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Livia Aumand  
AUTEUR DE LA THÈSE / AUTHOR OF THESIS  

M.Sc. (Chemistry)  
GRADE / DEGREE  

Department of Chemistry  
FACULTE, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT  

A. Studies Towards the Formation of Asymmetric Quaternary Centres via Radical Allylation  
B. Applications of Chiral Hydrazide Organocatalysts to Diels-Alder, Hydride Reduction, and  
   α-Chlorination Reactions  
C. Studies Directed Towards the Synthesis of Potential HIV-1 Reverse Transcriptase Inhibitors:  
   9-Alkylaryl TIBO Derivatives  

TITRE DE LA THÈSE / TITLE OF THESIS  

W. Ogilvie  
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR  

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR  

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS  

L. Barriault  
R. Ben  

Gary W. Slater  
LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES /  
DEAN OF THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES
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A thesis submitted to the Faculty of Graduate and Postdoctoral Studies

In partial fulfillment of the requirements for
The degree of Master of Science

Ottawa-Carleton Chemistry Institute
Department of Chemistry
University of Ottawa
Ottawa, Ontario
Canada

August 2005

Candidate
Livia M. Aumand

Supervisor
Dr. William W. Ogilvie

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<tr>
<td>AIBN</td>
<td>azaisobisbutyronitrile</td>
</tr>
<tr>
<td>BDE</td>
<td>bond dissociation energy</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1′-bi-2-naphthol</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>DCA</td>
<td>dichloroacetic acid</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization</td>
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<tr>
<td>er</td>
<td>enantiomeric ratio</td>
</tr>
<tr>
<td>GLC</td>
<td>gas-liquid chromatography</td>
</tr>
<tr>
<td>In'</td>
<td>radical initiator</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>iso</td>
<td>isopropanol</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>SOMO</td>
<td>single occupied molecular orbital</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethyl silyl</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Name</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>TCA</td>
<td>trichloroacetic acid</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFOH</td>
<td>trifluorosulfonic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TsOH</td>
<td>para-toluenesulfonic acid</td>
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Abstract

In part A, the attempts at synthesizing quaternary centres via radical reactions are described. Using tartrate acetals as chiral auxiliaries, tertiary bromides were submitted to radical allylation conditions in an effort to form 1,3-dicarbonyl compounds 27 possessing an asymmetric quaternary centre at C2.

![Chemical structure](image)

\[ R_1, R_2, R_3 \neq H \]

Part B describes the synthesis of chiral hydrazide 129 and its ability to catalyze the Diels-Alder reaction is examined. The application of chiral hydrazides 131 to the organocatalytic hydride reduction of \( \alpha,\beta \)-unsaturated aldehydes and the \( \alpha \)-chlorination of aldehydes is also recounted herein.
Finally, in Part C, efforts towards the synthesis of potential broad spectrum HIV-1 reverse transcriptase inhibitors are described. Compounds 161 are based on the TIBO family of compounds and possess a novel alkylaryl appendage.
Acknowledgements

I would first like to take the opportunity to thank my supervisor, Dr. Bill Ogilvie, for all of his support and guidance over the past few years. Throughout my Honour’s project and my Master’s degree, he has always been approachable and good-natured, even when chemistry wasn’t going as well as it could have! He inspires hard work in his students; whether it is in the lab or during preparation of the dreaded Master’s seminar. With regards to my seminar, I really appreciated all of Bill’s help and advice. Although I will not be continuing in science, I know that the oral presentation skills that I have learned from Bill will be instrumental in my future career.

Alison Lemay was also extremely helpful during the preparation of my seminar, not to mention during the past three years in and out of the lab. Despite her incredibly busy schedule, she always had time to give when it was needed. Ali, you are a very gifted chemist, but, more importantly, a wonderful person. I consider myself very lucky to be your friend.

I also benefited from the friendship of the other members of the Ogilvie group. Although he wasn’t in the lab for my Master’s degree, Joe Jebreen always offered me an ear to listen (or a garbage can to kick!) when I was frustrated. Joe, although you are now in “grande-ville” Montreal, I know that I can always count on your friendship. Ami Chin, whose MSc timeline has followed mine almost exactly, is the nicest and most generous person I have ever met. I wish you all the best in medical school and I hope that you are really happy in your chosen career- you deserve it. Although we were in different rooms for most of my MSc, Mathieu Lemay always had a kind word to give and glassware to give back dirty- er, “share.” All kidding aside, I am really happy that chemistry is now working out a little bit better for you. You put your nose to the grindstone and now you will reap the rewards, I am sure.

I would also like to thank former Ogilvie lab members: “Ma petite” Josée Cloutier, Patrick Beaulieu, Liz von Moos, Joe “Number 2” Moran, Ram Ananth, and Kat Vulic. All of you
made chemistry so much more enjoyable and I wish you all the best. Liz and Joe- I would also like to thank you guys for your continuing friendship!

I feel fortunate that the chemistry department at the University of Ottawa is such a friendly place to be. Not once did I ever feel hesitant to approach a professor for help and I benefited from their willingness to share their expertise. Dr. Louis Barriault was especially helpful during my seminar and I very much appreciated it. I would like to thank Dr. Tony Durst who has been extraordinarily helpful and kind during the past several years. His office door was always open and I have benefited from his advice and encouragement. When he “actually” retires, it will be a great loss to the University of Ottawa.

I would like to thank my family and friends for their support. My mother and father have always been at my side when I needed them. They are the people I admire and respect the most and I am lucky to have them as my parents. Vicky and Will- thank you for being my friends, as well as being my family. Finally, thank you to Matt for your love, patience, and friendship.
A. Studies Towards the Formation of Asymmetric Quaternary Centres via Radical Allylation

Chapter 1. Introduction

1.1 The Asymmetric Formation of Quaternary Centres

The asymmetric formation of quaternary centres has garnered increasing attention and synthetic efforts over the past few decades. It remains a significant challenge and several reviews have been devoted to the subject.\(^1\)

The great interest in quaternary centres can be said to stem from two sources. Firstly, there are not many reliable methods by which quaternary centres may be formed stereoselectively making this an irresistible synthetic challenge for the organic chemist. Secondly, since stereopure pharmaceuticals are preferred by drug regulatory agencies, it is of utmost importance to be able to develop syntheses that are highly stereoselective. Thus, methodologies to form asymmetric quaternary centres are of great interest to this industry. Two examples of pharmaceuticals on the market that possess asymmetric quaternary centres, along with a natural product that is a lead compound for potential medicinal use, are presented in Figure 1. Efavirenz 1 (Bristol-Myers-Squibb) is sold in enantiomerically pure form under the trade name Sustiva\(^2\) and is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of HIV.\(^2\) Pinnacic acid 2, isolated by Chou and coworkers from the marine organism Pinna muricata, is a potent specific inhibitor of cytosolic phospholipase A\(_2\) and is an interesting lead for the treatment of inflammatory disorders.\(^3\) Paclitaxel 3 (Bristol-Myers-Squibb), or Taxol\(^4\), is used in stereopure form in the treatment of cancer, specifically breast cancer.\(^4\)
Several methods to produce asymmetric quaternary centres are available, varying widely in efficiency and scope. Some of the methodologies rely on chiral auxiliaries to create the asymmetric centres; others rely on catalytic methods. In either case, few processes have utilized free radical chemistry to form these centres.

Radical reactions have several advantages over other methods, including that they generally proceed under mild and neutral conditions and, as a result, they tend to tolerate the presence
of many functional groups which would be sensitive to acidic or alkaline conditions present in other reaction classes (e.g. alkylation of enolates).\textsuperscript{5}

Nevertheless, it is only in the past fifteen years or so that radical addition reactions have been shown to proceed asymmetrically at all, let alone to form asymmetric quaternary centres. Radical addition reactions tend to suffer from the inherent nature of the carbon radical itself. The trigonal planar geometry of the carbon radical allows attack equally from above and below the plane (Figure 2). For example, in the addition of allyltributyltin to the radical derived from the alkylbromide shown, a racemate results.

**Figure 2. Non-selective radical allylation.**

Although the symmetric nature of the carbon-centered radical poses much difficulty in making it react asymmetrically, there has been some success in this area.\textsuperscript{6} Intramolecular reactions have been the most prevalent examples of asymmetric radical reactions generating quaternary centres.\textsuperscript{7} For example, in the synthesis of (+)-paraquinonic acid 6, Clive and
coworkers used an asymmetric radical cyclization to generate the quaternary centre present in this epimer of natural (-)-puraquinonic acid (Scheme 1).\textsuperscript{8}

**Scheme 1. Intramolecular radical cyclization resulting in the asymmetric formation of a quaternary centre in (+)-puraquinonic acid.**

The stereochemistry of the quaternary centre is a result of the stereoelectronic limits of the ring closure. Since the cyclization is 5-exo-trig and the alkene is contained in a 5-membered ring, the transition state geometry only allows the cis-fusion of the two five-membered rings.\textsuperscript{9} Consequently, the stereochemistry at the quaternary centre is dictated by the stereochemistry of the carbon bearing the bromoether moiety, which had been put in place earlier in the synthesis by way of an Evans’ aldol reaction.

Intermolecular radical reactions that generate asymmetric quaternary centres are less prevalent in the literature than radical cyclization reactions. This is, in part, due to the fact that the geometric constraints, which are often the source of the stereoselectivity of the intramolecular reactions (see Scheme 1), are not present in their intermolecular counterparts.
That being said, there have been some examples where the tendency of radicals to undergo non-selective addition reactions has been usurped. By the use of a chiral Lewis acid or a chiral auxiliary to favour addition from above or below the radical plane, asymmetric quaternary centres can be formed.

As shown in Scheme 2, Hoshino and coworkers demonstrated that by employing catalytic amounts of a BINOL-type ligand 8 and trimethylaluminum, the allylation of iodolactones 7 proceeded enantioselectively to preferentially produce the (R)-lactones 9. Although further studies on the nature of the radical intermediate are needed, it is believed that the chiral Lewis acid blocks one face of the lactone, and thus the allyl group can only be delivered via the opposite face.  

**Scheme 2. Asymmetric synthesis of quaternary centres on lactones.**

![Scheme 2 Diagram]

Although this result is impressive, this chemistry benefits from the fact that, in a cyclic molecule, C-C bond rotation is restricted, removing one of the more difficult elements in controlling stereoselectivity. Thus, to form asymmetric quaternary centres on acyclic molecules via radical processes is a great challenge.
1.2 Acyclic Stereocontrol in Radical Reactions

Asymmetric alkylations of acyclic, tertiary radicals have been achieved, albeit infrequently.\textsuperscript{11} In 1991, Guindon and coworkers noted excellent diastereoselectivity in the asymmetric formation of a quaternary carbon centre via radical allylation of an α-iodo ester 10 (Scheme 3).

Scheme 3. Asymmetric formation of a quaternary centre on an acyclic carbon via radical allylation.

\[ \text{O} \quad \text{H} \quad \text{CO}_2\text{Et} \quad \text{SnBu}_3 \xrightarrow{\text{AIBN, Hexane, } \Delta} \text{O} \quad \text{H} \quad \text{CO}_2\text{Et} \]

In fact, radicals situated adjacent to both a carbonyl group and a chiral centre have been the subject of much of the work concerning the asymmetric reactions of acyclic radicals. Over the past two decades, Guindon, Giese, Hart, and Curran\textsuperscript{11} have been pioneers in this field; developing excellent methodologies and insights into mechanistic aspects of these transformations.

Several studies have shown that radicals that are α to a carbonyl functionality (e.g. ketone, aldehyde, ester, or amide) are delocalized (Figure 3).

Figure 3. Delocalization of the α-carbonyl radical.

\[ R = \text{alkyl} \quad \text{or} \quad \text{alkoxy} \]
Bordwell and Harrelson, Jr.\textsuperscript{12} reported that the homolytic bond dissociation energy (BDE) for acetone (CH$_3$C(O)CH$_3$) is 94 kcal/mol, compared to 105 kcal/mol for methane.\textsuperscript{13} This supports the notion that the carbonyl group imparts some stability to the radical. The likelihood that this stability is due to resonance was illustrated by Fischer and coworkers, who showed that there were increased C$_\alpha$-C(O) rotational barriers for $\alpha$-carboalkoxy and $\alpha$-keto radicals.\textsuperscript{14}

Due to the partial double bond character present in the delocalized radical, its preferred conformation should be one that minimizes allylic (A$_{1,3}$) strain.\textsuperscript{15} Radical A, adjacent to a chiral centre possessing three groups of varying size (small (S), medium (M), and large (L)) could exist in three staggered conformations, as shown in Figure 4.\textsuperscript{16}

**Figure 4. Staggered conformations of a delocalized radical alpha to a chiral centre.**

To reduce A$_{1,3}$-strain, one would expect that for radical A the most energetically favourable conformer would be A$^1$, in which the largest group (R$_L$) is perpendicular to the radical plane and in which the smallest group (R$_S$) is approximately coplanar with the double bond (Figure 4$^*$. The coplanarity is expected to be approximate, since a staggered conformer would help to relieve A$_{1,2}$-strain between R$_L$ and R$'$ (in A$^1$).\textsuperscript{6a}

\textsuperscript{* It is important to mention that the relative sizes of the R groups are not necessarily what dictates which conformer is the lowest in energy. Electronic, rather than steric, factors may dominate, such as in the examples shown in Scheme 3 and 4. Although beyond the scope of this introduction, an excellent explanation is detailed in Reference 11c.
It is noteworthy to mention that positioning the R_L group perpendicular to the radical plane (in A¹) allows the overlap of the C-R_L sigma bond with the SOMO of the radical. This may stabilize the radical via hyperconjugation.¹⁷

The lowest energy ground state conformer is of great interest to chemists since it may help predict the nature of the transition state for radical reactions. Although the Curtin-Hammett principle states that the ratio of the products formed from conformational isomers is not determined by conformation population ratio, there are cases where the conformers can be predictive of the relative transition state energies. Most radical reactions, such as the asymmetric reduction or allylation of α-halo esters, are counted amongst such instances. Several studies have been done by Guindon and others to help confirm this in the case of the asymmetric radical reduction of α-bromo esters (Scheme 4).

**Scheme 4. Describing the effects of temperature on the diastereoselectivity of radical reduction.**

![Scheme 4](image)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>anti:syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>7:1</td>
</tr>
<tr>
<td>-10</td>
<td>11:1</td>
</tr>
<tr>
<td>-45</td>
<td>20:1</td>
</tr>
<tr>
<td>-78</td>
<td>32:1</td>
</tr>
</tbody>
</table>

Firstly, it was noted that the relative configuration between the carbon bearing the halide and the adjacent chiral centre had no effect on the extent or sense of diastereoselectivity. This implied that the addition of the hydride to the radical 13 (Step B), rather than the formation of the radical from 12 (Step A), is the asymmetric step of the reaction. By invoking Hammond’s postulate one may assume that, due to the relatively high energy of the radical intermediate, the transition state of the diastereoselective step is *early* and consequently has
significant radical character. Thus, the ground state radical conformation may give insight on the nature of the transition state of the reduction.

To confirm that it was in fact the relative energies of the transition states that determined the stereochemical outcome of the reduction (i.e. kinetic control) rather than the relative energies of the products (i.e. thermodynamic control), Guindon and coworkers performed the reduction at various temperatures (Scheme 4). It was found that as temperature decreased, diastereoselectivity increased. This demonstrated that the diastereoselective step was under kinetic control and the use of approximations of transition state geometries (i.e. radical conformers) to explain the stereoselectivity of the reduction was, indeed, appropriate.

Guindon and others have postulated that the lowest energy transition state of the radical reduction (or allylation) reactions resembles conformer $A^1$ (Figure 4), with the major product arising from the delivery of the hydride (or allyl group) from the face opposite that of the $R_L$ group (Figure 5). The minor product thus comes from the sterically-congested delivery of the hydride to the same face as the $R_L$ group.

**Figure 5. High and low energy transition states for radical reduction.**

Guindon and coworkers have postulated that the ability to block attack from the same face as $R_L$ can be increased by joining $R_M$ and $R_L$ in a ring, dubbed the “exocyclic effect” (Figure 6). By employing an ethyl group as the large group, one can see that the position of the methylene hydrogens in conformer $B$ aids in blocking $syn$ attack. However, rotation around the CH$_2$-CH$_3$ σ-bond results in conformer $B'$, which does not block $syn$ attack as efficiently. In structure $C$, however, the methylene hydrogens are effectively locked in the position which most efficiently blocks $syn$ attack.
As mentioned previously, few groups have applied the theories and trends detailed in Section 1.2 to the formation of asymmetric quaternary centres. One of these rare examples was reported in 1998 by Stoodley and coworkers.\textsuperscript{11de} They described an interesting methodology towards asymmetric quaternary centres via radical allylation which made use of a glucopyranosyl-based auxiliary.

### 1.3 Asymmetric Radical Allylation of Tertiary Bromides Employing a 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl Auxiliary

Stoodley’s auxiliary is derived from (D)-glucose and is attached to the substrate via the method shown in Scheme 5.\textsuperscript{18} A simple, commercially-available ketone or ester 15 is formylated regioselectively to produce the (E)-sodium salt 16. This reacts in an $S_{N}2$-like fashion with the acetobromoglucose 17 to produce the vinylogous ester or ketone 18.
Scheme 5. Formation of the glucopyranosyl-based vinyl ether 18.

At this stage, the glucoside 18 was bromoalkoxylated with good regioselectivity and stereoselectivity using N-bromosuccinimide and the appropriate alcohol. The bromination is believed to occur with the glucoside assuming a conformation similar to that depicted below in Scheme 6. The stereoselectivity is believed to arise from attack of NBS to the top face of the double bond, since the glucopyranosyl moiety effectively shields the bottom face.

Scheme 6. Facial and regioselective bromoalkoxylation of the vinyl ether 18.
The bromoalkoxy compounds (19 and 20) formed were regiopure, due to the attack of the alcohol at the bromonium carbon $\alpha$ to the OR* moiety rather than at the carbon $\alpha$ to the carbonyl group, since a partial positive charge is better stabilized at the former position. The $\alpha$-bromo-$\alpha$-dioxymethyl carbonyl compounds were formed as a mixture of diastereomers, 19 and 20. Prior to the radical allylation step, the major diastereomer, 19, could be isolated via fractional recrystallization in $>95\%$ diastereomeric excess and in modest yield.

The stereopure 19 analogs then underwent diastereoselective radical allylation to preferentially produce diastereomer 21, with modest to good stereoselectivity.$^{11d}$ The transition state of this reaction is believed to resemble the conformer shown in Scheme 7. As explained previously in section 1.2, the large glucopyranosyl moiety (OR*) is perpendicular to the radical plane and the hydrogen is approximately coplanar with the double bond to minimize $A_{1,3}$ strain. To reduce $A_{1,2}$ strain between R2 and OR*, the conformer is slightly staggered. The allyl group is delivered anti to the OR* group, due to steric effects, producing 21 as the major product. Diastereomer 22 is thought to arise from attack of the allyltributyl tin on the same side as OR*.

**Scheme 7. Diastereoselective radical allylation forming asymmetric quaternary centres.**

Unfortunately, only in some cases were the diastereomers 21 and 22 separable. Stoodley was successful, however, in removing the glucopyranosyl-based auxiliary via transacetalization using ethylene glycol or 1,2-ethanediol and a proton source (Scheme 8).
Scheme 8. Transacetalization of stereopure acetal 21 to enantioenriched acetal 23.

Although this methodology has its drawbacks, including poor yields, often only modest diastereoselectivities, and access to only one diastereomer, it is noteworthy to mention that Stoodley and coworkers were able to apply their findings to radical cyclization reactions, yielding highly stereopure quaternary centres.\textsuperscript{11e}

As shown in Scheme 9, stereopure 24 (prepared from 18 using NBS and propargyl alcohol) was cyclized in the presence of AIBN as initiator and 1-ethylpiperidinium hypophosphite as a source of hydrogen radicals to give 25. The glucopyranosyl auxiliary was then removed under methanolysis conditions to give 26 as a 2:1 mixture of anomers, in very good yields and excellent enantiomeric excesses.
Scheme 9. Asymmetric radical cyclization.

Inspired by both Stoodley’s results and the earlier findings of Guindon, Giese, and others, we sought to develop a novel methodology that would stereoselectively form quaternary centres using dialkyl tartrate acetals as chiral auxiliaries.

1.4 Objective

The goal of this project was to develop a route to acyclic 1,3-dicarbonyl compounds 27 with an enantiomerically-enriched quaternary centre at C2 (Figure 7).

Figure 7. Enantioenriched 1,3-dicarbonyl compound.
Although Stoodley essentially gave a route to this class of compound, his methodology required two stereoselective steps: the bromoalkoxylation (de = 46-78%), followed by fractional recrystallization to obtain the major diastereomer in stereopure form; and the radical allylation (de = 67-82%), in which the diastereomers were not always separable (see Section 1.1.3). Thus, overall the diastereomeric excess of this process is, at best, 64%. As mentioned in the previous section, only one of the two possible enantiomers of 23 (Scheme 8) can be synthesized.

Thus, we endeavoured to improve on Stoodley’s result, employing the knowledge garnered over the past 15 years regarding asymmetric radical reactions. We believed that by employing a chiral $C_2$-symmetric acetal, such as a tartrate acetal, as a chiral auxiliary, we could form an asymmetric quaternary centre (marked by an asterisk in Scheme 10).

**Scheme 10. Proposed asymmetric radical allylation using a tartrate acetal as a chiral auxiliary.**

![Diagram](image)

The asymmetry would result from the allylation step occurring from the lowest in energy of the possible transition states. Using L-dialkyl tartrate, one can see in Figure 8 that there are two conformers ($C^1$ and $C^2$) of the ground state radical that, based on the previous work of several groups (see Section 1.1.2), minimize the ground state energy.

Both conformers shown minimize allylic strain by placing the hydrogen on the carbon $\alpha$ to the radical approximately coplanar with the double bond. Both conformations are slightly
staggered, as complete coplanarity would result in \( A_{1,2} \) strain between \( R_2 \) and the oxygen that is perpendicular to the radical plane. By placing one of the C-O bonds in alignment with the SOMO of the radical, the stabilizing effects of hyperconjugation are allowed.

**Figure 8. Possible conformers in the transition state of the radical allylation reaction.**

Conformer \( C^1 \) should be energetically preferred over its \( 30^\circ \) rotamer \( C^2 \), since it is believed that \( C^2 \) would be subject to significant steric repulsion between \( R_2 \) and the \( \text{CO}_2 \text{R}_3 \) group coming out of the plane. As mentioned in Section 1.1.2, the favoured ground state conformer of the radical can be used to predict the transition state geometry due to the assumed early, reactant-like nature of the transition state. Thus, we would expect product 30, arising from bottom face attack, to be the major product, since it would arise from the lowest energy transition state.

Since tartaric esters are available in both chiral forms, simply using (D)-dialkyl tartrate, rather than the (L)-stereoisomer, should result in the formation of 31, rather than 30, as the
major product after radical allylation and acetal cleavage. Thus, we should have access to both enantiomeric forms of the 1,3-dicarbonyl compounds 27 via our methodology. From here, these useful synthons possessing two different carbonyl functionalities could then be applied to different chemical processes, such as the two displayed in Figure 9.

**Figure 9. Potential chemoselective reactions on the enantioenriched 1,3-dicarbonyl compounds.**
2.1 Formation of the α-Bromo Ester Tartrate Acetal

In order to test our methodology, we first had to design a synthesis of the α-halo tartrate acetal 28, which could then undergo the radical allylation. We decided to begin with the simple allylation precursor 34, with bromine as the halogen (X), a methyl group at R₂, the carbonyl moiety a methyl ester, and the inexpensive (L)-dimethyl tartrate as the tartaric ester (Figure 10).

**Figure 10. The radical allylation precursor 34.**

![Chemical structures](image)

As shown in Scheme 11, the α-bromo-β-acetal ester 34 should be formed in five synthetic steps. Based on a literature procedure, commercially available methyl methacrylate would be brominated and the addition product would then be treated immediately with sodium methoxide to form the dimethyl acetal 35. Under acid-catalyzed elimination conditions, the vinyl ether 36 would be formed, with the loss of methanol.
Scheme 11. First proposed synthetic route to 34.

The next step is based on Stoodley and coworkers bromoalkoxylation reaction using N-bromosuccinimide and methanol, shown in Scheme 6. We felt confident that this step would work, as the only difference between 36 and 18, is that a methoxy group is in place of the glucopyranosyl moiety (Figure 11).

Figure 11. Comparison between bromoalkoxylation substrate 37 and Stoodley’s bromoalkoxylation substrate.
After the formation of the α-bromo-β-dimethoxy ester 37, we would use a transacetalisation reaction to install the C₂-symmetric dimethyl tartrate acetal, forming 34 as a 1:1 mixture of diastereomers. At this point, we would be ready to test our methodology for creating asymmetric quaternary centres.

No amount of confidence in a particular synthesis, however, can force it to behave as planned and this case was no exception. Although the first two steps of the synthesis worked with ease, we began to run into minor problems forming 36. Without fail, the literature conditions always resulted in a poor yield and a 2:1 mixture of 36:35 (Scheme 12). Fractional distillation, unfortunately, did not prove to be a facile method of separating these compounds. In addition, not only did the volatility of both these compounds make column chromatography undesirable, but they migrated at the same Rf in all solvent systems tested.

**Scheme 12. Synthesis of 36 from methyl methacrylate.**

Fortunately, we were able to improve the yield and conversion of this reaction by performing the reaction in anhydrous benzene, rather than neat, and by changing the apparatus. The simple water-cooled condenser used in the literature procedure was replaced with a pressure-equalizing dropping funnel filled with activated 4Å molecular sieves. Fitted on top of this was a water-cooled condenser. The side-arm of the dropping funnel was wrapped with glass wool, as to insulate it, and its stopcock was left open (Figure 12).
Theoretically, the conversion of 35 to 36 should be reversible and, thus, by Le Chatelier’s principle, removing the methanol produced by the reaction should drive the reaction towards the product, 36. By using the apparatus shown above and heating to reflux, the methanol produced should azeotrope with benzene and this azeotrope should travel up the side-arm of the dropping funnel to the water-cooled condenser. Here, it will condense and travel back through the 4Å molecular sieves, removing the methanol, so that only benzene distills back into the reaction flask.
By performing the reaction in this manner, we were able to achieve 100% conversion and quantitative yield, obtaining 36 in sufficient purity to carry on with the next step in the synthesis (Scheme 13).

**Scheme 13. Improved synthesis of 36 from 35.**

Unfortunately, we were to have difficulties with the next step of the synthesis which proved to be less simple to resolve.

With Stoodley’s conditions, using N-bromosuccinimide and methanol (see Scheme 11), no reaction was observed. Incredulous, we repeated this reaction several times, but to no avail. Thus, we decided to attempt different bromination conditions as shown in Table 1.

**Table 1. Attempted bromination of 36 to form 37.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Br⁺ source</th>
<th>Conditions</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS</td>
<td>RT; 4h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1) AgNO₃</td>
<td>RT; 23h</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2) Br₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Br₂</td>
<td>RT; 12h</td>
<td>0</td>
</tr>
</tbody>
</table>
At this stage, we had no insight as to why the bromoalkoxylation worked so efficiently for Stoodley and not at all in our hands. It would become clear, however, a little further into the project and this discovery will be relayed later on in the manuscript.

In the meantime, we resolved to develop a new synthesis of our allylation precursor 34. We were intrigued to discover a recent publication in which β-acetal esters, similar to 34, had been successfully prepared.

Ballini and coworkers reported that from methyl propiolate 38 and a 1,2-diol or thiol, they could generate the corresponding acetal or thioacetal 39 (Scheme 14).

\[ \text{CO}_2\text{CH}_3 \rightarrow \text{CO}_2\text{CH}_3 \]

By controlling the reaction conditions, they could then successfully monomethylate α to the ester using potassium tert-butoxide as base and methyl iodide, thus forming 40.

**Scheme 14. Ballini and coworkers general route to β-acetal esters.**

Thus, our second route to allylation precursor 34 would begin with the base-catalyzed tandem Michael additions of (L)-dimethyl tartrate to commercially available methyl propiolate, forming 41 (Scheme 15). We would then attempt the methylation of 41 at C*. We believed that we could avoid methylating at the Cα and Cα' since both of these positions are more sterically hindered than C* and we would be using a bulky base.
Scheme 15. Proposed synthetic route to 34 from methyl propiolate.

Following the selective monomethylation, we hoped to be able to brominate 42 selectively at C* to form our allylation precursor 34. Although bromination conditions can often cause the oxidative cleavage of acetals to form the corresponding ester,²² Giordano and coworkers have reported selective bromination of tartrate acetals 43 without observing a significant amount of ester formation (Scheme 16).²³
Scheme 16. General scheme for Giordano and coworkers’ bromination of tartrate acetals.

The first step in our second route to 34 succeeded, albeit in poor yield (Scheme 17). However, we did not have any success in methylating at C*, although both potassium tert-butoxide and LDA were tried as bases (Table 2, Entries 1-2).

Scheme 17. Synthesis of the tartrate acetal 41 from methyl propiolate.

We then decided to investigate whether or not deprotonation was taking at C*, Cα, or Cα'. By adding D₂O, rather than MeI, we hoped to see by ¹H NMR if any of the ¹H peaks for protons at C*, Cα, and Cα' had disappeared, or if their relative integrations had decreased. We were surprised to find that deprotonation was not occurring at any of potential carbons.

At this point, we chose to try an additive in the methylation reaction. Using LDA as base, we would add TMEDA, an excellent lithium-chelator, which is well known to increase the
rate of organolithium reactions.\textsuperscript{24} Unfortunately, this modification was not successful and the formation of 42 was not observed (Table 2, Entries 3-5).

**Table 2. Attempted selective methylation of 41 to form 42.\textsuperscript{†}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive</th>
<th>Solvent</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOt-Bu</td>
<td>n/a</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>n/a</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>TMEDA</td>
<td>THF</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>TMEDA</td>
<td>Et\textsubscript{2}O</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>TMEDA</td>
<td>Toluene</td>
<td>0</td>
</tr>
</tbody>
</table>

Feeling frustrated with our results, we decided that since we were having difficulty forming the \( \alpha \)-bromo esters, we might be able to synthesize substrates that were different in structure, but should behave similarly in the radical allylation. We sought to replace the ester functionality with an aromatic ring, since it is known that radicals \( \alpha \) to aromatic groups are susceptible to \( A_{1,3} \) strain, similar to those \( \alpha \) to a carbonyl group.\textsuperscript{25} This is due to the partial double bond character between the C* and the ring (Figure 13). Thus, we expected to see good diastereoselectivity for the radical allylation of \( \alpha \)-bromo aromatic compounds, since we believed that the reaction would go through the lowest energy transition state, as shown previously in Figure 8.

\[ \text{In order to simplify the Table 2, experiments varying the temperature of the deprotonation and/or the methylation from -78 °C, which were also unsuccessful, were not included.} \]
Thus, our new goal was the synthesis of asymmetric quaternary centres flanked by an aldehyde and an aromatic ring. Although we had strayed from our original objective of synthesizing 1,3-dicarbonyl compounds, these new targets would also be synthetically useful (Scheme 18).

Scheme 18. Synthesis of α-aryl asymmetric quaternary centres via radical allylation.

As with our proposed syntheses of α-bromo ester compounds, we wished to initially synthesize a very simple radical allylation precursor, thus we chose a simple phenyl ring as our aromatic substituent. We would still use an (L)-dimethyl tartrate acetal as the chiral auxiliary and C* would be substituted by a bromine and a methyl group (50).

As shown in Scheme 19, from 2-phenylpropanal 48 we would form the dimethyl tartrate acetal 49 via acid catalysis. At this point, we would submit 49 to bromination conditions,
which should proceed selectively at the carbon α to the phenyl group, to form the radical allylation precursor 50.

Scheme 19. Proposed synthetic route to radical allylation precursor 50.

Initially, we heated 2-phenylpropanal in benzene, in the presence of catalytic CSA and (L)-dimethyl tartrate, using 4Å molecular sieves in the apparatus shown in Figure 12. However, this only gave 22% of the desired product 49. A superior method consisted of first irreversibly forming the dimethyl acetal using trimethylorthoformate and CSA as catalyst. At this point, dimethyl tartrate was added to the reaction mixture that was refluxed in the ubiquitous apparatus (Figure 12). This resulted in a much improved yield of 87% (Scheme 20).

Scheme 20. Synthesis of (L)-dimethyl tartrate acetal 49.

Unfortunately, free radical bromination of 49 to form 50 was unsuccessful (Table 3). Using molecular bromine and various initiators (light, benzoyl peroxide, and mercuric oxide\(^\text{26}\)), only starting material (49) was recovered (Entries 1, 4, 5). The result was the same using
NBS as bromine source and benzoyl peroxide or AIBN as radical initiators (Entries 2,3). Acid-catalyzed bromination either resulted in decomposition (Entry 6) or recovery of starting material (Entries 7 and 8).

Table 3. Attempted bromination of 49 to form 50.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Initiator/ Catalyst</th>
<th>Bromine Source</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Radical</td>
<td>hν</td>
<td>Br₂</td>
<td>RT</td>
<td>CH₂Cl₂</td>
<td>SM only</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>benzoyl peroxide</td>
<td>NBS</td>
<td>BP</td>
<td>CCl₄</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>AIBN</td>
<td>&quot;</td>
<td>BP</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>HgO</td>
<td>Br₂</td>
<td>BP</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>hν</td>
<td>&quot;</td>
<td>RT</td>
<td>CH₂Cl₂</td>
<td>&quot;</td>
</tr>
<tr>
<td>6</td>
<td>Acidic</td>
<td>HCl (anh.)</td>
<td>&quot;</td>
<td>RT</td>
<td>CCl₄</td>
<td>decomp.</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>CSA</td>
<td>NBS</td>
<td>RT</td>
<td>CH₂Cl₂</td>
<td>SM</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>CSA</td>
<td>Br₂</td>
<td>-78→rt</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Feeling frustrated by our lack of success, we returned to ponder our original synthetic route (Scheme 11). It still perplexed us as that the bromoalkoxilation, which worked so well for Stoodley, did not work for us. We decided to set up the reaction yet again, but, to be forthright, less care was taken with purification of starting materials, specifically N-bromosuccinimide. In our previous attempts, NBS was carefully recrystallized from water before use, but, in this case, we simply used it directly from a relatively old bottle. To our great surprise, this time, the reaction seemed to work (Scheme 21)! In addition to the NMR data supporting the formation of 37, we were able to ensure ourselves of this result via mass spectrometry. Although a molecular ion (M⁺) was undetectable, we did see two peaks at 211
(M⁺ - OMe) and 209 [(M⁺ - OMe) + 2], which are indicative of the presence of a bromine atom.

**Scheme 21. Successful bromomethoxylation of vinyl ether 36.**

Over time and with exposure to heat or light, HBr will form in NBS. An orange hue, rather than the white colour of NBS, indicates the presence of HBr. Since the NBS used directly from the bottle was a bright orange, we suspected that the bromoalkoxylation was actually acid-catalyzed and did not proceed via a similar mechanism to the one suggested by Stoodley (Scheme 22, A). Via mechanism A, the alkene 36 attacks the electrophilic NBS bromine to form a bromonium ion. Methanol then regioselectively opens the bromonium ion to give the product, 37. Since our result indicated that the reaction was actually acid-catalyzed, we propose the alternate mechanism, B. The carbonyl oxygen is protonated by the HBr, allowing an acid-catalyzed 1,4-Michael addition of methanol at the β-carbon to take place. The enol formed then attacks the electrophilic bromine to form 37. Although our interest did not lie in performing mechanistic studies on this reaction, one telling experiment would be to use recrystallized NBS and a trace of acid (e.g. CSA, TsOH). If the reaction did work in this case, then this would support our proposed mechanism, B.²

² It is noteworthy to mention that the reason for the observed facial selectivity in Stoodley’s reaction is not obvious via mechanism B. It has also been suggested that a catalytic amount of HBr in NBS is necessary for successful electrophilic bromination.²a In this proposal, the bromide anion from the HBr attacks the electrophilic bromine on the NBS to form molecular bromine, Br₂, and thus it is the Br₂ that is the actual brominating agent. In this case, Stoodley’s mechanism would not be incorrect. This mechanism would be supported if no reaction occurred in the experiment utilizing CSA or TsOH suggested above.
Scheme 22. Two alternate mechanistic pathways for the bromoalkoxylation reaction.

We could now attempt the transacetalisation reaction (Scheme 11) using (L)-dimethyl tartrate, an acid catalyst and the apparatus shown in Figure 12. As shown in Table 4 (Entries 1 and 2), attempting to form 34 in the same manner we had used to form 36, by refluxing in benzene in the presence of an organic acid and 4Å molecular sieves, proved to be fruitless. Stoodley’s method of transacetalisation, which consisted of stirring the 1,2-diol and the acetal in neat TFA (Scheme 8), was also attempted, but to no avail (Entry 3). We also tried a rather bizarre transacetalisation methodology, using 2,2-dimethoxypropane and CSA in catalytic amounts, but this, too, failed (Entry 4). Finally, by refluxing in toluene in the presence of 4Å molecular sieves (see Figure 12) and CSA or sulfuric acid, we were able to form 34 in modest yield (Entries 5 and 6). Sulfuric acid gave a cleaner reaction, thus we would continue to use this methodology to form 34.
Table 4. Transacetalisation conditions for the conversion of 37 to 34.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conditions</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CSA</td>
<td>C₆H₆</td>
<td>4Å sieves, Δ</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>TsOH</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>n/a</td>
<td>RT</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CSA, (Me)₂C(OMe)₂</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CSA</td>
<td>PhCH₃</td>
<td>4Å sieves, Δ</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>H₂SO₄</td>
<td>&quot;</td>
<td>&quot;</td>
<td>56</td>
</tr>
</tbody>
</table>

2.2 Radical Allylation of β-Acetal-α-Bromo Esters to Form Quaternary Centres

At last, we were ready to try our radical allylation on 34. Using AIBN or benzoyl peroxide as initiator, 34 was refluxed in toluene in the presence of allyltributyl tin. Although our yield was excellent, our diastereoselectivity proved to be poor, with a diastereomeric excess of 23% as measured by ¹H NMR. Since the diastereomers were inseparable and the diastereomeric excess low, we did not assign the relative configuration of the major diastereomer (Scheme 23).
Scheme 23. Radical allylation of 34 to form 51, bearing a quaternary centre.

Since a diastereomeric excess of 23% only implies a difference in transition state energies of 0.36 kcal/mol, we did not expect that lowering the temperature would provide a significant increase in diastereoselectivity. At -78 °C, we expected a diastereomeric excess of only 43%. However, we decided to perform a low temperature radical allylation experiment (Scheme 24). There was an increase in diastereoselectivity, although slightly less than we had predicted.

Scheme 24. Radical allylation of 34 at -78 °C.

---

5 This is based on the theory that, in a kinetically-controlled process, the ratio of products is equal to the ratio in rate constants for the transition states. From the Arrhenius equation ($\Delta G^\ddagger = -RT\ln k$) where $\Delta G^\ddagger$ is the transition state energy, $R = 1.987$ cal.mol$^{-1}$.K$^{-1}$, $T$ = the temperature in Kelvin, and $k$ is the rate constant, the ratio of the rate constants is proportional to the different in transition state energies:

$$\frac{k_a}{k_b} = e^{\frac{(\Delta G_b^\ddagger - \Delta G_a^\ddagger)}{RT}}$$

33
Our first inclination to improve the diastereoselectivity was to increase the bulk of the esters on the tartrate acetal. As may be recalled from Figure 8 in Section 1.4, we believe it is the steric hindrance between the tartrate ester group and R₂ that results in the diastereoselectivity. Thus, both (L)-diethyl tartrate (52) and L-diisopropyl tartrate (53) acetals were formed via transacetalisation in the same manner as 34 (Scheme 25). The yields of the tartrate acetals were slightly less than in the case of the dimethyl tartrate acetal 34, due to a transesterification side reaction that took place, replacing one or both of the ethyl or isopropyl groups, with a methyl group. This methyl group was believed to come from the methanol produced in the reaction. Placing the 4Å molecular sieves directly in the flask, rather than in the dropping funnel, did not alleviate this problem. Nevertheless, these side-products could be separated from our desired compounds 52 and 53.

Scheme 25. Formation of diethyl tartrate (52) and diisopropyl tartrate (53) acetals via transacetalisation.

We then attempted the radical allylation of 52 and 53, both at reflux and at -78 °C (Table 5). Although we saw a slight increase in diastereoselectivity at -78 °C for the diethyl tartrate acetal (de = 43% compared to de = 37% for dimethyl tartrate acetal), it was not a significant improvement. In the case of the diisopropyl tartrate acetal, the diastereomeric excess actually decreased slightly (de = 34%) as compared to the dimethyl tartrate acetal. Consequently, we began focusing our efforts at improving the diastereomeric excess of our allylation.
Table 5. Radical allylation of 52 and 53 at 110 °C and -78 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions</th>
<th>% Yield</th>
<th>% de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>benzoyl peroxide, PhCH₃, Δ</td>
<td>99</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>BE₄/O₂, CH₂Cl₂, -78°C</td>
<td>97</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>benzoyl peroxide, PhCH₃, Δ</td>
<td>99</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>BE₄/O₂, CH₂Cl₂, -78°C</td>
<td>94</td>
<td>34</td>
</tr>
</tbody>
</table>

2.3 Efforts to Improve the Diastereoselectivity of the Radical Allylation of α-Bromo Esters.

(i) Increasing the Bulk at R₂.

As described in section 1.4 (Figure 8) our model for diastereoselectivity in the radical allylation suggests that it is the steric hindrance between the R₂ group and the tartrate ester moiety that results in one ground state radical rotamer being preferred over the other. We wondered if the “R₂” group we employed in our first radical allylation trial, a methyl group, was too small to result in appreciable steric hindrance. Although it would slightly reduce the scope of our methodology, if bulkier groups were present at the R₂ position, perhaps the diastereoselectivity would increase to something synthetically useful. Thus, we decided to
design a synthetic route towards a radical allylation precursor with an isopropyl group at R₂. As we had observed the highest diastereomeric excess with diethyl tartrate, we decided to synthesize the (L)-diethyl tartrate acetal 56 (Figure 14).

**Figure 14. The radical allylation precursor 56 with increased bulk at R₂.**

Since methyl isopropylacrylate was not commercially available, we would have to design a synthetic route to our radical allylation precursor. We were initially intrigued by work done by Lapkin and Fotin, who made (E)-vinyl ethers 58 in one step from α-bromo esters 57 and dichloromethoxymethane using a Reformatsky-like reaction (Scheme 26).²⁸

**Scheme 26. Lapkin and Fotin’s synthesis of (E)-vinyl ethers.**

Although we were regretful that we had not come across this article for the synthesis of our previous radical allylation precursors (34, 52, 53), we were excited to have such a concise route to 56. As shown in Scheme 27, commercially available α-bromo valeric acid 59 would be converted into the methyl ester 60 using diazomethane. Using the literature procedure from Lapkin and Fotin, 60 would be converted to the vinyl ether 61. Bromomethoxylation of

36
61 using NBS and methanol would produce 62, which would then undergo a transacetalisation reaction to produce 56.

Scheme 27. Proposed synthetic route to radical allylation precursor 56.

Unfortunately, our optimism was short-lived. Although 60 was easily made in quantitative yield using diazomethane in ether, we could not reproduce the literature results to form 61. We tried two sources of freshly activated zinc (dust and 30 mesh) and several different reaction conditions, including sonication, which is reported to aid Reformatsky reactions, but to no avail. Therefore, we resigned ourselves to synthesizing the methyl isopropylacrylate via a literature procedure - essentially mimicking our route to 34, 52, and 53.
Scheme 28. Alternate proposed synthetic route to radical allylation precursor 56.

As shown above in Scheme 28, commercially available dimethylmalonate would be alkylated at C2 using isopropyl iodide to give 63. This would be converted via Stetter and Kuhlmann’s 3-step procedure to methyl isopropylacrylate 64. Bromine would then be added over the double bond to form a dibromo intermediate which, when treated with sodium methoxide, would produce the dimethyl acetal 65. This would then undergo an acid-catalyzed elimination to form the vinyl ether 61. At this point, the synthesis would proceed as in Scheme 27.

Thankfully, our proposed route went according to plan (Scheme 29). Using sodium hydride as base, dimethyl malonate was alkylated in 77% yield to produce 63. Stetter and Kuhlmann’s procedure to convert 63 to methyl isopropylacrylate (64) worked, but gave an inseparable mixture of starting material and product, in a modest crude yield. Since we did not believe that the presence of 63 would hinder the formation of 65 from 64, we pressed on

38
with the crude mixture. Thus, 65 was formed in 27% overall yield from 63. The CSA-catalyzed elimination reaction proceeded in quantitative yield to produce 61.

**Scheme 29.** Formation of vinyl ether 61 from dimethyl malonate.

![Scheme 29. Formation of vinyl ether 61 from dimethyl malonate.](image)

Shown in Scheme 30, the vinyl ether 61 was reacted with NBS in methanol to give the β-dimethylacetal-α-bromo ester in 77% yield. The radical allylation precursor 56 was formed in 47% yield, using our typical transacetalisation methodology.

**Scheme 30.** Synthesis of radical allylation precursor 56.

![Scheme 30. Synthesis of radical allylation precursor 56.](image)
We were now able to test the radical allylation methodology on our “bulkier” precursor 56. However, no increase in diastereomeric excess was seen, even at -78 °C (Scheme 31).

**Scheme 31. Radical allylation of 56 to form a quaternary centre.**

\[
\begin{align*}
\text{56} & \xrightarrow{\text{A or B}} \text{66} \\
\text{A: Benzoyl peroxide, PhCH₃, } & \Delta \\
\text{B: } & \text{BEt₃/O₂, CH₂Cl₂, -78} ° \text{C}
\end{align*}
\]

A: 95% yield, 20% de  
B: 95% yield, 33% de

This was a massive disappointment and it appeared that we were going to have to reevaluate our model for diastereoselectivity.

**(ii) Changing the Chiral Auxiliary**

Looking again at our model (Section 1.4, Figure 8), we wondered if free rotation around the carbon attaching the tartrate ester group would result in both the bulky OR₃ moiety and the carbonyl oxygen pointing away from the R₂ group (Figure 15). This would explain why we did not see any significant increase in diastereomeric excess between the different dialkyl tartrate acetals.
Figure 15. Reduced steric hindrance via rotation around C-C bond.

Thus, we sought a way to eliminate this problem. We felt that by replacing the ester groups with phenyl groups, bond rotation should not decrease the steric hindrance in the conformer shown in Figure 16.

Figure 16. Increased steric hindrance in a ground state radical conformer using hydrobenzoin acetal.
The \( C_2 \)-symmetric 1,2-diol, hydrobenzoin, would be used as chiral auxiliary for the radical allylation precursor. This diol is commercially available in both enantiomeric forms, so we would still have access to either enantiomer of the 1,3-dicarbonyl compounds after acetal cleavage (Scheme 32).

**Scheme 32. Proposed route to enantioenriched 1,3-dicarbonyl compounds 27 utilizing hydrobenzoin as chiral auxiliary.**

We anticipated that forming the hydrobenzoin acetal 68 from 37 using acid catalysis would be difficult based on the fact that hydrobenzoin would likely undergo pinacol-type rearrangements in the presence of acid. Not surprisingly, when hydrobenzoin was refluxed with 37 in benzene in the presence of CSA and 4Å molecular sieves an array of spots appeared on TLC and no product could be isolated from the crude mixture (Scheme 33).

**Scheme 33. Unsuccessful acid-catalyzed transacetalisation to form 68.**
Milder conditions, using boron trifluoride etherate as catalyst at 0 °C or room temperature, did not initiate any reaction. It was evident that a substantial driving force was needed to form the hydrobenzoin acetal, due, at least in part, to the bulky tertiary bromide adjacent to it. Since heating in protic conditions was not suitable as a driving force, we turned to the literature for aprotic methods. Noyori and coworkers had reported the formation of acetals under very mild conditions (aprotic, -78 °C) from the appropriate ketone or aldehyde, alkoxytrimethylsilane, and trimethylsilyl triflate.³² The alkoxytrimethylsilane was derived from the alcohol normally used in forming its respective acetal and the trimethylsilyl triflate acted as catalyst (Scheme 34).

**Scheme 34. Noyori and coworkers general route to acetals 70.**

Noyori was able to make both acyclic and cyclic acetals using this procedure. The driving force of the reaction is believed to be the high stability of the hexamethylsiloxane 71, which thus hinders the reverse reaction.³²

To synthesize the radical allylation precursor 68 using Noyori’s methodology, we would have to convert our dimethyl acetal 37 to the aldehyde 72 and hydrobenzoin to the ditrimethylsilyl ether derivative 73 (Scheme 35).
Scheme 35. Proposed synthetic route to radical allylation precursor 68.

The formation of 73 via a literature procedure\textsuperscript{33} proved to be quite simple. In the presence of triethylamine as base, chlorotrimethylsilyl was added to hydrobenzoin in dichloromethane, yielding 73 (24%, Scheme 36).

Scheme 36. Formation of ditrimethylsilyl ether 73 from hydrobenzoin.

However, cleavage of the dimethyl acetal proved to be impossible in our hands. Although a variety of conditions were tried, some of which are included in Table 6, generally only starting material was recovered.
Table 6. Attempted cleavage of dimethyl acetal 37.

```
\[
\begin{align*}
\text{Entry} & \quad \text{Conditions} & \quad \text{Result} \\
1 & \quad \text{HCl-activated Amberlite IR-120 ion-exchange resin; EtOH; RT} & \quad \text{SM} \\
2 & \quad \text{TFA-H}_2\text{O (1:1); RT} & \quad " \\
3 & \quad \text{H}_2\text{SO}_4-\text{H}_2\text{O (1:10); RT} & \quad " \\
4 & \quad \text{AcOH-H}_2\text{O (1:1); RT} & \quad " \\
5 & \quad \text{TsOH (2 eq); acetone-} & \quad " \\
\text{} & \text{H}_2\text{O (1:1); RT} & \quad " \\
6 & \quad \text{AcOH-H}_2\text{O (3:1), } & \quad \text{SM + decomp.} \\
\text{} & \Delta & \quad \text{SM + decomp.}
\end{align*}
```

Since, as mentioned previously, the driving force of the reaction is the formation of the stable hexamethylsiloxane, we did not believe that we would be successful in using Noyori’s methodology with the dimethyl acetal 37, rather than the aldehyde 72. If the reaction proceeded in the forward direction, two equivalents of methoxytrimethylsilane would be formed, rather than hexamethylsiloxane. The relative stability of the methoxytrimethylsilane may not be sufficient to drive the reaction in the direction of the hydrobenzoin acetal product. Nevertheless, we attempted this reaction, but were not surprised to observe no product (Scheme 37).
Scheme 37. Attempted formation of radical allylation precursor 68.

At this stage, we decided to resign ourselves to defeat in the formation of the hydrobenzoin acetal 68. However, we wished to try a different chiral auxiliary that we should also decrease rotation around the C-C bond attaching the ester moiety to the dioxolane ring (Figure 15).

(iii) Changing the Chiral Auxiliary: \(N,N'\)-Dibenzyl-\(N,N'\)-ethylenetartramide

Two postulates have been previously mentioned as to why the diastereoselectivity in the radical allylation was poorer than expected. Disappointingly, our first hypothesis, that the \(R_2\) group was not bulky enough, was not supported by our results, and our second could not be tested. A third theory is that it is not (or not solely) rotation about the bond connecting the tartrate ester to the dioxolane ring that results in reduced diastereoselectivity. In fact, we proposed that it may be the changeable conformation of the dioxolane ring that was the source of our poor diastereoselectivity.

As shown in Figure 17 below, a five-membered ring can exit in two conformations: the envelope or the half-chair. Up to this point, we had assumed that the dioxolane ring was in the envelope conformation and had neglected the possibility that, to avoid steric hindrance between the tartrate ester moiety and the \(R_2\) group, that the lower energy conformation of the ground state radical (and, by inference, the lowest energy transition state of the allylation) was actually the half-chair.
Figure 17. Two possible conformations of the dioxolane ring.

Thus, based on this assumption, for a significant increase in diastereoselectivity, the conformation of the dioxolane ring would have to be “locked” in the envelope conformation.

In 1985, Roush and coworkers utilized diisopropyl tartrate as a chiral auxiliary in the enantioselective allylboration of aldehydes. They proposed that the selectivity resulted from a destabilizing stereoelectronic interaction between the lone pairs on the aldehyde oxygen and the diisopropyl ester carbonyl oxygen. This would thus result in allylation occurring selectively from one face of the aldehyde (Figure 18).
Figure 18. Roush and coworkers explanation of selectivity for enantioselective allylboration of aldehydes.

Although they had reported modest diastereoselectivity using diisopropyl tartrate, for improved selectivity, the dioxolane would have to be “locked” in the envelope conformation so that the ester groups would be pseudoaxial. In addition, rotation of the bond connecting the ester group to the dioxolane ring would have to be limited. Thus, they endeavoured to “lock” the position of the carbonyl group by essentially joining the two ester groups in a cycle. To accomplish this, they synthesized $N,N'$-Dibenzyl-$N,N'$-ethylenetramide 74 from (L)-dimethyl tartrate (Figure 19).\textsuperscript{35}
Due to the eight-membered ring and the partial double bond character of the C-N amide bond, the carbonyl groups should be locked in a pseudoaxial position and bond rotation connecting the amide carbonyl to the dioxolane ring would be virtually disallowed.\textsuperscript{36}

Indeed, when Roush employed the tartramide auxiliary in the allylboration reaction, a substantial increase was seen in enantioselectivity as compared to using diisopropyl tartrate as chiral auxiliary.\textsuperscript{35} Thus, we were excited to use this new $C_2$-symmetric diol in our radical allylation reaction.

We followed Roush’s synthetic procedure to form tartramide 74 (Scheme 38). From benzaldehyde, the dimethyl tartrate acetal 75 was formed in 72% yield, by first forming the dimethyl acetal, and then performing a transacetalisation reaction with (L)-dimethyl tartrate in the same pot. This was then saponified to give the (L)-tartaric acid acetal 76 in 99% yield. Forming the octacycle with 76 and dibenzylethylenediamine was rather cumbersome, utilizing $N$-methyl-2-chloropyridinium iodide as catalyst in dilute anhydrous chloroform. This produced 77 in reproducibly poor yield (28%). Finally, the 1,2-diol was deprotected by refluxing in a solution of acetic acid and water to form 74 in 85% yield.
Scheme 38. Synthesis of chiral auxiliary 74 via Roush’s procedure.

To attach the tartramide 74 to the \(\alpha\)-bromo ester 37, we sought to utilize the procedure we had developed for attaching the dialkyl tartrate esters to 37. Unfortunately, we either observed starting material, or, in high boiling solvents such as dioxane and toluene, decomposition occurred (Scheme 39).
Although we were very frustrated to have been only able to test one of our postulated methods at improving diastereoselectivity, we decided to end the project after this latest disappointment. Our attention would soon be focused on other challenges in synthetic organic chemistry.
Chapter 3. Conclusions

Via radical allylation of α-bromo esters, we were successful in generating quaternary centres, albeit with poor diastereoselectivity. Dialkyl tartrate esters did not work effectively as chiral auxiliaries, even at low temperature.

```
-78°C, CH₂Cl₂

<table>
<thead>
<tr>
<th>R</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>37</td>
</tr>
<tr>
<td>Et</td>
<td>42</td>
</tr>
<tr>
<td>i-Pr</td>
<td>34</td>
</tr>
</tbody>
</table>
```

Unfortunately, attempts at replacing the dialkyl tartrate acetals with different chiral auxiliaries, such as hydrobenzoin or the Roush tarteramide, were not successful. In hindsight, even if our methodology had been successful, the biggest obstacle would have been making the acetals themselves, since their formation required harsh conditions (catalytic sulfuric acid in refluxing toluene).

Although the ultimate goal of this undertaking, the asymmetric synthesis of quaternary centres via radical allylation, was not reached, several novel compounds were synthesized which may prove useful in other synthetic endeavours. Most importantly, great deals of knowledge and experience have been gained by the candidate.
Chapter 4. Experimentals

Reactions were performed in oven- or flame-dried evacuated flasks under N₂ atmosphere and equipped with a magnetic stir bar and a rubber septum, unless otherwise noted. THF was freshly distilled from sodium/benzophenone, while dichloromethane, DMF, and toluene were freshly distilled from calcium hydride. Chloroform and benzene were dried over freshly activated 4Å molecular sieves for twenty-four hours before use. Reagents were purchased from Sigma-Aldrich, Lancaster, and Strem chemical companies. Triethylamine was freshly distilled over calcium hydride. Chlorotrimethylsilane was freshly distilled before use. Benzoyl peroxide was recrystallized from water. All other reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F254 precoated 0.25 mm thick aluminium plates. TLCs were visualized using ultraviolet light, potassium permanganate, ceric ammonium molybdate, and/or p-anisaldehyde stains. When necessary, products were purified using flash column chromatography on silica gel 60 (230-400 mesh) or preparatory TLC glass plates precoated with silica gel (Si250F). Solvents were evaporated on rotary evaporators.

¹H and ¹³C NMR spectra were acquired using either a Varian Gemini 200 MHz (¹H); or a Bruker Avance 300 MHz (¹H) and 75 MHz (¹³C). Infrared spectra were acquired on a Bomem Michaelson 100 FTIR spectrometer. Mass spectra were obtained using a Kratos IIH instrument using either CI or EI ionization techniques. Melting points were determined using an Electrotherm Meltemp® apparatus and are uncorrected.

Diazomethane was prepared from commercially available N-nitroso-N-methyl urea as follows. To a 250 mL plastic bottle was added a 40% aqueous solution of KOH (30 mL). After cooling to 0 °C, diethyl ether (100 mL) was added to the bottle. After stirring for 5 minutes, N-nitroso-N-methyl urea (7.0 g) was added in 4 portions over 15 minutes. The solution was stirred for an additional 5 minutes, after which the ether layer was decanted into a plastic bottle and cooled to -78 °C so that any remaining water would freeze. The cooled mixture was filtered through a cotton plug into a 100 mL plastic bottle containing KOH pellets. The yellow ethereal diazomethane solution was stored in the freezer.
2-(1-Bromo-1-methoxycarbonylethyl)-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid dimethyl ester

![Structural formula](image)

To a 25 mL flask containing 37 (0.410 mg, 1.70 mmol) in anhydrous toluene (17 mL) was added L-dimethyl tartrate (0.667 g, 3.74 mmol) and concentrated sulfuric acid (~1 drop). The reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (for setup, see diagram for 7). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed overnight, until reaction was deemed complete by TLC. After cooling, the reaction mixture was washed sequentially with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to afford a viscous, pale yellow oil which was purified via flash column chromatography (7:3 hexanes – ethyl acetate) to afford 34 (0.338 g, 56%), a viscous, colourless oil, as a 1:1 inseparable mixture of diastereomers. IR (thin film) 2960, 2848, 1753, 1443, 1278, 1221, 1113 cm⁻¹;¹H NMR (CDCl₃, 300 MHz) δ 5.81 (s, 0.5 H), 5.77 (s, 0.5 H), 4.94 (d, J = 6.2 Hz, 0.5 H), 4.92 (d, J = 6.6 Hz, 0.5 H), 4.79 (d, J = 4.0 Hz, 0.5 H), 4.77 (d, J = 4.4 Hz, 0.5 H), 3.85 (s, 1.5 H), 3.83 (s, 1.5 H), 3.82 (s, 1.5 H), 3.81 (s, 3 H), 3.80 (s, 1.5 H), 1.89 (s, 1.5 H), 1.88 (s, 1.5 H);¹³C NMR (CDCl₃, 75 MHz) δ 169.32 (C), 169.26 (C), 169.12 (C), 169.10 (C), 168.52 (C), 168.32 (C), 107.36 (CH), 107.28 (CH), 78.05 (CH), 77.96 (CH), 77.47 (CH), 77.44 (CH), 57.09 (C), 56.63 (C), 53.44 (CH₃), 53.42 (CH₃), 53.02 (CH₃), 52.98 (CH₃), 52.96 (CH₃), 52.92 (CH₃), 20.81 (CH₃), 20.15 (CH₃); MS (EI) m/z 355 (M + 2), 353 (M+), 189 (M+ - (Br)(CH₃)C(O)(CH₂)CH₃).
3,3-Dimethoxy-2-methylpropionic acid methyl ester$^{20}$

To a 100 mL flask containing methyl methacrylate (5.00 g, 49.9 mmol) at 0 °C was added bromine (7.98 g, 49.9 mmol) dropwise over 15 minutes. The reaction mixture was then allowed to warm to room temperature and was stirred for two hours. After cooling the reaction flask to 0 °C, a 25% w/w solution of sodium methoxide (8.09 g, 149.8 mmol) in methanol was then added via syringe pump over 20 minutes. The reaction mixture was then stirred overnight at room temperature at which time glacial acetic acid (2.94 mL, 49.9 mmol) was added. After stirring for 30 minutes, the reaction mixture was concentrated \textit{in vacuo} and was diluted with diethyl ether (300 mL). The resultant suspension was filtered through a pad of celite, rinsing several times with diethyl ether. The filtrate was washed with saturated sodium bicarbonate solution (200 mL), water (200 mL), and brine (200 mL), and then dried over anhydrous magnesium sulfate. Removal of solvent \textit{in vacuo} gave 35 (6.30 g, 78%) as a pale yellow oil whose spectral properties corresponded to those in literature.$^{20}$ $^1$H NMR (CDCl$_3$, 200 MHz) δ 4.43 (d, $J = 7.7$ Hz, 1H), 3.63 (s, 3H), 3.30 (s, 3H), 3.28 (s, 3H), 2.72 (dt, $J = 7.6$ Hz, 7.1 Hz, 1H), 1.10 (d, $J = 7.1$ Hz, 3H).
3-Methoxy-2-methylacrylic acid methyl ester

![Chemical Structure](image)

To a 500 mL flask containing 35 (4.91 g, 30.3 mmol) in anhydrous benzene (200 mL) was added camphor sulfonic acid (~10 mg). At this time, the reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (for setup, see diagram for 7). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed overnight, until reaction was deemed complete by TLC. The reaction mixture was then cooled and washed sequentially with saturated sodium bicarbonate solution (60 mL), water (60 mL), and brine (60 mL), and then dried over anhydrous magnesium sulfate. Removal of solvent in vacuo afforded 36 (3.93 g, 100%) as a pale yellow oil whose spectral properties corresponded to those in literature. \( ^{1}H \) NMR (CDCl\(_3\), 300 MHz) δ 7.31 (s, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 1.69 (s, 3H).

2-Bromo-3,3-dimethoxy-2-methylpropionic acid methyl ester

![Chemical Structure](image)

To a 100 mL flask containing 36 (1.00 g, 7.68 mmol) in dry methanol (40 mL) was added N-bromosuccinimide (3.28 g, 18.4 mmol) (non-recrystallized; slightly orange). The reaction mixture was stirred at room temperature overnight, or until deemed complete by TLC. After

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quenching the excess N-bromosuccinimide with 1 M sodium metabisulfite (50 mL), the methanol was removed in vacuo. The colourless aqueous solution was then extracted with dichloromethane (3 x 50 mL). The organic extracts were combined and washed sequentially with water (50 mL) and brine (50 mL) before being dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded 37 (1.38 g, 75%) as a pale yellow oil. IR (thin film) 2999, 2959, 2842, 1751 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.75 (s, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.48 (s, 3H), 1.79 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.83 (C), 107.87 (CH), 59.96 (CH₃), 59.84 (C), 58.21 (CH₃), 52.86 (CH₃), 19.87 (CH₃); MS (EI) m/z 211 (M⁺ - 29), 209 (M⁺ - 31).

2-Methoxycarbonylmethyl-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid dimethyl ester

![Chemical Structure](image)

To a 25 mL flask containing dimethyl tartrate (0.252 g, 1.19 mmol) in THF (4 mL) at 0 °C was cannulated a suspension of sodium hydride (0.029 g, 1.19 mmol) in THF (1 mL). The reaction mixture was stirred at 0 °C for 15 minutes before gradually adding methyl propiolate (0.100 g, 1.19 mmol) in THF (2 mL). The reaction mixture was gradually warmed to room temperature and stirred overnight until deemed complete by TLC. The mixture was then treated with brine (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of solvents in vacuo gave a viscous oil which was purified via flash column chromatography to afford 41 (0.047 g, 20%) as a pale yellow viscous oil. IR (thin film) 2963,
2846, 1767, 1441 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 5.66 (dd, \(J = 5.2, 5.2\) Hz, 1H), 4.78 (d, \(J = 3.3\) Hz, 1H), 4.71 (d, \(J = 3.3\) Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 2.83 (d, \(J = 5.5\) Hz, 1H), 2.82 (d, \(J = 5.0\) Hz, 1H); \(^1^\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 169.50 (C), 169.40 (C), 169.18 (C), 104.06 (CH), 77.38 (CH), 76.95 (CH), 52.85 (CH\(_3\)), 52.83 (CH\(_3\)), 51.94 (CH\(_3\)). 39.44 (CH\(_2\)), MS (EI) m/z 262 (M\(^+\)), 189 (M\(^+\) - CH\(_2\)CO\(_2\)CH\(_3\)).

2-(1-Phenylethyl)-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid dimethyl ester

To a 25 mL flask containing 2-phenylpropanal (0.150 g, 1.12 mmol) in anhydrous benzene (12 mL) was added trimethylorthoformate (0.134 mL, 1.23 mmol) and camphor sulfonic acid (0.010 g, 0.043 mmol). The reaction mixture was stirred at room temperature for 15 minutes, until disappearance of starting material was confirmed via TLC. L-Dimethyl tartrate (0.219 g, 1.23 mmol) was then added to the reaction mixture. At this time, the reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (see accompanying diagram). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed for nine hours, until reaction was deemed complete by TLC. After being cooled, the reaction mixture was sequentially washed with aqueous saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL), and then dried over anhydrous magnesium sulfate. Removal of the solvent in
vacuo afforded a viscous pale yellow oil which was purified using flash column chromatography (85% hexanes - 15% ethyl acetate) to yield 49 (0.280 g, 85%), a colourless viscous oil, as a 1:1 mixture of diastereomers. IR (thin film) 3087, 3062, 3030, 2955, 2907, 1743 cm⁻¹; $^1$H NMR (CDCl₃, 500 MHz) δ 7.25-7.31 (m, 5H), 5.35 (d, $J$ = 4.8 Hz, 0.5H), 5.32 (d, $J$ = 5.6 Hz, 0.5H), 4.78 (d, $J$ = 3.7 Hz, 0.5H), 4.77 (d, $J$ = 3.8 Hz, 0.5H), 4.67 (d, $J$ = 3.8 Hz, 0.5H), 4.64 (d, $J$ = 3.7 Hz, 0.5H), 3.74 (s, 1.5H), 3.73 (s, 1.5H), 3.72 (s, 1.5H), 3.71 (s, 1.5H), 3.08-3.14 (m, 1H), 1.35 (d, $J$ = 7.1 Hz, 1.5H), 1.34 (d, $J$ = 7.2 Hz, 1.5H); $^{13}$C NMR (CDCl₃, 125 MHz) δ 169.89 (C), 169.81 (C), 169.35 (C), 169.22 (C), 141.11 (C), 141.07 (C), 128.13 (CH), 128.08 (CH), 127.99 (CH), 126.61 (CH), 110.08 (CH), 109.79 (CH), 77.26 (CH), 76.95 (CH), 76.88 (CH), 76.65 (CH), 52.50 (CH₃), 52.47 (CH₃), 52.43 (CH₃), 43.35 (CH), 43.14 (CH), 15.36 (CH₃), 15.15 (CH₃); MS (Cl/iso) m/z 295 (MH⁺).

2-(1-Methoxycarbonyl-1-methyl-but-3-enyl)-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid dimethyl ester

![Diagram](image)

To a 10 mL flask equipped with a water-cooled condenser was added 34 (0.103 g, 0.290 mmol) in anhydrous toluene (3 mL). Allyltributyl tin (0.106 g, 0.319 mmol) was then added, followed by benzoyl peroxide (0.014 g, 0.058 mmol). The reaction mixture was then refluxed for 6 hours, until reaction was deemed complete by TLC. After cooling, the solvent
was removed *in vacuo* and the residue was immediately purified via gradient flash column chromatography (9:1 → 7:3 hexanes–ethyl acetate) to afford 51 (0.089 g, 98%), a pale yellow, viscous oil, as a 1.6 : 1 mixture of diastereomers. For characterization purposes, the product was purified via preparatory TLC (7:3 hexanes – ethyl acetate) to afford a clear, colourless, and viscous oil. IR (thin film) 3081, 2998, 2956, 1734, 1459, 1439 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.64-5.78 (m, 1H), 5.44 (s, 0.6H), 5.42 (s, 0.4H), 5.05-5.11 (m, 3H), 4.78-4.81 (m, 1H), 4.68-4.70 (m, 1H), 3.80-3.82 (m, 6H), 3.70-3.71 (m, 3H), 2.51-2.61 (m, 1H), 2.28-2.36 (m, 1H), 1.19-1.20 (m, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 173.47 (C), 173.44 (C), 169.91 (C), 168.95 (C), 132.87 (CH), 132.76 (CH), 118.60 (CH₂), 108.88 (CH), 108.62 (CH), 77.13 (CH), 76.94 (CH), 52.81 (CH₃), 52.04 (CH₃), 52.00 (CH₃), 49.90 (C), 49.88 (C), 39.88 (CH₂), 39.40 (CH₂), 14.91 (CH₃), 14.54 (CH₃); MS (Cl/iso) m/z 317 (MH⁺).

**General procedure for radical allylation at -78 °C.** To a 5 mL flask was added the 2-(1-bromo-1-methoxycarbonylethyl)-[1,3]-dioxolane-4,5-dicarboxylic acid dialkyl ester (0.28 mmol) in anhydrous dichloromethane (3 mL). The reaction mixture was brought to -78 °C and allyltributyl tin (0.17 mL, 0.56 mmol) was then added via syringe. Triethylborane (0.06 mL, 0.06 mmol), as a 1.0 M solution in hexanes, was then added. The reaction mixture continued to be stirred at -78 °C, adding additional triethylborane if necessary, until deemed complete via TLC. The solvent was then removed *in vacuo* and the residue was purified via gradient flash column chromatography (9:1 → 7:3 hexanes – ethyl acetate) to afford the 2-(1-methoxycarbonyl-1-methyl-but-3-enyl)-[1,3]-dioxolane-4,5-dicarboxylic acid dialkyl ester.
To a 25 mL flask containing 37 (0.300 g, 1.24 mmol) in anhydrous toluene (12 mL) was added L-diethyl tartrate (0.564 g, 2.74 mmol) and concentrated sulfuric acid (~1 drop). The reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (for setup, see diagram for 7). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed overnight, until reaction was deemed complete by TLC. After cooling, the reaction mixture was washed sequentially with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to afford a viscous, pale yellow oil which was purified via flash column chromatography (8:2 hexanes–ethyl acetate) to afford 52 (0.160 g, 34%), a viscous, colourless oil, as a 1:1 inseparable mixture of diastereomers. IR (thin film) 2989, 2958, 2942, 1745, 1452, 1373, 1274 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.82 (s, 0.5H), 5.79 (s, 0.5H), 4.90 (d, J = 4.2 Hz, 0.5H), 4.87 (d, J = 4.6 Hz, 0.5H), 4.75 (d, J = 4.0 Hz, 0.5H), 4.74 (d, J = 4.5 Hz, 0.5H), 4.22-4.34 (m, 4H), 3.82 (s, 3H), 1.90 (s, 1.5H), 1.89 (s, 1.5 H), 1.28-1.36 (m, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.18 (C), 169.14 (C), 168.89 (C), 168.83 (C), 168.12 (C), 167.93 (C), 107.29 (CH), 107.24 (CH), 78.22 (CH), 78.16 (CH), 77.61 (CH), 77.56 (CH), 62.25 (CH₂), 62.20 (CH₂), 57.06 (C), 56.77 (C), 53.41 (CH₃), 20.68 (CH₃), 20.16 (CH₃), 14.11 (CH₃), 14.08 (CH₃); MS (Cl/iso) m/z 383 (MH⁺).
2-(1-Bromo-1-methoxycarbonylethyl)-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid
diisopropyl ester

To a 25 mL flask containing 37 (0.300 g, 1.24 mmol) in anhydrous toluene (12 mL) was added L-diisopropyl tartrate (0.641 g, 2.74 mmol) and concentrated sulfuric acid (~1 drop). The reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (for setup, see diagram for 7). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed overnight, until reaction was deemed complete by TLC. After cooling, the reaction mixture was washed sequentially with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to afford a viscous, pale yellow oil which was purified via flash column chromatography (85:15 hexanes – ethyl acetate) to afford 53 (0.103 g, 31%), a viscous, colourless oil, as a 1:1 inseparable mixture of diastereomers. IR (thin film) 2984, 2940, 1758, 1453, 1376, 1278 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.80 (d, J = 1.1 Hz, 0.5H), 5.76 (d, J = 1.1 Hz, 0.5H), 5.04-5.16 (m, 2H), 4.79 (dd, J = 1.1, 4.5 Hz, 0.5H), 4.77 (dd, J = 1.1, 4.8 Hz, 0.5H), 4.64-4.66 (m, 1H), 3.81 (s, 1.5H), 3.80 (s, 1.5H), 1.88 (s, 3H), 1.26-1.29 (m, 12H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.18 (C), 169.13 (C), 168.40 (C), 168.33 (C), 167.60 (C), 167.42 (C), 107.16 (CH), 78.36 (CH), 78.30 (CH), 77.68 (CH), 77.64 (CH), 70.13 (CH), 70.08 (CH), 56.96 (C), 56.82 (C), 53.35 (CH₃), 21.63 (CH₃), 20.51 (CH₃), 20.11 (CH₃); MS (Cl/iso) m/z 411 (MH⁺).
2-(1-Methoxycarbonyl-1-methyl-but-3-enyl)-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid diethyl ester

To a 10 mL flask equipped with a water-cooled condenser was added 52 (0.090 g, 0.235 mmol) in anhydrous toluene (2.5 mL). Allyltributyl tin (0.156 g, 0.470 mmol) was then added, followed by benzoyl peroxide (0.006 g, 0.023 mmol). The reaction mixture was then refluxed for 2 hours, until reaction was deemed complete by TLC. After cooling, the solvent was removed in vacuo and the residue was immediately purified via gradient flash column chromatography (95:5 → 8:2 hexanes – ethyl acetate) to afford 54 (0.079 g, 99%), a pale yellow, viscous oil, as a 1.6:1 mixture of diastereomers. For characterization purposes, the product was purified via preparatory TLC (8:2 hexanes – ethyl acetate) to afford a clear, colourless, and viscous oil. IR (thin film) 3082, 2986, 2952, 1742, 1640, 1446, 1371, 1295, 1216 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.64-5.78 (m, 1H), 5.45 (s, 0.6H), 5.42 (s, 0.4H), 5.04-5.10 (m, 2H), 4.73-4.76 (m, 1H), 4.64-4.66 (m, 1H), 4.22-4.30 (m, 4H), 3.69-3.70 (m, 3H), 2.51-2.60 (m, 1H) 2.28-2.36 (m, 1H), 1.28-1.33 (m, 6H), 1.20 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 173.54 (C), 173.47 (C), 169.50, (C), 169.47 (C), 168.56 (C), 168.44 (C), 132.92 (CH), 132.83 (CH), 118.54 (CH₂), 108.81 (CH), 108.51 (CH), 77.29 (CH), 77.08 (CH), 61.95 (CH₂), 61.93 (CH₂), 52.00 (CH₃), 51.97 (CH₃), 49.93 (C), 39.86 (CH₂), 39.41 (CH₂), 14.82 (CH₃), 14.63 (CH₃), 14.09 (CH₃), 14.07 (CH₃); MS (CI/iso) m/z 345 (MH⁺)
2-(1-Methoxycarbonyl-1-methyl-but-3-enyl-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid diisopropyl ester

![Chemical Structure](image)

To a 5 mL flask equipped with a water-cooled condenser was added 54 (0.088 g, 0.214 mmol) in anhydrous toluene (2 mL). Allyltributyl tin (0.142 g, 0.428 mmol) was then added, followed by benzoyl peroxide (0.010 g, 0.043 mmol). The reaction mixture was then refluxed for 2 hours, until reaction was deemed complete by TLC. After cooling, the solvent was removed in vacuo and the residue was immediately purified via gradient flash column chromatography (95:5 → 85:15 hexanes – ethyl acetate) to afford 55 (0.079 g, 99%), a pale yellow, viscous oil, as a 1.6:1 mixture of diastereomers. For characterization purposes, the product was purified via preparatory TLC (8:2 hexanes–ethyl acetate) to afford a clear, colourless, and viscous oil. IR (thin film) 3082, 2985, 2943, 1738, 1634, 1461, 1377, 1288, 1223, 1146, 1103, 1022, 984, 919, 844 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.65-5.80 (m, 1H), 5.45 (s, 0.6H), 5.42 (s, 0.4H), 5.05-5.16 (m, 4H), 4.67 (dd, J = 4.4, 4.4 Hz, 1H), 4.59 (d, J = 4.6 Hz, 1H), 3.70-3.71 (m, 3H), 2.51-2.60 (m, 1H), 2.28-2.37 (m, 1H), 1.27-1.30 (m, 12H), 1.21 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 173.62 (C), 173.50 (C), 169.10 (C), 169.07 (C), 168.11 (C), 167.99 (C), 132.97 (CH), 132.89 (CH), 118.52 (CH₂), 108.74 (CH), 108.43 (CH), 77.46 (CH), 77.44 (CH), 77.25 (CH), 77.22 (CH), 69.80 (CH), 69.77 (CH), 52.01 (CH₃), 52.99 (CH₃), 49.98 (C), 49.95 (C), 39.85 (CH₂), 39.45 (CH₂), 21.66 (CH₃), 21.63 (CH₃), 14.76 (CH₃), 14.74 (CH₃); MS (Cl/iso) m/z 373 (MH⁺), 331 (MH⁺ - 42).
2-(1-Bromo-1-methoxycarbonyl-2-methylpropyl)-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid diethyl ester

To a 25 mL flask containing 62 (0.200 g, 0.743 mmol) in toluene (10 mL) was added L-diethyltartrate and 1 drop concentrated sulfuric acid. The reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (for setup, see diagram for #). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed overnight, until deemed complete by TLC. After being cooled to room temperature, the reaction mixture was washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL). The organic phase was dried over magnesium sulfate and the solvent was removed in vacuo to afford a pale brown viscous oil which was purified via flash column chromatography (85:15 hexanes-ethyl acetate) to afford 0.145 g 56 (0.145 g, 47%), a pale yellow viscous oil, as a 1:1 mixture of diastereomers. IR (thin film) 2980, 1754, 1467, 1436, 1392, 1372, 1224, 1167, 1129, 1093, 1027, 857, 834 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.62 (s, 0.5H), 5.58 (s, 1H), 5.00 (d, J = 4.3 Hz, 0.5H), 4.88 (d, J = 5.0 Hz, 0.5H), 4.67 (d, J = 4.4 Hz, 0.5H), 4.65 (d, J = 5.1 Hz, 0.5H), 4.21-4.30 (m, 4H), 3.80 (s, 1.5H), 3.77 (s, 1.5H), 2.41-2.59 (m, 1H), 1.27-1.34 (m, 6H), 1.11 (d, J = 6.6 Hz, 1.5H), 1.10 (d, J = 6.7 Hz, 1.5H), 0.99 (d, J = 6.7 Hz, 1.5H), 0.96 (d, J = 6.6 Hz, 1.5H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.27 (C), 169.07 (C), 167.78 (C), 167.66 (C), 167.64 (C), 167.47 (C), 108.24 (CH), 107.60 (CH), 77.72 (CH), 77.53 (CH), 77.21 (CH), 77.09 (C), 76.70 (CH), 62.06 (CH₂), 62.03 (CH₂),
53.53 (CH₃), 53.31 (CH₃), 35.61 (CH), 34.81 (CH), 19.25 (CH₃), 19.06 (CH₃), 19.04 (CH₃), 18.48 (CH₃), 14.07 (CH₃), 14.08 (CH₃); MS (Cl/iso) m/z 411 (MH⁺), 413 (MH⁺ + 2).

**Methyl 2-bromo-3-methylbutanoate**

![Methyl 2-bromo-3-methylbutanoate structure](image)

To a 100 mL flask containing 2-bromo-3-methylbutanoic acid in 30 mL diethyl ether was added a ~0.7 M solution of diazomethane (in diethyl ether) until a pale yellow colour persisted in the reaction flask. The reaction mixture was concentrated *in vacuo* (Note: Product very volatile) to afford 60 in quantitative yield as a pale yellow oil whose spectral properties corresponded to those in literature.³⁷¹H NMR (CDCl₃, 200 MHz) δ 4.03 (d, J = 7.9 Hz, 1H), 3.76 (s, 3H), 2.16-2.23 (m, 1H), 1.08 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H).
2-Methoxymethylene-3-methylbutyric acid methyl ester\textsuperscript{20}

![Chemical Structure](image)

To a 250 mL flask containing 65 (2.29 g, 12.037 mmol) in benzene (120 mL) was added camphor sulfonic acid (0.100 g, 0.430 mmol). The reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (for setup, see diagram for 7). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed overnight, until reaction was deemed complete by TLC. The reaction mixture was cooled to room temperature and washed sequentially with saturated sodium bicarbonate solution (100 mL), water (100 mL), and brine (100 mL). After drying over magnesium sulfate, the solvent was removed in vacuo to afford 61 (1.90 g, 100\%) whose spectral properties corresponded to literature values.\textsuperscript{28} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) \( \delta \) 7.15 (s, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 2.79-3.07 (m, 1H), 1.08 (d, \( J = 7.1 \) Hz, 3H).
2-Bromo-2-dimethoxymethyl-3-methylbutyric acid methyl ester

![Chemical structure](image)

To a foil-wrapped 100 mL flask containing 61 (0.327 g, 2.067 mmol) in methanol (10 mL) was added N-bromosuccinimide (1.47 g, 8.268 mmol) (non-recrystallized; slightly orange). After stirring overnight at room temperature, until deemed complete by T.L.C, the excess N-bromosuccinimide was quenched with saturated sodium metabisulfite solution (2 mL). The reaction mixture was stirred for 0.5 hour and the methanol was removed by rotovaparator. Water (20 mL) and dichloromethane (20 mL) were added to the resulting residue and the resulting layers were separated. Following extraction of the aqueous layer with dichloromethane (2 x 20 mL), the combined organic extracts were washed with water (20 mL) and brine (20 mL). Removal of the solvent in vacuo after drying over magnesium sulfate gave 62 (0.426 g, 77%) as a pale yellow oil which was used without further purification. For characterization purposes, the product was submitted to flash column chromatography (9:1 hexanes-ethyl acetate). IR (thin film) 2971, 2955, 2837, 1751, 1454, 1436, 1389, 1345, 1253, 1153, 1112, 1079, 976, 820 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.58 (s, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 3.55 (s, 3H), 2.40 (septet, \(J = 6.7\) Hz, 1H), 1.03 (d, \(J = 6.7\) Hz, 3H), 0.95 (d, \(J = 6.7\) Hz, 3H); \(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 168.49 (C), 108.23 (CH), 78.84 (C), 58.96 (CH\(_3\)), 58.67 (CH\(_3\)), 53.09 (CH\(_3\)), 35.34 (CH), 19.02 (CH\(_3\)), 18.99 (CH\(_3\)); MS (Cl/iso) m/z 269 (MH\(^+\)), 271 (MH\(^+\) + 2).
2-Isopropylmalonic acid dimethyl ester

To a 500 mL flask containing sodium hydride (3.85 g, 160.42 mmol) in 300 mL tetrahydrofuran at 0 °C was added dimethyl malonate (19.27 g, 145.83 mmol). After stirring for twenty minutes at 0 °C, isopropyl iodide (24.79 g, 145.83 mmol) was added to the reaction mixture. The reaction mixture was refluxed overnight, until deemed complete by TLC. After cooling to room temperature, the solvent was removed in vacuo and saturated ammonium chloride solution (200 mL) was added to the remaining residue. The suspension was extracted with diethyl ether (3 x 200 mL) and the combined organic extracts were washed with brine (200 mL). After drying over magnesium sulfate, the solution was concentrated to give an oil, which was purified via flash column chromatography (9:1 hexanes-ethyl acetate) to afford 63 (19.62 g, 77%) as a pale yellow oil, whose spectral properties corresponded to literature values.\textsuperscript{31} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) \( \delta \) 3.74 (s, 6H), 3.16 (d, \( J = 7.7 \), 1H), 2.12-2.43 (m, 1H), 0.97 (d, \( J = 7.6 \), 6H).
Potassium hydroxide (6.32 g, 112.7 mmol) in methanol (70 mL) was added over one hour, via dropping funnel, to a 500 mL flask containing 63 (19.62 g, 112.7 mmol) in methanol (70 mL). After stirring overnight at room temperature, the reaction mixture was concentrated and water (10 mL) was added. Concentrated hydrochloric acid (10 mL) was then added via dropping funnel over 20 minutes, followed by the addition of water (200 mL). The reaction mixture was then extracted with diethyl ether (3 x 50 mL), the combined organic extracts dried over magnesium sulfate, and the solvent removed in vacuo. The resulting residue was dissolved in pyridine (20 mL) and piperidine (0.96 g, 11.3 mmol) was added via syringe. After the addition of paraformaldehyde (2.81 g, 93.5 mmol), the reaction mixture was brought to reflux for 90 minutes. When cool, water (200 mL) and pentane (100 mL) were added to the reaction mixture and the layers were separated. The organic phase was washed sequentially with water (50 mL) and 10% hydrochloric acid solution (50 mL) until the pH of the aqueous washings was ~3. The organic phase was washed further with water (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL) before being dried over magnesium sulfate. After removing the solvent in vacuo, the resulting clear, colourless oil (10.03 g) was shown by $^1$H NMR to be a 7:3 mixture of methyl isopropylacrylate : 63 (product:SM). This mixture was immediately cooled to 0 °C** and bromine (12.51 g, 78.3 mmol) was added in portions over one hour. The reaction mixture was then warmed to room temperature and stirred for 2 hours. After cooling again to 0 °C, sodium methoxide (12.69 g, 234.9 mmol), as a 25% w/w solution in methanol, was then added in portions over 45

** If the methyl isopropylacrylate is to be stored for a period, 100 ppm hydroquinone should be added as a polymerization inhibitor.
minutes. The reaction mixture was warmed to room temperature and stirred overnight. Glacial acetic acid (4.61 mL, 78.3 mmol) was added to the reaction flask, followed by 0.5 hours of stirring. The reaction mixture was concentrated, and diethyl ether (500 mL) was added. The resulting slurry was filtered through celite, rinsing several times with diethyl ether. After concentrating the solution to ~200 mL, it was washed with water (100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic phase was dried with magnesium sulfate and concentrated in vacuo to yield 65 (5.69 g, 27%) as a clear colourless oil whose spectral properties corresponded to literature values. $^1$H NMR (CDCl$_3$, 200 MHz) δ 4.60 (d, $J = 8.2$ Hz, 1H), 3.77 (s, 1.5H), 3.76 (s, 1.5H), 3.65 (s, 1.5 Hz), 3.64 (s, 1.5 Hz), 3.33 (s, 1.5 Hz), 3.30 (s, 1.5 Hz), 2.63 (dd, $J = 6.1$, 8.4 Hz, 1H), 1.93-2.10 (m, 1H), 0.94 (d, $J = 7.3$ Hz, 3H), 0.91 (d, $J = 7.3$ Hz, 3H).

2-(1-Isopropyl-1-methoxycarbonylbut-3-enyl)-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid diethyl ester

![](image)

To a 10 mL flask equipped with a water-cooled condenser was added 56 (0.100 g, 0.243 mmol) in toluene (3 mL). Allyltributyl tin (0.161 g, 0.486 mmol) was added via syringe, followed by benzoyl peroxide (0.012 g, 0.0486 mmol). The reaction mixture was refluxed overnight, until deemed complete by TLC. After cooling to room temperature, it was loaded directly onto a column and purified via gradient flash column chromatography (95:5 → 80:20 hexanes-ethyl acetate) to afford # (0.086g, 95%), a pale yellow viscous oil, as a 0.6:0.4
mixture of diastereomers. For characterization purposes, 66 was purified by preparatory TLC (3:1 hexanes-ethyl acetate). IR (thin film) 3076, 2960, 1739, 1638, 1465, 1445, 1373, 1220, 1116, 1028, 962, 912, 860 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.91-6.06 (m, 1H), 5.58 (s, 0.4H), 5.53 (s, 0.6H), 4.93-5.04 (m, 2H), 4.72-4.73 (?): 4.60-4.64 (?), 4.21-4.30 (m, 4H), 3.71 (?), 3.70 (?), 2.50-2.70 (m, 2H), 2.17-2.29 (m, 1H), 1.28-1.33 (m, 6H), 0.95-1.04 (m, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 172.80 (C), 172.73 (C), 169.89 (C), 169.86 (C), 168.40 (C), 168.15 (C), 135.66 (CH), 116.35 (CH₂), 116.26 (CH₂), 108.39 (CH), 108.33 (CH), 77.43 (CH), 76.97 (CH), 76.60 (CH), 76.06 (CH), 61.89 (CH₂), 61.86 (CH₂), 61.82 (CH₂), 55.57 (C), 55.15 (C), 51.63 (CH₃), 51.58 (CH₃), 33.87 (CH₂), 32.92 (CH₂), 32.16 (CH), 31.66 (CH), 18.59 (CH₃), 18.30 (CH₃), 18.22 (CH₃), 18.08 (CH₃), 14.09 (CH₃), 14.07 (CH₃); MS (Cl/iso) m/z 373 (MH⁺).

(S,S)-1,2-Diphenyl-1,2-ethanediol bis(trimethylsilyl) ether³³

![Chemical Structure](image)

To a 10 mL flask containing (S,S)-hydrobenzoin (0.100 g, 0.467 mmol) in anhydrous dichloromethane (5 mL) was added triethylamine (0.109 g, 1.074 mmol), followed by the addition of chlorotrimethylsilane (0.127 g, 1.168 mmol). After stirring at room temperature for 3 hours, hexanes (15 mL) and ethyl acetate (5 mL) were added sequentially, resulting in the formation of a white precipitate. The solid powder was removed by suction filtration and the filtrate was concentrated. To the resulting residue was added hexanes (20 mL) and ethyl acetate (1 mL). The mixture was filtrated again and the filtrate concentrated in vacuo to afford 73 (0.157 g, 94%) as a white solid, whose spectral properties matched those in the literature.³³ ¹H NMR (CDCl₃, 200 MHz) δ 7.04-7.16 (m, 10H), 4.64 (s, 2H), -0.09 (s, 18H).
(R,R)-N,N'-Dibenzyl-N,N'-ethylenetramide\textsuperscript{35}

![Image of molecule 74]

To a 50 mL flask equipped with a water-cooled condenser was added 77 (0.400 g, 0.904 mmol) in a mixture of glacial acetic acid (12 mL) and distilled water (4 mL). The reaction mixture was refluxed overnight, until deemed complete by TLC. After cooling to room temperature, the solution was concentrated and azeotroped with toluene (2 x 10 mL). The solid yellow residue was then recrystallized using chloroform-ethanol (2:1) to afford 25 (0.273 g, 85%) as shiny white crystals, whose spectral properties corresponded to literature values.\textsuperscript{35} \textsuperscript{1}H NMR (CDCl$_3$, 200 MHz) \textsuperscript{d} 7.15-7.32 (m, 10H), 4.21 (s, 2H), 4.15 (d, $J = 14.1$ Hz, 2H), 3.99 (d, $J = 14.3$ Hz, 2H), 3.63-3.77 (m, 2H), 3.37-3.58 (m, 2H).

2-Phenyl-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid dimethyl ester

![Image of molecule 75]

To a 1000 mL flask containing benzaldehyde (15.00 g, 141.4 mmol) in anhydrous benzene (500 mL) was added trimethylorthoformate (15.50 g, 155.5 mmol) and camphor sulfonic acid (0.300 g, 1.29 mmol). After being stirred at room temperature for 1 hour, (L)-dimethyl
tartrate (27.70 g, 155.5 mmol) was added and the reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (for setup, see diagram for 7). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed overnight, until reaction was deemed complete by TLC. The reaction mixture was cooled to room temperature and washed sequentially with saturated sodium bicarbonate solution (150 mL), water (150 mL), and brine (150 mL). After drying over magnesium sulfate, the solvent was removed in vacuo to afford crude 75 (26.99 g, 72%) as an extremely viscous amber oil whose spectral properties corresponded to those in literature.\(^{38}\) \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 7.53-7.58 (m, 2H), 7.36-7.40 (m, 3H), 6.12 (s, 1H), 4.97 (d, \(J = 3.9\) Hz, 1H), 4.85 (d, \(J = 4.1\) Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H).

**2-Phenyl-[1,3]-dioxolane-(R,R)-4,5-dicarboxylic acid\(^{35}\)**

![Chemical Structure](image)

To a 250 mL flask containing 75 (4.76 g, 17.9 mmol) in methanol (75 mL) was added potassium hydroxide (4.11 g, 73.3 mmol) in 35 mL water. After stirring for 3 hours at room temperature, the reaction was deemed complete by TLC. Following the removal of methanol in vacuo, potassium dihydrogenphosphate (4.30 g, 31.6 mmol) was added to the reaction mixture with continuous stirring. The aqueous solution was then acidified (pH ~ 3) with concentrated hydrochloric acid and was extracted with ethyl acetate (3 x 100 mL). After drying over sodium sulfate, the solvent was removed in vacuo to afford 76 (4.23 g, 99%) as a white powder whose spectral properties corresponded to those in literature.\(^{35}\) \(^1\)H NMR
(acetone-$d_6$, 200 MHz) $\delta$ 7.61-7.66 (m, 2H), 7.38-7.45 (m, 3H), 6.11 (s, 1H), 5.04 (d, $J = 3.9$ Hz, 1H), 4.92 (d, $J = 3.9$ Hz, 1H).

2,3-Benzylidene-(R,R)-N,N'-dibenzyl-N,N'-ethylenetartramide$^{35}$

![Chemical structure](image)

To a two-necked 500 mL flask equipped with a water-cooled condenser was added N-methyl-2-chloropyridinium iodide in 135 mL anhydrous chloroform. After bringing the solution to reflux, a solution of 76 (2.00 g, 8.40 mmol), dibenzylethlenediamine (2.02 g, 8.396 mmol), and triethylamine (5.10 g, 50.38 mmol) in chloroform (135 mL) was added via syringe pump over 5 hours while continuously refluxing the reaction mixture. The reaction mixture was refluxed overnight, after which it was cooled to room temperature and washed sequentially with saturated sodium bicarbonate (200 mL), and water (2 x 200 mL). The organic phase was dried over magnesium sulfate and concentrated in vacuo to afford a sticky, orange solid. This was dissolved in dichloromethane (10 mL) and filtered through a small pad of silica, using ethyl acetate-hexanes (3:1) (1000 mL) as eluant. This was concentrated in vacuo to give a yellow foam which was recrystallized by dissolving in a minimal amount of hot dichloromethane and gradually adding hexanes dropwise until crystallization ensued. The crystals were obtained via suction filtration, rinsing several times with cold hexanes. After being dried in vacuo, 77 (1.03 g, 28%) was obtained as white needles whose spectral properties corresponded to those in literature.$^{35}$ $^{1}$H NMR (CDCl$_3$, 200
MHz) δ 7.66-7.70 (m, 2H), 7.33-7.39 (m, 3H), 7.21-7.26 (m, 10H), 6.20 (s, 1H), 4.93 (d, J = 6.3 Hz, 1H), 4.79 (d, J = 6.4 Hz, 1H), 4.67 (d, J = 14.3 Hz, 2H), 4.42 (d, J = 14.4 Hz, 2H), 3.13-3.35 (m, 4H).
B. Applications of Chiral Hydrazide Organocatalysts to Diels-Alder, Hydride Reduction, and α-Chlorination Reactions

1. Introduction

1.1 Asymmetric Organocatalysis

The use of small organic molecules to increase the rate of reactions is by no means a novel concept for synthetic organic chemists. On the other hand, significant interest in organic molecules that catalyse reactions asymmetrically has only blossomed in the past five years.\(^{39}\) Although an intriguing asymmetric intramolecular aldol reaction catalysed by (S)-proline 79 was reported independently by two groups in the early 1970s, both interest and significant advances in this area were slow to develop. This organocatalytic cyclization, known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, produced bicyclic ketones in good to excellent enantiomeric excesses (Scheme 40).\(^{40}\)

Scheme 40. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

This success notwithstanding, until recently asymmetric catalysts were usually metal-based, employing organic molecules as ligands. Although several of these methodologies are extremely useful and reliable, the use of metals in the pharmaceutical industry poses some problems. For toxicity reasons, metal impurities must be thoroughly removed and this
process is often quite difficult. Consequently, it is not surprising that asymmetric organocatalysis has finally become a major research area in synthetic organic chemistry.

Some examples of different organocatalysts and their respective mechanistic modes of actions are shown in Scheme 41. Using the tert-leucine-derived carbene precursor 83, Enders and Kallfass were able to perform the enantioselective benzoin condensation of benzaldehyde, producing 84 in quantitative yield and very good enantiomeric excess. Metzner and coworkers were able to form the enantioenriched epoxide 86 via a chiral sulfonium-ylide intermediate. Finally, asymmetric phase-transfer catalysis utilizing the spiroammonium catalyst 89 resulted in an enantioselective Michael addition of the glycine Schiff base 87 to the α,β-unsaturated ester 88.
Scheme 41. Examples of asymmetric organocatalysts.

(a) Carbene Catalysis:

(b) Sulfur-ylide Catalysis:

(c) Phase-Transfer Catalysis:

The above examples illuminate the great deal of effort that has been put forth of late in the field of asymmetric organocatalysis. Perhaps the most interest, however, has been directed towards secondary amine catalysts.
1.2 Chiral Secondary Amine Organocatalysts

Secondary amines have the ability to catalyze a wide variety of reactions involving carbonyl compounds. With the loss of water, a secondary amine, along with an acid co-catalyst, will react with a carbonyl group to form an iminium species (Scheme 42). The iminium is more reactive than the parent carbonyl compound in a variety of reactions, which will be discussed shortly. If the iminium possesses an enolizable proton, the reversible formation of an enamine can occur. Enamines are electron-rich at the α-carbon and thus, will react with electrophiles at this position.

Scheme 42. Iminium and enamine formation.

When an iminium forms from a secondary amine and an α,β-unsaturated carbonyl compound, its effect is to lower the energy of the LUMO of this conjugated system (Figure 20). This is also what is seen when a Lewis acid is added to an α,β-unsaturated carbonyl compound. Generally speaking, if the α,β-unsaturated carbonyl is the “electrophilic” component of a reaction, then the overlap between its LUMO and the HOMO of the “nucleophilic” component will be greater, thus resulting in a stabilizing effect.
Figure 20. Effects of an iminium ion on the LUMO energy and molecular orbital overlap energy of an $\alpha,\beta$-unsaturated carbonyl compound.

When the secondary amine is chiral, the resulting iminium ion may react asymmetrically to form stereoenriched products. Asymmetric iminium catalysis has been used in a wide variety of reactions involving $\alpha,\beta$-unsaturated carbonyl compounds including Diels-Alder$^{44}$ and [3+2] cycloadditions,$^{45}$ hydride reductions$^{46}$ and Friedel-Crafts alkylation.$^{47}$
As mentioned above, the reversible formation of an enamine from a carbonyl compound bearing an acidic α-proton allows the α-carbon to act as a nucleophile with various electrophiles (Scheme 43). Once again, if the secondary amine is chiral, these reactions may behave stereoselectively.

**Scheme 43. Electrophilic addition to an enamine.**

Aldol reactions, α-halogenations, and Mannich reactions, amongst many other synthetic transformations, have been rendered stereoselective via asymmetric enamine organocatalysis.

Two examples of asymmetric iminium catalysis: the Diels-Alder reaction and hydride reduction; as well as one example of enamine catalysis: α-halogenation of carbonyl compounds; will presently be discussed in detail.

### 1.3 Asymmetric Iminium Catalysis

**a) The Diels-Alder Reaction**

Although asymmetric organocatalysis of the Diels-Alder reaction using cinchona alkaloids had been reported as early as 1989, it was not until the introduction of MacMillan’s chiral imidazolidinone catalyst 91 in 2000 that stereoselectivities reached levels of synthetic utility.
MacMillan reported enantioselectivities of 83-96% in the Diels-Alder reaction of α,β-unsaturated aldehydes and dienes using 91 in the presence of hydrochloric acid as a co-catalyst (Table 7).

**Table 7. Highly enantioselective organocatalytic Diels-Alder reaction using MacMillan’s chiral imidazolidinone 91.**

<table>
<thead>
<tr>
<th>Diene</th>
<th>R</th>
<th>Major Product</th>
<th>Yield (%)</th>
<th>exo:endo</th>
<th>ee (major) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ph</td>
<td><img src="image" alt="Ph" /></td>
<td>99</td>
<td>1.3:1</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td><img src="image" alt="Me" /></td>
<td>75</td>
<td>n/a</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td><img src="image" alt="H" /></td>
<td>72</td>
<td>1:11</td>
<td>85</td>
</tr>
</tbody>
</table>

The catalytic cycle of the imidazolidinone-catalyzed Diels-Alder reaction is believed to proceed as shown in Figure 21. With the loss of water, the iminium is formed from the α,β-unsaturated aldehyde and the imidazolidinone 91 with the aid of the Brønsted acid co-catalyst. The [4+2] cycloaddition then occurs, followed by hydrolysis of the iminium ion which produces the cycloadduct and regenerates the imidazolidinone 91 and the acid co-catalyst. It
has been suggested that the rate-determining step of the cycle is the formation of the iminium ion,\textsuperscript{47b} although kinetic studies have not yet been reported.

**Figure 21. Catalytic cycle of imidazolidinone-catalyzed Diels-Alder reaction.**

The enantioselectivity of MacMillan’s organocatalytic Diels-Alder reaction is believed to be directly related to control of iminium geometry.\textsuperscript{44a} If the conformation and stereochemistry of the iminium ion is relatively fixed in the transition state for the cycloaddition, attack of the diene component may preferentially take place on one face of the $\alpha,\beta$-unsaturated species, resulting in an enantioselective reaction. The ground state geometry of the iminium ion is used to shed light on the geometry of the transition state. Although this assumption violates the Curtin-Hammett principle, it is widely used in the literature. It is most likely accepted
due to its accuracy in predicting the sense (e.g. \( R \) or \( S \)) of the stereoselectivity. For example, using computational chemistry methods, MacMillan and coworkers found that the iminium formed from propenal and 91 existed in the ground state conformation shown in Scheme 44.\(^{44a}\) The benzyl group on the iminium should selectively shield the top face of the dienophile from attack by the diene, resulting in the observed \((R)\)-enantioenriched cycloadduct.

**Scheme 44. Proposed source of enantioselectivity in MacMillan and coworkers’ organocatalytic Diels-Alder reaction.**

Kozlowski and Panda’s computational chemistry modeling of the transition state of the organocatalytic Diels-Alder reaction between \((E)\)-crotonaldehyde or \((E)\)-cinnamaldehyde and cyclopentadiene helped support the validity of using the ground state of the iminium ion to approximate the lowest energy transition state.\(^{52}\) In addition, they also found that the iminium existed in a conformation similar to that shown in Scheme 44. They suggested that a \(\pi-\pi\) interaction between the phenyl ring of the benzyl group and the olefin on the iminium ion helps to stabilize the transition state.

Interestingly, Houk and coworkers’ calculations revealed a different geometry for the most stable iminium ion.\(^{53}\) Although the \((E)\)-iminium was still found to be in the \(s\)-trans conformation, the benzyl group was not positioned over the olefinic component, but was instead over the imidazolidinone ring. Houk suggested that a \(\text{C-H} \cdots \pi\) interaction between the methyl group on the imidazolidinone ring and the phenyl ring of the benzyl group renders this conformation more stable (Figure 22). It is noteworthy to mention, however, that Houk
found that the ground state iminium conformation suggested by MacMillan and Kozlowski was only 0.5 kcal/mol higher in energy than the lowest energy conformation.

**Figure 22. Houk and coworkers lowest energy iminium geometries.**

Kinsman and Kerr successfully applied MacMillan’s methodology to the total synthesis of the natural product (+)-hapalindole Q (Scheme 45). Although the cycloaddition proceeded in only 35% yield and modest diastereoselectivity, the desired *endo* cycloadduct 94 was produced in 93% enantiomeric excess. Nine synthetic steps later, (+)-hapalindole Q was formed in 93% enantiomeric excess.
Scheme 45. Kinsman and Kerr’s total synthesis of (+)-hapalindole Q using MacMillan’s asymmetric organocatalytic Diels-Alder methodology.

Recently, MacMillan and coworkers reported a highly enantioselective Diels-Alder reaction with α,β-unsaturated ketones. Due predominantly to the lack of stereocontrol in the formation of Lewis acid-activated ketones (Scheme 46), few examples of asymmetric Diels-Alder reactions with α,β-unsaturated ketones are known.
Scheme 46. Selectivity in the Diels-Alder reaction of $\alpha,\beta$-unsaturated aldehydes versus ketones.

MacMillan and Northrup reported that although the use of catalyst 91 resulted in poor yields and enantioselectivities, a derivative of 91, imidazolidinone 95, generally gave very good yields, and excellent diastereoselectivities and enantioselectivities (Table 8).
Table 8. MacMillan’s enantioselective organocatalytic Diels-Alder reaction with \(\alpha,\beta\)-unsaturated ketones.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Diene</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>Major Product</th>
<th>Yield (%)</th>
<th>(endo:exo)</th>
<th>ee (major) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Me</td>
<td>Et</td>
<td>[Structure]</td>
<td>89</td>
<td>25:1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>(n)-Pr</td>
<td>Et</td>
<td>[Structure]</td>
<td>84</td>
<td>15:1</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>Et</td>
<td>[Structure]</td>
<td>88</td>
<td>&gt;200:1</td>
<td>96</td>
</tr>
</tbody>
</table>

Via computational chemistry methods, MacMillan and coworkers found that the \((Z)\)-iminium was favoured over the \((E)\)-iminium (Scheme 47). In addition, both faces of the \((E)\)-iminium are shielded from attack by the diene. Bottom face attack on the \((Z)\)-iminium by the 1,3-diene resulted in the observed stereochemistry of the major product.
Scheme 47. \((E)\)- and \((Z)\)-iminium geometries from ethyl vinyl ketone and 95.

Houk and coworkers’ computational chemistry calculations agree with MacMillan’s results for the minimum energy conformations of both the \((E)\)- and \((Z)\)-iminiums.\(^{53}\) They also support the proposal that the \((Z)\)-iminium is of slightly lower energy (0.4 kcal.mol) than the \((E)\)-iminium. Houk suggests that the benzyl ring is positioned over the olefinic moiety rather than over the imidazolidinone ring because the latter conformation is destabilized by a repulsive interaction between the benzene ring and the oxygen lone pair on the furan ring.

The uses of MacMillan’s chiral imidazolinone catalysts extend well beyond the Diels-Alder reaction.\(^{47,49a,56}\) One application is the asymmetric hydride reduction of \(\alpha,\beta\)-unsaturated aldehydes.\(^{46a}\)
(b) Hydride Reduction of $\alpha,\beta$- Unsaturated Aldehydes

The conversion of $\alpha,\beta$-unsaturated carbonyl compounds to their saturated counterparts is, no doubt, a synthetically useful reaction. If the $\beta$-position is disubstituted, an asymmetric hydrogenation would result in the production of a chiral centre at that position (Scheme 48). Unfortunately, since reduction of both the alkene moiety and the carbonyl group is possible, chemoselectivity in this reaction is often low. In addition, other functional groups (e.g. benzyloxy, nitro, or nitrile groups) that may be on the substrate are not typically tolerated in catalytic hydrogenation conditions. Thus, an improved process to chemoselectively reduce the olefinic component of $\alpha,\beta$-unsaturated carbonyl compounds would be a valuable methodology.

Scheme 48. Chemoselective reduction of $\alpha,\beta$- unsaturated carbonyl compounds.

In 2004, List and coworkers reported an organocatalytic transfer hydrogenation of $\alpha,\beta$-unsaturated aldehydes.\textsuperscript{57} This involved the conjugate addition of a hydride equivalent from the Hantzsch ester 98 to an iminium ion formed from the aldehyde 96 and dibenzylammonium trifluoroacetate. Very good to excellent yields were reported. In addition, nitro, benzyloxy, and nitrile groups were tolerated, as well as alkenes that were not conjugated to the aldehyde (Scheme 49).
Scheme 49. List and coworkers’ chemoselective organocatalytic transfer hydrogenation of α,β-unsaturated aldehydes.

The catalytic cycle of the organocatalytic hydride reduction, pictured in Figure 23, proceeds as follows. First, the reactive iminium ion 100 is formed from the trifluoroacetate salt of the secondary amine 97 and the α,β-unsaturated aldehyde 96. The β-position is now more activated for nucleophilic attack than it was on the parent aldehyde 96. The Hantzsch ester 98 reduces the iminium and is oxidized to the stable tetra-substituted pyridine 101. Hydrolysis of the iminium 102 releases the reduced aldehyde 99 and regenerates the amine catalyst 97.
Figure 23. Catalytic cycle of the organocatalytic reduction of $\alpha,\beta$-unsaturated aldehydes.

Not long after, two asymmetric versions of the organocatalytic reduction of $\alpha,\beta$-unsaturated aldehydes were reported by the List and MacMillan groups. Both achieved excellent yields and enantioselectivities using chiral imidazolidinone catalysts, although List’s methodology generally required a lower catalyst loading (Scheme 50).
Scheme 50. MacMillan and List’s methodologies for the asymmetric organocatalytic reduction of $\alpha,\beta$-unsaturated aldehydes.

The enantioselectivity of the hydride reduction is believed to arise from a facially-biased attack of the Hantzsch ester (98 or 105) on the iminium ion. List’s depiction of the transition state leading to the major product is shown in Figure 24. Due to the benzyl and tert-butyl groups positioned over top of the olefin, hydride delivery must occur from the bottom face of the iminium, leading to formation of the major product. It is assumed that the reduction catalysed by the imidazolidinone 104 occurs via a similar transition state.
Both groups observed a highly interesting phenomenon during their studies: List and MacMillan found that the geometry of the olefin of the α,β-unsaturated aldehyde did not affect the extent or sense of stereoselectivity. In fact, mixtures of (E) and (Z) isomers would give virtually the same enantioselectivity as stereopure (E)- or (Z)- olefins. As shown in Scheme 51, List demonstrated that whether the aldehyde 106 is pure (E)-, (Z)-, or a 1:1 mixture of the stereoisomers, the selectivity for the (R)-enantiomer of 107 remained the same.

Scheme 51. Enantioconvergence in the reduction of α,β-unsaturated aldehydes.

Both List and MacMillan suggested that there is rapid isomerism between the (E) and (Z) iminiums prior to hydride reduction. As shown in Scheme 52, the initial iminium (E)-108, formed from the condensation of the imidazolidinone 104 and the aldehyde (E)-106, can
isomerize to the iminium (Z)-108 via the enamine 109. In this case, the rate of the hydride reduction of (E)-108 (k_{(E)}) is assumed to be faster than the rate of the reduction of (Z)-108 (k_{(Z)}), so the aldehyde (R)-107 is formed as the major product.

Scheme 52. Explanation for enatioconvergence in the organocatalytic reduction.

Although neither List nor MacMillan have suggested an explanation for the difference in reaction rates, the enatioconvergent quality of this reaction is a vast improvement over
typical hydrogenations, in which the olefin geometry generally determines enantiospecific reductions. In sum, List and MacMillan’s enantioconvergent and chemoselective organocatalytic hydride reductions of α,β-unsaturated olefins are useful additions to the synthetic organic chemist’s arsenal.

1.4 Asymmetric Enamine Catalysis: α-Halogenation of Aldehydes

Halogenated compounds are extremely useful intermediates in synthetic organic chemistry. They are used in a wide variety of reactions, including the ubiquitous elimination and nucleophilic substitution reactions, organometallic coupling reactions, and the Reformatsky reaction, amongst many others. In addition to their use as intermediates in synthesis, halogenated compounds can be targets themselves. For example, fluorine is considered to be an isostere of hydrogen and is sometimes used in place of it in pharmaceutical compounds in order to change the metabolic or electronic properties of the drug without affecting steric.

Chlorine is also occasionally used as an isostere for methyl groups.

It is often synthetically useful to be able to make halogenated compounds in enantiopure form. Unfortunately, not many methods are known in which a halogen atom is introduced in a stereoselective manner. Recently, the MacMillan and Jørgensen groups have reported organocatalytic enantioselective α-chlorinations of aldehydes (Scheme 53). Both methodologies employed a chiral secondary amine to catalyze the asymmetric halogenation. MacMillan used his chiral imidazolidinone 91 and Jørgensen, the C2-symmetric pyrrolidine 113. MacMillan employed the quinone 111 as the chlorinating agent, while Jørgensen used N-chlorosuccinimide. Both achieved very good to excellent enantioselectivities and good yields, with the exception being Jørgensen’s synthesis of 112 (R = t-butyl) which gave only a 30% yield of product. Other than this case, all yields reported were over 70%. Although Jørgensen’s methodology required twice the catalyst loading of MacMillan’s (10 versus 5 mol%), the latter methodology necessitated lower temperatures.
Scheme 53. MacMillan’s and Jørgensen’s α-chlorination of aldehydes.

MacMillan and coworkers demonstrated the chemoselectivity of the α-chlorination, in that ketone functional groups were tolerated and not α-chlorinated themselves. In addition, both methodologies show a tolerance towards olefins and aromatic groups.

Although detailed mechanistic studies have not yet been disclosed, MacMillan suggests that the organocatalytic chlorination occurs via an enamine intermediate. The proposed catalytic cycle, shown below in Figure 25, begins with the condensation of the aldehyde 110 and the chiral imidazolidinone 91 to form the iminium 114. The iminium then isomerizes to give the protonated enamine 115 which attacks the quinone 111. The stable perchlorinated phenol 116 is expelled and the chlorinated iminium 117 is hydrolysed to release the α-chlorinated aldehyde 112, regenerating the organocatalyst 91.
Figure 25. Proposed catalytic cycle of the organocatalytic α-chlorination of aldehydes.

Although no model currently exists to explain the stereoselectivity of either Jørgensen’s or MacMillan’s α-chlorination methodologies, MacMillan did suggest a chair-like transition state for the chlorination (Figure 26).
Figure 26. Proposed transition state for the α-chlorination reaction.††

It is noteworthy to mention that Jørgensen reported the conversion of the α-chloro aldehydes 112 into a variety of products without any loss of optical purity (Scheme 54). Enantioenriched amino esters 120, amino alcohols 123, and terminal epoxides 122 were synthesized via simple synthetic transformations. The synthesis of these chiral building blocks illustrates the utility of the asymmetric organocatalytic α-chlorination of aldehydes.

†† For simplicity, the chiral imidazolidinone 91 has been replaced by pyrrolidine.
Scheme 54. Synthetic transformations of α-chloro aldehydes.

Very recently, both MacMillan\(^6\) and Barbas\(^5\) reported the enantioselective organocatalytic α-fluorination of aldehydes. Both groups obtained moderate to excellent yields and enantioselectivities using the imidazolidinone catalyst 123. Notable examples of MacMillan’s results are displayed in Scheme 55. A model explaining the stereoselectivity of the α-fluorination has not yet been reported, but MacMillan proposes that it proceeds via an enamine intermediate and a transition state similar to that shown in Figure 26.
Scheme 55. MacMillan’s asymmetric organocatalytic $\alpha$-fluorination of aldehydes.

The $\alpha$-chlorination and $\alpha$-fluorination reactions are excellent examples of the utility of chiral secondary amine catalysis. A better understanding of the mechanisms of these reactions will no doubt result in further organocatalyzed $\alpha$-substitution reactions of carbonyl compounds.

1.5 Objective

With the exception of MacMillan’s imidazolidinone catalysts (91, 95, 103, 104, 118) and perhaps proline, no other catalyst class has achieved excellent enantioselectivities in such a variety of synthetic transformations. However, a shortcoming of MacMillan’s chiral imidazolidinones is that often lengthy reaction times are required for complete conversion. For example, up to 4.5 days are necessary for some Diels-Alder reactions with $\alpha,\beta$-unsaturated ketones. A potential way of decreasing reaction time and increasing catalyst turn-over number (TON) is to accelerate the rate-limiting step of the catalytic cycle of the reaction in question.

As mentioned previously, it has been suggested that the rate-limiting step of secondary amine-catalyzed reactions may be the initial formation of the iminium ion (see catalytic cycles in Figures 21, 23, and 25). One method by which to increase the rate of formation of
the iminium would be to increase the nuclephilicity of the amine nitrogen atom. In hydrazine molecules, the α-nitrogen atom should have increased nucleophilicity as compared to a secondary amine due to the α-heteroatom effect.\textsuperscript{43,62}

When a nucleophilic atom is bound to an atom possessing a lone pair of electrons and the orbital containing this lone pair is able to overlap with the orbital containing the nucleophilic electrons, a splitting in energy is observed (Figure 27a). This raises the energy of the HOMO of the hydrazine relative to a secondary amine, which allows for better overlap between the hydrazine HOMO and the carbonyl LUMO (Figure 27b).

Figure 27. (a) The α-heteroatom effect in hydrazines. (b) Enhanced stabilization energy in reaction of hydrazine with a carbonyl compound compared to a secondary amine with the same compound.

We wished to design a potential organocatalyst bearing a hydrazine functionality, rather than the secondary amine seen in both MacMillan’s imidazolidinone catalysts and proline. In addition to the hydrazine functionality, the design of our catalyst would incorporate a few other key features. Firstly, the α-effect would be attenuated somewhat by the attachment of a carbonyl group to one of the nitrogens, making the catalyst a hydrazide. This was to ensure that the rate of hydrolysis of the iminium ion would still be swift. We also endeavoured to place the hydrazide functionality in a five-membered ring, based on the observation that both MacMillan’s catalysts and proline have the nucleophilic nitrogen embedded in a ring of that size. Finally, we would place a chiral centre α- to the nucleophilic nitrogen, whose optical
rotation should determine the sense of the selectivity. Since MacMillan has had significant success with a benzyl group at this position, our hypothetical catalyst would have this feature, as well.

**Figure 28. Hypothetical hydrazide catalyst.**

We wished to initially investigate the ability of the hydrazide to asymmetrically catalyze the Diels-Alder reaction. If success was achieved in this transformation, we would attempt the catalysis of other reactions, such as hydride reduction of α,β-unsaturated aldehydes and α-chlorination of aldehydes.
Chapter 2. Results and Discussion

2.1 Synthesis of Potential Hydrazide Catalyst 124 and the Diels-Alder Reaction

Since we envisioned that the chiral synthesis of the hydrazide 124 may not be trivial, we decided to first attempt the synthesis of the racemate. If good yields and rates were achieved using racemic 124, then a synthetic route to chiral 124 would be planned.

The racemic synthesis of 124 went smoothly in two steps (Scheme 56). Phenyl acetaldehyde was subjected to a Horner-Wadsworth-Emmons reaction using triethylphosphonoacetate to give the α,β-unsaturated ester in 93% yield. The ester was then heated in the presence of hydrazine monohydrate to form the racemic cyclic hydrazide 124 in good yield.

Scheme 56. Synthesis of racemic hydrazide 124.

The ability of 124 to catalyze the Diels-Alder reaction between cyclopentadiene and (E)-cinnamaldehyde was then tested. Using perchloric acid as co-catalyst, the reagents and catalysts were dissolved in a 9:1 methanol-water solution and the reaction was allowed to proceed for twenty-four hours. After this time, the extent of conversion, as well as the endo:exo ratio, were measured by 1H NMR.

Using 20 mol% catalyst, but no perchloric acid co-catalyst, negligible cycloaddition product was formed (Table 9, Entry 1). This was expected since the activated iminium ion would be slow in forming with no Brønsted acid present. In the absence of hydrazide 124, but with 20 mol% perchloric acid, the endo:exo ratio was 1.13:1 and the % conversion was only 7%
(Entry 2). This demonstrates that the perchloric acid alone is not an efficient catalyst of the cycloaddition. Unfortunately, trying both equimolar amounts of 124 and acid (Entry 3) and twice the amount of 124 than acid (Entry 4), resulted in a slight decrease in conversion. Thus, our catalyst was ineffective at significantly increasing the rate of the Diels-Alder reaction.

Table 9. Attempted 124-catalyzed Diels-Alder reaction and control experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol% 124</th>
<th>Mol% HClO₄</th>
<th>endo:exo</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>—</td>
<td>neg.</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.2</td>
<td>1.13:1</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
<td>1.3:1</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.1</td>
<td>1:1</td>
<td>2</td>
</tr>
</tbody>
</table>

We wondered if the free amide nitrogen was somehow interfering with the formation of the iminium ion. We decided to protect the amide nitrogen using a benzyl group via the synthesis shown in Scheme 57. The more nucleophilic nitrogen on 124 was first protected as a tert-butyl carbamate using Boc-anhydride to give 127 in 97% yield. The amide nitrogen was then benzylated using benzyl bromide to give 128. Finally, by treating 128 with trifluoroacetic acid, the nitrogen was deprotected to give 129, our proposed organocatalyst.
Scheme 57. Synthesis of the potential hydrazide catalyst 129.

As shown in Table 10, 129 was tested as an organocatalyst in the Diels Alder reaction between cyclopentadiene and (E)-cinnamaldehyde, using the same conditions employed for the testing of 124. The % conversion increased in almost all of the trials; however, it was still far from synthetically useful.

Table 10. Attempted 129-catalyzed Diels-Alder reactions and control experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol% 124</th>
<th>Mol% HClO₄</th>
<th>endo:exo</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>2:1</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.2</td>
<td>1:13:1</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.18</td>
<td>1:1:1</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.1</td>
<td>1:1:1</td>
<td>10</td>
</tr>
</tbody>
</table>
Our feelings of frustration were somewhat eased by the subsequent success of Mathieu Lemay, a PhD candidate in our laboratory. Lemay was inspired by the chiral hydrazides 131 (Figure 29) used by Yang and Chen\textsuperscript{63} as chiral auxiliaries in several stereoselective reactions, including diastereoselective allylation. These possessed a hydrazide moiety in a five-membered ring.

**Figure 29. The chiral hydrazides 131.**

![Image of chiral hydrazides 131]

The chiral hydrazides were easily synthesized in five steps from (+)-camphor sulfonic acid 132. Using the Bartlett and Knox’s procedure,\textsuperscript{64} (+)-ketopinoic acid was made by first converting 132 to the sulfonyl chloride, followed by its oxidation by potassium permanganate in aqueous base. The imine 134 was made via acid-catalyzed condensation of 133 with the appropriate alkyl hydrazine. Employing a Dean-Stark apparatus, 135 was produced by refluxing in high-boiling mesitylene. The imine double bond was then reduced using sodium cyanoborohydride in acidic conditions to form the chiral hydrazide derivatives 131.
Scheme 58. Synthesis of chiral hydrazide derivatives 131 from camphor sulfonic acid 132.

Lemay found that the chiral hydrazides 131 did in fact catalyze the Diels-Alder reaction efficiently and enantioselectively. The benzyl derivative (R = Bn) gave superior results. He was also surprised to see that enantioselectivity increased with decreasing pK_a of the acid co-catalyst, with triflic acid giving the largest enantiomeric excess.

A few examples of Lemay’s asymmetric Diels-Alder reaction are shown in Table 11. In general, good yields and enantioselectivities were achieved by performing the reaction in water, with a catalyst loading of 20 mol%. The use of water as solvent makes this methodology particularly appealing from an environmental perspective.
Table 11. Asymmetric catalysis of the Diels-Alder reaction by chiral hydrazide 136.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>R</th>
<th>Major Product</th>
<th>Yield (%)</th>
<th>exo:endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Ph</td>
<td></td>
<td>96</td>
<td>1.9:1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>i-Pr</td>
<td></td>
<td>84</td>
<td>2.6:1</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Ph</td>
<td></td>
<td>86</td>
<td>n/a</td>
<td>85</td>
</tr>
</tbody>
</table>

With this success, our attention was turned away from designing a novel chiral hydrazide catalyst to applying 136 to other synthetic transformations—specifically the hydride reduction of $\alpha,\beta$-unsaturated aldehydes.

2.2 Asymmetric Organocatalytic Hydride Reduction

We believed that chiral hydrazide 136 would be effective at asymmetrically catalyzing the hydride reduction of $\alpha,\beta$-unsaturated aldehydes after examining possible transition states for
the reaction. Like MacMillan, we used the geometry of the most stable iminium species to predict the geometry of the lowest-energy transition state.

Depending on the way in which the aldehyde approached the hydrazide 136, either the (E)- or the (Z)-iminium could form. Using 3-methyl-(E)-cinnamaldehyde 137, (E)-iminium 138 and (Z)-iminium 139 could be formed from condensation with 136, as shown in Scheme 59. Via an enamine species, 138 and 139 could isomerize to iminiums 140 and 141, respectively. Both 140 and 141 are expected to be destabilized relative to iminiums 138 and 139, which suffer from less A1,3-strain. Between 138 and 139, the (Z)-iminium 139 is expected to be the least stable due to steric interactions between the phenyl group and the hydrogen atom shown.
Scheme 59. Potential s-trans iminiums formed from condensation of 136 and 137.

For the most stable iminium species 138, there are two possible transition states (Scheme 60). Either the Hantzsch ester 98 could deliver the hydride equivalent from above the
conjugated iminium or from below. Attack from above is predicted to be hindered by the gem dimethyl groups on the camphor backbone. Thus, hydride delivery should occur selectively from the bottom, resulting in selectivity for the (R)-enantiomer of 142.

**Scheme 60. Transition states resulting in major and minor products.**

![Reaction Scheme]

Feeling confident concerning our hypothesis, we wished to first test the hydride reduction of α,β-unsaturated aldehydes on a simple substrate, thus we chose 3-methyl-(E)-cinnamaldehyde 137. Both MacMillan\(^{46a}\) and List\(^{46b}\) had reduced 137 in good yields and enantioselectivities, and it was also easily synthesized in three steps.

Using the procedure of Martín and coworkers,\(^{65}\) allylic alcohol 144 was synthesized in two steps from acetophenone (Scheme 61). First, a Horner-Wadsworth-Emmons reaction was carried out between acetophene and triethylphosphonacetetate to yield, after purification, the stereopure (E)-α,β-unsaturated ethyl ester 143 in modest yield. This was then reduced using DIBAL-H to the alcohol 144. Via a Swern reaction, 144 was oxidized to the (E)-α,β-unsaturated aldehyde 137 in excellent yield.
Scheme 61. Synthesis of hydride reduction substrate 137.

At this time, we could test the hydride reduction reaction. Since MacMillan had achieved very good yields and enantioselectivities in toluene, with TFA as co-catalyst, we decided to use these conditions. To simplify the procedure, we decided to run these initial trials at room temperature and for twenty-four hours. We would determine the percent conversion of the starting material 137 to the product 142 via $^1$H NMR and the enantiomeric excess via chiral GLC.

As shown in Table 12, using 20 mol% of 136 and TFA, we saw good conversion of 137 to 142 (Entry 1). We also observed some isomerisation of the (E)-stereoisomer of 137 to (Z)-137. Unfortunately, an enantiomeric excess of only 6% was observed. It can be seen from the control experiment without hydrazide 136, that the TFA co-catalyst alone did catalyze the reduction significantly (Entry 2). Since this acid-catalyzed background reaction would not be selective, it was possible that it was contributing to reducing the enantioselectivity, albeit to a small extent.

We decided to try a different acid, specifically triflic acid, since its use in Lemay’s Diels-Alder reaction (Section 2.1) had resulted in superior enantioselectivity. Although this change resulted in an increased conversion to product (98%), the enantioselectivity remained abysmal (Entry 3). Since the control reaction (Entry 4) showed very little conversion to
product 142, the triflic acid-catalyzed background reaction was certainly not contributing to our poor enantioselectivity.

Table 12. Investigating the ability of chiral hydrazide 136 to asymmetrically catalyze the reduction of 137.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol% 136</th>
<th>X</th>
<th>Mol% HX</th>
<th>% conversion to 142</th>
<th>% conversion to (Z)-137</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>CF₃COO</td>
<td>20</td>
<td>86</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>CF₃COO</td>
<td>20</td>
<td>20</td>
<td>9</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>CF₃SO₃</td>
<td>20</td>
<td>98</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>CF₃SO₃</td>
<td>20</td>
<td>5</td>
<td>17</td>
<td>n/a</td>
</tr>
</tbody>
</table>

While attempting to determine the cause of our low selectivity, we postulated that perhaps control of the iminium geometry was not as cut and dried as we had initially proposed in Scheme 59. Consequently, we decided to monitor iminium formation by ¹H NMR. In anhydrous deuterated benzene to simulate our reaction conditions, equimolar amounts of (E)-aldehyde 137, hydrazide 136, and triflic acid were dissolved and ¹H spectra were acquired at regular intervals.

During the fifteen minutes between preparing the NMR sample and running the first ¹H experiment, the iminium had formed completely. No peaks from either the catalyst 136 or
the aldehyde 139 were visible, including the CHO aldehyde peak. Lemay had also noted rapid formation of the iminium ion between 136 and (E)-cinnamaldehyde. In fact, he observed much faster iminium formation with hydrazide 136 than with MacMillan’s imidazolidinone species 91. Our observations, along with Lemay’s, supported our hypothesis that the rate of iminium formation is accelerated when using hydrazide catalysts.

The iminium species was monitored via $^1$H NMR at regular intervals for 135 minutes. There was no appearance of new peaks over time, nor were there any changes in chemical shift or relative integration of any peaks.

Simply by looking at the $^1$H NMR, it was evident that at least two iminiums had formed. Two sets of diastereotopic benzyl peaks (H$_A$, H$_A'$) could be seen, as well as two H$_B$ protons (Figure 30). Each “set” of peaks appeared to integrate for the same amount as the other (i.e. a possible 1:1 ratio of two iminium ions). However, “shoulders” could be seen on some of these peaks, indicating that more than one peak might actually be present at that chemical shift. Thus, at least two of the four iminiums shown in Scheme 59 were present in the reaction mixture. Since one major iminium species could not be identified, the spectrum was not interpreted further.

Figure 30. Highlighting specific protons on the iminium ion.

Since solvent choice may affect enantioselectivity, we decided to run a solvent scan on the hydride reduction of aldehyde 137 (Table 13). In general, more polar solvents (e.g. acetonitrile, DMF) gave higher enantioselectivities, while less polar solvents (e.g. THF,
chloroform, dichloromethane) gave greater conversion to product 142. In addition, a higher % conversion was generally accompanied by a lower or negligible enantiomeric excess and vice versa.

The lower conversion to product in polar solvents is most probably explained by the poor solubility of Hantzsch ester 98 in these solvents. This is supported by the observation that when the % conversion to 142 was low, the isomerism to (Z)-137 was high. This indicates that the iminium is readily formed in the polar solvents, but it often isomerizes and is hydrolysed before reduction can occur.

As for the higher enantioselectivity in acetonitrile and DMF, we wondered if more polar solvents allowed better control of iminium geometry than in benzene. We decided to look at the $^1$H NMR of the iminium in acetonitrile, since use of this solvent resulted in the largest enantiomeric excess (Entry 7).
Table 13. Effect of solvent on conversion and enantiomeric excess of hydride reduction.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>% conversion to 142</th>
<th>% conversion to (Z)-137</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₃</td>
<td>98</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>55</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>12</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>9</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>44</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>CHCl₃</td>
<td>47</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>CH₃NO₂</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>CH₃CN</td>
<td>12</td>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>i-PrOH</td>
<td>24</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

In fact, when equimolar amounts of hydrazide 136, aldehyde 137, and triflic acid were dissolved in deuterated acetonitrile, we observed a very different proton spectrum than in deuterated benzene. Initially, only one iminium ion could be observed and there was still unreacted 137 and 136 in solution. Over time, a second set of iminium peaks appeared and although the relative amount of starting materials 137 and 136 decreased somewhat, they did not disappear completely from the spectrum. After four hours, no new peaks appeared and
the relative integration of the peaks remained constant. The reaction was monitored for an additional ninety-five minutes to confirm that it had indeed reached equilibrium. At this time, the major iminium, minor iminium, and unreacted catalyst 136 existed in a 2.5: 1: 1.3 ratio. Since, unlike in benzene-\(d_6\), we had a definitive major iminium isomer, we decided to run \(^1\)H-\(^1\)H COSY and NOESY correlation experiments in an attempt to identify the structure of this isomer.

As shown in Figure 31, olefinic protons \(H_C\) and \(H_D\) were assigned, based on their chemical shift (8.14 and 6.66 ppm, respectively) and that they coupled with a frequency of 11.0 Hz. This coupling constant is indicative of protons at \(C_2\) and \(C_3\) of a 1,3-diene. \(H_C\) was assigned to the peak further downfield than \(H_D\), since \(H_C\) is attached to the deshielding iminium carbon.

**Figure 31. Highlighting specific protons on the iminium ion 138.**

The strong nOe interaction between \(H_D\) and both \(H_E\) and \(H_E'\), indicated that the major iminium was the \((E)-138\) rather than the \((Z)-139\) stereoisomer (Figure 32). This inference was also supported by the strong nOe interaction between \(H_C\) and \(H_A\) and \(H_{A'}\).
Figure 32. nOe correlations for iminium \((E)-138\) and structure of iminium \((Z)-139\).

The \((E)\)-isomer \(138\), rather than the isomerized \((E)\)-isomer \(140\) was assigned as the major isomer, due to additional nOe interactions (Figure 33). Proton \(H_C\) and the methyl group protons \((\text{CH}_3)^*\) displayed a strong nOe interaction. In addition, \(H_D\) interacted strongly with two of the protons on the conjugated phenyl group \(\text{Ph}^*\).

Figure 33. nOe correlations for iminium \((E)-138\) and structure of \((E)-140\).

The minor iminium isomer proved to be too difficult to accurately assign via NOESY or COSY experiments. It is postulated, however, that the minor iminium is the \((E)\)-iminium \(140\) which is produced from \(138\) via an enamine intermediate. This is hypothesized since the
$^1$H spectra showed that the (Z)-isomer of 137 was formed over time. The isomer (Z)-137 would have resulted from the hydrolysis of (E)-iminium 140 (Scheme 62).

Scheme 62. Hydrolysis of iminium (E)-140 to give (Z)-alkene 137.

The hydride reduction from the bottom face of iminium 140 would result in the (R)-enantiomer 142 being formed, rather than (S)-142 from iminium 138 (Scheme 63). In fact, the ratio of major:minor iminium isomers at equilibrium (2.5:1) is approximately the same as the enantiomeric ratio of the hydride reduction in acetonitrile (39% ee = 2.3:1 er). The iminium isomerism may indeed have been the cause of the poor enantioselectivity we had observed.
Scheme 63. Hydride reduction from the bottom face of (E)-iminiums 138 and 140.

That being said, the benzyl $^1$H peaks ($H_A$, $H_A'$) of the minor iminium isomer appeared to have “shoulders,” indicating that, in actuality, there may be minor isomers, such as the (Z)-iminium isomer 139. Although trying to prevent the enamine-derived isomerism seemed beyond our capabilities, hindering the formation of the (Z)-iminium isomer seemed an attainable goal.

As explained previously in Scheme 59, the (Z)-iminium ions 139 and 141 should be disfavoured energetically due to repulsive interactions between the $N$-benzyl group’s phenyl ring and the olefin hydrogen atom. However, due to free rotation about the $N$-C sigma bond,
this repulsion may not be as effective as desired (Scheme 64). Thus, we endeavoured to install a larger group than the benzyl moiety at this position, in hopes of decreasing \( (Z) \)-iminium formation and increasing enantioselectivity.

**Scheme 64. C-N bond rotation to decrease steric repulsion in \((Z)\)-iminium.**

![Diagram](image)

We chose to replace the \( N \)-benzyl group with an \( N \)-diphenylmethyl group, since free rotation around the latter moiety’s N-C bond should be less debilatory to iminium geometry control (Figure 34).

**Figure 34. \( N \)-diphenylmethyl camphor hydrazide catalyst 148.**

![Diagram](image)
The synthesis of the new catalyst would be almost identical to the original hydrazide 136, except diphenylmethylhydrazine 145 would be used in the condensation reaction with ketopinic acid 133 rather than benzylhydrazine.

Diphenylmethyl hydrazine was synthesized in one step from hydrazine monohydrate and diphenylmethyl chloride using the procedure of Kopecky and coworkers (Scheme 65).

**Scheme 65. Synthesis of diphenylmethylhydrazine 145.**

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Cl} & \quad \quad \text{H}_2\text{N-NH}_2, \text{H}_2\text{O} \\
\quad & \quad \text{NaHCO}_3, \text{DMSO} \\
\quad & \quad \text{Ph} \quad \quad \text{Ph} \\
145 & \quad \quad \text{NH}_2 \\
\quad & \quad \quad \quad \text{62}\% 
\end{align*}
\]

As shown in Scheme 66, the hydrazine 145 was subsequently condensed with 133 to form the imine 146 in 55% yield. Cyclization was achieved in refluxing mesitylene to give 147. Reduction of the C-N double bond using sodium cyanoborohydride in acidic conditions gave the hydrazide 148 in 91% yield.

We tested the catalytic ability of the chiral hydrazide 148 in three different solvents: toluene, since its use with catalyst 136 resulted in the largest % conversion to product (Entry 1, Table 13); acetonitrile, since with it the highest enantiomeric excess had been achieved (Entry 8, Table 13); and DMF, since using it gave the second highest % ee (Entry 4, Table 13). The same conditions were employed as for the previous hydride reductions: a twenty-four hour reaction time at room temperature.

In toluene, the % conversion to product 142 decreased from 98% using catalyst 136 to 60%, but the enantiomeric excess increased dramatically from 0 to 30% (Table 14). In DMF, the % conversion increased from 9 to 21% and the enantiomeric excess increased by 10% to 35%. Surprisingly, the enantiomeric excess actually decreased when employing acetonitrile as solvent, from 39 to 24%. The percent conversion decreased, as well, to 7% from 12%.
Table 14. The effect of solvent on the asymmetric hydride reduction of 137.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>% conversion to 142</th>
<th>% conversion to (Z)-137</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>136</td>
<td>toluene</td>
<td>98</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>148</td>
<td>toluene</td>
<td>60</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>CH₂CN</td>
<td>12</td>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>CH₂CN</td>
<td>7</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>136</td>
<td>DMF</td>
<td>9</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>148</td>
<td>DMF</td>
<td>21</td>
<td>16</td>
<td>35</td>
</tr>
</tbody>
</table>

To see whether or not the new hydrazide catalyst 148 was more effective at controlling iminium geometry, we monitored the iminium formation via ¹H NMR. As before, equimolar amounts of aldehyde 137, hydrazide 148, and triflic acid were dissolved in deuterated benzene. Initially, we could see four iminiums- one major and three minor (29: 2.2: 1.8: 1). We continued to acquire ¹H NMR spectra at regular intervals until no significant changes in the spectrum were observed. At this point, the ratio had changed to (14.3: 10: 1.8: 1). Thus, the ground state iminium geometry did not appear to be better controlled with hydrazide 148 than with 136, although this did not seem to negatively affect the enantioselectivities in DMF or toluene.

In any case, it did not appear that synthetically useful enantioselectivities could be achieved using either of the chiral hydrazide catalysts. Since there did not appear to be a definitive correlation between iminium geometry control and enantioselectivity, we wondered if the
gem dimethyl groups on the camphor backbone were too far away to block top attack of the Hantzsch ester (Figure 35).

Unlike the hydride reduction, Lemay’s organocatalytic Diels-Alder reaction involves both the α- and β-carbons. An attacking diene would probably experience more repulsion from the gem dimethyl groups than the Hantzsch ester. Thus, top attack would be more disfavoured in the Diels-Alder reaction, resulting in a more enantioselective reaction.

**Figure 35. Comparison between Diels-Alder and hydride reduction transition states.**

We began to look at the literature for secondary amine-catalysed reactions that might bring the attacking reagent closer to the gem dimethyl groups (i.e. attacking at the α-, rather than the β-position). One such reaction was MacMillan and Jørgensen’s asymmetric organocatalytic α-chlorination of aldehydes.

### 2.3 Asymmetric Organocatalytic α-Chlorination of Aldehydes

As explained in section 1.4, MacMillan’s α-chlorination of aldehydes is postulated to proceed via an enamine intermediate in a chair-like transition state. In both MacMillan and
Jørgensen’s methodologies, the exact manner in which enantioselectivity is induced is unknown. We too had no particular predictive model for enantioselectivity using our hydrazide catalysts, but hoped that our results would be as respectable as those previously reported.

The aldehyde substrate on which we wished to test the α-chlorination was hydrocinnamaldehyde 149. We expected that we might see some dichlorination product, since the α-H of the monochlorinated iminium 152 is more acidic than the nonchlorinated iminium 150, thus facilitating enamine formation (Scheme 67).

Scheme 67. Mono- and dichlorination in the organocatalytic α-chlorination of aldehydes.

We first attempted Jørgensen’s conditions, using no Brønsted acid co-catalyst and N-chlorosuccinimide as the electropositive chlorine source. As shown in Table 15, Entry 1, 136 was not a very effective catalyst in the absence of acid; although adding no catalyst gave no reaction at all (Entry 2).
Table 15. Organocatalytic α-chlorination by N-chlorosuccinimide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol% 136</th>
<th>Mol% CF$_3$SO$_3$H</th>
<th>% conversion to 153</th>
<th>% conversion to 156</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>20</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>20</td>
<td>32</td>
<td>26</td>
<td>n/a</td>
</tr>
</tbody>
</table>

In the presence of an equimolar amount of triflic acid, the extent of conversion to monochlorinated product 153 was increased to 31%, but the enantiomeric excess was still negligible (Entry 3). In the control reaction, using only acid as catalyst, the % conversion to 153 was surprisingly unchanged, but a significant amount of the dichlorinated product 151 was also produced. It appeared that while the hydrazone 136 did not increase the rate of the α-chlorination, it did suppress the second chlorination reaction. It is possible that hydrolysis of the iminium ion formed after the chlorination is faster than formation of the reactive enamine, rendering dichlorination unlikely (Scheme 68). Alternatively, the monochlorinated enamine may simply be too sterically congested to be chlorinated a second time.
Scheme 68. Hydrolysis versus enamine formation after first chlorination.

We were not altogether surprised at this lack of enantioselectivity, since MacMillan had observed similar results when using N-chlorosuccinimide as chlorine source, rather than the perchlorinated quinone 111 (Section 1.4). We decided to abandon the NCS methodology and try the α-chlorination reaction using MacMillan’s conditions.

In dichloromethane, using 20 mol% of catalyst 136 and triflic acid, excellent conversion to monochlorinated product 153 was observed, but the enantiomeric excess was a disappointing 8% (Table 16, Entry 1). Dichlorinated product 156 was not detected, unlike the control reaction using only triflic acid, for which only conversion to dichlorinated product was observed (Entry 2). In acetone, which was MacMillan’s solvent of choice, the conversion to 153 decreased to a modest 73%, while no enantioselectivity was observed (Entry 3). In the absence of catalyst 136, there was no reaction (Entry 4).
Table 16. Organocatalytic α-chlorination using quinone 111.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Mol% Hydrazide</th>
<th>Mol% CF₃SO₃H</th>
<th>Solvent</th>
<th>% conversion to 153</th>
<th>% conversion to 156</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>20</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>94</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>n/a</td>
<td>0</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>47</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>20</td>
<td>20</td>
<td>acetone</td>
<td>73</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>n/a</td>
<td>0</td>
<td>20</td>
<td>acetone</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CH(Ph)₂</td>
<td>20</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>60</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>CH(Ph)₂</td>
<td>20</td>
<td>20</td>
<td>acetone</td>
<td>47</td>
<td>0</td>
<td>36</td>
</tr>
</tbody>
</table>

Switching from catalyst 136 to 146, the % conversion dropped by approximately one third in both dichloromethane and acetone. This was not surprising, since 148 is bulkier than 136. On the other hand, the enantioselectivity increased quite significantly, to 29 and 36% in dichloromethane and acetone, respectively (Entries 5 and 6).

Although the highest enantioselectivities achieved in the α-chlorination using hydrazide catalyst 148 were far from synthetically useful, all variables have yet to be optimized. A
scan of different Brønsted acids, as well as solvents, could improve the results significantly. These may be attempted by another graduate student in the Ogilvie group in the future.
Chapter 3. Conclusions

The initial development of hydrazide compounds for organocatalysis appeared rather bleak, with compounds 124 and 129 exhibiting little, if any, catalytic activity in the Diels-Alder reaction. However, Mathieu Lemay’s discovery of the camphor hydrazide 131, an efficient catalyst of the asymmetric Diels-Alder reaction, gave us the new goal of applying 131 to other reactions.

![Chemical structures]

The hydrazide 131 did efficiently catalyze both the hydride reduction of α,β-unsaturated aldehydes and the α-chlorination of aldehydes. In addition, $^1$H NMR studies demonstrated that iminium formation was extremely rapid, supporting that the α-heteroatom effect did increase the rate of this step of the organocatalytic cycle. However, the enantioselectivity was poor in both reactions. The use of derivative 148 did improve enantioselectivities in both reactions, but not to synthetically useful levels. In addition, the conversion to product decreased, although longer reaction times could most likely alleviate this particular drawback.

It is evident that the development of a “privileged” structure, such as MacMillan’s imidazolidinones, that can catalyse a wide variety of reactions both efficiently and asymmetrically, is not a small feat. A combination of both sheer luck and immense effort is necessary in this extremely competitive field. Perhaps with a little of the former, the
application of chiral hydrazide catalysts to a broad scope of reactions will soon be as prevalent as other organocatalysts before them.
Chapter 4. Experimental

Reactions were performed in oven- or flame-dried evacuated flasks under N₂ atmosphere and equipped with a magnetic stir bar and a rubber septum, unless otherwise noted. THF was freshly distilled from sodium/benzophenone, while dichloromethane was freshly distilled from calcium hydride. Reagents were purchased from Sigma-Aldrich, Lancaster, and Strem chemical companies. Triethylamine was freshly distilled over calcium hydride. Chlorotrimethylsilane and (E)-cinnamaldehyde were freshly distilled before use. All other reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F₂₅₄ precoated 0.25 mm thick aluminium plates. TLCs were visualized using ultraviolet light, potassium permanganate, ceric ammonium molybdate, and/or p-anisaldehyde stains. When necessary, products were purified using flash column chromatography on silica gel 60 (230-400 mesh) or preparatory TLC glass plates precoated with silica gel (Si250F). Solvents were evaporated on rotary evaporators.

¹H and ¹³C NMR spectra were acquired using either a Varian Gemini 200 MHz (¹H); a Bruker Avance 500 MHz (¹H) and 125 MHz (¹³C); or a Bruker Avance 300 MHz (¹H) and 75 MHz (¹³C). Infrared spectra were acquired on a Bomem Michaelson 100 FTIR spectrometer. Mass spectra were obtained using a Kratos IIH instrument using either CI or EI ionization techniques. Melting points were determined using an Electrothermal Meltemp® apparatus and are uncorrected.
5-Benzylpyrazolidin-3-one

![Chemical Structure]

To a 500 mL flask containing 125 (10.00 g, 52.60 mmol) was added 200 mL methanol. Hydrazine monohydrate (3.95 g, 78.90 mmol) was then added and the mixture was brought to reflux for 17 hours or until deemed complete by TLC. The reaction mixture was then concentrated and subsequently diluted with diethyl ether (200 mL). After washing with brine, the solvent was removed in vacuo to give a pale yellow oil which was purified via flash column chromatography (5% MeOH in CHCl₃) to give 124 (7.60 g, 82%) as a pale, yellow oil. IR (thin film) 3403 (br), 3065, 3013, 2978, 1674, 1123 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.92 (br s, 1H), 7.13-7.28 (m, 5H), 4.15 (br s, 1H), 3.82-3.87 (m, 1H), 2.90 (dd, J = 6.9, 13.8 Hz, 1H), 2.75 (dd, J = 7.1, 13.8 Hz, 1H), 2.45 (dd, J = 7.2, 16.3 Hz, 1H), 2.24 (dd, J = 7.6, 16.4 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 176.84 (C), 137.18 (C), 129.04 (CH), 128.60 (CH), 126.75 (CH), 59.60 (CH), 39.43 (CH₂), 37.28 (CH₂); MS (EI) m/z 176 (M⁺).
**Ethyl (E)-4-phenylbut-2-enoate**

![Chemical Structure](image)

Triethylphosphonoacetate (9.80 g, 43.70 mmol) was added dropwise to a dispersion of sodium hydride (1.10 g, 45.78 mmol) in THF (150 mL). After stirring for 15 minutes, phenyl acetaldehyde (5.00 g, 41.61 mmol) was added via syringe. The reaction mixture was stirred at room temperature for 20 hours, until deemed complete via TLC. The reaction mixture was concentrated and ethyl acetate (200 mL) was added to the resulting viscous liquid. The solution was washed sequentially with saturated sodium bicarbonate solution (200 mL), water (200 mL), and brine (200 mL). After drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo* to afford a pale yellow oil. The crude product was purified via flash column chromatography (95:5 hexanes-ethyl acetate) to give 125 (6.88 g, 87%) whose spectral properties corresponded with literature values.\(^6\)\(^7\) \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 7.02-7.38 (m, 6H), 5.80 (dt, \(J = 1.6, 15.5\) Hz, 1H), 4.16 (q, \(J = 7.1\) Hz, 2H), 3.50 (d, \(J = 6.7\) Hz, 2H), 1.26 (t, \(J = 7.1\) Hz, 3H).
To a 100 mL flask containing **124** (0.500 g, 2.84 mmol) in dichloromethane (30 mL) was added t-butyl pyrocarbonate (0.650 g, 2.98 mmol). The reaction mixture was stirred at room temperature overnight until deemed complete by TLC. It was then washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL), before being dried over anhydrous sodium sulfate. Removing the solvent *in vacuo* afforded a pale yellow oil that was purified via flash column chromatography (5% methanol in chloroform) to yield **127** (0.757 g, 97%) as a pale yellow foam. IR (thin film) 3216, 3032, 2979, 2928, 1699, 1478, 1455, 1368, 1342, 1250, 1165, 1121 cm⁻¹; $^1$H NMR (CDCl₃, 300 MHz) δ 7.15-7.33 (m, 5H), 4.49-4.58 (m, 1H), 3.05 (dd, $J = 6.4, 13.4$ Hz, 1H), 2.72-2.87 (m, 2H), 2.31 (dd, $J = 2.6, 17.2$ Hz, 1H), 1.39 (s, 9H); $^{13}$C NMR (CDCl₃, 75 MHz) δ 170.72 (C), 153.19 (C), 136.47 (C), 129.41 (CH), 128.56 (CH), 126.81 (CH), 82.32 (C), 57.69 (CH), 40.45 (CH₂), 35.88 (CH₂), 28.05 (CH₃); MS (Cl/iso) m/z 277 (MH⁺), 176 (MH⁺ - t-Boc).
2,5-Dibenzy1-1-(tert-butoxycarbonyl)pyrazolidin-3-one

To a 25 mL flask containing sodium hydride (0.028 g, 1.177 mmol) in DMF (5 mL) was added 127 (0.250 g, 0.905 mmol) in DMF (3 mL) via cannula. After stirring at room temperature for 15 minutes, benzyl bromide (0.170 g, 0.996 mmol) was added via syringe, followed by tetrabutylammonium iodide (0.033 g, 0.0905 mmol). The reaction mixture was stirred at room temperature overnight, until deemed complete by TLC and then poured into a separatory funnel containing water (100 mL). The resulting suspension was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL) before being dried over anhydrous sodium sulfate. The crude yellow oil was purified via gradient flash column chromatography (15 → 30% ethyl acetate in hexanes) to yield 128 (0.242 g, 73%) as a pale yellow oil. IR (thin film) 3091, 3067, 3036, 2981, 2934, 1713, 1607, 1493, 1316, 1156, 1128, 1080 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.37-7.39 (m, 5H), 7.09-7.12 (m, 3H), 6.47-6.50 (m, 2H), 5.40 (d, J = 14.1 Hz, 1H), 4.53 (d, J = 14.1 Hz, 1H), 4.41-4.49 (m, 1H), 2.93 (dd, J = 8.6, 16.6 Hz, 1H), 2.07-2.34 (m, 3H), 1.30 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.38 (C), 155.64 (C), 136.89 (C), 135.99 (C), 129.90 (CH), 129.19 (CH), 128.64 (CH), 128.36 (CH), 128.07 (CH), 126.30 (CH), 82.22 (C), 59.05 (CH), 48.33 (CH₂), 39.90 (CH₂), 36.33 (CH₂), 27.85 (CH₃); MS (Cl/iso) m/z 367 (MH⁺), 266 (MH⁺ - t-Boc), 175 (266 – CH₃Ph).
2,5-Dibenzylpyrazolidin-3-one

To a 25 mL flask containing 128 (0.172 g, 0.470 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (1 mL). After stirring at room temperature for 3 hours, until deemed complete by TLC, the reaction mixture was concentrated and dichloromethane (20 mL) was added. Saturated sodium bicarbonate solution (10 mL) was then carefully added to neutralize any remaining TFA. The organic phase was separated from the aqueous phase and was washed sequentially with water (10 mL) and brine (10 mL). After drying over anhydrous sodium sulfate, the solvent was removed in vacuo to yield 129 (0.121 g, 97%) as a yellow oil. IR (thin film) 3482, 3093, 3064, 3029, 2919, 1678, 1496, 1454, 1404, 1357, 1082 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.18-7.38 (m, 8H), 7.02-7.05 (m, 2H), 4.63 (d, J = 14.6 Hz, 1H), 4.51 (d, J = 14.6 Hz, 1H), 3.95 (br. s, 1H), 3.67-3.76 (m, 1H), 2.83 (dd, J = 6.9, 13.7 Hz, 1H), 2.60-2.68 (m, 2H), 2.35 (dd, J = 6.4, 16.4 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.49 (C), 137.22 (C), 135.91 (C), 129.08 (CH), 128.70 (CH), 128.47 (CH), 128.39 (CH), 127.80 (CH), 126.66 (CH), 56.10 (CH), 47.95 (CH₂), 39.70 (CH₂), 38.03 (CH₂); MS (EI) m/z 266 (M⁺), 175 (M⁺ - CH₂Ph).

General procedures for Diels-Alder Reaction.

(a) Pyrazolidinone + acid: To a 10 mL flask was added (E)-cinnamaldehyde (0.050 g, 0.378 mmol) in methanol (3.4 mL) and the respective pyrazolidinone (0.076 mmol). Perchloric acid (0.20 mL, 0.076 mmol) was added as a 0.3734 M aqueous solution, followed by distilled water (0.18 mL). Cyclopentadiene was then added and the reaction mixture was stirred at room temperature and monitored via TLC. When ready for work-up, the reaction mixture was diluted with water (5 mL) and extracted
with diethyl ether (3 x 10 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL) before being dried over sodium sulfate. After removing the solvent by rotatory evaporator, chloroform (4 mL), water (2 mL), and trifluoroacetic acid (2 mL) were added in succession and the resulting mixture was stirred at room temperature for 24 hours. Saturated sodium bicarbonate solution (20 mL) was then added carefully until bubbling ceased. Diethyl ether (20 mL) was added to the neutralized mixture and the organic and aqueous phases were separated. The organic phase was washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was removed \textit{in vacuo} to yield an oil, which was invariably a mixture of (E)-cinnamaldehyde, pyrazolidinone, and cyclopentadiene, and Diels-Alder cycloadducts. The % conversion was determined via $^1$H NMR.

(b) \textbf{Pyrazolidinone only}: As above, except no acid was added and 0.38 mL of distilled water was added instead of 0.18 mL.

(c) \textbf{Acid only}: As above, except pyrazolidinone was not added.
To a 250 mL flask containing 135 (2.40 g, 8.943 mmol) in methanol (60 mL) was added glacial acetic acid (30 mL). Sodium cyanoborohydride (5.62 g, 89.432 mmol) was gradually added and the reaction mixture was stirred at room temperature and monitored by TLC. After 18 hours, 2 N sodium hydroxide solution (30 mL) was added to the reaction flask, and the resulting mixture was extracted with diethyl ether (3 x 80 mL). The combined organic extracts were washed with brine (150 mL) and dried over anhydrous magnesium sulfate. After removing the solvent in vacuo, the resulting white solid was purified via flash column chromatography (7:3 hexanes-ethyl acetate) to afford 131 (2.28 g, 94%) as a white crystalline powder. m.p. 109-111 °C; IR (thin film) 3210, 3032, 2958, 2876, 1656, 1454, 1389 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta 7.22-7.30\) (m, 5H), 4.68 (d, \(J = 14.3\) Hz, 1H), 4.41 (d, \(J = 13.97\) Hz, 1H), 3.86 (br. s, 1H), 3.48 (dd, \(J = 4.7, 8.3\) Hz, 1H), 2.14 (td, \(J = 4.8, 11.6\) Hz, 1H), 1.95-1.99 (m, 1H), 1.82-1.90 (m, 2H), 1.61 (dd, \(J = 8.4, 12.1\) Hz, 1H), 1.24-1.29 (m, 1H), 1.16-1.21 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 170.64\) (C), 135.94 (C), 128.61 (CH), 128.32 (CH), 127.69 (CH), 65.21 (C), 58.36 (C), 51.15 (C), 47.89 (CH\(_2\)), 46.71 (CH), 36.29 (C), 28.58 (CH\(_2\)), 26.61 (CH\(_2\)), 20.89 (CH\(_3\)), 20.24 (CH\(_2\)); HRMS (EI) calcd. for C\(_{17}\)H\(_{22}\)N\(_2\)O (M+) 270.1732; found 270.1723; \([\alpha]_D = +12.6^o\) (c 1.03, CHCl\(_3\)).
To a 500 mL flask fit with a water-cooled condenser and base trap was added (1S)-(+)10-camphor sulfonic acid (100.00 g, 430.48 mmol). Thionyl chloride (100 mL, # mmol) was carefully added and the resulting suspension was heated in a steam bath for 45 minutes. The reaction was cooled to room temperature and poured onto ice. The resultant white precipitate was filtered by suction and rinsed several times with cold water. The crude sulfonyl chloride intermediate was dried overnight in vacuo before being converted to (+)-ketopinoic acid 133. To a 3000 mL flask equipped with a water-cooled condenser was added sodium carbonate (100.00 g, 943.57 mmol) in distilled water (800 mL). While heating in a steam bath, potassium permanganate (33.00 g, 208.82 mmol) and hot water (250 mL) were added to the reaction mixture. At this point, approximately 1/3 of the crude acyl chloride was added, followed by 15 minutes of stirring. This process was repeated twice, so that a total of 100.00 g (632.79 mmol) of potassium permanganate and all the crude acyl chloride were added. The reaction mixture continued to be stirred for an additional 3 hours in the steam bath. After cooling to room temperature, the solution was made acidic by careful addition of 20% sulfuric acid solution (400 mL). At this point, the reaction mixture was replaced in the steam bath and sodium sulfite (100.00 g, 793.40 mmol) was added. After cooling, the resultant clear, colourless solution was extracted with diethyl ether (3 x 500 mL). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed in vacuo. The crude product could be carried on to the next synthetic step to form 133, or, if desired, can be purified via flash column chromatography (1:1 hexanes-ethyl
acetate). m.p. 197 °C (dec.); IR (Nujol mull) 2964, 1750, 1690, 1465 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 11.49 (br. s, 1H), 2.55 (dt, J = 3.9, 18.6 Hz, 1H), 2.34-2.40 (m, 1H), 2.12 (t, J = 4.3 Hz, 1H), 2.02-2.10 (m, 1H), 1.98 (d, J = 18.6 Hz, 1H), 1.75-1.81 (m, 1H), 1.39-1.44 (m, 1H), 1.14 (s, 3H), 1.11 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 212.66 (C), 174.91 (C), 67.08 (C), 49.66 (C), 44.06 (CH), 43.61 (CH₂), 26.80 (CH₂), 26.57 (CH₂), 20.82 (CH₃), 19.78 (CH₃); MS (EI) m/z 182 (M⁺).

(+)-2-(Benzylhydrazono)-7,7-dimethylbicyclo-[2.2.1]-heptane-1-carboxylic acid

To a 500 mL flask containing (+)-133 (3.36 g, 18.45 mmol) in dichloromethane (200 mL) was added benzyl hydrazine (3.38 g, 27.67 mmol) and glacial acetic acid (0.22 mL, 3.69 mmol). The reaction mixture was stirred at room temperature overnight, concentrated, and azeotroped with toluene (3 x 10 mL) to remove the acetic acid. The crude oil was then purified via flash column chromatography (65:35 hexanes-ethyl acetate) to yield (+)-134 (5.30 g, 100%) as a pale yellow, viscous oil. IR (thin film) 3282, 3095, 3069, 3032, 2971, 2630, 1743, 1494, 1453, 1390, 1328, 1284, 1233 cm⁻¹; ¹H (CDCl₃, 500 MHz) δ 7.28-7.36 (m, 5H), 4.33 (s, 2H), 2.41 (td, J = 4.0, 12.0 Hz, 1H), 2.35 (dt, J = 3.5, 17.2 Hz, 1H), 2.03-2.10 (m, 1H), 1.99 (t, J = 4.4 Hz, 1H), 1.81 (d, J = 17.1 Hz, 1H), 1.69-1.74 (m, 1H), 1.27-1.33 (m, 1H), 1.23 (s, 3H), 0.81 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 172.81 (C), 159.44 (C), 138.27 (C), 128.71 (CH), 128.26 (CH), 127.68 (CH), 59.63 (C), 55.11 (CH₂), 51.50 (C),
44.36 (CH), 32.70 (CH₂), 32.16 (CH₂), 28.18 (CH₂), 20.04 (CH₃), 19.66 (CH₃); HRMS (El) calcd. for C₁₇H₂₂N₂O₂ (M⁺) 286.1681 found 286.1692; [α]D = +53.7° (c 1.10, CHCl₃).

(+) -3-Benzyl-10,10-dimethyl-3,4-diazatricyclo-[5.2.1.0¹⁵]dec-4-en-2-one

To a 500 mL flask equipped with a Dean-Stark apparatus was added 134 (3.43 g, 11.943 mmol) in mesitylene (200 mL). The reaction mixture was brought to reflux and was heated until complete by TLC (approx. 22 hours). After cooling to room temperature, the mesitylene solution was loaded onto a column and the mesitylene was removed by eluting with hexanes (500 mL). The solvent system was then changed to 7:3 hexanes-ethyl acetate to afford 135 (2.56 g, 80%) as a white crystalline solid. m.p. °C; IR (thin film) 3097, 3042, 2962, 2906, 2879, 1690, 1630, 1499, 1455, 1419, 1388, 1320, 1264 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.20-7.29 (m, 5H), 4.79 (s, 2H), 2.52 (dt, J = 3.5, 17.7 Hz, 1H), 2.26 (td, J = 4.5, 12.0 Hz, 1H), 2.20 (t, J = 4.3 Hz, 1H), 2.05-2.12 (m, 1H), 2.08 (d, J = 17.6 Hz, 1H), 1.61-1.66 (m, 1H), 1.42-1.47 (m, 1H), 1.18 (s, 3H), 0.87 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 174.39 (C), 173.52 (C), 137.10 (C), 128.46 (CH), 127.72 (CH), 127.34 (CH), 63.57 (C), 49.75 (C), 49.16 (CH), 47.86 (CH₂), 31.86 (CH₂), 26.88 (CH₂), 25.24 (CH₂), 19.01 (CH₃), 18.51 (CH₃); HRMS (El) calcd. for C₁₇H₂₀N₂O (M⁺) 268.1576; found 268.1589; [α]D = +28.0° (c 1.04, CHCl₃).
3-Methyl-(E)-cinnamaldehyde

To a 100 mL flask containing dichloromethane (20 mL) was added oxaly chloride (1.03 g, 8.103 mmol). The reaction mixture was cooled to -78 °C and dimethyl sulfoxide (1.27 g, 16.205 mmol) was added gradually via syringe. After stirring for 15 minutes at -78 °C, 144 (1.00 g, 6.752 mmol) in dichloromethane (10 mL) was gradually added to the reaction mixture. Following an additional 15 minutes of stirring at -78 °C, triethylamine (3.28 g, 32.411 mmol) was added via syringe. The reaction mixture was stirred at this temperature for an additional 2 hours, until deemed complete by TLC. At this point, a white precipitate was removed via suction filtration and the resulting clear, colourless solution was washed sequentially with 10% hydrochloric acid (20 mL), saturated sodium bicarbonate solution (20 mL), water (20 mL), and brine (20 mL). After being dried over anhydrous magnesium sulfate, the solvent was removed in vacuo to afford an oil which was purified via flash column chromatography (9:1 hexanes-ethyl acetate). The spectral properties of the resultant clear, colourless oil 137 (0.910 g, 92%) corresponded to those in literature.\(^{68}\)\(^{1}\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 10.15 (d, \(J = 7.9\) Hz, 1H), 7.50-7.52 (m, 2H), 7.37-7.39 (m, 3H), 6.36 (d, \(J = 7.9\) Hz, 1H), 2.53 (s, 3H).
(+/-)-3-Phenylbutyraldehyde

To a 10 mL flask containing 137 (0.050 g, 0.342 mmol) in THF (4 mL) was added 10% palladium on carbon (0.005 g). The resulting suspension was stirred under an atmosphere of H₂ at room temperature for 2 hours, until the reaction was deemed complete by TLC. After purging the reaction mixture several times with N₂ to remove H₂, it was filtered over a celite pad. The celite was carefully rinsed several times with dichloromethane and was disposed of with caution. The filtrate was concentrated and dried in vacuo to afford (+/-)-142 (0.047 g, 92%) as a clear colourless oil whose spectral properties corresponded to those in literature.⁶⁹

The two enantiomers could be separated on an Agilent 6890 Series gas chromatograph equipped with a split-mode capillary injection system and a flame ionization detector using Agilent/J&W CycloSil-B column (100-200 °C at 5 °C/min, 3.0 mL/min); (-) isomer tᵣ = 11.3 min and (+) isomer tᵣ = 11.4 min.¹ H NMR (CDCl₃, 300 MHz) δ 9.69 (t, J = 1.9 Hz, 1H), 7.19-7.32 (m, 5H), 3.31-3.38 (m, 1H), 2.74 (ddd, J = 1.9, 6.9, 16.7 Hz, 1H), 2.64 (ddd, J = 2.2, 7.7, 16.7 Hz, 1H), 1.30 (d, J = 7.0 Hz, 3H).

(E)-Ethyl 3-phenylbut-2-enoate⁶⁵

To a 100 mL flask containing a suspension of sodium hydride (0.264 g, 11.00 mmol) in THF (20 mL) was gradually added triethylphosphonoacetate (2.24 g, 10.00 mmol) via syringe.
After stirring at room temperature for 15 minutes, acetophenone (1.20 g, 10.00 mmol) was gradually added via syringe. The reaction mixture was stirred for 3 hours, or until deemed complete by TLC. Diethyl ether (30 mL) and water (30 mL) were added to the reaction flask and the organic phase was separated from the aqueous phase. The aqueous phase was extracted with diethyl ether (2 x 30 mL) and the combined organic fractions were washed with brine (50 mL) and then dried over anhydrous magnesium sulfate. After removing the solvent in vacuo, the resulting oil was purified via flash column chromatography (98:2 hexanes-ethyl acetate) to yield 143 (0.912 g, 48%) as a clear, colourless oil, whose spectral properties corresponded to those in literature.\textsuperscript{70} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) \textdelta 7.42-7.50 (m, 2H), 7.33-7.38 (m, 3H), 6.13 (q, \textit{J} = 1.3 Hz, 1H), 4.15-4.27 (q, \textit{J} = 7.1 Hz, 2H), 2.57 (d, \textit{J} = 1.3 Hz, 3H), 1.30 (t, \textit{J} = 7.2 Hz, 3H).

\textit{(E)-3-Phenyl-but-2-en-1-ol}\textsuperscript{65}

\begin{center}
\includegraphics[width=0.2\textwidth]{144.png}
\end{center}

To a 500 mL flask containing 143 (6.84 g, 35.98 mmol) in THF (200 mL) at 0 °C was gradually added a 1.0 M solution of DIBAL-H in hexanes (76 mL, 75.55 mmol). The reaction mixture was warmed to room temperature and stirred for 6 hours, or until deemed complete by TLC. Saturated sodium-potassium tartrate solution (200 mL) was carefully added to the reaction mixture, which was then stirred vigorously until the appearance of two clear layers. The organic phase was separated from the aqueous, which was then extracted with diethyl ether (2 x 200 mL). The combined organic fractions were washed with saturated sodium-potassium tartrate solution (200 mL) and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo, the product was purified via flash column chromatography (3:1 hexanes-ethyl acetate) to yield 144 (5.10 g, 96%) as a clear colourless oil, whose spectral properties corresponded to those in the literature.\textsuperscript{68} \textsuperscript{1}H NMR (CDCl\textsubscript{3},
200 MHz) δ 7.26-7.44 (m, 5H), 5.99 (tq, J = 1.3, 6.7 Hz, 1H), 4.35 (d, J = 6.6 Hz, 2H), 2.74 (br. s, 1H), 2.06 (d, J = 1.2 Hz, 3H).

**General procedures for hydride reduction of α,β-unsaturated aldehydes.**

(a) **Pyrazolidinone + acid:** To a 5 mL flask was added the appropriate pyrazolidinone catalyst (0.0342 mmol) and solvent (0.85 mL). Triflic acid (0.005 g, 0.0342 mmol) was then added via syringe, followed by 137 (0.025 g, 0.1711 mmol). Finally, the Hantzsch ester 98 (0.048 g, 0.1882 mmol) was added to the reaction mixture which was then stirred for 20 hours. At this time, diethyl ether (10 mL) was added and the resultant solution was washed sequentially with 10% hydrochloric acid solution (10 mL), saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo* and the resultant oil or sticky solid was analyzed via $^1$H NMR and chiral GC.

(b) **Acid only:** As above, except no pyrazolidinone catalyst was added.

**Diphenylmethyl hydrazine**

![Diphenylmethyl hydrazine structure](image)

To a 100 mL flask containing hydrazine monohydrate (20.00 g, 399.52 mmol) in dimethyl sulfoxide (40 mL) was added sodium bicarbonate (10.35 g, 97.66 mmol). A solution of diphenylmethyl chloride (18.00 g, 88.78 mmol) in dimethyl sulfoxide (15 mL) was added dropwise to the reaction flask over 20 minutes. After stirring overnight at room temperature, the reaction mixture was poured into cold water (100 mL) and extracted with
dichloromethane (3 x 100 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL) and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo and the resulting pale yellow sticky solid was pumped overnight to yield 145 (10.90 g, 62%) whose spectral properties corresponded to those in literature. \(^{66}\) \(^1\)H NMR (DMSO-\(d_6\), 200 MHz) \(\delta\) 7.20-7.39 (m, 10H), 4.85 (d, \(J = 3.6\) Hz, 1H), 3.36 (br. s, 3H).

\[
\text{(+) \text{-2-(Diphenylmethylhydrazono)-7,7-dimethylbicyclo-[2.2.1]-heptane-1-carboxylic acid}}
\]

To a 100 mL flask containing crude (~70% pure) 133 (0.500 g, 2.75 mmol) in dichloromethane (25 mL) was added 145 (0.817 g, 4.118 mmol). Glacial acetic acid (0.030 mL, 0.549 mmol) was then added via syringe and the reaction mixture was stirred overnight at room temperature. After removal of solvent in vacuo, the resulting sticky yellow oil was purified via flash column chromatography (3:1 hexanes-ethyl acetate) to afford 146 (0.549 g, 55%) as a pale yellow foam. IR (thin film) 3268, 3088, 3066, 3036, 2972, 2668, 1735, 1667, 1495, 1450, 1330, 1232 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.31-7.38 (m, 8H), 7.24-7.29 (m, 2H), 5.53 (s, 1H), 2.36-2.46 (m, 2H), 2.03-2.11 (m, 1H), 2.01 (t, \(J = 4.3\) Hz, 1H), 1.88 (d, \(J = 17.2\) Hz, 1H), 1.66-1.71 (m, 1H), 1.27-1.33 (m, 1H), 1.22 (s, 3H), 0.81 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 172.57 (C), 141.41 (C), 141.07 (C), 128.71 (CH), 128.61 (CH), 127.65 (CH), 127.61 (CH), 127.42 (CH), 67.77 (CH), 59.64 (C), 51.49 (C), 44.36 (CH), 32.91
(CH₂), 32.02 (CH₂), 28.17 (CH₂), 20.00 (CH₃), 19.63 (CH₃); MS (EI) m/z 362 (M⁰); [α]D = +5.94° (c 1.0, CHCl₃).

(-)-3-Diphenylmethyl-10,10-dimethyl-3,4-diazatricyclo-[5.2.1.0¹,⁵]-dec-4-en-2-one

To a 100 mL flask equipped with a Dean-Stark apparatus was added 146 (0.502 g, 1.386 mmol) in mesitylene (50 mL). The reaction mixture was brought to reflux and was heated until complete by TLC (approx. 36 hours). After cooling to room temperature, the mesitylene solution was loaded onto a column and the mesitylene was removed by eluting with hexanes (100 mL). The solvent system was then changed to 8:2 hexanes-ethyl acetate to afford 147 (0.294 g, 62%) as an off-white powder. m.p. 156-158 °C; IR (thin film) 3091, 3052, 3036, 2962, 2939, 2884, 1694, 1630, 1496, 1456, 1371, 1337, 1179 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.26-7.37 (m, 10H), 6.64 (s, 1H), 2.59 (m, 1H), 2.09-2.35 (m, 4H), 1.64-1.72 (m, 1H), 1.45-1.53 (m, 1H), 1.22 (s, 3H), 0.88 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 174.19 (C), 173.64 (C), 139.93 (C), 139.51 (C), 128.53 (CH), 128.30 (CH), 128.28 (CH), 128.22 (CH), 127.38 (CH), 127.27 (CH), 63.52 (C), 59.75 (CH), 50.05 (C), 49.19 (CH), 32.17 (CH₂), 26.96 (CH₂), 25.26 (CH₂), 19.07 (CH₃), 18.60 (CH₃); HRMS (EI) exact mass calculated for C₂₃H₂₄N₂O requires m/z 344.1890, found 344.1881; [α]D = +0.23° (c 1.0, CHCl₃).
(-)-3-Diphenylmethyl-10,10-dimethyl-3,4-diazatricyclo-[5.2.1.0^1.5]-decan-2-one

To a 100 mL flask containing 147 (0.760 g, 2.208 mmol) in methanol (20 mL) was added sodium cyanoborohydride (2.78 g, 44.157 mmol). Glacial acetic acid (10 mL) was then added via syringe and the reaction was stirred at room temperature for 42 hours, or until deemed complete by TLC. A 2N solution of sodium hydroxide (10 mL) was carefully added to the reaction mixture, which was then extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo, the resulting off-white solid was purified via flash column chromatography (8:2 hexanes-ethyl acetate) to afford 148 (0.698 g, 91%) as a white powder. m.p. 178-179 °C; IR (thin film) 3336, 3060, 2994, 2967, 2924, 1675, 1447, 1387, 1297 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.26-7.36 (m, 10H), 6.65 (s, 1H), 3.62 (dd, \(J = 4.7, 8.3\) Hz, 1H), 2.15-2.24 (m, 1H), 1.87-2.00 (m, 3H), 1.71 (dd, \(J = 8.4, 13.1\) Hz, 1H), 1.22-1.39 (m, 2H), 1.07 (s, 3H), 0.90 (s, 3H); \(^13\)C NMR (CDCl\(_3\), MHz) \(\delta\) 171.40 (C), 138.58 (C), 138.44 (C), 129.45 (CH), 128.46 (CH), 128.35 (CH), 127.86 (CH), 127.62 (CH), 127.29 (CH), 66.02 (CH), 59.33 (CH), 57.98 (C), 50.97 (C), 46.97 (CH), 35.63 (CH\(_2\)), 28.88 (CH\(_2\)), 26.58 (CH\(_2\)), 21.22 (CH\(_3\)), 20.15 (CH\(_3\)); HRMS (EI) exact mass calculated for C\(_{23}\)H\(_{26}\)N\(_2\)O requires m/z 346.2047, found 346.2056; [\(\alpha\)]\(_D\) = -71.10° (c 1.0, CHCl\(_3\)).
To a 25 mL flask equipped with a water-cooled condenser was added chlorotrimethyl silane (0.972 g, 8.949 mmol) in dichloromethane (10 mL). Triethylamine (1.81 g, 17.898 mmol) was added to the stirred solution, followed by 3-phenylpropanal (1.00 g, 7.458 mmol). The reaction mixture was refluxed for 45 hours and then cooled to room temperature. Hexanes (50 mL) was added to the reaction flask and the resulting solution was washed with cold saturated sodium bicarbonate solution (3 x 50 mL). The organic phase was quickly washed with 10% hydrochloric acid solution (50 mL) and then saturated sodium bicarbonate solution (50 mL). After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to afford a pale yellow oil which was immediately dissolved in dichloromethane (50 mL) was added N-chlorosuccinimide (0.947 g, 7.094 mmol). After stirring at room temperature for 6 hours, the solvent was removed in vacuo and the resulting sticky solid was purified via flash column chromatography (8:2 hexanes-diethyl ether) to afford (±)-153 (0.913 g, 60%) as a pale yellow oil, whose spectral properties corresponded to literature values. The two enantiomers could be separated on an Agilent 6890 Series gas chromatograph equipped with a split-mode capillary injection system and a flame ionization detector using Agilent/J&W CycloSil-B column (100 °C isotherm, 2.0 mL/min); isomer A tR = 77.7 min and isomer B tR = 79.2 min. 1H NMR (CDCl3, 200 MHz) δ 9.53 (d, J = 2.2 Hz, 1H), 7.20-7.38 (m, 5H), 4.38 (ddd, J = 2.2, 5.7, 8.2 Hz, 1H), 3.37 (dd, J = 5.9, 14.5 Hz, 1H), 3.07 (dd, J = 8.2, 14.4 Hz, 1H).
General procedure for α-chlorination of aldehydes.

(a) Pyrazolidinone + acid: To a 5 mL flask containing the pyrazolidinone catalyst (0.03729 mmol) in the solvent (1.9 mL) was added triflic acid (0.005 g, 0.03729 mmol). 2,3,4,5,6,6-Hexachlorocyclohexa-2,5-dienone (0.067 g, 0.2237 mmol), followed by 3-phenylpropanal (0.025 g, 0.1864 mmol) were added to the reaction mixture, which was then stirred for 12 hours at room temperature. Sodium bicarbonate (0.010 g, 0.09346 mmol) was then added to the reaction flask, which was stirred for an additional 10 minutes before being filtered by suction. The filtrate was concentrated in vacuo and the crude oil/sticky solid that resulted was analysed by $^1$H NMR and chiral GC.

Acid only: As above, but no pyrazolidinone was added.
C. Studies Directed Towards the Synthesis of Potential HIV-1 Reverse Transcriptase Inhibitors: 9-Alkylaryl TIBO Derivatives

Chapter 1. Introduction

1.1 The Human Immunodeficiency Virus Type 1

Despite strong efforts in education and science, the instance of Acquired Immunodeficiency Syndrome (AIDS) infection is still alarmingly high. This is particularly true in the developing world, where there is little AIDS or sex education. Thus, it is not surprising that there is a wealth of scientific research in this area, in an attempt to better understand this disease and develop new treatments.

AIDS develops as a result of Human Immunodeficiency Virus (HIV) infection. The two strains of HIV: HIV-1 and HIV-2; are both transmitted as virions from one organism to another via bodily fluids. While HIV-1 is the most common form of the virus, HIV-2 is mostly restricted to West African countries and is considered to be less pathogenic than HIV-1. It is thus not surprising that the focus of current antiretroviral research is HIV-1.

HIV-1 concentrates its pathogenic effects on the immune system of an infected person, specifically the helper T lymphocytes, or CD4+ cells. These cells are involved in detecting the presence of foreign antigens, so that the immune system can overcome the infection before it causes significant harm. HIV-1 infection depletes the number of CD4+ cells, which hampers the response of the immune system to potential threats. With the resultant compromised immune response, an infection that a healthy immune system could overcome could be deadly for an HIV or AIDS patient.

The progress of HIV to AIDS is monitored by the number of healthy CD4+ cells that an infected person possesses. A healthy person will have between 500 and 1500 CD4+ cells per
milliliter of blood, while AIDS is diagnosed if a count of less than 200 CD4+ cells/mL blood is measured. Therefore, to slow the development of disease, the rate of CD4+ cell infection must be decreased. This can be done by interrupting the life cycle of an HIV-1 virion, shown in Figure 36.

The HIV-1 life cycle and CD4+ infection begin with the binding of the free virion to surface membrane proteins on the CD4+ cell (Step 2, Figure 36). Once bound, the virion’s lipid-envelope coat fuses with the plasma membrane of the CD4+ cell, which allows the virion’s contents to spill into the cell (Step 3, Figure 36). The fusion of the HIV-1 virion to the CD4+ cell can be interrupted with the use of a fusion inhibitor, such as enfuvirtide, also known as Fuzeon® (Roche/Trimeris). Enfuvirtide is a linear synthetic peptide that binds to a glycoprotein in the virion’s coat, disallowing the conformational changes that are necessary for fusion of the CD4+ cell to the virion.
The contents of the HIV virion, now in the CD4+ cytoplasm, include several enzymes, other proteins, and the HIV-1 genome, which is encoded as RNA. One of the enzymes is known as HIV-1 reverse transcriptase (HIV-1 RT). This enzyme transcribes the HIV-1 RNA genome into DNA (Step 4, Figure 36). Reverse transcription can be inhibited by two classes of HIV-1 inhibitors. Nucleoside reverse transcriptase inhibitors (NRTIs) mimic the structure of “normal” DNA nucleosides (deoxyadenosine, deoxyguanosine, deoxycytidine, and
deoxythymidine) so that they are incorporated into the nascent DNA strand, but do not allow replication to continue. Thus, replication is prematurely terminated. Some examples of NRTIs which are currently used to treat HIV-1 infection are didanosine, or Videx™ (Bristol-Myers Squibb); lamivudine, or Epivir™ (GlaxoSmithKline); and emtricitabine, or Emtriva™ (Gilead Sciences).

The second class of HIV-1 reverse transcriptase inhibitors, dubbed non-nucleoside reverse transcriptase inhibitors (NNRTIs), bind to an allosteric site on the enzyme, located 10 Å away from the active site. This causes a repositioning of a β-sheet containing three catalytic aspartic acid residues that are needed for reverse transcriptase activity. The repositioning of this structure prevents the enzyme from adopting the conformation necessary for reverse transcription to occur. The three NNRTIs that are currently on the market are nevirapine, or Viramune™ (Boehringer Ingelheim); delavirdine, or Rescriptor™ (Pfizer); and efavirenz, or Sustiva™ (Bristol-Myers Squibb).

After the DNA has been synthesized by reverse transcriptase, it is brought into the CD4+ cell nucleus, where it is integrated into the CD4+ genomic DNA by the HIV-1 protein integrase (Step 5, Figure 36).

The viral DNA may not be expressed as viral proteins for some time- this is known as the dormancy phase of the HIV-1 life cycle. Eventually, a poorly understood signal causes the CD4+ cell’s own machinery to commence transcribing the HIV-1 DNA into mRNA. The mRNA is then translated into HIV-1 proteins (Step 6, Figure 36). The nascent polypeptides aggregate near the cellular membrane before “budding” from the cell as new HIV-1 virions (Steps 7-9, Figure 36). The HIV-1 enzyme protease then cleaves the long polypeptides into functional HIV-1 proteins. The virion is now mature and able to infect another CD4+ cell. Protease inhibitors that are currently used in treatment include saquinavir, or Invirase™ (Hoffmann-La Roche); indinavir, or Crixivan™ (Merck); and fosamprenavir, or Lexiva™ (GlaxoSmithKline).
The replicative cycle of the HIV-1 virus is believed to be related to apoptosis, or programmed cell death. In addition, viral budding slowly destroys CD4+ cellular membranes, thus killing the cells. Syncytia, or multinucleated cell formation, caused by the expression of viral proteins on the surface of the infected CD4+ cells, is also a fatal process. Thus, over time, the body’s supply of CD4+ cells is decreased significantly, causing increased susceptibility to a wide variety of diseases.

Unfortunately, none of the drugs currently available can completely suppress the progress of the virus. This is due, in part, to drug-induced selection for HIV-1 mutations that cause the drugs to be less effective. The rapid selection for drug-resistant mutants is due to two intrinsic characteristics of HIV-1. Firstly, HIV-1 reverse transcriptase does not have any proofreading ability; if it inserts the incorrect nucleotide when converting the HIV-1 RNA into DNA, it cannot correct its mistake. This is unlike most DNA polymerases, including mammalian DNA polymerases, which possess proofreading, or 3'-5' exonuclease, activity. HIV-1 reverse transcriptase has been found to make an error once per 10 000 nucleotides in vivo, or about once per HIV-1 genome.⁷⁴ This high error rate is coupled with the brevity of the HIV-1 life cycle (0.3 days on average), which accelerates the process of Darwinian selection. Since, when replicating in the presence of HIV-1 inhibitors such as NNRTIs, drug-resistant viral mutants survive, while wild-type HIV-1 virions cannot replicate, the mutants are selected by the HIV-1 drugs.⁷⁸

The most efficacious way in which to reduce the rate of formation of HIV-1 mutants is to arrest the HIV-1 life cycle. Administering only one of the available HIV-1 medications to an infected person results in rapid selection for drug-resistant mutants, thus combination therapy is used. For example, combining an NNRTI with an NRTI and a PI has a synergistic effect, resulting in improved inhibition of the appearance of resistant virus.

That being said, combination therapy brings about its own problems. In addition to the inconvenience of taking many pills or injections every day, there are side effects associated with each of the drugs, including nausea, redistribution of body lipids, dizziness, and rashes. To avoid, for example, the CNS effects often observed with efavirenz, a patient may opt to
skip a dose. This decreases the suppression of viral replication, so that drug-resistant HIV-1 mutants can form. Therefore, a goal of current antiretroviral research is to produce a drug with minimal side-effects that, ideally, is potent enough to be used as monotherapy.

1.2 The Development of Broad-Spectrum Nevirapine Analogue

When developing inhibitors for a specific HIV-1 enzyme, such as reverse transcriptase, the primary goal is to have the compound interact with as many amino acid residues that are necessary for the enzyme’s function. These residues are usually conserved, even in mutants, since, without them, the enzyme may perform poorly, or not at all. Such an HIV-1 inhibitor should have prolonged efficacy and hinder the development of resistant mutants.

Recently, it was reported that introducing an aryl group connected via a linker to position 8 of the core structure of the NNRTI nevirapine 157 resulted in improved potency against a wide variety of drug-resistant mutants. These mutants included those that nevirapine was known to have induced in vitro and in vivo, and mutations that are triggered by other NNRTIs (Figure 37).79,80

Figure 37. Nevirapine 157 and its broad spectrum derivative 158.

Initially, it was found that aryl groups attached to the 8 position of the nevirapine core via an ethyl linker greatly improved the inhibition of resistant HIV-1 reverse transcriptase mutants, while its activity against the wild-type enzyme was retained.79 Further SAR studies
produced the superior 2-halo-8-aryloxymethyl derivatives 158, which also performed well in preliminary metabolic testing.

It was hypothesized that, with the nevirapine derivatives 158, new interactions were formed between the 8-aryl sidechain and amino acid residues in the NNRTI binding site. By analyzing the crystal structure of HIV-1 reverse transcriptase, it appeared that the novel sidechain may form favourable π-π interactions with several aromatic amino acid residues, such as Phe 227, Trp 229, and Tyr 232. The residue Trp 229 is highly conserved throughout various resistant HIV-1 reverse transcriptase mutants. In addition, point mutation of this residue to alanine resulted in a significant decrease in reverse transcriptase activity, indicating that Trp 229 may be a residue that is necessary for the enzymatic activity. As noted previously, favourable interactions with conserved residues should reduce the rate of selection for nevirapine-resistant HIV-1 mutants.

Since all NNRTIs are known to bind to the same site on the enzyme where they interact with many of the same residues, we wondered if other NNRTIs could benefit from the addition of an aryl sidechain similar to the one on the nevirapine derivative 158. We decided to look at a series of compounds known as the TIBO family, which were some of the first NNRTIs to be discovered.

1.3 Analyses of the X-ray Crystal Structures of Nevirapine and 9-Cl TIBO Complexed with HIV-1 reverse transcriptase

In 1989, researchers at the Janssen Research Foundation discovered the potent HIV-1 reverse transcriptase inhibitory activity of 4,5,6,7-tetrahydro-5-methylimidazo-[4,5,1-jk]-[1,4]-benzodiazepin-2-(1H)-one (TIBO) derivative 159.\(^1\) Out of over 600 compounds screened, 159 was the only compound to inhibit the enzyme at concentrations below cytotoxic levels. Several studies were undertaken to optimize the activity, resulting in TIBO derivative 160, whose 50% inhibitory concentration (IC\(_{50}\)) was 0.0043 µM.\(^2\)
Figure 38. The lead TIBO derivative 159 and the optimized derivative 160.

As mentioned previously, all known NNRTIs have been shown to bind similarly to the hydrophobic pocket located 10 Å from the active site of reverse transcriptase. The mode of binding involves the inhibitors assuming a two-ring hinge system or “butterfly-like” conformation in order to interact with the surrounding, mainly hydrophobic, amino acid residues. This conformation can be seen in the X-ray structure of nevirapine 158 complexed with HIV-1 reverse transcriptase, shown in Figure 39.

Figure 39. X-ray crystal structure of nevirapine bound to HIV-1 reverse transcriptase.
The TIBO skeleton, which is relatively flat, did not appear to be able to assume this shape, although biochemical and resistant mutation studies indicated that it must bind similarly to the other NNRTIs. However, an X-ray crystallographic study of the TIBO analogues suggested that they do, in fact, assume a similar conformation to the other NNRTIs.\textsuperscript{83} The phenyl and imidazolidinone rings comprise one ring of the two-hinged ring model, while the dimethylallyl substituent mimics the second ring (Figure 40).

**Figure 40. X-ray crystal structure of 9-CI TIBO complexed with HIV-1 reverse transcriptase.**

Since the conformations of nevirapine and TIBO derivatives complexed with reverse transcriptase bore such similarity, we wondered if a similar alkylaryl substitution that improved nevirapine activity could also provide an increase in broad-spectrum potency for the TIBO compounds. By superimposing the X-ray crystal structures of nevirapine and TIBO bound to reverse transcriptase, we deduced that there were two positions where an aryl group might interact with surrounding aromatic amino acid residues.
Figure 41. Overlay of nevirapine-HIV-1 reverse transcriptase complex and 9-Cl-TIBO-HIV-1 reverse transcriptase complex.

Shown above in Figure 41, since there is not perfect overlap of the 8-position of nevirapine (highlighted with a green arrow) with a particular position on the TIBO molecule, there is some ambiguity about the ideal location for the alkylaryl pharmacophore. Close inspection of the overlay suggested the installation of the side chain on either the 9- or 10- position on the TIBO skeleton (shown with pink arrows). Thus, the synthesis of both the 9-alkylaryl and 10-alkylaryl analogues must be undertaken (Figure 42).
1.4 Summary of 2003 Honour’s Project: “Studies Directed Towards the Synthesis of 9-Alkylaryl TIBO Derivatives”

For the author’s Honour’s project, under the supervision of Dr. W.W. Ogilvie, a synthetic route to the 9-alkylaryl TIBO derivatives was proposed. The features of the optimized TIBO derivative 160 that were known to be necessary for potency, including the thioimidazolidinone, the (S)-methyl group, and the dimethylallyl group, would be retained. We envisioned the use of a palladium-catalyzed coupling, such as the Sonogashira reaction, to attach the alkylaryl moiety.

The Janssen Research Foundation had already established a synthetic route to the 9-chloro TIBO derivative 163 from chloroisatoic anhydride 162 (Scheme 69). Since aryl chlorides do not undergo palladium coupling as readily as aryl iodides, we would use the Janssen synthesis as inspiration, but use iodoisatoic anhydride as starting material.
Scheme 69. The 9-chloro TIBO derivative 163 from chloroisatoic anhydride 162.

We decided to first attempt the synthesis of 9-phenethyl TIBO derivative 172 (Scheme 70). If this was successful, we would then apply the route to other alkylaryl TIBO derivatives. We wished to build the skeleton of the TIBO molecule as much as possible before installing the side chain, since this would simplify the syntheses of multiple derivatives. Illustrated in
Scheme 70 is the initial synthetic route, although only the first three steps were successful in practice.

Beginning with the commercially available 2-amino-5-iodobenzoic acid 164, iodoisatoic anhydride 165 was formed in 92% yield via a literature procedure.\textsuperscript{85} This was followed by an amide coupling with (L)-alanine methyl ester to produce 166 in 80% yield. Refluxing 164 in the presence of pyridinium hydrochloride formed the benzodiazepinedione 167 in 62% yield.
Scheme 70. Initial attempt to synthesize 9-phenethyl TIBO derivative 172.

The nitration of 167 did not go as smoothly as the initial steps of the synthesis. Although several nitration conditions were tried, the best yield that could be obtained was a mere 16%.
This poor yield, so early in our synthesis, led us to propose a new synthetic approach to 9-phenethyl TIBO 172.

Once again, we benefited from the abundance of chemistry developed by the Janssen Research Foundation in the development of our new synthetic route. This route involved the linkage of two building blocks via an amide coupling, followed by a nucleophilic aromatic substitution (S_NAr) reaction (Scheme 71).

**Scheme 71. Amide coupling-S_NAr route to benzodiazepinone skeleton.**

The first building block 176 was synthesized in three steps from commercially available methyl 2,5-dibromobenzoate 173 since the diiodo derivative was not readily available (Scheme 72). The methyl ester 173 was saponified using lithium hydroxide to give 2,5-dibromobenzoic acid 174 in 99% yield. Nitration then followed using fuming nitric acid to give 175 in a modest 40% yield. Finally, the carboxylic acid functionality was converted into an acyl chloride 176 using oxalyl chloride and a catalytic amount of DMF.
Scheme 72. Synthesis of acyl chloride building block 176 for second synthetic route to 9-phenethyl TIBO 172.

The second building block required for our synthesis was the monoprotected chiral diamine 181 which was synthesized via a modified literature procedure (Scheme 73). From Cbz-protected (L)-alanine, the amide 178 was produced in 87% yield in a two-step, one-pot reaction. The amide was converted into the nitrile 179 using cyanuric chloride. This was reduced in borane and the resulting primary amine was immediately protected as a tert-butyl carbamate to give 180 in 84% yield. Finally, the Cbz-protected amine was selectively deprotected using hydrogenolysis conditions to give the monoprotected chiral diamine 181.
Scheme 73. Synthesis of chiral monoprotected diamine 179 to be used in second synthetic route to 9-phenethyl TIBO 170.

As illustrated below, the benzoyl chloride 176 and the amine 181 were then coupled to produce 182 in a respectable 79% yield (Scheme 74). After deprotection of the Boc-protected amine using trifluoroacetic acid, 183 was produced via cyclization in dilute DMF at 90 °C.
Unfortunately, due to time constraints, our efforts in the synthesis of 9-phenethyl TIBO derivative 172 had to be temporarily abandoned. However, with the commencement of the author’s MSc in the fall of 2003, the project was resumed.

1.5 Objective

The main goal of this project was to devise a feasible route to 9-phenethyl TIBO 172. We would initially attempt the completion of the synthetic route shown in Scheme 74. After this was completed variations in the length and character of the alkyl linker moiety would then be attempted, such as propyl or ether linkages to the phenyl group. The aromatic group would
also be varied in an attempt to improve the potency of the derivatives. If subjection of these compounds to purified wild-type and mutant HIV-1 reverse transcriptase assays indicated reasonable potency, then the analogues would be tested in HIV-1 infected cells. In addition, a synthetic route towards the 10-alkylaryl TIBO derivatives would be a long-term goal.
Chapter 2. Results and Discussion

2.1 Synthetic route to the 9-phenethyl TIBO derivative 172: The amide coupling - S_NAr approach

To complete the synthesis of 9-phenethyl TIBO 172, shown in its entirety in Scheme 75, the amide and nitro groups of benzodiazepinone 183 would be simultaneously reduced using lithium aluminum hydride. The imidazolidinone ring would then be put in place with diphosgene, to give compound 184. After protection of the secondary amine as a “Boc” group, a Sonogashira coupling with phenylacetylene would result in the formation of 171. Hydrogenation of the alkyne would be followed by deprotection of the secondary amine using trifluoroacetic acid. The free amine would then be alkylated using dimethylallyl bromide to give 171. The conversion of the imidazolidinone to a thioimidazolidinone using P_2S_5 would complete the synthesis of 172.
Scheme 75. Complete synthetic route to 9-phenethyl TIBO 172.

It had been reported that similar amide functionalities to that of 183 were difficult to reduce. Harsh conditions, such as refluxing in high-boiling solvents in the presence of
multiple equivalents of lithium aluminium hydride, were required to give the triamines such as 185. Since the Janssen group never reported the isolation of triamines like 185, and Pfaendler and Weisner\textsuperscript{89} reported a similar triamine as air-sensitive, we decided not to attempt its isolation. Instead, we would immediately subject it to the imidazolidinone-forming conditions, using diphosgene and $N$-methyImorpholine, followed by refluxing in a water-dioxane solution. Similar conditions were utilized by the Pfaendler and Janssen groups in forming similar TIBO analogues, with variable success (36-79\%).\textsuperscript{84,89}

**Scheme 76. Proposed synthetic route to 184.**

Unfortunately, we were not successful in producing 184, demonstrated by a few examples of our attempts shown in Table 17. We tested different reducing reagents- lithium aluminium hydride (Entries 1,2), aluminum trihydride (Entry 2) and borane (Entry 4), with no luck. Attempts to purify the crude product obtained after the final step via flash column chromatography or recrystallization only led to smaller amounts of impure material that could not be identified via NMR or mass spectrometric methods.
Table 17. Examples of reduction conditions used in the attempted synthesis of 184.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Agent</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄</td>
<td>Dioxane</td>
<td>100 °C; 24 h</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH₄</td>
<td>THF</td>
<td>0 °C; 2 h</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>AlH₃</td>
<td>THF</td>
<td>RT; 24 h</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>BH₃·THF</td>
<td>THF</td>
<td>60 °C; 20 h</td>
<td>0%</td>
</tr>
</tbody>
</table>

Although, without a doubt, there were several other variables with which we could experiment, such as replacing diphosgene with phosgene, triphosgene, or carbonyl diimidazole, we wondered if we ought to try our organometallic coupling at this stage, instead. The aromatic ring in compound 183 is more electron-poor and, thus, is more activated towards oxidative addition than compound 184. We decided to take the inability to synthesize 184 as an initiative to modify our synthetic route.

As shown in Scheme 77, 183 would be coupled with phenylacetylene under Sonogashira conditions to produce 186. This would be hydrogenated to reduce both the nitro group and the alkyne to diamine 187. The imidazolidinone-ring formation would then be attempted using the previously described conditions. Finally, after alkylation of the secondary amine 188, the carbonyl group would be replaced with a thionyl group using P₂S₅.
Scheme 77. Modified synthetic route to 9-phenethyl TIBO 172.

The optimized Sonogashira reaction between 183 and phenylacetylene utilised [1,1’-bis(diphenylphosphino)ferrocene]dichloropalladium(II) as the palladium source, copper iodide, and diisopropylethylamine as base to give 186 in 57% yield (Scheme 78). A significant amount of homocoupled phenylacetylene was observed, despite careful deoxygenation of all liquid reagents. This was observed under both nitrogen and argon atmospheres and necessitated the addition of a large excess of phenylacetylene (>10 equivalents) to force the reaction to completion. Since the starting material and product were unresolvable via TLC, HPLC, or GC-MS, the reaction was followed via $^1$H NMR.
Scheme 78. Sonogashira coupling of 183 and phenylacetylene to produce 186.

Our attempts to hydrogenate the alkyne and nitro group catalysed by palladium on carbon were not fruitful. The reaction seemed to stall, requiring several equivalents of catalyst and the “product” that was observed on TLC was unisolable. It was at this point that our synthetic route’s biggest flaw became clear: it was far too long, cumbersome, and often low yielding for it to not work perfectly as on paper. Although we had scaled-up the synthesis of 183 as to have an abundance in case of potential road blocks, the S_NAr cyclization step was much lower yielding on a large scale (47% compared to 89%). In addition, the sheer length of the synthesis (17 steps including the synthesis of building blocks 179 and 181) was not particularly practical. If our aim was to devise a short and simple synthesis to be applied to multiple derivatives, we were falling very short. Thus, we began to explore other synthetic routes.

2.2 Synthetic route to the 9-phenethyl TIBO derivative 172: The bromoisatoic anhydride approach

At this time, we began to look at our original synthetic route to the 9-phenethyl TIBO derivative 172 (Scheme 70). Long after we had abandoned it, we had discovered an explanation as to why the nitration reaction proceeded so poorly. A review by Nightingale on anomalous nitration reactions suggested that polysubstituted halobenzenes could undergo oxidative decomposition side reactions when exposed to nitronium ions. If an electron-donating group, such as a mildly activating acetonilide group, is ortho or para to the halogen, the halogen may be eliminated via an oxidative mechanism (Scheme 79). The halogen cation generated is extremely unstable and will react with oxidizeable species in the reaction mixture; thus resulting in several side products.
Scheme 79. Anomalous nitration side-reaction of polysubstituted halobenzenes.

This reaction is most often observed with polysubstituted iodobenzenes and less frequently seen with other halogenated benzenes (I>Br>Cl>F). Since the Janssen Research Foundation had observed a 95% yield in the nitration reaction of chloro-substituted 192,86 we wondered if we might achieve better results with the bromo-derivative, than we had with the iodo-derivative (Scheme 80).

Scheme 80. Nitration of 9-halobenzodiazepine-2,5-diones.

Since the synthesis of bromo-192 would only require three steps, we could test this postulate quickly. Thus, our modified synthetic route (Scheme 81) to 9-phenethyl TIBO 172 combined aspects of those routes shown in Schemes 70 and 77.
Commercially available isatoic anhydride 194 would be brominated to give 195. After amide coupling with (L)-alanine methyl ester, 195 would be cyclized to form the benzodiazepine-2,5-dione 196. This compound would be subjected to nitration conditions to give 198. Sonogashira coupling of 198 with phenylacetylene would produce 199, which would be hydrogenated to reduce both the nitro and alkyne functionalities. Both amide functionalities of 200 would be reduced and then treated with diphosgene to give the imidazolidinone 188. Alkylation followed by the conversion of the imidazolidinone into a thioimidazolidinone would give our target 172.
Scheme 81. New synthetic route to 9-phenethyl TIBO derivative 172.

The first four steps of the synthesis went according to plan. Using a literature procedure,\textsuperscript{97} 194 was brominated to give bromoisatoic anhydride 195 in 82\% yield. Coupling 195 with
(L)-alanine methyl ester gave 196 in good yield. The cyclization in the presence of an excess of pyridinium hydrochloride and 4 Å molecular sieves to trap the methanol produced, gave benzodiazepine-2,5-dione 197 in 86% yield. Using the optimized conditions of a 1:1 mixture of fuming nitric acid – sulfuric acid at 0 °C, the nitration of 197 proceeded quickly producing 198 in a very respectable 79% yield. We were able to confirm the regioselectivity of the nitration via $^1$H NMR. The two aromatic protons coupled with a frequency of 2.4 Hz, which is in the typical range for meta coupling constants (1-3 Hz).\textsuperscript{91}

Scheme 82. Synthesis of benzodiazepin-2,5-dione 198.

Surprisingly, similar Sonogashira conditions to those used in the successful synthesis of 186 gave nothing but a mixture of starting material, decomposition products, and/or large amounts of homocoupled phenylacetylene. Several other Sonogashira conditions were attempted, including copper-free methodologies,\textsuperscript{92} which are known to reduce homocoupling (Table 18). Unfortunately, none of these were successful in producing 199. We found this
to be very surprising, since the aromatic ring of compound 199 is even more activated than 183 (Scheme 78), thus oxidative addition of the bromobenzene to the palladium (0) species should be rapid. Presumably, another step in the catalytic cycle was slow and/or the benzodiazepine-2,5-dione was unstable in Sonogashira conditions. In any case, we were not limited to the Sonogashira reaction to attach our phenethyl moiety and decided to investigate the Heck reaction as a means to attach this group.

Table 18. Attempted Sonogashira coupling between 195 and phenylacetylene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Source</th>
<th>Cul</th>
<th>Additives</th>
<th>Base</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(dppf)</td>
<td>yes</td>
<td>n/a</td>
<td>DIPEA</td>
<td>DMF; 70 °C 20 h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂(PPh₃)₂</td>
<td>yes</td>
<td>n/a</td>
<td>piperidine</td>
<td>THF; reflux 24 h</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>no</td>
<td>DABCO</td>
<td>Cs₂CO₃</td>
<td>MeCN; RT 48 h</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>PdCl₂(PPh₃)₂</td>
<td>no</td>
<td>no</td>
<td>piperidine</td>
<td>neat; 70 °C 24 h</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>no</td>
<td>no</td>
<td>piperidine</td>
<td>MeCN; RT 24 h</td>
<td>0</td>
</tr>
</tbody>
</table>

We decided to apply Littke and Fu’s conditions for the Heck coupling of styrene to 199, since they had observed excellent yields using both activated and deactivated aryl bromides and chlorides. The air-stable solid tri-*tert*-butylphosphonium tetrafluoroborate was used as the source for the tri-*tert*-butylphosphine ligand, which was formed after deprotonation with base. With tris(dibenzylideneacetone)dipalladium(0) as palladium source and
dicyclohexylmethylamine as base, 199 was coupled with styrene to produce 201 in excellent yield (Scheme 83).

**Scheme 83. Heck coupling of 199 and styrene to produce 201.**

Both the alkene and nitro groups were reduced simultaneously using hydrogen gas and palladium on carbon as catalyst to afford our desired product 200 in a reasonable 70% yield (Scheme 84).

**Scheme 84. Hydrogenation of 201 to afford aniline 200.**

Compound 200 was submitted to reductive conditions using borane in refluxing THF to give the triamine intermediate 202. Hall’s conditions for the oxidative cleavage of borane-amine adducts using iodine was found to be superior to acidic cleavage using aqueous hydrochloric acid. The triamine 202 was immediately reacted with diphosgene in the presence of N-methylmorpholine as base, and then refluxed in a water-dioxane solution to give 188 in a relatively low yield. Using lithium aluminium hydride in refluxing dioxane as reduction conditions, only afforded 188 in 5% yield.
Scheme 85. Synthesis of imidazolidinone 188 from 200.

Initial attempts to alkylate the secondary amine 188 using dimethylallyl bromide have been fruitless. The addition of potassium iodide or tetrabutylammonium iodide to catalyze the reaction did not result in synthesis of 203. Some starting material was recovered, along with trace amounts of two unidentified compounds, whose \(^1\)H NMR spectra did not resemble desired product 203.

Scheme 86. Unsuccessful alkylation of 188.

Efforts are currently underway in the Ogilive lab to devise alkylation conditions that will give 203, as well as optimizing the synthesis of imidazolidinone 188.
Chapter 3. Conclusions

After several setbacks in the attempt at synthesizing 9-phenethyl TIBO derivative 172 via the initial amide coupling-S_NAr route, this route was abandoned. It had become apparent that the route was too long and cumbersome to be suitable for making multiple 9-alkylaryl TIBO derivatives, even it was eventually successful.

Fortunately, we revisited a route previously explored in 2003, which involved two sequential amide couplings to form the benzodiazepine core. In this modified synthesis, a slight variation in the starting material was made in order to avoid oxidative side-reactions during the nitration reaction. A high-yielding Heck reaction successfully attached the phenethyl moiety. Although the synthesis of 172 has not yet been accomplished, only two steps remain. With minimal optimization of reaction conditions, we are confident that the synthesis will be completed successfully.

After the synthesis of 172 is achieved, the future direction of this project includes application of the synthetic route to other 9-alkylaryl derivatives. The development of a synthetic route to the 10-alkylaryl derivatives is also an imminent goal.
Chapter 4. Experimentals

Reactions were performed in oven- or flame-dried evacuated flasks under N₂ atmosphere and equipped with a magnetic stir bar and a rubber septum, unless otherwise noted. THF was freshly distilled from sodium/benzophenone, while dichloromethane and DMF were freshly distilled from calcium hydride. Pyridine was dried over 4 Å molecular sieves for 24 hours before use. Reagents were purchased from Sigma-Aldrich, Lancaster, and Strem chemical companies. Triethylamine and diisopropylethylamine were freshly distilled over calcium hydride. Styrene was distilled under vacuum before use. Phenylacetylene was distilled before use. N-methylmorpholine was freshly distilled over sodium. All other reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F₂₅₄ precoated 0.25 mm thick aluminium plates. TLCs were visualized using ultraviolet light, potassium permanganate, ceric ammonium molybdate, and/or p-anisaldehyde stains. When necessary, products were purified using flash column chromatography on silica gel 60 (230-400 mesh) or preparatory TLC glass plates precoated with silica gel (Si250F). Solvents were evaporated on rotary evaporators.

¹H and ¹³C NMR spectra were acquired using either a Varian Gemini 200 MHz (¹H); a Bruker Avance 500 MHz (¹H) and 125 MHz (¹³C); or a Bruker Avance 300 MHz (¹H) and 75 MHz (¹³C). Infrared spectra were acquired on a Bomem Michaelson 100 FTIR spectrometer. Mass spectra were obtained using a Kratos I1H instrument using either CI or EI ionization techniques. Melting points were determined using an Electrothermal Meltemp® apparatus and are uncorrected.
2,5-Dibromobenzoic acid

To a 250 mL flask containing methyl 2,5-dibromobenzoate (3.32 g, 11.2 mmol) was sequentially added THF (60 mL), methanol (20 mL), and water (20 mL). Lithium hydroxide monohydrate (1.17 g, 30.0 mmol) was added to the solution, which was then stirred vigorously for 2.5 hours, until deemed complete by TLC. The reaction mixture was concentrated to ~50 mL, followed by acidification (pH ~3) using concentrated hydrochloric acid. The solution was extracted with dichloromethane (4 x 100 mL) and the organic extracts were washed with brine (80 mL) and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded 174 (3.13 g, 99%) as a white powder. $^1$H NMR (acetone-$d_6$, 300 MHz) δ 7.98 (d, $J = 2.3$ Hz, 1H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.63 (dd, $J = 8.6$, 2.3 Hz, 1H).
2,5-Dibromo-3-nitrobenzoic acid

To a 500 mL flask equipped with a drying tube was added 174 (18.69 g, 66.79 mmol). Fuming nitric acid (175 mL) and concentrated sulfuric acid (~1 mL) were added sequentially and the reaction was stirred at room temperature for 4.5 hours, until deemed complete by TLC. The orange solution was carefully poured over ice (~500 g) and stirred until the ice was fully melted. Water (1000 mL) was then added, followed by isolation of the precipitate via suction filtration, rinsing several times with water. The collected solid was dried in vacuo to afford 175 (9.86 g, 45%) as an off-white solid. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\) 8.34 (d, \(J=2.3\) Hz, 1H), 8.02 (d, \(J=2.3\) Hz, 1H).

\(N\)-Carbobenzyloxy-(L)-alaninamide\(^{88}\)

To a 500 mL flask containing CBZ-(L)-alanine (24.76 g, 110.9 mmol) in THF (250 mL) at 0 °C was added triethylamine (16.2 mL, 116.5 mmol), followed by ethylchloroformate (11.6 mL, 121.1 mmol). The reaction mixture was stirred for 1 hour at 0 °C, after which time
concentrated ammonium hydroxide (15.8 mL, 221.8 mmol) was added via syringe. After warming gradually to room temperature, the reaction was stirred for an additional 15 hours. The solvent was then removed in vacuo and ethyl acetate (200 mL) and water (200 mL) were added to the reaction flask. After separating the organic phase from the aqueous, the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic fractions were washed sequentially with saturated sodium bicarbonate solution (200 mL), distilled water (200 mL), and brine (200 mL). After drying over anhydrous sodium sulfate, the solvent was removed in vacuo to afford 178 (21.52 g, 87%) as a white powder whose spectral properties corresponded to those in the literature.\textsuperscript{94} \textsuperscript{1}H NMR (acetone-\textit{d}_6, 300 MHz) \( \delta \) 7.26-7.38 (m, 5H), 7.02 (br s, 1H), 6.54 (br s, 2H), 5.06 (s, 2H), 4.20 (dq, \( J = 7.4, 7.4 \) Hz, 1H), 1.33 (d, \( J = 7.6 \) Hz, 3H).

\textit{N-(Carbobenzyloxy)-(S)-2-aminopropionitrile}\textsuperscript{88}

To a 500 mL flask containing 178 (20.00 g, 90.0 mmol) in a minimal amount of DMF (100 mL) was added cyanuric chloride (8.30 g, 45.0 mmol). After stirring for 0.5 hours at room temperature, the reaction was deemed complete by TLC and was quenched with water (100 mL). While stirring for an additional 0.5 hour, a white precipitate formed, which was isolated via suction filtration, rinsing several times with distilled water. The precipitate was dried in vacuo to give 179 (14.34 g, 78%) as a fluffy white powder whose spectral properties corresponded to literature values.\textsuperscript{95} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \( \delta \) 7.29-7.38 (m, 5H), 5.12 (br s, 3H), 4.65 (t, \( J = 7.6 \) Hz, 1H), 1.52 (d, \( J = 7.4 \) Hz, 3H).
(S)-(2-benzylxycarbonylamino-propyl)carbamic acid tert-butyl ester

To a 500 mL flask containing a solution of 179 (6.60 g, 32.3 mmol) in THF (200 mL) at 0 °C was added a 1.0 M solution of borane in THF (64.6 mL, 64.6 mmol). The reaction mixture was warmed to room temperature and stirred for 19 hours. After quenching with methanol (100 mL), the reaction mixture was concentrated. To the resulting viscous oil was again added methanol (200 mL) and the reaction mixture was allowed to stir for 12 hours. After removal of the solvent in vacuo, the resultant clear, colourless oil was dissolved in THF (150 mL). Di-tert-butyl dicarbonate was added, followed by triethylamine (4.86 mL, 34.9 mmol). After stirring for 7 hours at room temperature, the solvent was removed in vacuo and ethyl acetate (100 mL) and water (50 mL) were added. The organic phase was separated from the aqueous, which was subsequently extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the crude product was recrystallized from 30:1 hexanes-ethyl acetate (100 mL). The resulting white solid was collected by suction filtration, rinsing several times with hexanes and dried in vacuo to afford 180 (8.23 g, 84%) as a white solid. 

$^1$H NMR (acetone-$d_6$, 300 MHz) $\delta$ 7.28-7.35 (m, 5H), 6.26 (d, $J$ = 6.5 Hz, 1H), 6.13 (br s, 1H), 5.04 (s, 2H), 3.76 (dq, $J$ = 6.5, 6.5 Hz, 1H), 3.14 (t, $J$ = 6.3 Hz, 2H), 1.39 (s, 9H), 1.12 (d, $J$ = 6.7 Hz, 3H).
To a solution of 180 (1.68 g, 5.45 mmol) in ethanol (99%) (40 mL) was added 10% palladium on carbon (0.17 g). The resulting suspension was stirred under an atmosphere of H₂ at room temperature for 6.5 hours, until the reaction was deemed complete by TLC. The apparatus was then purged with N₂ several times to remove H₂ and the black suspension was filtered by suction through a celite pad. The celite pad was carefully rinsed several times with dichloromethane and was disposed of with caution. The filtrate was concentrated and dried in vacuo to afford 181 (0.78 g, 82%) as a pale brown oil, whose spectral properties corresponded to literature values. ¹H NMR (CDCl₃, 300 MHz) δ 5.07 (br s, 1H), 3.06-3.12 (m, 1H), 2.91-3.01 (m, 1H), 2.79-2.87 (m, 1H), 1.75 (s, 2H), 1.38 (s, 9H), 1.02 (d, J = 6.3 Hz, 3H).
(S)-[2-(2,5)-Dibromo-3-nitro-benzoylamino)-propyl]carbamic acid tert-butyl ester

To a 100 mL flask containing 175 (0.884 g, 2.72 mmol) in dichloromethane (25 mL) was added oxalyl chloride (0.24 mL, 3.91 mmol). The addition of two drops of DMF resulted in the production of gas. After stirring for 0.5 hours at room temperature, the reaction mixture was concentrated and dried in vacuo to yield a pale yellow solid, which was immediately dissolved in dichloromethane (20 mL). The reaction mixture was cooled to 0 °C and 181 (0.474 g, 2.72 mmol) was added, followed by N,N-diisopropylethylamine (0.78 mL, 4.49 mmol). A catalytic amount of N,N-dimethylaminopyridine (0.025 g, 0.204 mmol) was then added and the reaction mixture was stirred at 0 °C for one hour, until deemed complete by TLC. After being washed sequentially with 10% hydrochloric acid solution (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL), the organic phase was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave an off-white powder which was purified via flash column chromatography (65:35 hexanes-ethyl acetate) to afford 182 (0.77 g, 79%) as a white powder. m.p. 187-188 °C; IR (thin film) 3342, 3297, 3058, 2936, 2975, 1693, 1661 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 8.52 (d, J = 8.2 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 6.96 (t, J = 6.1 Hz, 1H), 3.90-4.06 (m, 1H), 2.99-3.13 (m, 2H), 1.39 (s, 9H), 1.07 (d, J = 6.7 Hz, 3H); ¹³C NMR (DMSO-d₆, 75 MHz) δ 164.62 (C), 158.81 (C), 152.28 (C), 143.89 (C), 134.78 (CH), 128.10 (CH), 121.93 (C), 110.52 (C), 78.58 (C), 46.60 (CH), 45.26 (CH₂), 29.17 (CH₃), 18.26 (CH₃); MS (Cl) m/z 484 (M⁺ + 4), 482 (M⁺ + 2), 480 (M⁺).
To a 25 mL flask containing 182 (0.30 g, 0.62 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1.2 mL). The resultant solution was stirred at room temperature for 4 hours, until deemed complete by TLC. The reaction mixture was stripped of solvent and excess trifluoroacetic acid was removed by azetotropically distillation with benzene (3 x 10 mL). The product was dried in vacuo to obtain the crude trifluoroacetate salt of the primary amine, which was immediately dissolved in DMF (80 mL). Triethylamine (0.26 mL, 1.86 mmol) was added and the reaction mixture was heated to 90 °C for 4 hours, until the reaction was deemed complete by TLC. After cooling, the light brown solution was added to a separatory funnel containing water (600 mL). This was extracted with ethyl acetate (4 x 150 mL). The combined organic fractions were washed with distilled water (100 mL) and brine (100 mL) before being dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a bright orange powder which was purified via flash column chromatography (3:1 ethyl acetate-hexanes) to afford 183 (0.16 g, 86%) as a bright orange powder. m.p. 193 °C; IR (Nujol) 3314, 3170, 3105, 3052, 2925, 1667 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 8.99 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.45 (d, J = 2.6 Hz, 1H), 7.17 (s, 1H), 3.77-3.83 (m, 1H), 3.64 (dd, J = 13.5 Hz, 6.1 Hz, 1H), 3.52 (qd, J = 7.5, 3.2 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.20 (C), 144.98 (CH), 143.17 (C), 135.48 (C), 133.82 (CH), 123.67 (C), 107.26 (C), 53.64 (CH₂), 48.49 (CH), 19.06 (CH₃); MS (El) m/z 301 (M⁺ + 2), 299 (M⁺).
(S)-3-Methyl-9-nitro-7-phenylethynyl-1,2,3,4-tetrahydrobenzo[e]-[1,4]-diazepin-5-one

To a 10 mL flask was added 183 (0.056 g, 0.187 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.015 g, 0.0187 mmol), and copper iodide (0.007 g, 0.0373 mmol). Via syringe, DMF (2 mL) and DIPEA (0.241 g, 0.748 mmol) were added and the reaction mixture was then sparged with N₂ for one hour. Phenylacetylene (0.029 g, 0.280 mmol) was added and the reaction was heated to 80 °C. After 22.5 hours, the reaction was deemed complete by ¹H NMR, water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed sequentially with water (20 mL) and brine (20 mL) before being dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, the solid product was purified via flash column chromatography (3:1 ethyl acetate-hexanes) to afford 186 (0.034 g, 57%) as a bright red powder. m.p. 210-212 °C; IR (thin film) 3386, 3320 (br), 3065, 2959, 2925, 2855, 2247, 1655, 1528, 1442, 1414, 1353, 1252 cm⁻¹; ¹H NMR (DMSO-d₆, 500 MHz) δ 8.94 (s, 1H), 8.47 (d, J = 3.5 Hz, 1H), 8.33 (s, 1H), 7.54-7.56 (m, 2H), 7.40-7.41 (m, 3H), 3.59-3.69 (m, 2H), 3.43-3.50 (m, 1H), 1.14 (d, J = 6.2 Hz, 3H); ¹³C NMR (DMSO-d₆, 125 MHz) δ 165.54 (C), 143.43 (CH), 143.04 (C), 134.31 (C), 132.39 (CH), 131.23 (CH), 128.68 (CH), 128.64 (CH), 123.05 (C), 122.12 (C), 108.01 (C), 88.30 (C), 87.33 (C), 52.71 (CH₂), 46.92 (CH), 18.06 (CH₃); MS (EI) m/z 321 (M⁺).
5-Bromoisatoic anhydride\textsuperscript{97}

\[ \text{195} \]

To a 1000 mL flask containing isatoic anhydride (20.00 g, 122.66 mmol) was added water (320 mL). The resulting suspension was heated to 50 °C and bromine (19.99 g, 125.12 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred for an additional 60 minutes at 50 °C, after which it was cooled to room temperature. The solid was isolated via suction filtration, rinsing several times with water and acetone, until the observed colour of the solid was off-white. The solid was dried \textit{in vacuo} overnight to yield \textbf{195} (24.36 g, 82\%) as an off-white powder whose spectral properties matched literature values.\textsuperscript{97} \textsuperscript{1}H NMR (DMSO-\textit{d}_6, 200 MHz) \( \delta \) 11.85 (s, 1H), 7.84-7.95 (m, 2H), 7.04-7.10 (m, 1H).

\[(S)-2-(2-Amino-5-bromobenzoylamino)propionic acid methyl ester\]

\[ \text{196} \]

To a 1000 mL flask containing \textbf{195} (23.30 g, 96.30 mmol) in DMF (300 mL) was added (L)-alanine methyl ester·HCl (14.79 g, 105.93 mmol). Diisopropylethylamine (37.34 g, 288.90
mmol) was added, followed by hydroxybenzotriazole (19.52 g, 144.45 mmol). The reaction was stirred at room temperature for 20 hours, until deemed complete by TLC. At this point, the reaction mixture was poured into a beaker containing 2500 mL of water. The resulting precipitate was filtered off, rinsing several times with water. After drying overnight in vacuo, 196 (24.77 g, 85%) was obtained as an off-white powder which was used without further purification. m.p.122-123 °C; IR (thin film) 3459 (br), 3366, 2994, 1736, 1638, 1483, 1216 cm⁻¹; ¹H NMR (acetone-δ₆, 300 MHz) δ 7.95 (br s, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.27 (dd, J = 2.3, 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.37 (br s, 2H), 4.60 (qd, J = 7.3, 7.3 Hz, 1H), 3.69 (s, 3H), 1.47 (d, J = 7.3 Hz, 3H); ¹³C NMR (acetone-δ₆, 75 MHz) δ 174.95 (C), 169.63 (C), 151.10 (C), 136.42 (CH), 132.09 (CH), 120.39 (CH), 117.64 (C), 107.35 (C), 53.27 (CH), 50.10 (CH₃), 18.39 (CH₃); MS (El) m/z 302 (M⁺ + 2), 300 (M⁺).
(S)-7-Bromo-3-methyl-3,4-dihydro-1H-benzo[e]-[1,4]-diazepine-2,5-dione

To a 1000 mL flask containing **196** (18.92 g, 62.85 mmol) in pyridine (200 mL) was added pyridinium hydrochloride (15.66 g, 62.85 mmol). The reaction flask was equipped with a dropping funnel (stopcock open) containing activated 4 Å molecular sieves to which was attached a water-cooled condenser (see accompanying diagram). The side-arm of the dropping funnel was wrapped with cotton and the reaction was refluxed for 42 hours, until deemed complete by TLC. After cooling to room temperature, the yellow solution was poured into a beaker containing ice water (2500 mL). The resulting off-white precipitate was isolated via suction filtration, washing several times with water. After drying the solid overnight *in vacuo*, **197** (14.54 g, 86%) was obtained as an off-white powder, which was used without further purification. m.p. 285 °C (dec.); IR (thin film) 3397 (br), 2906, 1675, 1636, 1482, 1429 cm⁻¹; ¹H NMR (DMSO-d₆, 500 Mhz) δ 10.47 (s, 1H), 8.55 (d, J = 5.1 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 2.5, 8.6 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 3.83-3.88 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H); ¹³C NMR (DMSO-d₆, 125 MHz) d 171.89 (C), 166.27 (C), 136.08 (C), 134.76 (CH), 132.50 (CH), 127.97 (C), 123.08 (CH), 115.60 (C), 47.14 (CH), 13.63 (CH₃); MS (EI) m/z 270 (M⁺ + 2), 268 (M⁺).
To a 250 mL flask equipped with a drying tube was added 197 (14.43 g, 53.62 mmol). Fuming nitric acid (100 mL) was added and the reaction mixture was cooled to 0 °C. Concentrated sulfuric acid (100 mL) was added gradually and the reaction was stirred for a further 15 minutes at 0 °C, until deemed complete by TLC. The orange solution was poured into ~1000 g ice. The resulting pale yellow powder was isolated via suction filtration, rinsing several times with cold water. Drying in vacuo overnight yielded 198 (13.31 g, 79%) as a pale yellow powder, which was used without further purification. m.p. 218 °C (dec.); IR (Nujol) 3331, 3264, 1723, 1670, 1459, 1379 cm⁻¹; ¹H NMR (DMSO-d₆, 500 MHz) δ 10.09 (s, 1H), 8.89 (d, J = 5.6 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 3.99-4.04 (m, 1H), 1.25 (d, J = 6.7 Hz, 3H); ¹³C NMR (DMSO-d₆, 125 MHz) δ 171.24 (C), 164.83 (C), 141.31 (C), 137.67 (CH), 132.15 (C), 130.73 (CH), 129.29 (C), 115.76 (C), 46.82 (CH), 13.11 (CH₃); MS (El) m/z 315 (M⁺ + 2), 313 (M⁺).
(S)-8-Methyl-4-phenethyl-6,7,8,9-tetrahydro-2H-2,7,9a-triazabenz[c,d]azulen-1-one

To a 250 mL flask equipped with a condenser and containing 200 (1.50 g, 4.85 mmol) in THF (50 mL) was added a 1.0 solution of borane in THF (97 mL, 97.03 mmol). The solution was refluxed for 48 hours, after which it was cooled to room temperature. At this time, Hall’s oxidative work-up procedure was used to cleave the borane-amine adducts. Triethylamine (3.63 g, 35.87 mmol), glacial acetic acid (7.5 mL, 127.5 mmol), and iodine (2.72 g, 10.70 mmol) were added sequentially to the reaction mixture. After stirring at room temperature for 2 hours, the flask’s contents were poured into a separatory funnel containing concentrated sodium hydroxide solution (50 mL) and a saturated sodium thiosulfate solution (50 mL). After ensuring that the pH was >11 (additional NaOH pellets were added, if necessary), the solution was extracted with diethyl ether (4 x 100 mL). The combined organic extracts were washed with brine (200 mL) and dried over anhydrous magnesium sulfate. After removal of the solvent on rotovaporator, the pale yellow oil was dried overnight in vacuo. At this time, the viscous oil was dissolved in dichloromethane (50 mL) and N-methylmorpholine (1.52 g, 15.04 mmol) was added. The reaction mixture was brought to 0 °C and a solution of diphosgene (0.96 g, 4.85 mmol) in dichloromethane (10 mL) was added over 15 minutes. The reaction mixture was stirred for an additional 30 minutes at 0 °C and was warmed to room temperature for one hour. The solution was concentrated and the resulting off-white solid was suspended in an 85:15 water-dioxane solution (50 mL). The flask was equipped with a water-cooled condenser, and the reaction mixture was refluxed for one hour. After cooling to room temperature, the pale yellow
solution was washed with dichloromethane (20 mL) and then was rendered basic (pH>10) using concentrated ammonium hydroxide solution. The resulting cloudy white mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), before being dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, the product was purified via flash column chromatography (3% methanol in chloroform) to yield 188 (0.527 g, 35%) as an off-white powder. m.p. 188-190 °C; IR (thin film) 3450 (br), 3192, 3030, 2966, 2922, 1692 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 10.31 (s, 1H), 7.16-7.31 (m, 5H), 6.85 (s, 1H), 6.63 (s, 1H), 4.33 (dd, J = 2.1, 13.2 Hz, 1H), 4.23 (d, J = 16.5 Hz, 1H), 4.15 (d, J = 16.5 Hz, 1H), 3.36 (dd, J = 9.9, 13.2 Hz, 1H), 3.14-3.24 (m, 1H), 2.88 (s, 4H), 1.77 (br s, 1H), 1.33 (d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 156.13 (C), 141.66 (C), 135.21 (C), 128.67 (C), 128.38 (CH), 128.32 (CH), 127.10 (C), 125.91 (CH), 125.01 (C), 119.71 (CH), 107.55 (CH), 54.17 (CH), 53.81 (CH₂), 53.27 (CH₂), 38.39 (CH₂), 37.79 (CH₂), 20.92(CH₃); MS (El) m/z 307 (M⁺).

(S)-9-Amino-3-methyl-7-phenethyl-3,4-dihydro-1H-benzo[e]-[1,4]-diazepine-2,5-dione

To a 1000 mL flask containing 201 (2.56 g, 7.593 mmol) in methanol (250 mL) was added 10% palladium on carbon (0.100 g). The resulting suspension was stirred under an atmosphere of H₂ at room temperature for 12 hours, until the reaction was deemed complete by TLC. After purging the reaction mixture several times with N₂ to remove H₂, it was filtered over a celite pad. The celite was carefully rinsed several times with dichloromethane and was disposed of with caution. After removal of the solvent in vacuo, the crude product
was purified via flash column chromatography (3% methanol in chloroform) to afford 200 (1.64 g, 70%) as an off-white powder. m.p. 121-123 °C; IR (thin film) 3447, 3372, 3260 (br), 3080, 3061, 3027, 2921, 1705, 1651, 1454, 1307, 1270 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 9.36 (s, 1H), 7.99 (d, J = 5.0 Hz, 1H), 7.24-7.28 (m, 2H), 7.13-7.19 (m, 4H), 6.67 (s, 1H), 4.14 (br s, 2H), 3.90 (m, 1H), 2.77-2.88 (m, 4H), 1.46 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 172.95 (C), 170.08 (C), 141.44 (C), 139.80 (C), 138.57 (C), 128.36 (CH), 128.35 (CH), 127.62 (C), 125.97 (CH), 121.16 (C), 119.89 (CH), 119.73 (CH), 48.00 (CH), 37.39 (CH₂), 37.20 (CH₂), 13.61 (CH₃); MS (EI) m/z 309 (M⁺).

(S)-3-Methyl-9-nitro-7-styryl-3,4-dihydro-1H-benzo[e]-[1,4]-diazepine-2,5-dione

To a 100 mL flask containing 198 (0.485 g, 1.544 mmol), tri-tert-butylphosphonium tetrafluoroborate (0.045 g, 0.154 mmol), and tris(dibenzylideneacetone)dipalladium(0) (0.071 g, 0.0772 mmol) was added anhydrous dioxane (20 mL). After sparging the solution with nitrogen for 30 minutes, N,N-dicyclohexylmethylamine (0.664 g, 3.397 mmol) and styrene (0.193 g, 1.853 mmol) were added sequentially. The reaction was stirred at room temperature overnight, until deemed complete by TLC. The reaction mixture was filtered through a celite pad, rinsing several times with ethyl acetate. After removal of the solvent in vacuo, the crude product was purified via flash column chromatography (5% methanol in chloroform) to yield 201 (0.507 g, 97%) as a bright orange powder. m.p. 254 °C (dec.); IR (Nujol) 3381, 3342, 3074, 2955, 2923, 1700, 1661, 1458, 1376, 1246, 1170 cm⁻¹; ¹H NMR (DMSO-d₆, 500 MHz) δ 10.06 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.45 (d, J = 2.1 Hz, 1H),
8.27 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 7.3 Hz, 2H), 7.29-7.53 (m, 5H), 3.98-4.07 (m, 1H), 1.26 (d, J = 6.7 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ 171.44 (C), 166.12 (C), 141.21 (C), 136.36 (C), 134.03 (C), 132.72 (CH), 131.23 (CH), 130.90 (C), 128.76 (CH), 128.52 (C), 128.29 (CH), 126.81 (CH), 125.51 (CH), 125.00 (CH), 46.98 (CH), 13.27 (CH$_3$); MS (EI) $m/z$ 337 (M$^+$).
Claims to Original Research

1. Prepared several substrates in order to investigate the use of dialkyl tartrate acetals as chiral auxiliaries in the asymmetric formation of quaternary centres.

2. Examined the catalytic ability of hydrazide compounds in the Diels-Alder reaction, hydride reduction of $\alpha,\beta$-unsaturated aldehydes, and the $\alpha$-chlorination of aldehydes.

3. Investigated two synthetic routes to the novel 9-phenethyl TIBO derivative.
References


15. For reviews on $\lambda_{1,3}$ strain see: (a) Johnson, F. *Chem. Rev.* 1968, 68, 375. (b) Hoffmann, R.W. *Chem. Rev.* 1989, 89, 1841.


