A Radical Conjugate Addition Approach to the Total Synthesis of Celogentin C

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A RADICAL CONJUGATE ADDITION APPROACH TO THE TOTAL SYNTHESIS
OF CELOGENTIN C

by

Steven Gene Capps

A thesis submitted to the faculty of
Brigham Young University
In partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry and Biochemistry
Brigham Young University
December 2008
of a thesis submitted by

Steven Gene Capps

This thesis has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

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ABSTRACT

A RADICAL CONJUGATE ADDITION APPROACH TO THE TOTAL SYNTHESIS OF CELOGENTIN C

Steven Gene Capps

Department of Chemistry and Biochemistry

Master of Science

The synthesis of five chiral DBFOX (dibenzofuran-oxazoline) ligands with either aryl or benzyl substituents will be presented. The requisite amino alcohols were obtained with high enantioselectivity either commercially (DBFOX/Bn), via Sharpless asymmetric aminohydroxylation (DBFOX/Nap, DBFOX/\textit{t}-BuPh, DBFOX/Pip), or via phase-transfer catalyzed asymmetric alkylation (DBFOX/MeNap). These ligands, complexed with
Mg(NTf₂)₂, were used as Lewis acid promoters of enantioselective radical conjugate additions to α/β-unsaturated nitro-amides/esters. A summary of these results is presented and discussed.

These findings led us to believe that our initial binding model between metal, ligand, and substrate was flawed. Thus, we figured that if we started with a functionality known to bind to both nitro groups and carbonyls, and then introduced a chiral element for control, we may be able to improve the β-carbon enantioselectivity. We have tried to accomplish this via hydrogen-bonding ligands (ureas and thioureas). Initial studies on achiral versions of this concept are discussed.
ACKNOWLEDGEMENTS

First note must definitely go to Dr. Castle, without whom I would never have finished this work. His constant pressure to move forward and patience with me allowed me to focus on completing this project. I wish to thank my associates in the Castle lab for encouragement and problem-solving.

I also wish to thank Dr. Liwen He, who pioneered the work with DBFOX/Ph, and was able to teach me a great deal of laboratory technique before he moved on. While I never really mastered tin chemistry, the skills he passed on to me definitely helped push the reactions forward. Also, Dr. Biplab Banerjee and Jay Kang deserve thanks for working on the reactions and making intermediates for the ligands.

Finally, I wish to thank my family, especially my mother, Donna L. Shambaugh, who was always there to provide encouragement whenever a setback or failed reaction occurred. I dedicate this thesis to her, as she always joked that it was her name that should have been on my scholastic projects.
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CHAPTER 1. INTRODUCTION

1.1 Celogentin C

Celogentin C (I, Figure 1), isolated by Kobayashi and co-workers from the seeds of *Celosia argentea*, is known to inhibit polymerization of microtubule protein (IC$_{50}$ = 0.8 μM), and is the most potent natural product within the Moroidin family (Figure 2). This renders Celogentin C a promising anti-mitotic and anti-tumor agent. Structurally, Celogentin C is a bicyclic octapeptide with two fused rings, possessing two unusual linkages, the first being the C-N bond between tryptophan and histidine residues to form the right-hand ring.

The second interesting feature of I is the C-C leucine-tryptophan linkage in the left-hand ring. This linkage forms a functionality known as a β-substituted amino acid. Since a conventional peptide coupling reaction would be unsuitable for this bond formation, a strategy for forming the core left-hand ring structure with an alkene, then installing the isopropyl group via a radical conjugate addition with high enantioselectivity, has been designed. To date, no total synthesis of this natural product has been published, though a model synthesis of the right-hand ring was published by the Castle group in 2006. Two other researchers in the field, Moody and Hutton, have also worked toward and published results in the pursuit of this attractive synthetic target.
Figure 1. Celogentin C (1)

Figure 2. Moroidin and Other Celogentins

Moroidin

Celogentin A, $R = \text{OH}$
Celogentin B, $R = \text{His}$
1.2 Radical Conjugate Addition

The field of radical chemistry has blossomed within the past ten years, leading to a great deal of research. Traditionally, radicals have been thought of as mostly neutral, non-polar species. However, this paradigm has shifted, and recent work in radical donors and acceptors has been widespread, leading to a type of radical reaction known as a radical conjugate addition (RCA). The RCA is the use of a nucleophilic radical, often alkyl, which adds to an electron-deficient radical acceptor, such as an $\alpha, \beta$-unsaturated carbonyl compound. In 2001, Zhang published a review on intramolecular RCA reactions, and Castle published another review in 2005. The scope and utility of RCA reactions is wide, with macrocyclizations, alkyl additions, and radical cascade mechanisms, with reagents such as SmI$_2$ or R$_3$SnH. Sibi was particularly noteworthy as a pioneer in Lewis-acid- promotion of intermolecular RCA reactions, especially using chiral auxiliaries and chiral Lewis acid complexes to promote stereoselectivity via oxazolidinones and bis-oxazolines (Scheme 1). His research also led to milder conditions for many products of other major reactions, such as aldol-type products.

Scheme 1. Sibi’s Early Work with Enantioselective RCA Reactions
In 2005, the Castle group published work that detailed how the DBFOX/Ph ligand, developed by Kanemasa and Curran (2, Figure 4)\textsuperscript{15} was effective at facilitating the enantioselective synthesis of $\beta$-substituted $\alpha$-amino acids via a Lewis acid-promoted RCA (Scheme 1).\textsuperscript{16} This substructure is a commonly-occurring motif in many natural products, including 1.\textsuperscript{17} Such structures are also attractive synthetic targets as constrained analogues of natural $\alpha$-amino acids.\textsuperscript{18} While other methods exist for constructing these analogues,\textsuperscript{19} the radical conjugate addition is attractive due to the mild conditions that do not interfere with acidic protons, such as peptide amide hydrogens.\textsuperscript{20} Thus, one could generate a library of $\beta$-substituted $\alpha$-amino acids from complex peptidic structures containing a radical acceptor, such as an electron-deficient alkene, by varying the nature of the radical.

![Figure 3. DBFOX/Ph (2)](image)

**Scheme 2.** Mg/DBFOX-promoted Enantioselective Radical Conjugate Additions

\[ R^1 = \text{NHBn or OMe}, R^2 = \text{H, OMe, or F} \]

50–88\% ee, \textit{syn/anti} = 1.4-2.6:1
1.3 Initial Results

After using a Knoevenagel condensation to prepare the requisite \( \alpha \)-nitro, \( \alpha,\beta \)-unsaturated esters, a wide range of Lewis acids were tested in the RCA. Mg and Zn gave the most promising initial results, but the most important factor of this stage was the observation of a slow addition in the absence of any Lewis acid promoter, as long as a large excess of alkyl iodide was used (20 eq). This crucial observation allowed a calculation of relative rates of acceleration for various conditions.

In order to determine if a stereoselective RCA would be possible, the Castle group experimented with Bu\(_3\)SnD. The \( \alpha \)-hydrogen in the product which is installed via hydrogen atom abstraction is quite acidic, due to conjugation with the carbonyl and the presence of the nitro group. Thus, the RCA would be ill-suited to applications in organic synthesis, if epimerization of the newly-formed stereocenter could not be prevented. By substituting Bu\(_3\)SnD for Bu\(_3\)SnH, previous group members were able to observe D-H exchange in the products when H\(_2\)O was used in the workup of amide substrates, or when SiO\(_2\) chromatography was employed in purification. Hydrogenation of the NO\(_2\) group in the crude products, followed by \( N \)-Cbz protection, allowed purification of amide and ester products with \( \alpha \)-D labels, indicating that the stereocenter was not epimerizing. This finding set the possibility for using chiral Lewis acid complexes to control the H atom abstraction, and potentially the addition, in a stereoselective RCA.

Work on determining the best chiral Lewis acid complex was next. Previous group members tried using variations of Curran’s DBFOX/Ph ligand with various R groups \( \alpha \) to the phenyl group (Figure 4). Dimethyl- or dibutyl-DBFOX ligands proved to
be less effective than the parent ligand (2), presumably because the added bulk interfered in the complexation with both Lewis acid and substrate.

![Figure 4. DBFOX/Ph-like Ligands (R = H, Me, n-Bu)](image)

In order to accurately assess the selectivity of their methodology, the Castle group had to determine the absolute stereochemistry of their addition products. This was accomplished by reduction of the nitro group to an amine, then hydrolysis of the benzyl amide to an acid, to form known amino acids (Scheme 3).

![Scheme 3. Absolute Configuration Determination](image)
Comparison of resulting products’ NMR and optical rotation data allowed them to quantify the amount of syn product and anti product (named as shown in Scheme 3) obtained from the RCA. From this data, they were able to determine the selectivity at the \(\alpha\)-carbon and the \(\beta\)-carbon of the nitroalkene, which they dubbed “\(\alpha\) ee” and “\(\beta\) ee.” The results of their research were that they could obtain a high \(\alpha\) ee (up to 83%), but the \(\beta\) ee was low (up to 25%).

### 1.4 Empirical Substrate-Lewis Acid Binding Model

The main disadvantage to the DBFOX/Ph-promoted radical conjugate additions is the lack of stereoselectivity at the \(\beta\)-carbon. This leads to a poor diastereomeric ratio, even though the enantiomeric excess of each diastereomer is good. Based on these findings, the Castle group suggested a binding model of the metal/ligand/substrate that explained the differences in selectivity between the two carbon stereocenters (Figure 5). The octahedral magnesium complex possessed a literature precedent,\(^{21}\) and also helped to explain why the hydrogen abstraction by the \(\alpha\)-carbonyl radical is more selective than the alkyl radical addition to the \(\beta\)-carbon. This model postulates that the aryl group (phenyl in this case) is used to shield one face of the alkene. Thus, by increasing the size of the aryl group, we could increase the effective shielding at the \(\beta\)-carbon, thereby increasing the diastereomeric ratios.
Figure 5. Substrate-Lewis Acid Binding Model

1.5 References


CHAPTER 2. LIGAND PREPARATION

2.1 Amino Alcohol Preparation

The simplest way in which to increase the bulk of the aryl group attached to the DBFOX backbone structure was to vary the amino alcohol used and then follow the synthesis of 2 by Curran and Kanemasa. With five modified DBFOX ligands in mind, we set out to synthesize the five amino alcohol precursors (Figure 1). For the first three ligands (3-5), we envisioned a simple two-step synthesis to install the functional groups and stereocenter.

![Proposed DBFOX Ligands](image)

**Figure 1.** Proposed DBFOX Ligands
Naphthyl Cbz amino alcohol (Cbz Nap, 11) was synthesized in two steps from 2-vinyl naphthalene (8) via Sharpless asymmetric aminohydroxylation (SAA)\(^1\) as previously reported in moderate yields and excellent enantioselectivity (Scheme 1).\(^2\) The \(p\)-tBuPh Cbz amino alcohol (Cbz tBu, 12) was synthesized in the same manner, with slightly lower yields, but excellent selectivity (>99% ee). The benzodioxole Cbz amino alcohol (Cbz Pip, 13) was obtained in the same way with moderate yield, but again, excellent selectivity (95% ee).

![Scheme 1. SAA Reaction](image)

One source of the low yields in the SAA reaction is the formation of the regioisomeric amino alcohol. By keeping the reaction at 0 ºC, this byproduct is minimized, affording a 3:1 ratio or better favoring the desired product. The exact amount of regioisomer formed in each case was not quantified, but was roughly calculable from crude \(^1\)H NMR by the differences in methylene hydrogen chemical shifts.

With the SAA products in hand, the Cbz protecting group was removed via hydrogenolysis with 10% Pd/C, 1 atm of H\(_2\), and NH\(_4\)OAc to increase the palladium turnover, presumably by dissociating the Pd/amine complex. Due to the nature of the
hydrogenation as a heterogeneous mixture, the rate was variable, but the reaction was usually done within 24 hours. A 20% loading of Pd/C did not seem to accelerate the reaction, but adding more than three equivalents of NH₄OAc resulted in sluggish reactivity. Using a higher pressure of H₂ proved to be counterproductive and removed the benzylic amine entirely. The crude product, with conversion verified by TLC and NMR, was taken directly on to the next stage of synthesis.

The fourth amino alcohol was commercially available at >99% ee as D-phenylalaninol (14, Figure 2). The fifth amino alcohol was neither commercially available nor did it have an available vinyl precursor. Methylenenaphthyl amino alcohol (16)³ was synthesized in three steps from 2-(bromomethyl)naphthalene (15) via a chiral phase-transfer-catalyzed alkylation (Scheme 2).⁴ The resulting iminoester (95% ee) was first hydrolyzed in dilute acid, then reduced with LiBH₄ to give the S-amino alcohol, whereas all the others were R-amino alcohols. This choice of stereochemistry was made based on availability of cinchonidine-derived phase-transfer catalyst. Initial reductions were carried out using LAH in refluxing THF overnight, but yields were typically low (50–70%). Fortunately, Dr. Biplab Banerjee, a co-worker in the Castle lab, was able to develop the borohydride conditions shown in Scheme 2 to improve the yield of this step.

![Figure 2. D-phenylalaninol (14)](image-url)
2.2 Bisoxazoline Formation

With all five amino alcohols in hand, we proceeded to follow the synthesis laid out by Curran and Kanemasa for 2. From commercially available dibenzofuran, a directed ortho-metallation, followed by installing a carboxylate at those two positions, gave the diacid. Conversion to the diacid chloride proceeded smoothly to provide the precursor (17) for the DBFOX ligand formation.

The amidation of 17 with amino alcohols 18 and 21 proceeded smoothly within a day at room temperature, analogous to the procedure outlined for DBFOX/Ph. Amidations with amino alcohols 19, 20, and 22 were sluggish and often low-yielding. This was remedied by elevating the temperature up to 90 °C and allowing for longer reaction times. Presumably, the added bulk of the amino alcohols led to the decreased reactivity relative to phenylglycinol, though this does not help to explain the relative rates of Nap and MeNap. Furthermore, there were multiple cases of mono-amidated intermediate being isolated (as R-COCl or R-CO2H), indicating that the second amidation was much more sluggish than the first.
Table 1. DBFOX/R Amidations

<table>
<thead>
<tr>
<th>R</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Prd</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nap (18)</td>
<td>CHCl₃</td>
<td>35</td>
<td>24</td>
<td>23</td>
<td>91</td>
</tr>
<tr>
<td>tBu (19)</td>
<td>DMF</td>
<td>90</td>
<td>68</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>Pip (20)</td>
<td>DMF</td>
<td>90</td>
<td>67</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>Bn (21)</td>
<td>THF</td>
<td>45</td>
<td>107</td>
<td>26</td>
<td>79</td>
</tr>
<tr>
<td>MeNap (22)</td>
<td>DMF</td>
<td>120</td>
<td>86</td>
<td>27</td>
<td>67</td>
</tr>
</tbody>
</table>

We speculated that one possibility as to the relative reactivity of the tBu and Pip amino alcohols compared to phenylglycinol could be attributed to the residual ammonium acetate used in the hydrogenolysis of the Cbz protecting group prior to the amidation. NH₄OAc is only mildly soluble in CDCl₃, and NMR’s obtained of crude amino alcohols show roaming ammonium peaks, which is no surprise. However, what is surprising are occasional shifts of 0.1–0.2 ppm of the acetate peak were observed in some samples. This suggests that an acetate salt could have been slowing the nucleophilic attack of the nitrogen lone pair to the benzodioxole acid chloride. Further experimentation would be needed to verify or disprove this hypothesis.
The final step from the Curran-Kanemasa synthesis of 2 is a cyclodehydration mediated by diethylaminosulfur trifluoride (DAST).\textsuperscript{5} Applied to the new amides, DAST cyclodehydrations were unreliable and often low-yielding. The original procedure reported that the purity of the diamide precursor was essential to the success of the DAST procedure. Due to the scale of many of the ligand preparations, recrystallization was impractical and often failed. The majority of the amides were purified by column chromatography (SiO\textsubscript{2}), which likely left trace impurities responsible for the capricious yields.

A second procedure was reported by Evans and Woerpel in which they cyclodehydrated similar alkyl amino amides via tosyl chloride, Et\textsubscript{3}N, and dimethylamino pyridine (DMAP).\textsuperscript{6} This procedure allowed activation of the sulfoxide with DMAP, driving the tosylate formation to induce the nucleophilic attack of the amide oxygen in cyclization. While this procedure proved to be more reliable and robust than the DAST-mediated procedure, reactions were more sluggish (2-3 days) and lower-yielding. Increasing the amount of DMAP to stoichiometric amounts remedied this issue, but quickly became impractical, due to the difficulty of monitoring the reaction by TLC and NMR from DMAP overlapping product signals.

Fortunately for us, an article was discovered around the same time that dealt with highly-activated DMAP analogues, particularly 4-pyrrolidinopyridine (PPY).\textsuperscript{6} A catalytic amount (10 or 20 mol %) of PPY mediated the cyclodehydration of amides 23-27 within 24 hours with good yields (Table 2).
Table 2. DBFOX/R Cyclodehydrations

![Chemical Structure]

<table>
<thead>
<tr>
<th>R</th>
<th>Time (hrs)</th>
<th>Prd</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nap (23)</td>
<td>19</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>tBu (24)</td>
<td>19</td>
<td>4</td>
<td>58</td>
</tr>
<tr>
<td>Pip (25)</td>
<td>20</td>
<td>5</td>
<td>64</td>
</tr>
<tr>
<td>Bn (26)</td>
<td>19</td>
<td>6</td>
<td>83</td>
</tr>
<tr>
<td>MeNap (27)</td>
<td>23</td>
<td>7</td>
<td>82</td>
</tr>
</tbody>
</table>

2.3 References


CHAPTER 3. RADICAL CONJUGATE ADDITIONS WITH NEW DBFOX LIGANDS

3.1 Ligand Evaluation on Model Substrate

With five new DBFOX ligands in hand, the next step of the project was to test each of these ligands in place of DBFOX/Ph (2) on the model substrate. All other conditions were kept constant. Since achieving high selectivity in both the addition and H-atom abstraction steps were key, the full three-step sequence to inhibit epimerization at the α-carbon was performed (Scheme 1). Only one change was made to the procedure as constituted in the 2005 paper: the ligand and Lewis acid were stirred overnight in order to ensure complexation. Early trials resulted in a large percentage of products characterized by the reduction of the double bond, rather than the radical addition. We theorized that one possible cause of this increase in byproducts was a lack of association between the new ligands, which are bulkier than 2, and Mg(NTf₂)₂. Thus, without the electron-rich DBFOX ligands to lower the Lewis acidity of the Mg, conjugate reduction by Bu₃SnH was favored, a hypothesis supported by observations from the initial work, where stronger Lewis acids promoted the conjugate reduction at a slow rate.

Upon increasing the initial complexation time, the percentage of reduction product was minimized and yields of addition product were increased. The kinetic extent of complexation was first monitored by NMR, but it soon became apparent that an easier visual cue could be used: Initial solubility of Mg(NTf₂)₂ in CH₂Cl₂ was minor, resulting in a cloudy suspension. Upon complexation with the ligand, it dissolved and the solution cleared.

It was our initial hypothesis that these bulkier DBFOX ligands would increase the diastereoselectivity of the addition step over the results reported with 2. Initial trials with
DBFOX/Nap (3) and DBFOX/p-tBuPh (4) confirmed this hypothesis (Table 1). DBFOX/Bn (6) and DBFOX/MeNap (7) also showed increased selectivity at the β-carbon stereocenter. Surprisingly, DBFOX/Pip (5) showed worse selectivity than 2, leading to a possible theory that the heteroatoms in the dioxole ring participated in some way to our detriment. Also surprising was the significantly lower yields obtained when 7 was used. Since the improvements over 2 were minimal (and less than those observed with 3), this was never optimized. Perhaps the lower yields are due to an even slower rate of ligand-Mg complexation, and could potentially be remedied by a longer initial stirring before substrate addition.

Table 1. Ligand Evaluation in Radical Conjugate Addition

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% Yield</th>
<th>syn/anti</th>
<th>% ee (syn, anti)$^a$</th>
<th>α ee, β ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2$^b$</td>
<td>76</td>
<td>1.4:1</td>
<td>88, 76</td>
<td>83, 20</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>1.8:1</td>
<td>96, 97</td>
<td>96, 30</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>1.6:1</td>
<td>84, 79</td>
<td>28, 28</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>1.2:1</td>
<td>76, 79</td>
<td>78, 12</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>1.5:1</td>
<td>82, 80</td>
<td>81, 25</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>1.6:1</td>
<td>92, 90$^c$</td>
<td>91, 25</td>
</tr>
</tbody>
</table>

$^a$ Determined by chiral HPLC (see Ch. 5 for details). $^b$ Data from Ref. 1. $^c$ Major enantiomers were opposite those obtained from reactions with 3–6.
3.2 Substrate Scope of DBFOX/Nap-Mediated Additions

With the improvements observed at both stereocenters using 3, we set out to investigate if these trends held with the other amide and ester radical acceptors used in the initial studies with 2 (Table 2). Amide substrates 35 and 37 underwent the Mg/3-promoted radical conjugate addition with improved enantio- and diastereoselectivity. The best results were still from 33, which contained the more electron-rich \( p \)-methoxyphenyl alkene \( \beta \)-substituent. However, when esters 39, 41, and 43 were employed, lower yields and lower selectivities were observed for all three substrates.

One possible explanation for this flip-flop in the trend could be the carbonyl-Lewis acid complex interaction. Amides have a stronger tendency to bind to Lewis acids\(^2\) because of the resonance between the nitrogen lone pair and carbonyl oxygen, which results in a greater negative charge on the more electronegative oxygen (Figure 1). Esters do not share this level of resonance, since the oxygen is less prone to lone pair donation. This difference alone does not serve as an adequate explanation for the significant changes observed in the radical conjugate additions between the amide and ester substrates, as well as the trend differences in data resulting from the switch from DBFOX/Ph to DBFOX/Nap.
### Table 2. Reaction Scope of DBFOX/Nap (3)

![Chemical Structures]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligand</th>
<th>% Yield</th>
<th>syn/anti</th>
<th>% ee (syn, anti)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 (R = p-OMePh)</td>
<td>2$^b$</td>
<td>76</td>
<td>1.4:1</td>
<td>88, 76</td>
</tr>
<tr>
<td>33 (R = Ph)</td>
<td>3</td>
<td>65</td>
<td>1.8:1</td>
<td>96, 97</td>
</tr>
<tr>
<td>35 (R = Ph)</td>
<td>2$^b$</td>
<td>66</td>
<td>1.4:1</td>
<td>64, 62</td>
</tr>
<tr>
<td>35 (R = Ph)</td>
<td>3</td>
<td>60</td>
<td>1.7:1</td>
<td>73, 71</td>
</tr>
<tr>
<td>37 (R = p-OMePh)</td>
<td>2$^b$</td>
<td>59</td>
<td>1.6:1</td>
<td>72, 50</td>
</tr>
<tr>
<td>37 (R = Ph)</td>
<td>3</td>
<td>63</td>
<td>2.0:1</td>
<td>80, 61</td>
</tr>
<tr>
<td>39 (R = p-OMePh)</td>
<td>2$^b$</td>
<td>75</td>
<td>2.6:1</td>
<td>21, 28</td>
</tr>
<tr>
<td>39 (R = Ph)</td>
<td>3</td>
<td>38</td>
<td>2.2:1</td>
<td>11, 15</td>
</tr>
<tr>
<td>41 (R = p-OMePh)</td>
<td>2$^b$</td>
<td>60</td>
<td>1.7:1</td>
<td>9, 17</td>
</tr>
<tr>
<td>41 (R = Ph)</td>
<td>3</td>
<td>28</td>
<td>1.3:1</td>
<td>2, 5</td>
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<tr>
<td>43 (R = p-OMePh)</td>
<td>2$^b$</td>
<td>66</td>
<td>1.7:1</td>
<td>6, 12</td>
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<tr>
<td>45 (R = p-OMePh)</td>
<td>3</td>
<td>17</td>
<td>1.4:1</td>
<td>3, 3</td>
</tr>
</tbody>
</table>

$^a$ Determined by chiral HPLC (See Ch. 5 for details). $^b$ Data from Ref. 1
3.3 Methodology Considerations

Faced with these findings, we began to wonder if our empirical binding model might be inaccurate, because the carbonyl difference had such a major effect on the reaction, which suggests a primarily monodentate substrate-auxiliary interaction instead of the postulated bidentate interaction. Although nitro-Lewis acid complexation has been reported previously,\textsuperscript{3} the data, which show a minimal improvement in the stereoselectivity at the β-carbon of the amide substrates, combined with a sharp decline of selectivity with the ester substrates, argue against this model.

The reactions summarized in Tables 1 and 2 were all conducted with a substantial quantity of Bu\textsubscript{3}SnH (three additions, 2.5 equivalents each) to ensure complete conversion. The goal of this project was to enhance the scope, value, and practicality of this methodology, so we explored the same reaction of the DBFOX/Nap–Mg(NTf\textsubscript{2})\textsubscript{2}–directed addition of isopropyl radical to 33 with one-half the amount of tin per loading (Scheme 2). While yields were slightly lower, the dr and ee values remained comparable. No other values were changed. Further optimization and experimentation could restore the reaction to its previous levels of yield or higher in the future. These findings are fortuitous, as the only troublesome reagent in the radical
conjugate addition sequence is the tin. However, its impact can be minimized by employing a procedure published by Harrowven, in which a 10% w/w mixture of ground KF in silica gel was used in the purification to remove a significant level of tin byproduct impurity from the Cbz-protected amino amides and esters.

Scheme 1. Radical Conjugate Addition with Reduced Tin Loadings

3.4 References


CHAPTER 4. INITIAL EXAMINATION OF HYDROGEN-BONDING CATALYSTS

4.1 Ureas and Thioureas

Evidence was obtained through experimentation that suggested our hypothesized binding model was inaccurate. Thus, we began to explore the possibility of other systems that are known to interact with both nitro groups and carbonyls, such as hydrogen bond donors. Hydrogen bonding reagents have been extensively used in chemistry, and have received special attention in recent literature as part of a complex chemical scaffold to bring two reacting elements together.\(^1\) We wanted to use these same principles to hydrogen bond to both Lewis basic groups, inducing a conformational change that would twist the carbonyl out of the plane from the rest of the nitroalkene (Figure 1). Removal of this conjugation may cause the amino portion of the amide to preferentially shield one face of the alkene from radical attack. One reason this might occur is that the dipole alignment in the natural planar conformation between the nitro group and carbonyl group destabilizes the compound. By hydrogen bonding to a rigid backbone, a twist can be imposed to bring these two dipoles out of plane with each other, relieving that electronic interference. Of course, it is difficult to predict which functional group will twist.

![Proposed Catalyst-Substrate Binding](image)

**Figure 1.** Proposed Catalyst-Substrate Binding
Rigid hydrogen bond donors would be the best option for the proposed binding shown in Figure 1. A fixed backbone combined with a chiral element away from the binding site would be able to transfer that chirality via steric to the proposed “twisted” binding model. We decided to survey a series of ureas and thioureas, as these functional groups have exhibited hydrogen bonding to nitro groups.\(^2\)\(^-\)\(^4\) Takenaka recently discovered an aminopyridinium ion that also complexes well with nitroalkenes.\(^5\) A set of seven donors were proposed as simple, achiral ligands to test the extent to which hydrogen bonding will catalyze the radical conjugate addition (Figure 2). We hoped that the thioureas would act as the better catalyst, since thioureas are more Lewis acidic than ureas. However, we are aware that the thiocarbonyl may interfere with the radical chemistry.

![Figure 2. Hydrogen Bond Donors](image)

### 4.2 Radical Conjugate Additions with Achiral Hydrogen Bond Donors

Compounds 41–47 were synthesized and we performed the radical conjugate addition as outlined previously, substituting the DBFOX/Mg complex with the various
hydrogen bond donors. Since 41–47 are achiral, we performed only the radical conjugate addition, unlike the previous studies where precautions were taken to prevent epimerization by reducing the nitroalkene product to an amine, then protecting with CbzCl before purifying.

Initial results on the screening process were difficult to unravel, as tin removal became a major problem. Nonetheless, we were able to see the peaks corresponding to the substrate starting material and the addition product on both MS and 1H NMR. Using ligand 45, we saw an approximate two to one ratio of product to starting material, with no evidence of reduction byproducts. Masses for these fractions are unreliable still, due to the tin contamination and multiple purification attempts.

4.3 Conclusions

The syntheses of five new DBFOX ligands were accomplished, and these ligands were then tested in a radical conjugate addition reaction. DBFOX/Nap exhibited minor increases in enantio- and diastereoselectivity over DBFOX/Ph with α/β-unsaturated-α-nitroamide substrates, but the corresponding nitroesters exhibited decreased yields and selectivities. This data caused us to revisit our empirical binding model, which had postulated an octahedral magnesium complex with a bidentate complexation to the substrate. With the major differences between substrate reactivity, we had to consider that the carbonyl–Lewis acid coordination was major compared to the nitro–Lewis acid complexation, which may or may not exist. We then began model studies utilizing hydrogen-bond donors, which are known to bind to both nitro groups and carbonyls. The results of these studies are still in progress.
4.4 References


CHAPTER 5. EXPERIMENTAL AND SPECTROSCOPIC DATA

5.1 General Methods

Tetrahydrofuran, N,N-dimethylformamide, triethylamine, methylene chloride, and methanol were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina.\(^1\) Flash chromatography was carried out using 60–230 mesh silica gel. \(^1\)H NMR spectra were obtained on a Varian 500 MHz spectrometer, with chloroform (7.27 ppm) or tetramethylsilane (0.00 ppm) as an internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). \(^1\)C NMR spectra were obtained on a Varian spectrometer operating at 125 MHz, with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on a Nicolet Avatar 360 FT-IR Spectrometer. Optical rotations were obtained using a Perkin-Elmer 241 Polarimeter. Mass spectral data were obtained using ESI techniques from the Brigham Young University mass spectrometry facility.

5.2 Experimental Details

\((R)-\)Benzyl 2-hydroxy-1-(naphthalene-2-yl)ethylcarbamate (11). To a stirred solution of benzyl carbamate (1.47 g, 9.74 mmol) in 1-propanol (13 mL) was added freshly prepared sodium hydroxide solution (414 mg in 13 mL H\(_2\)O), with a 3 mL aliquot set aside. Freshly prepared sodium hypochlorite (1.20 g, 11.0 mmol) was then added, followed by (DHQD)\(_2\)PHAL (40 mg, 0.05 mmol). The mixture was stirred until homogeneous, then immersed in a 0 °C ice bath. After 10 minutes, 2-vinylnaphthalene
(502.3 mg, 3.26 mmol, 8) was added. The aliquot of NaOH solution was used to dissolve the K₂OsO₂(OH)₄ (25.4 mg, 0.07 mmol). This was then added to the bulk solution. The solution was stirred at 0°C for 4.5 hours, at which time the stirring ceased and the flask was cooled to -25°C to precipitate product. The product was collected by filtration, washed with cold 1:1 nPrOH-H₂O, and dried overnight on the benchtop to afford product (288.3 mg, 0.90 mmol, 68%) as a white solid. *If product did not precipitate*, the solution was quenched with satd. aq. sodium sulfite, then stirred at 0°C for 15 mins. The aqueous layer was separated and extracted with 3 x 15 mL of EtOAc. The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Flash chromatography (SiO₂, 2 x 20 cm, 30-50% EtOAc/hexane gradient elution) provided product, occasionally contaminated with regioisomer. Spectral data for 11 were identical to those previously reported.²

**(R)-Benzyl 1-(4-tert-butylphenyl)-2-hydroxyethylcarbamate (12).** Prepared from *p*-tert-butylstyrene (9, 150 μL, 135 mg, 0.83 mmol) according to the procedure given for the preparation of 11. Compound 12 (109.5 mg, 0.33 mmol, 40%) was obtained as a white solid: [α]D₂⁵ –3.6 (c 0.50, EtOH); ¹H NMR (CDCl₃, 500 MHz) δ 7.40–7.27 (m, 9H), 5.20–5.12 (m, 1H), 5.13 (s 2H), 4.86–4.80 (m, 1H), 3.62–3.54 (m, 1H), 3.37–3.31 (m, 1H), 2.52 (s, 1H), 1.32 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 157.3, 151.3, 138.7, 136.6, 128.8 (2C), 128.44 (2C), 128.40, 125.9 (2C), 125.8 (2C), 73.7, 67.2, 48.6, 34.8, 31.6 (3C); IR (film) ν_max 3377, 3260, 3062, 2924, 2855, 1696, 1282, 1157, 1084, 989 cm⁻¹; HRMS (ESI) m/z 328.19092 (MH⁺, C₂₀H₂₅NO₂H requires 328.19072). 12 was obtained in >99% ee, as analyzed by HPLC (Chiralcel OD-H, 65:35 hexane:i-PrOH, 0.70 mL/min; t_R = 7.9 min, 9.4 min (major)).
(R)-Benzyl 1-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethylcarbamate (13).

Prepared from 5-vinylbenzo[d][1,3]dioxole \(^3\) (10, 96 mg, 0.65 mmol) according to the procedure given for the preparation of 11. Compound 13 (102 mg, 0.32 mmol, 50%) was obtained as an off-white solid: \([\alpha]_{25}^{25} -10.9\) (c 1.0, EtOH); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.40–7.27 (m, 5H), 6.80–6.76 (m, 3H), 5.95 (s 2H), 5.44 (d, \(J = 3.5\) Hz, 1H), 5.13 (d, \(J = 12.0\) Hz, 1H), 5.08 (d, \(J = 12.0\) Hz, 1H), 4.80–4.71 (m, 1H), 3.91–3.75 (s, 2H), 2.10 (s, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 156.5, 148.3, 147.5, 136.4, 133.2, 128.8 (2C), 128.5 (3C), 120.1, 108.8, 107.3, 101.4, 67.3, 66.8, 57.1; IR (film) \(v_{\text{max}}\) 3395, 3310, 3090, 3050, 2950, 2895, 2780, 1697, 1504, 1440, 1370, 1320, 1244, 1038, 940 cm\(^{-1}\); HRMS (ESI) \(m/z\) 338.09908 (MNa\(^+\), C\(_{17}\)H\(_{17}\)NO\(_5\)Na requires 338.09989). 13 was obtained in 95% ee, as analyzed by HPLC (Chiralcel OD-H, 80:20 hexane: \(i\)-PrOH, 0.80 mL/min; \(t_R = 10.0\) min (major), 15.5 min).

**Hydrogenolysis of the Cbz group:** To a solution of 11 (16.2 mg, 0.050 mmol) in MeOH (2 mL) was added solid ammonium acetate (12 mg, 0.15 mmol). After stirring for a minute, 10% Pd/C (2.3 mg, 20% w/w to substrate) was added. The vial was evacuated, then a positive pressure of H\(_2\) was applied. This was repeated twice more to ensure the absence of air in the reaction container. The positive pressure of H\(_2\) was kept on the system for 23 hours, at which time the flask was evacuated and opened and the solution was run through a plug of Celite to remove the Pd/C. The solution was washed with 5 mL water to remove NH\(_4\)OAc. Reaction completion was verified by NMR and TLC.

(S)-tert-Butyl 2-(diphenylmethylenaminoo)-3-(naphthalene-2-yl)propanoate (15): A solution of N-(diphenylmethylene)glycine tert-butyl ester (50.0 mg, 0.17 mmol) and N-(2’,3’,4’-trifluoro)benzylhydrocinchonidinium bromide \(^4\) (9.5 mg, 0.017 mmol) in
PhCH₃–CHCl₃ (7:3, 750 μL) was treated with 2-(bromomethyl)naphthalene (96.6 mg, 0.423 mmol). The solution was then cooled to –20 °C, treated with 50% aqueous KOH (250 μL), and stirred at –20 °C for 12 h. The resultant mixture was diluted with Et₂O (20 mL), washed with H₂O (3 × 5 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 1.5 × 25 cm, 10% EtOAc–hexanes elution) afforded 15 (62.0 mg, 0.14 mmol, 84%) as a yellow oil. Spectral data for this compound were identical to those previously reported.⁵ 15 was obtained in 95% ee, as analyzed by HPLC (Chiralcel OD-H, 99.8:0.2 hexane:i-PrOH, 1.0 mL/min; t_R = 9.5 min (major), 15.6 min).

(S)-2-Amino-3-(naphthalene-2-yl)propan-1-ol (16). A solution of 15 (150 mg, 0.34 mmol) in THF (2.0 mL) was treated with HCl (2 N, 500 μL) and stirred at rt for 4 h. The resultant mixture was treated with sat aq NaHCO₃ (1.5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography (SiO₂, 1.0 × 18 cm, 100% EtOAc elution) afforded the free amine (77.0 mg, 0.28 mmol, 83%).

A solution of this amine (40 mg, 0.15 mmol) in anhydrous Et₂O (2.0 mL) was treated with anhydrous CH₃OH (8.8 μL, 7.0 mg, 0.22 mmol) followed by LiBH₄ (4.8 mg, 0.22 mmol). The resultant mixture was stirred at rt under Ar for 16 h, then treated with H₂O (0.5 mL) and CH₃OH (0.3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated in vacuo to afford 16 (26.9 mg, 0.13 mmol, 91%) as an off-white solid. Spectral data for this compound were identical to those previously reported.⁶

N⁴,N⁶-bis((R)-2-Hydroxy-1-(napthalen-2-yl)ethyl)dibenzo[b,d]furan-4,6-dicarboxamide (18): A flask with magnetic stirbar was charged with diacid chloride 17
(74.7 mg, 0.25 mmol) and anhydrous solvent (CHCl₃, pre-treated with basic alumina, 2 mL). This was placed into a 0°C ice bath under argon and stirred for 5 minutes. A solution of deprotected naphthyl amino alcohol (90 mg, 0.48 mmol), Et₃N (0.08 mL, 0.51 mmol), and CHCl₃ (1 mL) was added dropwise to the dibenzofuran. The flask was then heated in an oil bath to 35°C for 24 hours. Solid ammonium chloride (50 mg) was added to quench the reaction, and this was stirred at room temperature for 30 mins. Then, the solution was filtered. The solid was stirred in THF for an additional 30 mins, and then filtered again. The combined organic extracts were concentrated in vacuo. Flash chromatography (SiO₂, 1.5 x 20 cm, 50%/80%/100% EtOAc-hexanes gradient elution) afforded 18 (133.9 mg, 0.23 mmol, 91%) as a yellow oil: [α]²⁵ D +131 (c 0.1, 95% EtOH); ¹H NMR (CDCl₃, 500 MHz) δ 8.14 (d, J = 7.5 Hz, 2H), 8.04 (d, J = 7.5 Hz, 2H), 8.01 (d, J = 6.5 Hz, 2H), 7.87 (s, 2H), 7.80–7.72 (m, 8H), 7.53–7.47 (m, 4H), 7.44–7.39 (m, 2H), 5.45 (dd, J = 10.0, 6.5 Hz, 2H), 4.10–4.04 (m, 2H), 4.02–3.97 (m, 2H), 3.34 (br s, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 164.5 (2C), 153.4 (2C), 136.5 (2C), 133.3 (2C), 132.9 (2C), 128.6 (2C), 127.9 (2C), 127.6 (2C), 127.5 (2C), 126.2 (2C), 125.9 (2C), 125.6 (2C), 124.8 (2C), 124.3 (2C), 124.2 (2C), 123.6 (2C), 118.9 (2C), 66.0 (2C), 56.6 (2C); IR (film) νmax 3325, 2920, 2349, 1731, 1695, 1682, 1658, 1641, 1592, 1539, 1531, 1462, 1060, 954, 806, 737, 617, 559 cm⁻¹; HRMS (ESI) m/z 595.22258 (MH⁺, C₃₈H₃₀N₂O₅H requires 595.22275).

N⁴,N⁶-bis((R)-1-(4-tert-Butylphenyl)-2-hydroxyethyl)dibenzo[b,d]furan-4,6-dicarboxamide (19). Compound 19 was prepared from deprotected p-tert-butyl phenyl amino alcohol (200 mg, 1.03 mmol) and 17 (160 mg, 0.54 mmol) according to the procedure given for the preparation of 18, with the exceptions that DMF (6 mL total) was
used as the reaction solvent and the reaction was stirred at 90 °C for 68 h. Compound 19 (240 mg, 0.39 mmol, 72%) was obtained as a light yellow solid: \( [\alpha]_{D}^{25} +0.8 \) (c 0.25, EtOH); \(^1\)H NMR (CDCl₃, 500 MHz, mixture of rotamers) \( \delta \) 8.30 and 8.21 (2d, \( J = 7.5 \) and 7.5 Hz, 2H), 8.09 and 8.02 (2d, \( J = 8.0 \) and 8.0 Hz, 2H), 7.98–7.94 and 7.86–7.82 (2m, 2H), 7.52 and 7.48 (2t, \( J = 7.5 \) and 7.5 Hz, 2H), 7.40–7.36 (m, 8H), 5.09 (d, \( J = 9.5 \) Hz, 2H), 4.31–4.21 (m, 2H), 4.07 and 4.01 and 3.71 (3 br s, 2H), 3.51 (t, \( J = 11.5 \) Hz, 2H), 1.34 (s, 18H); \(^{13}\)C NMR (CDCl₃, 125 MHz, mixture of rotamers) \( \delta \) 164.2 and 164.0 (2C), 152.6 and 152.4 (2C), 151.0 (2C), 138.7 and 138.6 (2C), 129.6 and 129.3 (2C), 125.7 (4C), 125.5 (4C), 124.2 and 124.1 (2C), 124.0 (2C), 123.9 and 123.8 (2C), 118.5 (2C), 73.1 and 72.9 (2C), 47.6 and 47.5 (2C), 34.6 (2C), 31.3 (6C); IR (film) \( \nu \) max 3418, 2961, 2868, 1644, 1543, 1426, 1407, 1298, 1270, 1181, 1157, 1108, 1084, 910 cm⁻¹; HRMS (ESI) \( m/z \) 607.31665 (MH⁺, \( C_{38}H_{42}N_{2}O_{5}H \) requires 607.31341).

\( N^4,N^6\)-bis(\((R)-1\)-(Benzo[\(d\])[1,3]dioxol-5-yl)-2-hydroxyethyl)dibenzo[\(b,d\)]furan-4,6-dicarboxamide (20). Compound 20 was prepared from deprotected piperonal amino alcohol (9.0 mg, 0.050 mmol) and 17 (7.9 mg, 0.027 mmol) according to the procedure given for the synthesis of 18, with the exceptions that DMF (3 mL total) was used as the reaction solvent and the reaction was stirred at 90 °C for 67 h. Compound 20 (13.9 mg, 0.024 mmol, 88%) was obtained as white solid: \( [\alpha]_{D}^{25} +7.6 \) (c 0.25, EtOH); \(^1\)H NMR (CDCl₃, 500 MHz) \( \delta \) 8.11 (d, \( J = 7.5 \) Hz, 2H), 7.99 (d, \( J = 7.5 \) Hz, 2H), 7.85 (d, \( J = 6.5 \) Hz, 2H), 7.49–7.45 (m, 2H), 6.93–6.90 (m, 4H), 6.79 (dd, \( J = 7.5 \), 2.0 Hz, 2H), 5.92 (s, 4H), 5.21 (d, \( J = 3.5 \) Hz, 2H), 4.04–3.98 (m, 2H), 3.96–3.89 (m, 2H), 3.33 (s, 2H); \(^{13}\)C NMR (CDCl₃, 125 MHz) \( \delta \) 164.4 (2C), 153.4 (2C) 148.0 (2C), 147.1 (2C), 133.1 (2C), 127.4 (2C), 124.4 (2C), 124.3 (2C), 123.7 (2C), 120.1 (2C), 118.8 (2C), 108.5 (2C),
107.3 (2C), 101.1 (2C), 66.2 (2C), 56.2 (2C); IR (film) $\nu_{\text{max}}$ 3274, 2920, 2868, 1638, 1542, 1488, 1440, 1233, 1191, 1040, 932 cm$^{-1}$; HRMS (ESI) $m/z$ 583.17130 (MH$^+$, C$_{32}$H$_{26}$N$_2$O$_9$H requires 583.17111).

$N^4, N^6$-bis((R)-1-Hydroxy-3-phenylpropan-2-yl)dibenzo[\textit{b, d}]furan-4, 6-dicarboxamide (21). Compound 21 was prepared from 14 (19.1 mg, 0.12 mmol) and 17 (18.5 mg, 0.063 mmol) according to the procedure given for the synthesis of 18, with the exceptions that THF (2 mL total) was used as the reaction solvent and the reaction was stirred at 45 °C for 107 h. Compound 21 (26.1 mg, 0.050 mmol, 79%) was obtained as a white solid: $[\alpha]^{25}_{D} +75$ (c 0.50, EtOH); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.05 (d, $J$ = 7.5 Hz, 2H), 7.92 (d, $J$ = 8.0 Hz, 2H), 7.52 (d, $J$ = 7.5 Hz, 2H), 7.44 (t, $J$ = 8.0 Hz, 2H), 7.38–7.29 (m, 8H), 7.24 (t, $J$ = 7.5 Hz, 2H), 4.49–4.39 (m, 2H), 3.90 (d, $J$ = 10.0 Hz, 2H), 3.79 (d, $J$ = 12.0 Hz, 2H), 3.45 (s, 2H), 3.16 (dd, $J$ = 13.5, 6.0 Hz, 2H), 3.05 (dd, $J$ = 13.5, 8.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 164.6 (2C), 153.4 (2C), 138.2 (2C), 129.7 (4C), 128.9 (4C), 127.7 (2C), 126.9 (2C), 124.6 (2C), 124.4 (2C), 123.9 (2C), 119.2 (2C), 63.3 (2C), 53.8 (2C), 37.2 (2C); IR (film) $\nu_{\text{max}}$ 3390, 2924, 2853, 1657, 1629, 1538, 1457, 1261, 1194, 1086, 1035 cm$^{-1}$; HRMS (ESI) $m/z$ 523.22020 (MH$^+$, C$_{32}$H$_{30}$N$_2$O$_5$H requires 523.22275).

$N^4, N^6$-bis((S)-1-Hydroxy-3-(naphthalen-2-yl)propan-2-yl)dibenzo[\textit{b, d}]furan-4, 6-dicarboxamide (22). Compound 22 was prepared from 16 (34.0 mg, 0.17 mmol) and 17 (23.4 mg, 0.080 mmol) according to the procedure given for the synthesis of 18, with the exceptions that DMF (5 mL total) was used as the reaction solvent and the reaction was stirred at 120 °C for 86 h. Compound 22 (33.2 mg, 0.053 mmol, 67%) was obtained as a yellow oil: $[\alpha]^{25}_{D} -19$ (c 0.17, EtOH); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.10
(d, J = 7.5 Hz, 2H), 7.96 (d, J = 7.5 Hz, 2H), 7.84–7.78 (m, 6H), 7.78–7.74 (m, 2H), 7.61
(d, J = 7.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.48–7.42 (m, 6H), 4.57–4.49 (m, 2H), 3.94
(dd, J = 11.5, 3.0 Hz, 2H), 3.84 (dd, J = 11.5, 4.0 Hz, 2H), 3.35 (dd, J = 13.5, 6.0 Hz,
2H), 3.23 (dd, J = 13.0, 8.5 Hz, 2H), 2.97 (br s, 2H); 13C NMR (CDCl3, 125 MHz) δ
164.3 (2C), 153.3 (2C), 135.6 (2C), 133.7 (2C), 132.3 (2C), 128.3 (2C), 128.0 (2C),
127.8 (2C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 126.1 (2C), 125.5 (2C), 124.4 (2C),
124.2 (2C), 123.7 (2C), 119.0 (2C), 62.9 (2C), 53.6 (2C), 37.1 (2C); IR (film) νmax 3392,
2923, 2869, 1651, 1536, 1399, 1375, 1325, 1245, 1200, 1195, 1080, 1025, 1015, 1003,
925 cm–1; HRMS (ESI) m/z 623.25377 (MH+, C40H34N2O5H requires 623.25405).

4,6-bis((R)-4-(Naphthalen-2-yl)-4,5-dihydroxyazol-2-yl)dibenzo[b,d]furan (23). A solution of 18 (59.2 mg, 0.10 mmol) in anhydrous CH2Cl2 (1.5 mL) was treated
with Et3N (40 μL, 29.1 mg, 0.29 mmol) and 4-pyrrolidinopyridine (4.8 mg, 0.032 mmol).
The mixture was stirred at 0 °C for 10 min, then treated dropwise with a solution of TsCl
(45.9 mg, 0.23 mmol) in anhydrous CH2Cl2 (1.5 mL). The resultant mixture was
vigorously stirred at rt for 19 h, then treated with sat aq NH4Cl (7 mL) and extracted with
CH2Cl2 (3 x 10 mL). The combined organic layers were dried (Na2SO4) and
concentrated in vacuo. Flash chromatography (SiO2, 1.5 x 19 cm, 20–100% EtOAc in
hexanes gradient elution) afforded 23 (49.1 mg, 0.088 mmol, 88%) as an off-white solid:
[α]25D -28 (c 0.13, 95% EtOH); 1H NMR (CDCl3, 500 MHz) δ 8.24 (d, J = 8.0 Hz, 2H),
8.17 (d, J = 7.5 Hz, 2H), 7.87 (s, 2H), 7.80 (d, J = 8.0 Hz, 4H), 7.77 (d, J = 8.5 Hz, 2H),
7.53–7.48 (m, 4H), 7.44–7.36 (m, 4H), 5.68 (t, J = 9.0 Hz, 2H), 4.96 (t, J = 9.0 Hz, 2H),
4.40 (t, J = 8.0 Hz, 2H); 13C NMR (CDCl3, 125 MHz) δ 162.5 (2C), 154.4 (2C), 145.3
(2C), 139.8 (2C), 133.4 (2C), 132.8 (2C), 128.8 (2C), 128.6 (2C), 127.9 (2C), 127.7 (2C),
125.5 (2C), 124.4 (2C), 123.7 (2C), 119.0 (2C), 62.9 (2C), 53.6 (2C), 37.1 (2C); IR (film) νmax 3392,
126.2 (2C), 125.8 (2C), 125.5 (2C), 124.9 (2C), 124.8 (2C), 123.9 (2C), 123.1 (2C), 74.8 (2C), 70.1 (2C); IR (film) νmax 2928, 1650, 1494, 1427, 1185, 1124, 984, 747, 700 cm⁻¹; HRMS (ESI) m/z 559.20263 (MH⁺, C₃₈H₂₆N₂O₃H requires 559.20162).

**4,6-bis((R)-4-(4-tert-Butylphenyl)-4,5-dihydrooxazol-2-yl)dibenzo[b,d]furan** (24). Compound 24 was prepared from 19 (2.9 mg, 0.0048 mmol) according to the procedure given for the synthesis of 23. Compound 24 (1.6 mg, 0.0028 mmol, 58%) was obtained as an off-white solid: [α]D²⁵ +36 (c 0.05, 95% EtOH); ¹H NMR (CDCl₃, 500 MHz) δ 8.15 (t, J = 7.5 Hz, 4H), 7.50–7.32 (m, 10H), 5.70 (dt, J = 18.0, 9.0 Hz, 2H), 4.66–4.58 (m, 2H), 4.25–4.15 (m, 2H), 1.32 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz) δ 161.0 (2C), 154.4 (2C), 151.2 (2C), 137.9 (2C), 128.5 (2C), 125.9 (4C), 125.6 (4C), 124.8 (2C), 123.6 (2C), 123.0 (2C), 113.5 (2C), 80.6 (2C), 63.4 (2C), 34.6 (2C), 31.3 (6C); IR (film) νmax 2959, 1651, 1427, 1185, 1120, 1059 cm⁻¹; HRMS (ESI) m/z 571.29856 (MH⁺, C₃₈H₃₈N₂O₃H requires 571.29552).

**4,6-bis((R)-4-(Benzo[d][1,3]dioxol-5-yl)-4,5-dihydrooxazol-2-yl)dibenzo[b,d]furan** (25). Compound 25 was prepared from 20 (19.1 mg, 0.0328 mmol) according to the procedure given for the synthesis of 23. Compound 25 (11.9 mg, 0.0210 mmol, 64%) was obtained as a beige solid: [α]D²⁵ −2.5 (c 0.12, EtOH); ¹H NMR (CDCl₃, 500 MHz) δ 8.16 (d, J = 7.5 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 6.98 (s, 2H), 6.87 (d, J = 7.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 5.92 (d, J = 6.0 Hz, 4H), 5.46 (t, J = 9.5 Hz, 2H), 4.91 (t, J = 9.0 Hz, 2H), 4.35 (t, J = 8.5 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 162.2 (2C), 154.3 (2C), 147.9 (2C), 146.9 (2C), 136.5 (2C), 128.7 (2C), 124.8 (2C), 123.8 (2C), 123.0 (2C), 120.0 (2C), 113.2 (2C), 108.3 (2C), 107.4 (2C), 101.0 (2C),
74.8 (2C), 69.6 (2C); IR (film) $\nu_{\text{max}}$ 2924, 1654, 1489, 1428, 1248, 1188, 1039, 935, 749 cm$^{-1}$; HRMS (ESI) $m/z$ 547.14990, (MH$^+$, C$_{32}$H$_{22}$N$_2$O$_7$H requires 547.14998).

4,6-bis((R)-4-Benzyl-4,5-dihydrooxazol-2-yl)dibenzo[\textit{b,d}] furan (26). Compound 26 was prepared from 21 (66.4 mg, 0.13 mmol) according to the procedure given for the synthesis of 23, with the exception that 0.20 equiv of 4-pyrrolidinopyridine were employed. Compound 26 (50.0 mg, 0.11 mmol, 83%) was obtained as a beige solid: $[\alpha]_{D}^{25} –43$ (c 0.26, EtOH); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.12 (t, $J = 7.5$ Hz, 4H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.35–7.29 (m, 8H), 7.26–7.21 (m, 2H), 4.78–4.70 (m, 2H), 4.52 (t, $J = 8.5$ Hz, 2H), 4.25 (t, $J = 8.0$ Hz, 2H), 3.39 (dd, $J = 14.0$, 4.5 Hz, 2H), 2.87 (dd, $J = 13.5$, 4.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 161.7 (2C), 154.2 (2C), 138.1 (2C), 129.3 (4C), 128.7 (4C), 128.6 (2C), 126.5 (2C), 124.8 (2C), 123.7 (2C), 123.0 (2C), 113.3 (2C), 72.0 (2C), 67.9 (2C), 41.7 (2C); IR (film) $\nu_{\text{max}}$ 2923, 1651, 1494, 1427, 1185, 1125, 984 cm$^{-1}$; HRMS (ESI) $m/z$ 487.20193 (MH$^+$, C$_{32}$H$_{26}$N$_2$O$_3$H requires 487.20162).

4,6-bis((S)-4-(Naphthalen-2-ylmethyl)-4,5-dihydrooxazol-2-yl)dibenzo[\textit{b,d}] furan (27). Compound 27 was prepared from 22 (36.8 mg, 0.059 mmol) according to the procedure given for the synthesis of 23, with the exception that 0.20 equiv of 4-pyrrolidinopyridine were employed. Compound 27 (28.3 mg, 0.048 mmol, 82%) was obtained as a beige solid: $[\alpha]_{D}^{25} +72$ (c 0.17, 95% EtOH); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.12–8.10 (m, 4H), 7.78–7.74 (m, 6H), 7.72 (s, 2H), 7.47–7.41 (m, 8H), 4.86–4.80 (m, 2H), 4.48 (t, $J = 9.0$ Hz, 2H), 4.26 (t, $J = 8.5$ Hz, 2H), 3.51 (dd, $J = 14.0$, 5.0 Hz, 2H), 3.03 (dd, $J = 14.0$, 9.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 161.7 (2C), 154.2 (2C), 135.5 (2C), 133.5 (2C), 132.3 (2C), 128.7 (2C), 128.2 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 126.1 (2C), 125.5 (2C), 124.8 (2C), 123.7 (2C), 123.1 (2C), 123.0 (2C),
113.3 (2C), 71.9 (2C), 67.8 (2C), 41.8 (2C); IR (film) $\nu_{\text{max}}$ 3052, 2925, 2853, 1652, 1507, 1427, 1185, 1124, 984 cm$^{-1}$; HRMS (ESI) $m/z$ 587.23438 (MH$^+$, C$_{40}$H$_{30}$N$_2$O$_3$H requires 587.23292).

5.3 References

   Organometallics 1996, 15, 1518.


3. Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R.
   Tetrahedron 2006, 62, 4214


5.4 Selected NMR Spectra and HPLC Traces
$^1$H (CDCl$_3$, 500 MHz)
$^{13}$C NMR

Pulse: XP
Pulse Sequence: stpp1

$26$ (CDCl$_3$, 500 MHz)
**SAMPLE INFORMATION**

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Sample Type: Unknown  
Vial: 1  
Injection #: 2  
Injection Volume: 20.00 µl  
Run Time: 30.0 Minutes  
Sample Set Name: 

Acquired By: System  
Date Acquired: 7/14/2006 2:18:16 PM  
Acq. Method Set: Chiral AA  
Date Processed: 7/14/2006 3:38:25 PM  
Processing Method: Chiral  
Channel Name: Extract 254.0  
Proc. Chnl. Descr.: PDA 254.0 nm

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**Report Method: Chiral**

Sample Information

Sample Name: SGC-RCA-Naph-1b
Sample Type: Unknown
Vial: 1
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Injection Volume: 20.00 ul
Run Time: 50.0 Minutes
Sample Set Name:

Acquired By: System
Date Acquired: 4/24/2007 8:10:10 PM
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Date Processed: 4/24/2007 9:04:03 PM
Processing Method: Chiral Aldol
Channel Name: WinCh2
Proc. Chnl. Descr.: PDA 254.0 nm

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Processing Method: Chiral Aldol  
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Proc. Chnt. Descr.: PDA 254.0 nm

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Page: 1 of 1
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- **Injection Volume:** 20.00 ul
- **Run Time:** 40.0 Minutes
- **Sample Set Name:**

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Injection #: 4
Injection Volume: 20.00 ul
Run Time: 40.0 Minutes
Sample Set Name: 

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Processing Method: Chiral Aldol
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Page: 1 of 1
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Injection Volume: 20.00 ul
Run Time: 40.0 Minutes

Acquired By: System
Date Acquired: 5/26/2008 5:18:07 PM
Acq. Method Set: Chiral Aldol
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Processing Method: Chiral Aldol
Channel Name: WLin Ch4
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Proc. Chnl. Descr.: PDA 235.0 nm

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**Date Processed:** 4/22/2008 12:13:38 PM

**Processing Method:** Chiral Aldol
**Channel Name:** WvlN Ch4
**Proc. Chnl. Descrip.:** PDA 254.0 nm

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(contaminated with syn 42 )
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- Peak Results

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