Expanding the
Organocatalyzed α-Chlorination-Aldol Reaction

by
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Abstract

Organocatalysis, while still a relatively new field in organic chemistry, now plays an indispensable role in organic synthesis. Transformations not accessible by classical synthetic methods are now not only routine, but mild, high yielding and increasingly sophisticated in what they can achieve. One such reaction is the α-chlorination-aldol reaction developed by the Britton group in 2013. This reaction has been demonstrated to provide access to stereochemically rich chlorohydrins from readily available and achiral starting materials. The reaction has found extensive utility in the concise synthesis of imino-cyclitols and carbohydrate analogues.

In this thesis a more general approach to the tandem α-chlorination-aldol with different electrophiles or ketones is investigated. Within, we show that azodicarboxylates can be used as electrophiles to functionalize aldehydes prior to submission to an aldol reaction. These aminated aldol adducts are further investigated for their utility in synthesizing imino-cyclitols, and their ability to form cyclic, polyhydroxylated hydrazones.

As well, new substrates are investigated for their propensity to engage in an α-chlorination-aldol reaction. Four new substrates are demonstrated to form the corresponding chlorinated aldol adducts in moderate yields and high enantioselectivity. Furthermore, we demonstrate that these new aldol adducts can provide access to novel, natural product-like scaffolds.

Keywords: organocatalysis; methodology; proline; amination; aldol
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# Table of Contents

Approval........................................................................................................................................... ii
Abstract.............................................................................................................................................. iii
Acknowledgements.......................................................................................................................... iv
Table of Contents............................................................................................................................ v
List of Tables....................................................................................................................................... viii
List of Figures..................................................................................................................................... ix
List of Schemes.................................................................................................................................... x
List of Abbreviations........................................................................................................................ xii

## Chapter 1. Introduction ......................................................................................................................... 1

1.1. Asymmetric Catalysis .................................................................................................................... 1
1.2. Asymmetric Organocatalysis .......................................................................................................... 2
  1.2.1. Introduction to Organocatalysis .............................................................................................. 2
  1.2.2. Organocatalyzed Aldol Reactions .......................................................................................... 4
  1.2.3. Organocatalyzed α-Functionalization of Aldehydes ............................................................... 8
  1.2.4. Mechanism of Enamine Catalysis ........................................................................................... 11
  1.2.5. Kinetic and Dynamic Kinetic Resolutions Facilitated by Secondary Amines .................... 15
1.3. Britton DKR α-Chlorination-Aldol Reaction ................................................................................ 16
1.4. Thesis Overview ........................................................................................................................... 17

## Chapter 2. Azodicarboxylates in a Tandem Aldol Reaction and Potential Applications ....................... 19

2.1. α-Amination-Aldol Exploration .................................................................................................... 19
  2.1.1. Discovery and Optimization .................................................................................................... 19
  2.1.2. Determination of DKR ........................................................................................................... 21
2.2. Elaboration of Amination-Aldol Adducts .................................................................................... 23
  2.2.1. Strategies to Prepare Pyrrolidines .......................................................................................... 23
  2.2.2. Synthesis of Hydrazones and Characterization ..................................................................... 29
2.3. Conclusion .................................................................................................................................... 29
2.4. Experimental Information .......................................................................................................... 29
  2.4.1. General Considerations .......................................................................................................... 29
  2.4.2. General Procedures ............................................................................................................... 30
  2.4.3. Preparation and Characterization Data ................................................................................... 31
    Preparation of Hydrazone (45) ....................................................................................................... 31
    Preparation of Hydrazone (59) ....................................................................................................... 32
    Preparation of Acylated-Hydrazone (57) ...................................................................................... 34
    Reduction of Acylated Hydrazine (58) ........................................................................................... 34
  2.4.4. NMR Spectra ......................................................................................................................... 36
  2.4.5. HPLC Traces ......................................................................................................................... 40

## Chapter 3. Expanding the Ketone Scope of the α-Chlorination-Aldol Reaction .................................... 41

3.1. Exploration of Potential Aldol Donors ......................................................................................... 41
List of Tables

Table 2.1  Abbreviated Optimization Table of α-Amination-Aldol reaction ............ 20
Table 2.2  Outcome of DKR Determination Experiments. .................................. 22
Table 2.3  Reduction Conditions for N-N Bond Cleavage................................. 24
Table 2.4  Boc-Deprotection Conditions of Hemiaminal (56) ............................ 27
Table 3.1  Increasing Conversion with Increasing Purity of Thiopyranone ............ 49
Table 3.2  Optimizing Equivalents of Ketone and Aldehyde. .............................. 49
Table 3.3  Solvent Optimization for α-Chlorination-Aldol Reaction ..................... 50
Table 3.4  Workups and Purifications for Crude Cyclohexanone Aldol Adduct ...... 51
Table 3.5  Effect of Water Concentration on Conversion .................................... 53
List of Figures

Figure 1.1  (R) and (S) Enantiomers of thalidomide respectively………………………………1
Figure 1.2  Zimmerman-Traxler Transition State (36) Proposed by List for Proline
Catalyzed Aldol Reactions. ..............................................................................................12
Figure 1.3  Modelled Houk-List Transition States for Acetone and Cyclohexanone..13
Figure 1.4  Seebach-Eschenmoser Mechanism and Oxazolidinone (37a,b). ..........13
Figure 1.5  Generally Accepted Mechanism for Proline Catalysis..............................14
Figure 1.6  Kinetic Resolution and Dynamic Kinetic Resolution, where k1≠k2 ..........15
Figure 2.1  1H NMR (400 MHz) of the Purified Aldol adduct (43a) by Adamson. ......20
Figure 2.2  Equilibrium between Cyclized Aminal and Aldol Adduct .......................25
Figure 2.3  Synthesis of Hydrazones (45) and (59). ......................................................29
Figure 3.1  Visual Purity of Thipyranone: (L-R) Commercially available, Purified with
just Charcoal, Purified with Charcoal and Silica Plug. .................................................48
Figure 3.2  Crude 1H NMR of Proposed Intermediate (Compound (84) or (85)) with
zoom. .................................................................................................................................52
Figure 3.3  Visual Differences in Water Concentration (L-R: 0 vol%, 0.5 vol%, 1.0
vol%, 3.0 vol%, 5.0 vol% and 10 vol%). .........................................................................53
Figure 3.4  Scope of α-Chlorination-Aldol Reaction ( Compound (81) isolated as diol
after reduction). ..............................................................................................................54
Figure 3.5  Synthesis of THFs (94), (95), (96), (97), and (98). .................................56
Figure 3.6  Synthesis of Pyrrolidines (99), (100), and (101).................................57
List of Schemes

Scheme 1.1 Eder-Sauer-Wiechert (1971) and Hajos-Parrish (1974) Reactions respectively. ................................................................. 3
Scheme 1.2 First Organocatalyzed Intermolecular Aldol by List (2000) .................. 3
Scheme 1.3 MacMillan’s Organocatalyzed Diels-Alder Reaction (2000).............. 4
Scheme 1.4 List’s Mannich and Aldol Reactions using Hydroxyacetone ............... 5
Scheme 1.5 Cordova’s and Ender’s Reactions of Dihydroxylated Ketones in Aldol
Reactions ................................................................................................................. 6
Scheme 1.6 Cyclohexanone (23) in an Aldol Reaction ........................................... 7
Scheme 1.7 Ward’s Thiopyranone (24) Aldol reaction and Application to Polyketide
synthesis ...................................................................................................................... 7
Scheme 1.8 MacMillan Demonstrating Aldehydes as Aldol Reaction Donors ........ 8
Scheme 1.9 Amination of Aldehydes by List and Jørgensen (2002) ....................... 9
Scheme 1.10 Amination of Aldehydes and Applications to the Synthesis of Evan’s
Auxiliary and a Protected Amino-acid ................................................................. 9
Scheme 1.11 Hayashi and Coworkers Aminooxylation Reaction ......................... 10
Scheme 1.12 Jørgensen’s Sulfenylation of Aldehydes ........................................... 10
Scheme 1.13 α-Chlorination of Aldehydes by MacMillan and Jørgensen ............. 11
Scheme 1.14 Iminium and Enamine activation modes facilitated by Proline .......... 12
Scheme 1.15 Blackmond’s Proposed Mechanism for the Decomposition of
Oxazolidinone ........................................................................................................... 14
Scheme 1.16 Ward’s DKR Aldol Reaction using Thiopyran Aldehydes ................ 16
Scheme 1.17 Britton DKR α-Chlorination-Aldol Reaction .................................... 16
Scheme 1.18 Currently Understood Mechanism for α-Chlorination-Aldol Reaction .... 17
Scheme 1.19 Current applications of α-Chlorination-Aldol .................................. 17
Scheme 1.20 Goal of this thesis- a more general tandem methodology .................. 18
Scheme 2.1 Amination Aldol Reaction Developed by Adamson ......................... 19
Scheme 2.2 Possible Outcomes of Aldol Reaction with Aldehyde Adducts Formed by
D-proline ................................................................................................................... 21
Scheme 2.3 Determination of Configuration by nOe coorelations ......................... 22
Scheme 2.4 Initial Strategy for Pyrrolidine Synthesis ......................................... 23
Scheme 2.5 Elimination Strategy for Cleaving N-N bond ................................... 24
Scheme 2.6 New Protecting group Strategy using bis-Boc Azodicarboxylate (52) ...... 25
Scheme 2.7 Acylation of Amination-Aldol Adducts .............................................. 26
Scheme 2.8 Reduction to Compound (56) using Raney Nickel ......................... 26
Scheme 2.9 Reducing Presumed Aminal (56) ...................................................... 27
Scheme 2.10 Boc Deprotection of Presumed Hemiaminal (56) ............................. 27
Scheme 2.11 Acylation of Hydrazone (45) ............................................................. 28
Scheme 2.12 Samarium (II) Diiodide Reduction Leading to Hydrazine (58) ....... 28
Scheme 3.1  The Goal of the Research Presented in this Chapter. ........................................41
Scheme 3.2  Investigating Aldehydes as Donors in α-Chlorination-Aldol.................42
Scheme 3.3  α-Chlorination-Aldol with Cyclopentanone gave poor Diastereoselectivity. .................................................................43
Scheme 3.4  α-Chlorination-Aldol Reaction with Cyclohexanone.........................43
Scheme 3.5  Preparation of TBS protected ketones (69-71). ........................................44
Scheme 3.6  bis-TBS protected Dihydroxyacetone (70) in an Aldol Reaction........44
Scheme 3.7  TBS-protected Hydroxyacetone (69) Aldol Reaction............................45
Scheme 3.8  Preparation of α-nitrogen Ketones..........................................................45
Scheme 3.9  Azidoacetone (76) in an α-Chlorination-Aldol reaction..................46
Scheme 3.10 Thiopyranone in α-Chlorination-Aldol Reaction.............................46
Scheme 3.11 Newly Identified Ketones for α-Chlorination-Aldol Reaction...........47
Scheme 3.12 Formation of Sulfite Salts with Aldehydes........................................47
Scheme 3.13 Procedure for Isolating Pyranone Aldol Adducts..............................51
Scheme 3.14 Determination of Enantiomeric Excess by Formation of PNB-esters (92). .................................................................55
Scheme 3.15 Synthesis of THF Rings from Chlorohydrins.......................................56
Scheme 3.16 Reductive Amination-Cyclization to form Pyrrolidines from Chlorohydrins. ........................................................................56
Scheme 3.17 Retrosynthetic Analysis of Hyacynthacine Derivative (102)...............58
Scheme 3.18 Cyclization of the Free Primary Alcohol (106) after Deprotection.......58
Scheme 3.19 Reductive Amination of Aldol Adduct (105)........................................59
Scheme 3.20 Protection-deprotection sequence to Access Primary Alcohol (109)...59
Scheme 3.21 Oxidation of Primary Alcohol (109) with Parikh-Doering and Dess-Martin conditions..............................................................60
Scheme 3.22 Attempted Aldol Reaction of (111).........................................................60
Scheme 3.23 Adamson’s work on Aldehydes Containing Protected β-hydroxy group.61
List of Abbreviations

[\alpha]_D^{20} \quad \text{Specific rotation at the sodium D line (589 nm) at 20°C}
°C \quad \text{Degrees Celsius}
Ac \quad \text{Acetyl}
AcOH \quad \text{Acetic Acid}
Ar \quad \text{Aryl}
Bn \quad \text{benzyl}
Boc \quad \text{tert-Butyloxycarbonyl}
c \quad \text{Concentration}
Cbz \quad \text{Carboxybenzyl}
DBnAD \quad \text{Dibenzyl azodicarboxylate}
DtBAD \quad \text{Ditertbutyl azodicarboxylate}
DFT \quad \text{Density functional theory}
DIC \quad \text{N,N′-Diisopropylcarbodiimide}
DKR \quad \text{Dynamic kinetic resolution}
DMAP \quad \text{Dimethylaminopyridine}
DMF \quad \text{Dimethyl formamide}
DMSO \quad \text{Dimethyl sulfoxide}
DMP \quad \text{Dess-Martin periodane}
ee \quad \text{Enantiomeric excess}
eq \quad \text{Equivalents}
EtOAc \quad \text{Ethyl acetate}
HPLC \quad \text{High-performance liquid chromatography}
KIE \quad \text{Kinetic isotope effect}
KR \quad \text{Kinetic resolution}
MeOH \quad \text{Methanol}
NCS \quad \text{N-chlorosuccinimide}
NEt}_3 \quad \text{Triethylamine}
NMR \quad \text{Nuclear magnetic resonance}
nOe \quad \text{Nuclear Overhauser effect}
Ph \quad \text{Phenyl}
Ra-Ni \quad \text{Raney Nickel}
TBAF \quad \text{Tetrabutylammonium fluoride}
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td>tert-butyl dimethyl silyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-Toluenesulfonic acid monohydrate</td>
</tr>
<tr>
<td>VWD</td>
<td>Variable wavelength detector</td>
</tr>
</tbody>
</table>
Chapter 1.

Introduction

1.1. Asymmetric Catalysis

In chemistry, chirality refers to a geometric property of molecules relating to their symmetry. Chirality often originates through unique structural features in a molecule, and can manifest in point chirality, plane chirality or axial chirality, none of which permit an improper axis of rotation. The physical and chemical properties of chiral molecules cannot be distinguished in an achiral environment, but enantiomeric molecules often have unique interactions in a chiral environment, such as enzymatic active sites. For example, thalidomide (1+2) was a drug marketed as a sedative to pregnant women to aid with morning sickness (Figure 1.1). Tragically, it was discovered that the racemic drug caused teratogenic effects. Thus, while one enantiomer was indeed effective against morning sickness, the other caused birth defects. Further complicating the use of thalidomide, the drug undergoes racemization in vivo, precluding the use of enantiomerically pure material. Considering the importance of chirality in drug leads and natural products, significant effort has been expended in the development of new means to selectively and intentionally introduce chirality in organic synthesis.

![Figure 1.1](image)

Figure 1.1 (R) and (S) Enantiomers of thalidomide respectively.

Catalysis is defined as a process by which chemical reactions are accelerated using a catalyst. Catalysts facilitate reactions by opening new mechanistic pathways via formation of distinct intermediates between the catalyst and its substrate. A central tenet of catalysis is that the catalyst itself is regenerated in the reaction and can therefore be cycled through a reaction multiple times, allowing for its use in sub-stoichiometric...
amounts. In this way, catalysis is both an atom and resource efficient means to perform chemical reactions and is a common tool for organic synthesis.

One of the first examples of asymmetric catalysis is the asymmetric hydrogenation of alkenes using rhodium complexes demonstrated by Knowles and coworkers at Monsanto in 1977. Here, they showed that rhodium complexes adorned with appropriate chiral ligands could induce high levels of enantioselectivity in a hydrogenation reaction of several different prochiral olefins. The process was later commercialized and used in the industrial synthesis of L-DOPA, an important drug for treating Parkinson’s disease symptoms. For his work, Knowles, along with Noyori (asymmetric hydrogenation) and Sharpless (asymmetric oxidations) shared the 2001 Nobel Prize in Chemistry.

Currently, three main categories of asymmetric catalysis include organometallic catalysis, which employs metal complexes with chiral ligands to induce asymmetry, enzyme catalysis, and organocatalysis, which uses small organic molecules as catalysts.

1.2. Asymmetric Organocatalysis

1.2.1. Introduction to Organocatalysis

Organocatalysis can often provide distinct advantages over organometallic catalysis or enzyme catalysis that include reduced sensitivity to moisture, absence of toxic metals, and broad applicability. The often cited first examples of organocatalysis are the Hajos-Parrish and Eder-Sauer-Wiechert reactions described in 1974 and 1971 respectively (Scheme 1.1). Each of these reactions employs proline as a catalyst, which promotes an intramolecular aldol reaction. In the case of the Eder-Sauer-Wiechert reaction, the aldol reaction is followed by dehydration to give enone 5, while the Hajos-Parish reaction provides hydroxyl-dione 7 in high optical purity.
After the initial discovery of the proline-catalyzed intramolecular aldol reaction, little else was done in this field until the turn of the century. In 2000, the intermolecular aldol reaction was described by List, Lerner and Barbas (Scheme 1.2). Using acetone 9 and various α-branched aldehydes, the authors were able to promote an intermolecular aldol reaction using proline 8. This seminal publication also explored different amino acid-based catalysts, showing proline to be the best catalyst for both yield and enantioselectivity.

Shortly after, MacMillan demonstrated the first organocatalyzed Diels-Alder reaction (Scheme 1.3). While proline was not employed in this reaction, several proline-like molecules were examined as catalysts, including proline methyl ester and a C₂ symmetric proline derivative. The optimal catalyst for this reaction was determined to be
an imidazolidinone derived catalyst 11, which promoted Diels Alder reactions between various α,β-unsaturated aldehydes and cyclopentadiene 10 in excellent yield and enantioselectivity. This type of imidazolidinone catalyst has since been utilized in a wide variety of asymmetric organocatalytic reactions. Notably, this report by MacMillan also marked the first appearance of the word organocatalysis in the literature. Together, the publications by List and MacMillan marked the beginning of an organocatalysis “gold rush”, as countless additional processes have since been developed.


\[
\begin{align*}
\text{H} & \text{C} = \text{C} \quad + \\
\text{MeOH-H}_2\text{O} & 16-24 \text{ h} \\
\text{CHO} \quad + \\
\text{R} & \text{CHO} \\
5 \text{ mol\% 11} & \text{80-99\% yield} \\
\text{83-96\% ee} & \text{11} = \\
\end{align*}
\]


1.2.2. Organocatalyzed Aldol Reactions

The next significant development in proline organocatalysis was List’s variation of the Mannich reaction (Scheme 1.4). This was the first example of an organocatalyzed reaction using an imine as an electrophile, rather than an aldehyde or ketone. This iteration of the Mannich reaction also demonstrated that preformation of the imine acceptor was not necessary, and the reaction could be carried out in one pot with remarkable efficiency. As well, this was the first demonstration that ketones other than acetone could participate as nucleophiles in an organocatalytic aldol reaction. List was able to further demonstrate the utility of hydroxyacetone as a suitable substrate for an aldol reaction in his publication detailing the synthesis of 1,2-diols (Scheme 1.4).
Cordova and coworkers investigated dihydroxyacetone 16 as a substrate in the proline-catalyzed aldol for its potential utility in synthesizing carbohydrates and carbohydrate analogues (Scheme 1.5).\textsuperscript{24} While conversions were generally high, poor diastereoselectivity was observed for many substrates. These limitations were overcome three years later when Enders successfully demonstrated the aldol reaction between aldehyde 17 and 2,2-dimethyl-1,3-dioxan-5-one (dioxanone) 20 in excellent yield and enantioselectivity.\textsuperscript{25,26} Enders applied this methodology in the synthesis of polyols such as D-psicose 22.

Scheme 1.4  List’s Mannich and Aldol Reactions using Hydroxyacetone.
In their initial investigations, List and Barbas each independently reported that alkyl ketones made suitable substrates for proline aldol reactions (Scheme 1.6). Each showed that cyclohexanone 23 could engage in aldol reactions with moderate yields and excellent enantioselectivity. Additionally, both List and Barbas noted the poor reactivity of 3-pentanone.
Recognizing the potential of an organocatalytic 3-pentanone aldol and its applications in polyketide synthesis, Ward and coworkers adapted the lithium promoted tetrahydro-4H-thiopyran-4-one (thiopyranone) aldol reaction to be compatible with organocatalysis in 2004 (Scheme 1.7).\cite{32,33,34,35,36} After considerable optimization, the aldol adducts of thiopyranone could be isolated in up to 97% yield with excellent enantioselectivity and diastereoselectivity. This aldol reaction could also be performed iteratively to build up larger molecules that were subsequently reduced with Raney Nickel to provide access to polyketide-like scaffolds. This strategy has been used in the synthesis of several polyketide-derived natural products.\cite{37}

\textit{Ward (2004)}

As noted by MacMillan, an aldol between two aldehydes is a challenging synthetic problem due to the tendency of aldehydes to polymerize uncontrollably, and the difficulty
in distinguishing the donor and acceptor aldehydes. Using organocatalysis, MacMillan was able to demonstrate a controlled dimerization of aldehydes employing proline as the organocatalyst (Scheme 1.8). Specifically, MacMillan was able to take advantage of the mild reaction conditions inherent to organocatalysis to avoid polymerization of the aldehydes, while the issue of selectivity was addressed by adding the desired electrophilic partner via syringe pump to the reaction mixture. This iteration provided access to β-hydroxy-aldehydes, which are valuable synthetic intermediates as was demonstrated in MacMillan’s application of these adducts in the synthesis of differentially protected hexoses. This newfound control of aldehydes as nucleophiles inspired a new subset of organocatalysis.

\[ 
\text{MacMillan (2002)} 
\]

\[
\begin{align*}
&\text{R}_1 \quad \text{H} \\
&\text{O} \\
&\text{R}_2 \\
&\text{O} \\
&\text{H} \\
&\text{R}_1 \\
&\text{OH} \\
&\text{R}_2 \\
&\text{DMF, 4°C} \\
&\text{10 mol\% L-proline (8)} \\
&\begin{cases}
75-88\% \text{ yield} \\
91-99\% \text{ ee}
\end{cases}
\end{align*}
\]

Scheme 1.8 MacMillan Demonstrating Aldehydes as Aldol Reaction Donors.

1.2.3. Organocatalyzed α-Functionalization of Aldehydes

α-Functionalized aldehydes are versatile building blocks for the synthesis of biologically relevant scaffolds. To this end, organocatalysis has enabled the α-halogenation, -amination, -hydroxylation, and -sulfenylation of aldehydes. The first demonstrations of this were by List and Jørgensen, in their adaptations of the amination reaction to organocatalytic conditions (Scheme 1.9). Each independently reported the proline-catalyzed α-amination of several alkyl aldehydes utilizing azodicarboxylates 26a-c as electrophiles to yield α-aminated aldehydes in excellent yields and enantioselectivity. α-Aminated aldehydes are useful building blocks in the synthesis of natural products containing chiral C-N stereocentres including amino acids, alkaloids and carbohydrate scaffolds. This was demonstrated in Jørgensen’s short synthesis of an enantioenriched amino acid 29 (Scheme 1.10). Furthermore, the amination reaction has been demonstrated with ketones by Jørgensen and applied to the synthesis
of enantioenriched oxazolidinones (e.g., compound 28), which are valuable as chiral auxiliaries (Scheme 1.10).

\[
\begin{align*}
\text{25} & \quad + \quad \text{26} & \quad \xrightarrow{10 \text{ mol\% L-proline} (8)} & \quad \text{27} \\
\text{26a} R = \text{-Bn} & & & \\
\text{26b} R = \text{-B} \text{Bu} & & & \\
\text{26c} R = \text{-Et} & & & \\
\text{27a} R = \text{-Bn} & & \text{(99\% yield, 86\% ee)} & \\
\text{27b} R = \text{-B} \text{Bu} & & \text{(97\% yield, 92\% ee)} & \\
\text{27c} R = \text{-Et} & & \text{(83\% yield, 93\% ee)} & \\
\end{align*}
\]

Scheme 1.9 Amination of Aldehydes by List and Jørgensen (2002).

Several organocatalytic methods for \(\alpha\)-hydroxylation and -sulfenylation of aldehydes have been developed. Notable examples by MacMillan\textsuperscript{19}, Cordova\textsuperscript{43}, Hayashi\textsuperscript{44}, and others\textsuperscript{42,46} have led to useful methods for the synthesis of \(\alpha\)-hydroxy
aldehydes which are useful synthetic building blocks for the preparation of carbohydrates.\textsuperscript{35} In each case, nitrosobenzene \textbf{30} is employed as the electrophilic oxygen source to enable aminooxylations of both ketones and aldehydes in excellent yield and enantioselectivity (Scheme 1.11). The N-O bond can be subsequently cleaved using hydrogenation conditions\textsuperscript{42}, or CuSO\textsubscript{4}\textsuperscript{43} to give 1,2-diols.

\begin{center}
\begin{align*}
\text{H}^+ & + \text{N}^+\text{O}_\text{Ph} & \text{10 mol\% L-proline (8)} & \text{CH}_3\text{CN} \\
\text{30} & \rightarrow & \text{H}^+ & \text{N}^+\text{O}_\text{Ph} \\
\text{30} & \rightarrow & \text{H}^+ & \text{N}^+\text{O}_\text{Ph} i) \text{NaBH}_4 \\
& & \text{ii) CuSO}_4 & \text{H}_2, \text{PtO}_2
\end{align*}
\end{center}

\textbf{Scheme 1.11 Hayashi and Coworkers Aminooxylations Reaction.}

In 2005, Jørgensen and coworkers reported the analogous asymmetric α-sulfenylation of simple aldehydes (Scheme 1.12).\textsuperscript{45} For this purpose, Jørgensen designed a novel proline-derived organocatalyst \textbf{32} (now known as Jørgensen’s catalyst) to overcome the poor yields and enantioselectivity observed when using proline or other proline derivatives. The increased steric bulk of the catalyst imparted greater bias for the addition of incoming nucleophiles. Additionally, the silyl protecting group increased the efficiency of the catalyst by preventing undesired reactivity of the exposed alcohol. Since this first disclosure, Jørgensen’s catalyst has found utility in many other organocatalyzed reactions.\textsuperscript{47}

\begin{center}
\begin{align*}
\text{H}^+ & + \text{N}^+\text{N}^+\text{S}^+\text{Bn} & \text{10 mol\% 32} & \text{toluene} \\
\text{31} & \rightarrow & \text{H}^+ & \text{N}^+\text{O}_\text{Ph} \\
\text{31} & \rightarrow & \text{H}^+ & \text{N}^+\text{O}_\text{Ph} \text{N}^+\text{O}_\text{Ph} i) \text{NaBH}_4 \\
& & \text{ii) CuSO}_4 & \text{H}_2, \text{PtO}_2
\end{align*}
\end{center}

\textbf{Scheme 1.12 Jørgensen’s Sulfenylation of Aldehydes.}

MacMillan’s seminal work on the synthesis of enantioenriched α-chloroaldehydes relied on use of imidazolidinone catalyst \textbf{11} and a quinone-derived electrophilic chlorinating reagent \textbf{33}.\textsuperscript{37} Shortly after, Jørgensen reported using prolinamide \textbf{35} and N-chlorosuccinimide (NCS) \textbf{34} to effect the same transformation.\textsuperscript{38} Interestingly, proline was
reported to give moderate to excellent conversions of the $\alpha$-chloroaldehydes, but with poor enantiostereoselectivity ($<10\%$). Jørgensen demonstrated the utility of the $\alpha$-chloroaldehyde building block in a short synthesis of protected amino acids.$^{38}$

*MacMillan (2004)*

\[ \text{RCHO} + \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl}
\end{array}
\end{array} \overset{\text{5mol\% 11}}{\rightarrow} \begin{array}{c}
\text{RCl}
\end{array} \]

acetone, $-30^\circ C$

71-94% yield
80-95% ee

*Jorgensen (2004)*

\[ \text{RCHO} + \text{34} \overset{\text{10mol\% 35}}{\rightarrow} \begin{array}{c}
\text{RCl}
\end{array} \]

CH$_2$Cl$_2$, rt

30-90% yield
81-97% ee

Scheme 1.13 $\alpha$-Chlorination of Aldehydes by MacMillan and Jørgensen.

**1.2.4. Mechanism of Enamine Catalysis**

It is generally agreed that the first step in proline-catalyzed reactions is the condensation of proline with the carbonyl of the donor molecule whether it is an aldehyde or ketone. Upon condensation, proline can form an iminium ion as well as the tautomer enamine, each of which can facilitate different types of reactivity (Scheme 1.14).$^{20,48}$ The initially formed iminium ion has a LUMO which is lower in energy than the original carbonyl, thus making it more susceptible to direct nucleophilic addition. Tautomerization to the enamine allows for HOMO-raising activation of the substrate. Experimental confirmation of the existence of these intermediate enamines has been achieved via crystallization of enamines between proline and different ketones.$^{49}$
Scheme 1.14 Iminium and Enamine activation modes facilitated by Proline.

There are different models for how secondary amine organocatalysis directs the facial selectivity of reactions depending on the catalyst employed. In the cases of Jørgensen and MacMillan’s catalysts, steric shielding by the bulky substituents on the catalyst favours addition of the incoming electrophile to the less hindered face. Proline on the other hand, does not sterically shield one face over another but instead directs selectivity via hydrogen bonding to the incoming electrophile. The initial proposal by List suggested that the reaction proceeds through an enzyme like transition state, invoking a Zimmerman-Traxler structure 36, with the carboxylic acid of proline hydrogen bonding to the aldehyde carbonyl.\(^{14}\)

Figure 1.2  Zimmerman-Traxler Transition State (36) Proposed by List for Proline Catalyzed Aldol Reactions.

This transition state was modeled using DFT by Houk and coworkers who suggested that this mode of hydrogen bonding seemed a likely model to explain the high enantioselectivity of proline catalyzed reactions (Figure 1.3).\(^{50}\) Furthermore, DFT modelling confirmed that proline encourages HOMO-raising reactivity of the donor, and facilitates LUMO lowering of the incoming electrophiles with the Lewis acidic nature of the hydrogen bonding.
There is further debate as to whether this model fully encapsulates all the intermediate species in the catalytic cycle. A low energy intermediate oxazolidinone 37a was modelled by Houk, and its role in the catalytic cycle is still the subject of debate. Some suggest that the oxazolidinone is a “dead end” intermediate, playing no role in the reaction. Others, including Seebach, suggest that the oxazolidinone plays a key role in the formation of the enamine species. Seebach has even suggested the oxazolidinone 37b is involved in the stereodetermining step, as demonstrated in the Seebach-Eschenmoser mechanism (Figure 1.4).

DFT and NMR studies by Gschwind indicate that both the enamine and oxazolidinone species exist in solution during the reaction, though the concentrations of these intermediates depend heavily on the identities of the solvent, catalyst, and aldehydes. As well, kinetics studies by Blackmond of proline catalyzed aldol reactions corroborate previous studies, and further reveal that the intermediate oxazolidinones can decompose to form irreversibly deactivated species of proline and aldehyde (Scheme 1.15). Recent mechanistic studies by Blackmond and Christmann of the α-chlorination reaction, using MacMillan’s and Jorgensen’s catalysts, have revealed the presence of a reversibly forming succinimide-catalyst-aldehyde adduct which could play a similar role in the mechanism to the oxazolidinone.

Both Gschwind and Blackmond report a dependence on water for the concentrations of these types of intermediates in solution. Attempts have been made to
elucidate the role of water in the catalytic cycle of organocatalysis, but no agreed upon universal mechanism has been identified. For example, it has been suggested that water suppresses the formation of the intermediate oxazolidinone,\(^5^9\) that water increases the rate of hydrolysis of the catalyst, or that water is explicitly involved in the transition state for addition.

![Scheme 1.15 Blackmond’s Proposed Mechanism for the Decomposition of Oxazolidinone.](image)

The currently accepted mechanism invokes the Houk-List transition state as the stereodetermining step (Figure 1.5). As well, it is the consensus of recent literature that the Seebach-Eschenmoser oxazolidinone 38 should be included in the mechanistic pathway for proline catalyzed reactions, though its exact role in the mechanism is not definitively known.

![Figure 1.5 Generally Accepted Mechanism for Proline Catalysis.](image)
1.2.5. Kinetic and Dynamic Kinetic Resolutions Facilitated by Secondary Amines

Kinetic resolutions take advantage of differing reaction rates for each enantiomer of a starting material with a chiral reagent and derive from the differences in energy of resulting diastereomeric transition states. The differing reaction rates allow for the introduction of enantioenrichment in a product from a racemic starting material. A major limitation of this process is that the theoretical maximum yield is 50% if the starting material is a racemate. A dynamic kinetic resolution (DKR) introduces an interconversion between each of the starting enantiomers. In this way, the theoretical conversion is 100% (Figure 1.6).

\[
\begin{align*}
\text{SM}_{(R)} & \xrightarrow{k_1} P_{(R)} & \text{SM}_{(R)} & \xrightarrow{k_1} P_{(R)} \\
\text{SM}_{(S)} & \xrightarrow{k_2} P_{(S)} & \text{SM}_{(S)} & \xrightarrow{k_2} P_{(S)}
\end{align*}
\]

**Figure 1.6** Kinetic Resolution and Dynamic Kinetic Resolution, where \( k_1 \neq k_2 \).

There have been few examples of DKR reactions in synthetic chemistry utilizing secondary amine catalysts. In Ward’s organocatalyzed aldol reaction using thiopyran aldehydes, a DKR process is facilitated by proline (Scheme 1.16). Ward initially aimed to effect a kinetic resolution of racemic thiopyran aldehydes by taking advantage of the ability of the proline catalyzed aldol to discriminately react with each enantiomer of the aldehyde. Surprisingly, they were able to isolate a single diastereomer of the aldol adduct in excellent yield, enantioselectivity and diastereoselectivity. Ward rationalized the high diastereoselectivity of the reaction using Evan’s model for double stereodifferentiating partners in aldol reactions. The reaction of the matched aldehyde would occur much faster, leading to the kinetic resolution. Crucially, proline was also able to facilitate the racemization of the aldehyde, leading to a DKR.
1.3. Britton DKR α-Chlorination-Aldol Reaction

The Britton DKR α-chlorination-aldol reaction facilitates the one-pot chlorination of an aldehyde followed by a proline catalyzed DKR aldol reaction with dioxanone 20 (Scheme 1.17). It has been shown that this reaction takes advantage of a DKR, such that the poorly stereoselective chlorination reaction with proline is inconsequential, and leads to excellent diastereoselectivity for the reaction.

Scheme 1.17 Britton DKR α-Chlorination-Aldol Reaction.

The currently understood mechanism and rationalization for the stereoselectivity of this reaction invokes the Houk-List transition state for aldol reactions to explain the exclusive anti-aldol selectivity that is observed for these aldol reactions. To rationalize the typically moderate-excellent selectivity for the syn-chlorohydrin, a transition state is proposed whereby steric repulsion between the R-group of the aldehyde and the enamine, and electrostatic repulsion between the oxygen of dioxanone and the chloro-substituent of the aldehydes are minimized (Scheme 1.18).
Currently Understood Mechanism for α-Chlorination-Aldol Reaction.

In further studies, the utility of this method was demonstrated in the concise synthesis of both THF’s and iminocyclitols (Scheme 1.19).\textsuperscript{69−71} By reduction of the ketone and subsequent cyclization of the diol, carbohydrates and analogues can be readily formed after the closure of the THF ring. Similarly, after a reductive amination-cyclization sequence the corresponding pyrrolidines can also be formed.

Current applications of α-Chlorination-Aldol.

1.4. Thesis Overview

While the α-chlorination-aldol reaction has extensive utility in the synthesis of the discussed systems, it is limited in utility to production of compounds that occupy a narrow region of chemical space, namely carbohydrates and carbohydrate analogues. The topic of this thesis is the exploration and expansion of the α-chlorination-aldol reaction in each of the ketone and electrophile dimensions (Scheme 1.20). In Chapter 2, the compatibility of the α-amination of aldehydes with the dioxanone aldol is investigated as well as the potential applications towards pyrrolidine synthesis. The proposed synthesis would access similar pyrrolidines as the α-chlorination-aldol, but with altered stereochemistry in a concise manner. The focus of the research presented in Chapter 3 is the exploration of the ketone dimension of the α-chlorination-aldol reaction and optimization of the reaction conditions such that four different ketones can engage in the reaction.
Scheme 1.20 Goal of this thesis - a more general tandem methodology.
Chapter 2.

Azodicarboxylates in a Tandem Aldol Reaction and Potential Applications

2.1. α-Amination-Aldol Exploration

2.1.1. Discovery and Optimization

In the interest of expanding the concept of the tandem α-chlorination-alcohol methodology to other electrophiles, the compatibility of the α-amination of aldehydes developed by List and Jørgensen was explored with a dioxanone aldon by Chris Adamson (MSc: 2016) (Scheme 2.1). Adamson noted simple alkyl aldehydes (41a, 41b) worked well as monitored by thin-layer chromatography (TLC). However, the crude 1H NMR spectra of 43a and 43b were difficult to interpret – this did not improve upon purification. We suspected that rotamers of each carbamate broaden the peaks as shown in Figure 2.1.

Scheme 2.1  Amination Aldol Reaction Developed by Adamson.
The scope of the amination-aldol reaction was examined with respect to the aldehyde component by Adamson. Unfortunately, other substrates were isolated in poor yields. The known scope of the amination is quite narrow and limited primarily to alkyl aldehydes. Consequently, this limited the scope of the corresponding $\alpha$-amination-aldol process. Optimization of the reaction revealed that changing the reaction solvent to MeNO$_2$ (entry 4) led to a significant increase in the conversion to aldol product (Table 2.1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst Loading</th>
<th>Concentration</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>80mol%</td>
<td>0.1 M</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>80mol%</td>
<td>0.5 M</td>
<td>92%</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>80mol%</td>
<td>0.5 M</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>MeNO$_2$</td>
<td>50mol%</td>
<td>0.5 M</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2.1    Abbreviated Optimization Table of $\alpha$-Amination-Aldol reaction
2.1.2. Determination of DKR

Considering the Britton group’s previously developed α-chlorination-aldol proceeded via a DKR, it was important to identify if a DKR was operative in the α-amination-aldol reaction. Literature precedent indicated that α-aminoaldehydes do not racemize in the presence of a proline catalyst.\(^{72}\) However, we sought to demonstrate this under our reaction conditions.

To assess the potential role of a DKR in this process, both enantiomers of the α-aminoaldehyde were synthesized and isolated according to the procedure published by Jørgensen.\(^ {41}\) Subsequently, in separate experiments, the D- and L- α-aminoaldehydes were submitted to aldol conditions using L-proline as the catalyst. If these reactions involved a DKR, then the same product 43a should be isolated from reaction of both +/- 44 regardless of initial aldehyde configuration (Scheme 2.2). That is, proline should effect racemization of the aldehydes (+)-44 and (-)-44, and the proline-catalyzed aldol reaction should allow for discrimination via diastereomeric transition states. If a DKR does not operate under these conditions, then we should observe 45 when (+)-44 is submitted to the aldol reaction and 43a when (-)-44 is submitted to the reaction.

Scheme 2.2 Possible Outcomes of Aldol Reaction with Aldehyde Adducts Formed by D-proline.
Table 2.2  Outcome of DKR Determination Experiments.

When (+)-44 was submitted to the aldol reaction with L-proline, we observed very little product formation (<10%). Furthermore, the aldol adduct was formed as a 1:1 mixture of diastereomers at the N-stereocentre. This observation suggests that a very slow racemization of the α-aminoaldehyde occurs and is consistent with Jørgensen’s observation that the enantiomeric excess of α-aminoaldehydes decreases after prolonged exposure to proline.41 In our case, while racemization of the α-aminoaldehyde by proline occurs, this process is too slow to be compatible with a DKR. That is, $K_{eq}$ is slow to equilibrate, and $k_1 >> k_2$ (Scheme 2.2). To validate our experimental method, (-)-44 was submitted to identical reaction conditions, and 43a was indeed isolated in yields comparable to the normal reaction conditions.

The stereochemistry of the aldol adducts was confirmed by nOe experiments on the corresponding hydrazones 46 and 47. After hydrogenation to remove the Cbz protecting groups, the aldol adducts cyclize rapidly to the hydrazones 46 and 47 (Scheme 2.3). This bicyclic system is rigid and allows for assignment of stereochemistry by observation of key transannular nOe correlations. Stereochemical assignment of compound 47 was assigned through analogy, that is, it was a diastereomer of 46. As the anti-aldol stereochemistry is set, the only possible diastereomer is that shown on 47.

Scheme 2.3 Determination of Configuration by nOe correlations.
2.2. Elaboration of Amination-Aldol Adducts

2.2.1. Strategies to Prepare Pyrrolidines

The Britton group has ongoing projects concerning the synthesis of libraries of pyrrolidine structures and envisioned using this methodology in a concise synthesis of new pyrrolidine scaffolds. Presumably, after N-N bond cleavage followed by intramolecular reductive amination, pyrrolidines could be synthesized in a 3-step total sequence from cheap and achiral starting materials (Scheme 2.4). Importantly, these pyrrolidines 48 would differ in configuration at the 2-position when compared to the pyrrolidines synthesized by Bergeron-Brlek and coworkers (e.g., 49).\(^{70}\)

![Scheme 2.4 Initial Strategy for Pyrrolidine Synthesis.](image)

First, we attempted the cleavage of the N-N bond via an alkylation-elimination sequence using an α-bromo ketone 51 (Scheme 2.5).\(^{73-76}\) We envisioned alkylation of the free amide in the presence of base would give ketone 50. The subsequent addition of base is reported to facilitate an elimination reaction upon heating to give the N-N bond cleavage product. Unfortunately, we did not observe any alkylated product under the established reaction conditions.
Scheme 2.5  Elimination Strategy for Cleaving N-N bond.

Other reducing agents are known to cleave N-N bonds, including SmI$_2$, Raney-Nickel and Birch reduction with sodium metal. Furthermore, other hydrogenation conditions with Pd/C were attempted in efforts to optimize the conditions for N-N bond cleavage as shown in Table 2.2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reduction</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SmI$_2$</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Ra-Ni</td>
<td>hydrazone</td>
</tr>
<tr>
<td>3</td>
<td>Na, NH$_3$</td>
<td>hydrazone</td>
</tr>
<tr>
<td>4</td>
<td>H$_2$, Pd/C (0.01M-0.1M AcOH)</td>
<td>hydrazone</td>
</tr>
<tr>
<td>5</td>
<td>Zn dust, conc. AcOH</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

Table 2.3  Reduction Conditions for N-N Bond Cleavage.

As indicated in table 2.2 (entry 1), when SmI$_2$ was employed for cleavage of the N-N bond, we did not observe any identifiable organic material after reaction work up. The combination of Zn dust and concentrated acetic acid (entry 5) was also found to remove the acetonide protecting group and we observed formation of the triol followed by further decomposition (entry 5).

In entries 2-4, the hydrazone was the only isolable product. This indicated that the -Cbz protecting group was too labile under most reduction conditions for the direct cleavage of the N-N bond to be possible. Ideally, the N-protecting group would be retained upon cleaving the N-N bond for the subsequent intramolecular reductive amination step.

The amination-aldol reaction sequence was subsequently attempted using a different electrophile, the bis-Boc azodicarboxylate 52, which proceeded in a similar
manner to the corresponding aldol reaction using Cbz-protected reagent 42 (Scheme 2.6).
Interestingly, the NMR spectra of the product were well resolved for 53a, but indicated a mixture of compounds, even after repeated purification.

Scheme 2.6 New Protecting group Strategy using bis-Boc Azodicarboxylate (52).

We hypothesized that in the case of a 1,6 relationship between an amine and carbonyl, that there could be an intramolecular cyclization occurring, as depicted in Figure 2.2, resulting in formation of a hemi-aminal. Both diastereomers at the aminal center would be present, leading to two structures observable by $^1$H NMR spectroscopy.

Figure 2.2 Equilibrium between Cyclized Aminal and Aldol Adduct.

This also explained the failure of our initial N-N bond cleaving strategies, as these reactions require accessibility of the proton on the nitrogen. Further, the presence of diastereomeric hemiaminals also explains the complicated $^1$H NMR spectrum of 53 (Figure 2.1), which included both rotamers and hemiaminals. Unfortunately, we were unable to trap the aminal 53 in the ketone or open form. For example, attempts to acylate the nitrogen with acetic anhydride resulted in a mono-acylated product 54, observed by mass spectrometry (Scheme 2.7).
Scheme 2.7 Acylation of Amination-Aldol Adducts.

Based on this insight, we shifted focus to reducing agents capable of cleaving the N-N bond in hemi-aminal 55. Initial attempts at hydrogenation using Raney Nickel failed. Upon sonication of the reaction mixture, a new spot appeared by TLC, and after 8 hours showed ~90% conversion to the new spot. Column chromatography of this spot yielded a product with a complex and difficult to interpret $^1$H NMR spectrum. Based on both the Rf (0.4 in 50:50 Hexanes:EtOAc) and m/z of the compound we hypothesized that this product was again a diastereomeric mixture of hemiaminals 56 formed after cleavage of the N-N bond (Scheme 2.8).

Scheme 2.8 Reduction to Compound (56) using Raney Nickel.

Unfortunately, reduction of 56 using known procedures for reducing hemi-aminals were unsuccessful. For example, reaction with sodium borohydride returned starting materials. We also investigated a reduction involving triethylsilane accompanied by a strong Lewis acid (BF$_3$) and unfortunately observed none of the desired pyrrolidine.
Scheme 2.9 Reducing Presumed Aminal (56).

As typical reduction conditions failed to provide further insight into the structure of compound 56 or afford the pyrrolidine product, we reasoned that deprotection of the -Boc group first should give the imine, which when followed by hydride reduction should afford the desired product (Scheme 2.10).

Scheme 2.10 Boc Deprotection of Presumed Hemiaminal (56).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA</td>
<td>Acetonide deprotection</td>
</tr>
<tr>
<td>2</td>
<td>I₂</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>3</td>
<td>FeCl₃</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>4</td>
<td>Heat</td>
<td>Starting material recovered - decomposition</td>
</tr>
</tbody>
</table>

Table 2.4 Boc-Deprotection Conditions of Hemiaminal (56).

As indicated in Table 2.3, (entry 1) we found that the acetonide was more labile than the Boc protecting group under TFA conditions. Diluting the TFA did not improve this result. Mild Lewis acids were investigated (entries 2 and 3) to promote Boc deprotection, but only returned starting materials. It has been reported that Boc groups can be removed thermally\(^8\), unfortunately in our case the temperature was increased until the compound decomposed without any observable loss of the Boc protecting group prior to decomposition.
Investigation of strategies to cleave the N-N bond from the hydrazones represented an alternative approach to pyrrolidine structures. This strategy relies on activation of the N-N bond by introducing an electron-withdrawing group on the free secondary-amine followed by an intramolecular reductive amination. In this event, acylation of the hydrazone 45 proceeded smoothly to give 57 (Scheme 2.11).

Scheme 2.11 Acylation of Hydrazone (45).

When the acetylated-hydrazone 57 was exposed to SmI\(_2\) in THF, the only isolable product was the acetylated hydrazine 58 (Scheme 2.12). This experiment demonstrated that C=N bond was also readily reduced, and more susceptible to reduction than the N-N bond. Since our goal was to synthesize pyrrolidines via a reductive amination sequence, maintaining the oxidation state of the hydrazone carbon was crucial. At this point we determined there was no reasonable synthetic sequence that could give us access to the desired pyrrolidine structures. It is notable that hydrazines such as 58 are known to be inhibitors of α-L-fucosidases and this three-step synthesis represents an efficient means to prepare such scaffolds.\(^{85}\)

Scheme 2.12 Samarium (II) Diiodide Reduction Leading to Hydrazine (58).
2.2.2. Synthesis of Hydrazones and Characterization

The amination-aldol procedure was adapted into a three-step process to synthesize hydrazones for ease of purification and characterization. To evaluate scope, this three-step process was applied to two different aldehydes, and two resulting hydrazone products 45 and 59 were isolated in moderate yields and high enantiomeric excess (Figure 2.3).

![Figure 2.3 Synthesis of Hydrazones (45) and (59).](image)

2.3. Conclusion

A novel synthetic method has been developed that combines a proline-catalyzed aldehyde amination reaction developed by List and Jørgensen, with an organocatalytic aldol reaction. These aldol adducts were investigated for their potential applications in the synthesis of pyrrolidines. Unfortunately, incompatible protecting groups and formation of stable hemi-aminals prevented N-N bond cleavage. The amination-aldol was shown to be useful in the synthesis of cyclic hydrazones 45 and 59 and the concise synthesis of hydrazine 58.

2.4. Experimental Information

2.4.1. General Considerations

L- and D- proline (99% purity) were purchased from Sigma-Aldrich. All other reagents were purchased from Sigma-Aldrich or TCI and used without purification unless indicated. All reactions described were performed at ambient temperature and open to atmosphere unless otherwise indicated.
NMR spectra were recorded using CDCl₃ as the solvent. Signal positions are given in ppm relative to tetramethylsilane and were calibrated using the residual solvent signal ('H NMR: CDCl₃ 7.26 ppm; ¹³C NMR: CDCl₃ 77.0 ppm). 'H NMR multiplicities are given as (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dddd, doublet of doublet of doublet m, multiplet; bs, broad singlet). 'H and ¹³C NMR are recorded on a Bruker 600, Bruker 500 or Bruker 400. Diastereomeric ratios are based on analysis of crude 'H NMR spectra.

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum Two FTIR spectrometer. Only selected wavenumbers are provided for each compound. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 at 589 nm at 20°C. HPLC analysis was performed on an Agilent 1100 HPLC equipped with a variable UV-Vis wavelength detector. Enantiomeric excess was determined as indicated for each compound. High resolution mass spectra were measured on an Agilent 6210 TOF LC/MS using ESI-MS.

2.4.2. General Procedures

General Procedure A (One-Pot Organocatalytic Amination-Aldol)

L-proline (0.8 eq) was stirred in nitromethane (0.5 M). To the suspension was added aldehyde (1.1 eq). To this suspension was added azodicarboxylate (1.0 eq). The resulting suspension was stirred until consumption of starting material was observed visually (yellow solution turns colourless) and confirmed by TLC. Once consumption of starting material was observed, 2,2-dimethyl-1,3-dioxan-5-one (2.0 eq) was added. The reaction was monitored by TLC until consumption of intermediate aminated aldehyde was noted. The reaction mixture was diluted with CH₂Cl₂, washed with water, brine and then dried with MgSO₄. The resulting organic layer was concentrated using a rotary evaporator. The crude product was either purified as indicated or subjected to hydrogenation.

General Procedure B (Hydrogenation of Amination-Aldol Adducts)

Crude product from procedure A was dissolved in MeOH (with 1% AcOH, 0.1 M). To this solution is added 25% w/w Pd/C. The resulting suspension was put under H₂
atmosphere by evacuating the reaction vessel and backfilling with H$_2$ balloon three times. The reaction was stirred until consumption of crude product is observed by TLC. The reaction mixture was filtered through Celite to remove Pd/C, and the Celite was rinsed with more MeOH. The mixture was concentrated on a rotary evaporator, then purified as indicated.

2.4.3. Preparation and Characterization Data

*Preparation of Hydrazone (45)*

According to General Procedure A, L-proline (46 mg, 0.4 mmol) was stirred in nitromethane (1.2 mL). To the suspension was added isovaleraldehyde (54 μL, 0.55 mmol), and dibenzyl azodicarboxylate (DBnAD) (149 mg, 0.5 mmol). Once consumption of DBnAD was observed, dioxanone (130 mg, 1.0 mmol) was added. The reaction was monitored by TLC until consumption of intermediate aminated aldehyde was noted (2 days). The reaction mixture was diluted with 2 mL of CH$_2$Cl$_2$, washed with sequentially with 5 mL water, then 5 mL brine and then dried with MgSO$_4$. The resulting organic layer is concentrated using a rotary evaporator.

Following General Procedure B, the crude product was dissolved in 4 mL of MeOH containing 1% v/v AcOH. To this solution is added 25% w/w Pd/C (100 mg). The resulting suspension is put under H$_2$ atmosphere and stirred until consumption of crude product is noted. The reaction mixture was filtered through Celite, rinsed with more MeOH, and concentrated on a rotary evaporator. Purification of crude by flash chromatography on silica (60:40 hexanes:EtOAc and 1% NEt$_3$) afforded hydrazone 45 as a white solid (146 mg, 64% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ=5.33 (bs, 1H), 4.41 (m, 1H), 4.39 (d, J = 15.6 Hz, 1H), 4.22 (d, J = 15.6 Hz, 1H), 4.03 (m, 1H), 2.71 (d, J = 9.4 Hz, 1H), 2.47 (bs, 1H), 1.99 (m, 1H), 1.52 (s, 3H), 1.43 (s, 3H), 1.00 (d, J = 6.8 Hz, 6H)
C NMR (100 MHz, CDCl₃): δ = 139.4, 99.78, 66.4, 62.77, 62.14, 61.8, 27.4, 27.2, 21.6, 19.5, 19.0

HRMS (ESI) m/z calcd for C₁₁H₂₁N₂O₃ [M+H]⁺ 229.1547, found 229.1534

IR: 3359, 2961, 2872, 1643, 1380, 1372, 1165, 1074, 862 cm⁻¹

[α]D²⁰: -22.9 (c = 31.9 mg/mL in CHCl₃)

**Determination of Enantiomeric Excess of Hydrazine (45)**

A racemic sample of hydrazine 45 was prepared using racemic proline. The racemic hydrazine was separated by chiral HPLC using Phenomenex Lux (3μm) Cellulose-3 column; flow rate 0.4 mL/min; eluent: hexanes-iPrOH 80:20; detection at 254 nm; retention time = 10.6 min and 20.1 min. The enantiomeric excess of the optically-enriched hydrazine was determined using the same method (85% ee).

**Preparation of Hydrazine (59)**

![Hydrazine structure]

According to General Procedure A, L-proline (46 mg, 0.4 mmol) was stirred in nitromethane (1.2 mL). To the suspension was added valeraldehyde (54 μL, 0.55 mmol), and dibenzyl azodicarboxylate (DBnAD) (149 mg, 0.5 mmol). Once consumption of DBnAD was observed, dioxanone (130 mg, 1.0 mmol) was added. The reaction was monitored by TLC until consumption of intermediate aminated aldehyde is noted (2 days). The reaction mixture was diluted with 2 mL of CH₂Cl₂, washed with sequentially with 5 mL water, then 5 mL brine and then dried with MgSO₄. The resulting organic layer was concentrated using a rotary evaporator.

Following General Procedure B, the crude product was dissolved in 4 mL of MeOH containing 1% v/v AcOH. To this solution was added 25% w/w Pd/C (100 mg). The
resulting suspension was put under H$_2$ atmosphere and stirred until consumption of crude product is noted. The reaction mixture was filtered through Celite, rinsed with more MeOH, and concentrated on a rotary evaporator. Purification of crude by flash chromatography on silica (60:40 hexanes:EtOAc and 1%NEt$_3$) afforded hydrazone 59 as a white solid (103 mg, 45% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 5.13 (bs, 1H), 4.43 (m, 1H), 4.40 (d, $J = 14.6$ Hz, 1H), 4.22 (d, $J = 14.6$ Hz ,1H), 3.87 (m, 1H), 3.14 (dd, $J = 7.1$, 6.8 Hz, 1H), 2.46 (bs, 1H), 1.69 (m, 1H), 1.53 (s, 3H), 1.44 (s, 3H) 1.69-1.39 (m, 3H), 0.96 (t, $J = 7.6$ Hz 3H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$= 139.6, 99.9, 66.1, 63.1, 62.9, 55.9, 31.7, 27.2, 21.6, 18.8, 14.1

HRMS (ESI) m/z calcd for C$_{11}$H$_{21}$N$_2$O$_3$ [M+H]$^+$ 229.1547, found 229.1529

IR: 3348, 2989, 2871, 1648, 14555, 1373, 1167, 1074, 862 cm$^{-1}$

$[\alpha]_{D}^{20}$: -24.5 (c = 17.5 mg/mL in CHCl$_3$)

**Determination of Enantiomeric Excess of Hydrazone (59)**

A racemic sample of hydrazone 59 was prepared using racemic proline. The enantiomeric hydrazone was separated by chiral HPLC using Phenomex Lux (3$\mu$m) Cellulose-3 column; flow rate 0.4 mL/min; eluent: hexanes-$i$PrOH 80:20; detection at 254 nm; retention time = 11.5 min and 16.5 min. The enantiomeric excess of the optically enriched hydrazone was determined using the same method (98% ee).
Preparation of Acylated-Hydrazine (57)

Hydrazone 45 (20 mg, 0.09 mmol) was submitted to neat Ac$_2$O (0.1 M, 1 mL) with 1.0 eq of DMAP (11 mg, 0.09 mmol) and stirred overnight. The reaction was diluted with 5 mL of EtOAc and quenched using aqueous NaHCO$_3$. The organic layer was washed several times with aqueous NaHCO$_3$. The organic layer was then dried with brine and NaSO$_4$ and concentrated using a rotary evaporator. Purification by column chromatography on silica (60:40 hexanes:EtOAc) afforded 37 mg (86% yield) of a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 5.24 (m, J = 5.6$ Hz, 1H), 4.57 ($dd$, $J = 8.0, 5.6$ Hz, 1H), 4.50 ($d$, $J = 14.6$ Hz, 1H), 4.29 ($d$, $J = 14.6$ Hz, 1H), 2.55 ($m$, 1H), 2.25 ($s$, 3H), 2.10 ($s$, 3H), 1.49 ($s$, 3H), 1.40 ($s$, 3H), 1.04 ($d$, $J = 6.8$ Hz, 3H), 0.82 ($d$, $J = 6.8$ Hz, 3H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 171.5, 169.8, 153.4, 101.1, 69.5, 62.5, 62.3, 55.7, 26.5, 26.1, 21.5, 21.4, 20.7, 20.1, 19.8$

HRMS (ESI) $m/z$ calcd for C$_{15}$H$_{28}$N$_3$O$_5$ [M+NH$_4$]$^+$ 330.2023, found 330.2050

IR: 3476, 2965, 2936, 1744, 1681, 1402, 1373, 1231, 1166, 1072, 1044 cm$^{-1}$

$[\alpha]_D^{20}$: -69.6 (c = 47 mg/mL in CHCl$_3$)

Reduction of Acylated Hydrazine (58)

SmI$_2$ was prepared according to a literature procedure.$^{86}$ A 250 mL round bottom flask was flame-dried and put under N$_2$ atmosphere. To the flask was added solid Sm metal chunks (1.65 g, 11.0 mmol) and 1,2-diiodoethane (1.55 g, 5.5 mmol). 55 mL of
anhydrous THF was added to the flask via syringe and the suspension was stirred. The flask was evacuated and backfilled with N\textsubscript{2} several times over the course of 1 h to remove liberated ethylene gas. After 1 h the gas line was removed, the flask sealed, and the solution stirred overnight. The yellow solution slowly turns blue. The next morning the solution was dark blue and can be used as a saturated solution of SmI\textsubscript{2} (~0.06 M).

Acylated hydrazone 57 (10 mg, 0.03 mmol) was dissolved in 0.5 mL MeOH (0.1 M) and added to a flame-dried flask. The flask was put under N\textsubscript{2} atmosphere. 4mL of prepared SmI\textsubscript{2} solution was added to the flask. As blue colour disappears, another 4mL of SmI\textsubscript{2} was added and the blue colour remained. The reaction was monitored by TLC until consumption of starting material is complete. The crude reaction was washed with water and the aqueous layer extracted three times with CH\textsubscript{2}Cl\textsubscript{2}. Purification by flash chromatography on silica (60:40 hexanes:EtOAc) yielded a clear oil (1.2 mg, 12% yield).

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta = 4.86 \ (dd, J = 5.8, 2.9 \text{ Hz, 1H}), 4.45 \ (dd, J = 10.2, 5.8 \text{ Hz, 1H}), 4.38 \ (d, J = 12.2 \text{ Hz, 1H}), 4.25 \ (m, J = 2.9, 1.7 \text{ Hz, 1H}), 4.11 \ (dd, J = 12.6, 2.9 \text{ Hz 1H}), 3.85 \ (dd, J = 12.6, 1.4 \text{ Hz 1H}), 2.64 \ (m, 2H), 2.19 \ (s, 3H), 2.10 \ (s, 3H), 1.44 \ (s, 3H), 1.43 \ (s, 3H), 1.13 \ (d, J = 6.6 \text{ Hz, 3H}), 0.84 \ (d, J = 6.6 \text{ Hz, 3H})

\textbf{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3})}: \(\delta = 172.9, 170.1, 98.9, 71.2, 66.1, 61.9, 54.0, 52.7, 29.7, 29.5, 27.9, 25.6, 21.1, 20.9, 18.0

\textbf{HRMS (ESI) m/z calcd for C\textsubscript{15}H\textsubscript{26}N\textsubscript{2}O\textsubscript{5} [M+H]+ 315.1914, found 315.1923

\textbf{IR}: 2926, 1743, 1660, 1496, 1376, 1234, 1199, 1090, 1044 cm\textsuperscript{-1}

\textbf{[a]\textsubscript{D}\textsuperscript{20}: }-32.1 \ (c =1.2 \text{ mg/mL in CHCl\textsubscript{3}})
2.4.4. NMR Spectra

NMR of Hydrazone (45)
NMR of Hydrazone (59)
NMR of Hydrazine (57)
NMR of Hydrazine (58)
2.4.5. HPLC Traces

HPLC Traces for Racemic (Left) and Enantioenriched (Right) (45)

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<th>Height (nA.U.)</th>
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HPLC Traces for Racemic (Left) and Enantioenriched (Right) (59)

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<td>0.6037</td>
<td>3250.41846</td>
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<td>50.2142</td>
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<tr>
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<td>5.84761</td>
<td>0.9159</td>
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<tr>
<td>2</td>
<td>16.559</td>
<td>0.5943</td>
<td>1.6723245</td>
<td>436.26291</td>
<td>99.0841</td>
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Chapter 3.

Expanding the Ketone Scope of the α-Chlorination-Aldol Reaction

3.1. Exploration of Potential Aldol Donors

3.1.1. Background

α-Chloroaldehydes are valuable synthetic building blocks and have found extensive application in natural product synthesis. One useful reaction of α-chloroaldehydes involves nucleophilic addition of organometallic reagents to give 1,2-anti-chlorohydrins that can be used in the synthesis of various natural products containing epoxides, tetrahydrofurans and pyrrolidines. In particular, it has been found that lithium enolates engage in aldol reactions with α-chloroaldehydes with good to excellent diastereoselectivity favouring formation of 1,2-anti-chlorohydrins.

As discussed in Chapter 1, a significant development in the reactions of α-chloroaldehydes was the report of a one-pot organocatalyzed α-chlorination-aldol reaction. The conditions for these reactions are mild, and effect both chlorination and C-C bond formation with excellent yields and control of stereochemistry. The organocatalyzed α-chlorination-aldol reaction has found application in the synthesis of small molecules and other natural products. Considering the limitations to the organocatalyzed α-chlorination-aldol reaction that include only using dioxanone as the ketone partner and “Cl+” as the electrophile, we sought to expand the scope of this reaction and enable production of more diverse families of tetrahydrofurans and pyrrolidines (Scheme 3.1).

![Scheme 3.1](image-url)

Scheme 3.1 The Goal of the Research Presented in this Chapter.
Based on the established utility of DMSO as a solvent for proline-catalyzed aldol reactions and CH$_2$Cl$_2$ as a solvent for organocatalyzed α-chlorination-aldol reactions, we initiated our studies with a solvent mixture of DMSO:CH$_2$Cl$_2$ (1:1). Additionally, we began by exploring reactions in a one pot but stepwise manner, unlike the previous α-chlorination-aldol methodology. In the α-chlorination-aldol with dioxanone, the rate of chlorination of the aldehyde was sufficiently fast to ensure that chlorination of dioxanone would not occur. In the present study it was not clear that the additional ketones would not undergo chlorination. We also chose isovaleraldehyde as the model aldehyde, as it demonstrated high levels of diastereoselectivity in previous α-chlorination-aldol and other proline catalyzed aldol reactions.$^{94,95,68}$ This choice also made analysis of crude reaction products by $^1$H NMR spectroscopy more straightforward.

### 3.1.2. Alkyl ketones and aldehydes

Initially, aldehydes were explored as aldol donors, following work reported by MacMillan involving the use of two aldehydes in an aldol reaction.$^{33}$ We first submitted isovaleraldehyde 25 to α-chlorination, followed by the addition of propanal 61 (Scheme 3.2). The reaction yielded a single product was identified as enal 62. Presumably, an aldol reaction occurred, but underwent elimination to form the enal product. Unfortunately, further attempts to optimize this reaction failed to give the desired aldol adduct.

![Scheme 3.2](image)

**Scheme 3.2 Investigating Aldehydes as Donors in α-Chlorination-Aldol.**

Moving forward, and given our previous success with dioxanone, we examined other cyclic ketones in attempt to develop a more general α-chlorination-aldol reaction. As depicted in Scheme 3.3, we found that cyclopentanone 63 reacted with 2-chloroisovaleraldehyde to provide a 1:1:1 mixture of diastereomers of the aldol adduct 64 in 14% yield (Scheme 3.3). Column chromatography allowed removal of one diastereomer, while the other two diastereomers remained inseparable. This prevented assignment of
stereochemistry, or any further optimization of the reaction. Poor diastereoselectivity is a noted problem with cyclopentanone in aldol reactions. This is likely due in part to the increased reactivity of a 5-membered ring under organocatalytic conditions. The increased angle strain imparted by the smaller ring angles could lead to less discrimination between diastereomeric transitions states leading to product chlorohydrins. This would be observed as poor diastereoselectivity.

Scheme 3.3 α-Chlorination-Aldol with Cyclopentanone gave poor Diastereoselectivity.

Gratifyingly, cyclohexanone 23 reacted well with aldehyde 25 under the identical reaction conditions to give chlorohydrin 65 (Scheme 3.4). Good conversions and diastereoselectivity were observed by 1H NMR spectroscopic analysis of crude reaction mixtures, all while employing a modest excess of the ketone. This is unlike many previous reports of organocatalytic aldol reactions that typically employ alkyl ketones in large excess, or as a solvent as in List’s first intermolecular aldol reaction. The relative stereochemical assignment of compound 65 was based on literature precedent for the observed configuration, and was confirmed by nOe experiments on the reduced and cyclized adducts (compound 97, p. 55).

Scheme 3.4 α-Chlorination-Aldol Reaction with Cyclohexanone.
3.1.3. Synthesis and Investigation of α-substituted Ketones in α-Chlorination-Aldol Reactions

Building on the previous successes with dioxanone 20, other protected α-hydroxy ketones were prepared (Scheme 3.5). We determined that the α-hydroxy ketones should be protected to maximize solubility and avoid side reactions of the free alcohol function. The choice of a TBS protecting group was based on literature precedent for organocatalytic aldol reactions of silyl-protected hydroxy-ketones, which typically demonstrate the highest reactivity among protected hydroxy-ketone derivatives.94

Scheme 3.5 Preparation of TBS protected ketones (69-71).

Firstly, bis-TBS-protected dihydroxyacetone 71 was prepared, and submitted to the aldol reaction conditions (Scheme 3.6). In this case, the conversion to 72, and diastereoselectivity were quite low, which is line with observations reported by Barbas in proline catalyzed aldol reactions of this substrate. However, this reaction demonstrates the possibility to access differently protected dihydroxyacetone derivatives such as 72 using the α-chlorination-aldol methodology.

Scheme 3.6 bis-TBS protected Dihydroxyacetone (70) in an Aldol Reaction.

Analysis of the crude product derived from the reaction of methyl ketone 69 and 2-chloroisovaleraldehyde by 1H NMR spectroscopy revealed both good conversion and diastereoselectivity (14:1) to compound 73 (Scheme 3.7). Here, the regioselectivity of the
The aldol reaction favors aldol reaction on the silyloxy-substituted side of the ketone. TBS-protected hydroxyacetophenone 70 was also prepared but unfortunately, did not engage in aldol reactions with 2-chloro-isovaleraldehyde.

\[
\begin{align*}
\text{O} & \quad \text{H} \quad \text{C} \\
\text{25} & \quad \text{C} \quad \text{O} \quad \text{H} \\
\text{i) NCS, 80 mol\% L-proline (8)} & \quad \text{Me} \quad \text{O} \quad \text{CH}_2\text{Cl}_2 \\
\text{ii) DMSO, Me} & \quad \text{C} \quad \text{O} \quad \text{Me} \quad \text{TBS} \\
\text{69} & \quad \text{OH} \quad \text{TBS} \\
\text{73} & \quad \text{Cl}
\end{align*}
\]

58% yield
14:1 d.r.
97% ee

**Scheme 3.7  TBS-protected Hydroxyacetone (69) Aldol Reaction.**

A protected α-amino ketone were also prepared via displacement of chloride from chloroacetone (75) with the potassium salt of succinimide 74 (Scheme 3.8). Unfortunately, we observed no aldol reaction between this ketone 76 and 2-chloro-isovaleraldehyde. We suspect that in this case the succinimide protecting group is too bulky, and thus prevents condensation of proline or the subsequent approach of the electrophile.

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{74} & \quad \text{H} \\
\text{i) KOH, EtOH} & \quad \text{C} \quad \text{O} \\
\text{ii) 75, DMF} & \quad \text{O} \quad \text{N} \quad \text{O} \\
\text{76} & \quad \text{Cl}
\end{align*}
\]

54% yield

**Scheme 3.8  Preparation of α-nitrogen Ketones.**

In search of a smaller nitrogen protecting group, azidoacetone 77 was prepared by the reaction of chloroacetone with sodium azide. Unfortunately, this substrate reacted with itself too quickly when exposed to proline and there was no indication of reaction with 2-chloro-isovaleraldehyde. The product of two or more molecules of azidoacetone reacting with each other would be quite dangerous and unstable, and so this compound was not isolated nor characterized.
Scheme 3.9 Azidoacetone (76) in an α-Chlorination-Aldol reaction.

At this point, we had identified three compatible ketones for the α-chlorination aldol reaction. Each of these ketones would enable the synthesis of new classes of natural products that either lack a primary alcohol function (i.e., 1-silyloxyacetone) or include other ring systems (e.g., cyclohexanone). Notably, we found that ketones reacted best when constrained in a six-membered ring and anticipated that other 6-membered rings would be suitable substrates for this reaction.

3.1.4. Six-membered rings in the α-Chlorination Aldol Reaction

Inspired by Ward’s thiopyranone aldol, we explored the use of thiopyranone 24 in the α-chlorination aldol reaction (Scheme 3.10). Here, thiopyranone reacted with isovaleraldehyde 25 in 45% yield and excellent diastereoselectivity (10:1) (79). Similarly, pyranone 78 also engaged in the α-chlorination aldol reaction providing the unusual adduct 80 in 50% yield and excellent diastereoselectivity (12:1).

Scheme 3.10 Thiopyranone in α-Chlorination-Aldol Reaction.

At this point it was determined we had identified a satisfactory scope of new ketones that could be used for this process and we moved forward to further optimize these reactions (Scheme 3.11).
3.2. Optimization of α-Chlorination-Aldol Reaction

3.2.1. Purity of Starting Materials

**Purification of Aldehydes**

At the outset of this project, we had concerns regarding the quality of commercially available aldehydes. As the α-chlorination-aldol reaction is extremely sensitive to quality of starting materials, this warranted further investigation.

Firstly, upon investigation of the aldehydes, we found that many had undergone oxidation (~30-40%) by reaction with atmospheric oxygen, providing the corresponding carboxylic acids. To purify these aldehydes, we attempted to form sulfite salts of the aldehydes using sodium sulfite (Scheme 3.12). Exposure of the contaminated aldehyde, such as hydrocinnamaldehyde 81 to aqueous sodium sulfite in ethyl acetate resulted in the precipitation of the corresponding sodium sulfite salt (e.g., 82). Filtration of the salt allowed for easy removal of other organic soluble contaminants.

Reforming the aldehyde proved to be more challenging than expected. Polar aldehydes proved to have significant water solubility and were difficult to isolate following aqueous extraction. Additionally, recovery of volatile aldehydes was made difficult by the necessary concentration (rotary evaporation) after extraction. However, in general, this purification procedure proved useful for non-volatile, less polar aldehydes such as 81. Alternatively, we found that washing organic solutions of crude aldehydes with saturated
aqueous sodium carbonate was sufficient to remove the corresponding carboxylic acid impurities. Once the aldehydes were determined to be of sufficient purity, we began to investigate the purity of the commercially available ketones.

**Purification of Thiopyranone**

Thiopyranone did not match the literature description of its physical form. According to SDS, thiopyranone is a white powder while the commercially available material was purchased as a brown/orange solid. While the $^1$H NMR spectrum of this material was consistent with literature reported spectra, we decided to investigate the effect of purifying the ketone on the subsequent aldol reaction. The colour was removed by dissolving thiopyranone in ethyl acetate and mixing with decolourizing charcoal, which afforded a yellow powder after filtration and concentration. Additional filtration of the ethyl acetate solution through a short plug of silica gel followed by concentration provided a mostly white powder (Figure 3.1)

![Visual Purity of Thiopyranone: (L-R) Commercially available, Purified with just Charcoal, Purified with Charcoal and Silica Plug.](image)

The first and third samples of ketone were submitted to an α-chlorination-aldol reaction to determine the effect of purity on the aldol reaction. In fact, the conversions increased significantly as shown in table 3.1 from entry 1 to entry 2.
### Table 3.1 Increasing Conversion with Increasing Purity of Thiopyranone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Purity</th>
<th>Yield</th>
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<tr>
<td>1</td>
<td>Commercially pure</td>
<td>24%</td>
</tr>
<tr>
<td>2</td>
<td>Charcoal + SiO₂ plug</td>
<td>35%</td>
</tr>
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#### 3.2.2. Optimization of reaction conditions

The thiopyranone aldol reaction was further optimized using internal standard (1,3,5-trimethoxybenzene) for reaction monitoring by ¹H NMR spectroscopy. First, the equivalents of ketone and aldehyde were varied, to determine which reagent should be employed in excess, and by how much. As summarized in Table 3.2 (entry 2), using the aldehyde in excess gave very little desired product while (entry 3) increasing the equivalents of ketone had a modest effect on conversion. Further increases in equivalents of ketone (entries 4 and 5) led to modest increases in conversions. In the end, 3 equivalents of ketone (entry 4) was chosen as optimal, as purification of the final product was complicated by excess ketone present in the crude reaction mixture.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio (aldehyde:ketone)</th>
<th>Conversion</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>2:1</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>1:3</td>
<td>28%</td>
</tr>
<tr>
<td>5</td>
<td>1:5</td>
<td>34%</td>
</tr>
</tbody>
</table>

#### Table 3.2 Optimizing Equivalents of Ketone and Aldehyde.

Different solvent systems were examined for the aldol reaction (Table 3.3) and it was found that a chlorinated solvent is necessary for the α-chlorination reaction as no chlorination was observed in DMSO or DMF (entry 2). This observation was also made by Jørgensen’s in their initial disclosure of the aldehyde α-chlorination reaction.³⁸ Using only CH₂Cl₂ as a reaction solvent provided less final aldol product than the 1:1 CH₂Cl₂:DMSO. We also investigated different ratios of CH₂Cl₂: DMSO and CH₂Cl₂: DMF and found small variances in product yield. In the end, for ease of workup and handling of crude reaction mixtures, a 9:1 mixture of CH₂Cl₂: DMSO was chosen as the optimal solvent system (entry 5).
### Table 3.3 Solvent Optimization for α-Chlorination-Aldol Reaction.

<table>
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<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion</th>
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<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>No α-chlorination</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂: DMSO (1:1)</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂: DMSO (1:9)</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂: DMSO (9:1)</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂: DMF (1:1)</td>
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</tbody>
</table>

Catalyst loading was also examined, and larger equivalents of proline led to higher conversions to aldol product. Beyond 80 mol%, additional proline was found to be insoluble in the optimal solvent system and therefore 80 mol% of proline was chosen as optimal.

### 3.2.3. Purification of New Aldol Adducts

The workup and purifications for the new aldol adducts was intended to be minimal to avoid product loss and thus our goal was to apply each crude reaction mixture (after evaporation of volatiles) directly to a silica gel column and purify the products by flash chromatography. This procedure worked well for the mono-OTBS ketone 69, bis-OTBS ketone 70 and thiopyranone 24.

Conversely, aldol products from cyclohexanone 23 and pyranone 78 gave mixtures of diastereomers after flash chromatography. Critically, diastereomeric mixtures isolated following chromatography were not observed in ¹H NMR spectra recorded on crude reaction products indicating that these aldol adducts underwent extensive decomposition and epimerization during column chromatography (Table 3.4 entries 3 and 4). Washing the reaction mixture with saturated aqueous NH₄Cl or NaCl to remove DMSO prior to column chromatography prevented decomposition, but not epimerization in these cases (entries 1 and 2). Ultimately, we found that washing the crude reaction mixture with saturated aqueous NH₄Cl (to remove the DMSO), followed by a wash with saturated aqueous NaHCO₃, concentration and column chromatography on silica gel allowed facile purification (entry 5). Acidification of the NaHCO₃ aqueous layer and re-extraction with CH₂Cl₂ allowed examination of organic components that were removed from the crude reaction product. Analysis of these extracted materials by ¹H NMR spectroscopy indicated predominantly succinimide and suggested that succinimide played a role in degradation.
or epimerization of these particularly sensitive aldol adducts during purification by flash column chromatography on both silica and alumina.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Workup/Purification</th>
<th>Result</th>
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<tbody>
<tr>
<td>1</td>
<td>Wash with NH₄Cl, SiO₂ column</td>
<td>Epimerization</td>
</tr>
<tr>
<td>2</td>
<td>Wash with NaCl, SiO₂ column</td>
<td>Epimerization</td>
</tr>
<tr>
<td>3</td>
<td>Direct application to SiO₂ column</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>Direct application to basic alumina column</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>Wash with NH₄Cl, then NaHCO₃, then apply to SiO₂ column</td>
<td>No epimerization</td>
</tr>
</tbody>
</table>

**Table 3.4 Workups and Purifications for Crude Cyclohexanone Aldol Adduct.**

After applying these optimized purification and workup procedures to pyranone, we found the aldol adduct 80 remained unstable to column chromatography on both silica and alumina stationary phases. Frustratingly, the ¹H NMR spectrum recorded on crude pyranone aldol 80 indicated excellent purity and conversion. Thus, the pyranone aldol adduct was isolated as diol 83 after reduction of the intermediate ketone 80. The latter material proved stable and was readily isolated in good yield over the two steps by flash column chromatography (Scheme 3.13).

**Scheme 3.13 Procedure for Isolating Pyranone Aldol Adducts.**

### 3.3. Byproduct Formation and Effect of H₂O on the Reaction

#### 3.3.1. Observation of Proline-Aldehyde Byproducts

While optimizing the aldol reaction, a consistent pattern in the chlorination reaction was observed. A white precipitate would form during chlorination, only to disappear after 1 hour leaving behind a homogenous solution. Filtering off the white solid before it disappeared and analysis by ¹H NMR spectroscopy allowed us to determine that there was in fact an adduct forming between the α-chloroaldehyde and proline (Figure 3.2).
Different adducts between proline and aldehydes have been reported, including oxazolidinones (85)\textsuperscript{58}, and adducts involving succinimide (84).\textsuperscript{63}

![Diagram of molecules](image)

**Figure 3.2** Crude \(^1\)H NMR of Proposed Intermediate (Compound (84) or (85)) with zoom.

This observation further supports our previous finding that proline reacts readily with \(\alpha\)-chloroaldehydes and effects racemization critical to the DKR process. Further, this suggests that the catalyst prefers to exist covalently bound to the \(\alpha\)-chloroaldehyde rather than free in solution and prompted us to examine the effect of water on the reaction, which would presumably assist in solubilizing free proline and unveiling \(\alpha\)-chloroaldehydes for reaction. It is a known phenomenon that water concentration can affect the concentration of these intermediates in solution\textsuperscript{58}, and thus the addition of water can perturb this equilibrium and perhaps enhance the reaction rate.
3.3.2. Effect of $\text{H}_2\text{O}$ on $\alpha$-Chlorination-Aldol Reaction

Although water was investigated in the original chloro-aldol methodology, it was not used at high concentrations (0.5 eq of water). The effect of water is known to show effects continuing from sub-stoichiometric amounts, until water is used as a reaction solvent. Ward’s DKR aldol of thiopyranone employs “wet DMSO” or “wet DMF” which is reported as 0.8 ml water per 6 ml dry DMSO (~12 vol%). Others have reported optimizing the water content for each substrate, in a range of 15-30 eq of water (~9 vol%).

With this in mind, we investigated increasing water concentration from 0% (dry) up to 10 vol%. Here we found significant differences in reaction profiles or “cleanliness” as well as colour changes. The source of colour was not identified, though it should be noted that the products of this aldol reaction are colourless oils or white solids. As expected, the solubility of proline increased with increasing water concentration.

![Visual Differences in Water Concentration](image)

**Figure 3.3** Visual Differences in Water Concentration (L-R: 0 vol%, 0.5 vol%, 1.0 vol%, 3.0 vol%, 5.0 vol% and 10 vol%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>vol%$\text{H}_2\text{O}$</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0%</td>
<td>21%</td>
</tr>
<tr>
<td>2</td>
<td>0.5%</td>
<td>17%</td>
</tr>
<tr>
<td>3</td>
<td>1.0%</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>3.0%+</td>
<td>0% (biphasic)</td>
</tr>
</tbody>
</table>

**Table 3.5** Effect of Water Concentration on Conversion.

As summarized in Table 3.5, the difference in reaction yield (determined by analysis of $^1\text{H}$ NMR spectra with internal standard recorded on crude reaction products) was significant up to 3 vol% of water (entry 3). At higher concentrations of water, we found reaction conversion decreased and the reactions became biphasic (entry 4). Based on
these results, we repeated several other aldol reactions with 1.0 vol% water and noted increased conversions, cleaner crude reactions and easier purification.

3.4. Demonstrating the Scope of the New Ketones

With the optimized reaction conditions in hand, we set out to demonstrate the applicability of the methodology. With the assistance of Terry Rai (undergraduate student 2018) and Bharanishashank Adluri (PDF) (86, 89), we were able to demonstrate the generality of the methodology by applying the optimized reaction conditions to the compounds shown in figure 3.4.

Figure 3.4  Scope of α-Chlorination-Aldol Reaction (Compound (81) isolated as diol after reduction).
3.4.1. Determination of Enantiomeric Excess

The enantiomeric excess of the aldol adducts was determined in most cases by reducing the ketone function and isolating the corresponding diol (Scheme 3.14). Formation of the bis-\(p\)-nitrobenzoate (PNB) esters 92 was then effected under standard conditions.98 Reduction of the ketone was necessary, as elimination products 93 were observed when PNB protection was attempted on the aldol adducts themselves. Once the PNB esters 92 were formed, the UV-absorbing products compounds were amenable to separation by HPLC and detection by a variable wavelength detector (VWD).

![Scheme 3.14 Determination of Enantiomeric Excess by Formation of PNB-esters (92).](image)

3.4.2. Synthesis of Novel Small Molecules

To demonstrate the utility of the new aldol adducts, we synthesized a panel of small molecules with the assistance of Lexi Gower-Fry (93) (an undergraduate student). THF scaffolds are prevalent throughout nature and found within carbohydrates and polyketides.96,99 These new aldol reactions provide access to an increased diversity of THFs. Additionally, this exercise provided a means to determine the relative stereochemistry of the chlorohydrins, as nOe correlations could be observed in many of the bicyclic systems (see Experimental). After reduction of aldol adducts to the corresponding diols, cyclization under microwave conditions68 yielded a range of THFs. Using this synthetic sequence, we were able to generate a small library of THF molecules (Scheme 3.15).
Scheme 3.15 Synthesis of THF Rings from Chlorohydrins.

Additionally, following the procedure established by Bergeron-Brlek\textsuperscript{71}, reductive amination with benzylamine followed by cyclization under thermal conditions was employed to generate a small library of pyrrolidines with Bharanhishashank Adluri (PDF) and Terry Rai (undergraduate student) (96, 97, 98). A small library of pyrrolidines was generated and characterized.

Scheme 3.16 Reductive Amination-Cyclization to form Pyrrolidines from Chlorohydrins.
3.5. Studies Towards a Short Synthesis of Hyacinthacine C Derivatives

3.5.1. Initial Strategy to Synthesize Hyacinthacine C Derivative

To further demonstrate the utility of these new aldol adducts, we designed a short synthesis of a member of the hyacinthacine C family 102 (Scheme 3.17). Our initial strategy involved using the previously established dioxanone methodology to provide chlorohydrin 105. Following deprotection and oxidation to aldehyde 104, we could then carry out a second aldol to afford 103. After deprotection, reductive amination and cyclization this sequence should afford 102. While we were excited to find that deprotection of the known aldol adduct 105 proceeded smoothly, we were unfortunately not able to oxidize the primary alcohol function to aldehyde 104. We suspected that here, the free alcohol cyclizes to form the corresponding hemiacetal 107 and, consequently, a revised strategy was designed to prevent such processes.
3.5.2. Revised strategy

Based on the observations detailed above, a revised synthetic route was designed to avoid hemiacetal formation. By switching the order of steps, we anticipated that we could avoid hemiacetal formation. Following the procedures established by Bergeron-Brlek, we effected reductive amination of the aldol adduct 105 to give 108 as shown in scheme 3.19.
A simple benzylidene protecting group strategy was designed to protect the amine and the secondary alcohol. By mixing 108 in acetonitrile with a large excess of benzaldehyde, MgSO₄ and catalytic acetic acid, we were able to isolate a mixture of two diastereomers at the benzylidene position (Scheme 3.20) in good yield. Deprotection of the TBS-alcohol with TBAF proceeded smoothly to give 109.

Oxidation of the primary alcohol 109 under Parikh-Doering conditions gave a mixture of four aldehydes (Scheme 3.21). We expected two diastereomers at the benzylidene centre and two diastereomers at the α-chloro stereocentre. Fortunately, this was easily remedied following the work of Kang where a Dess-Martin periodane (DMP) oxidation was employed to prevent racemization of the chloromethine-stereocentre. In this case, two diastereomers of the α-chloroaldehyde were isolated, one for each epimer at the benzylidene position.
Scheme 3.21 Oxidation of Primary Alcohol (109) with Parikh-Doering and Dess-Martin conditions.

With the α-chloroaldehyde 111 in hand, we attempted the key step, an aldol reaction with one of the new ketones described in this thesis. Unfortunately, upon submission of the aldehyde to the optimized aldol reaction conditions with ketone 69, we observed rapid decomposition of the aldehyde (Scheme 3.22).

Scheme 3.22 Attempted Aldol Reaction of (111).

Given the lability of the protected hydroxy group under organocatalytic conditions and propensity for this material to undergo elimination this process would require an alternative protecting group strategy. Notably, in the work of Adamson, considerable optimization of the hydroxyl protecting groups was necessary to find a compatible substrate for an organocatalyzed aldol reaction involving a β-hydroxyaldehyde,\textsuperscript{102} which ultimately led to the use of a TIPS protecting group (Scheme 3.23).
Adamson’s work on Aldehydes Containing Protected β-hydroxy group.

3.6. Conclusion

The scope of the α-chlorination-aldol reaction was expanded to include four new ketones (TBS-protected hydroxyacetone 69, thiopyranone 24, pyranone 78, and cyclohexanone 23). After identification of these new ketones, a general set of reaction conditions were optimized for this set of substrates. The effect of water on the reaction was investigated and found to have a substantial impact on both the conversions and cleanliness of the reaction. After optimization, ten aldol adducts were synthesized in moderate yields, poor to high diastereoselectivity and high enantioselectivity. The aldol adducts were then used to synthesize a library of eight small molecules (94-101). Furthermore, studies towards the concise synthesis of hyacinthacine C natural products using this methodology were examined. Unfortunately, the key reaction utilizing this methodology failed due to an elimination reaction of a protected β-hydroxy group on the intermediate aldehyde.

3.7. Experimental Information

3.7.1. General Considerations

L- and D- proline (99% purity) were purchased from Sigma-Aldrich. All other reagents were purchased from Sigma-Aldrich or TCI and used without purification unless indicated. All reactions described were performed at ambient temperature and open to atmosphere unless otherwise indicated.

Aldehydes were purified by crystallization of bisulfite adducts and regeneration with aqueous K₂CO₃ (1.0 M) or by washing with saturated aqueous Na₂CO₃ prior to
reaction. TBS-protected hydroxyacetone (mono and bis) were synthesized according to literature procedures.\textsuperscript{103} 4H-tetrahydrothiopyranone was purchased from TCI America and purified before use by swirling with decolourizing charcoal and filtering with silica plug. All other ketones were purchased from Sigma-Aldrich and used without purification.

NMR spectra were recorded using CDCl\textsubscript{3} as the solvent. Signal positions are given in ppm relative to tetramethylsilane and were calibrated using the residual solvent signal (\textsuperscript{1}H NMR: CDCl\textsubscript{3} 7.26 ppm \textsuperscript{13}C NMR: CDCl\textsubscript{3} 77.0 ppm). \textsuperscript{1}H NMR multiplicities are given as (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; bs, broad singlet). \textsuperscript{1}H and \textsuperscript{13}C NMR are recorded on a Bruker 600, Bruker 500 or Bruker 400. Diastereomeric ratios are based on analysis of crude \textsuperscript{1}H NMR spectra.

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum Two FTIR spectrometer. Only selected wavenumbers are provided for each compound. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 at 589nm. HPLC analysis was performed on an Agilent 1100 HPLC equipped with a variable UV-Vis wavelength detector. Enantiomeric excess was determined as indicated for each compound. High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS using ESI-MS.

\textbf{3.7.2. General Procedures}

\textbf{General Procedure C (Organocatalyzed One-pot \(\alpha\)-Chlorination-Aldol)}

NCS (1.05 eq) and proline (0.8 eq) were suspended in CH\textsubscript{2}Cl\textsubscript{2} (0.56 M) at 0\textdegree C. To this suspension was added aldehyde (1 eq). The suspension was allowed to stir at 0\textdegree C for 1h. After 1h, ketone (3 eq.), DMSO (final concentration of aldehyde 0.5M, DMSO:CH\textsubscript{2}Cl\textsubscript{2} (1:9)) and 1% v/v H\textsubscript{2}O were all added to the reaction mixture. The reaction was allowed to warm to room temperature. The reaction was monitored by \textsuperscript{1}H NMR until disappearance of \(\alpha\)-chloro-aldehyde is noted. The reaction was worked up and purified as indicated.
General Procedure D (Reduction of Aldol Adduct)

Dissolve aldol adduct in MeOH (0.5 M) and cool to 0°C. Add 2 eq NaBH₄. The reaction was stirred at 0°C until consumption of starting material was observed by TLC (~1 h). The reaction was quenched at 0°C by slow addition of saturated NH₄Cl until bubbling ceased. The reaction mixture was diluted with H₂O to ensure all solids were dissolved. The crude mixture was extracted 3x with CH₂Cl₂. The organic layer was dried with brine, and Na₂SO₄. The organic layer was concentrated under reduced pressure and purified as indicated.

General Procedure E (Cyclization of Diol)

Chlorodiol was dissolved in MeOH (0.5 M) and placed in a microwave vial. The vial was sealed in a CEM Discover LabMate microwave reactor and subjected to microwave radiation. The vial was heated for 5 minutes at 90°C, then for 5 minutes at 110°C, before heating for 1.8 h at 120°C (pressure was kept below 300 psi). The vial was cooled and analyzed by TLC to ensure complete consumption of starting material. The crude mixture was concentrated under reduced pressure and then purified by column chromatography on silica as indicated.

General Procedure F (Synthesis of PNB-esters for Determination of Enantiomeric Excess)

Either the chlorodiol or aldol adduct (depending on stability) was dissolved in 1:1 CH₂Cl₂:NEt₃ (0.4M). To this was added 2 eq of PNB-Cl per alcohol on substrate (2 or 4eq). A spatula tip of DMAP was added to the solution, which was allowed to stir overnight. The reaction mixture was washed with each of H₂O, 1.0M aqueous HCl and brine, dried with Na₂SO₄ and concentrated under reduced pressure. The adducts were purified by column chromatography on silica as indicated.
General Procedure G (Reductive Amination)

Chlorohydrin was dissolved in dry THF (0.1 M) with 1 eq of AcOH. Amine (2 eq) was added and allowed to stir for ~1 hour or until most of the chlorohydrin has been consumed by TLC. NaBH₃CN (2 eq) was added and the reaction was stirred for another 1 h, or until intermediate imine is consumed by TLC. The reaction was quenched with water and the organic layers were separated. Extract the aqueous layer 3x with CH₂Cl₂ and dry with brine, then Na₂SO₄. Concentrate and purify as indicated.

3.7.3. Preparation and Characterization Data of Aldol Adducts

Preparation of Chlorohydrin (73)

According to general procedure C, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH₂Cl₂ (0.9 mL) at 0°C, before adding isovaleraldehyde (0.5 mmol, 54 μL). After 1 h, add ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H₂O (10 μL). Reaction was stirred for 24 h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO₂ column. Purification by flash chromatography (hexanes-EtOAc-NEt₃ 95%:4%:1%) afforded (180 mg, 58%) of a pale-yellow oil.

¹H NMR (500 MHz, CDCl₃) δ = 3.96 (dd, J = 7.3, 2.0 Hz, 1H), 3.94 (d, J = 8.2 Hz, 1H), 3.82 (d, J = 8.2 Hz, 1H), 2.26 (bs, 1H), 2.20 (s, 3H), 2.12 (m, J = 6.8 Hz, 1H), 1.07 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H)

¹³C NMR (125 MHz, CDCl₃) δ = 209.7, 79.0, 73.0, 70.8, 32.5, 25.6, 25.5, 20.3, 20.0, 18.0, -4.9, -5.2 ppm

HRMS (ESI) m/z calcd for C₁₄H₃₀ClO₃Si [M+H]⁺ 309.1647, found 309.1666

IR: 3453, 2956, 2930, 1718, 1254, 1102, 835, 777 cm⁻¹

αD²⁰ = -18.9 (c = 64 mg/mL in CHCl₃)
Determination of Absolute Stereochemistry for Chlorohydrin (73)

Determination of Enantiomeric Excess of Chlorohydrin (73)

Preparation of Chlorohydrin (91)
Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO_2 column and purified using (90:10 hexanes:EtOAc) to give white solid (108 mg, 56% yield).

^1H NMR (500 MHz, CDCl_3) δ= 7.28 (m, 2H), 7.21 (m, 3H), 4.15 (ddd, J = 1.6, 4.0, 10.2 Hz, 1H), 3.94 (d, J = 8.6 Hz, 1H), 3.63 (m, J = 1.6, 8.5, 10.4 Hz, 1H), 2.91 (m, J = 5.0, 7.5, 12.9 Hz, 1H), 2.78 (m, J = 7.3, 8.6, 13.9 Hz, 1H), 2.29 (m, J = 5.0, 7.4, 10.3, 14.3 Hz, 1H), 2.20 (s, 3H), 2.13 (d, J = 11.0 Hz, 1H), 2.07 (m, 1H), 0.80 (s, 9H), 0.00 (s, 6H)

^13C NMR (125 MHz, CDCl_3) δ= 209.4, 140.3, 128.6, 128.6, 126.3, 79.0, 75.0, 63.1, 36.5, 32.5, 25.6, 25.3, 17.9, -4.9, -5.3

HRMS (ESI) m/z calcd for C_{19}H_{25}ClO_{3}NSi [M+NH_4]^+ 388.2069, found 388.2041

IR: 3362, 2958, 2927, 2856, 1708, 1104, 1074, 834, 698 cm^{-1}

m.p.: 70-73°C

α_20^D = -9.7 (c=20 mg/mL in CHCl_3)

Determination of Relative Stereochemistry for Chlorohydrin (91), preparation of (96)

According to general procedure D, chlorohydrin 91 (0.5 mmol, 194 mg) was reduced to the corresponding chlorodiol with NaBH_4 (1.0 mmol, 37 mg) in MeOH (1 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH_4Cl (5 mL) and extracted 3x with 10 mL of CH_2Cl_2. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure E, without purification, the crude reduction product was subjected to microwave irradiation.
After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO$_2$. Purification by column chromatography (60:40 Hexanes:EtOAc) to give a white solid in 18% yield (20 mg, 0.09 mmol).

The cyclic diol was stirred in acetone (0.1 M) with TsOH (0.1 eq, 30 mg) and two heaping spatula tips of MgSO$_4$ to form the acetonide protected THF. The crude product was purified by column chromatography (60:40 hexanes:EtOAc) to yield (18 mg, 0.08 mmol) a clear oil in 17% overall yield from aldol adduct. Relative stereochemistry was determined by 2D NOE analysis. Key NOE correlations are shown above.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$= 7.29 (m, 2H), 7.21 (m, 3H), 4.37 (dd, $J = 4.9, 7.2$ Hz, 1H), 4.27 (dd, $J = 5.0, 7.2$ Hz, 1H), 3.92 (m, 1H), 3.83 (td, $J = 4.9, 6.7$ Hz, 1H), 2.78 (m, 1H), 2.72 (m, 1H), 1.93 (m, 2H), 2.53 (s, 3H), 1.34 (s, 3H), 1.33 (d, $J = 7.7$ Hz, 3H)

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$= 141.6, 128.4, 128.3, 125.8, 114.9, 86.2, 85.3, 83.3, 79.9, 35.4, 31.8, 29.7, 27.3, 25.4, 19.0

HRMS: (ESI) m/z calcd for C$_{16}$H$_{23}$O$_3$[M+H]$^+$ 263.1642, found 263.1635

IR: 3027, 2957, 2929, 2871, 1708, 1381, 1210, 1074, 865, 699, 512 cm$^{-1}$

$\alpha_D^{20}$ = -14.7 (c = 22 mg/mL in CHCl$_3$)

**Determination of Enantiomeric Excess of Chlorohydrin (91)**

According to general procedure F, the corresponding PNB esters of chlorohydrin 85 were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 μm) Amylose-5 column; flow rate 0.4 mL/min; eluent: hexanes-$i$PrOH 95:5; detection at 254 nm; retention time = 3.24 min and 3.71 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (97% ee).
Preparation of Chlorohydrin (89)

According to general procedure C, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH$_2$Cl$_2$ (0.9 mL) at 0°C, before adding in valeraldehyde (0.5 mmol, 54 μL). After 1h, ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H$_2$O (10 μL) were added. The reaction was stirred for 24h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then the crude reaction was applied to SiO$_2$ column (5-10-15% EtOAc in hexanes gradient) to give pale yellow oil (44 mg, 27% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ = 4.28 (ddd, J = 1.8, 5.2, 9.2 Hz, 1H), 3.97 (d, J = 8.5 Hz, 1H), 3.67 (ddd, J = 1.7, 8.5, 10.3 Hz, 1H), 2.23 (s, 3H), 2.08 (d, J = 10.5 Hz, 1H), 1.92 (m, J = 4.6, 9.3, 14.3 Hz, 1H), 1.78 (m, J = 5.3, 6.7, 8.9, 14.0 Hz, 1H), 1.54 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 209.5, 79.1, 74.4, 63.8, 37.0, 25.6, 25.4, 19.9, 18.0, 13.2, -4.8, -5.1

HRMS: (ESI) m/z calcd for C$_{14}$H$_{33}$ClO$_3$NSi[M+NH$_4$]$^+$ 326.1913, found 326.1889

IR: 3446, 2958, 2931, 1716, 1254, 1099, 837, 778, 672 cm$^{-1}$

$\alpha$$_{D}^{20}$ = -0.8 (c = 13 mg/mL in CHCl$_3$)

Determination of Enantiomeric Excess of Chlorohydrin (89)

According to general procedure F, the corresponding PNB esters of chlorohydrin 83 were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 μm) i-Cellulose-5 column; flow rate 0.2 mL/min; eluent: hexanes-iPrOH 97:3; detection at 254 nm; retention time = 2.61 min and 3.30 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (97% ee).
**Preparation of Chlorohydrin (90)**

![Chemical Structure](image)

According to general procedure C, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH₂Cl₂ (0.9 mL) at 0°C, before adding in 4-pentenal (0.5 mmol, 42 mg). After 1h, ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H₂O (10 μL) were added. The reaction was stirred for 24h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO₂ column and purified by flash chromatography (80:20 hexanes:EtOAc) to give a clear oil (51 mg, 49% yield)

**¹H NMR (400 MHz, CDCl₃)** δ= 5.83 (m, J = 6.9, 10.2 Hz, 1H), 5.20 (m, 2H), 4.26 (m, J = 1.9, 7.2 Hz, 1H), 3.97 (d, J = 8.5 Hz, 1H), 3.73 (m, J = 1.9, 8.5, 10.3 Hz, 1H), 2.65 (m, 2H), 2.23 (s, 3H), 2.09 (d, J = 10.3 Hz, 1H), 0.92 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H)

**¹³C NMR (100 MHz, CDCl₃)** δ= 209.4, 133.6, 118.5, 78.9, 73.8, 62.8, 39.3, 25.6, 25.4, 18.0, -4.9, -5.1

**HRMS:** (ESI) m/z calcd for C₁₄H₂₈ClO₃Si [M+H]⁺ 307.1491, found 307.1504

**IR:** 3443, 2955, 2929, 2858, 1716, 1641, 1255, 1097, 837, 778 cm⁻¹

αD²₀ = -27.7 (c=18.4 mg/mL in CHCl₃)

**Determination of Enantiomeric Excess of Chlorohydrin (90)**

According to general procedure F, the corresponding PNB esters of chlorohydrin 84 were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 μm) i-Cellulose-5 column; flow rate 0.4 mL/min; eluent: hexanes-iPrOH 95:5; detection at 254 nm; retention time = 1.18 min and 1.50 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (95% ee).
Preparation of Chlorohydrin (86)

According to general procedure C, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH₂Cl₂ (0.9 mL) at 0°C, before adding in 4-pentynal (0.5 mmol, 41 mg). After 1h, ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H₂O (10 μL) were added. The reaction was stirred for 24h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO₂ column and the product purified by flash chromatography (70:30 hexanes:EtOAc) to give a clear oil (75 mg, 49% yield).

¹H NMR (500 MHz, CDCl₃) δ = 4.30 (m, 1H), 3.97 (bs, 2H), 2.83 (m, J = 1.3, 2.7, 6.8 Hz, 2H), 2.25 (s, 3H), 2.18 (s, 1H), 2.14 (m, J = 2.7 Hz, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H)

¹³C NMR (125 MHz, CDCl₃) δ = 209.7, 79.4, 78.7, 73.1, 71.5, 60.4, 25.6, 25.5, 25.1, 18.0, -4.8, -5.1

HRMS: (ESI) m/z calcd for C₁₄H₂₅ClO₃NSi [M+NH₄]⁺ 322.1600, found 322.1604

IR: 3450, 3311, 2954, 2929, 1716, 1255, 1101, 837, 778, 635, 505 cm⁻¹

αD²₀ = -34.3 (c = 8 mg/mL in CHCl₃)

Determination of Enantiomeric Excess of Chlorohydrin (86)

According to general procedure F, the corresponding PNB esters of chlorohydrin 86 were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomenex Lux (3 μm) i-Cellulose-5 column; flow rate 0.4 mL/min; eluent: hexanes-iPrOH 99:1; detection at 254 nm; retention time = 3.06 min and 3.79 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (97% ee).
Preparation of Chlorohydrin (79)

According to general procedure C, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH₂Cl₂ (0.9 mL) at 0°C, before adding isovaleraldehyde (0.5 mmol, 54 μL). After 1h, thiopyranone (1.5 mmol, 174 mg), DMSO (0.1 mL) and H₂O (10 μL) were added. The reaction was stirred for 48h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then the crude reaction was applied to SiO₂ column and product purified by flash chromatography (80:20 hexanes:EtOAc) to give a white solid (53 mg, 45% yield).

¹H NMR (400 MHz, CDCl₃) δ= 4.31 (m, J = 3.7, 7.4 Hz, 1H), 3.68 (dd, J = 2.5, 8.0 Hz, 1H), 3.07 (m, 1H) 3.00-2.90 (m, 4H), 2.84-2.70 (m, 3H), 2.19 (m, J = 2.0, 6.6 Hz, 1H), 1.10 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ= 210.8, 70.7, 70.5, 56.5, 44.1, 32.2, 31.9, 30.5, 20.3, 20.1

HRMS: (ESI) m/z calcd for C₁₀H₂₁ClO₂NS[M+NH₄]⁺ 254.0976, found 254.0957

IR: 3539, 2970, 2926, 2872, 1684, 1323, 1307, 1248, 1057, 638, 560, 526 cm⁻¹

m.p.: 91-93°C

αD²⁰ = -37.4 (c=32.5 mg/mL in CHCl₃)

Determination of Relative Stereochemistry for Chlorohydrin (79), preparation of (98)

According to general procedure D, chlorohydrin 79 (1.0 mmol, 250 mg) was reduced to the corresponding chlorodiol with NaBH₄ (2.0 mmol, 74 mg) in MeOH (2 mL).
After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH₄Cl (5 mL) and extracted 3x with 10 mL of CH₂Cl₂. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure E, without purification, the crude reduction product was subjected to microwave irradiation. After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO₂. Purification by column chromatography (80:20 hexanes:EtOAc) gave a white solid (30 mg, 15% yield). Relative stereochemistry was determined by 2D NOE analysis. Key NOE correlations are shown above.

^1H NMR (600 MHz, CDCl₃) δ= 4.06 (m, 1H), 3.43 (d, J = 6.5 Hz, 1H), 3.38 (ddd, J = 3.7, 10.95, 10.94 Hz, 1H), 2.84 (dd, J = 11.6, 13.0 Hz, 1H), 2.73-2.61 (m, 3H), 2.46 (m, J = 3.5, 11.1 Hz, 1H), 1.74 (m, 1H), 1.66 (m, 1H), 1.60 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H)

^13C NMR (150 MHz, CDCl₃) δ= 91.9, 78.7, 74.7, 49.9, 33.6, 31.0, 27.3, 18.4, 18.3

HRMS: (ESI) m/z calcd for C₁₀H₁₉O₂S[M+H]^+ 203.1100, found 203.1098

IR: 3398, 2924, 1437, 1382, 1072, 1015, 945, 880, 634 cm⁻¹

m.p.: 82-86°C

αD²₀ = +4.7 (c=27 mg/mL in CHCl₃)

**Determination of Enantiomeric Excess of Chlorohydrin (79)**

According to general procedure F, the corresponding PNB esters of chlorohydrin 77 were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomenex Lux (3 μm) Amylose-3 column; flow rate 0.4 mL/min; eluent: hexanes-iPrOH 90:10; detection at 254 nm; retention time = 10.77 min and 16.02 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (94% ee).
Preparation of Chlorohydrin (87)

According to general procedure C, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH₂Cl₂ (0.9 mL) at 0°C, before adding valeraldehyde (0.5 mmol, 54 μL). After 1h, thiopyranone (1.5 mmol, 174 mg), DMSO (0.1 mL) and H₂O (10 μL) were added. The reaction was stirred for 48h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then the crude reaction was applied to SiO₂ column and the product purified by flash chromatography (80:20 hexanes:EtOAc) to give a clear oil. (17 mg, 15% yield)

¹H NMR (400 MHz, CDCl₃) δ= 4.13 (m, J = 2.3, 6.3, 8.4 Hz, 1H), 4.00 (m, J = 2.3, 5.0, 9.0 Hz, 1H), 3.10 (m, 1H), 3.03-2.90 (m, 4H), 2.86-2.66 (m, 4H), 1.95 (m, 1H), 1.82 (m, 1H), 1.58 (m, 1H), 1.45 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ= 210.1, 72.3, 63.5, 56.3, 44.2, 37.0, 32.0, 30.6, 20.0, 13.5

HRMS: (ESI) m/z calcd for C₁₀H₁₈ClO₂S[M+H]⁺ 237.0711, found 237.0732

IR: 3442, 2958, 2929, 1705, 1427, 1072, 1052, 752, 618 cm⁻¹

αD²₀ = -15.0 (c = 17.8 mg/mL in CHCl₃)

Preparation of Chlorohydrin (65)

According to general procedure C, NCS (1.05 mmol, 142 mg) and L-proline (0.80 mmol, 92 mg) were stirred in CH₂Cl₂ (1.8 mL) at 0°C, before adding in isovaleraldehyde (1.0 mmol, 108 μL). After 1h, ketone (2.0 eq, 2.0 mmol, 200 μL) in solution of DMSO (0.2mL) and H₂O (20 μL) was added. The reaction was stirred, and allowed to warm to
room temperature. The reaction was monitored by $^1$H NMR until consumption of starting material was noted (2d).

**Workup:** Volatiles were evaporated by rotary evaporation. To the crude reaction mixture was added ~2 mL of saturated aqueous NH$_4$Cl. The aqueous phase was extracted with Et$_2$O 2x. The combined organic layers were washed with saturated aqueous NaHCO$_3$, then brine. The organic layer was dried with Na$_2$SO$_4$ and concentrated by rotary evaporation. The crude product was purified by flash chromatography on SiO$_2$ column (90:10 hexanes:EtOAc). The product was isolated as a pale yellow oil (104 mg, 48% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 4.09 (dd, $J = 2.0$, 8.4 Hz, 1H), 3.58 (dd, $J = 1.8$, 8.7 Hz, 1H), 3.51 (bs, 1H), 2.76 (m, 1H), 2.47-2.27 (m, 2H), 2.22 (m, 1H), 2.12 (m, 2H), 1.91 (m, 1H), 1.68 (m, 2H), 1.32 (m, 1H), 1.11 (dd, $J = 1.7$, 6.8 Hz, 3H), 1.02 (dd, $J = 2.0$, 6.5 Hz, 3H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 215.2, 70.9, 70.6, 54.4, 42.6, 32.2, 29.5, 27.5, 24.5, 20.8, 20.1

**HRMS:** (ESI) $m/z$ calcd for C$_{11}$H$_{20}$ClO$_2$[M+H]$^+$ 219.1146, found 219.1135

**IR:** 3530, 2939, 2870, 1695, 1241, 1131, 1603, 732, 531 cm$^{-1}$

$\alpha^20$ = -13.2 (c = 79 mg/mL in CHCl$_3$)

**Determination of Relative Stereochemistry of Chlorohydrin (65), preparation of (97)**

According to general procedure D, chlorohydrin 65 (100 mg, 0.45 mmol) was reduced to the corresponding chlorodiol with NaBH$_4$ (2.0 mmol, 74 mg) in MeOH (2 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH$_4$Cl (5 mL) and extracted 3x with 10 mL of CH$_2$Cl$_2$. The crude mixture was
concentrated by rotary evaporation. Subsequently, according to general procedure E, after microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO₂. Purification by column chromatography (80:20 Hexanes:EtOAc) to gave a white solid (60 mg, 74% yield). Key NOE correlations are shown above.

**¹H NMR (600 MHz, CDCl₃)** δ = 3.97 (m, 1H), 3.47 (m, J = 6.5 Hz, 1H), 3.39 (m, J = 4.9, 11.0 Hz, 1H), 2.15 (m, 1H), 1.84-1.70 (m, 5H), 1.37-1.17 (m, 4H), 1.13 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H)

**¹³C NMR (150 MHz, CDCl₃)** δ = 93.1, 79.4, 76.6, 50.2, 31.5, 31.1, 25.5, 23.9, 23.3, 18.49, 18.47

**HRMS**: (ESI) m/z calcd for C₁₁H₂₁O₂[M+H]⁺ 185.1536, found 185.1541

**IR**: 3368, 2931, 2865, 1446, 1081, 1070, 978, 641 cm⁻¹

**αD²⁰**: +4.7 (c = 42.3 mg/mL in CHCl₃)

**Determination of Enantiomeric Excess of Chlorohydrin (65)**

Firstly, according to procedure D, the chlorohydrin was reduced to the corresponding diol. Then, according to general procedure F, the corresponding PNB esters of chlorohydrin 65 were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3μm) Amylose-5 column; flow rate 0.250 mL/min; eluent: hexanes-iPrOH 97:3; detection at 254 nm; retention time = 6.46 min and 7.08 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (98% ee).
**Preparation of Chlorohydrin (88)**

According to general procedure C, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH$_2$Cl$_2$ (0.9 mL) at 0°C, and then valeraldehyde (0.5 mmol, 54 μL) was added. After 1 h, ketone (2 eq, 1.0 mmol, 100 μL) in solution of DMSO (0.1 mL) and H$_2$O (10 μL) was added. The reaction was stirred and allowed to warm to room temperature. The reaction was monitored by $^1$H NMR until consumption of starting material was noted (2d).

Workup: Volatiles were removed by rotary evaporation. The crude product was mixed with 2 mL of saturated aqueous NH$_4$Cl and extracted with 5 mL of Et$_2$O 2x. The combined organic layers were washed with saturated aqueous NaHCO$_3$, then brine. The organic layers were dried with Na$_2$SO$_4$ and then concentrated by rotary evaporation. The crude product was purified by flash chromatography on a SiO$_2$ column (90:10 hexanes:EtOAc) to give a pale yellow oil (30 mg, 28% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 3.93 (m, 2H), 3.64 (m, $J = 1.4$, 3.7 Hz, 1H), 2.76 (m, $J = 1.2$, 5.8, 8.3 Hz, 1H), 2.49-2.29 (m, 2H), 2.14 (m, 2H), 2.03-1.88 (m, 2H), 1.85-1.50 (m, 4H), 1.48-1.30 (m, 3H), 0.94 (t, $J = 7.4$ Hz, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 215.2, 72.7, 63.4, 54.1, 42.6, 37.0, 29.5, 27.5, 24.6, 20.0, 13.5

HRMS: (ESI) m/z calcd for C$_{11}$H$_{20}$ClO$_2$[M+H]$^+$ 219.1146, found 219.1126

IR: 3512, 2934, 2865, 1698, 1449, 1309, 1278, 1132, 1063, 612, 541 cm$^{-1}$

$\alpha^{20}$ = +10.0 (c = 100.6 mg/mL in CHCl$_3$)
**Preparation of Chlorohydrin (83)**

According to general procedure C, NCS (1.05 mmol, 142 mg) and L-proline (0.80 mmol, 90 mg) were stirred in CH$_2$Cl$_2$ (1.8 mL) at 0°C, and valeraldehyde (1.0 mmol, 108 µL) was added to this suspension. After 1h, tetrahydropyranone (3.0 mmol, 330 µL) in solution of DMSO (0.2 mL) and H$_2$O (20 µL) was added. The reaction mixture was stirred, and allowed to warm to room temperature. The reaction was monitored by $^1$H NMR until consumption of starting material (2d).

After complete consumption of α-chloro-aldehyde, the reaction was quenched by addition of saturated aqueous NH$_4$Cl. The aqueous layer was extracted 3x with CH$_2$Cl$_2$. The combined organic layers were dried with brine, then Na$_2$SO$_4$ and concentrated by rotary evaporation. Then according to general procedure D, the crude aldol product was dissolved in MeOH (2 mL) and cooled to 0°C. To the reaction was added NaBH$_4$ (2.0 mmol, 74 mg). After consumption of aldol adduct is noted by TLC (1 h), the reaction was quenched with 5 mL of saturated aqueous NH$_4$Cl. The aqueous layer was extracted 3x with 10 mL of CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried with Na$_2$SO$_4$ and concentrated by rotary evaporation. The crude product was purified by flash chromatography on SiO$_2$ (60:40 hexanes:EtOAc) to yield a white solid (98 mg, 44% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ= 3.99-3.86 (m, 3H), 3.78 (m, $J= 3.2, 6.4, 7.6$ Hz, 1H), 3.65 (m, $J= 3.2, 7.5$ Hz, 1H), 3.41-3.33 (m, 2H), 3.18 (d, $J= 6.4$ Hz, 1H), 3.08 (dd, $J= 11.0$ Hz, 1H), 2.17 (m, $J= 6.7$ Hz, 1H), 2.01-1.89 (m, 2H), 1.65 (m, 1H), 1.06 (d, $J= 6.7$ Hz, 3H), 1.02 (d, $J= 6.7$ Hz, 3H)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ= 74.0, 72.5, 71.3, 67.4, 66.4, 46.4, 34.6, 31.7, 20.3, 19.6

HRMS: (ESI) m/z calcd for C$_{10}$H$_{20}$ClO$_3$[M+H]$^+$ 223.1095, found 223.1082

IR: 3380, 2965, 2872, 1217, 1088, 996, 749, 665, 617 cm$^{-1}$

m.p.: 68-72°C
\[ \alpha_{D}^{20} = -9.3 \text{ (c = 66.3 mg/mL in CHCl}_3 \] 

**Determination of Relative Stereochemistry of Chlorohydrin (83), preparation of (94)**

According to general procedure E, 81 (20 mg, 0.09 mmol) was submitted to microwave radiation to effect the cyclization. The cyclized product was purified by flash chromatography on SiO\(_2\) (97:3 CH\(_2\)Cl\(_2\):MeOH) to yield (11.1 mg, 60% yield) of a clear oil.

**\(^1\)H NMR (600 MHz, CDCl\(_3\))** \(\delta =\)

- 4.17 (m, 2H),
- 4.03 (m, \(J = 4.5, 11.7\) Hz, 1H),
- 3.70 (m, \(J = 4.2, 11.0\) Hz, 1H),
- 3.52 (m, 1H),
- 3.30 (m, \(J = 2.2, 12.0\) Hz, 1H),
- 2.11 (m, 1H),
- 1.76 (m, 1H),
- 1.69 (m, 1H),
- 1.39 (bs, 1H),
- 0.97 (d, \(J = 6.0\) Hz, 3H),
- 0.94 (d, \(J = 6.0\) Hz, 3H)

**\(^13\)C NMR (150 MHz, CDCl\(_3\))** \(\delta =\)

- 93.0,
- 77.2,
- 73.6,
- 67.2,
- 65.5,
- 48.9,
- 33.1,
- 31.0,
- 18.6,
- 18.4

**HRMS:** (ESI) \(m/z\) calcd for C\(_{10}\)H\(_{22}\)O\(_3\)N[M+NH\(_4\)]\(^+\) 204.1594, found 204.1600

**IR:** 3349, 2969, 2924, 1084, 1046, 880, 635 cm\(^{-1}\)

\[ \alpha_{D}^{20} = +8.9 \text{ (c=11.1 mg/mL)} \]

**Determination of Enantiomeric Excess of Chlorohydrin 83**

The cyclized product was used to determine the enantiomeric excess. According to general procedure F, the corresponding PNB esters of the THF 94 were prepared of each a racemic and enantioenriched sample. Preparation of the bis-PNB ester of the chlorohydrin was necessary to prevent elimination of the \(\beta\)-PNB group of the ketone. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3\(\mu\)m) Cellulose-3 column; flow rate 0.4mL/min; eluent: hexanes-\(i\)PrOH 90:10; detection at 254 nm; retention time = 1.57 min and 2.50 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (93% ee).
**Preparation of THF (93)**

According to general procedure D, chlorohydrin 65 (100 mg, 0.45 mmol) was reduced to the corresponding chlorodiol with NaBH₄ (2.0 mmol, 74 mg) in MeOH (2 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH₄Cl (5 mL) and extracted 3x with 10 mL of CH₂Cl₂. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure E, After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO₂. Purification by column chromatography (80:20 Hexanes:EtOAc) to gave a white solid (60 mg, 74% yield). Key NOE correlations are shown above.

According to general procedure D, chlorohydrin 87 (33 mg, 0.14 mmol) was reduced to the corresponding chlorodiol with NaBH₄ (0.28 mmol, 10 mg) in MeOH (0.5 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH₄Cl (2 mL) and extracted 3x with 5 mL of CH₂Cl₂. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure E, After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO₂. Purification by column chromatography (80:20 hexanes:EtOAc) to give a clear oil (8.3 mg, 29% yield).

**¹H NMR (400 MHz, CDCl₃)** \(\delta = 4.00 \) (bs, 1H), 3.70 (m, 1H), 3.42 (m, J = 3.7, 11.0 Hz, 1H), 2.87 (dd, J = 11.6, 13.0 Hz, 1H), 2.80-2.53 (m, 4H), 2.48 (m, J = 3.5, 11.0 Hz, 1H), 1.68 (m, 3H), 1.63-1.30 (m, 7H), 0.95 (t, J = 7.2 Hz, 3H)

**¹³C NMR (100 MHz, CDCl₃)** \(\delta = 86.6, 78.9, 49.5, 36.5, 36.2, 33.9, 27.4, 27.3, 19.0, 14.0\)

**HRMS:** (ESI) \(m/z\) calcd for C₁₀H₁₉O₈S[M+H]⁺ 203.1100, found 203.1099

**IR:** 3401, 2955, 2974, 2871, 1716, 1429, 1051, 754, 636 cm⁻¹

\(\alpha_D^{20} = -2.4\) (c = 17.6 mg/mL in CHCl₃)
Preparation of Pyrrolidine (99)

According to general procedure G, chlorohydrin 89 (95 mg, 0.29 mmol) was dissolved in dry THF (3 mL) with AcOH (17 μL, 0.29 mmol). Benzylamine (84 μL, 0.8 mmol) was added and allowed to stir for 1 hour. NaBH₃CN (49 mg, 0.8 mmol) was added and the reaction mixture stirred for another 1 h. The reaction was quenched with 5 mL of water and the organic layers separated. The aqueous layer was extracted 3x with CH₂Cl₂ and dried with brine, then NaSO₄. The crude product was concentrated and purified by flash chromatography (90:10 hexanes:Et₂O) to give a clear oil (24 mg, 21% yield).

¹H NMR (500 MHz, CDCl₃) δ = 7.29 (m, 4H), 7.22 (m, 1H), 3.76 (d, J = 14.2 Hz, 1H), 3.72 (d, J = 14.2 Hz, 1H), 3.64 (m, J = 3.3, 5.7 Hz, 1H), 3.60 (m, J = 5.5, 6.7 Hz, 1H), 2.67 (m, 2H), 2.61 (d, J = 3.3 Hz, 1H), 1.41 (bs, 1H), 1.49-1.36 (m, 2H), 1.31-1.16 (m, 2H), 1.02 (d, J = 6.2 Hz, 3H), 0.91 (s, 9H), 0.85 (t, J = 7.1 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H)

¹³C NMR (125 MHz, CDCl₃) δ = 139.5, 129.0, 127.0, 126.7, 77.8, 74.6, 70.1, 62.9, 56.8, 35.8, 25.7, 18.9, 18.1, 18.0, 14.3, -4.6, -4.8

HRMS: (ESI) m/z calcd for C₂₁H₃₈NO₂Si[M+H]+ 364.2666, found 364.2668

IR: 3549, 2956, 2929, 1253, 1123, 835, 776, 732, 698 cm⁻¹

α⁺D = +12.3 (c = 23 mg/mL in CHCl₃)

Preparation of Pyrrolidine (100)

According to general procedure G, chlorohydrin 90 (54 mg, 0.18 mmol) was dissolved in dry THF (0.1M, 2 mL) with (10 μL, 0.18 mmol) AcOH. Benzylamine (49 μL,
0.46 mmol) was added and allowed to stir for 1 hour. NaBH$_3$CN (28 mg, 0.46 mmol) was added and stirred for another 1 h. The reaction was quenched with 5 mL of water and the organic layers separated. The aqueous layer was extracted 3x with CH$_2$Cl$_2$ and dried with brine, then NaSO$_4$. The crude product was concentrated and purified by flash chromatography (90:10 hexanes:EtOAc) to give a clear oil (16 mg, 25% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ= 7.29 (m, 4H), 7.23 (m, 1H), 5.85 (m, 1H), 5.02 (m, J = 1.7, 13.8 Hz, 2H), 3.80 (d, J = 14.1 Hz, 1H), 3.71 (d, J = 14.1 Hz, 1H), 3.68 (m, 1H), 3.60 (m, J = 5.3, 6.8 Hz, 1H), 2.80 (m, J = 3.5, 7.4 Hz, 1H), 2.72 (m, J = 6.3 Hz, 1H), 2.57 (d, J = 3.6 Hz, 1H), 2.13 (m, J =1.1, 3.5, 7.3, 13.8 Hz, 1H), 2.00 (m, J = 1.3, 7.8, 14.3 Hz, 1H), 1.01 (d, J = 6.2 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) δ= 139.8, 135.6, 128.9, 128.0, 126.8, 116.4, 77.8, 74.1, 69.7, 63.3, 57.4, 37.7, 25.8, 18.3, 18.0, -4.6, -4.8

HRMS: (ESI) m/z calcd for C$_{21}$H$_{36}$NO$_2$Si[M+H]$^+$ 362.2510, found 362.2501

IR: 3550, 3028, 2065, 2955, 2928, 1253, 1124, 1092, 835, 776, 698 cm$^{-1}$

α$_D^{20}$ = +21.4 (c=14 mg/mL in CHCl$_3$)

**Preparation of Pyrrolidine (101)**

![TBSO](https://example.com/tbs.png)

According to general procedure G, chlorohydrin 86 (24 mg, 0.07 mmol) was dissolved in dry THF (0.1 M, 1 mL) with AcOH (4.5 μL, 0.07 mmol). Benzylamine (22 μL, 0.21 mmol) was added and allowed to stir for 1 hour. NaBH$_3$CN (12.5 mg, 0.21 mmol) was added and stirred for another 1 h. The reaction was quenched with 5 mL of water and the organic layers separated. The aqueous layer was extracted 3x with CH$_2$Cl$_2$ and dried with brine, then NaSO$_4$. The crude product was concentrated and purified by flash chromatography (80:20 hexanes:EtOAc) to give (9 mg, 32% yield) a clear oil.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 7.36\text{-}7.27\ (m, 4H), 7.23\ (m, 1H), 3.89\text{-}3.81\ (m, 2H), 3.75\ (m, J = 4.8, 6.2\ Hz, 1H), 3.71\ (d, J = 13.8\ Hz, 1H), 2.91\ (m, J = 2.8, 4.2, 6.9\ Hz, 1H), 2.80\ (m, J = 6.3\ Hz, 1H), 2.62\ (d, J = 3.3\ Hz, 1H), 2.19\ (m, J = 2.7, 4.1, 16.9\ Hz, 1H), 2.05\ (m, J = 2.6, 6.8, 16.9\ Hz, 1H), 1.94\ (t, J = 2.6\ Hz, 1H), 1.04\ (d, J = 6.2\ Hz, 3H), 0.92\ (s, 9H), 0.12\text{-}0.11\ (s, 6H)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta = 139.7, 128.9, 128.1, 126.9, 82.2, 77.8, 74.6, 69.2, 68.7, 63.3, 57.5, 25.8, 23.5, 18.2, 18.0, -4.6, -4.7\)

**HRMS:** (ESI) \(m/z\) calcd for C\(_{21}\)H\(_{34}\)NO\(_2\)Si[M+H]\(^+\) 360.2353, found 360.2348

**IR:** 3547, 3310, 2955, 2928, 2119, 1253, 1130, 835, 777, 699, 632 cm\(^{-1}\)

\(\alpha_{D}^{20} = +12.6\) (c=11 mg/mL in CHCl\(_3\))
3.7.4. NMR Spectra

NMR Spectra of Chlorohydrin (73)
NMR Spectra of Chlorohydrin (91)
NMR Spectra of THF (96)
NMR Spectra of Chlorohydrin (89)
NMR Spectra of Chlorohydrin (90)
NMR Spectra of Chlorohydrin (86)
NMR Spectra of Chlorohydrin (79)
NMR Spectra of THF (98)
NMR Spectra of Chlorohydrin (87)
NMR Spectra of Chlorohydrin (65)
NMR Spectra of THF (97)
NMR Spectra of Chlorohydrin (88)
NMR Spectra of Chlorohydrin (83)
NMR Spectra of THF (94)
NMR Spectra of THF (93)
NMR Spectra of Pyrrolidine (100)
NMR Spectra of Pyrrolidine (101)
NMR Spectra of Pyrrolidine (102)
3.7.5. HPLC Traces

HPLC Trace of PNB-(73) (Racemic Left, Enantioenriched Right)

HPLC Trace of PNB-(91) (Racemic Left, Enantioenriched Right)

HPLC Trace of PNB-(89) (Racemic Left, Enantioenriched Right)
HPLC Trace of PNB-(90) (Racemic Left, Enantioenriched Right)

HPLC Trace of PNB-(86) (Racemic Left, Enantioenriched Right)

HPLC Trace of PNB-(79) (Racemic Left, Enantioenriched Right)
HPLC Trace of PNB-(65) (Racemic Left, Enantioenriched Right)

HPLC Trace of PNB-(94) (Racemic Left, Enantioenriched Right)
3.7.6. Preparation and Characterization of Hyacinthacine synthesis compounds

*Preparation of Amino-Alcohol (108)*

![Chemical Structure](image)

Compound 105 was synthesized according to literature procedures.\(^{71}\) All spectral data matched that reported previously.

*Preparation of Primary Alcohol (109)*

![Chemical Structure](image)

Compound 108 (0.2mmol, 90mg) was stirred in CH\(_2\)CN (0.5M, 4mL) with benzaldehyde (10eq, 2.0mmol, 202\(\mu\)L), AcOH (2eq, 0.4mmol, 23\(\mu\)L) and a spatula tips of MgSO\(_4\) for 48h. After TLC indicated reaction progression had stalled, the crude mixture was filtered through cotton and put under vacuum and all volatiles evaporated. The crude was purified by column chromatography (80:20 Hexanes:EtOAc) and taken directly to the next step.

The crude product was dissolved in THF (0.1M, 2mL) and 1.0M TBAF in THF (2eq., 0.6mL) was added at 0\(^\circ\)C. The reaction was allowed to warm to room temperature, and stirred for 1 hour. After 1 hour, THF was evaporated by rotary evaporation. The crude was dissolved in EtOAc and filtered through a short SiO\(_2\) plug. The product was purified by flash chromatography (80:20 Hexanes:EtOAc) to afford a clear oil (64% yield). Characterization data is all reported as a mixture of diastereomers (3:1) at the benzylidene position.

\(^1\)H NMR (CDCl\(_3\), 500MHz) \(\delta=7.6-7.3\ (m, 7H), 7.2\ (m, 8H), 5.52\ (bs, 1H minor), 5.26\ (bs, 1H major), 4.40\ (m, J = 2.7, 9.0 Hz, 1H minor), 4.4-4.23\ (m, 2.5H), 4.13\ (m, 1H), 3.97\ (m, 1H), 3.89\ (m, 2.3H), 3.81\ (m, 1H minor), 3.67\ (d, 1H major), 3.59\ (m, 1.5H), 3.53\ (m, 2H),
3.31 (ddd, \( J = 5.0, 10.8, 10.9 \) Hz, 1H minor), 3.07 (ddd, \( J = 5.0, 10.1, 10.2 \) Hz, 1H major), 1.53 (s, 3H minor), 1.48 (s, 3H major), 1.39 (s, 3H minor) 1.36 (s, 3H major)

\textbf{\( ^{13}\text{C NMR} \) (CDCl\(_3\), 150MHz)} \( \delta = 140.4, 138.0, 128.9, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.5, 127.3, 127.1, 127.1, 126.7, 99.5, 99.3, 95.1, 79.1, 73.4, 65.2, 64.8, 64.6, 63.8, 63.2, 62.1, 62.0, 61.5, 60.7, 52.1, 50.3, 29.3, 19.4, 19.2, 14.1

\textbf{HRMS:} (ESI) \( m/z \) calcd for C\(_{23}\)H\(_{29}\)ClNO\(_4\)[M+H]\(^+\) 418.1780, found 418.1767

\textbf{IR:} 3424, 2993, 2939, 1702, 1602, 1495, 1453, 1087, 907, 728, 699, 647 cm\(^{-1}\)

\( \alpha_D^{20} = -37.6 \) (c=40 mg/mL in CHCl\(_3\)
Preparation of Aldehyde (111)

Primary alcohol 109 (0.05mmol, 20mg) was dissolved in CH$_2$Cl$_2$ (0.5mL, 0.1M). Solid NaHCO$_3$ (0.4mmol, 40mg) was added to the vial. To this suspension was added DMP (0.58mmol, 25mg). The suspension was stirred for 1 hour, monitoring conversion by TLC. When starting material no longer appeared by TLC, the reaction was quenched with H$_2$O and the aqueous layer extracted with CH$_2$Cl$_2$ 3x. The organic layer was dried with brine and Na$_2$SO$_4$. The crude organic product was concentrated by rotary evaporation. Product decomposed by TLC and this crude mixture was used in all further experiments with aldol reactions. Ideally, the next isolable intermediate after the aldol reaction would be characterized, as proper purification of the aldehyde proved difficult. Provided is the crude NMR of aldehyde 111 after oxidation and workup.
References


(64) Pellissier, H. Tetrahedron 2016, 72, 3133–3150.


