5 Modes of Cyclization

The substrate 13 employed provided a dually activated structure, and with this was chosen for use within this work. It was predicted that nucleophilic addition to a
benzo-tethered carbonyl 13 or imino moiety 16 could be done selectively (Scheme 4). Subsequently at C(3) (labeled in Scheme 3, Section 1.3), the adjacently bound alkyne moiety could discriminately be activated for annulation to the resultant alcohol or amine. The efficiency of this process, with regards to following a CTC or STC pathway, would be determined. Addition to the alkyne could occur at C(3') by a 5-exo-dig mechanism to form dihydro-isobenzofuran 14 or 1-hydro-isoindole 17; or at C(2') by a 6-endo-dig mechanism to form 1H-isobenzopyran 15 or 1,2-dihydro-isoquinoline 18 (Scheme 4). These cyclizations were hypothesized to occur with retention of the chiral centre implemented at C(1).

Scheme 4. Modes of cyclization for the chosen substrates for the utilization within CTC or STC parameters.

Literature precedence led to the use of Lewis acids as alkyne activators.\textsuperscript{16-21} The most predominant sources of Lewis acids, used for amino or hydroxylic cyclizations to alkynes, are silver (I), silver (II) and palladium (II) salts.\textsuperscript{16-21} Recently, gold (I) and gold (III) salts have also shown great utility for similar activation.\textsuperscript{56-59}
Gold salts have presented greater substrate application and require lower catalytic loadings.$^{56-59}$

Some of the most promising literature that discussed the cyclization of alcohols to alkynes is presented herein. Pale et al. used gold (I) chloride (AuCl) [10 mol\%] for the synthesis of aurones.$^{16}$ Gabriele et al. utilized palladium (II) iodide (PdI$_2$) [10 mol\%] in the oxidative carbonylation and cyclization of 2-alkynylbenzylalcohols and similar substrates.$^{17}$ Belmont et al. performed a comparison of silver versus gold tandem reactions for the cyclization of carbonyl moieties to alkynes. They identified silver trifluoromethanesulfonate (AgOTf) and silver oxide (Ag$_2$O) as selective for 5-exo-dig and 6-endo-dig closures, pending alkynyl substitution.$^{18}$ Aponick et al. demonstrated the cyclization of monoallylic diols with the unique combination of chlorotriphenylphosphine gold (I) (ClAuPPh$_3$) and AgOTf to generate gold (I) trifluoromethanesulfonate (AuOTf) \textit{in situ}, with an impeccable catalyst loading of 1 mol\%.$^{19}$

Amine cyclizations have also been well-documented by Asao et al. and Takemoto et al. whereby tandem nucleophilic addition and cyclization was achieved with imine substrates, analogous to compound 16, under Lewis acid catalysis with AgOTf and indium (III) trifluoromethanesulfonate (In(OTf)$_3$), respectively.$^{20,21}$

The above documents that similar achiral substrates to those chosen for the research within this thesis (13 & 16), have undergone 5-exo-dig and 6-endo-dig cyclizations induced by catalytic quantities of Lewis acids.
1.6 Enantioselective Allylation Chemistry

The allyl group is commonly utilized as a functionalized site that can be easily transformed to other desired components. Some examples include the derivation to aldehydes through ozonolysis or oxidation; epoxidation and cross-olefin methathesis can also be conducted. The versatility of possible chemical modifications of an allyl moiety provides a reactive site to expand upon, when integrated through nucleophilic addition to the basic skeletal structure of the employed substrate 13.

The allylation of carbon-carbon, carbon-oxygen and carbon-nitrogen centres are comprehensively studied reactions, as these transformations are often conducted with a great deal of ease, selectivity and efficiency. The methodology conveyed within this thesis is a contribution to the area of research in carbonyl and imino allylations.

Enantioselective allylation of carbonyl compounds is one of the most effective and common methods for the synthesis of chiral homoallylic alcohols. These procedures are predominantly carried out under stoichiometric metal-mediated conditions and, less so, catalytically. Denmark and Fu reviewed and developed three general types of carbonyl allylations. Type I is the addition of allylic trichlorosilanes catalyzed by Lewis bases, which append diastereoselectively with anti/syn geometry that reflects the Z/E geometry of the allyl silane. Type II is the addition of allylic organometallic reagents (Sn, Si, B) catalyzed by Lewis acids, forming predominantly the syn geometry, regardless of the starting allyl geometry. Type III is the addition of organometallic reagents (Cr, Zn, In) generated in situ from allylic halides and
catalyzed by chelating ligands, which are predominantly anti-selective independent of the allyl geometry (Figure 4).\textsuperscript{22}

![Chemical representation of Denmark and Fu's types of carbonyl allylations with the predominantly formed stereochemistry.](image)

Over the past fifteen years, catalytic enantioselective allylation methods have been developed, and one of the most frequently used methods is a combination of type II and type III allylations, under Denmark and Fu's classifications.\textsuperscript{22} This method involves the combination of chiral chelating ligands and Lewis acids with allylic organometallic reagents. Two transition states are commonly proposed for these enantioselective allylations: closed, or internal Lewis acid activation \textsuperscript{19}, and open, or external Lewis acid activation \textsuperscript{20} (Figure 5). The ligand employed and Lewis acid nature of the additive, are case-specific to which mechanism they follow during the reaction course. These transition states are also comparable for those of imines.
An established complex for ligand-Lewis acid catalysis contains one of the cheaper, most stable and easily modified ligands, 1,1'-bi(2-naphthol) (BINOL 21) or its phosphine analog 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP 22) (Figure 6). The oxygen and phosphorus atoms act as chelators to Lewis acid additives and/or metals. Both ligands 21 and 22 have been used with Lewis acids in the catalytically activated asymmetric allyl transfer to carbonyl/imino functionalities, from a stoichiometric quantity of achiral organometallic species.

These ligands are also distinguished for their formation of closed transitions states and high enantioinduction. Mikami et al.\textsuperscript{23} and Carreira et al.\textsuperscript{24,25} have independently thoroughly studied BINOL-titanium complexes for the stannane and
silane-mediated allylations of aldehydes. Their work established catalytic methodologies that provided good yields (65-95%) and high enantioinduction (> 80% excess).\textsuperscript{23,24,25} This work also stimulated the investigations of different metals, such as zirconium; and the effect of ligand substitutions at C(3) or C(7) of BINOL. These modifications could improve reactivity in terms of temperature modification, reaction times, and mole loadings of the catalytic complex.

Allyl-metal reactivity towards various substrates, such as aryl or aliphatic aldehydes, ketones and imines, could also be increased.\textsuperscript{22,26,27} Loh \textit{et al.} established stannane allylations of aryl-ketones with (\textit{R})-BINOL-In (III) complexes (20 mol\%) providing moderate yields (50-80\%) and high enantiomeric excesses (e.e.'s) (>80\%).\textsuperscript{28} The work of Walsh \textit{et al.} is another reported example of stannane-mediated allylation of ketones, with greater yields (>80\%) employing titanium (IV)-BINOL complexes in 20-30 mol\% catalyst loading.\textsuperscript{29} Based on these reports, and the independent works of Schaus \textit{et al.}\textsuperscript{30} and Yamamoto \textit{et al.},\textsuperscript{31-34} the research presented within this thesis was initiated. Schaus \textit{et al.} documented the optimized allylboration of ketones catalyzed by chiral diols, identifying 3,3'-dibromo-substituted BINOL (3,3'-Br\textsubscript{2}-BINOL) as the most effective ligand (see Section 2.1, Scheme 5).\textsuperscript{30} Yamamoto \textit{et al.} have also made a large contribution to the silver (I)-BINAP catalyzed allylsilylation of aldehydes in terms of method optimization, substrate scope, and mechanistic elucidation (see Section 3.2, Scheme 17).\textsuperscript{31,32,33,34}

It was envisioned that arylalkynyl- imines, ketones and aldehydes could easily be allylated under BINOL/BINAP catalyzed methods. In the presence of a Lewis
acid, it was hypothesized that concurrent tandem catalysis could also occur to form an isobenzofuran, isoquinoline, or other natural product precursors.

The work presented herein has three highlighted advantages that are limited in the works discussed thus far. Allylation was conducted with a catalytic quantity of Lewis acid and ligand; allylation was done enantioselectively; and the substrate employed was systematically designed to undergo concurrent/sequential catalytic cyclization to form a second profile of entirely different compounds. This work would then be applied towards natural product synthesis in the partial synthesis of the natural product (+)-spirolaxine methyl ether.
2. Enantioselective Allylboration

2.1 Introduction

There is a multitude of allylboration methodologies for nucleophilic addition to aldehydes, ketones, and imines.\(^{22,50}\) Recall Denmark and Fu's allylation classifications discussed in Section 1.6, under which allylboration qualifies as type II allylation of carbonyl compounds and other electrophiles (e.g. imines).\(^{22}\) These procedures are generally regioselective; however they are often limited in that they are not enantioselective or require stoichiometric quantities of Lewis acids in order to activate the borane or boronate for allyl transfer.

Nevertheless, several independent research groups have reported successful enantioselective allylborations. These works were pioneering and have been utilized frequently by others for the enantioselective allylation of aldehydes, ketones, and imines.\(^{35-41}\) The general structures of such active boronate and borane species involve the oxy-boron centre being tethered to form cyclic diols from chiral alcohols, or they are stereoelectronically confined, so that substrate orientation occurs preferentially in one geometry.

Soderquist et al. have utilized a conformationally rigid cyclic allylborane \(^{23}\) for the allylation of ketones with yields of 70-92 % and e.e.'s of >80%, as well as for the allylation of trimethylsilyl-aldimines and ketimines with yields of 50-82% and e.e.'s of >90%.\(^{35,36}\) Brown et al. have also utilized a chiral alkyl substituted allylborane \(^{24}\) for the allylation of aldehydes with 70-80% yields and with e.e.'s of >88%.\(^{37,38}\) Moreover, Roush et al.\(^ {39}\) developed chiral tartrate ester allyl boronates, the
derivatives of which are frequently used for enantioselective allylation. Tartrate allyl boronates are among the most frequently used enantioselective allylboration reagents and are superseded in application only by BINOL and its related chiral alcohols.\textsuperscript{22,50} Roush \textit{et al.}'s reagent 25 afforded aldehyde allylation with yields of 55-95\% and e.e.'s of 70-90\%.\textsuperscript{39} Similarly to Roush \textit{et al.},\textsuperscript{39} Hall \textit{et al.} have constructed chiral, cyclic, diol-based allyl boronates 26 for the allylation of aldehydes, catalyzed by the addition of scandium (III) trifluoromethanesulfonate (10 mol\%) (\textbf{Figure 7}).\textsuperscript{40,41} Hall \textit{et al.}'s\textsuperscript{40,41} boronate diol is more useful than those previously mentioned. The inclusion of substituted allyl moieties has shown to not only confer enantioinduction, but to impart a high degree of diastereoselection as well. Yields were moderate (>50-85\%); diastereomeric ratios (d.r.'s) were >95\% and e.e.'s were substantial (>80\%).\textsuperscript{40,41}

\textbf{Figure 7.} Various chiral tethered allyl boranes and boronates conventionally used for the allylation of aldehydes, ketones and imines. 23, Soderquist \textit{et al.}'s borane\textsuperscript{35,36}; 24, Brown \textit{et al.}'s borane\textsuperscript{37,38}; 25, Roush \textit{et al.}'s boronate\textsuperscript{39}; and 26, Hall \textit{et al.}'s boronate.\textsuperscript{40,41}

All the mentioned methodologies do, however, contain undesirable properties, such as limited reactivity towards aromatic substrates and sensitivities to air and temperature. It was the intent within this work to formulate a generalized methodology without these limitations and to provide products in quantitative yields and with ideal e.e.'s.
The construction of a generalized methodology was influenced by the work of Schaus et al., where ligand exchange of acyclic allylalkylboronate 27 with (R)-3,3'-dibromo-BINOL, was accomplished under facile conditions to enantioselectively transfer the allyl moiety to ketones 28 (Scheme 5). This was actually the first report of ketone allylboration that used catalytic quantities of BINOL and its derivatives.

![Scheme 5](image)

**Scheme 5.** Schaus et al.'s asymmetric allylboration of ketones.

To summarize, the majority of enantioselective allylation approaches to date have generally been limited to aliphatic substrates or require complex borane/boronate species that are difficult to work with. To overcome these limitations for the allylation of various aromatic electrophiles, the work within this thesis combined a catalytic quantity of chiral aromatic diol ligands with a stoichiometric quantity of Lewis acidic diisopropylallylboronate. As stated in Chapter 1, the electrophilic aromatic substrates were also specifically chosen to undergo nucleophilic addition and subsequent cyclization to form natural product precursors (Scheme 6). This methodology is also complementary to an atom-economic approach, with the removal of an added Lewis acid for boron activation.
2.2 General Synthetic Approach

The reactivity of a carbonyl group is comparable to that of an imine, and the two functionalities undergo nucleophilic addition in a similar manner. Aldehydes and imines are similar in reactivity and both are more reactive than ketones. This reactivity trend presented three types of electrophiles for enantioselective nucleophilic allylation and tandem electrophilic cyclization.

The strategy of enantioselective allylation and cyclization of imino-benzoalkynes 16 and carbonyl-benzoalkynes 13 is highly advantageous for the formation of Cl-chiral 1,2-dihydro-isoquinolines, 1-hydro-isoindoles, 1H-isobenzofurans and 1H-isobenzopyrans. These aromatic heterocycles are valuable as potential precursors for the construction of medicinal/natural products. Enantioselective allylboration was then carried out on alkynyl- arylimines, arylaldehydes and arylketones for the synthesis of Cl-chiral aromatic heterocycles.

As stated in Section 2.1, the initial approach with boron-mediated allylations
was influenced by the work of Schaus et al. (Scheme 5), utilizing imines instead of ketones for allylboration.\(^{30}\) It was anticipated that the imine functionality would have similar reactivity as its keto-counterpart.

Other influential work for the boron-mediated allylation approach used within, came from Chong et al.\(^ {42,43}\) The combination of derivatized BINOL with allylboronates presented by Chong et al., had previously been the only documented use of BINOL/ boronate. It involved stoichiometric quantities of the reagent for the allylation of aldehydes and ketones (Scheme 7).\(^ {42}\) Chong et al. have also amended their methodology by using a 3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-BINOL allylboronate 29 for the allylation of cyclic imines to furnish chiral tetrahydroisoquinolines.\(^ {43}\) It was anticipated that this methodology could potentially be applied to the acyclic imine substrates used herein, as well. High yields (>80%) and exceptional enantiomeric ratios (>90%) were reported from both methodologies.\(^ {42,43}\)

\[ \text{R} = \text{aryl} \]
\[ \text{R}' = \text{H or CH}_3 \]

Scheme 7. Chong et al.'s approach to allylboration of aldehydes and ketones.\(^ {42}\)
As mentioned previously, allylboronates are strong enough Lewis acids to accomplish alkylation without a Lewis acid additive. It was expected that the alkylborate byproduct 30 could be acidic enough to promote the intramolecular cyclization of the alcohol and alkyne (Scheme 8).

**Scheme 8.** Anticipated ring closure promoted by alkylborate byproduct 30.

With the anticipated activation of alkynes for cyclization by the alkylborate byproduct 30, and the reputable alkylation methods of Schaus et al.\(^{30}\) and Chong et al.,\(^{42,43}\) the pursuit of a CTC methodology of nucleophilic alkylation/cyclization for the construction of chiral benzo-heterocycles began.
2.3 Results and Discussion

2.3.1 Imine Allylations

All imines 33 were synthesized from the condensation of ethynyl-benzaldehydes or ethynyl-acetophenones 31 with the suitably reactive primary amines 32, in the presence of a water scavenger (Scheme 9). The inclusion of a water scavenger was required for the preparation of the imines, as they are hygroscopic and less stable in comparison to their carbonyl equivalents. Initially, common primary amines were used, equipped with a functional group that could potentially be selectively and easily removed from the dihydro-isoquinoline product to generate the free amine. Benzylamine (32, R₃ = CH₂Ph) and para-anisidine (32, R₃ = p-methoxyphenyl) were the ideal substrates, and could be removed through hydrogenolysis or oxidation, respectively. Upon isolation of the imines 33 they were incorporated into the conditions discussed in Section 2.1 for allylboration catalyzed by (R)-BINOL or one of its derivatives (Scheme 6).

![Scheme 9](image)


The reaction’s molarity, solvents, reactant and ligand mole quantities were those used from Schaus et al.’s optimized conditions (Scheme 5).
The allyldiisopropyl boronate 27 used for the reactions was chemically labile and challenging to characterize. The initial procedure for its synthesis was followed directly from the literature (Scheme 10).\(^{45}\)

![Scheme 10. Scheme for the preparation of diisopropylallylboronate 27.\(^{45}\)](attachment)

The desired allylboration reactions required a mixed solvent system of nonpolar toluene (PhMe) and \(\alpha,\alpha,\alpha\)-trifluorotoluene (PhCF\(_3\)) (Table 1). The ethereal allylboronate 27 required concentration and subsequent solvation in PhMe. When this was attempted, visible formation of insoluble boric acid crashed out of solution. The molarity of the resultant PhMe solution was then not measured accurately. The high volatility and moisture sensitivity of the diisopropylallylboronate promoted its degradation or evaporation. The allylboronate was stored in the Et\(_2\)O and concentrated with PhMe on a small scale (20 mL ethereal boronate) as needed per reaction. The solution integrity could be maintained for a month or more, and reduced the required quantity of allyldiisopropyl boronate added for the allylations.

At reduced temperatures \((<0^\circ\text{C})\), the imine allylations (Table 1) were incomplete even after 8 hours as determined by thin layer chromatography (TLC). At that point, the reactions were left to warm to room temperature (rt) overnight. Starting materials were always consumed, yet product isolation was difficult. Yields above
40% were not achieved, and what was isolated by column chromatography easily underwent racemization.

Table 1. Results summation of attempted imine allylboration utilizing (R)-BINOL and allyldiisopropyl borate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield %</th>
<th>Reaction Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td><img src="image" alt="Substrate" /></td>
<td>12</td>
<td><img src="image" alt="Yield" /> [α] = -39°; sample racemized on exposure to chloroform or residual boric acid</td>
</tr>
<tr>
<td>37</td>
<td><img src="image" alt="Substrate" /></td>
<td>-55</td>
<td><img src="image" alt="Yield" /> only product isolated</td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Substrate" /></td>
<td>9</td>
<td><img src="image" alt="Yield" /> [α] = 0°; sample degradation after column chromatography</td>
</tr>
<tr>
<td>39</td>
<td><img src="image" alt="Substrate" /></td>
<td>-45</td>
<td><img src="image" alt="Yield" /> only product isolated</td>
</tr>
<tr>
<td>40</td>
<td><img src="image" alt="Substrate" /></td>
<td>-40</td>
<td><img src="image" alt="Yield" /> only product isolated</td>
</tr>
</tbody>
</table>
Optical activity was initially assessed by the products’ optical rotation. The product 1-allyl-2-(4-methoxy-phenyl)-1,2-dihydro-isoquinoline 36 was determined to be optically active, however, with a fluctuating (unstable) measured rotation. The product 36 was then left over a period of days, after which optical rotation was measured again. It was then elucidated that the compound was a racemic mixture. To rationalize this conundrum it was hypothesized that the residual acid present in the chloroform utilized for NMR and optical rotation, was enough to cause racemization of the chiral centre through tautomerization, accompanied by the resonant forces of aromaticity within the product 34 (Scheme 11). The residual acid may have also likely originated from the boric acid byproduct 30, undetected even after multiple purifications. Washing of the crude reactions with 2.0 M sodium hydroxide was done to try and remove the residual acid and remove the remaining (R)-BINOL, to simplify purification during chromatography. BINOL was removed but the boric acid byproduct 30 persisted as seen by NMR, and all isolated products had fluctuating optical activity. Attempts were then made to account for the losses in mass recovery.

Scheme 11. One of the proposed actions of a trace amount of acid on the isolated 1,2-dihydro-isoquinoline.
One other predominant product was detected by TLC; its isolation and characterization was pursued. This other major product accounted for almost all the mass where the yields of 1,2-dihydro-isoquinolines were low. It was also found to be more stable, and according to nuclear magnetic resonance spectroscopy and mass spectrometry (NMR and MS) it was identified as the allylated parent aldehyde 35, that was utilized for condensation to formulate the imines (Scheme 12).

Scheme 12. 1-(2-Phenylethynyl-phenyl)-but-3-en-1-ol 35, major product isolated from the attempted allylation of 2-phenylethynyl-benzylimines.

The results of all attempted imine allylations are summarized in Table 1. It was seen that small quantities of the desired 1-allyl-1,2-dihydroisoquinolines (Entries 36 and 38) could be isolated from imines formed from terminal alkynes. When phenyl substituted ethynyl-benzaldehydes were used, allylation of the imine did not occur, which subsequently led to the exclusive formation of 1-(2-phenylethynyl-phenyl)-but-3-en-1-ol (35) (Scheme 12). Substitution at the termini of the ethyne impeded the progress of the reaction, thus no further substituted ethynes were used. The substitution (R = Ph, allyl, Ts, PMP, Table 1) of the imine also offered no
enhancement in reactivity or stability. It was then concluded that this was not the most plausible route for the allylation of imines. It was deemed more advantageous to use more reactive aldehydes as substrates, and to focus the research attention on applying the same method in producing C1-chiral dihydro-benzoisofurans and 1H-benzoisopyrans (Scheme 8).

2.3.2 Carbonylallylations

The same allylboration procedure and conditions applied to the imines was extended to 2'-substituted- ethynylbenzaldehydes and ethynylacetophenones based on the work of Schaus et al. (Scheme 6). Reactions of the aldehydes were found to go to completion within one hour, as determined by TLC, which contrasts with that of the imines. This rapid reaction rate resulted in racemic compounds when conducted at 0 °C. To optimize the reaction conditions, different temperatures were employed for the aldehyde allylations: -40 °C and -78 °C. Despite the temperature alterations the reaction outcome was always the same; reactions were completed within one hour and compounds were racemic. This lack of optical induction is likely a reason why Schaus et al. did not include any aldehyde substrates within their work. It was observed that aldehydes react too fast with the allylboronate, to the point where boronate disproportionation and association with (R)-BINOL does not occur.

It was anticipated that the electronic and steric constraints of the ethynylarylaldehyde substrates would compensate for the lack of reaction control. However, the aldehyde substrates, despite any electronic modifications of the 2'-ethynyl functionality and reduction in temperature, had an uncatalyzed background
rate of allylation that was too fast, and all products obtained were found to be either optically insignificant or inactive. The results of the aldehyde allylations are summarized in Table 2.

Table 2. Results of aldehyde allylations under (R)-3,3'-Br₂-BINOL catalysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>[α]D²⁰</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>[α]D²⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td></td>
<td>45</td>
<td>0</td>
<td>44</td>
<td></td>
<td>38</td>
<td>+2</td>
</tr>
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<td></td>
<td>51</td>
<td>+7.5</td>
<td>45</td>
<td></td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>43</td>
<td></td>
<td>49</td>
<td>+2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The substrate 2'-ethynylbenzaldehyde and the catalyst (R)-BINOL, were used for determining the reaction success. Yields were decent (>60%) but it was found that (R)-BINOL offered no enantioinduction. It was more promising to utilize the diol
ligand \((R)-3,3'-\text{Br}_2\text{-BINOL}\), that Schaus \textit{et al.} had reported to be most effective for the allylation of ketones.\(^{30}\) Yields were approximately 20\% greater when \((R)-3,3'-\text{Br}_2\text{-BINOL}\) was used, however, there was no apparent change in enantioinduction (see Table 2). The difference in mass recovery was not determined, and it was assumed that the loss in yield was in the reaction workup and purification. Removal of the catalyst was not accomplished with a base wash. The catalyst had the same retention as the products by column chromatography, which required multiple columns for removal. The low yields were also reasoned to be due to the presence of the boric acid byproduct 30, promoting intermolecular polymerization of the alkynyl moieties to generate a complex unidentifiable mixture.

Before abandoning 2'-ethynylbenzaldehydes as substrates, cyclization of the homoallylic alcohols was attempted to assess the plausibility of a CTC or STC pathway. As shown in Table 2 the isolated product was consistently the homoallylic alcohol. Concurrent catalytic annulation, by CTC definitions, was not achieved.

A scan of different Lewis acids to promote cyclization, chosen from literature prevalence, was initiated.\(^{16-21}\) The Lewis acids were added in 10 mol\% and up to stoichiometric quantities in order to judge the catalytic reactivity. They were added to the reaction in a sequential manner, after allylation was determined to be complete by TLC. Boric acid \((\text{B(OH)}_3)\), triflic acid \((\text{TfOH})\), \(p\)-toluenesulfonic acid \((\text{PTSA})\), copper (I) triflate \((\text{CuOTf})\), iodine/potassium carbonate \((\text{I}_2/\text{K}_2\text{CO}_3)\), \text{AgOTf}, gold (III) chloride \((\text{AuCl}_3)\) and \(\text{In(OTf)}_3\) were screened; however, no successful additive was found. \(\text{TfOH}\) caused substrate and product polymerization. The \(\text{I}_2/\text{K}_2\text{CO}_3\)
combination caused closure of the allyl moiety with the alcohol, forming cyclic ether 46 (Scheme 13). All other additives had no effect on the reaction.

The solvation of the Lewis acids was limited in PhMe and co-solvent PhCF₃. The combined effects of solvent and the reaction components caused the sequestering of the added Lewis acid and cyclization did not occur in a STC manner. Cyclizations of the pure isolated alcohols with the same additives, were not pursued at this time.

![Chemical structure](image)

**Scheme 13.** The undesired cyclization product formed when I₂/K₂CO₃ was used as a mild electrophilic annulation promoter.

With all the results in perspective, it was established that this allylboration was also inappropriate for the selected 2'-ethynylaldehydes. As such, attention turned towards examining the chemical reactivity of arylethynyl ketones under these allylboration conditions.

Reaction conditions remained the same to those presented by Schaus et al. and utilized for the imines and aldehydes (Scheme 5). The reaction temperature was assessed to be best at -40 °C and left to warm to rt after ~8 hours. Both (R)-BINOL (15 mol%) and (R)-3,3'-Br₂-BINOL (10 mol%) were scanned to determine which was the most effective catalyst. The results of (R)-BINOL catalysis corroborated the conclusions made with the analogous aldehydes and reported by Schaus et al., that
there was no enantioinduction under set reaction conditions.\textsuperscript{30} Reactions carried out with (\textit{R})-3,3'-Br\textsubscript{2}-BINOL gave low yields for all products isolated (\textbf{Entries 48-51}) and there was little optical activity (\textbf{Table 3}). Similar problems to those of the aldehyde allylations were also encountered with cyclization and purification of the ketone allylations.

STC annulation of the generated homoallylic alcohols with AgOTf did occur for the electron-donating alkynyl substituents PMP 50, and thiophenyl 51. However, neither CTC nor STC annulation occurred with the electron withdrawing or deficient ethynylphenyl 48, or ethynylhexyl 49, substituents. Some optical activity was observed in the products 50 and 51. It was noted that the addition of In(OTf)\textsubscript{3} at the beginning of the allylation provided CTC product 1-allyl-1-methyl-3-[1-phenyl-meth-(\textit{Z})-ylidene]-1,3-dihydro-isobenzofuran (47). Unfortunately, the product was isolated with disappointing yields (<20\%), and was racemic.

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{47}
\caption{Chemical structure of 1-allyl-1-methyl-3-[1-phenyl-meth-(\textit{Z})-ylidene]-1,3-dihydro-isobenzofuran (47).}
\end{figure}

As stated, (\textit{R})-3,3'-Br\textsubscript{2}-BINOL persisted throughout purification and pure homoallylic alcohols and benzoisopyrans were not obtained. It was also noted that any measured optical activity would be inaccurate due to the presence of the catalyst.
in the sample. All samples from both carbonyl allylation procedures were deemed racemic due to compromised or non-existent optical activity.

**Table 3.** Results summation of ketone allylborations using (R)-3,3'-Br₂-BINOL as the catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield %</th>
<th>$\left[\alpha\right]^{20}_{D}$</th>
<th>Entry</th>
<th>Product</th>
<th>Yield %</th>
<th>$\left[\alpha\right]^{20}_{D}$</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td>21</td>
<td>+71</td>
<td>50</td>
<td></td>
<td>22</td>
<td>+55</td>
</tr>
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<td></td>
<td><img src="image1.png" alt="Product 1" /></td>
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<td></td>
<td></td>
<td><img src="image2.png" alt="Product 2" /></td>
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<tr>
<td>49</td>
<td></td>
<td>29</td>
<td>+6</td>
<td>51</td>
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<td>8</td>
<td>+37</td>
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<td></td>
<td></td>
<td><img src="image4.png" alt="Product 4" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* values (x) are from reactions where In(OTf)$_3$ was added in 5 mol% to the reaction; attempted CTC

It was speculated that the lack of enantioinduction was due to catalyst sequestering by the product upon allyl transfer and could not be turned over to continue in the catalytic cycle (Figure 9).
Figure 9. Representation of catalyst sequestering during allyl transfer and probable cause for the lack of enantioinduction.

Figure 9 illustrates the association of allyldiisopropyl boronate with (R)-3,3'-Br₂-BINOL, through ligand exchange of an isopropoxy group for a BINOL hydroxyl group. A closed, chair transition state then forms with the electrophilic substrate, 52. Upon the allyl transfer to the electrophile (carbonyl or imine), there is no release of the associated boronate from the product to regenerate the catalytic ligand and release the homoallylic alcohol, 53. If the homoallylic alcohol is still effectively associated with the boronate, then the oxygen becomes deactivated, and regardless of the electrophilic enhancement of the alkyne by the Lewis acid, the interaction is not as strong as the boron-oxygen bond. This results in no cyclization. This would explain the low yields, production of the racemic compounds and the null effect of the sequential addition of a Lewis acid.

Kobayashi and Schneider recognized that the catalytic addition of indium (I) iodide assisted in activating pinacolyl allylboronates, for the construction of homoallylic alcohols from ketones. It was anticipated that this metal might also
function similarly within these reaction conditions to activate the boronate 27, and increase catalyst turnover. InI may also promote annulation of the alcohol to the alkyne in a CTC manner. Unfortunately this method did not resolve any of the limitations from catalyst turnover and provided no increase in reactivity, yield, or enantioinduction.

As was discussed in Section 2.1, the work of Chong et al.\textsuperscript{43} could be utilized as an alternate method to enantioselectively allylate aldehydes, ketones, and imines (Scheme 7). This method employs stoichiometric quantities of (R)-BINOL, which is costly and complicated to derive the allylboronate. A trial allylation was attempted with a stoichiometric quantity of (R)-BINOL-allylboronate and the substrate 2'-phenylethynyl acetophenone. Similar to the former allylboration, this method did not work well with arylethynyl-ketone substrates. The yield was 21\% with (R)-3,3'-Br\textsubscript{2}-BINOL catalysis: it was reduced to 11\% isolated product in the (R)-BINOL-allylboronate reaction. The optical purity was also lower with optical rotations changing from 71\° to 30\°. Further attempts using Chong et al.'s optimal 3,3'-trifluoromethyl-BINOL complex were not done at this time.\textsuperscript{43} It was of greater practicality and benefit to employ a more robust method for allylation; as well the focus of this method development was to be maintained, in a catalytic concurrent or sequential tandem manner.

Thus this supplementary technique for constructing Cl-chiral dihydroisoquinolines, dihydro-benzoisofurans and dihydro-isobenzopyrans had been exhausted.
2.4 Conclusion and Future Work

All attempts described above to overcome the encountered limitations with the allylboration of imines, aldehydes, and ketones had been unsuccessful within the context of BINOL-allyldiisopropyl boronate methodology. At this time, it was considered more constructive to commence work with a complementary methodology in the form of allylsilylation, to achieve our target products, addressed in the following chapter.

Future work within the allylboration methodology includes the composition of a more stable allylboronate species for allyl transfer. As well, further investigations should be focused on the allylation of ketones, and the resulting formation of chiral quaternary carbon-centres. Compounds with such chiral centres have proven to be synthetically challenging to prepare, thus a more convenient synthetic methodology would be beneficial.

Other extended works could include the incorporation of substituted allylating reagents, to introduce the aspect of a diastereoselective methodology. This could actually prove advantageous for the aldehyde substrates. Steric hindrance around the nucleophilic carbon may slow the reaction process and allow for allylboronate coordination with the ligand, so that allyl transfer may occur stereoselectively. This approach is preceded by an array of promising literature regarding the construction of 3,3-disubstituted allylboronates. The preparation of 3,3-disubstituted allylboronates is often extensive in preparation, but provide stable boronate species.\(^{40,41,48,49,50}\)
3. Enantioselective Allylsilylation

3.1 Introduction

Complementary to allylboration is allylsilylation, which is frequently favoured for the stability of the reagents employed. Denmark and Fu class allylsilylation the same as allylboration, that is, Type II (Recall Section 1.6).\(^{22}\) Allylic silane additions generally occur through Lewis acid activation of electrophilic carbonyl or imine moieties. Enantioselection can be directed through silane coordination to a chiral ligand. The spacial interactions of the Lewis acid, its counter-ion and a ligand are determining factors for the stereochemical outcome of these types of allylations. The organization of these electronic and steric forces around the silicon centre, affect the proximal positioning of the nucleophile for allyl transfer to the electrophile. Recall that stereoinduction occurs from one of two basic modes of internal or external interactions in one of the transition states (Figure 5). The Lewis acid and its counter-ion, along with the capacity for ligand association, determine the orientations of associated internal and external interactions in most cases.\(^{22}\)

As discussed in Section 1.6, BINOL and its derivatives are among the most widely used ligands for the allylation of aldehydes, ketones, and imines. Two of the most prominently used allyl reagents with BINOL based ligands are trialkoxy-silanes and trialkyl-stannanes. Stannanes are less preferred due to their toxicity and difficulty in removal of byproducts during purification.

The results, in terms of yield and optical purity, obtained from both allylating reagents are comparable. The works of Yamamoto \textit{et al.} have demonstrated this.\(^{31,51}\)
They presented the asymmetric allylation of aldehydes with BINAP-silver(I) complexes and allyltributylstannane.\textsuperscript{31} Previously moisture sensitive chiral alkyloxyboranes and fastidious BINOL-titanium(IV) complexes were the most frequently used catalysts for asymmetric allylations; currently Yamamoto \textit{et al.}'s catalytic methods are favoured.\textsuperscript{22,31-34,51}

A comparison ensued for the use of BINAP with other chiral phosphines, and the determination of the effect of the silver (I) counter ion on the overall yield and enantioinduction. The highest yields (50-95\%) and e.e.’s (>90\%) resulted from the use of BINAP, AgOTf, and allyltributylstannanes.\textsuperscript{51} Attempts to expand this methodology and remove the use of allylstannanes, Yamamoto \textit{et al.} subsequently explored the BINAP·Ag(I) reactivity with allyltrimethoxysilane.\textsuperscript{31} This proved advantageous, with comparable yields and equivalent e.e.’s. Their work with silanes also showed that the use of AgOTf gave low yield and no enantioinduction.\textsuperscript{31,32} With the insight that fluoride activates silanes, silver fluoride was used, resulting in a dynamic effect on the reactivity and providing homoallylic alcohols in >70\% yields with e.e.’s >80\%, substantiating that the nature of the metal counter-ion is pertinent to reactivity.\textsuperscript{31}

To recount the objective of this thesis, it is the pursuit of a tandem catalytic nucleophilic addition/cyclization on a deliberately designed substrate in a chiral fashion to assemble \textit{C}(1)-chiral dihydro-isobenzofurans or dihydro-isoquinolines (Scheme 4).

Previously domino allylations and cyclizations of \textit{ortho}-alkynylaryl-imines or aldehydes, have been conducted in an achiral fashion, described below. To support
the formation of STC and CTC methodologies, the work of Takemoto et al. was considered, where they performed the synthesis of 1,2-dihydroisoquinolines and 1H-isochromenes in a tandem sequence, catalyzed by Lewis acids.\(^{52}\) They used In(III) and allyltributylstannane as shown in Scheme 14, producing almost exclusively cyclized product in yields of >80% within 12-48 hours.\(^{52}\)

![Scheme 14. Representation of Takemoto et al.'s tandem nucleophilic addition and cyclization.](image)

Asao et al. have also used Pd(II)-Cu(II) catalysis in the nucleophilic addition of allyltrimethylsilane to alkynylbenzaldehydes \((\text{Scheme 15}).\)\(^{53}\) Yields were only moderate (30-80%) and reaction conditions were mild (room temperature), completed within 12-24 hours.

Both contributions support the choice of substrate and the reaction pathway selected herein for tandem allylation/annulation.

![Scheme 15. Representation of Asao et al.'s tandem nucleophilic addition and cyclization.](image)
Expanding on enantioselective tandem catalysis is important for broadening the limited available literature. To the best of our knowledge to date, there is only one other method for the formation of C(1)-chiral 1,3-dihydro-isobenzofurans, conducted in a tandem addition/cyclization manner. Wang et al. reported the use of organozinc reagents and a re-usable dendritic chiral ligand (Scheme 16). This chemistry falls short of being classed as CTC, because heating was required after addition was complete. It is maintained in a tandem fashion and would be classed as STC. Their yields were respectable (>70%), with moderate e.e.'s (>80%).

\[
\begin{align*}
R' &= \text{aryl, alkyl} \\
R'' &= \text{H or F}
\end{align*}
\]

Scheme 16. Representation of Wang et al.'s asymmetric tandem nucleophilic addition/cyclization.

The use of BINAP and allylsilylation remains beneficial in comparison to Wang et al.'s method, due to the incorporation of a prefunctionalized nucleophile (allyl group) and greater stability of the catalyst and nucleophilic reagent employed.
3.2 General Synthetic Approach

The initial reaction conditions utilized were those developed by Yamamoto et al.\textsuperscript{31} and were modified by trial and error accordingly for our substrates (Scheme 17).

\begin{align*}
\text{R} = \text{aryl, alkyl} \\
\text{Scheme 17. Representation of Yamamoto et al.'s allylsilylation conditions.}^{31}
\end{align*}

It is proposed that aldehyde substrate 54 first become associated with the BINAP·Ag(I) complex 55, and then the slow addition of allyltrimethoxysilane 56 permits allyl transfer to the carbonyl carbon, 57. The intermediate aldehyde-silane complex 57 becomes protonated by methanol (MeOH) and liberates fluorotrimethoxysilane 58, as an intermediate that subsequently transfers fluoride to the BINAP·Ag-OMe complex 59, to regenerate the active catalyst (Scheme 18).\textsuperscript{55}
Scheme 18. Mechanistic proposal for the asymmetric allylation of aldehydes by BINAP-F complex.

The silicon atom does not possess the same Lewis acid character as that of boron. It was anticipated that a Lewis acid additive would be required in order to promote cyclization. It would be assessed whether this could be done concurrently (added at the beginning of the reaction) or sequentially (added after the nucleophilic addition is complete). It was hypothesized under these allylsilylation conditions on 2'-arylethynyl aldehydes and with the addition of a Lewis acid, chiral natural product precursors 1,3-dihydrobenzofurans would be synthesized under CTC or STC (Scheme 19).
3.3 Results and discussion

3.3.1 Condition optimization

Reaction optimization was based on the conditions that produced the highest yields of isolated product, with the largest measured optical activity. The aim of this synthetic approach was to design a CTC reaction (Scheme 19).

Scheme 19. Reaction proposal for allylsilylation and subsequent cyclization.

Under Yamamoto et al.'s conditions (Scheme 17),\textsuperscript{31} allylated products were isolated in insufficient quantities (<20%). In all cases for reaction condition optimization and complete chemical characterization, the homoallylic alcohols (63-72) were used. These homoallylic alcohols displayed the highest stability and were isolated with greater yields than their corresponding 1\textit{H}-isobenzofurans (76-85). Optimization began with the evaluation of the optimal temperature, which was assessed by the quantity of optical rotation induced in the product. It was found that at room temperature the uncatalyzed background reaction was too fast, and there was insignificant optical rotation. At \(-20^\circ\text{C}\) the reaction proceeded well within 2-8 hours.
and the optical rotations were of significant caliber (Table 4). At −40 °C the reaction rate was decreased approximately by one half of that at −20 °C, taking 4-16 hours. The optical rotations remained equal to those conducted at -20 °C. Finally, at −78 °C, the reaction rates were inefficiently prolonged (>24 hours) and offered no increase in optical rotation. Thus −20 °C was chosen as the optimal temperature to conduct these experiments.

Yamamoto et al. reported p-tolyl-BINAP as the best ligand for their enantioselective allylsilylations. The most effective chiral ligand under our conditions, was then evaluated. A comparison of the allylalcohol product (63) optical rotations utilizing (S)-BINAP·AgF and (S)-p-tolyl-BINAP·AgF was conducted. It was found that there was no significant increase in optical activity from the former ligand. Based on ligand cost and effectiveness, (S)-BINAP was selected as the optimal ligand.

The mole ratio of reagents was subsequently determined. Mechanistic studies conducted by Kobayashi et al. and within our own group, have elucidated that the active catalytic complex is proposed to be the bis-AgF·(S)-BINAP complex 62. This was in accord with the reagent stoichiometry for optimal stereoinduction, with a 2:1 ratio of AgF:BINAP.

Figure 10. Three proposed active catalytic species as determined by NMR and MS.
There are three complexes shown in Figure 10, which have been identified by NMR and MS. An equilibrium exists between all three at room temperature, with complex 61 being the most predominant. At -20°C, complex 62 is the predominant species, and corresponds to the only NMR peak to shift upon addition and association of the substrate aldehyde and silane. This NMR shift confirms the some involvement of 62 within the reaction.

The next optimization step was to survey the reagent stoichiometry of catalysts that would provide the greatest optical activity. Yamamoto et al. reported 10 mol% AgF: 5 mol% BINAP as the most effective ratio for enantioinduction. The use of 5 mol% AgF: 2.5 mol% (S)-BINAP and stoichiometric amounts of the reactants, were also examined. There was a significant decrease in optical activity, ~50% less optical rotation, with 5 mol% AgF: 2.5 mol% (S)-BINAP. Between stoichiometric amounts and 10 mol% AgF: 5 mol% (S)-BINAP, there was an insignificant difference of ~5% in optical rotation. After this, no further quantities were explored and 10 mol% AgF: 5 mol% BINAP was chosen to be the most effective mole stoichiometry. The amount of silane was maintained at 1.5 equivalents to ensure reaction completion, as well as the reaction molarity (0.16 M).

Despite employing optimized conditions, the yields of isolated alcohols (63-72) were unacceptably low (<40%) for all substrates. To overcome this, the reaction conditions were modified, employing the methods of Yamamoto et al. with the use of BINAP, AgOTf, KF, and 18-crown-6 Et2O in THF. The yield was improved from 35% to 65%, however, the optical purity of the isolated product was slightly decreased.
by a few degrees of measured rotation. What was noted from this procedure was the marked increase in yield when conducted in THF. It was proposed that in pure MeOH, the solvent reacts with the alkynyl moieties to promote intermolecular polymerization (Scheme 20). The increase in yields when THF was utilized was proposed to come from decreasing the effective concentration of MeOH around the substrate/product, and decreasing the rate of the undesired pathway and polymerization.

![Desired pathway; product cleaved and catalyst turned over](image)

![Undesired product; negative charge induces polymerization](image)

**Scheme 20.** Proposed mechanism for the undesired intermolecular polymerization of alkynes.

THF was then used instead of MeOH. The yield was improved, however, the product lacked any optical activity. Mechanistic reports from Kobayashi *et al.*, suggested that MeOH is required for product release and regeneration of the catalytic complex 58, shown previously in **Scheme 18**. The next modification was to successively add equivalents of MeOH to THF. With the addition of 3-6 equivalents of MeOH, the yields were still moderate to high (>60%). The rate of uncatalyzed achiral allylation remained high, and there was still no optical induction.
To summarize reactions in 100% MeOH were low yielding with high enantioinduction and required 2-8 hours for completion. In contrast, reactions in THF with 3-6 equivalents of MeOH were high yielding and resulted in no enantioinduction with prolonged reaction times 6 to >8 hours. Continued solvent modification showed that the greater the MeOH concentration, the greater the optical rotation of the product. Yields were also substantially higher, compared to reactions carried out in just MeOH (2-5 fold greater). It was found that 3 parts MeOH to 1 part THF provided optimal enantioinduction with moderate yields (Table 4). This optimized solvent system was then applied to all allylsilylations.
Table 4. Results summary of all homoallylic alcohols generated for cyclization to form C(1)-chiral phthalans.

\[
\text{R} = \text{alkyl or aryl} \\
\text{R}_1 = \text{H, F, OCH}_3
\]

\[
\begin{array}{cccc|cccc}
\text{Entry} & \text{Product} & \text{Yield} & [\alpha]_D^{20} & \text{ee}^a & \text{Entry} & \text{Product} & \text{Yield} & [\alpha]_D^{20} & \text{ee}^a \\
\text{\%} & \overset{\circ}{\circ}\text{C} & \% & \% & \text{\%} & \overset{\circ}{\circ}\text{C} & \% & \% & \\
\hline
63 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 86 & -103 & 82% & 68 & \begin{array}{c}
\text{F} \\
\text{H}
\end{array} & 60 & -89 & 83% \\
64 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 59 & -102 & 83% & 69 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 62 & -86 & 89% \\
65 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 51 & -79 & 80% & 70 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 27 & -67 & 87% \\
66 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 63 & -90 & 91% & 71 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 37 & -58 & 69% \\
67 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 43 & -53 & 55% & 72 & \begin{array}{c}
\text{HO} \\
\text{H}
\end{array} & 43 & -111 & 87%
\end{array}
\]

\( a - \text{ee \% determined by } { }^{31}\text{P Q NMR and application of Horeau Principle.} \) ee = p x 100\%, p = (K-1)/(K+1). K = ratio homochiral peak area/ ratio heterochiral peak areas, see Experimental Section for further details.
3.3.2 Substrate Scope

With temperature, ligand, and reagent mole stoichiometries established, scanning of the general substrate scope of this reaction began (substrates and results shown in Table 4). The methodology proved to be robust for substrates that varied in substitution site and functionality with the exclusion of one: 2,4-dimethoxy-6-phenylethynyl-benzaldehyde (68), results not shown.

When there was bis-methoxy substitution at C(4) and C(6) of the substrate, the ability for the catalytic complex to associate with the aldehyde substrate was hindered. The reaction did not proceed at reduced temperature and was left to warm to rt, overnight. At that point, the uncatalyzed allylation was considered responsible for the product formation, in that what was isolated 74 was racemic (Scheme 21).

![Scheme 21. Substrate incompatibility for the allylsilylation procedure.](image)

Substitution at C(5) of the substrate with an electron withdrawing substituent (fluoride) did not alter the optical rotation and yield. Electron donating groups (methoxy) at C(5) and C(3) of the benzene ring also resulted in products with high optical activity and yield, consistent with the results from substrates without benzene substitution. Benzodioxolane was also allylated with high optical activity and moderate yield. The remaining different substitutions occurred at the 2′-ethynyl
functionality of the benzaldehydes, which resulted in distinct trends of the products' optical purity and yields, discussed below (results in Table 4).

A trend was observed based of the 2'-ethynyl substitution results. All alkyl-substituted ethynes required longer reaction times and were isolated in lower yields and optical purities. The difference in results from different substituents is derived from two forces within the transition state.

Figure 11 is a depiction of the closed (internally activated) transition state formed between the catalytic complex, silane, and aldehyde. The first destabilizing force within the transition state comes from the free rotation of the substituents of C(1'). This rotation electronically and more effectively, sterically, impedes the transition state formation. In Figure 11, R represents the alkyl or aryl substituent at C(1'). Rotation about this carbon, when alkyl substituted, would impede on the allyl association and transfer. If, however, R is an aryl substituent, it remains rigid, planar, and immobile towards impeding on allyl transfer.

The second interaction involves that of the core benzene ring, C(2)-C(7), and aromatic π-stacking with the phenyl substituents on the phosphines of (S)-BINAP. The latter force is effective towards positioning of the aldehyde within the transition state and allyl transfer in an enantioselective manner.
Figure 11. Portrayal of a closed transition state between aldehyde and silane substrates.

The extent of which different substrates successfully react within this allylation methodology is encouraging for the generation of functionalized and derivatized 1,3-dihydro-isobenzofurans and 1H-isochromenes. All isolated alcohols were indefinitely bench-top stable.

3.3.3 Cyclization to phthalans

Isolation of stable homoallylic alcohols was seemingly trivial by column chromatography. However, the yields of all compounds were unsatisfactory when the reactions were conducted in MeOH (~10-40%). Despite the low yields and before condition optimization, it was attempted to sequentially add a Lewis acid to the crude reactions after allylation in MeOH, to promote and assess the plausibility of cyclization. Lewis acid selection was based upon an extensive literature survey (results shown in Table 5). The most common and successful methods identified were those that utilized the salts of silver (I), gold (I) and gold (III), in chemical systems most similar to that used herein. 56,57,58,59
AgOTf was successful for the cyclizations of most of the substrates that had aromatic substituents on the ethyne, but not for those with alkyl substituents (Table 6). Gold (I) chloride did prove effective for the cyclization of the alkyl substituted ethynes. All metal mediated cyclizations were identified to undergo 5-exo-dig ring closure. The substrates 2'-phenylethynyl 63, 2'-p-methoxyphenylethynyl 64, and 2'-thiophenylethynyl 70, all displayed ring closure over time without the addition of a Lewis acid. This was thought to be due to the electron rich ethyne substituent. It was observed with these self-mediated concurrent closures that they were no longer regioselective, and small quantities of the 6-endo-dig products were detected. These isomers were inseparable by column chromatography and necessitated the addition of a Lewis acid for regioselective annulation. Similarly to their parent homoallylic alcohols, the yields of the isolated phthalans were unacceptably low in MeOH (~5-30%). The solvent was previously identified as deleterious to product formation, and the cyclizations needed to be done with THF as the co-solvent.

When the solvent was changed it was quickly observed that there was another limitation of the methodology. The results of cyclization with the use of AgOTf remained the same. However, AuCl no longer cyclized the electron deficient (alkyl) substituted ethynes in a sequential one-pot manner. The mixed solvent system impeded the solvation of the Lewis acid additive, and limited its interaction with the alkyne moiety, preventing activation and cyclization. Different Lewis acids were then scanned with the purified homoallylic alcohols in 3:1 ratio, MeOH:THF. If no reaction was observed after 24 hours, heating to reflux was implemented for the next 24 hours. At that point, the reactions were either degraded or no reaction was
occurring. If no reaction was occurring the solvent was removed and replaced with higher boiling PhMe or acetonitrile. Stirring was then continued for another 24 hours at room temperature, and then 24 hours at reflux before concluding that under these conditions, the Lewis acid was not an activator for cyclization. The results of the Lewis acids that were scanned are presented in Table 5.

It was noted that substrates that had undergone one-pot sequential cyclization, with the addition of AgOTf, could no longer be further cyclized after they were isolated. It was established that there was some component in the one-pot alkylation/cyclization that was required to form the phthalans, and the pure homoallylic alcohols could not undergo Lewis acid catalyzed cyclization. It was found that the BINAP-phosphines themselves were indirectly required for cyclization. When triphenylphosphine was added to the purified 1-(2-phenylethynyl-phenyl)-but-3-en-l-ol (63) with AgOTf in MeOH:THF, 5-exo-dig ring closure was observed, however, incomplete and resulted in a mixture of phthalan 76 and 63. When it was established that the catalytic complex played some role in activating the alcohol or alkyne for annulation, the project focus then returned to the addition of Lewis acids to the one-pot reactions.
Table 5. Results from Lewis acid screening for the cyclization of purified homoallylic alcohols to form the 6-endo-dig or 5-exo-dig products.

![Lewis acid reaction diagram]

<table>
<thead>
<tr>
<th>Lewis acid additive</th>
<th>Quantity</th>
<th>Substrate for cyclization and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgOTf</td>
<td>10 mol% stoichiometric</td>
<td>5-exo-dig product</td>
</tr>
<tr>
<td>Ag₂O</td>
<td>stoichiometric</td>
<td>no rxn</td>
</tr>
<tr>
<td>AgSbF₆</td>
<td>stoichiometric</td>
<td>no cyclization</td>
</tr>
<tr>
<td>Zn(OTf)₂</td>
<td>10 mol% stoichiometric</td>
<td>no rxn</td>
</tr>
<tr>
<td>CuOTf</td>
<td>10 mol% stoichiometric</td>
<td>no rxn</td>
</tr>
<tr>
<td>In(OTf)₃</td>
<td>10 mol% stoichiometric</td>
<td>&lt;10% product</td>
</tr>
<tr>
<td>InI</td>
<td>10 mol% stoichiometric</td>
<td>no rxn</td>
</tr>
<tr>
<td>GaCl₂</td>
<td>10 mol% stoichiometric</td>
<td>no rxn</td>
</tr>
<tr>
<td>AuCl</td>
<td>10 mol% stoichiometric</td>
<td>&lt;10% product</td>
</tr>
<tr>
<td>AuCl₃</td>
<td>10 mol% stoichiometric</td>
<td>&lt;10% product</td>
</tr>
<tr>
<td>ClAuPPh₃</td>
<td>10 mol% stoichiometric</td>
<td>no rxn</td>
</tr>
<tr>
<td>PTSA</td>
<td>stoichiometric</td>
<td>no rxn</td>
</tr>
<tr>
<td>TfOH</td>
<td>stoichiometric</td>
<td>polymerization</td>
</tr>
</tbody>
</table>
As previously stated, AgOTf promoted cyclization in the one-pot reactions providing the 5-exo-dig product exclusively, except in the case of the phenyl substituted 76, which contained a mixed formation of 6-endo-dig product. This was likely generated from concurrent cyclization after allylation, and before Lewis acid addition. It is possible that the 6-endo-dig product was formed from a different reaction mechanism, whereby the aldehyde substrate forms a pyrylium species 75, which is then allylated (Scheme 22).\(^{60}\) If the isochromene product could be isolated and identified as racemic, this alternate pathway would be confirmed. All attempts thus far to isolate the 6-endo-dig product, however, have only resulted in its degradation.

\[
\begin{align*}
\text{R} & = \text{H or Me} \\
\text{R'} & = \text{alkyl or aryl}
\end{align*}
\]

**Scheme 22.** Generation of a pyrylium species, 75, for the formation of racemic isochromene.

It was observed that electron withdrawing substituents like trifluorotolyl, and electron neutral substituents like all alkyls, do not cyclize with AgOTf. Gold salts have been shown to exhibit great affinity for alkynes\(^{59,60}\) and promoting their addition to heteroatoms. However, AuCl could not promote complete cyclization in the presence of THF. Recall, the work of Aponick *et al.* demonstrated the cyclization of electron deficient monoallylic diols. This was done with a mixture of AgOTf and
ClAuPPh₃ that generated AuOTf *in situ*, and was utilized as prepared in solution.¹⁹ When the two metals were added sequentially to the described allylation, minimal (<20%) cyclization occurred. When the two metals were added as a solution, complete cyclizations of the alkyl and trifluorotolyl substituted alkynes was observed, generating the 5-*exo-dig* phthalan products. At this point all allylated products had undergone STC to form chiral phthalans. Results are summarized in Table 6.
Table 6. Results summary of chiral phthalans synthesized and isolated from STC conditions.

\[
\begin{align*}
&\text{R = alkyl or aryl} \\
&\text{R}_1 = \text{H, F, OCH}_3
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield %</th>
<th>([\alpha]^{20}_D)</th>
<th>[(a)]</th>
<th>Entry</th>
<th>Product</th>
<th>Yield %</th>
<th>([\alpha]^{20}_D)</th>
<th>[(a)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>76</td>
<td><img src="image" alt="Product 76" /></td>
<td>37(^a)</td>
<td>+40</td>
<td></td>
<td>81</td>
<td><img src="image" alt="Product 81" /></td>
<td>65(^a)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td><img src="image" alt="Product 77" /></td>
<td>10(^b)</td>
<td>+82</td>
<td></td>
<td>82</td>
<td><img src="image" alt="Product 82" /></td>
<td>21(^b)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td><img src="image" alt="Product 78" /></td>
<td>42(^b)</td>
<td>+160</td>
<td></td>
<td>83</td>
<td><img src="image" alt="Product 83" /></td>
<td>65(^a)</td>
<td>+162</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td><img src="image" alt="Product 79" /></td>
<td>16(^a)</td>
<td>NA</td>
<td></td>
<td>84</td>
<td><img src="image" alt="Product 84" /></td>
<td>11(^b)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td><img src="image" alt="Product 80" /></td>
<td>11(^b)</td>
<td>NA</td>
<td></td>
<td>85</td>
<td><img src="image" alt="Product 85" /></td>
<td>36(^b)</td>
<td>+43</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) not available due to decomposition
The methodology seemed successful, however, almost all of the isolated chiral phthalans had been observed to be quite air sensitive and instantaneously began degrading upon exposure to air. Physical changes were noticeable with a change in colour from clear and colourless oils to slightly yellow oils. Spectroscopic methods confirmed the phthalans undergo significant decomposition.

It was thought that residual acid from the deuterated chloroform was contributing to the degradation, as was the case with the 1,2-dihydro-isoquinolines. The $d$-chloroform was then passed through a plug of basic alumina for purification; however, the result remained the same. Pure phthalans were thus never obtained and fully characterized, except for compounds 76, 77, 78, 83, and 85. The other product yields were inaccurate, even though they were retrieved clean from column chromatography; by the time NMR analysis began, there was significant decomposition. The major products were the allylated phthalans. NMR results reported in the experimental section correspond to the major product. However, optical rotation would be skewed and was not reported, as the decomposition products could not be identified.

Pyridinium chlorochromate (PCC) oxidation of the isolated phthalan 86 directly upon concentration from chromatographic purification was done to produce the more stable lactone 87 (Scheme 23). The oxidation procedure, however, only worked where the phthalan possessed the phenyl-vinyl ether substitution. When alkyl-vinyl ether substituted phthalans were subjected to the same conditions, complete product decomposition occurred, and what was recovered was unidentifiable.
Scheme 23. The oxidation of phthalans with phenyl-vinyl ether composition, 86, to lactones, 87.

One allylic alcohol did provide a stable phthalan, being 1-allyl-4,6-dimethoxy-3-[1-phenyl-meth-(Z)-ylidene]-1,3-dihydro-isobenzofuran (85). This compound and methodology were then applied to natural product construction through the partial synthesis of (+)-spirolaxine methyl ether (93, Figure 13). To complete this task the benzofuran 85 required oxidation with PCC.

With PCC oxidation, the product lactone 89 was cleanly afforded although with an unfavourable yield of 30%. This lactone was the only compound that had available literature characterization data. Phthalide 89 was then characterized to confirm that there was no loss in optical purity when the homoallylic alcohols were cyclized. Optical rotation was used to confirm optical purity. The optical rotation was measured but could not be precisely compared to the literature due to the decreased concentration from low product isolation. The measured value was $[\alpha]_D^{20} = -10^\circ$ (c. 0.8 g/100 mL, CHCl$_3$) and literature value was $[\alpha]_D^{20} = +68^\circ$ (c. 1.2 g/100 mL, CHCl$_3$). Thus confirmation of the optical purity for compound 89, was not successful, but it did conclude that in order to make the required stereoisomer 88 (Figure 12), (R)-BINAP was required, not (S)-BINAP.
When the reactions were repeated with (R)-BINAP the phthalan 85 was isolated with a 58% yield, and the phthalide 88, with a yield of 25%. The optical rotation $[\alpha]_D^{20} = +57^\circ$ (c. 2.0 g/100 mL, CHCl$_3$) confirmed the optical purity as compared to the literature.

\[ \text{Figure 12. } 88 \text{ was the required intermediate compound for the total synthesis of (+)-Spirolaxine methyl ether; } 89 \text{ was the phthalide generated from PCC oxidation of 85.} \]

The values for optical purity were obtained for the homoallylic alcohols by the application of Horeau's principle of enantioenrichment (see Section 3.3.4) and compound ratio determination by $^{31}$P NMR. After the confirmed enantiopurity of 88, it was implied that the other homoallylic alcohols (63-72) also maintained their enantiopurity upon cyclization (76-85). Thus the e.e.'s reported in Table 4 for the alcohols remained consistent for the phthalan counterparts in Table 6. A successful CTC methodology had thus been constructed for the synthesis of C(1)-chiral 1,3-dihydro-isobenzofurans.

3.3.4 Optical Purity Determination

Application of the Horeau Principle within chemical or NMR analysis of optically enriched samples is conceptually useful for the determination of enantiopurity, or the excess of an enriched enantiomer within a sample. It involves
the use of an achiral bifunctional duplicating reagent. In other words, an achiral reagent is used that is capable of reacting twice indiscriminately between monomeric units (R and S enantiomers). For NMR analysis of alcohols, phosphorus trichloride or methylphosphonothioic dichloride, are predominantly used. For chemical analysis or chiral resolution, a variety of other reagents can be utilized, such as oxalyl chloride or carbonic acid diethyl ester. Both approaches work based on the formation of optically active homochiral (RR or SS), and mesomeric heterochiral (RS and SR) dimers of the optically enriched sample. Diastereomers are formed and can be measured quantitatively by NMR, or chemically separated and quantified to identify the ratio of dimers and optical purity (Scheme 24).

![Scheme 24. Diastereomers formed from treatment of enantiomERICally enriched homoallylic alcohols with phosphorus trichloride.](image)

The reactions between monomers and the achiral reagent must be irreversible, thus no equilibria are formed. There are also three critical assumptions that are made in order to apply the Horeau principle: 1) the outcome of the first reaction must have no influence on the second reaction, or no chiral recognition between bound monomer and achiral linker with the incoming monomer; 2) there must be no rate difference
between the enantiomers during the reaction with the achiral linker; and 3) there must be no interference by side reactions, so all mass is effectively accounted for.\textsuperscript{61} To determine the optical purity of the homoallylic alcohols (63-72), PCl\textsubscript{3} was employed as the achiral linker. Dimer formation of the alcohols was quantified by \textsuperscript{31}P-\textsuperscript{1}H decoupled NMR, and the ratio of peaks was analyzed for optical purity (results reported in Table 4). The procedure followed was adapted from Feringa et al.\textsuperscript{62,63} and the analysis of optical purity was followed by the simplified expression put forth by Marsaioli et al. (See Section 4.3).\textsuperscript{64}

### 3.3.5 Application to Natural Product Synthesis – Partial Synthesis of (+)-Spirolaxine Methyl Ether

To the best of our knowledge, there are only four reported total syntheses for the natural product (+)-spirolaxine methyl ether (93, Figure 13), which is a secondary metabolite produced by and isolated from cultures of the white-rot fungus *Sporotrichum laxum*.\textsuperscript{66-69} The bioactivity of the spirolaxines has been assayed across several therapeutic remedies such as lowering cholesterol, cytotoxicity inhibition, tumor growth suppression, antibiotics, and inhibitory activity against the ulcer causing *Helicobacter pylori*.\textsuperscript{65} The development of a convenient synthesis for this natural product could likely lead to its pharmaceutical application.
Figure 13. Chemical structure of natural product and potential pharmaceutical, (+)-spirolaxine methyl ether, 93.

The allylation/cyclization procedure from this thesis was directly applied in the construction of the phthalide intermediate 88, which has been incorporated within two of the four reported total syntheses of 93. It was envisioned to obtain this intermediate with similar yields, but advantageously in shorter time and milder conditions (Scheme 25).

Scheme 25. Overview of applied allylation/cyclization procedure to develop the shared intermediate phthalide, 88, from other convergent syntheses of (+)-spirolaxine methyl ether.

The four present methodologies each have their own unique contribution to the total synthesis, from one aspect or another. The unique and most important transformations from each synthesis are described briefly herein.
The first published synthesis was that of Robinson and Brimble, whereby they applied the convergent approach of combining a chiral phthalide-aldehyde and spiroacetal sulfone. They accomplished this in 21 steps overall, six of these employed in the construction of the chiral phthalide-aldehyde, which similarly enough, did require the use of quantitative (+)-BINOL·TiF₄ complex and allyltrimethylsilane for alkylation. This same convergent approach was employed by Keaton and Phillips, however, the construction of the spiroketal differed and was completed in less than half the steps to that of Robinson and Brimble. They employed a Kulinkovich cyclopropanation, ring opening and further subunit coupling reactions. Outline in Scheme 26 are the main features of the two approaches of Robinson and Brimble and Keaton and Phillips.

**Scheme 26.** Route A is Robinson & Brimble's convergent approach to 93. Route B is Keaton and Phillips convergent approach to 93.

The other two total syntheses differ greatly in the approach taken to achieve the same product 93. Dallavalle *et al.* reported another convergent approach of a
phthalide and a spiroketal, however, the introduction of the key chiral centres was quite distinct from those previously mentioned.\textsuperscript{68} A regioselective intramolecular ring closure formed the spiroketal and then coupling of a phosphonate derivative of the phthalide, followed by stereoselective hydrogenation provided the target natural product (Scheme 27).\textsuperscript{68}

![Scheme 27](image)

\textbf{Scheme 27.} Representation of Dallavalle \textit{et al.}'s total synthesis of 93 and the highlighting the key transformation steps.\textsuperscript{68}

The last contribution of total synthetic methodologies came from Trost and Weiss in 2007.\textsuperscript{69} It was an ingenious approach for the synthesis of (+)-spirolaxine methyl ether 93. The chemistry developed therein allows for greater substitution and variation in the composition of spirolaxine derivatives. It is a completely linear synthetic approach, carried out over 13 steps. The key transformations are the enantioselective alkynylation and subsequent reduction in the formation of the
phthalide; the phthalide is then expanded upon and functionalized with an appropriately positioned alkyne for intramolecular cyclization in a regioselective manner to complete the spiroketal unit (Scheme 28).  

![Scheme 28. Representation of Trost and Weiss' total synthesis of (+)-spirolaxine methyl ether 93, and the key transformation steps.](image)

Work within our group is being undertaken to develop an alternate strategy for the construction of the spiroketal component for coupling with the phthalide, in the generation of another total synthesis of (+)-spirolaxine methyl ether.

The synthesis of 88 comprises just one of the potential applications of the reported enantioselective allylation/cyclization methodology (Scheme 25) for the construction of natural products and pharmaceutical compounds.
3.4 Conclusions and Future Work

The development of a methodology for the asymmetric generation of homoallylic alcohols that can sequentially undergo cyclization to formulate C1-chiral phthalans was successfully completed. The limitation of the methodology, which remains to be improved, is the isolation of stable phthalan products. However, it was shown that when phthalans were chemically transformed upon isolation, to remove the vinyl ether component, the product is stable and can then be utilized for further synthetic elaboration (recall Scheme 23). Other treatments to isolate stable products includes the concentration of the phthalans under vacuum or by distillation to exclude moisture. Alternatively, the product could be hydrogenated, however, this may reduce the allyl to propyl and remove the reactive functionality, limiting its expansion to form larger products.

Another promising expansion of this work involves the use of substituted allyl reagents for the regioselective and enantioselective addition to aldehydes and other similarly reactive electrophiles. This methodology may also be applied to ketones and imines for the construction of chiral tertiary homoallylic alcohols and C1-chiral isoquinolines respectively.
4. Experimental Section

4.1 General Procedures for Allylboration Chemistry

General Information All reactions were carried out under nitrogen with previously oven-dried glassware. Methanol was purchased anhydrous in a Sureseal package from Aldrich, triethylamine was distilled fresh from sodium hydroxide and tetrahydrofuran was obtained from an Innovative Technology Inc. “PureSolv” system. All stock solvents were purchased from Caledon or EMD Chemicals and used untreated. All reagents were purchased from Sigma-Aldrich, Fluka, Alfa Aesar or Acros and used as received. Column chromatography was carried out on 10% water deactivated silica gel 60 Å (70-230 mesh) from Sigma-Aldrich. Thin layer chromatography was performed on aluminum backed silica gel 60 F254 sheets from EMD Chemicals Inc. (Merck KgaA). TLC plates were visualized with UV light or stained with iodine or phosphomolybdic acid. $^1$H NMR spectra were recorded at 300 MHz, $^{13}$C NMR spectra at 75 MHz and $^{31}$P NMR at 121 MHz on a Bruker Avance DPX-300 Digital NMR with chemical shifts reported in ppm relative to d-chloroform (7.26 ppm for $^1$H NMR & 77.0 ppm for $^{13}$C NMR). Multiplicity of spectra signals: s = singlet, d = doublet, t = triplet, q = quartet. Mass spectra were obtained using a Kratos Concept 1S Double Focusing Spectrometer. IR were recorded with a Class Ila Laser Product-ATI Mattson Research Series FT-IR. Optical rotations were measured with an Autopol III Automatic Polarimeter from Rudolph Research.
General procedure for the synthesis of arylethynyl-aldehydes and ketones (Sonogashira Coupling) Substrates 2'-bromobenzaldehyde or 2'-bromoacetophenone (one equivalent) were dissolved in freshly distilled triethylamine (Et$_3$N) (0.25 M) under N$_2$ and 1.2 equivalents of commercially available mono-substituted ethyne were added. Dichloro-bis(triphenylphosphine) palladium (II) (0.02 equivalents) was then added and the mixture was allowed to stir for ~10 minutes. The rbf was then covered in foil and 0.01 equivalents of copper (II) iodide were added and the mixture was heated to ~50°C for 3-6 hours depending on the substituted ethyne; completion was determined by TLC and the disappearance of the aldehyde. The reaction was then cooled to room temperature and Et$_3$N was removed by a rotary evaporator. The crude oil was then adsorbed on SiO$_2$ gel and purified by column chromatography with a mixtures of hexanes and ethyl acetate. The spectral data from $^1$H and $^{13}$C NMR matched that of the literature$^{52,70,71,72}$ except for the following compounds.

2-Iodo-3,5-dimethoxy-benzaldehyde$^{73}$

1.0 Equiv. of 3,5-dimethoxybenzaldehyde and 1.1 equiv. of silver trifluoroacetate were dissolved in DCM under N$_2$. Subsequently 1.2 equiv. of iodine were added and the reaction was left to stir ON at rt. Completion was determined by TLC and the disappearance of aldehyde. The yellow ppt was filtered and washed with DCM. The combined organic phase was washed with water, dried with Na$_2$SO$_4$ and concentrated. The resulting solid was dissolved in EtOAc and adsorbed on SiO$_2$ gel. It was then filtered on a small pad of SiO$_2$ gel and eluted with 3:1 Hex: EtOAc and concentrated for NMR. Cream solid; $^1$H NMR (CDCl$_3$) $\delta$ 10.20

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(s, 1H), 7.08 (d, J = 3.0 Hz, 1H), 6.68 (d, J = 3.0 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H);

$^{13}$C NMR (CDCl$_3$) δ 196.3, 161.3, 159.0, 136.6, 105.0, 104.7, 77.2, 56.8, 55.8.

3,5-Dimethoxy-2-phenylethynyl-benzaldehyde

The preparation was the same as for the general coupling procedure above. Yellow solid; $^1$H NMR (CDCl$_3$) δ 10.65 (s, 1H), 7.56-7.60 (m, 2H), 7.34-7.40 (m, 3H), 7.05 (d, J = 3.0 Hz, 1H), 6.69 (d, J = 3.0 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ 191.7, 161.7, 160.8, 137.9, 131.5, 128.6, 128.4, 123.0, 110.1, 104.5, 101.1, 99.1, 81.0, 56.3, 55.8.

2-Bromo-4,6-dimethoxy-benzaldehyde

The spectral data matched that of the literature$^{74}$; the procedure was as follows. 1.0 Equiv. of 1-bromo-3,5-dimethoxybenzene was dissolved in DMF (1.93M) and cooled to 0 °C. 2.5 Equiv. of phosphorus oxychloride were then added and the reaction was heated to 100 °C for 4 hours. Reaction completion was determined by TLC and the disappearance of the aryl bromide. The reaction was cooled to rt then poured onto ice and left to sit ON. The resulting ppt was filtered, washed with water and then dried in vacuo. The ppt was then recrystallized from Hex:EtOAc, and dried to yield a cream-coloured solid which was then used.
2,4-Dimethoxy-6-phenylethynyl-benzaldehyde

Preparation\textsuperscript{75}: 1.0 Equiv. of 2-bromo-4,6-dimethoxy-benzaldehyde, 0.05 equiv. of tetrakis(triphenylphosphine) palladium (0) and 0.05 equiv. of copper iodide were weighed into a rbf covered in foil then dissolved in DMF (1.2 M) under N\textsubscript{2}. 1.2 Equiv. of phenyl acetylene were added followed by Et\textsubscript{3}N (2.4 M) and the reaction was heated to 70 °C for 6 h, completion determined by TLC and disappearance of aldehyde. The reaction was then setup for distillation under reduced pressure to removed the DMF and Et\textsubscript{3}N. The resulting oil was passed through a plug of SiO\textsubscript{2} gel, rinsed with 1:1, Hex:EtOAc. The filtrant was reduced and then re-crystallized from EtOAc. Pale yellow solid; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) 10.59 (s, 1H), 7.58-7.63 (m, 2H), 7.35-7.53 (m, 3H), 6.76 (d, \( J = 3.0 \) Hz, 1H), 6.49 (d, \( J = 3.0 \) Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \( \delta \) 188.9, 164.4, 162.8, 131.9, 128.9, 128.4, 122.6, 119.4, 116.5, 110.0, 99.3, 95.6, 86.9, 56.0, 55.7.

**General procedure for the synthesis of allyldiisopropyl borate** A dried 3-neck rbf was equipped with a pressure equalized addition funnel and filled with N\textsubscript{2}. 1.0 Equiv. of triisopropyl borate was dissolved in Et\textsubscript{2}O (0.33 M) the solution was then cooled to -78°C. 1.04 equivalents of a 1.0 M solution of allylmagnesium bromide in Et\textsubscript{2}O was the added dropwise and left to stir for 3 hours further at -78°C. The reaction was then placed in an ice bath and 3.0 equivalents of 3.0 M HCl was added and the solution left to stir for one more hour in the ice bath. The organic layer was separated and the
aqueous was extracted 3 times with Et₂O, dried with Na₂SO₄; the Na₂SO₄ was washed twice with Et₂O. All volumes of Et₂O were split among the reaction and washes to give a total solution molarity of ~0.1, which was then purged with N₂ and stored in the freezer until needed. Solution integrity ~30 days. The spectral data from ¹H and ¹³C NMR matched that of the literature.³⁰,⁴⁵

**General procedure for the allylboration of aldehydes and ketones** Aldehyde or ketone substrates were measured into a rbf (1.0 equiv.). 15 mol% of (R)-(+) -BINOL was then added and under N₂ dry toluene and α,α,α-trifluorotoluene (ratio 1:3) was added (0.2 M). The resulting solution was then cooled to −78°C. Separately 3.0 equiv. of 0.1M etheral solution of allyldiisopropylboronate was mixed with dry toluene (1.0 M) and concentrated on the rotary evaporator at room temperature with the water aspirator to remove the ether. The toluene solution was then added to the aldehyde/ketone and BINOL at −78°C and left to stir for up to 8 hours and then left to warm to rt ON if needed as determined by TLC. When reactions were completed they were washed with 2.0 M NaOH to remove the BINOL, the aqueous phase was extracted 2 times with toluene then dried with Na₂SO₄ and concentrated. The crude oils were adsorbed on SiO₂ gel and columned with Hexanes/EtOAc.
4.2 Physical Data of Allylboration

1-Allyl-2-(4-methoxyphenyl)-1,2-dihydro-isoquinoline
(31, Table 1, 12% yield).

Yellow oil; \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 7.20 (d, \( J = 3.0 \) Hz, 1H), 6.90-7.13 (m, overlapping, 7H), 6.58 (d, \( J = 3.0 \) Hz, 1H), 5.72-5.85 (overlapping d & m, 3H), 5.03-5.08 (overlapping s & t, 2H), 4.95 (t, \( J = 6.0 \) Hz, 1H), 3.82 (s, 3H), 2.45-2.78 (m, 2H); \( ^13C \) NMR (CDCl\(_3\)) \( \delta \) 154.5, 139.5, 134.7, 131.7, 129.7, 129.4, 127.3, 126.3, 125.0, 123.2, 118.0, 117.6, 114.7, 103.6, 61.0, 55.6, 37.7.

1-Allyl-(toluene-4-sulfonyl)-1,2-dihydro-isoquinoline
(33, Table 1, 9% crude yield).

Yellow oil; degraded after chromatography and during NMR in CDCl\(_3\).

1-(2-Ethynyl-phenyl)-but-3-en-1-ol (36, Table 2, 45% yield).

Yellow solid; \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 7.39-7.62 (m, 3H), 7.13-7.28 (m, 2H), 5.86-5.97 (m, 1H), 5.70-5.78 (m, 1H), 4.87-5.14 (m, 3H), 3.36 (s, 1H), 2.40-2.60 (m, 2H), 1.73 (d, \( J = 3.0 \) Hz, 1H); \( ^13C \) NMR (CDCl\(_3\)) \( \delta \) 135.4, 135.0, 134.9, 134.7, 134.4, 132.5, 132.3, 129.1, 126.8, 126.6, 125.7, 125.5, 119.2, 119.1, 117.3, 114.3, 114.1, 82.0, 81.5, 81.4, 72.6, 42.7, 24.5.
1-(2-Phenylethynyl-phenyl)-but-3-en-1-ol (37, Table 2, 51\% yield).

White solid; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.55-7.61 (m, 4H), 7.38-7.42 (m, 4H), 7.29 (t, \(J = 9.0\) Hz, 1H), 5.89-6.03 (m, 1H), 5.19-5.37 (m, 3H), 2.73-2.82 (m, 1H), 2.54 (quintet, 1H), 2.43 (d, \(J = 3.0\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 145.8, 134.8, 132.2, 131.5, 128.8, 128.5, 127.1, 125.3, 123.1, 120.5, 118.3, 94.6, 87.1, 71.4, 42.9

1-[2-(4-Methoxy-phenylethynyl)-phenyl]-but-3-en-1-ol (38, Table 2, 49\% yield).

Cream solid; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.47-7.58 (overlapping mult., 4H), 7.37 (dt, \(J = 9.0, 3.0\) Hz, 1H), 7.27 (dt, \(J = 9.0, 3.0\) Hz, 1H), 5.89-5.99 (m, 1H), 5.17-5.33 (overlapping mult., 3H), 3.86 (s, 1H), 2.72-2.80 (m, 1H), 2.52 (quintet, 1H), 2.30 (d, \(J = 3.0\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 159.8, 145.5, 134.8, 132.9, 132.0, 128.4, 127.1, 125.3, 120.8, 118.2, 115.2, 114.1, 94.6, 85.7, 71.4, 55.3, 42.8.

1-(2-Pent-1-ynyl-phenyl)-but-3-en-1-ol (39, Table 2, 38\% yield).

C/c oil; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.49 (d, \(J = 3.0\) Hz, 1H), 7.40 (d, \(J = 3.0\) Hz, 1H), 7.31 (t, \(J = 9.0\) Hz, 1H), 7.20 (t, \(J = 6.0\) Hz, 1H), 5.82-5.96 (m, 1H), 5.15-5.22 (m, 3H), 2.64-2.70 (m, 1H), 2.47 (quintet,
3H), 2.34 (d, $J = 3.0$ Hz, 1H), 1.67 (quintet, 2H), 1.08 (t, $J = 6.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 145.4, 134.9, 132.2, 127.9, 126.9, 125.2, 121.3, 118.0, 95.7, 78.4, 71.4, 42.6, 22.2, 21.6, 13.6.

1-(4,5-Dimethoxy-2-phenylethynyl-phenyl)-but-3-en-1-ol (40, Table 2, 35% yield).

White solid; $^1$H NMR (CDCl$_3$) $\delta$ 7.49-7.56 (m, 2H), 7.36-7.42 (m, 3H), 7.11 (s, 1H), 7.02 (s, 1H), 5.87-6.01 (m, 1H), 5.18-5.32 (m, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 2.68-2.78 (m, 1H), 2.45-2.55 (m, 1H), 2.21 (d, $J = 3.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 149.8, 147.7, 139.4, 134.8, 131.3, 128.4, 128.2, 118.3, 114.3, 112.2, 108.3, 93.2, 71.2, 56.0, 43.1.

2-(2-Phenylethynyl-phenyl)-pent-4-en-2-ol (48, Table 3, 21% yield).

C/c oil; $^1$H NMR (CDCl$_3$) $\delta$ 7.60-7.66 (m, 1H), 7.54-7.57 (m, 2H), 7.33-7.42 (m, 3H), 7.25-7.30 (m, 2H), 5.58-5.72 (m, 1H), 5.15 (t, $J = 12.0$ Hz, 2H), 3.30-3.36 (m, 1H), 2.95 (s, 1H), 2.75-2.82 (m, 1H), 1.81 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 160.1, 148.7, 134.5, 134.0, 131.2, 128.6, 128.5, 126.7, 125.7, 123.1, 119.3, 119.1, 95.2, 74.4, 46.3, 31.6, 22.7.
2-(2-Oct-1-ynyl-phenyl)-pent-4-en-2-ol (49, Table 3, 29% yield).

C/c oil; \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 7.36-7.55 (m, 2H), 7.27 (dt, \(J = 9.0, 3.0\) Hz, 1H), 7.19 (dt, \(J = 9.0, 3.0\) Hz, 1H), 5.58-5.65 (m, 1H), 5.07-5.14 (m, 2H), 3.12-3.19 (m, 1H), 2.67-2.75 (m, 1H), 2.48 (t, \(J = 6.0\) Hz, 1H), 1.70 (s, 3H), 1.43-1.67 (m, 2H), 1.43-1.53 (m, 2H), 1.23-1.36 (m, 4H), 0.86-0.94 (m, 2H); \(^1^C\) NMR (CDCl\(_3\)) \(\delta\) 153.5, 148.5, 134.6, 134.3, 129.0, 127.7, 126.5, 125.5, 121.1, 120.2, 118.5, 80.6, 74.5, 46.3, 44.4, 31.3, 28.7, 27.2, 22.6.

1-Allyl-3-(4-methoxy-phenyl)-1-methyl-1H-isochromene (50, Table 3, 22% yield).

C/c oil; \(^1^H\) NMR (CDCl\(_3\)) \(\delta\) 7.71 (d, \(J = 3.0\) Hz, 2H), 7.08-7.25 (m, 2H), 6.93 (d, \(J = 6.0\) Hz, 2H) 6.30 (s, 1H), 5.82-5.95 (m, 1H), 5.08 (t, \(J = 12.0\) Hz, 2H), 3.86 (s, 3H), 2.80-2.87 (m, 1H), 2.56-2.63 (m, 1H); \(^1^C\) NMR (CDCl\(_3\)) \(\delta\) 151.2, 135.0, 133.4, 131.0, 127.6, 126.5, 126.1, 123.9, 123.2, 118.2, 113.7, 98.6, 80.2, 55.3, 43.4, 29.8, 24.7.
1-Allyl-1-methyl-3-thiophen-2-yl-1H-isochromene

(51, Table 3, 8% yield).

C/c oil; $^1$H NMR (CDCl$_3$) $\delta$ 7.50-7.53 (m, 2H), 7.43 (d, $J = 3.0$ Hz, 1H), 7.29-7.36 (m, 3H), 7.20-7.23 (m, 1H), 6.02 (s, 1H), 5.75-5.84 (m, 1H), 5.06-5.11 (m, 2H), 2.61-2.71 (m, 2H), 1.64 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 149.6, 142.4, 137.9, 136.6, 130.7, 126.8, 126.4, 125.6, 125.0, 123.9, 122.8, 114.4, 93.7, 67.9, 46.4, 24.3.
4.3 General Procedures for Allylsilylation Chemistry

General procedure for the preparation of homoallylic alcohols (S)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (5 mol%) and silver fluoride (10 mol%) were weighed into a rbf covered with foil. The catalysts were then dissolved in MeOH (total reaction 0.16 M, 3 MeOH:1 THF) under N₂ and left to stir at room temperature for 10 minutes. The reaction was then cooled to −20°C and the aldehyde was added in THF followed by the dropwise addition of allyltrimethoxysilane (1.5 equivalents). Reactions were left to stir 1-2 hours at −20°C and monitored for completion by TLC and the disappearance of aldehyde. The reaction was then directly adsorbed onto SiO₂ gel and columned with hexane/ethyl acetate.

General procedure for the preparation of phthalans The general reaction set-up is identical to that of the homoallylic alcohols except when reaction completion is assessed, the cold bath is removed and 10 mol% of the Lewis acid additive was added, and the reaction was left to stir at rt until cyclization was complete, as determined by TLC. For aromatic substituents AgOTf was added; for aliphatic substituents Au(I)OTf was added. Cyclization times varied from 2-24 h as determined by TLC.

Preparation of gold (I) trifluoromethanesulfonate The solution of Au(I)OTf was prepared according to literature procedure.¹⁹ 1.0 Equiv. of chloro(triphenylphosphine)gold (I) and 1.0 Equiv. of silver trifluoromethanesulfonate were dissolved in DCM (0.004 M) under N₂ and stirred for ~10 minutes at room temperature before use. 10 mol% of DCM solution was added the aliphatic allylations
to promote STC annulation to the phthalan. Solutions were prepared fresh for each use.

**General procedure for the determination of optical purity** The optical purity of the isolated homoallylic alcohols were assessed by the adapted methods of Marsaioli *et al.*$^{64}$ and Feringa *et al.*$^{62,63}$ The isolated alcohols (3 equivalents) were dissolved in CDCl$_3$ (0.3M). Ten equivalents of pyridine were added to the mixture with stirring. One equivalent of phosphorus trichloride was then dissolved in CDCl$_3$ (0.1M) then added to the alcohol with stirring. Stirring was continued for ~10 minutes then $^{31}$P NMR spectra were recorded; $^{31}$P Q parameters and $^{31}$P-$^1$H coupled parameters were measured and are reported. The optical purity was calculated by the methods reported by Feringa *et al.*$^{62}$ Enantiomeric excess = $p \times 100\%$. $p^2 = (K-1)/(K+1)$, where K equals the peak area of the homochiral compound divided by the sum of the peak areas of heterochiral compound 1 and heterochiral compound 2 as determined by $^{31}$P Q parameters. Recall the identification of homochiral and heterochiral compounds from Scheme 17.

**General procedure for the oxidation of 1-[1-Phenyl-meth-(Z)-ylidene]-1,3-dihydro-isobenzofurans to phthalans**

Reaction conditions followed from the literature.$^{54}$ 1.0 Equiv. of the dihydrobenzofuran was dissolved in DCM (0.05 M) under N$_2$. 1.2 Equiv. of pyridinium chlorochromate were added and the reaction was left to stir at rt for 2 h. Reaction completion was determined by TLC. When complete the solution was filtered
through celite and rinsed with DCM and then concentrated. The resulting oil was dissolved in EtOAc, adsorbed on SiO₂ gel and filtered through a plug of SiO₂ gel, rinsing with EtOAc. The filtrate was the concentrated and dried on the high vacuum and analyzed by NMR.
4.4 Physical Data for Allylsilylation Products

1-(2-Phenylethynyl-phenyl)-but-3-en-1-ol (63, Table 4, 86% yield).

Cream solid: mp 75-77°C ; [α]_D^{20} = -103 (c. 5.0 g/100 mL, CHCl₃). ^1H NMR (CDCl₃) δ 7.55-7.61 (m, 4H), 7.38-7.42 (m, 4H), 7.29 (dt, J = 9.0, 1.5 Hz, 1H), 5.89-6.03 (m, 1H), 5.19-5.37 (m, 3H), 2.73-2.82 (m, 1H), 2.54 (quintet, 1H), 2.43 (d, J = 3.0 Hz, 1H); ^13C NMR (CDCl₃) δ 145.8, 134.8, 132.2, 131.5, 128.8, 128.5, 127.1, 125.3, 123.1, 120.5, 118.3, 94.6, 87.1, 71.4, 42.9; IR (CHCl₃) 3683, 3606, 3455, 3019, 2400, 1521, 1424, 1216, 757, 669 cm⁻¹; HRMS (EI, m/z): calculated for C₁₈H₁₆O: 248.1201; found: 248.1201.

Enantiomeric Excess Determination: ^31P Q NMR δ 5.12 (s), 5.18 (s), 5.36 (s); ^31P-^1H coupled NMR δ 2.23 (t, J = 9.7 Hz), 8.01 (t, J = 9.7 Hz); ee 82%.

1-[2-(4-Methoxy-phenylethynyl)-phenyl]-but-3-en-1-ol (64, Table 4, 59% yield).

Cream solid: mp 53-55°C ; [α]_D^{20} = -102 (c. 4.0 g/100 mL, CHCl₃). ^1H NMR (CDCl₃) δ 7.47-7.58 (overlapping mult., 4H), 7.37 (dt, J = 9.0, 1.5 Hz, 1H), 7.27 (dt, J = 9.0, 1.5 Hz, 1H), 5.89-5.99 (m, 1H), 5.17-5.33 (overlapping mult., 3H), 3.86 (s, 1H), 2.72-2.80 (m, 1H), 2.52 (quintet, 1H), 2.30 (d, J = 3.0 Hz, 1H); ^13C NMR (CDCl₃) δ 159.8, 145.5, 134.8, 132.9, 132.0, 128.4, 127.1, 125.3, 120.8, 118.2, 115.2, 114.1, 94.6, 85.7, 71.4, 55.3,
42.8; IR (CHCl₃) 3684, 3596, 3436, 3019, 2279, 1647, 1513, 1424, 1215, 761, 670 cm⁻¹; HRMS (EI, m/z): calculated for C₁₉H₁₈O₂: 278.1307; found: 278.1307.

Enantiomeric Excess Determination: \(^{31}\)P Q NMR δ 5.04 (s), 5.15 (s), 5.30 (s); \(^{31}\)P-\(^{1}\)H coupled NMR δ 2.15 (t, \(J = 9.7\) Hz), 7.96 (t, \(J = 9.7\) Hz); ee 83%.

**1-[2-(4-Trifluoromethyl-phenylethynyl)-phenyl]-but-3-en-1-ol (65, Table 4, 51% yield).**

Yellow solid: mp 68-71 °C; [α]\(D^20\) = −79 (c. 3.0 g/100 mL, CHCl₃). \(^1\)H NMR (CDCl₃) δ 7.60-7.64 (overlapping s and d, 4H), 7.55 (d, \(J = 3.0\) Hz, 2H), 7.43 (t, \(J = 6.0\) Hz, 1H), 7.30 (t, \(J = 6.0\) Hz, 1H), 5.86-6.00 (m, 1H), 5.18-5.35 (overlapping mult., 3H), 2.70-2.78 (m, 1H), 2.52 (quint., 1H), 2.28 (d, \(J = 3.0\) Hz, 1H); \(^{13}\)C NMR (CDCl₃) δ 146.0, 134.6, 132.3, 131.6, 129.3, 127.2, 126.9, 119.8, 118.4, 93.0, 89.4, 71.3, 43.0; IR (CHCl₃) 3387, 3019, 2400, 2289, 1521, 1425, 1215, 1031, 759, 670 cm⁻¹; HRMS (EI, m/z) calculated for C₁₉H₁₅F₃O: 316.1075; found: 316.1075.

Enantiomeric Excess Determination: \(^{31}\)P Q NMR δ 5.22 (s), 5.37 (s), 5.49 (s); \(^{31}\)P-\(^{1}\)H coupled NMR δ 2.31 (t, \(J = 9.7\) Hz), 8.17 (t, \(J = 9.7\) Hz); ee 80%.

**1-(6-Phenylethynyl-benzo[1,3]dioxol-5-yl)-but-3-en-1-ol (66, Table 4, 63% yield).**

White solid: mp 142-145°C; [α]\(D^20\) = −90 (c. 4.0 g/100 mL,
CHCl₃). ¹H NMR (CDCl₃) δ 7.49-7.52 (m, 2H), 7.36-7.39 (m, 3H), 7.07 (s, 1H), 6.96 (s, 1H), 5.88-6.00 (overlapping s and m, 3H), 5.17-5.30 (overlapping mult., 3H), 2.64-2.72 (m, 1H), 2.47 (quintet, 1H), 2.29 (d, J = 3.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 148.4, 146.4, 141.3, 134.6, 131.3, 128.4, 128.3, 123.2, 118.3, 113.4, 111.3, 106.1, 101.4, 93.1, 87.0, 71.1, 43.0; IR (CHCl₃) 3669, 3610, 3456, 3019, 2400, 1520, 1424, 1218, 772, 670 cm⁻¹; HRMS (EI, m/z) calculated for C₁₉H₁₆O₃: 292.1099; found: 292.1099.

Enantiomeric Excess Determination: ³¹P Q NMR δ 5.30 (s), 5.40 (s), 5.72 (s); ³¹P-¹H coupled NMR δ 2.40 (t, J = 9.7 Hz), 8.20 (t, J = 9.7 Hz); ee 91%.

1-(2-Pent-1-ynyl-phenyl)-but-3-en-1-ol (67, Table 4, 43% yield).

Light yellow oil: [α]D²⁰ = -53 (c. 4.0 g/100 mL, CHCl₃).

¹H NMR (CDCl₃) δ 7.49 (d, J = 3.0 Hz, 1H), 7.40 (d, J = 3.0 Hz, 1H), 7.31 (t, J = 9.0 Hz, 1H), 7.20 (t, J = 6.0 Hz, 1H), 5.82-5.96 (m, 1H), 5.15-5.22 (m, 3H), 2.64-2.70 (m, 1H), 2.48 (quintet, 3H), 2.34 (d, J = 3.0 Hz, 1H), 1.67 (quintet, 2H), 1.08 (t, J = 6.0 Hz, 3H); ¹³C NMR (CDCl₃) δ 145.4, 134.9, 132.2, 127.9, 126.9, 125.2, 121.3, 118.0, 95.7, 78.4, 71.4, 42.6, 22.2, 21.6, 13.6; IR (CHCl₃) 3684, 3611, 3450, 3019, 2400, 1521, 1424, 1218, 1047, 928, 771, 670 cm⁻¹; HRMS (EI, m/z) calculated for C₁₅H₁₈O: 214.1358 found: 214.1358.

Enantiomeric Excess Determination: ³¹P Q NMR δ 4.98 (s), 5.13 (s), 5.36 (s); ³¹P-¹H coupled NMR δ 7.86 (t, J = 9.7 Hz), 2.10 (t, J = 9.7 Hz); ee 55%;
1-(5-Fluoro-2-phenylethynyl-phenyl)-but-3-en-1-ol (68, Table 4, 60% yield).

White solid: mp 91-93°C; [α]D²⁰ = -89 (c. 3.0 g/100 mL, CHCl₃). ¹H NMR (CDCl₃) δ 7.49-7.54 (m, 1H), 7.28-7.41 (overlapping mult., 4H), 6.97 (dt, J = 9.0, 1.5 Hz, 1H), 5.86-5.97 (m, 1H), 5.20-5.30 (overlapping mult., 3H), 2.72-2.81 (m, 1H), 2.47 (quintet, 1H), 2.31 (d, J = 3.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 164.6, 161.2, 148.8, 148.7, 134.3, 134.0, 133.9, 131.4, 128.5, 122.9, 118.8, 116.3, 114.5, 114.2, 112.9, 112.6, 94.2, 86.0, 70.9, 42.7; IR (CHCl₃) 3686, 3610, 3490, 3019, 2400, 2360, 2341, 1521, 1424, 1424, 1218, 928, 772, 669 cm⁻¹; HRMS (EI, m/z) calculated for C₁₈H₁₅FO: 266.1107 found: 266.1107.

Enantiomeric Excess Determination: ³¹P Q NMR δ 5.42 (s), 5.49 (s), 5.71 (s); ³¹P-¹H coupled NMR δ 2.58 (t, J = 9.7 Hz), 8.41 (t, J = 9.7 Hz); ee 83%.

1-[2-(3,3-Dimethyl-but-1-ynyl)-phenyl]-but-3-en-1-ol (69, Table 4, 62% yield).

Light yellow oil: [α]D²⁰ = -86 (c. 4.0 g/100 mL, CHCl₃). ¹H NMR (CDCl₃) δ 7.49 (d, J = 3.0 Hz, 1H), 7.38 (dd, J = 6.0, 1.5 Hz, 1H), 7.31 (t, J = 9.0 Hz, 1H), 7.20 (dt, J = 9.0, 1.5 Hz, 1H), 5.83-5.97 (m, 1H), 5.14-5.24 (overlapping mult., 3H), 2.65-2.73 (m, 1H), 2.45 (quintet, 1H), 2.34 (d, J = 3.0 Hz, 1H), 1.36 (s, 9H); ¹³C NMR (CDCl₃) δ 145.5, 134.9, 132.0, 127.9, 126.9, 125.1, 121.0, 118.0, 104.0, 76.9, 71.4, 42.6, 31.0, 28.2; IR (CHCl₃) 3421, 3018, 2400, 2240, 1629, 1516,
1474, 1424, 1216, 1047, 928, 757, 670 cm\(^{-1}\); HRMS (EI, \(m/z\)) calculated for C\(_{16}\)H\(_{20}\)O: 228.1514; found: 228.1514.

Enantiomeric Excess Determination: \(^{31}\)P Q NMR \(\delta\) 4.97 (s), 5.29 (s), 5.33 (s); \(^{31}\)P-\(^{1}\)H coupled NMR \(\delta\) 2.10 (\(t, J = 9.7\) Hz), 7.85 (\(t, J = 9.7\) Hz); ee 89%.

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\text{H}_2\text{OH}
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\text{H} \quad \text{O}
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1-(2-Thiophen-2-ylethynyl-phenyl)-but-3-en-1-ol (70, Table 4, 27% yield).

Cream solid: mp 70-72°C; \([\alpha]_D^{20} = -67\) (c. 2.0 g/100 mL, CHCl\(_3\)). \(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 7.58-7.65 (m, 2H), 7.39-7.48 (m, 2H), 7.34 (dt, \(J = 9.0, 1.5\) Hz, 1H), 7.28 (d, \(J = 3.0\) Hz, 1H), 5.93-6.07 (m, 1H), 5.24-5.38 (overlapping mult. 3H), 2.76-2.85 (m, 1H), 2.58 (quintet, 1H), 2.40 (d, \(J = 3.0\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 145.7, 134.8, 132.1, 129.7, 128.7, 128.6, 127.1, 125.6, 125.3, 122.1, 120.4, 118.2, 89.7, 86.6, 71.4, 42.8; IR (CHCl\(_3\)) 3596, 3450, 3019, 2400, 1640, 1521, 1423, 1215, 1046, 759, 670 cm\(^{-1}\); HRMS (EI, \(m/z\)) calculated for C\(_{16}\)H\(_{14}\)SO: 254.0765; found: 254.0765.

Enantiomeric Excess Determination: \(^{31}\)P Q NMR \(\delta\) 5.05 (s), 5.08 (s), 5.30 (s); \(^{31}\)P-\(^{1}\)H coupled NMR \(\delta\) 2.15 (\(t, J = 9.7\) Hz), 7.94 (\(t, J = 9.7\) Hz); ee 87%.

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\text{H}_2\text{OH}
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\text{H} \quad \text{O}
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1-(2-Cyclohexylethynyl-phenyl)-but-3-en-1-ol (71, Table 4, 37% yield).

Light yellow oil: \([\alpha]_D^{20} = -58\) (c. 3.0 g/100 mL, CHCl\(_3\)). \(^{1}\)H
NMR (CDCl₃) δ 7.49 (d, J = 3.0 Hz, 1H) 7.40 (d, J = 3.0 Hz, 1H), 7.31 (t, J = 9.0 Hz, 1H), 7.20 (t, J = 6.0 Hz, 1H), 5.82-5.96 (m, 1H), 5.16-5.22 (m, 3H), 2.66-2.73 (m, 1H), 2.47 (quintet, 1H), 2.33 (d, J = 3.0 Hz, 1H), 1.88-1.93 (m, 2H), 1.78-1.79 (m, 2H), 1.57-1.64 (m, 3H), 1.40-1.46 (m, 3H); 

13C NMR (CDCl₃) δ 145.4, 134.9, 132.2, 127.8, 126.9, 125.2, 121.2, 118.1, 99.9, 78.2, 71.4, 42.6, 32.7, 29.8, 25.9, 24.8; IR (CHCl₃) 3602, 3558, 3450, 3019, 2400, 1517, 1424, 1215, 1030, 928, 758, 669 cm⁻¹; HRMS (EI, m/z) calculated for C₁₈H₂₂O: 254.1671 found: 254.1671

Enantiomeric Excess Determination: ³¹P Q NMR δ 4.96 (s), 5.13 (s), 5.30 (s); ³¹P-¹H coupled NMR δ 2.08 (t, J = 9.7 Hz), 7.83 (t, J = 9.7 Hz); ee 69%.

1-(3,5-Dimethoxy-2-phenylethynyl-phenyl)-but-3-en-1-ol
(72, Table 4, 43% yield).

White solid: mp 67-69 °C; [α]Dⁿ⁻²⁰ = -111 (c. 2.0 g/100 mL, CHCl₃). ¹H NMR (CDCl₃) δ 7.52-7.55 (m, 2H), 7.32-7.39 (m, 3H), 6.76 (d, J = 3.0 Hz, 1H), 6.39 (d, J = 3.0 Hz, 1H), 5.87-6.01 (m, 1H), 5.18-5.31 (overlapping mult., 3H), 3.91 (s, 3H), 3.86 (s, 3H), 2.71-2.80 (m, 1H), 2.48 (quintet, 1H), 2.36 (s, 1H); ¹³C NMR (CDCl₃) δ 161.3, 161.1, 149.1, 134.8, 131.3, 128.3, 128.0, 123.8, 118.2, 102.2, 101.8, 97.7, 97.3, 83.3, 71.4, 56.0, 55.5, 42.6; IR (CHCl₃) 3682, 3608, 3450, 3019, 2400, 1710, 1520, 1424, 1215, 758, 670 cm⁻¹; HRMS (EI, m/z) calculated for C₂₀H₂₀O₃: 308.1412; found: 308.1412.

Enantiomeric Excess Determination: ³¹P Q NMR δ 5.44 (s), 5.52 (s), 5.77 (s); ³¹P-¹H coupled NMR δ 2.63 (t, J = 9.7 Hz), 8.41 (t, J = 9.7 Hz); ee 87%.
1-Allyl-3-[1-phenyl-meth-(Z)-ylidene]-1,3-dihydro-isobenzofuran (76, Table 6, yield of mixture 37%).

Slightly yellow oil: $[\alpha]_D^{20} = +40$ (c. 3.0 g/100 mL, CHCl$_3$). $^1$H NMR (CDCl$_3$) $\delta$ 7.80 (d, $J = 3.0$ Hz, 1H), 7.60 (d, $J = 3.0$ Hz, 1H), 7.32-7.50 (m, 5H), 7.20 (t, $J = 9.0$ Hz, 1H), 5.90-6.01 (m, 2H), 5.75 (t, $J = 6.0$ Hz, 1H), 5.16-5.28 (overlapping mult., 2H), 2.63-2.84 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 155.3, 142.0, 136.5, 135.1, 132.8, 128.7, 128.4, 128.3, 128.0, 125.2, 121.5, 119.9, 118.5, 96.0, 85.1, 40.3.

1-Allyl-3-[1-(4-methoxy-phenyl)-meth-(Z)-ylidene]-1,3-dihydro-isobenzofuran (77, Table 6, 10% yield).

C/c oil: $[\alpha]_D^{20} = +82$ (c. 0.7 g/100 mL, CHCl$_3$). $^1$H NMR (CDCl$_3$) $\delta$ 7.71 (d, $J = 3.0$ Hz, 2H), 7.25 (dt, $J = 9.0$, 1.5 Hz, 2H), 7.17 (dt, $J = 9.0$, 1.5 Hz, 1H), 7.05-7.12 (m, 2H), 6.94 (d, $J = 6.0$ Hz, 2H), 6.33 (s, 1H), 5.89-6.08 (m, 1H), 5.35 (q, $J = 3.0$ Hz, 1H), 5.12-5.18 (overlapping mult., 2H), 3.86 (s, 3H), 2.87 (quintet, 1H), 2.60 (quintet, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 157.4, 153.7, 141.7, 135.3, 133.0, 129.4, 129.0, 128.2, 126.7, 121.4, 119.6, 118.4, 113.9, 95.6, 84.8, 55.3, 40.4.
1- Allyl-3-[1-(4-trifluoromethyl-phenyl)-meth-(Z)-ylidene]-1,3-dihydro-isobenzofuran (78, Table 6, yield 42%).

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\text{C/c oil: } [\alpha]_D^{20} = +160 \text{ (c. 3.0 g/100 mL, CHCl}_3)\].
\[\text{^1H NMR (CDCl}_3\text{) } \delta 7.84 \text{ (d, } J = 3.0 \text{ Hz, 2H)}, 7.57-7.62 \text{ (m, 3H), 7.33-7.42 (m, 3H), 5.84-5.95 (m overlap s, 2H), 5.76 (t, } J = 6.0 \text{ Hz, 1H), 5.22 (dt, } J = 12.0, 3.0 \text{ Hz, 2H), 2.61-2.84 (m, 2H)}\]; \[\text{^13C NMR (CDCl}_3\text{) } \delta 157.2, 142.4, 134.6, 132.5, 129.3, 128.5, 127.6, 125.2, 121.5, 120.3, 118.7, 94.8, 85.5, 40.1\].

5- Allyl-7-[1-phenyl-meth-(Z)-ylidene]-5,7-dihydro-furo[3',4',4,5]benzo[1,2-d][1,3]dioxole (79, Table 6, yield 16%).

\[\text{C/c oil: } \text{^1H NMR (CDCl}_3\text{) } \delta 7.73 \text{ (d, } J = 3.0 \text{ Hz, 2H), 7.35 (t, } J = 9.0 \text{ Hz, 2H), 7.15 (t, } J = 6.0 \text{ Hz, 1H), 6.96 (s, 1H), 6.73 (s, 1H), 6.05 (s, 2H), 5.85-5.96 (m, 2H), 5.72 (s, 1H), 5.61 (t, } J = 6.0 \text{ Hz, 1H), 5.22 (dt, } J = 12.0, 3.0 \text{ Hz, 2H), 2.60-2.74 (m, 2H)}\]; \[\text{^13C NMR (CDCl}_3\text{) } \delta 155.5, 149.1, 148.6, 136.7, 136.4, 132.7, 128.8, 128.3, 127.6, 124.9, 118.6, 101.8, 101.7, 99.9, 94.5, 84.7, 40.3\].
1-Allyl-3-but-(Z)-ylidene-1,3-dihydro-isobenzofuran (80, Table 6, yield 11%).

C/c oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.16-7.28 (m, 2H), 7.15 (t, $J = 6.0$ Hz, 1H), 7.09 (t, $J = 3.0$ Hz, 1H), 6.95 (t, $J = 9.0$ Hz, 1H), 5.84-5.98 (m, 1H), 5.61 (s, 1H), 5.10-5.24 (m, 3H), 2.71-2.78 (m, 1H), 2.44-2.52 (m, 1H), 2.17 (dt, $J = 9.0$, 1.5 Hz, 2H), 1.62 (quintet, 2H), 0.98 (t, $J = 6.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 156.0, 134.3, 131.0, 130.0, 127.8, 125.5, 124.1, 122.8, 117.4, 100.1, 50.9, 38.8, 35.9, 20.1, 13.7.

3-Allyl-5-fluoro-1-[1-phenyl-meth-(Z)-ylidene]-1,3-dihydro-isobenzofuran (81, Table 6, yield 65%).

Yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.75 (d, $J = 3.0$ Hz, 2H), 7.52 (q, $J = 3.0$ Hz, 1H), 7.37 (t, $J = 9.0$ Hz, 1H), 7.19 (t, $J = 3.0$ Hz, 1H), 7.09 (dt, $J = 9.0$, 1.5 Hz, 1H), 7.01 (d, $J = 3.0$ Hz, 2H), 5.85-5.96 (overlapping s and m, 2H), 5.69 (t, $J = 6.0$ Hz, 1H), 5.19-5.27 (m, 2H), 2.62-2.78 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 144.1, 136.3, 132.3, 128.4, 128.0, 121.6, 118.9, 116.2, 115.9, 108.9, 108.6, 95.8, 84.5, 79.5, 60.4, 40.1.

1-Allyl-3-[2,2-dimethyl-prop-(Z)-ylidene]-1,3-dihydro-isobenzofuran (82, Table 6, yield 21%).

C/c oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.19 (dt, $J = 9.0$, 1.5 Hz, 1H), 7.11 (dt, $J = 9.0$, 1.5 Hz, 1H), 6.95 (dd, $J = 6.0$, 3.0 Hz, 2H), 5.84-5.98
(m, 1H), 5.67 (s, 1H), 5.09-5.17 (m, 3H), 2.68-2.83 (m, 1H), 2.49-2.58 (m, 1H), 1.19 (s, 9H); $^{13}$C NMR (CDCl$_3$) $\delta$ 163.4, 134.5, 131.3, 130.0, 127.8, 125.5, 124.0, 117.4, 96.7, 38.3, 35.2, 27.9.

1-Allyl-3-[1-thiophen-3-yl-meth-(Z)-ylidene]-1,3-dihydro-isobenzofuran (83, Table 6, 65% yield).

Yellow oil: $[\alpha]_{D}^{20} = +162$ (c. 4.0 g/100 mL, CHCl$_3$). $^1$H NMR (CDCl$_3$) $\delta$ 7.53-7.55 (m, 2H), 7.30-7.43 (m, 5H), 6.04 (s, 1H), 5.88-6.00 (m, 1H), 5.71 (t, $J = 6.0$ Hz, 1H), 5.22 (dt, $J = 15.0$, 3.0 Hz, 2H), 2.58-2.80 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 154.5, 142.2, 137.0, 134.7, 133.0, 128.5, 128.4, 128.3, 124.6, 121.4, 120.4, 119.7, 118.4, 90.9, 84.9, 40.4.

1-Allyl-3-[1-cyclohexyl-meth-(Z)-ylidene]-1,3-dihydro-isobenzofuran (84, Table 6, yield 11%).

C/c oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.24-7.29 (m, 1H), 7.19 (dt, $J = 9.0$, 1.5, 1H), 7.10 (dt, $J = 9.0$, 1.5 Hz, 1H), 6.94-6.97 (m, 2H), 5.84-5.97 (m, 1H), 5.58 (s, 1H), 5.08-5.17 (m, 3H), 2.69-2.79 (m, 1H), 2.44-2.54 (m, 1H), 2.04-2.11 (m, 1H), 1.89-1.93 (m, 2H), 1.79-1.82 (m, 2H), 1.70-1.74 (m, 2H), 1.15-1.40 (m, 5H); $^{13}$C NMR (CDCl$_3$) $\delta$ 160.4, 134.4, 131.1, 130.1, 127.8, 125.4, 124.1, 123.0, 117.4, 97.9, 42.2, 38.6, 30.7, 30.6, 26.2.
1-Allyl-4,6-dimethoxy-3-[1-phenyl-meth-(Z)-ylidene]-
1,3-dihydro-isobenzofuran (85, Table 6, yield 36%).

Slight yellow oil: $[\alpha]_D^{20} = +43$ (c. 0.1 g/100 mL, CHCl$_3$).

$^1$H NMR (CDCl$_3$) $\delta$ 7.78 (dd, $J = 6.0$, 1.5 Hz, 2H), 7.28-7.41 (m, 3H), 6.73 (s, 1H), 6.40 (d, $J = 3.0$ Hz, 1H), 6.27 (d, $J = 3.0$ Hz, 1H), 5.94-6.05 (m, 1H), 5.28 (q, $J = 6.0$ Hz, 1H), 5.11-5.18 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.79-2.89 (m, 1H), 2.47-2.56 (m, 1H); $^1$H NMR (CDCl$_3$) $\delta$ 159.5, 154.7, 148.5, 135.1, 134.3, 133.2, 128.2, 128.0, 127.8, 124.8, 117.6, 113.2, 101.3, 97.5, 94.9, 77.7, 55.5, 55.4, 38.2.

3-Allyl-5,7-dimethoxy-3$H$-isobenzofuran-1-one (88, yield 30 %).

Slight yellow oil: $[\alpha]_D^{20} = -10^\circ$ (c. 0.7 g/100 mL, CHCl$_3$). $^1$H NMR (CDCl$_3$) $\delta$ 6.45 (d, $J = 3.0$ Hz, 2H), 5.71-5.85 (m, 1H), 5.36 (t, $J = 6.0$ Hz, 1H), 5.14-5.23 (m, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 2.68-2.77 (m, 1H), 2.55-2.64(m, 1H); $^1$H NMR (CDCl$_3$) $\delta$ 168.2, 166.6, 159.6, 154.4, 131.4, 119.4, 107.0, 98.8, 97.7, 78.8, 56.0, 55.9, 38.8; IR (CHCl$_3$) 3450, 3427, 3020, 2976, 2400, 2361, 2341, 1749, 1614, 1431, 1219, 1043, 927, 771, 669 cm$^{-1}$; HRMS (EI, m/z) calculated for C$_{13}$H$_{14}$O$_4$: 234.0892 found: 234.0892.
References


4 Clark, A.; Natural Products as a Resource for New Drugs Pharmaceutical Res. 1996, 13, 1133-1141.


22 Denmark, S.E.; Fu, J.; Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones Chem. Rev. 2003, 103, 2763-2793.


75 Wei, W-G; Zhang, Y-X; Yao, Z-J; Efficient Construction of Novel α-Keto Spiro Ketal and the Total Synthesis of (+/-)-Terreinol Tetrahedron 2005, 61, 11882-11886.