Stereoselective Nucleophilic Additions to α-Amino Aldehydes: Application to Natural Product Synthesis

Per Restorp

KTH Chemical Science and Engineering

Doctoral Thesis

Stockholm 2006

Abstract

This thesis deals with the development and application of new synthetic methodology for stereo- or regioselective construction of carbon-carbon bonds in organic synthesis.

The first part of this thesis describes the development of a divergent protocol for stereoselective synthesis of chiral aminodiols by employing Mukaiyama aldol additions to syn- and anti-α-amino-β-silyloxy aldehydes. The stereoselectivity of the nucleophilic attack is governed by either chelation to the α-amino moiety or by nucleophilic attack in the Felkin-Anh sense. This study is also directed towards the elucidation of the factors that dictate aldehyde π-facial selectivity in substrate-controlled nucleophilic additions to these and similar systems.

In the second part, a highly stereoselective [3 + 2]-annulation reaction of N-Ts-α-amino aldehydes and 1,3-bis(silyl)propenes for stereoselective construction of densely functionalized pyrrolidines is presented. In addition, this methodology is also implemented as a keystep in a synthetic approach towards the polyhydroxylated pyrrolidine and pyrrolizidine alkaloids DGDP and (+)-alexine from a common late pyrrolidine intermediate.

Finally, a divergent protocol for regioselective opening of vinyl epoxides using alkyne nucleophiles is described, in which the regioselectivity of the nucleophilic attack is controlled by the choice of reaction conditions. The regioselectivities of the $S_N2$ and $S_N2'$ processes are, however, significantly influenced by the nature of the alkyne substituents and the best results are obtained using ethoxyacetylene. The $S_N2$ opening of vinyl epoxides with ethoxyacetylene as nucleophile is also shown to provide a straightforward entry to functionalized γ-butyrolactones.


Keywords: Stereoselective synthesis, Substrate-control, α-Amino aldehydes, Mukaiyama aldol, Allylsilanes, [3 + 2]-Annulation, (+)-Alexine, DGDP, Vinyl epoxides, Regioselectivity, Alkyne nucleophiles.
Abbreviations

DGDP: (2S,3R,4R,5R)-2,5-bis(hydroxymethyl)pyrrolidine-3,4-diol
DMDP: (2R,3R,4R,5R)-2,5-bis(hydroxymethyl)pyrrolidine-3,4-diol
DMP: Dess-Martin periodinane
equiv: equivalent
ee: enantiomeric excess
dr: diastereomeric ratio
Im: imidazol
KHMDS: potassium hexamethyldisilazane
LA: Lewis acid
PCC: pyridinium chlorochromate
THP: tetrahydropyran
TS: transition state
List of Publications

This thesis is based on the following papers, referred to in the text by their Roman numerals I-V.

I. Diastereoselective Aldol Additions to α-Amino-β-Silyloxy Aldehydes. Divergent Synthesis of Aminodiols
   Per Restorp and Peter Somfai

II. Stereoselective Synthesis of Functionalized Pyrrolidines via a [3 + 2]-Annulation of N-Ts-α-Amino Aldehydes and 1,3-Bis(silyl)propenes
    Per Restorp, Andreas Fischer and Peter Somfai

III. Synthetic Studies Toward the Polyhydroxylated Alkaloids DGDP and (+)-Alexine utilizing a [3 + 2]-Annulation Reaction of N-Ts-α-Amino Aldehydes and 1,3-Bis(silyl)propenes
    Per Restorp and Peter Somfai
    *Preliminary manuscript.*

IV. Regioselective and Divergent Opening of Vinyl Epoxides with Ethoxyacetylene
    Per Restorp and Peter Somfai

V. Regioselective and Divergent Opening of Vinyl Epoxides with Alkyne Nucleophiles
    Per Restorp and Peter Somfai
The Author’s Contribution to Papers I-V

I. I contributed to the formulation of the research problems, performed the experimental work and wrote the manuscript.

II. I contributed to the formulation of the research problems, performed the experimental work excluding the X-ray crystallographic analysis and wrote the manuscript.

III. I contributed to the formulation of the research problems, performed the experimental work and wrote the manuscript.

IV. I contributed to the formulation of the research problems, performed the experimental work and wrote the manuscript.

V. I contributed to the formulation of the research problems, performed the experimental work and wrote the manuscript.
# Table of Contents

1. Introduction..................................................................................................... 1

2. Stereodivergent Synthesis of Aminodiols 
   2.1 Introduction................................................................................................. 5
   2.2 Asymmetric induction models ................................................................. 5
       2.2.1 Asymmetric 1,2- and 1,3-induction models under
       non-chelating conditions .............................................................................. 6
       2.2.2 Merged model for 1,2- and 1,3-asymmetric induction ......................... 7
       2.2.3 Asymmetric 1,2- and 1,3-induction models under
       chelating conditions ..................................................................................... 8
   2.3 Diastereoselective synthesis of aminodiols................................................. 9
       2.3.1 Synthesis of $\alpha$-amino-$\beta$-silyloxy aldehydes............................... 10
       2.3.2 Mukaiyama aldol additions to $\alpha$-amino-$\beta$-silyloxy aldehydes .......... 11
       2.3.3 Determination of the relative stereochemistry ................................... 13
   2.4 Discussion of the observed diastereoselectivity ........................................ 14
   2.5 Conclusions and outlook ........................................................................... 16

3. Stereoselective Synthesis of Functionalized Pyrrolidines
   3.1 Introduction............................................................................................... 19
       3.1.1 Allylsilanes as 1,3-dipole equivalents in annulation reactions ..........20
       3.1.2 Allylsilanes as 1,2-dipole equivalents in annulation reactions ..........20
   3.2 Stereoselective synthesis of functionalized pyrrolidines........................... 21
       3.2.1 [3 + 2]-Annulation reactions of N-Ts-$\alpha$-amino aldehydes and
       1,3-bis(silyl)propenes ................................................................................. 21
       3.2.2 Stereochemistry determination and rationalization of the
       selectivity ..................................................................................................... 25
   3.3 Conclusions and outlook ........................................................................... 27

4. Synthetic Approaches Toward DGDP and (+)-Alexine
   4.1 Introduction............................................................................................... 29
   4.2 Synthetic approaches toward DGDP and (+)-alexine ............................... 30
       4.2.1 Retrosynthetic analysis ....................................................................... 30
       4.2.2 Synthesis of DGDP ............................................................................. 31
       4.2.3 Towards the synthesis of (+)-alexine ................................................. 32
   4.3 Conclusions and outlook ........................................................................... 36

5. Regioselective and Divergent Opening of Vinyl Epoxides
   5.1 Introduction............................................................................................... 37
   5.2 Regioselective opening of vinyl epoxides with alkynes......................... 38
       5.2.1 Attack according to the $S_n2$ manifold ............................................ 38
       5.2.2 Attack according to the $S_n2'$ manifold ............................................ 41
       5.2.3 $\gamma$-Butyrolactones in natural product synthesis .............................. 45
   5.3 Conclusions and outlook ........................................................................... 46

6. Concluding remarks ..................................................................................... 47

7. Acknowledgements........................................................................................ 49

8. Appendix ....................................................................................................... 51
Organic chemistry is the study of carbon containing compounds and their properties. As a science, it bridges biology and medicine as well as material science and physics and provides a crucial platform for drug discovery and developments in agriculture, polymer and petroleum industry. Organic chemistry is also of fundamental importance for gaining a better understanding of the basic mechanisms of natural systems, including life itself.

Synthetic organic chemistry is the art and science concerned with the construction of structurally complex organic molecules from readily available starting materials by a series of rationally designed synthetic transformations. The ability of carbon to form up to four chemical bonds with other atoms allows for the construction of a seemingly infinite array of molecules for a wide variety of applications which is reflected in the enormous structural and functional diversity of organic compounds.

![Molecules](image)

**Figure 1.** Natural products prepared through organic synthesis.

During the last decades, organic synthesis has grown exponentially (if not explosively) and new methods allow for the synthesis of complex organic structures, which previously seemed unattainable. The synthetic efforts toward many natural products have largely been driven by their intriguing chemical structures and interesting biological properties.¹ For instance, epothilone B (1) and Taxol® (2) are powerful anti-cancer agents, thienamycin (3) has potent antibiotic properties and brevetoxin B (4) is a marine neurotoxin (Figure 1).

---

However, organic chemists are by no means limited to naturally occurring compounds for their synthetic endeavours. At the heart of organic synthesis lies its truly explorative and creative nature, allowing organic chemists to design and construct fundamentally new compounds with functions and properties that merely their imagination and the available synthetic methods set the boundaries for.\textsuperscript{2}

The world around us is chiral\textsuperscript{3} and the same holds true for many organic compounds. In order to synthesize a chiral compound with a defined relative and absolute stereochemistry, its connectivity and three-dimensional structure must be considered. The spatial distribution of the substituents in a chiral compound can have a significant impact on the interactions toward other chiral molecules (for instance biological receptors) and there are numerous examples where two enantiomers of a given molecule show fundamentally different behaviour in living systems.\textsuperscript{4} Different strategies can be employed to access optically active products including resolution of a racemic mixture, utilization of the chiral pool, or by employing asymmetric synthesis. Asymmetric synthesis can further be divided into three subgroups:

\textit{Reagent-control:}

The formation of a new stereogenic center is governed by a chiral reagent or catalyst not covalently bound to the substrate.

\textit{Auxiliary-control:}

The formation of a new stereogenic center is controlled by a stoichiometric amount of a chiral auxiliary covalently bound to the substrate but not part of the final structure.

\textit{Substrate-control:}

The formation of a new stereogenic center is controlled by chirality already present in the substrate.

Today, an immense number of organic transformations are available to the organic chemist for the purpose of complex molecules synthesis but the further need for efficient and highly selective transformations remains undisputed. The aim of this doctoral work is to develop new synthetic methodology for stereo- or regioselective construction of carbon-carbon bonds in organic synthesis and apply this methodology to tackle synthetic problems encountered in natural product synthesis. Specifically, the synthetic methodologies presented in chapters 2-4 have been developed to address the synthesis of polyhydroxylated


\textsuperscript{3} Chiral, greek; handed. Body with non-superimposable mirror images.

alkaloids by employing substrate-controlled stereoselective additions of nucleophiles to \( \alpha \)-amino aldehydes.

*Chapter 2* describes our efforts to develop a divergent protocol for stereoselective synthesis of chiral aminodiols by exploring substrate-controlled diastereoselective additions of nucleophiles to \( \alpha \)-amino-\( \beta \)-silyloxy aldehydes.

*Chapter 3* deals with the development of a highly stereoselective synthesis of densely functionalized pyrrolidines by a \([3 + 2]\)-annulation reaction of \( N \)-Ts-\( \alpha \)-amino aldehydes and \( 1,3 \)-(bis)silylpropenes.

*Chapter 4* presents the use of the \([3 + 2]\)-annulation methodology introduced in chapter 3 in our synthetic studies toward the polyhydroxylated pyrrolidine and pyrrolizidine alkaloids DGDP and \((+)-alexine\).

*Chapter 5* describes our efforts to develop a divergent protocol for regioselective opening of vinyl epoxides with alkyne nucleophiles, which provides an efficient entry to functionalized \( \gamma \)-butyrolactones.
2

Stereodivergent Synthesis
of Aminodiols

Paper I

2.1 Introduction

Nucleophilic carbonyl addition reactions have evolved as a versatile tool in organic synthesis for stereoselective C-C bond formation. In aldehydes, the two carbonyl faces are heterotopic and nucleophilic additions to the different C=O π-faces give rise to stereoisomeric products (Figure 2). In the absence of any chiral influence, the two faces are enantiotopic and nucleophilic Re- or Si-face attacks are equally probable inevitably resulting in the formation of a racemic mixture. However, if the aldehyde R-group contains a stereogenic center the Re- and Si-faces become diastereotopic and nucleophilic attack to either C=O π-face is associated with a different activation energy barrier and unequal formation of the two diastereomeric products is expected.

![Figure 2. Nucleophilic additions to the heterotopic faces of an aldehyde.](image)

The ability to predict and control the stereochemical outcome in nucleophilic additions to aldehydes containing a proximal stereocenter has a major impact on synthetic planning and design, and much work has been directed towards the elucidation of the factors that dictate carbonyl π-facial selectivity.

2.2 Asymmetric induction models

Over one hundred years ago, Emil Fischer and coworkers added sodium cyanide to chiral aldehyde moieties in carbohydrates and observed an unequal formation

---

5 Except formaldehyde.
6 This can also be achieved by employing chiral Lewis acids or chiral nucleophiles. For further discussion, see (a) Mander, L. N. In Stereochemistry of Organic Compounds; Eliel, E., Wilen, L., Eds.; Wiley: New York, 1994, pp 858-894. (b) Gawley, R. E.; Aube, J. Principles of Asymmetric Synthesis; Elsevier Science: New York, 1996.
of the corresponding diastereomeric cyanohydrins and concluded that “further synthesis with asymmetric systems proceeds in an asymmetric manner”. Over the following decades several models emerged to rationalize the stereochemical outcome in nucleophilic additions to aldehydes containing a proximal stereocenter. Based on the structure of the aldehyde and reaction conditions used, the nucleophilic additions can proceed under chelation or non-chelation control. The stereochemical models are further divided into 1,2- or 1,3-asymmetric induction models depending on whether the α- or β-stereocenter exerts the major stereodirecting effect. More recently, integrated models for 1,2- and 1,3-asymmetric induction have been developed.

2.2.1 Asymmetric 1,2- and 1,3-induction models under non-chelating conditions

The stereochemical outcome in additions to aldehydes containing an α-stereocenter can be rationalized by the Felkin-Anh model. In this model, the largest group (L) is for steric or electronic reasons oriented perpendicular to the C=O framework and nucleophilic attack is expected to proceed via transition state A in order to avoid steric interactions between the

![Scheme 1. 1,2-asymmetric induction models under non-chelating conditions.](image)

Fischer, E. Chem. Ber. 1894, 27, 3189-3232, see p. 3210 “dass bei asymmetrischen Systemen auch die weitere Synthese in asymmetrischen Sinn vor sich geht”.


If the L-group is a polar heteroatom, this effect is due to a hyperconjugative delocalization of the forming bond (HOMO) with the LUMO of the C-L bond. This stabilization is maximized if the incipient bond between the nucleophile and the carbonyl group is oriented antiperiplanar to the C-L bond. For further discussion, see Anh, N. T.; Eisenstein, O. Nouv. J. Chim. 1977, 1, 61-70.
\( \alpha \)-substituent (M) and the approaching nucleophile thus affording the 1,2-\textit{syn} isomer (Scheme 1, TS A).

If the L-group is a highly electronegative heteroatom,\(^{11}\) recent computational\(^{12}\) and experimental\(^{13}\) data instead supports the Cornforth model,\(^{14}\) which predicts the same stereochemical outcome but recognizes an overall dipole-minimization of the substrate by orienting the aldehyde carbonyl and the electronegative heteroatom (L) antiparallel (Scheme 1, TS B).

In nucleophilic additions to aldehydes containing a polar \( \beta \)-heteroatom, a different model is included to account for the influence of the remote stereocenter. It is believed that nucleophilic attack proceeds via conformation C, in which both steric and electronic repulsions are minimized, thus affording the 1,3-\textit{anti} isomer as the major product (Scheme 2).\(^{15}\)

![Scheme 2. 1,3-asymmetric induction model under non-chelating conditions.](image)

### 2.2.2 Merged model for 1,2- and 1,3-asymmetric induction

In an extensive investigation, Evans and coworkers studied additions to \( \alpha \)-methyl-\( \beta \)-alkoxy aldehydes and demonstrated that the stereoselectivity is influenced by both stereocenters and that their stereodirecting effects can be mutually reinforcing or attenuating (Scheme 3).\(^{9a,16}\) From these results, an integrated stereoinduction model based on the Felkin-Anh\(^{8b,c}\) and the polar 1,3-induction models\(^{15}\) was proposed which correctly accounts for the combined stereodirecting effects of the \( \alpha \)-methyl and \( \beta \)-alkoxy substituents.

If H\(^1\) in structure C is replaced by a Me-group, the \( \alpha \)- and \( \beta \)-substituents operate in concert and promote nucleophilic attack to the same aldehyde \( \pi \)-face and

---

11 Theoretical studies of enolborane additions to \( \alpha \)-heteroatom substituted aldehydes have shown that highly electronegative substituents (F, Cl, OMe) favor Cornforth transition states whereas less electronegative substituents (PMe\(_2\), SMe\(_2\), NMe\(_2\)) favor Felkin-Anh transition states, see reference 12.


14 Cornforth, J. W.; Cornforth, R. W.; Mathew, K. \textit{K. J. Chem. Soc.} \textbf{1959}, 112-127. The Cornforth model has recently been modified from its original version to incorporate the concepts of a staggered rearrangement and a \( >90^\circ \) angle of the incoming nucleophile, see ref 12.


nucleophilic additions to anti-α-methyl-β-alkoxy aldehydes 5 afford uniformly high diastereoselectivities in favor of the Felkin-Anh products 6 (Scheme 3, TS D). If H^2 in structure C is replaced by a Me-group, the stereodirecting effects of the α- and β-stereocenters are now opposing and nucleophilic additions to syn-α-methyl-β-alkoxy aldehydes 7 proceed with variable levels of aldehyde π-facial selectivity depending on the steric demands of the nucleophile and the solvent polarity (TS E). It has been shown that sterically demanding enolates respond to the steric effects exerted by the α-stereocenter and afford predominately Felkin-Anh adduct 8, whereas addition of “smaller” enolates are controlled by the dipolar effects of the β-stereocenter and produce anti-Felkin-Anh adduct 9 as the major product. Not surprisingly, these dipolar effects are more pronounced in less polar solvents.9a

Scheme 3. Evans merged model for 1,2- and 1,3-stereinduction.

2.2.3 Asymmetric 1,2- and 1,3-induction models under chelating conditions

If the aldehyde contains an α-substituent capable of chelation (L) and the reaction is carried out under conditions allowing for chelation-control a rigid 5-membered cyclic chelate is formed between the α-substituent and the carbonyl moiety (Scheme 4). This is followed by nucleophilic attack on the sterically most accessible carbonyl π-face, thus affording the anti-adduct.9b It should be noted that the consequence of a monodentate Felkin-Anh activation (Scheme 1) or a chelate carbonyl activation (Scheme 4) has a direct bearing on the stereochemical outcome of the reaction.

Scheme 4. 1,2-asymmetric induction under chelation-control.
Previous studies have shown that aldehydes containing a β-substituent capable of chelation form a rigid 6-membered cyclic chelate when treated with a chelating Lewis acid, followed by nucleophilic attack to afford the 1,3-anti adduct (Scheme 5). In this case, the chelation-controlled model and the 1,3-polar induction model predict the same stereochemical outcome (compare Schemes 2 and 5).

![Scheme 5](image)

**Scheme 5.** 1,3-asymmetric induction under chelation-control.

Recently, a merged stereochemical model for 1,2- and 1,3-induction in chelation-controlled additions to α-methyl-β-alkoxy aldehydes was developed.

### 2.3 Diastereoselective synthesis of aminodiols

The aminodiol subunit is a common structural feature in several iminosugars, polyhydroxylated pyrrolidine, pyrrolizidine and indolizidine alkaloids. An interesting approach towards these densely functionalized compounds would be a diastereoselective addition of nucleophiles to α-amino-β-silyloxy aldehydes 10 and 11 using the inherent diastereofacial bias imposed on the aldehyde by the α- and β-substituents to control the stereochemical outcome (Scheme 6). Ideally, we were interested in developing a divergent protocol for selective synthesis of all isomeric aminodiols 12-15 with high levels of stereochemical control. In addition, we were interested in investigating the merged impact of the α- and β-substituents on the stereochemical outcome of the nucleophilic additions in these systems.

---

We reasoned that in nucleophilic additions to aldehydes 10 and 11 (R’=Bn) the α-NTsBn moieties would act as the large substituents for both steric and electronic reasons and exert the major stereodirecting effect, thus affording Felkin-Anh adducts 14 and 15. Since the 1,3-polar induction model predicts the formation of the 1,3-anti adduct, we speculated that the α- and β-substituents would be mutually reinforcing in additions to syn-aldehydes 11. In additions to anti-aldehydes 10 the individual stereodirecting effects of the α- and β-substituents promote nucleophilic addition to opposite aldehyde π-faces and were expected to be mutually non-reinforcing. Furthermore, we envisioned that aminodiols 12 and 13 could be obtained from 10 and 11 (R’=H) in a chelation-controlled addition.

2.3.1 Synthesis of the α-amino-β-silyloxy aldehydes

The α-amino-β-silyloxy aldehydes 10 and 11 were prepared from the corresponding vic-vinylc amino alcohols syn- and anti-16 using standard transformations (Scheme 7).

Scheme 7. Synthesis of aldehydes 10 and 11.

2.3.2 Mukaiyama aldol additions to α-amino-β-silyloxy aldehydes

With aldehydes 10 and 11 in hand, initial focus was directed towards the investigation of the stereochemical outcome in Mukaiyama aldol additions\(^{21}\) of silylenol ether 17 to anti-aldehyde 10a and 10b (R\(^3\)=H) using either a monodentate (Table 1, entries 1, 3) or a chelating Lewis acid (entry 2).

**Table 1.** Diastereoselective Mukaiyama aldol additions to anti-α,β-disubstituted aldehydes 10a-d\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>10a</th>
<th>Lewis acid</th>
<th>Yield(^b) (%)</th>
<th>(dr) (12:14)(^f)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>BF(_3)-OEt(_2)</td>
<td>91</td>
<td>92:8</td>
<td>12a, 14a</td>
</tr>
<tr>
<td>2</td>
<td>10a</td>
<td>TiCl(_4)</td>
<td>85</td>
<td>90:10</td>
<td>12a, 14a</td>
</tr>
<tr>
<td>3</td>
<td>10b</td>
<td>BF(_3)-OEt(_2)</td>
<td>94</td>
<td>&gt;98:2</td>
<td>12b</td>
</tr>
<tr>
<td>4</td>
<td>10c</td>
<td>BF(_3)-OEt(_2)</td>
<td>92</td>
<td>&lt;2:98</td>
<td>14c</td>
</tr>
<tr>
<td>5(^d)</td>
<td>10d</td>
<td>BF(_3)-OEt(_2)</td>
<td>81</td>
<td>&lt;2:98</td>
<td>14d</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: To 10 (1 equiv) in CH\(_2\)Cl\(_2\) at -60 °C were added Lewis acid (3 equiv) and 17 (2 equiv) and the resulting mixture was stirred for 18 h. \(^b\)Isolated yield. \(^c\)Determined by \(^1\)H NMR analysis of the crude reaction mixture. \(^d\)The reaction time was 24 h.

In all three cases the reactions proceeded in excellent yields and stereoselectivities in favor of the α-chelation controlled products 12a, b (entries 1-3). Addition to NTsBn-protected anti-aldehyde 10c afforded the expected Felkin-Anh adduct, aminodiol 14c as a single diastereomer in excellent yield (entry 4). The diastereoselectivity was not affected by increasing the steric demands of the R-substituent, but a slight decrease in reaction rate was observed (entry 5).

With these results in hand, we turned our attention to the nucleophilic additions of 17 to syn-aldehydes 11a-d (Table 2). Addition to NTsTs protected syn-aldehydes 11a and 11b afforded the chelation-controlled products,

aminodiols 13a and 13b, in good yields and diastereoselectivities (entries 1, 2). These results are analogous to the additions to anti-aldehydes 10a and 10b.

**Table 2. Diastereoselective Mukaiyama aldol additions to syn-α,β-disubstituted aldehydes 11a-d**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yieldb (%)</th>
<th>drc (13:15)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a BF₃OEt₂</td>
<td>88</td>
<td>&gt;98:2</td>
<td>13a</td>
</tr>
<tr>
<td>2</td>
<td>11b BF₃OEt₂</td>
<td>89</td>
<td>88:12</td>
<td>13b,15b</td>
</tr>
<tr>
<td>3</td>
<td>11c BF₃OEt₂</td>
<td>26d</td>
<td>49:51</td>
<td>13c, 15c</td>
</tr>
<tr>
<td>4e</td>
<td>11c BF₃OEt₂</td>
<td>91</td>
<td>47:53</td>
<td>13c, 15c</td>
</tr>
<tr>
<td>5</td>
<td>11d BF₃OEt₂</td>
<td>-f</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6e</td>
<td>11d BF₃OEt₂</td>
<td>49g</td>
<td>44:56</td>
<td>13d, 15d</td>
</tr>
</tbody>
</table>

* Reaction conditions: To 11 (1 equiv) in CH₂Cl₂ at -60 °C were added BF₃OEt₂ (3 equiv) and 17 (2 equiv) and the resulting mixture was stirred for 18 h. b Isolated yield. c Determined by ¹H NMR analysis of the crude reaction mixture. d Conversion after 18 h at -60 °C according to ¹H NMR analysis. e Reaction carried out at -40 °C for 40 h. f No reaction, 11d was recovered. g Conversion after 40 h at -40 °C according to ¹H NMR analysis.

In sharp contrast, additions to syn-aldehyde 11c (R’ = Bn) gave a considerably lower reaction rate and, more interestingly, no diastereofacial selectivity was observed (entry 3). Increasing the temperature to -40 °C resulted in complete conversion but equally low stereoselectivity (entry 4). With bulkier R-substituents even lower reaction rates and similar diastereoselectivities were observed (entries 5, 6).
2.3.3 Determination of the relative stereochemistry

The relative stereochemistry of aminodiol 12a was determined by desilylation using TBAF followed by intramolecular acetalization to afford 18 (Scheme 8).\(^{22}\) The relative stereochemistry of 18 was assigned by analyzing the \(^1\)H NMR coupling constants. The chelation-controlled adducts 12b, 13a and 13b were assigned in analogy to this result.

![Scheme 8. Determination of the relative stereochemistry of 12a.](image)

Attempts to desilylate Felkin-Anh adduct 14c proved much more difficult than initially anticipated. All attempts to use fluoride-based methods failed and, in addition, the OTBS-group in 14c proved surprisingly stable towards acidic conditions.

![Scheme 9. Determination of the relative stereochemistry of 14c.](image)

Instead, 14c was transformed into oxazolidinone 19 by a stereoselective reduction of the ketone,\(^{23}\) followed by detosylation and oxazolidinone formation (Scheme 9).\(^{24}\) The relative stereochemistry of Felkin-Anh adduct 14d was assigned in analogy to this result.


\(^{24}\) The observed coupling constant is in agreement with a *cis*-oxazolidinone, see Mikami, K.; Kaneko, Y.; Loh, T.-P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 3909-3912.
2.4 Discussion of the observed diastereoselectivity

The stereochemical outcome of the Mukaiyama aldol additions to \textit{anti}-aldehydes 10a, b and \textit{syn}-aldehydes 11a, b (R' = H) can be rationalized in terms of a chelation-controlled reaction mechanism. However, since BF\textsubscript{3}⋅OEt\textsubscript{2} is incapable of chelation, these reactions proceed via a monodentate Lewis acidic activation. The rigid 5-membered cyclic chelate is formed due to the presence of a hydrogen-bond between the NHTs and C=O moieties, which is followed by nucleophilic attack on the sterically most accessible C=O Si-face (Scheme 10).\textsuperscript{25} This study also demonstrates that the relative stereochemistry of the \textit{α}-amino-\textit{β}-silyloxy aldehydes has an insignificant influence on the stereoselectivity in the chelation-controlled reactions since additions to \textit{anti}-aldehydes 10a, b and \textit{syn}-aldehydes 11a, b proceed with comparable levels of \textit{syn}-stereoselectivities (Tables 1, 2).

\begin{equation}
\begin{array}{c}
\text{Nu:} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{R}
\end{array}
\begin{array}{c}
\text{NHTs} \\
\text{Nu:} \\
\text{BF}_3\cdot\text{OEt}_2 \\
\text{R} \\
\text{Nu}
\end{array}
\begin{array}{c}
\text{H} \\
\text{F}_3\text{B} \\
\text{R} \\
\text{H} \\
\text{O}
\end{array}
\begin{array}{c}
\text{Nu:} \\
\text{F}_3\text{B} \\
\text{Nu} \\
\text{H} \\
\text{NHTs}
\end{array}
\begin{array}{c}
\text{R} \\
\text{OH} \\
\text{Nu}
\end{array}
\end{equation}

\textbf{Scheme 10.} Hydrogen-bonding model for chelation-controlled additions to \textit{α}-NHTs aldehydes.

In contrast, in the Felkin-Anh additions to 10c, d and 11c, d (R' = Bn) the polar \textit{β}-OTBS substituent has a large influence on the stereoselectivity of the nucleophilic additions since the diastereoselectivities in the additions to \textit{anti}-aldehydes 10c, d and \textit{syn}-aldehydes 11c, d differ significantly. To determine the inherent stereodirecting effect of the \textit{α}-NTsBn substituent in the absence of a \textit{β}-OTBS substituent, aldehyde 20 was subjected to the same reaction conditions (Scheme 11). This gave \textit{anti}-amino alcohol 21 as a single diastereomer,\textsuperscript{26} showing that the diastereofacial bias imposed on the carbonyl moiety by the \textit{α}-NTsBn substituent is sufficiently strong to direct the approaching nucleophile according to the Felkin-Anh model.

\begin{equation}
\begin{array}{c}
\text{Nu:} \\
\text{OTMS} \\
\text{BF}_3\cdot\text{Et}_2\text{O} \\
\text{85\%}
\end{array}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{T} \\
\text{sBn}
\end{array}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{Bu}
\end{array}
\begin{array}{c}
\text{Bu} \\
\text{OB} \\
\text{TMS}
\end{array}
\begin{array}{c}
\text{Bu} \\
\text{OH} \\
\text{OB}
\end{array}
\begin{array}{c}
\text{R} \\
\text{OH} \\
\text{Nu}
\end{array}
\begin{array}{c}
\text{H} \\
\text{F}_3\text{B} \\
\text{R} \\
\text{H} \\
\text{O}
\end{array}
\begin{array}{c}
\text{Nu:} \\
\text{F}_3\text{B} \\
\text{Nu} \\
\text{H} \\
\text{NHTs}
\end{array}
\begin{array}{c}
\text{R} \\
\text{OH} \\
\text{Bu}
\end{array}
\end{equation}

\textbf{Scheme 11.} Felkin-Anh addition to \textit{α}-NTsBn aldehyde 20.


\textsuperscript{26} The relative stereochemistry of 21 was determined by transformation to the corresponding \textit{cis}-oxazolidinone in analogy to 14c. The measured coupling constant was 7.6 Hz.
Consequently, in the Felkin-Anh additions to anti-aldehydes 10c, d the β-OTBS substituent exerts an insignificant or cumulative stereodirecting effect (Table 1, entries 3, 4) whereas in additions to syn-aldehydes 11c, d the α- and β-stereocenters are strongly opposing resulting in a diminished stereoselectivity (Table 2, entries 3-6). It stands clear that these results can not be accounted for by merging the individual stereodirecting effects of the α-substituent (Felkin-Anh) and the β-substituent (1,3-polar induction model), since this analysis would predict the opposite outcome (non-reinforcing α- and β-stereocenters in additions to anti-aldehydes and reinforcing in additions to syn-aldehydes) as discussed previously.

To learn more about nucleophilic additions to these and similar systems an investigation of Mukaiyama aldol additions to aldehydes containing different polar α- and β-substituents was initiated. The first experiments in this study were directed toward nucleophilic additions to α,β-bisbenzyloxy aldehydes 20a, b, which followed the same trend (Scheme 12).

![Scheme 12. Nucleophilic additions to syn- and anti-α,β-bisbenzyloxy aldehydes.](image)

During the course of this investigation, Evans and coworkers published an extensive study of diastereoselective additions to α,β-bisalkoxy aldehydes observing the same trends,27 grounding our investigation to a halt. According to their results, additions to α,β-bisbenzyloxy aldehydes respond to dipole minimization effects and are best rationalized by the Cornforth model. However, we believe that additions to α-amino-β-silyloxy aldehydes 10c, d and 11c, d instead proceed according to the Felkin-Anh mechanism.11

According to Evans’ investigation, developing syn-pentane interactions28 between a non-hydrogen β-substituent and the approaching nucleophile is prohibitive.27 In line with this, anti-aldehydes 10c, d react through transition state F whereas syn-aldehydes 11c, d react through transition state G (Scheme 13). However, in both F and G destabilizing syn-pentane interactions are developed between the C=O moiety and either the R- (anti-aldehydes 10c, d) or β-O moieties (syn-aldehydes 11c, d). These interactions are energetically

---

28 A destabilizing syn-pentane interaction is created when a hydrocarbon chain is folded in such a way as C1-C5 in a cyclohexane chair-conformation.
more unfavourable for $\text{C}=\text{O}\leftrightarrow R$ than $\text{C}=\text{O}\leftrightarrow O$, a fact that would imply that nucleophilic additions to *anti*-aldehydes 10c, d should be less favourable than additions to *syn*-aldehydes 11c, d. This is, however, contradicted by the experimental results and more factors are clearly involved in dictating the stereochemical outcome in additions to 10c, d and 11c, d. A computational study has shown that the orientation of the $\beta$-stereocenter in G is more unfavourable than in F, due to a destabilizing dipolar interaction between the polar $\beta$-OTBS and C=O bonds. 29 This effect could be responsible for the diminished stereoselectivity in nucleophilic additions to *syn*-aldehydes 11c, d.

To test the validity of this hypothesis, the $\beta$-OTBS group in *syn*-aldehydes 11c, d should be replaced with a less polar group (for instance alkyl). If this model is accurate, the nucleophilic attack is then expected to proceed with high level of Felkin-Anh stereoselectivity. An alternative approach would be to employ a solvent of high polarity, which could more efficiently stabilize unfavourable dipolar interactions as in G. 30

![Scheme 13. Felkin-Anh additions to *syn*- and *anti*-α-amino-β-silyloxy aldehydes.](image)

### 2.5 Conclusions and Outlook

In this chapter, the stereoselective construction of chiral aminodiols has been realized by diastereoselective Mukaiyama aldol additions to α-amino-β-silyloxy aldehydes. The relative stereochemistry of the nucleophilic additions was controlled by chelation to the α-NHTS moiety or by addition in a Felkin-Anh sense. In the latter case, the stereoselectivity was significantly influenced by the

30 The impact of a polar $\beta$-heteroatom on the stereoselectivity in nucleophilic additions to aldehydes is more pronounced in solvents of low polarity. For further discussion, see references 9a and 16.
relative stereochemistry of the aldehyde $\alpha$- and $\beta$-substituents and based on literature precedence, a model was presented to account for this observation. The long history of success in rationalizing and predicting the stereochemical outcome in nucleophilic additions to chiral aldehydes containing one proximal stereocenter (Section 2.2) has resulted in a general belief that the factors dictating carbonyl $\pi$-facial selectivity are well understood. However, recent studies, including our investigation, demonstrate that this is not the case and show that the stereochemical outcome in nucleophilic additions to chiral aldehydes containing multiple stereocenters is not always the sum of the stereodirecting effects of the individual substituents. Clearly, more research is needed in this area before the contributing electronic, steric, and torsional effects responsible for carbonyl $\pi$-facial selectivity in nucleophilic addition reactions can be identified and more accurate stereochemical models developed.
Stereoselective Synthesis of 
Functionalized Pyrrolidines 
Papers II and III

3.1 Introduction

Allylsilanes are versatile reagents in organic synthesis for stereoselective C-C bond construction.\(^{31}\) A prominent feature of the allylsilane reactivity is the ability of C-Si bonds to stabilize adjacent carbocations. This \(\sigma \rightarrow \pi\) hyperconjugative stabilization of \(\beta\)-carbocations is often referred to as the silicon \(\beta\)-effect and is responsible for the regioselectivity and nucleophilicity of allylsilanes toward electrophiles.

The Sakurai-Hosomi allylation of carbonyl compounds is an important transformation in organic synthesis (Scheme 14). From a mechanistic point of view, the allylsilane attacks the activated C=X \(\pi\)-bond (X=O, NR\(^{''}\)) to transiently form \(\beta\)-silylcation A. This is followed by silyl group elimination to afford the corresponding homoallylic alcohol or protected amine. Due to the low Lewis acidity of allylsilanes, an external activation is generally needed and efficient asymmetric induction has been realized by employing chiral Lewis acids or Lewis bases.\(^{32}\)

![Scheme 14. Addition of allylsilanes to activated C=X \(\pi\)-bonds (X=O, NR\(^{''}\)).](image)

Allylsilanes have also successfully been utilized for the construction of functionalized 5-membered heterocyclic ring systems by intramolecular nucleophilic interception of \(\beta\)-silylcation intermediate A. In these [3 + 2]-annulation reactions, two distinct reaction pathways can be identified. The

---

32 Denmark, S. E.; Fu, J. P. Chem. Rev. 2003, 103, 2763-2793.
allylsilane can either function as a 1,3-dipole equivalent with a net 1,2-silyl shift or as a 1,2-dipole equivalent proceeding with no migration of the silyl group.

3.1.1 Allylsilanes as 1,3-dipole equivalents in annulation reactions

The Lewis acid promoted [3 + 2]-annulation reactions of chiral allylsilanes and aldehydes to afford functionalized THF-rings have been extensively studied by the groups of Roush and Panek. In their approaches, the stereogenic Si-center acts as a dominant stereodirecting element and the reactions proceed via a stepwise addition of the allylsilane to the aldehyde to form β-silylcation intermediate B (Scheme 15). This is followed by a 1,2-silyl migration and intramolecular ether formation furnishing functionalized THF-rings in good yields and excellent diastereoselectivities. In the approach developed by Roush and coworkers, the 2,5-relative stereochemistry of the THF-ring can be controlled by the choice of Lewis acid and this reaction was recently implemented in the total synthesis of the annonaceous acetogenins asimicin.

\[
\begin{align*}
& \text{R}^1\text{H} + \text{R}^2\text{S}i\text{R}'_3 \xrightarrow{\text{LA}} \text{B} \\
& \quad \xrightarrow{\text{1,2-silyl shift}} \xrightarrow{\text{Annulation}} \text{R}^2\text{S}i\text{R}'_3
\end{align*}
\]

Scheme 15. Chiral allylsilanes as 1,3-dipole equivalents in [3 + 2]-annulation reactions to form THF-rings.

Similarly approaches have also been developed for the construction of 2-pyrrolidinones (γ-lactams) or pyrrolidines through [3 + 2]-annulation reactions of chiral allylsilanes and chlorosulfonyl isocyanates or N-acyl imines, respectively.

3.1.2 Allylsilanes as 1,2-dipole equivalents in annulation reactions

Annulation reactions of allylsilanes to form 5-membered heterocycles, proceeding without silyl-group migration have received less attention and require that the β-silylcation intermediate is intercepted by a nucleophile other than the Lewis acid complexed alkoxide or nitrogen. An interesting example of such a transformation concerns the synthesis of functionalized pyrrolidines by a [3 + 2]-

annulation reaction of allyltrimethyl silane and N-Cbz-α-amino aldehydes developed by Kiyooka and coworkers (Scheme 16).37

\[ \text{R} \text{H} \text{O} \text{NHCbz} + \text{Allylation} \xrightarrow{\text{BF}_3 \cdot \text{Et}_2\text{O}} \text{Annulation} \]

\[ \begin{align*}
\text{R} \text{O} & \text{NHCbz} \\
\text{BF}_3 \cdot \text{Et}_2\text{O} & \rightarrow 70-75 \% \\
\text{dr} & >20:1
\end{align*} \]

**Scheme 16.** Allylsilanes as 1,2-dipole equivalents in [3 + 2]-annulation reactions to form pyrrolidines.

### 3.2 Stereoselective synthesis of functionalized pyrrolidines

Functionalized pyrrolidines are common substructures in a variety of natural products18 and have also found wide applications as chiral ligands38 and organocatalysts39 in asymmetric synthesis. Consequently, the development of efficient methods for stereoselective synthesis of functionalized pyrrolidines with defined stereochemistry and derivatizable functional groups is an important area of research in synthetic organic chemistry.40

#### 3.2.1 [3 + 2]-Annulation reactions of N-Ts-α-amino aldehydes and 1,3-bis(silyl)propenes

Based on the study by Kiyooka and coworkers,37 we envisioned that densely functionalized pyrrolidines 25, containing four contiguous stereocenters, could be prepared from protected α-amino aldehydes 23 and 1,3-bis(silyl)propenes 24 by a [3 + 2]-annulation reaction (Scheme 17). Initial focus was directed towards investigating the effects of different silicon substituents and α-amino aldehyde N-protecting groups on the annulation reaction. Treatment of N-Ts-α-amino aldehyde 23a and silane 24a (SiR'₃ = SiMe₃) with BF₃·OEt₂ at -78 °C afforded, to our delight, pyrrolidine 25a as a single diastereomer in 77% isolated yield.

---

(Table 3, entry 1). In this reaction, silane 24 functions only as a 1,2-dipole equivalent since pyrrolidine 25a was formed exclusively (scheme 17, path a) and no piperidine formation derived from a 1,2-silyl shift of the terminal silyl moiety could be detected (path b).

Scheme 17. Pathway for the synthesis of functionalized pyrrolidines 25.

The sterically more demanding silane 24b (SiR’3 = SiPr3) failed to participate in the [3 + 2]-annulation reaction (entry 2). Instead, after prolonged stirring at -78 °C compound 26 could be isolated as a single diastereomer in excellent yield. This kind of α-amino aldehyde dimerization reflects the nucleophilic character of the sulfonamide nitrogen, which is an important feature of the [3 + 2]-annulation reaction. This is to the best of our knowledge unprecedented in the literature.41

However, the synthetic utility of this methodology would be significantly increased if the silyl moieties in 25 could be oxidized to hydroxyl groups via a stereospecific Tamao-Fleming oxidation.42 Alkylsilane moieties, as in 25a, can generally not be oxidized to hydroxyl moieties. In contrast, the dimethylphenylsilyl group is a known hydroxyl group equivalent.43 However, treatment of aldehyde 23a and silane 24c (R’3 = SiMe2Ph) with BF3⋅OEt2 at -60 °C afforded pyrrolidine 27, lacking the C4 Si moiety, along with the desired pyrrolidine 25b in low yields although as single diastereomers (entry 3).44 Protodesilylation of unactivated C(sp3)-SiMe2Ph moieties as in 25b are typically

41 For a very recent example of a related dimerization of aziridine aldehydes, see Hili, R.; Yudin, A. K. J. Am. Chem. Soc. ASAP, DOI:10.1021/ja065898s.
44 No reaction was observed at -78 °C. This result was expected since silane 25c is less reactive than silane 25a, see Mayr, H.; Hagen, G. J. Chem. Soc. Chem. Commun. 1989, 91-94.
performed under basic conditions at elevated temperatures. Accordingly, it is more likely that protodesilylation of the vinylsilane moiety in silane \(24c\) occurs prior to the nucleophilic attack to aldehyde \(23a\). This is followed by nucleophilic attack of the mono-desilylated nucleophile which would, in agreement with the study reported by Kiyooka and coworkers account for the formation of pyrrolidine \(27\). The reason for the increased propensity for protodesilylation of silane \(24c\) compared to silane \(24a\) remains unclear.

Table 3. Optimization of the [3 + 2]-annulation

<table>
<thead>
<tr>
<th>Entry</th>
<th>23 (R)</th>
<th>24 (SiR’(^3))</th>
<th>Lewis acid</th>
<th>Yield(^a) (%)</th>
<th>(dr^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a (Ts)</td>
<td>a (SiMe(_3))</td>
<td>BF(_3)OEt(_2)</td>
<td>25a (77)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>2</td>
<td>a (Ts)</td>
<td>b (SiPr(_3))</td>
<td>BF(_3)OEt(_2)</td>
<td>26 (95)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>3(^e)</td>
<td>a (Ts)</td>
<td>c (SiMe(_2)Ph)</td>
<td>BF(_3)OEt(_2)</td>
<td>25b (15)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>4</td>
<td>a (Ts)</td>
<td>c (SiMe(_2)Ph)</td>
<td>Me(_2)AlCl</td>
<td>25b (25)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>5</td>
<td>a (Ts)</td>
<td>c (SiMe(_2)Ph)</td>
<td>MeAlCl(_2)</td>
<td>25b (67)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28 (18)</td>
<td>(E/Z) &gt;98:2</td>
</tr>
<tr>
<td>6</td>
<td>b (Cbz)</td>
<td>c (SiMe(_2)Ph)</td>
<td>MeAlCl(_2)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>c (Bz)</td>
<td>c (SiMe(_2)Ph)</td>
<td>MeAlCl(_2)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield \(^b\) Determined by \(^1\)H NMR analysis of the crude reaction mixture. \(^e\) The reaction temperature was -60 °C.

To avoid this undesired protodesilylation, a variety of Lewis acids were screened, none of which yielded pyrrolidines \(25b\) or \(27\). Pleasingly, Me\(_2\)AlCl and MeAlCl\(_2\) promoted the formation of pyrrolidine \(25b\) with no sign of the

47 No protodesilylated adduct was observed with aldehyde \(23a\) and silane \(24a\) using the same conditions (BF\(_3\)OEt\(_2\), CH\(_2\)Cl\(_2\), -60 °C). This is puzzling since a previous study has shown that trimethylsilyl groups are protodesilylated faster than dimethylphenylsilyl groups in allylsilanes, see reference 46.
48 Lewis acids: BCl\(_3\), TMSOTf, TiCl\(_4\), SnCl\(_4\), Sc(OTf)\(_3\).
desilylated pyrrolidine 27 (entries 4, 5). The best result was obtained using MeAlCl2, furnishing pyrrolidine 25b in 67% yield as a single detected diastereomer along with the formation of diene 28 (entry 5). Finally, the effect of nitrogen protecting groups was studied, but neither NHCbz (entry 6) nor NHBz (entry 7) afforded any pyrrolidine formation. Instead, a mixture of unidentified elimination products was obtained, probably due to the lower nucleophilicity of the nitrogen atom in these functional groups thus favoring elimination over annulation.49

At this point, we investigated the scope and limitations of the optimized procedure and N-Ts-α-amino aldehydes 23a, d-h were selected for further investigation (Table 4).50

**Table 4. Stereoselective [3 + 2]-annulation of silane 24c and aldehydes 23a, d-h**

<table>
<thead>
<tr>
<th>Entry</th>
<th>23 (R)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; 25 (%)</th>
<th>&lt;i&gt;dr&lt;/i&gt;&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a (iPr)</td>
<td>b (67)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>2</td>
<td>d (Me)</td>
<td>d (33)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>3</td>
<td>e (Ph)</td>
<td>e (69)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>4</td>
<td>f (CH2OTBS)</td>
<td>f (57)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>5</td>
<td>g (CH2CH=CH2)</td>
<td>g (35)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>6</td>
<td>h (CH2CH2OTBDPS)</td>
<td>h (61)</td>
<td>&gt;98:2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup> Low yield due to instability of the aldehyde.

The [3 + 2]-annulation with silane 24c proceeded in all cases in moderate to good yields with excellent stereoselectivity, furnishing densely functionalized pyrrolidines 25b, d-h containing four contiguous stereocenters and derivatizable functional groups with complete diastereoselectivity. In addition, chiral HPLC analysis showed no sign of racemization of aldehyde 23a during either the oxidation or the [3 + 2]-annulation reaction.51

49 The nitrogens in NHCbz or NHBz are more electron-deficient due to more efficient resonance stabilization in these functional groups compared to in NHTs. This has been quantified by measuring the nitrogen inversion-barriers of carbamate, amide and sulphonamide-protected aziridine invertomers, see Gilchrist, T. L. *Heterocyclic Chemistry*, Longman Scientific & Technical: Essex, 1985, see p. 36.

50 N-Ts-α-amino aldehydes 23a-h were prepared from the corresponding amino alcohols, see Ocejo, M.; Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Synlett* **2005**, 2110-2112.

51 The [3 + 2]-annulation of (S)-23a and 24c afforded 25b with ee >97% according to chiral HPLC analysis (Chiracel OD-H, hexane/iPrOH 99:1, 1 mL/min).
With a method for stereoselective synthesis of pyrrolidines in hand, we became interested in investigating whether the same methodology could be applied for the construction of functionalized piperidines through a mechanistically related [4 + 2]-annulation reaction. However, subjecting N-Ts-β-amino aldehyde 29 and silane 24c to the optimized reaction conditions resulted in no piperidine formation (Scheme 18). Instead, diene 30 was isolated in 51% unoptimized yield as a single detected stereoisomer.

Scheme 18. Attempted [4 + 2]-annulation reaction.

3.2.2 Stereochemistry determination and rationalization of the selectivity

To our delight, pyrrolidine 25b was crystalline and its relative stereochemistry was determined by X-ray crystallographic analysis to be (2S*, 3R*, 4R*, 5R*) (Figure 3). The relative stereochemistry of pyrrolidines 25a, d-h was assigned in analogy with this result.

Figure 3. Crystal structure of pyrrolidine 25b.

To account for the observed stereochemical outcome of the [3 + 2]-annulations, the diastereofacial bias imposed on the aldehyde C=O by the α-NHTs substituent (C3-selectivity) and the orientation of silane 25 in the transition state (C4-selectivity) have to be considered (Figure 4).

---

The C3-selectivity can be rationalized by a chelation-controlled mechanism proceeding via a monodentate Lewis acidic activation and by invoking a hydrogen bond between the $\alpha$-NHTs and C=O moieties. This is followed by nucleophilic attack on the least hindered Si-face as discussed in chapter 2. Attack of silane 24 in a Felkin-Anh sense would result in the formation of the C3-epimeric pyrrolidine (see Chapter 2.2.1).

Keck and coworkers have studied transition state geometries in BF$_3$⋅OEt$_2$ promoted crotylstannane additions to aldehydes. They concluded that syn-synclinal transition states, in which the silyl methylene moiety is oriented gauche to the aldehyde C=O, are the lowest energy pathways due to the presence of favorable secondary orbital interactions. $^{53}$ It has also been argued that the most sterically demanding quadrant of space in these structures is that occupied by the carbonyl complexed Lewis acid. $^{33b}$ In order to minimize these unfavorable steric interactions with the approaching nucleophile, we propose that the reactions proceed through syn-synclinal TS A that accounts for the observed C4-selectivity. $^{33b}$ The alternative syn-synclinal TS B suffers from unfavorable steric interactions between the carbonyl complexed Lewis acid and silane 24 and predicts the formation of the C4 epimeric pyrrolidine. The transiently formed $\beta$-silylcation C is then trapped by the NHTs moiety. It should be noted that the observed C5 stereochemistry indicates that the nucleophilic attack of the sulfonamide on the $\beta$-silyl cation is faster than C4-C5 bond rotation.

As shown in Figure 4, silane 24 reacts through an open transition state. Altering the alkene geometry of the silane from E to Z is not expected to influence the overall C3-C4 relative stereochemistry of 25. $^{54}$ However, if the nucleophilic

---


$^{54}$ Addition of (E)- or (Z)-crotylsilanes to aldehydes give predominantly syn-selectivity, although the selectivity is generally higher for (E)-crotylsilanes, see Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. Tetrahedron Lett. 1983, 24, 2865-2868.
attack by the sulfonamide is indeed faster than C4-C5 bond rotation, this could provide an entry to the C5 epimeric pyrrolidine. To test this notion, aldehyde 23a was treated with silane 31 under the optimized reaction conditions for the [3 + 2]-annulation but, somewhat disappointingly, this resulted in no pyrrolidine formation (Scheme 19). Instead, diene 28 was isolated as the major product in 54% yield as a single stereoisomer.

Scheme 19. Addition of (Z)-silane 31 to aldehyde 23a.

### 3.3 Conclusions and Outlook

A method for stereoselective synthesis of densely functionalized pyrrolidines containing four contiguous stereocenters and derivatizable functional groups by a [3 + 2]-annulation of N-Ts-α-amino aldehydes and 1,3-bis(silyl)propenes has been developed. In this approach, silane 24 functions only as a 1,2-dipole equivalent and no 1,2-silyl migration was observed. The use of 1,3-bis(silyl)propenes in Lewis acid or Lewis base promoted additions to aldehydes is unprecedented in the literature. Future work will focus on annulation reactions of these nucleophiles with different electrophiles to evaluate the possibilities for the construction of other functionalized carbo- and heterocyclic ring systems, for instance THF-rings by additions to α-silyloxy aldehydes. The effect of varying the silicon-substituents of 1,3-bis(silyl)propenes in Lewis acid and Lewis base promoted additions to aldehydes will also be evaluated.
4

Synthetic Approaches Toward
DGDP and (+)-Alexine

Paper III

4.1 Introduction

The \([3 + 2]\)-annulation reaction of \(N\)-Ts-\(\alpha\)-amino aldehydes and 1,3-bis(silyl)propenes for stereoselective construction of functionalized pyrrolidines was introduced in Chapter 3. In the following chapter, the implementation of this reaction in natural product synthesis of polyhydroxylated alkaloids will be discussed.

Polyhydroxylated pyrrolidine and pyrrolizidine alkaloids are a class of naturally occurring compounds that have attracted considerable attention due to their significant biological activity. Many of these compounds display powerful glycosidase inhibitory properties, anti-cancer and anti-viral activities and are therefore potential drug targets for HIV and cancer therapy.

\[
\text{(+)-alexine (32)} \quad \text{(+)-casuarine (34)} \quad \text{DMDP (36)}
\]

\[
\text{(+)-australine (33)} \quad \text{Hyacinthacine A1 (35)} \quad \text{DGDP (37)}
\]

Figure 5. Structurally related pyrrolidine and pyrrolizidine alkaloids.


Noteworthy members of this important class of compounds are (+)-alexine (32), (+)-australine (33), (+)-casuarine (34), and hyacinthacine A1 (35) (Figure 5), which are all structurally related differing only in relative stereochemistry (compare 32 and 33) and the level of hydroxylation (compare 34 and 35). They can formally be derived from the same monocyclic glycosidase inhibitors DMDP (36) and DGDP (37). From a synthetic standpoint, these alkaloids are densely functionalized compounds, containing at least four contiguous stereocenters, and have attracted considerable attention from the synthetic community. Due to their structural resemblance to sugars, many synthetic approaches have exploited the highly oxygenated architecture and intrinsic chirality of carbohydrates as starting points for their synthetic approaches.\(^5^7\) Asymmetric routes from achiral starting materials have also been developed, which to date mainly rely on stereoselective reductions of pyrroles.\(^5^8\) Sharpless aminohydroxylations\(^5^9\) and dihydroxylations,\(^6^0\) ring-closing metathesis\(^6^1\) and tandem [4 + 2]/[3 + 2] cycloaddition reactions of nitroalkenes.\(^6^2\) Recently, a synthesis of polyhydroxylated pyrrolidine alkaloids based on asymmetric allylic alkylations of butadiene epoxide with amines was reported by Trost and coworkers.\(^6^3\)

4.2 Synthetic approaches toward DGDP and (+)-alexine

4.2.1 Retrosynthetic analysis

We reasoned that the [3 + 2]-annulation methodology introduced in the previous chapter would be an ideal starting point for an expedient synthesis of (+)-alexine (32) and DGDP (37), since dimethylphenylsilyl groups can be oxidized to the corresponding hydroxyl moieties with retention of the stereochemistry (Scheme 20). Accordingly, we envisioned that pyrrolidine 25f, which contains all the requisite stereocenters with the correct absolute and relative stereochemistry for DGDP, would serve as a common precursor. The additional C7 stereocenter of (+)-alexine (32) would be installed by a substrate-controlled stereoselective allylation or vinylation of the corresponding aldehyde.

---

The preparation of pyrrolidine 25f from aldehyde 23f and silane 24c by the [3 + 2]-annulation methodology was described in Chapter 3.

![Chemical Structures](image)

Scheme 20. Retrosynthetic analysis of (+)-alexine and DGDP.

4.2.2 Synthesis of DGDP

The synthesis of DGDP (37) started from aldehyde 23f and silane 24c which smoothly underwent a highly stereoselective [3 + 2]-annulation reaction to afford pyrrolidine 25f as a single diastereomer (Scheme 21). Desilylation of pyrrolidine 25f under acidic conditions followed by a stereospecific Tamao-Fleming oxidation42 furnished the polyhydroxylated pyrrolidine 38 in 50% yield over two steps. Attempts to detosylate 38 using sodium naphthalenide at -78 °C in THF resulted in no reaction and only recovered starting material could be isolated. Instead, detosylation could be realized by treatment with Li/NH3(l) in THF at -78 °C, which afforded DGDP (37) in only three steps from 25f. The spectroscopic data for 37 was in full accordance with literature data.64

---

Scheme 21. Synthesis of DGDP.

4.2.3 Towards the synthesis of (+)-alexine

The synthesis of (+)-alexine also started from pyrrolidine 25f (Scheme 22). Desilylation under acidic conditions furnished pyrrolidine 39 in excellent yield. Different oxidation methods were evaluated for accomplishing a chemoselective oxidation of the primary hydroxyl moiety in pyrrolidine 39 to aldehyde 40, and the best results were obtained by treatment of 39 with TEMPO/NaOCl, which cleanly furnished aldehyde 40 in quantitative yield with no sign of oxidation of the secondary alcohol or aldehyde epimerization.

65 Oxidation of 39 using DMP, PCC or Swern conditions afforded 40 in lower yields.
At this point we set out to examine substrate-controlled diastereoselective additions of nucleophiles to aldehyde 40 to set the C7 stereocenter of (+)-alexine (Scheme 22, 32). We envisioned that the correct C7 stereochemistry for (+)-alexine could be installed by a nucleophilic addition in a Felkin-Anh sense, where the α-sulfonamide moiety acts as the large group and exerts the major stereodirecting effect (compare Scheme 11, Chapter 2). Alternatively, a chelation-controlled nucleophilic addition to a 6-membered cyclic chelate, as previously described for TiCl$_4$ promoted additions of allylsilanes to β-alkoxy aldehydes was also expected to furnish the correct C7 stereochemistry for (+)-alexine (See Scheme 5, Chapter 2).

Treatment of aldehyde 40 with vinylmagnesium bromide at -78 °C afforded pyrrolidine 41 in excellent yield but as an inseparable 6:1 mixture of C7 stereoisomers (Table 5, entry 1). Lowering the reaction temperature to -100 °C resulted in only slightly higher diastereoselectivity (entry 2). Pleasingly, treatment of aldehyde 40 with allyltrimethylsilane and the chelating Lewis acid TiCl$_4$ afforded pyrrolidine 42 in 70% as a single detected stereoisomer. The use of the less reactive Lewis acid analogue TiCl$_4$(OiPr)$_2$ afforded pyrrolidine 42 with similar stereoselectivity in a somewhat diminished yield and the reaction temperature had to be increased to -50 °C to ensure full conversion of the aldehyde (entry 4). Further attempts to optimize this reaction by employing other monodentate and chelating Lewis acids (BF$_3$·OEt$_2$ and MeAlCl$_2$) gave inferior results.
Table 5. Stereoselective allylation/vinylation of aldehyde 40

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu:</th>
<th>Lewis acid</th>
<th>T (°C)</th>
<th>dr(^a ) / Yield (%)(^b )</th>
<th>Product (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^c )</td>
<td>R(\text{MgBr} )</td>
<td>N/A</td>
<td>-78</td>
<td>86:14 (90)</td>
<td>(\text{CH}=\text{CH}_2 )</td>
</tr>
<tr>
<td>2(^c )</td>
<td>R(\text{MgBr} )</td>
<td>N/A</td>
<td>-100</td>
<td>90:10 (85)</td>
<td>(\text{CH}=\text{CH}_2 )</td>
</tr>
<tr>
<td>3(^e )</td>
<td>R(\text{TMŞ} )</td>
<td>Ti(\text{Cl}_4 )</td>
<td>-78</td>
<td>&gt;95:5 (70)</td>
<td>(\text{CH}_2\text{CH}=\text{CH}_2 )</td>
</tr>
<tr>
<td>4(^f )</td>
<td>R(\text{TMŞ} )</td>
<td>Ti(\text{Cl}_4(\text{OiPr})_2 )</td>
<td>-78 to -50</td>
<td>&gt;95:5 (56)</td>
<td>(\text{CH}_2\text{CH}=\text{CH}_2 )</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR analysis of the crude reaction mixtures. \(^b\) Isolated yield after flash chromatography. \(^c\) Vinyl magnesium bromide (5 equiv) was added to a solution of aldehyde 40 in \(\text{Et}_2\text{O} \) at the indicated temperature. \(^d\) Product not fully characterized. \(^e\) Allyltrimethyl silane (3 equiv) was added to a solution of aldehyde 40 and Ti\(\text{Cl}_4 \) (1.5 equiv) in \(\text{CH}_2\text{Cl}_2 \). \(^f\) Allyltrimethyl silane (3 equiv) was added to a solution of aldehyde 40 and Ti\(\text{Cl}_4(\text{OiPr})_2 \) (3 equiv) in \(\text{CH}_2\text{Cl}_2 \).

At this point, the alcohol functionalities in pyrrolidine 42 were protected as benzyl ethers by treatment with KHMDS and Bn\(\text{Br} \) to smoothly furnish pyrrolidine 43 in excellent yield (Scheme 23). The terminal olefin in 43 was cleaved to the corresponding aldehyde by a Lemieux-Johnson oxidation,\(^{67} \) followed by in situ reduction using NaBH\(_4 \) to give alcohol 44 in 72% yield over two steps. The tosyl protecting group in 44 could readily be cleaved by treatment with sodium naphthalenide in THF at -78 °C for 5 minutes to furnish amine 45 in excellent yield.

Different conditions were evaluated for the 5-exo-tet ring-closure of pyrrolidine 45 to afford pyrrolizidine 46. Donohoe and coworkers have recently reported a method for cyclization of a similar system in their synthesis of 1-epi australine and hyacinthacine A\(_1 \) using Ms\(\text{Cl} \), which is believed to proceed via a chemoselective mesylation of the primary alcohol followed by cyclization.\(^{58} \) However, treatment of pyrrolidine 45 with Ms\(\text{Cl} \) at 0 °C resulted in the formation of a complex mixture of products indicating that mesylation of 45 did not proceed chemoselectively. Instead, cyclization of pyrrolidine 45 could be accomplished by converting the primary hydroxyl moiety in 45 into the corresponding alkyl bromide in situ using C\(\text{Br}_4 \), P\(\text{Ph}_3 \), and NE\(\text{T}_3 \) followed by cyclization to afford pyrrolizidine 46 in good yield.

---


---

34
Scheme 23. En route to (+)-alexine

Only two steps remained in our synthesis of (+)-alexine, a stereospecific Tamao-Fleming oxidation of the silyl moieties in 46 proceeding with retention of the stereochemistry and deprotection of the benzyl ethers by a Pd/C hydrogenolysis.

The Tamao-Fleming oxidation of dimethylphenylsilyl moieties can be realized by a one-pot procedure using an electrophilic agent (Hg$^{2+}$ or Br$_2$) in AcOOH/AcOH.42 From a mechanistic point of view, the oxidation proceeds via an electrophilic aromatic ipso substitution of the electrophile on the phenyl ring to generate a heteroatom substituted silane that is subsequently oxidized by AcOOH (Scheme 24). In this case, oxidation of the tertiary amine in 46 could potentially be a problem.42

Scheme 24. Tamao-Fleming oxidation of dimethylphenylsilyl moieties.

Alternatively, the oxidation can be performed in a two-step sequence by transforming the dimethylphenylsilyl moieties into the corresponding silylfluorides through a protodesilylation reaction ($E^+ = H^+$) using BF$_3$·AcOH or HBF$_4$·OEt$_2$ in CH$_2$Cl$_2$ or AcOH. The silylfluorides can in a subsequent step be
converted to the corresponding hydroxyl moieties by using H₂O₂ as oxidant, which is reported to be less prone to oxidize tertiary amines.⁴²,⁴³

We reasoned that the amine in 46 would be protonated under the reaction conditions, thus making N-oxide formation unlikely. However, treatment of 46 with Br₂ (generated in situ from KBr) or Hg(OTf)₂ in AcOOH/AcOH gave in both cases a complex mixture of products with no sign of pyrrolizidine 47.⁶⁸ To circumvent this problem, we turned our attention to the two-step procedures described above, which have previously been used for oxidation of dimethylphenylsilyl groups in the presence of tertiary amines.⁶⁹ Disappointingly, treatment of 46 with BF₃·AcOH or HBF₄·OEt₂ in CH₂Cl₂ or AcOH at ambient temperature resulted only in recovered starting material. Attempts to heat pyrrolizidine 46 and BF₃·AcOH or HBF₄·OEt₂ to reflux in CH₂Cl₂ resulted in rapid decomposition. These somewhat disappointing results forced us to reconsider our synthetic strategy and it was decided to oxidize the silyl moieties earlier in the synthesis. Pleasingly, treatment of pyrrolidine 44 with Hg(OTf)₂ in AcOOH/AcOH smoothly furnished pyrrolidine 48 in 60% yield and the synthesis of (+)-alexine by this slightly modified approach is currently in progress in the Somfai group (Scheme 25).⁷⁰

![Scheme 25. Tamao-Fleming oxidation of pyrrolidine 44.](image)

### 4.3 Conclusions and Outlook

In this chapter, our efforts toward the synthesis of polyhydroxylated alkaloids have been described by exploiting the potential of the [3 + 2]-annulation reaction introduced in Chapter 3. So far, this has resulted in the synthesis of the pyrrolidine alkaloid DGDP as well as a nearly completed synthesis of the pyrrolizidine alkaloid (+)-alexine. Since the Tamao-Fleming oxidation of the silyl moieties in pyrrolidine 44 worked satisfactorily, there is good reason to believe that the synthesis of (+)-alexine will be completed in the near future.

---

⁶⁸ For a successful oxidation of a dimethylphenylsilyl moiety in a similar system, see reference 56.
⁷⁰ This experiment was performed by Dr. Martina Dressel.
5
Regioselective and Divergent
Opening of Vinyl Epoxides
Papers IV and V

5.1 Introduction

Vinyl epoxides are common building blocks in organic synthesis and they have often been employed as starting materials and advanced intermediates in the construction of more complicated target molecules. Since vinyl epoxides belong to the class of allylic electrophiles, nucleophilic attack can occur either at the allylic carbon according to the $S_N2$ manifold (figure 6, attack at a) or in a conjugate fashion by a $S_N2'$ attack (attack at b). Controlling the mode of nucleophilic attack is therefore a pivotal aspect of the chemistry of vinyl epoxides and much work has been devoted to develop processes that proceed regioselectively.

![Figure 6. Nucleophilic attack on a vinyl epoxide according to the (a) $S_N2$ or (b) $S_N2'$ manifolds.](image)

Attack according to the $S_N2'$ manifold by carbon-based nucleophiles can generally be accomplished in Pd-catalyzed allylic alkylations using soft anions, by employing organocopper reagents or by Cu(I)-catalyzed additions of organomagnesium or organozinc compounds. Regioselective $S_N2$ attacks can be realized by the use of Grignard reagents, the combination of R-Li and BF$_3$·OEt$_2$, or trialkylinzincates and aluminates, although the regioselectivity is sometimes moderate.

---

However, few regiodivergent approaches have been developed that allow for selective nucleophilic addition to either the $S_N2$ or $S_N2'$ position. Smith and coworkers have developed a protocol for regioselective addition of dithiane nucleophiles based on a steric differentiation between the $S_N2$ and $S_N2'$ manifolds. In this approach, sterically encumbered dithianes add to the more accessible terminal position ($S_N2'$) whereas “smaller” dithianes attack the activated allylic position ($S_N2$), both processes proceeding in yield and with high regioselectivity (Scheme 26). Inspired by this investigation, we embarked on a study towards the development of a divergent protocol for regioselective opening of vinyl epoxides using alkyne nucleophiles. Due to the unencumbered nature of these nucleophiles, we reasoned that this process would instead require an electronic differentiation between the $S_N2$ and $S_N2'$ pathways, since it is known that hard nucleophiles prefer $S_N2$ attack whereas soft nucleophiles attack according to the $S_N2'$ manifold. In the ideal case, we envisioned that the regioselectivity of the process could be controlled by a judicious choice of reaction conditions.

![Scheme 26. Regioselective opening of vinyl epoxides with lithiated dithianes.](image)

### 5.2 Regioselective opening of vinyl epoxides with alkynes

#### 5.2.1 Attack according to the $S_N2$ manifold

Previous studies have demonstrated that hard nucleophiles are mainly influenced by coulombic attractions with the substrate and react under charge control with the electrophilic allylic carbon according to the $S_N2$ manifold. In line with this, we initiated our study by investigating how the electronic properties of the alkyne nucleophiles affected the regioselectivity of the nucleophilic attack. For this purpose, four alkyne anions 49a-d with different electronic properties were selected as representative nucleophiles (Table 6).

---


Nucleophilic addition of lithium acetylides 49a-d to vinyl epoxide 50a resulted in low conversion and regioselectivity at -20 °C in Et₂O (entries 1, 2). Attempts to optimize the process by changing solvent and temperature met with no success; no reaction was observed in THF and in PhMe vinyl epoxide 50a decomposed. Lithium acetylide 49c gave no addition product at -20 °C and increasing the temperature again resulted in decomposition of vinyl epoxide 50a (entry 3). Pleasingly, lithium acetylide 49d, derived from ethoxyacetylene added to 50a with complete S_N2 regioselectivity and stirring at -78 °C for 1 h resulted in complete conversion of vinyl epoxide 50a (entry 4). From these experiments, it appears that electron-donating substituents increase the reactivity and S_N2 regioselectivity in the nucleophilic additions of lithium acetylides to vinyl epoxide 50a (compare entries 1, 2 and 4).

To determine if this observation was a general trend, the influence of the structure and configuration of the vinyl epoxides was studied and 50b-g were selected for further investigations (Table 7). To our delight, reaction with lithium acetylide 49d afforded exclusively the S_N2 adducts, homoallylic alcohols 53 and 56-61 in 52-65% yield, irrespective of the nature of the R-groups or epoxide configurations (Table 7, entries 1-7).
Table 7. Regioselective S<sub>N</sub>2 opening of vinyl epoxides 50a-g with lithium ethoxyacetylide 49d<sup>a</sup>

![Reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>50</th>
<th>R</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>S&lt;sub&gt;N&lt;/sub&gt;2:S&lt;sub&gt;N&lt;/sub&gt;2′&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;O&lt;TBDPS</td>
<td>64</td>
<td>&gt;98:2</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>61</td>
<td>&gt;98:2</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;TBDPS</td>
<td>62</td>
<td>&gt;98:2</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OBn</td>
<td>52</td>
<td>&gt;98:2</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>c-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>61</td>
<td>&gt;98:2</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>c-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>63</td>
<td>&gt;98:2</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;O&lt;TBDPS</td>
<td>65</td>
<td>&gt;98:2</td>
<td>61</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 49d (2.5 equiv), 50 (1 equiv) and BF<sub>3</sub>·Et<sub>2</sub>O (2.5 equiv) in Et<sub>2</sub>O at -78 °C.

<sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis of the crude product.

The stereochemical outcome of the nucleophilic additions to vinyl epoxides 50 was established via chemical correlation. Homoallylic alcohol 53 was transformed into γ-butyrolactone 62 by a retro-ene reaction<sup>81</sup> followed by intramolecular trapping of the resulting ketene (Scheme 27). The cis-configuration of 62<sup>82</sup> showed that nucleophilic attack takes place with inversion of the configuration at the allylic position via a S<sub>N</sub>2 mechanism. Accordingly, the relative stereochemistry of the homoallylic alcohols 53 and 56-61 is directly related to the cis- or trans-stereochemistry of the vinyl epoxides thus providing a synthetic route to cis- or trans-β,γ-disubstituted-γ-butyrolactones, respectively.


<sup>82</sup> Lactone 62 was desilylated (TBAF, 97%) to give 78 with spectroscopic data in complete accordance with literature data, see Nubbemeyer, U. Synthesis 1993, 1120-1128.
5.2.2 Attack according to the $S_N2'$ manifold

Conjugated alkylations of vinyl epoxides, with organocopper reagents have been extensively studied and proceed generally with high regioselectivities. However, since alkynyl groups are not transferred from organocopper reagents in Michael additions to enones, this approach for $S_N2'$ alkynylations of vinyl epoxides is not viable. In contrast, alkynylalanes have previously been used for opening of epoxides and the soft character of these regents has enabled Michael additions of alkynes to enones. Importantly, alkynylalanes are also readily prepared in situ from lithium acetylides thus allowing a divergent strategy.

Addition of alanes 63a and 63b to vinyl epoxide 50a proceeded in excellent yields to afford a regioisomeric mixture of the $S_N2$ and $S_N2'$ adducts (Table 8, entries 1, 2). In contrast to the $S_N2$ additions (Table 6, entries 1, 2), the regioselectivities in these cases were not influenced by the electronic properties of the aromatic substituent. To our delight, conjugate additions of alanes 63c and 63d to trans-vinyl epoxides 50a-e proceeded with complete $S_N2'$ regioselectivity and afforded allylic alcohols 64-68 in 59-76% yield (entries 3-8).

---

Table 8. Conjugate additions of alkynylalane 63 to vinyl epoxides 50a-g*

![Diagram of conjugate additions of alkynylalane to vinyl epoxides]

<table>
<thead>
<tr>
<th>Entry</th>
<th>50</th>
<th>63 (R’=)</th>
<th>Sₐ2:Sₐ2’</th>
<th>E:Z</th>
<th>Yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>a (Ph)</td>
<td>29:71</td>
<td>70:30</td>
<td>84</td>
<td>51, 54</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>b (4-MeOPh)</td>
<td>30:70</td>
<td>70:30</td>
<td>90</td>
<td>52, 55</td>
</tr>
<tr>
<td>3</td>
<td>a</td>
<td>c (TMS)</td>
<td>&lt; 2:98</td>
<td>84:16d</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>a</td>
<td>d (OEt)</td>
<td>&lt; 2:98</td>
<td>22:78</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>b</td>
<td>d (OEt)</td>
<td>&lt; 2:98</td>
<td>70:30</td>
<td>59f</td>
<td>66c</td>
</tr>
<tr>
<td>6</td>
<td>c</td>
<td>d (OEt)</td>
<td>&lt; 2:98</td>
<td>70:30g</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>d</td>
<td>d (OEt)</td>
<td>&gt; 98:2</td>
<td>N/A</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>e</td>
<td>d (OEt)</td>
<td>&lt; 2:98</td>
<td>22:68</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>f</td>
<td>d (OEt)</td>
<td>34:66</td>
<td>&gt;98:2</td>
<td>55</td>
<td>60, 69</td>
</tr>
<tr>
<td>10</td>
<td>g</td>
<td>d (OEt)</td>
<td>62:38</td>
<td>&gt;98:2</td>
<td>65</td>
<td>61, 70</td>
</tr>
</tbody>
</table>

* Reaction conditions: 50 (1 equiv) and 63 (2 equiv) in PhMe for 12 h at 25 °C. b Determined by ¹H NMR analysis of the crude product. c Isolated yield. d E:Z isomers could be separated by flash chromatography. e Compound 71 formed as byproduct, see text. f Combined yield of 66 and 71. g Ratio of stereoisomers, E:Z assignment not possible.

The Sₐ2’ adducts were the only obtained products in the additions of 63c, d to trans-vinyl epoxides 50a-e with two exceptions (entries 5, 7). The Sₐ2’ addition of alane 63d to vinyl epoxide 50b afforded alcohol 71 along with the expected Sₐ2’ adduct 66 (Scheme 28). Compound 71 is most likely the result of a Lewis acid promoted Friedel-Crafts type of intramolecular opening of vinyl epoxide 50b and has previously been observed under similar conditions. ⁸⁶

Scheme 28. S$_{N}$2' alkynylation of vinyl epoxide 50b with alane 63d.

Addition of alane 63d to vinyl epoxide 50d afforded only the S$_{N}$2 adduct, homoallylic alcohol 58 in 62% yield (entry 7). This reversal in regioselectivity is most likely due to complexation of alane 63d to the benzyloxy moiety of 50d, thereby directing the nucleophilic attack. This undesired complexation could be suppressed by using the sterically more demanding TBDPS protecting group, which gave only the desired S$_{N}$2' adduct (entry 4).

The S$_{N}$2' additions of alanes 63c, d to trans-vinyl epoxides 50a-e resulted in complete S$_{N}$2' regioselectivity. These products were, however, obtained as a mixture of E/Z isomers (entries 3-8). In contrast, additions to cis-vinyl epoxides 50f, g gave a diminished regioselectivity but complete E stereoselectivity (entries 9, 10). To rationalize these results, we propose that the S$_{N}$2' alkynylation proceed by complexation of the alkynylalane to the epoxide oxygen followed by intramolecular delivery of the alkyne nucleophile. In trans-vinyl epoxides 50a-e, the conjugate S$_{N}$2' additions are likely to proceed through both $s$-trans conformer A and $s$-cis conformer B, resulting in the formation of an E/Z isomeric mixture (Scheme 29).

In contrast, in the S$_{N}$2' additions to cis-vinyl epoxides 50f, g $s$-cis conformer C suffers from severe steric interactions (Scheme 30). As a consequence, conjugate additions to cis-vinyl epoxides 50f, g proceed exclusively through $s$-trans conformer D resulting in complete E stereoselectivity. Previous studies have shown that Michael additions of alkynylalanes to enones can only proceed when the complex between the vinyl epoxide and the alkynylalane can adopt a conformation in which the reacting alkyne and alkene moieties are in close

---

proximity in space.\textsuperscript{84} For steric reasons, complexation of the alkynylalane to cis-vinyl epoxides is likely to occur \textit{trans} to the vinyl moiety as in conformation E, which results in a less efficient orbital overlap. This is likely to retard the S\textsubscript{N}2' pathway with concomitant diminished regioselectivity as a result.

![Scheme 30](image)

\textit{Scheme 30.} Regio- and stereoselectivity in the S\textsubscript{N}2' alkynylations of cis-vinyl epoxides 50f, g.

To expand the scope of this method, the effect of adding a substituent on the terminal alkene was explored (Scheme 31). Success in this approach would also provide valuable insight into the reaction mechanism, and prove whether the conjugate S\textsubscript{N}2' additions indeed proceed via complexation of the alane to the epoxide oxygen followed by intramolecular delivery of the nucleophile. If this assumption is correct, the alkyne nucleophile would be expected to add to cis-vinyl epoxide 72 through conformation D to furnish S\textsubscript{N}2' adduct 74. However, subjecting 72 to the optimized S\textsubscript{N}2' conditions did not result in the formation of the expected conjugate addition product. Instead, the S\textsubscript{N}2 adduct 73 was isolated as the sole detected product, probably due to increased steric hindrance at the alkene terminus (Scheme 31).

![Scheme 31](image)

\textit{Scheme 31.} Attempted S\textsubscript{N}2' addition of alane 63d to cis-vinyl epoxide 72.
5.2.3 γ-Butyrolactones in natural product synthesis

The γ-butyrolactone is a common substructure in many natural products. In addition, these compounds have frequently been used as valuable intermediates in the construction of more complex molecules in organic synthesis. An interesting example on this theme is the synthesis of prostaglandin PGF$_{2\alpha}$ from D-glucose reported by Gilbert Stork and coworkers (Scheme 32). In this approach, compound 75 was used as an advanced intermediate.89

\[ \text{α-D-Glucose} \xrightarrow{17 \text{ steps}} \xrightarrow{\text{C}_4\text{H}_9} \xrightarrow{\text{HO}} \xrightarrow{\text{HO}} \xrightarrow{\text{OH}} \xrightarrow{\text{CO}_2\text{H}} \text{PGF}_{2\alpha} \]

**Scheme 32.** Synthesis of PGF$_{2\alpha}$ by Stork and coworkers.

To demonstrate the utility of the regioselective S$_2$2 opening of vinyl epoxides with ethoxyacetylene, 75 was prepared in three steps from γ-butyrolactone ent-62 using a cross-metathesis (CM) approach. Cross-metathesis has gained an increasingly important role in organic synthesis for the construction of olefinic C-C bonds, triggered by the rapid development of efficient catalysts with high functional group tolerance. Initially, we reasoned that lactone 75 could be prepared from ent-62 and alcohol 76a by a cross-metathesis reaction using Grubbs’ 2nd catalyst. However, this reaction resulted in low yield of 77 even after prolonged reaction times (Table 9, entry 1). Disappointingly, attempts to increase the conversion by employing higher reaction temperatures led to rapid decomposition of the starting material (entries 2, 3). Protection of the allylic alcohol as the TBDPS ether 76b also met with no success (entries 4, 5).

Surprisingly, desilylation of γ-butyrolactone ent-62 using TBAF to furnish alcohol 78 followed by CM resulted in the formation of lactone 75 ($E/Z >20:1$) in 57% isolated yield after stirring for 2.5 h at rt (entry 6). This approach provides a facile, convergent synthesis of γ-butyrolactone 75.

---

Table 9. Optimization of the CM reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>76</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ent-62</td>
<td>a</td>
<td>rt</td>
<td>60</td>
<td>26b (77)</td>
</tr>
<tr>
<td>2</td>
<td>ent-62</td>
<td>a</td>
<td>40</td>
<td>15</td>
<td>c</td>
</tr>
<tr>
<td>3d</td>
<td>ent-62</td>
<td>a</td>
<td>80</td>
<td>3</td>
<td>c</td>
</tr>
<tr>
<td>4</td>
<td>ent-62</td>
<td>b</td>
<td>rt</td>
<td>3</td>
<td>c</td>
</tr>
<tr>
<td>5f</td>
<td>ent-62</td>
<td>b</td>
<td>40</td>
<td>6</td>
<td>c</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>a</td>
<td>rt</td>
<td>2.5</td>
<td>57 (75)</td>
</tr>
</tbody>
</table>

*Grubbs’ 2nd cat. (0.1 equiv), ent-62/78 (1 equiv) and 76 (2 equiv) in CH2Cl2 at the indicated temperature and reaction time. b Conversion according to 1H NMR analysis of the crude reaction mixture. Product 77 was not isolated from the crude mixture and characterized. c Starting material decomposed. d PhMe was used as solvent. e No reaction, ent-62 was recovered. f Compound 76a was added over 1.5 h.

5.3 Conclusions and Outlook

In this chapter, a divergent protocol for regioselective addition of alkynes to vinyl epoxides has been described. The combination of lithium acetylides and BF3·OEt2 resulted predominately in Sn2 attack whereas alkynylalanes mainly afforded the Sn2’ adducts. The regioselectivity of both processes was significantly influenced by the nature of the alkyne substituent. The best results were obtained with ethoxyacetylene, which added with complete regioselectivity under both Sn2 and Sn2’ conditions and the Sn2 adducts could be transformed into γ-butyrolactones. The synthetic utility of these processes were demonstrated by an expedient synthesis of γ-butyrolactone 75, an advanced intermediate in Stork’s synthesis of PGF2α. A possible extension of this project could be to study regioselective Sn2 and Sn2’ alkynylations of other allylic electrophiles, for instance allyl chlorides or acetates. However, due to the limitations in nucleophile scope encountered in this investigation this was not performed.
Concluding Remarks

This thesis deals with the development of new methodology in organic synthesis for stereo- or regioselective construction of carbon-carbon bonds.

Specifically, substrate-controlled stereoselective additions of nucleophiles to α-amino aldehydes have been studied to identify the factors that dictate carbonyl π-facial selectivity in nucleophilic additions to these and similar systems. This investigation also resulted in the development of a method for stereocontrolled synthesis of chiral aminodiols, which are common substructures in many polyhydroxylated alkaloids. In addition, a highly stereoselective [3 + 2]-annulation reaction to afford densely functionalized pyrrolidines with complete diastereoselectivity was developed. This approach is ideal for the synthesis of polyhydroxylated alkaloids and was also implemented as a keystep in a synthetic approach towards the polyhydroxylated pyrrolidine and pyrrolizidine alkaloids DGDP and (+)-alexine from a common late pyrrolidine intermediate.

In addition, a protocol for regioselective opening of vinyl epoxides using alkyne nucleophiles was developed. The regioselectivity of the processes is controlled by the choice of reaction conditions. This approach provides a straightforward entry to functionalized γ-butyrolactones, which was demonstrated by an expedient synthesis of an advanced intermediate in Stork’s synthesis of PGF₂α.

To conclude, the development of new synthetic methodology continues to occupy a prominent position in organic chemistry research and the further need for efficient, highly selective and environmentally benign processes remains undisputed. It is expected that future progress in the field of complex molecules synthesis will continue to ultimately depend on the synthetic methodologies available.
Acknowledgement

A journey is always easier when you travel together. In the following list there are a number of people to whom I would like to express my deepest gratitude for their support during these years:

First of all, I would like to thank my supervisor Professor Peter Somfai for giving me the opportunity to come to KTH, for teaching me how good research is conducted and for sharing his great knowledge in chemistry. It has been a rewarding experience in many aspects to work in your group for the last 5 years.

Staffan, Daniel, Tessie, Tobias, Olof, Emilie, Martina, Dr. Berit Olofsson and Professor Christina Moberg for rewarding discussions and valuable comments on this thesis. Henry Challis, Lena Skowron and the staff at Organic Chemistry for all your help!

The Aulin-Erdtman foundation, KTH and the Nobel foundation for travel grants for the conferences in Philadelphia, San Francisco and Lindau.

All the past and present coworkers of the Somfai lab for creating a nice and stimulating working environment. Special thanks to Daniel, Staffan and Janne B for all your good advice and for always lending a hand. Thanks to Sebastian, Olaf and Pavel for the champagne, the cinnamon buns and for putting up with me when I abuse your language. Thanks also to Tessie and Martina for all your help with the research projects when it was needed the most.

Dr. Andreas Fischer for the X-ray analysis. Dr. Ulla Jacobsson and Anders Frölander for always taking time to help me with the NMRs.

All the present and former coworkers at Organic Chemistry for rewarding discussions, innebandy (Strykpojkarna Sthlm) and occasional Friday beer.

All my friends from outside the lab. Special thanks to Christian for all the good laughs and for being the BEST captain when sailing in the archipelago. Tobbe for being a great friend, for sharing laughs and frustration and for all your good advice on my work. Janne, for all the inline trips. Hornstull is not the same anymore! Jenny and Olof for being good friends from my very first week as a chemistry undergraduate in Lund and through it all. All my old friends from Lund, especially Nisse and Norpan for all the good times and late nights out. Mari for being so close, although so far away…

My family, for a lifetime of love and support.
Appendix

This appendix contains experimental and/or spectroscopic data for compounds mentioned in this thesis but not reported in publications I-V.

Compound 18

To a stirred solution of 12a (29 mg, 0.05 mmol) in THF (1 mL) at 0 °C was added TBAF (20 mg, 0.06 mmol) and the solution was stirred at rt for 90 minutes. The reaction mixture was filtered through an Extrelut NT3® column and concentrated.

To a stirred solution of the crude product obtained in the previous step and CH(OEt)3 (115 µl, 1 mmol) in dry MeOH (1mL) was added PPTS (cat.) and the solution was stirred at rt for 2h. The reaction mixture was filtered through an Extrelut NT3® column and concentrated. Flash chromatography of the residue (SiO2, CH2Cl2:MeOH 98:2) yielded compound 18 as a colorless oil (15 mg, 67%).

1H NMR (400 MHz, CDCl3) δ 7.76 (d, J = 8.3 Hz, 2H), 7.27-7.09 (m, 5H), 7.01 (d, J = 8.3 Hz, 2H), 4.59 (d, J = 9.5 Hz, 1H), 3.77 (m, 1H), 3.22 (m, 4H), 2.74 (q, J = 9.5 Hz, 1H), 2.60 (m, 2H), 2.41 (m, 1H), 2.25 (s, 3H), 2.12 (dd, J = 13.2, 5.0 Hz, 1H), 1.59 (m, 1H), 1.52 (m, 1H), 1.24 (m, 1H), 1.01 (s, 9H); 13C NMR (100 MHz, CDCl3): 144.0, 141.6, 137.3, 129.8, 128.2, 128.1, 127.2, 125.7, 126.2, 125.4, 71.5, 69.4, 61.3, 51.8, 39.9, 36.8, 33.3, 31.3, 26.5, 21.5; IR (neat) 3400, 1160 cm⁻¹; HRMS (FAB+) calcd for C25H36NO5S (M+H): 462.2314, found: 462.2314.

Compound 19

1H NMR (400 MHz, CDCl3) δ 7.25-7.01 (m, 10H), 4.91 (d, J = 15.6 Hz, 1H), 4.70 (m, 1H), 4.14 (d, J = 15.6 Hz, 1H), 3.90 (t, J = 6.0 Hz, 1H), 3.57 (d, J = 8.0 Hz, 1H), 3.47 (m, 1H), 2.67 (m, 1H), 2.44 (m, 1H), 1.96 (m, 1H), 1.77 (m, 2H), 1.54 (m, 2H), 0.83 (s, 9H), 0.80 (s, 9H), 0.01 (s, 3H), -0.16 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 158.2, 141.1, 136.6, 128.7, 128.6, 128.3, 127.6, 127.4, 126.2, 76.2, 75.5, 46.4, 35.1, 34.7, 32.5, 30.6, 25.9, 25.4, 18.0, -4.9, -4.8; IR (neat) 3430, 2950, 1740 cm⁻¹; HRMS (FAB+) calcd for C31H48NO4Si (M+H): 526.3353, found: 526.3353.

Stereochemistry determination of compound 21.

To a stirred solution of 21 (19 mg, 63 µmol) in MeCN:AcOH 1:1 (2 mL) at 0 °C was added Me₄NBH(OAc)₃ (83 mg, 315 µmol) and the solution was stirred for 30 min. The mixture was diluted with H₂O (10 mL) and extracted with Et₂O.
(2x15 mL). The combined organic phases were dried, filtered and evaporated to give a colorless oil. Flash chromatography of the residue (SiO₂, pentane:EtOAc 5:1) yielded the desired compound as a single diastereomer (26 mg). To a THF solution (2 mL) of the alcohol obtained in the previous step cooled to -78 °C was added Na⁺C₁₀H₈⁺ in DME until the black color persisted. The solution was stirred for an additional 30 min followed by quenching with EtOH (1 mL) and H₂O (5 mL) and extracted with Et₂O (2x15 mL). The combined organic phases were dried, filtered and evaporated to give a white solid. Flash chromatography of the residue (SiO₂, pentane:EtOAc 2:1 + 1% NH₃) yielded the desired amine (9 mg). To a CH₂Cl₂ solution (1 mL) of the amine obtained in the previous step (7 mg, 24 μmol) was added triphosgene (11 mg, 36 μmol) and DIEA (9 μl, 50 μmol) and the reaction was stirred at rt over night. The reaction mixture was filtered through an Extrelut NT3® column and concentrated. Flash chromatography of the residue (pentane:EtOAc 10:1) afforded the corresponding oxazolidinone as a colorless oil (7.5 mg, 82% over three steps).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta 7.32 (m, 5H), 5.11 (d, J = 15.4 Hz, 1H), 4.76 (ddd, J = 10.8, 7.6, 2.9 Hz, 1H), 4.07 (d, J = 15.4 Hz, 1H), 3.60 (ddd, J = 10.9, 4.8, 1.7 Hz, 1H), 3.42 (dd, J = 7.6, 2.3 Hz, 1H), 1.96 (m, 2H), 1.70 (m, 1H) 1.53 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H); \]

\[ ^13C \text{ NMR (100 MHz, CDCl}_3 \delta 158.7, 136.2, 128.8, 127.8, 75.6, 61.4, 47.6, 34.7, 30.7, 28.5, 25.4, 21.3, 17.1; IR (neat) 3430, 2960, 1730 cm}^{-1}; \text{HRMS (FAB+) calcd for C}_{19}H_{30}NO_3 (M+H): 320.2226, found: 320.2234. \]

\[ \text{Compound 22a} \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta 9.74 (s, 1H), 7.37-7.26 (m, 10H), 4.72 (d, J = 11.8 Hz, 1H), 4.63 (m, 2H), 4.55 (d, J = 11.8 Hz, 1H), 3.92 (dd, J = 3.7, 1.9 Hz, 1H), 3.77 (m, 1H), 1.73 (m, 1H), 1.54 (m, 1H), 1.29-1.21 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3 \delta 203.5, 138.5, 137.6, 128.9, 128.8, 128.4, 128.3, 128.1, 85.0, 80.3, 73.3, 72.7, 32.1, 31.3, 29.6, 25.7, 23.0, 14.5; \]

\[ \text{Compound 22b} \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \delta 9.77 (s, 1H), 7.37-7.24 (m, 10H), 4.80 (d, J = 12.1 Hz, 1H), 4.53 (m, 3H), 3.84 (m, 1H), 3.72 (m, 1H), 1.68 (m, 1H), 1.61 (m, 1H), 1.29-1.20 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3 \delta 202.5, 138.3, 137.5, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 84.2, 79.7, 73.6, 72.9, 32.1, 30.6, 29.6, 25.9, 23.0, 14.5; \]

\[ \text{Compound 73} \]

\[ ^1H \text{ NMR (CDCl}_3, 500 MHz) \delta 7.70 (m, 4H), 7.39 (m, 6H), 5.60 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.68 (d, J = 9.6Hz, 2H), 3.61 (d, J = 9.7 Hz, 1H), 2.72 (s, 1H), 2.47 (m, 1H), 1.62 (dd, J = 6.3, 1.0 Hz, 3H), 1.34 (t, J = 7.1Hz, 3H), 1.09 (s, 9H); \]

\[ ^13C \text{ NMR (CDCl}_3, 125 MHz) \delta 135.7, 135.6, 133.1, 133.0, 129.8, 127.7, 126.9, 125.1, 93.5, 74.5, 71.1, 70.4, 39.2, 36.4, 26.8, 19.3, 14.3, 13.2; \]