Part I:

The First Asymmetric Total Synthesis of Nigerone

Part II:

Catalytic, Enantioselective Claisen Rearrangements

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Dedication

To Andy, for everything
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Abstract

Part I:

The First Asymmetric Total Synthesis of Nigerone

Part II:

Catalytic, Enantioselective Claisen Rearrangements

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Part I. The first enantioselective synthesis of the chiral bisnaphthopyrone natural product nigerone and its enantiomer, ent-nigerone, has been achieved. The synthesis of nigerone highlights the asymmetric oxidative biaryl coupling with 1,5-diaza-cis-decalin copper complexes that was developed by the Kozlowski group. It was found that constrained 2-naphthols were necessary to produce the highly functionalized chiral 1,1'-binaphthols in high enantioselectivity. The key eight-step isomerization process to form the natural product proceeded with retention of the biaryl configuration. The axial configurations of bisisonigerone and nigerone were definitively established through a combination of circular dichroism (CD) measurements and quantum chemical CD calculations.
Part II. Catalytic, enantioselective Claisen rearrangements have been studied. The first of the [3,3'] sigmatropic rearrangements utilized a bisamidinium catalyst, featuring a dual hydrogen-bonding array that can coordinate a singular oxygen atom on the Claisen substrate. It was found that the dual hydrogen donor was key, as acceleration of the Claisen rearrangement was far greater than with using twice as much of a mono hydrogen bond donor.

Next, the first catalytic, enantioselective Meerwein-Eschenmoser Claisen rearrangement has been developed. Both copper(II) and palladium(II) catalysts were employed. The reaction was optimized to afford the oxindole product bearing a quaternary stereocenter at C3 in high enantiomeric excess.
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Chapter 1. Asymmetric Total Synthesis of Nigerone

1.1 Biaryls in Nature

There are a myriad of natural products that contain a biaryl bond (Figure 1.1.1).\(^1\) Not only do methodologies that are able to install the axial chirality give access to these complex molecules, but they open the door to new classes of ligands as well.\(^2\) Therefore, any methods to generate these molecules in high yields and enantioselectivities would be highly valuable to the synthetic community.

Figure 1.1.1 Biaryls in Nature

1.1 (aR)-2'-methoxyvinaxanthone

1.2 Bikoenquinone-A

1.3 Skyrin

1.4 Schizandrin

1.5 Sporandol

1.2 Nonoxidative Biaryl Couplings

Due to the lack of a universal method to create a biaryl bond in an asymmetric fashion, chemists have found other means to generate these biaryls. One such way in which the biaryl bond has been constructed stereoselectively is through the use of a chiral auxiliary. For example, Meyers and co-workers synthesized the natural product gossypol 1.9 (Scheme 1.2.1)\(^3\) through such a gambit. The tert-butyl oxazoline, was used to direct the axial chirality via an Ullmann coupling, generating the biaryl 1.8 in 81% yield, with
an 11:1 diastereomeric ratio. With the axial stereochemistry installed, the auxiliary was removed and the biaryl was further elaborated to generate gossypol.

**Scheme 1.2.1 Synthesis of Gossypol**

A different approach to asymmetric biaryl bond formation was used by Bringmann and co-workers in the first total synthesis of knipholone 1.13 (Scheme 1.2.2). A palladium-catalyzed intramolecular biaryl coupling provided the lactones 1.11a-b in 68% yield. It was found that the lactones were conformationally unstable and thus were able to interconvert. An atrop-enantioselective ring opening of 1.11a-b was then performed with enantiopure oxazaborolidine. Once cleaved, the biaryl 1.12a-b would not atropisomerize, allowing the desired (S)-enantiomer to be converted to the natural product.
1.3 Kozlowski Group Oxidative Asymmetric Biaryl Coupling Reaction

To solve the problem of synthesizing complex biaryl natural products, our group developed an oxidative asymmetric biaryl coupling reaction, using a chiral 1,5-diaza-cis-decalin copper catalyst 1.15. There are many advantages to using this methodology. The reaction proceeds under mild conditions (either at room temperature or 40 °C); therefore the reaction is tolerant of a wide variety of functional groups. This distinguishes it from other catalytic, asymmetric methods to generate chiral biaryls, such as the Kumada, Negishi, and Suzuki couplings. The low temperatures also allow one to synthesize the biaryl without fear that it would atropisomerize. The reaction is not sensitive to trace air or trace moisture, with oxygen serving as the oxidant and water as the only byproduct. There is also full control over the stereochemical outcome of the product. From fifty
cases, the \((R,R)\)-diamine catalyst has been found to yield the \((S)\)-biaryl, and the \((S,S)\)-diamine the \((R)\)-biaryl.

Substitution at the C3 position was necessary for chelation to the catalyst (Table 1.1 entry 1 versus entry 10). In addition, the chelating group also serves as an electron-withdrawing substituent, which increases the naphthalene oxidation potential and allows the biaryl coupling to proceed with high selectivity. Esters proved to be optimal, but other functionality was tolerated as well, such as ketones, phosphonates, and sulfonyls.

**Table 1.1 Scope of C3 Substitution in Biaryl Coupling**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>(R^1)</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO(_2)Me</td>
<td>((S,S))</td>
<td>85</td>
<td>93 ((R))</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CO(_2)Bn</td>
<td>((R,R))</td>
<td>79</td>
<td>90 ((S))</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CO(_2)t-Bu</td>
<td>((R,R))</td>
<td>85</td>
<td>90 ((S))</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CON(_2)Et</td>
<td>((S,S))</td>
<td>48</td>
<td>72 ((R))</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CON(CH(_2))(_4)</td>
<td>((S,S))</td>
<td>50</td>
<td>73 ((R))</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>COPh</td>
<td>((S,S))</td>
<td>88</td>
<td>89 ((R))</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OBn</td>
<td>((S,S))</td>
<td>77</td>
<td>38 ((R))</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>P(O)OMe(_2)</td>
<td>((S,S))</td>
<td>76</td>
<td>92 ((R))</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>SO(_2)C(_6)H(_4)-4-OMe</td>
<td>((S,S))</td>
<td>57</td>
<td>75 ((R))</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>((S,S))</td>
<td>81</td>
<td>16 ((S))</td>
<td></td>
</tr>
</tbody>
</table>

This method is also very tolerant of functionality at other positions (Table 1.2). Too many electron-donating groups, such as OMe, cause the reaction to proceed quickly and in high yield, however the enantioselectivities suffered, due to rapid enantiomerization (entry 1). Replacement of the OMe at C4 with an electron-withdrawing OAc (entry 2) increased the enantiomeric excess to 90%. This methodology
made it possible to couple a large number of substrates effectively, providing functionalized 1,1'-binaphthalene-2,2'-diols in high yield and enantioselectivity as shown with a few representative examples in Table 1.2.

**Table 1.2 Copper-Catalyzed Coupling of Substituted 2-Naphthols**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$R^4$</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>CMe</td>
<td>(S,S)</td>
<td>83</td>
<td>3 (S)</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>(R,R)</td>
<td>72</td>
<td>90 (S)</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>OAc</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>(S,S)</td>
<td>75</td>
<td>45 (R)</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>OAc</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>(R,R)</td>
<td>38</td>
<td>22 (S)</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>(S,S)</td>
<td>71</td>
<td>86 (R)</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>n-propyl</td>
<td>(S,S)</td>
<td>85</td>
<td>87 (R)</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>$\equiv$-TMS</td>
<td>(S,S)</td>
<td>85</td>
<td>82 (R)</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>I</td>
<td>(R,R)</td>
<td>80</td>
<td>81 (R) (99)</td>
</tr>
</tbody>
</table>

Other asymmetric catalytic oxidative couplings exist as well. Uang,\textsuperscript{10} Chen,\textsuperscript{11} and Sasai\textsuperscript{12} have all developed naphthol couplings using various vanadium catalysts. However, the naphthols coupled bore no substitution at C3, nor any electron withdrawing groups. In addition, long reaction times (up to seven days) were required. Katsuki has successfully coupled naphthol monomers bearing substitution at C3,\textsuperscript{13} however when the electron-withdrawing ester was present, they saw no reaction. Due to the necessary substitution pattern, as well as the electronics of the requisite naphthol, the copper-catalyzed asymmetric biaryl coupling reaction was chosen to synthesize the natural product nigerone (the synthesis of which will be discussed in the following sections).
1.4 Retrosynthetic Analysis

The natural product nigerone \(1.19\) (Figure 1.4.1) is a yellow pigment that was isolated along with isonigerone \(1.20\), from the fungus *Aspergillus Niger*.\(^{14}\) While it has never been synthesized previously, the isolation paper found that nigerone had a stable biaryl core, such that after refluxing in acetic acid for 3 hours, no isomerization of the axial stereochemistry was observed.\(^{14}\) Although nigerone was found to have moderate anti-tumor\(^{15}\) and anti-bacterial activity,\(^{16}\) the molecule was chosen to be synthesized to demonstrate the utility of the Kozlowski group’s oxidative asymmetric biaryl coupling reaction (Table 1.2).

Figure 1.4.1 Natural Products Nigerone and Isonigerone

![Figure 1.4.1](image)

The retrosynthesis of nigerone consisted of a formal Claisen condensation using the enolate of acetone \(1.22\), to generate the pyrone ring (Scheme 1.4.1). The bisnaphthol \(1.21\) was envisioned to stem from the functionalized monomer \(1.23\). The monomer contained substitution at both the C4 and C5 positions, corresponding to the substitution pattern of the natural product.
1.5 Substitution Effects on Biaryl Coupling

This particular substitution pattern was a concern due to previous examples of coupling highly functionalized monomers (Figure 1.5.1).² Having substitution at the C4, C5, and C6 positions produced a steric gearing effect that caused a non-optimal coordination to the copper catalyst, as shown with 1.25, which in turn, led to the poor conversion and low selectivity of 1.24. However, when substitution at C5 was removed, the ester at C3 was able to bind to the copper, giving the biaryl 1.26 in 90% ee.

While substitution was needed at both the C4 and C5 positions to synthesize nigerone, there was no functionalization at the C6 (Scheme 1.4.1). It was hoped that the lack of substitution at this position would be sufficient to relieve the steric crowding toward the coordinating ester. The monomer 1.27 was synthesized, and subjected to the biaryl coupling conditions to generate 1.29 (Scheme 1.5.1). While the enantioselectivity
did improve (from 27 to 45% ee), it was still not sufficient to continue on the route to nigerone.  

Scheme 1.5.1 Coupling of C4, C5 monomer

Our theory of steric inhibition to chelation was tested by the use of a constrained monomer. The use of a cyclic protecting group should allow the C3 ester to optimally coordinate to the copper catalyst. Initial attempts to constrain the substitution at C4 and C5 were unsuccessful (Figure 1.5.2), as the monomers were either unstable (dioxenone 1.30), or were labile during the biaryl coupling (1.31-1.32).  

Figure 1.5.2 Initial Constrained Monomers

Gratifyingly, a methylene bridge between C4 and C5 proved sufficiently stable to the oxidative biaryl coupling (Scheme 1.5.2). The naphthalene diol 1.33 was treated with boron tribromide to yield the triol 1.34 in 93% yield, which was then protected using pivaloyl chloride, to provide the C4 naphthol. This material was then converted to the diol by removal of the C5 pivalate group, using potassium carbonate in methanol. With both the C4 and C5 OH’s revealed, diiodomethane was employed to install the methylene bridge to give 1.35 in 24% yield over three steps. Next, the pivalate group at C2 was
removed to afford the free naphthol, followed by the oxidative asymmetric biaryl coupling. With the substitution at C4 and C5 sufficiently constrained, binaphthol 1.36 was formed in 96% conversion and 66% ee.\textsuperscript{18}

**Scheme 1.5.2 Installation and Coupling of Methylene Bridge Substrate 1.35**

As shown in Figure 1.5.3, the substitution pattern of the requisite monomer had a dramatic effect on the enantioselectivity. The addition or removal of just one methoxy group can vary the enantiomeric excess by 63%. Even so, the enantioselectivity was still not sufficiently high to proceed along the planned route to the natural product. Therefore, a revised route to nigerone was needed.
Figure 1.5.3 Enantioselectivities of Various Binaphthols

1.6 Revised Route to Nigerone
The monomers flavasperone 1.37 and heminigerone 1.38 were isolated along with the natural product (Figure 1.6.1). Therefore it is believed a phenol oxidative coupling of the monomers leads to the dimeric pigments.\textsuperscript{14}

Figure 1.6.1 Isolated Monomers

It was speculated that the constrained naphthopyrone would couple with high selectivity under our asymmetric biaryl coupling conditions.\textsuperscript{19} Flavasperone was treated with the copper-diamine catalyst 1.15, and rewardingly bisisonigerone 1.40 was generated in 60\% yield and 80\% ee (Scheme 1.6.1). Unfortunately, the reaction proceeded sluggishly, thus a full equivalent of the copper complex was necessary.
Scheme 1.6.1 Biaryl Coupling of Flavasperone to Generate Bisisonigerone

With bisisonigerone in hand, the final step of the synthesis was investigated. A base-mediated isomerization to generate nigerone from bisisonigerone was envisioned. To determine whether an isomerization would be feasible, we first needed to know if the product was more stable than the starting material. Pleasingly, energy calculations showed that nigerone 1.19 was the more stable conformer, due to stronger hydrogen bonds in 1.19 relative to 1.40 (Figure 1.6.2).

Figure 1.6.2 Energy Values for Bisisonigerone and Nigerone

We next needed to ascertain if there was a pathway for the isomerization that would lead to nigerone. We envisioned an eight-step isomerization from bisisonigerone to nigerone (Scheme 1.6.2). A hydroxyl anion could undergo a conjugate addition to the α,β-unsaturated carbonyl, followed by a retro-conjugate addition to open the pyrone ring.
giving 1.42. Rotation about the C3 bond puts the OH at C2 in position to add to the α,β-unsaturated carbonyl, where a second retro-conjugate addition would close the pyrone ring to give isonigerone 1.20. Duplication of this pathway on the bottom half of the molecule would furnish the natural product.

Scheme 1.6.2 Eight-Step Isomerization to Nigerone

1.7 Comparison of Synthetic Nigerone to Isolated Nigerone

With (S)-nigerone in hand, the optical rotation was determined and compared to the value in the isolation paper. At higher concentrations, the value was of the same sign as in the isolation paper, but the magnitude was vastly different (Figure 1.7.1). At lower concentrations, the optical rotation of synthetic nigerone reversed signs, with the magnitude more closely matching the reported value.
To clear up the confusion about the absolute stereochemical assignment of nigerone, the (R)-enantiomer of nigerone was synthesized (Scheme 1.7.1). Starting from commercially available 3,5-dimethoxybenzoic acid 1.43, a reduction/oxidation sequence furnished the carboxylic acid 1.44 in 60% yield over 4 steps. The acid was then converted to the acid chloride, followed by addition of the dimethylmalonate anion to generate the diester, followed by a Friedel-Crafts cyclization to produce the diol 1.45. Protection of the newly generated diol with acetic anhydride, and subsequent selective deprotection of the C2 OH afforded the free naphthol 1.27 in 62% yield over 5 steps. Naphthol 1.27 was converted to the ether using MOMCl, followed by addition of the dimethyl anion, to generate the keto-sulfoxide 1.46. A cyclization was performed using acetaldehyde, and then the MOM ether was cleaved using BCl3 to produce flavasperone in 57% yield over 4 steps. With flavasperone in hand, the oxidative asymmetric biaryl coupling reaction was performed, creating bisisonigerone in 60% yield and 80% ee, after stirring at 40 °C over 6 days. Bisisonigerone was then isomerized to nigerone under basic conditions. After stirring overnight at 70 °C, the natural product was obtained in 50% yield and 77% ee. However, after one trituration using 50% ethyl acetate/hexanes, the enantiomeric excess was increased to 90%.
With both enantiomers of nigerone in hand, the optical rotations of synthetic nigerone were compared to the isolated natural product (Figure 1.7.2). The optical rotations for synthetic (S)-nigerone and synthetic (R)-nigerone were of equal magnitude and opposite signs, indicating they are enantiomers of one another. In addition, the sign for (R)-nigerone matches that of the reported value, signifying that isolated nigerone is the (R)-configuration.

**Figure 1.7.2 Comparison of Synthetic (S)- and (R)-Nigerone to Isolated Nigerone**

The absolute configurations of bisisonigerone (1.40) and nigerone (1.19) had been assigned based upon the highly stereoregular nature of the copper catalyzed coupling.
reaction. However, the CD spectrum of the synthesized (S)-nigerone did not match the spectrum of the natural product.\textsuperscript{14} Computational calculations were used to independently confirm the stereochemical assignments.

Originally, the isolated natural product’s CD spectrum was compared to other bisnaphthopyrones, which led (erroneously) to nigerone being assigned the (S) configuration.\textsuperscript{14} Synthesis of (R)-nigerone provided a material that matched the natural product CD spectrum. The configurations were further established by means of quantum chemical CD calculations using the exciton chirality method.\textsuperscript{20} The calculated CD spectra for (R)-nigerone and (R)-bisisonigerone matched very well with the experimental CD curves (Figure 1.7.3) whereas those of the (S)-enantiomers did not,\textsuperscript{18} allowing the absolute configuration to be assigned as (R).

\textbf{Figure 1.7.3 CD Spectra of Isolated and Synthetic Nigerone}
1.8 Conclusion

In conclusion, the first total synthesis of nigerone (1.19) has been achieved, demonstrating the utility of the catalytic, asymmetric biaryl coupling reaction developed by the Kozlowski group. Nigerone was synthesized in 15 steps and 6% overall yield.
1.9 Experimental Section

General Synthetic Procedures. Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N₂ in dried glassware. When necessary, solvents and reagents were dried prior to use. Toluene and CH₂Cl₂ were de-oxygenated by purging with N₂ and then dried by passing through activated alumina. THF was distilled from sodium benzophenone ketyl. CH₃CN, TMEDA, and hexanes were distilled from CaH₂. Benzene was distilled from sodium. Solvents for the preparation of the catalyst complexes and for the oxidative coupling reactions were usually used without purification although acid-free halogenated solvents are required (if necessary, trace acid can be removed by filtering through basic Al₂O₃). Enantiomerically pure diaza-cis-decalin was prepared as previously described. The Cu(TMEDA)Cl(OH) catalyst was prepared and used in the oxidative biaryl coupling reactions to prepare the racemic samples of the biaryl products.

Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 60-F plates. Visualization was accomplished with UV light. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh).

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC), performed on a Waters 600 HPLC with UV detection at 254 nm. An analytical Chiralpak AD column (0.46 cm x 25 cm) from Daicel was used. ¹H NMR spectra were recorded on Bruker AM-500 (500 MHz), AM-360 (360 MHz), AM-250 (250 MHz), or AM-200 (200 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance (CDCl₃ 7.26 ppm).
Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Decoupled $^{13}$C NMR spectra were recorded on a Bruker AM-500 (125 MHz) spectrometer. IR spectra were taken on a Perkin-Elmer FT-IR spectrometer using a thin film on NaCl plates or a CHCl$_3$ solution. Melting points were obtained on Thomas Scientific Unimelt apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 with a sodium lamp and are reported as follows $[\alpha]_D^{23}$ (c g/100 mL, solvent). CD spectra were recorded on a Jasco J-720 spectrophotometer equipped with a NESLABR TE-11 variable temperature circulator. CD measurements were performed at 20 °C using a 1 mL quartz cuvette of 0.1 cm path length and the following parameters: scanned optical range, 240-400 nm; scan band width, 1 nm; scanning speed, 100 nm/min, response, 1 sec; accumulations, 5. Data were processed using Jasco Spectra Manager V. 1.51.

Methyl 1,3,8-trihydroxy-6-methoxynaphthalene-2-carboxylate (1.34): A solution of the naphthalene diol (see p 22 for procedure) 1.33 (0.050 g, 0.179 mmol) in CH$_2$Cl$_2$ was cooled to 0 °C, at which time a 1 M BBr$_3$ solution in CH$_2$Cl$_2$ (0.358 mL) was added. After 1 h, water was added and the layers separated. The aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated to afford the naphthalenetriol 1.34 (0.044 g) in 93% as a yellow solid 0.044 g (93%); mp 180-185 °C, decomposition; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 11.10$ (bs, 1H), 9.42 (s, 1H), 8.80 (bs, 1H), 6.61 (s, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 6.35 (d, $J = 2.2$ Hz, 1H).
Hz, 1H), 4.12 (s, 3H), 3.87 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 171.2, 163.2, 158.4, 153.2, 141.4, 104.9, 102.8, 101.5, 99.8, 97.7, 94.7, 55.3, 53.1; IR (film): $\nu$ = 3474, 3405, 3281, 1660, 1621, 1517 cm$^{-1}$; HR-MS (ES): $m/z$ = 287.0535, calcd for C$_{13}$H$_{12}$O$_6$Na [M+Na]$^+$: 287.0532.

![Methyl 8-methoxy-5-(pivaloyloxy)naphtho[1,8-de][1,3]dioxine-4-carboxylate (1.35):](image)

Methyl 8-methoxy-5-(pivaloyloxy)naphtho[1,8-de][1,3]dioxine-4-carboxylate (1.35): A solution of naphthalenetriol 1.34 (0.020 g, 0.075 mmol) in CH$_2$Cl$_2$ (500 µL) was cooled to 0 °C. Trimethylacetyl chloride was added (26 µL in 50 µL of CH$_2$Cl$_2$) followed by triethylamine (29 µL in 50 µL of CH$_2$Cl$_2$). After 30 min, the same portions of trimethylacetyl chloride and triethylamine were added again. After a further 1 h at 0 °C, 1 M HCl was added and the mixture was extracted with CH$_2$Cl$_2$. The organic layers were combined, dried with Na$_2$SO$_4$, and concentrated. The bispivaloyl product was obtained as a yellow solid (0.023 g) in 70% yield.

A 0 °C solution of bispivalate (0.020 g, 0.046 mmol) in CH$_2$Cl$_2$ (500 µL) was added to a 0 °C solution of K$_2$CO$_3$ (0.006 g) in MeOH (300 µL). After 1 h the reaction mixture was allowed to warm to room temperature. After 30 min, 1 M HCl was added and the reaction mixture was extracted with CH$_2$Cl$_2$. The organic layers were combined, dried with Na$_2$SO$_4$, and concentrated. The monopivaloyl product was obtained as a yellow solid (0.016 g) in 100% yield.
To a solution of the above monopivaloyl product (0.015 g, 0.043 mmol) in dimethylformamide (400 μL) CH₂I₂ (30 μL) was added, followed by K₂CO₃ (0.029 g). The resulting reaction mixture was heated to 60 °C. After 8 h, 1 M HCl was added and the mixture was extracted with EtOAc. The organic layers were combined, dried with Na₂SO₄, and concentrated. The residue was chromatographed (25% EtOAc/hexanes) to afford 1.35 as a yellow solid (0.044 g) in 34% yield: mp 133-135 °C; ¹H NMR (500 MHz, CDCl₃): δ = 7.05 (s, 1H), 6.76 (d, J = 1.7 Hz, 1H), 6.61 (d, J = 1.6 Hz, 1H), 5.58 (s, 2H), 3.89 (s, 6H), 1.35 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ = 176.7, 164.1, 161.1, 151.7, 150.6, 147.7, 136.3, 112.2, 108.2, 107.3, 101.3, 100.1, 91.2, 55.6, 52.3, 39.2, 27.1; IR (film) 2976, 2937, 1752, 1725, 1640, 1594, 1467 cm⁻¹; HRMS (Cl): m/z = 360.1202, calcd for C₁₉H₂₀O₇ [M]+: 360.1209.

(R)-(−)-Dimethyl-5,5’-dihydroxy-8,8’-dimethoxy-[6,6’]bi[naptho[1,8-de][1,3]dioxinyl]-4,4’-dicarboxylate (1.36): A solution of 1.35 (0.024 g, 0.067 mmol) in THF/MeOH (700 μL/200 μL) at 0 °C was treated with a solution of NaOMe/MeOH (140 μL, 2.5 M). After slowly warming to ambient temperature and then stirring 30 min, the reaction was quenched with 1 M HCl. After extracting with EtOAc, the organic layers were combined, dried over Na₂SO₄, and concentrated. The residue was chromatographed (15% EtOAc/hexanes) to afford the free naphthol as a yellow solid; yield: 0.014 g (78%).
To a solution of naphthol (0.002 g, 0.007 mmol) in CH$_2$Cl$_2$ (200 µL) was added (S,S)-1.28 (0.003 g, 0.0007 mmol). The mixture was sonicated and allowed to stir at room temperature under air. After 4 h, 1 M HCl was added, and the mixture was extracted with CH$_2$Cl$_2$. The organic layers were combined, dried over Na$_2$SO$_4$, and concentrated, to afford the product 1.36 in 96% conversion (measured by $^1$H NMR and HPLC) and 66% ee (measured by HPLC): CSP HPLC (Chiralpak ODH, 1.0 mL min$^{-1}$, hexanes:i-PrOH = 92:8): $t_R$(SM) = 15.5 min, $t_R$(S-1.36) = 43.5 min, $t_R$(R-1.36) = 56.2 min; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 11.40 (s, 2H), 6.41 (d, $J$=2.2, 2H), 6.11 (d, $J$ = 2.2, 2H), 5.70 (d, $J$ = 5.0, 2H), 5.62 (d, $J$ = 5.0, 2H), 3.99 (s, 6H), 3.59 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 170.1, 162.2, 156.1, 154.1, 152.6, 138.8, 108.8, 105.1, 98.6, 98.1, 97.6, 90.8, 55.4, 52.5; IR (film) 3053, 2926, 2856, 1664, 1633, 1586, 1444 cm$^{-1}$; HRMS (ES): $m/z$ = 573.0999, calcd for C$_{28}$H$_{22}$O$_{12}$Na [M+Na]$^+$: 573.1100.

![2-(3,5-Dimethoxyphenyl) acetic acid (1.44) structure](image)

2-(3,5-Dimethoxyphenyl) acetic acid (1.44): A solution of 3,5-dimethoxy benzoic acid 1.43 (5.6 g, 30.7 mmol) in THF (250 mL) was cooled to 0 °C. LiAlH$_4$ (2.33 g, 61.4 mmol) was slowly added. After 3 h at room temperature, a saturated solution of Na/K tartrate (50 mL) was added. After 1 h at room temperature, the layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over MgSO$_4$, filtered, and concentrated. The benzylic alcohol (4.8 g) was obtained in quantitative yield as a white solid. The $^1$H NMR spectrum matches that of the reported compound.$^{24}$
A solution of the benzylic alcohol from above (4.8 g, 30.7 mmol) in CH₂Cl₂, was cooled to 0 °C, at which time PBr₃ (3.07 mL) was added. After 1 h at room temperature, NaHCO₃ was added dropwise and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated to afford the benzylic bromide (6.2 g) in 94% yield as an oil. The ¹H NMR spectrum matches that of the reported compound.²⁵

To a solution of the benzylic bromide from above (6.2 g, 26.8 mmol) in DMF, was added NaCN. After 1 h water was added and the aqueous layer was extracted with EtOAc. The organic layers were washed three times with water and brine, dried over MgSO₄, and concentrated to afford the benzylic nitrile (4.2 g) in 89% yield as a white solid. The ¹H NMR spectrum matches that of the reported compound.²⁶

A concentrated solution of HCl was added to the benzylic nitrile from above (4.2 g, 26.8 mmol). After 2.5 h at reflux, water (100 mL) was added and the reaction was cooled to room temperature. The aqueous phase was extracted three times with CH₂Cl₂, dried over MgSO₄, filtered and concentrated. Crystallization from EtOAc/hexanes gave phenyl acetic acid 1.44 (4.2 g) in 90% yield as white crystals. The ¹H NMR spectrum matches that of the reported compound.²⁷

Methyl 1,3-dihydroxy-6,8-dimethoxynaphthalene-2-carboxylate (1.33): To a solution of phenyl acetic acid 1.44 (0.429 g, 2.19 mmol) in CH₂Cl₂, SOCl₂ (0.319 mL) was added. After 1 h at reflux, the solution was concentrated. To a suspension of NaH (95%, 0.16 g, 6.56 mmol) in THF (13 mL) under Ar was slowly added dimethyl malonate (73 µL, 6.38
mmol). After refluxing under Ar for 1 h, the dimethyl malonate solution was cooled to room temperature and a solution of the above acid chloride in THF was added. After stirring for 17 h at room temperature 1 M HCl and EtOAc were added. The layers were separated and the aqueous layer was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was chromatographed (SiO₂; 85% Hexanes/EtOAc) to afford the intermediate tricarbonyl (0.650g) as a clear oil.

To a solution of the intermediate tricarbonyl in methane sulfonic acid (10 mL), was added P₂O₅ (0.600 g). After 3 h at room temperature, ice was added and the resulting precipitate was filtered and dried in an oven overnight to yield naphthalene diol 1.33 (0.500 g) in 82% yield as a grey solid: mp 162-164 °C; ¹H NMR (500 MHz, CDCl₃) δ 11.13 (s, 1H), 10.70 (s, 1H), 6.64 (s, 1H), 6.48 (d, J = 2.2 Hz, 1H), 6.28 (d, J = 2.2 Hz, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.89 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3, 160.7 (2), 158.8, 157.7, 141.1, 105.1, 102.0, 97.9, 97.4, 95.8, 56.1, 55.3, 52.4; IR (film) 3443, 3304, 2953, 1664, 1594 cm⁻¹; HRMS (ES) calcd for C₁₄H₁₅O₆ (MH⁺) 279.0868, found 279.0880. This sequence matches that of another synthesis but no experimental procedures or characterizations were reported.

**Methyl-1-acetoxy-3-hydroxy-6,8-dimethoxynapthalene-2-carboxylate (1.27):** To a round-bottomed flask containing the naphthalene diol 1.33 (0.50 g, 1.80 mmol), Ac₂O (2.54 mL) and pyridine (2.50 mL) were added. After 4 h at room temperature, The solution was poured over ice to quench any excess Ac₂O. EtOAc was added and the
organic layer was subsequently washed with 1M HCl, water, brine, dried over MgSO₄, filtered, and concentrated. Methanol was added to this material along with sufficient 1M NaOMe solution until TLC analysis indicated no remaining diacetate compound. 1 M HCl was subsequently added and the aqueous layer was extracted three times with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was chromatographed (SiO₂; 70% hexanes/EtOAc) to afford naphthol 1.27 (0.44 g) in 76% yield as a yellow solid: mp 168-169 °C; ¹H NMR (500 MHz, CDCl₃) δ 10.83 (s, 1H), 7.06 (s, 1H), 6.52 (d, J = 2.2 Hz, 1H), 6.29 (d, J = 2.2 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 2.37 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.0, 169.5, 161.1, 158.1, 157.4, 149.9, 141.1, 111.2, 109.3, 107.3, 97.8, 97.1, 56.1, 55.4, 52.9, 20.9; IR (film) 3134, 3007, 2957, 2845, 1760, 1671, 1629, 1571 cm⁻¹; HRMS (ES) calcd for C₁₆H₁₆O₇Na (MNa⁺) 343.0794, found (MNa⁺) 343.0797.

1,3-Dimethoxy-6-(methoxymethoxy)-7-(2-(methylsulfinyl)acetyl)naphthalene-8-yl-acetate (1.46): A solution of 1.27 (0.250 g, 0.780 mmol) in DMF (4 mL) was cooled to 0 °C at which time NaH (0.028 g, 1.17 mmol) was added. After 20 min, MOMCl (0.099 mL) was added in one portion. After 2 h at room temperature, EtOAc and 1 M HCl were added. The organic layer was washed three times with water and brine to remove DMF. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was chromatographed (SiO₂; 70% hexanes/EtOAc) to afford the MOM-protected naphthol (0.270 g) in 94% yield as a white powder: mp 140-141 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.22 (s, 1H), 6.65 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 5.28 (s, 2H), 3.92 (s, 3H),
3.87 (s, 3H), 3.86 (s, 3H), 3.51 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.3, 165.8, 159.9, 157.3, 152.5, 145.6, 138.8, 116.8, 110.4, 107.9, 98.8, 98.6, 95.1, 56.6, 56.3, 55.6, 52.7, 20.9; IR (film) 3067, 2989, 1772, 1714, 1629, 1586 cm$^{-1}$; HRMS (ES) calcd for C$_{18}$H$_{20}$O$_8$Na (MNa$^+$) 364.1158, found 364.1164.

Benzene (10 mL) and DMSO (3.1 mL) were added to a round bottom flask containing NaH (0.296 g, 12.33 mmol). After 1 h at reflux, the reaction mixture was allowed to cool to room temperature and a solution of the MOM-protected naphthol (0.642 g, 1.76 mmol) in benzene was added. After 1 h at 45 °C, the solution was concentrated at which time water and acetic acid were added dropwise until a precipitate formed. The precipitate was collected by filtration and dried to afford 1.46 (0.600 g) in 96% yield as a yellow powder: mp 145-146 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 14.05 (s, 1H), 6.73 (s, 1H), 6.54 (d, $J = 2.2$ Hz, 1H), 6.36 (d, $J = 2.2$ Hz, 1H), 5.35 (dd, $J = 9.7$, $J = 6.8$, 2H), 4.84 (d, $J = 14$ Hz, 1H), 4.30 (d, $J = 14$ Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.56 (s, 3H), 2.77 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 194.6, 165.3, 162.3, 160.7, 154.0, 141.6, 108.1, 107.3, 100.2, 99.1, 97.2, 94.8, 68.6, 56.8, 56.2, 55.4, 39.9; IR (film) 3003, 2968, 3397, 1625, 1583 cm$^{-1}$; HRMS (ES) calcd for C$_{17}$H$_{20}$O$_7$SNa (MNa$^+$) 368.0930, found 368.0937.

**Flavasperone (1.37):** To a solution of 1.46 (0.192 g, 0.523 mmol) in toluene (10 mL), one drop of piperdine was added. The solution was warmed to 45 °C and newly purchased acetaldehyde (0.375 mL) was added. After 3 h at reflux, the mixture was
allowed to cool to room temperature upon which time EtOAc and 1 M HCl were added. The organic layer was washed with water and brine. To the unpurified product was added CH₂Cl₂ (3.80 mL) and the reaction mixture was cooled to −78 °C. The cooled solution was treated with BCl₃ (0.476 mL, 3.00 mmol) and was allowed to stir for 20 minutes at which time NaHCO₃ was added. The reaction mixture was then allowed to warm to room temperature. The organic layer was washed with water and brine. The residue was chromatographed (SiO₂; 4% EtOAc/CH₂Cl₂) to afford 1.37 (0.036 g) in 65% yield as a yellow solid: (500 MHz, CDCl₃) δ 12.83 (s, 1H), 6.89 (s, 1H), 6.60 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 2.2 Hz, 1H), 6.29 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 2.51 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 182.9, 166.4, 161.7, 159.6, 155.9, 154.7, 140.6, 110.6, 110.4, 108.6, 105.2, 97.0, 96.8, 56.0, 55.2, 20.5. ¹H NMR matches that of reported compound.²⁹

(R)-Bisisonigerone (1.40): To a solution of 1.37 (0.030 g, 0.010 mmol) in 1:1 CH₃CN/CH₂Cl₂ (3 mL), CuI-(S,S)-1,5-diaza-cw decalin catalyst 1.28 (0.036 g, 0.010 mmol) was added. After 6 d at 40 °C, 1 M HCl was added and the aqueous layer was extracted three times with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was chromatographed (SiO₂; 60% hexanes/EtOAc) to afford 1.40 (0.018 g) in 60% yield along with 1.37 (0.009 g) as a
**yellow solid: mp 180-185 °C decomposition; [$\alpha$]$^D_2$ +72.58 (c 0.25, 80% ee, CHCl$_3$);**

$^1$H NMR (500 MHz, CDCl$_3$)  $\delta$ 13.19 (s, 1H), 6.45 (d, $J = 2.2$ Hz, 1H), 6.33 (s, 1H), 6.21 (d, $J = 2.2$ Hz, 1H), 4.02 (s, 3H), 3.55 (s, 3H), 2.56 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$)  $\delta$ 182.9, 166.4, 161.7, 159.7, 156.1, 154.6, 140.5, 110.5, 110.3, 108.6, 104.3, 96.9, 96.7, 56.0, 55.2, 29.7, 20.5; IR (film) 3366, 3003, 2926, 1656, 1610, 1579, 1517 cm$^{-1}$; HRMS (ES) calcd for C$_{32}$H$_{26}$O$_{10}$Na (MNa$^+$) 571.1604, found 571.1624; CSP HPLC (Chiralpak AD, 1.0 mL/min, 90:10 hexanes:i-PrOH): $t_R(S) = 40.6$ min, $t_R(R) = 109.9$ min.

**(R)-Nigerone (1.19):** A solution of 1.40 (0.026 g) in MeOH (22 mL) was heated with satd aq NaOH solution (0.22 mL) and was placed in a 70 °C oil bath. After 18 h, 1M HCl was added and the aqueous layer was extracted three times with CH$_2$Cl$_2$. The organic layers were combined, dried over MgSO$_4$, filtered, and concentrated. The residue was chromatographed (SiO$_2$; 60% hexanes/EtOAc) to afford 1.19 (0.013 g) in 50% yield as yellow solid: mp > 200 °C decomposition; [$\alpha$]$^D_2$ -114.0 (c 0.10, 70% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$)  $\delta$ 15.31 (s, 1H), 6.44 (d, $J = 7$ Hz, 2H), 6.07 (d, $J = 7$ Hz, 1H), 6.00 (s, 1H), 4.06 (s, 3H), 3.49 (s, 3H), 2.03 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$)  $\delta$ 184.5, 167.6, 163.1, 161.9, 161.2, 151.3, 140.7, 108.8, 107.3 105.5, 104.3, 97.2, 96.5, 56.2, 55.2, 20.6; IR (film) 3377, 2930, 2853, 1652, 1610, 1586, 1409; HRMS (ES) calcd for C$_{32}$H$_{26}$O$_{10}$Na (MNa$^+$) 571.1604, found 571.1624; CSP HPLC (Chiralpak AD, 1.0 mL/min, 90:10 hexanes:i-PrOH): $t_R(S) = 31.7$ min, $t_R(R) = 38.7$ min.
References:


(19) Flavasperone (1.37) has been synthesized previously by a different route: Bycroft, B. W.; Roberts, J. C. “Mycological Chemistry. XIV. Synthesis of Flavasperone” J. Chem. Soc. 1963, 4868-4872.


Chapter 2. Design and Use of a Bisamidinium Catalyst for Monodentate Substrates.

2.1 Background

The Claisen Rearrangement was first discovered in 1912 by Ludwig von Claisen, who observed “the thermal isomerization of an allyl vinyl ether 2.1 or of its nitrogen or sulfur containing analogue derivatives to afford a bifunctionalized molecule 2.2” (Scheme 2.1.1).\(^1\) This first work described the rearrangement of allyl phenyl ether 2.3 to produce the C-allyl phenol 2.4.

![Scheme 2.1.1 General Claisen Rearrangement](Image)

However, it was another twenty-five years before it was discovered that the rearrangement was applicable to aliphatic substrates through work done by Bergmann and Corte in 1935,\(^2\) and Lauer and Kilburn in 1937 (Scheme 2.1.2).\(^3\)

![Scheme 2.1.2 Aliphatic Claisen Rearrangement](Image)
2.2 Diastereoselective Claisen Rearrangements

As the Claisen rearrangement is known to proceed via a chair-like transition state (2.12),\(^4\) the stereochemistry of the product is determined by the stereochemistry of the allyl vinyl ether, as well as by the geometry of the original double bonds.\(^5\)

![Diastereoselective Claisen Rearrangement Diagram](image)

The use of enantiopure allyl vinyl ether 2.14 allows one to transfer the stereochemistry to the rearranged product, which in the case shown below affords phenol 2.15 with excellent enantioselectivity (Equation 2.1).\(^6\) The highly ordered cyclic transition state results in the observed high selectivity.

**Equation 2.1 Diastereoselective Claisen Rearrangement**

![Equation 2.1 Diagram](image)

2.3 Enantioselective Claisen Rearrangements

As Lewis acids were well known to accelerate the Claisen rearrangement (see Equation 2.1), the first successful, enantioselective Claisen rearrangements employed chiral Lewis acids. The first such example was reported in 1990.\(^7\) In this seminal paper, Yamamoto reported the use of a modified chiral aluminum-BINOL catalyst to afford the rearranged product 2.17 in up to 91% ee (Scheme 2.3.1). He found that at least one equivalent of catalyst was necessary due to the strong binding of the Lewis acidic aluminum to the aldehyde product.
Scheme 2.3.1 Yamamoto's Asymmetric Claisen Rearrangement

![Scheme 2.3.1 Yamamoto's Asymmetric Claisen Rearrangement](image)

In 1991, Corey reported the first enantioselective Ireland-Claisen rearrangement (Scheme 2.3.2). The use of an amine base in the presence of a chiral boron reagent afforded either 2.19a or 2.19b, which rearranged to the carboxylic acid 2.20. The reaction was optimized such that both the E and Z enolates could be accessed in geometrically pure form, which was necessary to produce the carboxylic acid product in high selectivity (97% ee).

![Scheme 2.3.2 Corey's Asymmetric Ireland-Claisen Rearrangement](image)

Both Yamamoto and Corey's work showed how successful Lewis acids are at creating an asymmetric environment to afford optically pure products. Yet these pioneering examples required a stoichiometric, or even excess amount of catalyst. Further research was needed to solve the important problem of turnover.

### 2.4 Catalytic, Enantioselective Claisen Rearrangements

While the Claisen rearrangement has enjoyed a long and rich history due to its widespread application in the synthesis of natural products, the development of a
general, catalytic, enantioselective variant has remained a challenge for synthetic chemists. Examples of catalytic, asymmetric Claisen rearrangements have suffered from low enantioselectivities, as well as a limitation of substrate scope. Seminal work done by Hiersemann and coworkers showed that 2-ester substituted allyl vinyl ether 2.21 rearranged to keto-ester 2.23 in excellent yield and selectivity, employing 5 mol% of the copper bis(oxazoline) catalyst (Scheme 2.4.1).\(^\text{10}\) The ester at C2 was necessary to bind the catalyst via a two-point binding mode with the copper catalyst (2.22).

Scheme 2.4.1 Hiersemann's Claisen Rearrangement

\[
\begin{array}{c}
\text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \\
\text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \\
\text{Me} \quad \text{Me} \\
\end{array}
\xrightarrow{\text{5 mol\%}}
\begin{array}{c}
\text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \\
\text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \\
\text{Me} \quad \text{Me} \\
\end{array}
\quad 99\% \text{ ee}
\]

Mikami and co-workers developed an asymmetric Claisen rearrangement using monodentate substrate 2.24 and 5 mol% of a palladium-BINAM catalyst to provide cyclohexanones 2.25a and 2.25b (Scheme 2.4.2).\(^\text{11}\) Unlike the asymmetric Ireland-Claisen (Scheme 2.3.2), the starting material was not geometrically pure; as a result, only moderate selectivity was observed. However, Mikami was able to achieve turnover in the rearrangement, employing 5 mol% of the catalyst.

Scheme 2.4.2 Mikami's Claisen Rearrangement

\[
\begin{array}{c}
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\end{array}
\xrightarrow{\text{Pd(OAc)}_2, \text{5 mol\%}, 60^\circ \text{C}}
\begin{array}{c}
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\end{array}
\quad 81\% \text{ ee}
\]

36
2.5 Hydrogen-Bonding Catalysts

The examples of enantioselective Claisen rearrangements, both stoichiometric and catalytic, employ Lewis acids as catalysts. However, there are limitations to this mode of activation, such as turnover (Scheme 2.3.1 and Scheme 2.3.2), or the need for a bidentate substrate (Scheme 2.4.1). Therefore, a different mode of catalysis was studied in order to develop a general catalytic, enantioselective Claisen rearrangement.

Unlike the highly developed field of Lewis acid catalysis, organocatalysis is undergoing a resurgence; only recently has the efficiency, selectivity, and scope of these catalysts been appreciated.\textsuperscript{12} Similarly, the field of hydrogen bond accelerated catalysis, a subset of organocatalysis, has also seen an explosion in recent years.\textsuperscript{13} Hydrogen bonding serves to not only catalyze a reaction; it can also be used to introduce stereochemistry. There are numerous instances reported of reactions utilizing chiral hydrogen bonding catalysts, with several examples shown below (Scheme 2.5.1).\textsuperscript{14,15,16}

Scheme 2.5.1 Examples of Enantioselective Hydrogen Bond Catalysis

<table>
<thead>
<tr>
<th>Strecker</th>
<th>Michael</th>
<th>Aza-Henry</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Strecker Reaction" /></td>
<td><img src="image" alt="Michael Reaction" /></td>
<td><img src="image" alt="Aza-Henry Reaction" /></td>
</tr>
</tbody>
</table>

2.6 Hydrogen Bond Acceleration of the Claisen Rearrangement

Historically, turnover has been problematic when Lewis acid catalysts are used, as illustrated in Scheme 2.3.1 and Scheme 2.3.2. It was postulated that the use of hydrogen
bond donors as catalysts could solve this important problem. This idea was supported by earlier work done by Curran in which the rearrangement of an allyl vinyl ether, 2.34, bearing a methoxy group at C6 was accelerated using ureas and thioureas as catalysts (Scheme 2.6.1). A five-fold rate increase was observed when 40 mol% of the urea catalyst was used, though elevated temperatures were required.

**Scheme 2.6.1 Curran's H-Bond Accelerated Claisen Rearrangement**

![Scheme 2.6.1](image)

The hypothesis that hydrogen bond donors could accelerate the Claisen rearrangement was inspired by calculations from Jørgensen and Hillier. Their results showed that water could serve as a dual hydrogen bond donor to the sp³ oxygen with an OHN bond angle of approximately 170° (Figure 2.6.1a). Yet MM2* calculations of 2.38 revealed that the coordination of the urea to the allyl vinyl ether was not optimal, resulting in an OHN bond angle of only 130° (Scheme 2.6.1b). It was theorized that the rate of the Claisen rearrangement could be accelerated even further if a catalyst was designed to provide the optimal 170-180° OHN bond angle.

**Figure 2.6.1 Hydrogen Bonding Structures in Claisen Rearrangements**

- **a) Jørgensen & Hillier**
  ![Structure](image)
  
  O-H bond distance = 2.0 Å
  O-...H-N bond angle = -170°

- **b) MM2* Calculations**
  ![Structure](image)
  
  O-H bond distance = 2.2 Å
  O-...H-N bond angle = 130°

- **c) Hiersemann & Strassner**
  ![Structure](image)
  
  O-H bond distance = 1.95 Å
  O-...H-N bond angle = 162°
Hiersemann asserted that to achieve optimal binding of the catalyst with a urea, one needed a substrate capable of a two-point interaction (Figure 2.6.1c),\textsuperscript{21} in his case 2-alkoxycarbonyl-substituted allyl vinyl ether \(2.39\). Subsequent studies by Jacbosen revealed a similar hydrogen-bonding network. The use of 20 mol\% chiral guanidinium barfate afforded keto-ester \(2.42\) in good yield and high selectivity (Scheme 2.6.2).\textsuperscript{22}

**Scheme 2.6.2 Jacbosen's Claisen Rearrangement**

\[
\begin{align*}
\text{O}^\text{OMe} & \quad \text{2.40} \\
\text{R} & \quad \text{2.41} \\
\text{O}^\text{OMe} & \quad \text{2.42}
\end{align*}
\]

Yet the necessity of a bidentate substrate precludes the development of a general catalytic Claisen rearrangement. The sp\(^3\) oxygen on the allyl vinyl ether bears two lone pairs, thus, a monodentate substrate is also capable of a two-point interaction. A bidentate allyl vinyl ether is not required.

### 2.7 Design of a Two-point Interaction Catalyst

Based on the examples shown in Section 2.6, several key points needed to be addressed in the design of a hydrogen bonding catalyst for the Claisen rearrangement. First, the lowest energy catalyst conformation should be the active species. Second, the catalyst should bind to the substrate in the most favorable fashion in order to achieve optimal activation. Third, coordination to the starting material should be more favorable than coordination to the product to facilitate turnover (Scheme 2.7.1). Finally, the catalyst should provide an enantiodiscriminating catalytic environment to realize asymmetric induction.
Scheme 2.7.1 Coordination of $sp^2$ versus $sp^3$ oxygen to Hydrogen Bonding Catalyst

The optimal orientation and distance of an amide N–H bond with ether 2.45 was used to identify a catalyst capable of undergoing a two-point interaction with a substrate bearing a single Lewis basic atom. A dual hydrogen bond donor benefits from increased strength and directionality, relative to single hydrogen bond donor.\textsuperscript{13} Spartan was used to model the complex between dimethyl ether and two molecules of acetamide (Figure 2.7.1).\textsuperscript{23}

Figure 2.7.1 Optimal Positions for Hydrogen Bond Donors

The OHN bonds were used as vectors for the database-mining program CAVEAT. The resulting template was entered into the Cambridge Crystal Database to find substructures that contain the necessary vectors.\textsuperscript{24} The lead compounds were then translated into readily synthesizable structures (Figure 2.7.2). Compound 2.48 was the most promising candidate, inspiring the design of bisamidine 2.49. The modular nature of the molecule would allow for easy derivatization. In addition, 2.49 avoided self-hydrogen bonding, while rotation about the aryl substituent bond led to degenerate
conformations.\textsuperscript{25} Finally, steric interactions would destabilize product coordination facilitating turnover.

Figure 2.7.2 Substructures Obtained from CAVEAT

2.8 First Generation Catalyst
To test the feasibility of a bisamidinium as a hydrogen bond donor catalyst, an achiral variant was first synthesized. 1,3-dicyanobenzene \textsuperscript{2.52} was treated with ethylenediamine and sulfur to afford bisamidine \textsuperscript{2.53} in 67\% yield. To increase the solubility of the catalyst, the bisamidine was converted to the bisamidinium via the chloride salt, which was formed in quantitative yield. Anion exchange with sodium barfate afforded \textsuperscript{2.54} in 90\% yield. The doubly cationic nature of \textsuperscript{2.54} provided a superior set of hydrogen bond donors by increasing the acidity of the protons on the nitrogens.

Scheme 2.8.1 Synthesis of First Generation Bisamidinium Catalyst
A suitable substrate was needed to test the reactivity of the bisamidinium catalyst. Previous work done by Dr. Annamalai showed that when 2.55 was subjected to the Claisen rearrangement a mixture of both the 3,3’ and 1,3’ products was observed. This result arises from the highly polarized transition state (Scheme 2.8.2). It was known that installation of a CF₃ group allowed for a more synchronous pathway, consequently, allyl vinyl ether 2.59 was chosen to avoid formation of a 1,3’ rearranged product. The CF₃ prevented the formation of the enolate/allylic cation pair and favored the concerted rearrangement pathway, which led to the 3,3’ sigmatropic rearrangement product 2.61.

Scheme 2.8.2 Mechanism of the Claisen Rearrangement

To synthesize 2.59, cinnamyl alcohol 2.62 was reacted with trifluoroacetic anhydride 2.63 to afford the trifluoromethyl acetate 2.64 in 73% yield (Scheme 2.8.3). 2.64 was then subjected to the Takai reaction to produce necessary Claisen starting material 2.59 in 50% yield.

Scheme 2.8.3 Synthesis of Claisen Substrate

With substrate 2.59 in hand, a catalytic Claisen rearrangement was attempted using catalyst 2.54 (Scheme 2.8.4). Despite the use of the bisamidinium barfate salt, the
catalyst was still insoluble in a number of organic solvents. No rearrangement was observed when 50 mol% of bisamidinium 2.54 was used.

**Scheme 2.8.4 Claisen Rearrangement with 2.54**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Hexanes</th>
<th>Het. Mix.</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂CN</td>
<td>Homogeneous</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>CHCl₃</td>
<td>Het. Mix</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>PhCH₃</td>
<td>Het. Mix.</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>PhCF₃</td>
<td>Het. Mix.</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>tBuOCH₃</td>
<td>Het. Mix.</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

2.9 **Second Generation Catalyst**

It was believed that if the solubility of the catalyst could be increased, then the rearrangement would proceed much more readily. To that end, a catalyst with a tert-butyl group on the aromatic ring was desired (Scheme 2.9.1). 5-tert-Butylbenzene-1,3-dioic acid 2.65 was converted to the acid chloride, followed by addition of ethanolamine to afford the diamide 2.66. The bisimidoyl chloride was obtained after reaction with thionyl chloride, followed by liquid ammonia to generate bisamidine 2.67 in 64% yield over four steps. Bisamidinium 2.68 was synthesized from bisamidine 2.67 in 90% yield.

**Scheme 2.9.1 Synthesis of Second Generation Catalyst**

Addition of the tert-butyl group dramatically improved the solubility of the catalyst. Low conversion to product was observed in acetonitrile, while the use of chloroform allowed the rearrangement to occur with 81% conversion after 6 days.
(Scheme 2.9.2). The use of dichloromethane and trifluorotoluene afforded 95% conversion to 2.61 with 25 mol% of the catalyst.

**Scheme 2.9.2 Claisen Rearrangement with 2.68**

Since the t-Bu group on the catalyst helped to increase the solubility, it was possible to run the reaction at a higher concentration and still retain a homogenous reaction mixture. The concentration of the reaction was doubled to 0.88 M and complete conversion to product was observed in just three days, compared to six days at 0.44 M (Scheme 2.9.2).

As expected for a catalyst that interacts via hydrogen bonding, there was a dramatic effect on the rate of the rearrangement when the solvents were varied. There was little to no background reaction in the absence of catalyst. It was found that nonpolar solvents were optimal, as ethereal solvents strongly inhibited the rearrangement. A significant rate increase was seen with both dichloromethane and trifluorotoluene (95- and 55-fold, respectively).
Figure 2.9.1 Effect of Solvent in the Claisen Rearrangement

In order to show the effectiveness of bisamidinium 2.68, a comparison to other hydrogen bonding catalysts was undertaken (Scheme 2.9.3). As stated previously, 25 mol% of the bisamidinium catalyst gave 95% conversion to product. The dual hydrogen bond nature of the catalyst was important as 50 mol% of monoamidinium 2.69 gave only 33% conversion, and ammonia salt 2.70 only 36%. Interestingly, the effectiveness of the catalyst was not solely a consequence of pKₐ; the stronger Brønsted acids 2.71 and 2.72 generated the product much more slowly than 2.68. Bisamidinium 2.68 was also much more effective than known Claisen catalysts 2.73 and 2.74.²²
Scheme 2.9.3 Use of Brønsted Acids to Catalyze the Claisen Rearrangement

\[
\text{CF}_3\text{O}^+ + \text{catalyst} \rightarrow \text{CF}_3\text{O}^+ + \text{PhCF}_3
\]

2.10 Catalytic, Enantioselective Hydrogen Bonding Catalyzed Claisen Rearrangement

The goal of designing a hydrogen bonding catalyst that allowed for turnover in the Claisen rearrangement had been achieved. It was next postulated that a chiral scaffold based on the achiral bisamidinium could be created to allow for both turnover, and to impart selectivity. To this end, Dr. Annamalai substituted (1S,2R)-2-amino-1,2-diphenylethanol for the achiral ethanolamine to synthesize enantiopure bisamidinium 2.77 (Scheme 2.10.1). He saw complete conversion to product and 20% enantiomeric excess when 50 mol\% of bisamidinium 2.77 was used. This is the first example of a hydrogen bond accelerated, enantioselective Claisen rearrangement using a monodentate substrate.
Scheme 2.10.1 Synthesis and Use of Enantiopure Bisamidinium 2.77 in the Claisen Rearrangement

In order to optimize the reaction and increase the enantiomeric excess, derivatives of the bisamidinium catalyst were needed in the hopes of creating a more stereodifferentiating environment for the Claisen rearrangement. Starting from the bisnitrile 2.52 allowed for a more streamlined synthesis of bisamidinium 2.80, using (1R,2R)-1,2-dicyclohexylethane-1,2-diamine instead of the aminoalcohol (1S,2R)-2-amino-1,2-diphenylethanol (Scheme 2.10.2). Unfortunately, after stirring at room temperature for eight days, bisamidinium 2.80 provided only 47% conversion and no enantioselectivity.26
Scheme 2.10.2 Use of Bisamidinium 2.80 to Catalyze the Claisen Rearrangement

It was concluded that the phenyl substituents on bisamidinium 2.77 played a role beyond increasing the steric bulk at those positions, possibly through a \( \pi \) bonding interaction with allyl vinyl ether 2.59.\[^{26}\]

2.11 Synthesis of Chiral Non-racemic 1,2-diamines

Optimization of the hydrogen bond accelerated Claisen rearrangement required the synthesis of analogues of the bisamidinium catalyst. This, in turn, necessitated new enantiomerically pure 1,2-diamines. Despite the widespread use of chiral diamines in stereoselective synthesis, and their use as chiral auxiliaries and ligands,\[^{29}\] only a limited number are commercially available. Thus, analogues of 2.77 are contingent upon the synthesis of chiral non-racemic vicinal diamines.

Recently, methodology for synthesizing \( C_2 \) symmetric 1,2-diamines, via a diaza-Cope rearrangement, was reported (Scheme 2.11.1).\[^{30}\] Condensation of diamine 2.81, then Cope rearrangement, followed by hydrolysis affords the new diamine 2.84. This reaction would allow one to access an array of diphenylethlenediamine analogues.
Scheme 2.11.1 Synthesis of C Symmetric 1,2-Diamines

The synthesis of diamine analogues required enantiopure (1R, 2R)-1,2-bis(2-hydroxyphenyl)-ethylenediamine. While 2.84 was commercially available, the cost was prohibitive. It was therefore necessary to synthesize 2.84 (Scheme 2.11.2). O-Anisaldehyde 2.85 was treated with aluminum and KOH, followed by DMSO and HBr to yield dione 2.86 in 50% yield. Condensation with cyclohexanone and ammonium acetate in acetic acid provided the diimine 2.87 in quantitative yield. Birch reduction, followed by hydrolysis, afforded the racemic diamine in 90% yield. Diamine 2.88 will be resolved using L-tartaric acid, to afford (R,R)-2.88 and (S,S)-2.88.

Scheme 2.11.2 Synthesis and Resolution of (1R, 2R)-1,2-Bis(2-hydroxyphenyl)-ethylenediamine

With enantiopure diamine 2.81 in hand, diphenylethylenediamine analogues 2.89a-c will be synthesized following the protocol described above (Scheme 2.11.3).
2.12 Conclusion

In conclusion, a hydrogen bond accelerated Claisen rearrangement of a monodentate substrate has been developed. Support for the dual hydrogen bonding catalyst was seen as lower reactivity was observed with the corresponding monamidinium. The reaction was optimized to take place in a reasonable timeframe. Continuing studies to optimize the enantioselective variant through derivatization of bisamidinium 2.91 are being undertaken.
2.13 Experimental Section

General Synthetic Procedures. Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N₂ in glassware that had been either flame dried in a stream of N₂ or dried in an oven (90 °C) for at least 6 h. When necessary, solvents and reagents were dried prior to use. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 60-F plates. Chromatography on silica gel was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). ¹H NMR spectra were recorded on Bruker AM-500 (500 MHz), Astra-500 (500 MHz), or DMX-360 (360 MHz) spectrometers. Chemical shifts are reported from the solvent resonance. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Mass spectra were obtained on a low resonance Micromass Platform LC in electron spray mode and high resonance VG autospec with an ionization mode of either CI or ES. IR spectra were taken on an ASI ReactIR 1000 with Si probe. Melting points were obtained on a Thomas Hoover Scientific Unimelt apparatus and are uncorrected.

Computational Procedures. Calculations were performed on SGI workstations using an R-4000 or R-10,000 processor. The computer programs used for all calculations are as follows: MacroModel V. 6.0 for the SGI,²⁰ Spartan V. 5.1.2 for the SGI,²³ FUNMAP,³¹ and CAVEAT V. 2.2.²⁴
CAVEAT search to find H-bond vectors. A minimized complex 2.45 consisting of two molecules of acetamide and one molecule of dimethyl ether was obtained via Spartan using an MM2* force field (Figure 2.13.1).

Figure 2.13.1 Structure and Resulting Vector used for CAVEAT Search.

Complex S1 was then used as the “target structure file” by CAVEAT to perform a database search. The atoms highlighted in red in Figure 2.13.1 was used to define two vectors with vector 1 being N1(base) to H1 (tip) and vector 2 being N2 (base) and H2 (tip). The base and tip for each vector was constrained to be nitrogen or hydrogen, respectively. The angle tolerance and position tolerance for each vector were 0.15 radians and 0.30 Å, respectively. The “linked” database was used in the CAVEAT search which corresponds to a subset of the Cambridge Structure Database. The search returned 26 hits meeting the above requirements. After scanning the list manually, the X-ray structures listed in Figure 2.13.2 were chosen as appropriate starting points for ligand construction with 2.48 leading to design of 2.49 as a hydrogen bonding catalyst.
4,5-dihydro-2-(3-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1H-imidazole (2.53):
Isophthalonitrile 2.52 (1.0 g, 7.8 mmol), ethylene diamine (6.3 mL), and sulfur (0.125 g, 3.9 mmol) were heated to reflux. After 12 h, the reaction mixture was cooled to room temperature, during which time a solid crashed out of solution. The solid was filtered and washed with water. The resulting crystals were recrystallized from ethylene diamine to yield 2.53 in 67% yield. $^1$H NMR matches that of the reported compound.\textsuperscript{32}

Bisamidinium catalyst (2.54): MeOH (8.5 mL) was cooled to 0 °C and acetyl chloride (8.5 mL) was added dropwise. The solution stirred at 0 °C for 1 h, and then warmed to room temperature and allowed to stir for 1 h. The solution was cooled back to 0 °C and 2.53 (0.14 g, 0.65 mmol) was added. The reaction stirred for 1 h at 0 °C and then...
overnight at room temperature, at which time it was concentrated under vacuum. $^1$H NMR matches that of the reported compound.\(^{32}\)

The resulting solid was dissolved in MeOH (7 mL) and NaBArF (0.79 g, 0.89 mmol) was added. The resulting mixture was allowed to stir overnight at which time it was concentrated and CH\(_2\)Cl\(_2\) was added to yield a precipitate. The precipitate was filtered and the mother liquor was concentrated to give a solid that was recrystallized from CH\(_2\)Cl\(_2\) and hexanes to yield a beige solid \textbf{2.54} (0.600 g) in 66\% yield. $^1$H NMR matches that of the reported compound.\(^{32}\)

\[
\text{Sodium Barfate (2.92): } 2.92 \text{ was synthesized via already published procedures. } ^1\text{H NMR matches that of the reported compound.}^{33}
\]

\[
\text{Cinnamyl 2,2,2-trifluoroacetate (2.64): To a solution of cinnamyl alcohol 2.62 (1.17 g, 8.77 mmol) in dry CH}_2\text{Cl}_2 (20 mL) was added Et}_3\text{N (1.48 mL, 10.52 mmol) followed by trifluoroacetic acetic anhydride 2.63 (1.22 mL, 8.77 mmol). The reaction was complete after 20 min at which time the reaction mixture was diluted with H}_2\text{O, and the organics were separated from the aqueous layer. The remaining aqueous layer was extracted twice with CH}_2\text{Cl}_2. The organics were combined, dried over Na}_2\text{SO}_4, and concentrated in vacuo. The resultant liquid was purified by flash column chromatography (5%}
\]

54
EtOAc/hexanes) to give **2.64** (1.57 g, 6.81 mmol) in 78% yield as a yellow oil. $^1$H NMR matches that of the reported compound.\(^{27}\)

![](image)

**1-((E)-3-(1,1,1-Trifluoroprop-2-en-2-yloxy)prop-1-enyl)benzene (2.59):** **2.59** was prepared from **2.64** via published procedures in 46% yield. $^1$H NMR matches that of the reported compound.\(^{27}\)

![](image)

**1,1,1-Trifluoro-4-phenylhex-5-en-2-one (2.61):** A solution of **2.59** (104.6 mg, 0.46 mmol) in toluene (5 mL) was heated at reflux for 24 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (100% hexanes > 1% ether/hexanes > 5% ether/hexanes) to give **2.61** (0.045 g, 0.20 mmol) in 43% yield as a pale yellow liquid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 (t, $J = 7.7$ Hz, 2H), 7.24 (t, $J = 7.7$ Hz, 2H), 7.21 (d, $J = 7.0$, 2H), 5.96 (ddd, $J = 16.9$ Hz, 10.3 Hz, 6.6 Hz, 1H), 5.13 (d, $J = 10.3$ Hz, 1H), 5.13 (d, $J = 16.9$ Hz, 1H), 4.00 (q, $J = 7.0$ Hz, 1H), 3.20 (dd, $J = 18.0$ Hz, 7.7 Hz, 1H), 3.11 (dd, $J = 18.0$ Hz, 7.7 Hz, 1H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 189.6 (q, $J = 34.8$ Hz), 141.7, 139.4, 129.0, 127.7, 127.3, 115.8, 115.7 (q, $J = 292.5$ Hz), 43.4, 42.1; IR (thin film) 3084, 3065, 3030, 2926, 2856, 1768, 1451 cm$^{-1}$; HRMS (CI) $m/z = 228.0762$ C$_{12}$H$_{11}$F$_3$O [M$^+$], found 228.0752.
5-tert-butyl-N1,N3-bis(2-hydroxyethyl)benzene-1,3-diamide (2.66): To a solution of 5-tert-butylbenzene-1,3-dioic acid 2.65 (1.0 g, 4.5 mmol) in PhCH3 (3.5 mL) and DMF (90 µL), SOCl2 (0.8 mL, 11.3 mmol) was added. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and the solvents were removed in vacuo. A separate round-bottom flask was charged with ethanolamine (0.54 mL, 9.0 mmol), Et3N (1.3 mL, 9.0 mmol), and CH2Cl2 (14 mL), and subsequently cooled to 0 °C. The concentrated acid chloride solution was dissolved in CH2Cl2 (3 mL), cooled to 0 °C, and transferred to the amino alcohol solution via syringe. The resulting mixture was allowed to warm up to room temperature and stirred overnight, at which time it was concentrated under reduced pressure. The product 2.66 was carried on unpurified to the next step.

2-(3-tert-butyl-5-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-1H-imidazole (2.67): A round-bottom flask was charged with 2.66 (1.39 g, 4.5 mmol) and SOCl2 (15 mL) and heated to reflux for 2 h. The solvent was then removed in vacuo and dissolved in CHCl3 (5 mL). A separate round bottom flask was cooled to −78 °C and charged with NH3 (g, excess) to form liquid ammonia. The CHCl3 solution of the previously generated intermediate was then slowly added to the solution of ammonia in CHCl3 (15 mL) at −78 °C. The mixture was allowed to stir and slowly warm to room temperature. After
stirring overnight, 10% aq. NaOH was added and the organic layer was separated. The aqueous layer was then extracted twice with CH₂Cl₂, dried over MgSO₄, and concentrated. The resulting solid was then recrystallized using CH₂Cl₂/hexanes mixture to yield 2.67 (0.76 g, 2.8 mmol) in 64% overall yield as a white solid. ¹H NMR matches that of the reported compound.³²

![Structure of Bisamidinium catalyst (2.68)](image)

**Bisamidinium catalyst (2.68):** MeOH (8.5 mL) was cooled to 0 °C and acetyl chloride (8.5 mL) was added dropwise. The solution stirred at 0 °C for 1 h, and then warmed to room temperature and allowed to stir for 1 h. The solution was cooled back to °C and 2.67 (0.14 g, 0.65 mmol) was added. The reaction stirred for 1 h at 0 °C and then overnight at room temperature, at which time it was concentrated under vacuum.

The resulting solid was dissolved in MeOH (7 mL) and NaBArF S3 (0.79 g, 0.89 mmol) was added. The resulting mixture was allowed to stir overnight at which time it was concentrated and CH₂Cl₂ was added to yield a precipitate. The precipitate was filtered and the mother liquor was concentrated to give a solid that was recrystallized from CH₂Cl₂ and hexanes to afford 2.68 (0.60 g, 0.30 mmol) in 66% overall yield as a beige solid. ¹H NMR (360 MHz, Acetone-d₈) δ 10.23 (bs, 4H), 8.99 (s, 1H), 8.51 (s, 2H), 7.79 (s, 16 H), 7.67 (s, 8H), 4.37 (s, 8H), 1.41 (s, 9H); ¹³C NMR (360 MHz, Acetone-d₈) δ 166.8, 162.8 (q, J = 49.6 Hz), 155.8, 135.7, 132.4, 130.2 (q, J = 97.7 Hz), 128.0, 125.8 (q, J = 270.3 Hz), 124.6, 118.6, 46.3, 36.5, 31.2; IR (film) 3698, 3466, 3134, 3057, 2980,
1633, 1613, 1579, 1355 cm\(^{-1}\); HRMS (ES) \(m/z = 863.0648\) calcd for \(C_{64}H_{24}B_{2}F_{4}Na\) \([\text{MNa}]^+\), found 863.0619.

\[
\begin{array}{c}
\text{CF}_3
\end{array}
\]

\(2.69\) was made following the same procedure as \(2.68\): \(^1\)H NMR (360 MHz, Acetone-\(d_8\)) \(\delta\)
9.75 (bs, 2H), 8.01 (m, 4H), 7.76 (bs, 8H), 7.64 (bs, 5H), 4.30 (s, 4H); \(^1^3\)C NMR (360 MHz, Acetone-\(d_8\)) \(d\) 166.8, 161.7 (q, \(J = 49.3\) Hz), 135.0, 134.6, 129.6, 128.9 (m), 128.3, 124.4 (q, \(J = 270.2\) Hz), 122.3, 117.5 (t, \(J = 3.7\) Hz), 45.0; IR (film) 3468, 3259, 1707, 1614, 1568, 1359, 1274, 1120 cm\(^{-1}\).

\[
\begin{array}{c}
\text{CF}_3
\end{array}
\]

\(2.70\) was made following the same procedure as \(2.68\): \(^1\)H NMR (360 MHz, Acetone-\(d_8\)) \(\delta\)
7.79 (bs, 8H), 7.68 (bs, 4H), 3.55 (t, \(J = 8.0\) Hz, 6H), 2.21 (quintet, \(J = 3.2\) Hz, 1H), 2.04 (m, 6H); \(^1^3\)C NMR (360 MHz, Acetone-\(d_8\)) \(d\) 161.7 (q, \(J = 49.6\) Hz), 134.6, 128.9 (m), 124.4 (q, \(J = 270.2\) Hz), 117.5 (t, \(J = 3.7\) Hz), 46.9, 22.7, 19.2; IR (film) 3383, 1707, 1654, 1359, 1274, 1120 cm\(^{-1}\).

\[
\begin{array}{c}
\text{CF}_3
\end{array}
\]

\(2.74\) was made following the same procedure as \(2.68\): \(^1\)H NMR matches that of the reported compound.\(^{22}\)
General procedure for the Claisen rearrangement of 2.59: Compound 2.59 (0.020 g, 0.088 mmol) was weighed into a 1 dram vial, followed by the addition of the appropriate catalyst (Table 2.1), followed by distilled PhCF₃ (100 μL). The vial was sealed and the reaction was allowed to stir at room temperature. Conversion to 2.61 was determined by ¹H NMR of aliquots removed during the course of the reactions.

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<th>Catalyst</th>
<th>Equiv</th>
<th>Amt. Catalyst</th>
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<th>Conv (48 h)</th>
<th>Conv (72 h)</th>
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<td>0.25</td>
<td>44 mg</td>
<td>ND</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td>2.69</td>
<td>0.50</td>
<td>44 mg</td>
<td>12</td>
<td>24</td>
<td>33</td>
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<tr>
<td>2.70</td>
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<td>42 mg</td>
<td>16</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>2.71</td>
<td>0.50</td>
<td>4 μL</td>
<td>10</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>2.72</td>
<td>0.50</td>
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<tr>
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<td>47 mg</td>
<td>19</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>No Catalyst</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
References:


(23) SPARTAN v5.0 (Wavefunction, Inc.; 18401 Von Karman Avenue, Suite 370; Irvine, CA 92612 U.S.A.).


(31) a) Lauri, G., FUNMAP. b) Kozlowski, M. C; Panda, M. "Computer-Aided Design of Chiral Ligands. Part 2. Functionality Mapping as a Method to Identify Stereocontrol Elements for Asymmetric Reactions" J. Org. Chem. 2003, 68, 2061-2076. c) The FUNMAP program incorporates the FUNGEN and CLASS modules and automates the entire process going from target and probe input to cluster locations, so a set of targets and standard probes can be fully evaluated consistently and routinely.


Chapter 3. First Catalytic, Enantioselective Meerwein-Eschenmoser Claisen Rearrangement to Generate Allyl Oxindoles.

3.1 Meerwein-Eschenmoser-Claisen Background

The Meerwein-Eschenmoser Claisen rearrangement is a specific type of Claisen rearrangement involving an enamine to generate an amide bond (Scheme 3.1.1). Typically the Eschenmoser-Claisen rearrangement is done at high temperatures; not to facilitate the rearrangement, but to generate the substrate via addition of the allyl alcohol to the iminium 3.2. Difficulty in isolation of the starting enamine 3.5 has hindered the development of an asymmetric variant.

Scheme 3.1.1 General Eschenmoser-Claisen Rearrangement

Unlike the typical Eschenmoser substrate, the allyl indole 3.9 illustrated in Scheme 3.1.2 can be constructed under mild conditions, which should allow one to isolate the material prior to the rearrangement. In addition, enamine 3.9 is stabilized by the aromatic system of the heterocycle, which should also slow the rearrangement. While this type of rearrangement to generate oxindole 3.10 has been seen in the literature, no enantioselective versions have been reported.
3.2 Approaches to Enantiopure Oxindoles

This variant of the Eschenmoser-Claisen rearrangement would potentially yield an enantiopure oxindole. Several methods to construct oxindoles bearing a quaternary stereocenter have been reported. One such example by Overman\(^5\) utilizes a Heck reaction to close the five-membered ring of the oxindole (Scheme 3.2.1). The use of 10 mol\% palladium-BINAP catalyst provided oxindole 3.12 in high yield and selectivity. However, five steps are required to synthesize the requisite starting material 3.11.

Scheme 3.2.1 Overman's Asymmetric Heck Reaction

Trost\(^6\) and co-workers have employed an asymmetric allylation reaction to generate enantiopure oxindoles such as 3.14 (Scheme 3.2.2), through the use of a molybdenum catalyst. As with the asymmetric Heck reaction, the nitrogen on oxindole 3.13 must be protected, in this case, with a Boc group.
A third example, carried out by Fu,\textsuperscript{7} took advantage of a known DMAP rearrangement to install the ester functionality at the 3-position of the oxindole (Scheme 3.2.3). A chiral ferrocenyl catalyst was used to generate oxindole 3.16 in good yield and excellent enantioselectivity.

Despite these successes, there are drawbacks to each of these methods. The necessary starting materials require three to five steps to synthesize. In addition, the nitrogen must be protected, which adds an extra deprotection step for generation of the oxindole product. Finally, the substitution patterns are limited; the ester/allyl combination at C3, which maps onto many natural products, is not available with high enantioselectivity.\textsuperscript{8}

There are many natural products,\textsuperscript{9,10,11,12,13} as well as therapeutic targets,\textsuperscript{14,15,16} that contain an oxindole moiety (Figure 3.2.1). Many of these natural products contain an allyl chain at C3, which could easily be installed in an asymmetric fashion utilizing the
Claisen methodology. Therefore, new methodologies to access enantiopure oxindoles would be very useful to synthetic chemists.

**Figure 3.2.1 Oxindole Natural Products and Therapeutics**

![Chemical structures of oxindoles and therapeutic agents.](image)

**3.3 Monodentate Substrates**

Following up on the work outlined in Chapter 2, the first substrates that were investigated were monodentate, bearing a nitrile at the C3 position. The nitrile on 3.24 and 3.25 also served as an electron-withdrawing group that would decelerate the Claisen rearrangement to allow isolation of 3.26 and 3.27 in pure form.\(^\text{17}\) Both allyl alcohol and methallyl alcohol were incorporated, as the steric of the alcohol are known to affect the rate of the rearrangement.\(^\text{2}\) It was found that neither Brønsted nor Lewis acids catalyzed the rearrangement of this monodentate substrate class (Scheme 3.3.1).
Scheme 3.3.1 Claisen Rearrangement of 3-nitrile Indole

![Scheme 3.3.1 Claisen Rearrangement of 3-nitrile Indole]

3.4 Brønsted Acids

Due to the lack of success of the monodentate substrate, bidentate substrates were investigated. It was envisioned that either a Brønsted or Lewis acid could coordinate to both the sp³ oxygen of the allyl chain as well as the sp² oxygen of a carbonyl substituent (Scheme 3.4.1).

Scheme 3.4.1 Coordination of Catalyst to a Bidentate Substrate

![Scheme 3.4.1 Coordination of Catalyst to a Bidentate Substrate]

Brønsted acid catalysts were screened first (Scheme 3.4.2). Complete conversion and 16% ee was observed with bisamidinium catalyst 3.32 (see Scheme 2.10.1). Bissulfonamide 3.33 gave racemic product, with 80% conversion. Urea 3.34 also gave 80% conversion with 6% enantiomeric excess. The low selectivity arises from the competing thermal reaction, with 60% conversion being observed without catalyst over the same timeframe.
3.5 Lewis Acid Screening: Copper bis(oxazolines)

Due to the facility of the uncatalyzed thermal reaction, Lewis acid catalysts, which have a much broader reactivity range, were investigated next. The first catalysts that were tested were the copper bis(oxazolines) (Scheme 3.5.1). 18

The enantioselectivity was dramatically affected by both the substitution on the oxazoline portion of the ligand, as well as the counterion on the copper. The tert-butyl bis(oxazoline) ligand 3.35 furnished 34% ee when Cu(OTf)2 was used, and 58% ee when Cu(SbF6)2, with less coordinating counterions, was employed. Phenyl bis(oxazoline) 3.36 also gave low selectivity with the triflate counterion, but increased to 54% ee with Cu(SbF6)2. The enantioselectivity improved to 67% when [Cu(S,S)-Bn-box](SbF6)2 3.37 was employed. Indanol bis(oxazoline) 3.38 gave 35% ee Cu(OTf)2, 52% ee with Cu(BF4)2, and 81% ee with Cu(SbF6)2. The same result was obtained with Cu(SbF6)2 indanol bis(oxazoline) complexes whether CuBr2 or CuCl2 was used as the initial copper source. All of these results employed stoichiometric copper complexes in order to gauge the inherent selectivity of the metal adducts.
Various solvents were screened during optimization (Scheme 3.5.2). Dichloromethane provided the best results affording complete conversion to 3.30 and 81% ee. It was necessary to use distilled solvents as trace HCl could catalyze the rearrangement. Dichloroethane provided slightly lowered enantioselectivity (78% ee). The use of toluene and chloroform decreased both the selectivity and the conversion to product. THF was screened as it was observed to inhibit the uncatalyzed thermal process. However, no conversion to product occurred when the copper bis(oxazoline) was employed with THF; nor did the rearrangement occur when dichloromethane was used as a co-solvent. The same trends were observed with acetonitrile.

Replacing the isopropylidene-bis(oxazoline) 3.39 with a spiro-bis(oxazoline) alters both the dihedral angle and the bite angle of the catalyst (Figure 3.5.1).
Increasing the ring size from cyclopropylidene to cyclohexylidene (3.40a-d) induces strain in the ligand that serves to decrease these angles. Isopropylidene-bis(oxazoline) 3.39 most closely matches the cyclopentylidene ligand 3.40a (n=3).

Figure 3.5.1 Known Dihedral and Bite Angles

<table>
<thead>
<tr>
<th>n</th>
<th>Φ (deg)</th>
<th>θ (deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120.6</td>
<td>97.7</td>
</tr>
<tr>
<td>2</td>
<td>115.8</td>
<td>98.3</td>
</tr>
<tr>
<td>3</td>
<td>113.2</td>
<td>95.7</td>
</tr>
<tr>
<td>4</td>
<td>111.5</td>
<td>94.9</td>
</tr>
</tbody>
</table>

Increasing the bite angle has been shown to improve the enantioselectivity of the Diels-Alder reaction,\(^1\) therefore cyclopropylidene ligand 3.40a, which has the largest bite angle, was synthesized to test in the Claisen rearrangement.\(^2\) Disappointingly, the selectivity improved only slightly, increasing from 81 to 83% (Scheme 3.5.3).

Scheme 3.5.3 Effect of Bite Angle on Selectivity

As the presumed coordination mode involves catalyst coordination to both the ester and the allyl chain (Scheme 3.4.1), changing the steric environment around the ester was proposed to affect the selectivity. In order to test this hypothesis, a series of esters were synthesized (Scheme 3.5.4). Indole 3.41 was protected using TIPS-Cl, followed by reaction with N-bromosuccinimide, to afford 3.42 in 75% yield. Lithium-halogen exchange, and then addition of the requisite chloroformate yielded the ethyl, benzyl, and isopropyl ester indoles (3.43-3.45). As tert-butyl chloroformate was not available, the
tert-butyl ester was synthesized in a different manner. Carboxylic acid 3.46 was converted to the acid chloride and then treated with tert-butanol to generate ester 3.48.

**Scheme 3.5.4 Synthesis of Ester Indole Series**

The four esters were then transformed to the necessary Claisen substrates through reaction with NCS and methallyl alcohol, affording the products in 34-66% yield (3.49-3.52).

**Scheme 3.5.5 Synthesis of Claisen Rearrangement Substrates**

These indole substrates were then screened against copper indanol bis(oxazoline) 3.38e (Scheme 3.5.6). Changing the steric environment around the coordinating carbonyl did affect the selectivity, with larger groups leading to lower selectivity. The methyl ester gave the best result with 81% ee, while the larger ethyl and benzyl esters lowered the enantioselectivity to 79% ee and 73% ee, respectively. The isopropyl ester decreased the ee further to 65%, and the tert-butyl ester provided only 42% ee.
As shown in Scheme 3.5.6, esters that are smaller in size afford better enantioselectivities. Therefore, it was hypothesized that replacing the methyl ester with a methyl ketone (3.57) might improve the selectivity (Scheme 3.5.7). Unfortunately, rearranged product 3.58 was not stable. While attempting to synthesize the racemate of the oxindole product the methyl ketone was cleaved, presumably via a facile retro-Claisen condensation, affording 3.61 as the sole product.

Installation of an amide at C3 was also investigated. The amide was generated in an analogous fashion to the ester series (Scheme 3.5.4), followed by reaction with N-chlorosuccinimide and allyl alcohol to afford the Claisen substrate 3.62. Disappointingly, copper(II) failed to catalyze the rearrangement with high enantioselectivity (Scheme 3.5.8). Most likely, allylic strain destabilizes the coordination mode needed (3.63) for good asymmetry transfer from the catalyst to the product.
A range of catalyst loadings were examined in an effort to further optimize the rearrangement (Scheme 3.5.9). No improvement was observed when 200 mol% catalyst loading was used, a likely indication that the thermal background reaction is not competing with the catalyzed pathway. When the catalyst loading was lowered to 50 mol%, almost complete conversion was observed, while the enantioselectivity was reduced to 77%. Decreasing the catalyst loading to 25 mol% lowered conversion (78%) and selectivity (76% ee), indicating the thermal rearrangement was intervening during the relatively slow turnover.

Due to poor turnover with copper(II) as the Lewis acid, other metals were screened as promoters for the rearrangement (Scheme 3.5.10). In particular, metals with different geometries were surveyed that would destabilize the product metal adduct 3.65. With the bis(oxazoline) scaffold, copper providing the highest enantioselectivities and complete conversion. Lower reactivity was observed with both nickel and zinc adducts, as well as lower selectivities. Interestingly, the opposite enantiomer of the product was
formed when zinc was employed, which is consistent with a change from square planar to tetrahedral coordination geometry. Promisingly, the palladium adduct exhibited reactivity on par to the copper adduct, along with high levels of selectivity (73% ee).

<table>
<thead>
<tr>
<th>M</th>
<th>Conv (%)</th>
<th>t</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuCl₂</td>
<td>100</td>
<td>35 min</td>
<td>81</td>
</tr>
<tr>
<td>CuBr₂</td>
<td>100</td>
<td>1 h 15 min</td>
<td>80</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>30</td>
<td>2 h</td>
<td>24*</td>
</tr>
<tr>
<td>NiBr₂</td>
<td>50</td>
<td>2 h</td>
<td>47</td>
</tr>
<tr>
<td>PdCl₂</td>
<td>100</td>
<td>1 h</td>
<td>73</td>
</tr>
</tbody>
</table>

*Opposite enantiomer

### 3.6 Lewis Acid Screening: Palladium Diphosphines

Since it was unclear how to further optimize the copper complexes for this transformation, attention was turned to the palladium complexes, which can accommodate a wider array of ligands (diamines, aminophosphines, and diphosphines). Building on the promising 73% ee with [Pd(S₅S)-Ind-box](SbF₆)₂ (Scheme 3.5.10), a number of diphosphine ligands were screened first (Scheme 3.6.1). BINAP 3.66, gave a promising 45% ee and complete conversion to product in just five minutes at room temperature. Lowering the temperature only slowed the reaction and did not increase the selectivity. More sterically encumbered ligands, specifically tol-BINAP 3.67 and xylyl-BINAP 3.68 provided no appreciable change observed in the enantioselectivity. Difluorphos 3.69, which has a smaller dihedral angle than that of BINAP, increased the selectivity to 56% ee. BIPHEP 3.70, gave moderate selectivity. Finally, DUPHOS 3.71 furnished only 11% ee.
In order to understand how the catalyst was binding to the substrate, it was necessary to determine the absolute configuration of the quaternary stereocenter that is formed during the course of the reaction. To this end, derivatives of the oxindole product were synthesized in an effort to obtain an X-ray crystal structure.

4-Bromobenzene-1-sulfonyl chloride was used to sulfonate the nitrogen on oxindole 3.30 that was 80% enantiomeric excess, resulting in the crystalline 3.72. A crystal structure of 3.72 was obtained. However, because this material was only 80% ee, there was a one in ten chance that the crystal structure was of the minor enantiomer. Therefore, two more crystal structures were obtained. All three crystals were of the same configuration. This means there was a 999 in 1,000 chance the crystals were of the major enantiomer. The X-ray crystal structure showed that 3.72 was of the (R)-configuration, indicating that 3.30 was of the (R)-configuration.
With the absolute configuration established, stereochemical models of proposed transition states were studied in an effort to further optimize the reaction and improve the enantioselectivity (Scheme 3.6.3). Two transition states are illustrated with the $C_2$-symmetric BINAP-derived catalyst coordinating to the indole starting material 3.76 (the BINAP backbone is represented as a line). As shown in TS2, there are steric interactions between the allyl group and the pseudoequatorial phenyl group of the phosphorus, as well as between the ester and the other pseudoequatorial phenyl group. On this basis, increasing the steric bulk of the ester might more strongly disfavor the formation of the minor enantiomer, serving to increase the enantioselectivity.

**Scheme 3.6.3 Stereochemical Model of the Asymmetric Rearrangement**
In order to test this theory, the series of esters synthesized previously (Scheme 3.5.4) were screened using the palladium-BINAP catalyst (Scheme 3.6.4). Gratifyingly, increasing the steric bulk at the C3 ester position did improve the enantioselectivity, as the isopropyl and tert-butyl esters furnished 63% and 85% ee, respectively. Also consistent with the model, decreasing the steric bulk at R<sup>1</sup> also improved the selectivity. While the ethallyl derivative afforded lower ee (35%), the allyl derivative 3.76 provided higher ee (71%). Similar results were seen with both the benzyl and isopropyl esters. The tert-butyl ester with allyl substitution afforded 3.73 in 89% ee. It is important to note that turnover was not problematic with palladium. As such, substoichiometric catalyst loadings (20 mol%) were employed with palladium-BINAP.

### Scheme 3.6.4 Substrate Scope with BINAP

![Scheme 3.6.4 Substrate Scope with BINAP](image)

In addition to Scheme 3.6.2, an oxindole of high optical purity (3.73, 90% ee) was derivatized using camphor sulfonyl chloride to sulfonate the nitrogen on 3.73, and attempts were made to grow crystals of the product (Scheme 3.6.5). Unfortunately, the
resultant sulfonamide was an oil. An attempt was made to react the camphor ketone with 2,4-dinitrophenylhydrazine (2,4-DNPH), since hydrazones tend to be crystalline. Instead, the ester on the oxindole transesterified during the course of the reaction. Since methyl ester 3.75 was crystalline, an X-ray crystal structure was obtained showing that 3.75 was the (S)-configuration. This is consistent with the HPLC traces, which show that copper-bis(oxazoline) and palladium-BINAP give opposite major enantiomers. All other structures were assigned by analogy from these two results.

Scheme 3.6.5 Crystal Structure of Derivatized Oxindole 3.75

As with copper (Scheme 3.5.1), the effect of the counterion on palladium was also investigated (Scheme 3.6.6). Here, changing the counterion did little to affect the enantioselectivity, but, in the case of more strongly coordinating anions such as OTf or OAc, the product formed very slowly. Presumably counterion binding to the metal inhibits coordination to the substrate.

Scheme 3.6.6 Effect of Counterion on Enantioselectivity
Lowering the catalyst loading to 20 mol% was not detrimental (Scheme 3.6.7), and complete conversion to product was observed in 10 minutes at room temperature. Decreasing the loading further to 5 mol% provided 3.56 in the same enantioselectivity, and did not substantially reduce the rate.

**Scheme 3.6.7 Effect of Catalyst Loading on Enantioselectivity**

<table>
<thead>
<tr>
<th>mol %</th>
<th>T</th>
<th>t (min)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0°C</td>
<td>10</td>
<td>84</td>
</tr>
<tr>
<td>20</td>
<td>rt</td>
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<td>82</td>
</tr>
<tr>
<td>20</td>
<td>0°C</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>rt</td>
<td>30</td>
<td>82</td>
</tr>
</tbody>
</table>

Using the optimized reaction conditions, difluorphos ligand 3.69 was reexamined with 3.81, the substrate that had given the highest ee with palladium-BINAP (Scheme 3.6.8). Pleasingly, 92% enantioselectivity was observed using 20 mol% of the palladium(II) catalyst.

**Scheme 3.6.8 Difluorphos ligand with Substrate x**

### 3.7 Lewis Acid Screening: Palladium Phosphinoxazolines

While the goal of high enantioselectivity with substoichiometric catalyst loadings in an Eschenmoser-Claisen rearrangement had been obtained, the high enantioselectivity was only observed when allyl alcohol was used, dramatically limiting the substrate scope of the reaction. Consequently, new ligands were screened to further optimize the reaction. The phosphinoxazoline ligands were investigated as they combine the
scaffolds of the diphosphine ligands, and the bis(oxazoline) ligands. The commercially available isopropyl ligand 3.82 was promising, giving 3.78 in 79% ee (Scheme 3.7.1). Good turnover was achieved with this catalyst system, and loadings of 20 mol% were used.

**Scheme 3.7.1 Initial Results with iPr-PHOX**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>t (min)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-Bu</td>
<td>H</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Me</td>
<td>15</td>
<td>76</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>Me</td>
<td>Et</td>
<td>15</td>
<td>79</td>
</tr>
</tbody>
</table>

The promising enantioselectivities observed with isopropyl-phosphino-oxazoline 3.82 prompted the synthesis of other phosphino-oxazoline ligands. The condensation of 2-fluorobenzaldehyde 3.83 with a chiral amino alcohol (3.84a-d) was performed using 4 Å molecular sieves, followed by an oxidation with N-bromosuccinimide (Scheme 3.7.2) to yield oxazolines 3.85a-d. Treatment with KPPh₂ provided 2-(o-diphenylphosphinophenyl)oxazolines 3.86a-d.

**Scheme 3.7.2 Synthesis of Phosphino-oxazoline Ligands**

With the phenyl- and benzyl-phosphino-oxazoline ligands, only moderate enantioselectivities were seen (Scheme 3.7.3). Phenyl-phosphino-oxazoline 3.86b gave 67% ee with tert-butyl ester 3.56 and only 49% ee with methyl ester 3.30. Benzyl-
phosphinoxazoline 3.86c gave almost the same selectivities with 3.56 and 3.30 showing 60 and 48% ee, respectively. Indanol ligand 3.86d gave similar results to the isopropyl, providing 3.30 in 72% ee.

**Scheme 3.7.3 Substrate Screening with PHOX Ligands**

As with the palladium(II) diphosphine ligands (Scheme 3.6.3), stereochemical models were studied in order to achieve the highest selectivities possible (Scheme 3.7.4). A steric interaction between the R group on the oxazoline portion of the ligand and the allyl chain was seen, which would disfavor TS2. Therefore it was postulated that if the steric bulk of R could be increased, formation of TS1 would be more strongly favored, thereby increasing the selectivity of the reaction.
To this end, tert-butyl-phosphino-oxazoline ligand 3.86a was used in the Eschenmoser-Claisen rearrangement (Scheme 3.7.5). Gratifyingly, this ligand afforded high selectivities over a range of substrates. Methyl ester with allyl alcohol (3.76) afforded 83% ee, while methyallyl alcohol (3.30) and ethallyl alcohol provided 89% and 92% ee, respectively. When the reaction was run on a 1 mmol scale, the enantioselection (91% ee) and yield (95%) improved. The use of the tert-butyl ester lowered the enantioselectivity and the yield. However, with the methyl ester, high enantioselection was retained with either electron-donor or electron-withdrawing substitution on the aromatic ring (3.87-3.90). Interestingly, a propargyl substrate rearranged to afford the allenyl product 3.91 in 100% conversion and 39% ee.
3.8 Deuterium Labeling

As palladium(II) catalysts were employed, the possibility of π-allyl cation chemistry (i.e., 3.92) needed to be considered. The substrates that have been utilized in the rearrangement would give the same product, regardless of whether a [3,3′] sigmatropic rearrangement or a [1′,3] sigmatropic rearrangement occurred (Scheme 3.8.1). Based on the results with other Lewis acids such as copper and zinc complexes (good to excellent enantioselectivity, but poor turnover), a Lewis acid-catalyzed mechanism seemed most likely. To test this hypothesis, a labeling experiment was devised.

Scheme 3.8.1 [3,3′] versus [1′,3]
A deuterium atom was installed on the allyl group of the indole starting material. A Luche reduction\textsuperscript{28} of 2-ethylacrolein 3.93 with sodium borodeuteride yielded deuterium-labeled allyl alcohol 3.94. The labeled allyl alcohol was used to produce deuterium-labeled Claisen substrate 3.96. When this substrate was subjected to the reaction conditions, only the [3,3'] rearranged product 3.97 was observed by \textsuperscript{1}H NMR, in 80% isolated yield, and 92% ee (Scheme 3.8.2). This supports a concerted [3,3'] rearrangement.

**Scheme 3.8.2 Deuterium Labeling Experiment**

\[
\begin{align*}
\text{O} & \quad \text{Et} \\
\text{3.93} & \quad \text{CeCl}_3 \cdot 7\text{H}_2\text{O} \quad \text{NaBD}_4 \quad \text{MeOH, 0 °C} \\
\text{Et} & \quad \text{3.94} \quad \text{HO} \\
\text{3.95} & \quad \text{2) HO} \\
\text{3.94} & \quad \text{Et} \\
\text{3.96} & \quad \text{Cl}_3\text{CCO}_2 \quad \text{Me-N} \quad \text{N-Me} \\
\text{3.97} & \quad \text{Et} \\
\text{D} & \quad \text{Et} \\
\end{align*}
\]

**3.9 Conclusions**

In conclusion, the first enantioselective, catalytic Eschenmoser-Claisen rearrangement has been developed. This method constitutes a mild entry to oxindole products bearing a quaternary stereocenter. Tert-butyl-phosphinooxazoline 3.86a afforded the best selectivity with the smaller C3 methyl ester and the larger R2 groups, while the diphosphine ligands provided higher selectivities with larger esters and smaller allyl alcohols (Scheme 3.9.1). The rearrangement proved to be general, as both electron-withdrawing and electron-donating groups were tolerated on the indole framework. In
addition, catalyst loadings as low as 5 mol% could be used. Future directions for this project will focus on optimizing the results of the allenyl substrate 3.91, as well as expansion into other heterocycles.

Scheme 3.9.1 Comparison of \( t \)-BuPHOX Ligand with BINAP Ligand
3.10 Experimental Section

General Considerations. Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N₂ in dried glassware. When necessary, solvents and reagents were dried prior to use. THF was distilled from sodium benzophenone ketyl. CH₃CN, CH₂Cl₂, TMEDA, and hexanes were distilled from CaH₂. Benzene was distilled from sodium.

Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 254-F plates. Visualization was accomplished with UV light. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh).²⁹ Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC), performed on a Waters 600 HPLC with UV detection at 254 nm. An analytical Chiralpak OD, AS and AD column (0.46 cm x 25 cm) from Daicel was used. ¹H NMR spectra were recorded on Bruker AM-500 (500 MHz), AM-360 (360 MHz), or AM-300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance (CDCl₃ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Decoupled ¹³C NMR spectra were recorded on a Bruker AM-500 (125 MHz) spectrometer. IR spectra were taken on a Perkin-Elmer FT-IR spectrometer using a thin film on NaCl plates or a CHCl₃ solution. Mass spectra were obtained on a low resonance Micromass Platform LC in electrospray mode and high resonance VG autospec with an ionization mode of either CI or ES. Melting points were obtained on Thomas Scientific Unimelt apparatus and are uncorrected. Optical rotations
were measured on a Perkin-Elmer Polarimeter 341 with a sodium lamp and are reported as follows $[\alpha]^{23}_D$ (c g/100 mL, solvent).

**Preparation of Claisen Substrate Precursors:**

3-Bromo-1-(triisopropylsilyl)-1H-indole (3.42): A solution of indole (2.0 g, 17.1 mmol) in THF (100 mL) was cooled to 0 °C, at which time NaH (60% in oil, 3.4 g, 85.5 mmol) was added. The mixture was stirred together for 5 min, followed by addition of TIPSCI (10 mL, 46.7 mmol). After 1 h stirring at room temperature, the mixture was cooled to 0 °C, then H$_2$O was added. The organic layer was washed with 1 M HCl and brine, dried over Na$_2$SO$_4$, and concentrated under vacuum.

A solution of the TIPS-indole (4.67 g, 17.1 mmol) in THF was cooled to -78 °C, then recrystallized N-bromosuccinimide (3.0 g, 17.1 mmol) was added. After stirring for 3 h, another aliquot of N-bromosuccinimide (1.5 g, 8.6 mmol) was added and stirring was continued for another 2 h. After warming to room temperature, pyridine (170 μL) and hexanes (30.7 mL) were added and the mixture was concentrated. The precipitate was washed thoroughly with hexanes and the combined filtrate was concentrated. The residue was chromatographed (SiO$_2$, 100% hexanes) to afford 3.42 (4.5 g, 12.8 mmol) in 75% yield over the 2 steps as a white solid: mp 56-58 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.58-7.57 (m, 1H), 7.50-7.48 (m, 1H), 7.25 (s, 1H), 7.22-7.19 (m, 2H), 1.72-1.65 (m, 3H), 1.17 (d, $J = 7.5$ Hz, 18H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 140.1, 130.0, 129.7,
122.5, 121.6, 119.1, 114.1, 93.6, 18.0, 12.8; IR (film) 2949, 2868, 1463, 1285 cm⁻¹; HRMS (Cl) m/z = 352.1109 calcd for C₁₇H₂₇BrNSi [MH]⁺, found 352.1018.

Ethyl 1H-indole-3-carboxylate (3.43): Indole 3.42 (0.30 g, 0.86 mmol) was dissolved in Et₂O (8.6 mL) and cooled to -78 °C. A solution of t-BuLi (1.5 M in pentane, 1.25 mL, 1.88 mmol) was added dropwise, allowed to stir for 15 minutes, and then ethyl chloroformate (100 µL, 1.03 mmol) was added. The reaction mixture stirred for 30 min at -78 °C, and then warmed to room temperature over 30 min. The mixture was quenched with NaHCO₃, washed with H₂O and brine, dried over Na₂SO₄, and concentrated under vacuum.

To a solution of the resultant carboxylate-indole (0.295 g, 0.86 mmol) in THF (10 mL) was added TBAF (1 M in THF, 0.86 mL, 0.86 mmol). After stirring 15 min, the mixture was quenched with NH₄Cl, washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The oil was chromatographed (SiO₂, 25% EtOAc/hexanes) to afford 3.43 (0.094 g, 0.50 mmol) in 58% yield over 2 steps. The ¹H NMR spectrum matches that of the reported compound.¹⁴

Benzyl 1H-indole-3-carboxylate (3.44): Using the procedure from compound 3.43 with benzyl chloroformate, 3.44 (0.35 g, 1.41 mmol) was obtained in 62% yield as a white
solid: mp 142-145°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.63 (bs, 1H), 8.23-8.18 (m, 1H), 7.96 (d, $J = 3.0$ Hz, 1H), 7.55-7.26 (m, 8H), 5.49 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.1, 136.7, 136.1, 131.4, 128.5, 128.0 (2), 127.0, 123.2, 122.1, 121.4, 111.6, 108.5, 65.6; IR (film) 3398, 3298, 3128, 3066, 2958, 2881, 1676, 1529, 1429, 1328, 1244 cm$^{-1}$; HRMS (ES) $m/z$ = 252.0946 calcd for C$_{16}$H$_{14}$NO$_2$ [MH]$^+$, found 252.1071.

**Isopropyl 1H-indole-3-carboxylate (3.45):** Using the procedure from compound 3.43 with isopropyl chloroformate, 3.45 (0.26 g, 1.28 mmol) was obtained in 90% yield as an oil. The $^1$H NMR spectrum matches that of the reported compound.$^{30}$

**tert-Butyl 1H-indole-3-carboxylate (3.48):** Oxalyl chloride (320 µL, 3.72 mmol) was added to a suspension of indole-3-carboxylic acid (0.20 g, 1.24 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL), followed by a catalytic amount of anhydrous DMF (2 drops). The suspension was stirred at rt for 3 h. Removal of the solvent in vacuo gave the crude acid chloride as a yellow oil. To this material was added slightly warmed $t$-BuOH (1.7 mL), followed by KOt-Bu (0.226 g, 2.02 mmol). The resulting mixture was stirred for 90 min, diluted with Et$_2$O and washed with satd aq NH$_4$Cl and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated under vacuum. The oil was purified by chromatography.
(SiO₂, 40% EtOAc/Hexanes) to yield **3.48** (0.27 g, 1.24 mmol) in 100% yield as a white solid. The ′H NMR spectrum matches that of the reported compound[^31].

![Chemical Structure](image)

**N,N-Dimethyl-1H-indole-3-carboxamide (3.99):** Using the procedure from compound **3.43** with dimethylcarbamic chloride, **3.99** (0.32 g, 1.70 mmol) was obtained in 30% yield as a beige solid. ′H NMR spectrum matches that of the reported compound[^32].

![Chemical Structure](image)

**Methyl 5-methoxy-1H-indole-3-carboxylate (3.100):** Pyridine (0.30 mL, 3.54 mmol) was added to a suspension of 5-methoxy-1H-indole (0.40 g, 2.72 mmol) in anhydrous THF (6 mL) at 0 °C. A solution of trichloroacetyl chloride (0.40 mL, 3.54 mmol) in THF (6 mL) was added dropwise via an addition funnel over 1 h. The reaction mixture was then allowed to warm to room temperature to stir for 16 h. The reaction mixture was quenched in 1 M HCl, dried over Na₂SO₄, and concentrated under vacuum. The resulting solid was then dissolved in MeOH (54 mL), and aq. KOH (50 % by wt., 0.20 mL) was added. The reaction mixture was heated to reflux for 5 h, then stirred at ambient temperature for 1 h, followed by concentration under vacuum. The solid was purified by chromatography (SiO₂, 25% EtOAc/Hexanes) to yield **3.100** (0.50 g, 2.45 mmol) in 90% yield as a off-white solid: mp 141-142 °C; ′H NMR (500 MHz, CDCl₃) δ 8.87 (bs, 1H), 7.86 (d, J = 2.9 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.91 (dd, J = 2.3 Hz, 8.8 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H); ′C NMR (125 MHz, CDCl₃) δ 165.9, 132.9, 129.1, 124.2, 116.2, 111.4, 107.2, 105.6, 103.5, 103.3, 99.7, 55.7, 55.3, 54.8, 54.5.
Methyl 5-bromo-1H-indole-3-carboxylate (3.101): Using the procedure from 3.100 with 5-bromo-1H-indole, 3.101 (0.65 g, 2.57 mmol) was obtained in 50% yield as an off-white solid: mp 212-214 °C; 1H NMR (500 MHz, CDCl3) δ 8.60 (bs, 1H), 8.34 (d, J = 1.3 Hz, 1H), 7.92 (d, J = 2.9 Hz, 1H), 7.38 (dd, J = 1.8 Hz, 8.6 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 165.0, 134.7, 131.7, 127.4, 126.3, 124.3, 115.7, 112.9, 108.8, 51.2; IR (film) 3290, 2943, 1684, 1529, 1452, 1359, 1189 cm⁻¹; HRMS (CI) m/z = 253.1323 calcd for C10H9BrNO2 [MH]+, found 253.9817.

Methyl 7-methoxy-1H-indole-3-carboxylate (3.102): Using the procedure from 3.100 with 7-methoxy-1H-indole, 3.102 (0.56 g, 2.72 mmol) was obtained in 100% yield as a white solid. 1H NMR spectrum matches that of the reported compound.33
Representative Procedure (A) for Installation of an Allyl Alcohol to Indole Substrates:

Methyl 2-(2-methylallyloxy)-1H-indole-3-carboxylate (3.31): To a flame-dried round-bottom flask was added 3.95 (3.0 g, 17.13 mmol). CH₂Cl₂ (15 mL) was added and upon cooling to 0 °C, distilled 1,4-dimethylpiperazine (1.29 mL, 9.60 mmol) and recrystallized N-chlorosuccinimide (2.52 g, 19.02 mmol) were added. The resulting solution was stirred at 0 °C for 2 h. In a separate flame-dried round bottom flask, methallyl alcohol (2.9 mL, 34.26 mmol) and trichloroacetic acid (0.67 g, 4.11 mmol) were dissolved in CH₂Cl₂ (15 mL). The solution was cooled to 0 °C, and transferred via cannula to the indole solution. This mixture was stirred for 2 h at 0 °C, at which time the reaction mixture was concentrated under vacuum. It was then loaded onto a base-washed SiO₂ column (1% Et₃N, 24% EtOAc, 75% Hexanes) and eluted with 25% EtOAc/Hexanes to afford 3.31 (2.5 g) in 60% yield as a white solid: mp 92-94 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.63 (bs, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.23-7.14 (m, 3H), 5.18 (s, 1H), 5.05 (s, 1H), 4.81 (s, 2H), 3.93 (s, 3H), 1.86 (s, 3H); ¹³C NMR (90 MHz, THF-d₈) δ 164.5, 156.9, 141.4, 131.0, 127.2, 121.5, 121.4, 121.1, 113.1, 110.6, 89.9, 76.8, 49.9, 19.0; IR (film) 3231, 2949, 1660, 1552, 1475 cm⁻¹; HRMS (ES) m/z = 268.0950 calcd for C₁₄H₁₃NO₃Na [MNa]⁺, found 268.0950.
2-(allyloxy)-1H-indole-3-carbonitrile (3.24): Following the general procedure (A) 3.24 (0.05 g, 0.27 mmol) was obtained in 38% yield (59% brsm) as a white solid: mp 98-100 °C. 1H NMR (500 MHz, CDCl₃) δ 8.53 (bs, 1H), 7.55-7.53 (m, 1H), 7.26-7.14 (m, 3H), 5.54 (dd, J = 1.2, 17.2 Hz, 1H), 5.40 (dd, J = 1.1, 10.5 Hz, 1H), 5.10 (dt, J = 1.3, 5.5 Hz, 2H); IR (film) 3227, 3204, 2212, 1559, 1471, 1347 cm⁻¹; HRMS (Cl) m/z = 199.0793 calcd for C₁₂H₁₁N₂O [MH]+, found 199.0878.

2-(2-methylallyloxy)-1H-indole-3-carbonitrile (3.25): Following the general procedure (A) 3.25 (0.056 g, 0.26 mmol) was obtained in 38% yield as a white solid: mp 104-106 °C. 1H NMR (500 MHz, CDCl₃) δ 8.05 (bs, 1H), 7.58 (d, J = 3.7 Hz, 1H), 7.24-7.18 (m, 3H), 5.20 (s, 1H), 5.10 (s, 1H), 5.03 (s, 2H), 1.89 (s, 3H); 13C NMR (90 MHz, THF-d₈) δ 157.0, 139.7, 130.1, 127.3, 121.7, 121.1, 117.4, 114.8, 113.1, 110.5, 107.7, 75.0, 18.3; IR (film) 3223, 3173, 2926, 2212, 1563, 1471 cm⁻¹; HRMS (Cl) m/z = 213.0950 calcd for C₁₃H₁₂N₂O [MH]+, found 213.0994.

Ethyl 2-(2-methylallyloxy)-1H-indole-3-carboxylate (3.49): Following the general procedure (A) 3.49 (0.06 g, 0.23 mmol) was obtained in 47% yield as beige solid: mp 90-91 °C. 1H NMR (500 MHz, CDCl₃) δ 9.16 (bs, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.24-7.12
(m, 3H), 5.15 (s, 1H), 5.00 (s, 1H), 4.77 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 1.81 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H); \(^1^3\)C NMR (90 MHz, THF-d\(_8\)) \(\delta\) 164.0, 156.8, 141.4, 131.0, 127.3, 121.4, 121.3, 121.2, 113.0, 110.5, 90.2, 76.9, 58.9, 19.1, 14.7; IR (film) 3231, 2980, 1660, 1552, 1471 cm\(^{-1}\); HRMS (Cl) m/z = 260.1208 calcd for C\(_{15}\)H\(_{18}\)NO\(_3\) [MH\(^+\)], found 260.1299.

**Benzyl 2-(2-methylallyloxy)-1H-indole-3-carboxylate (3.50):** Following the general procedure (A) 3.50 (0.073 g, 0.23 mmol) was obtained in 45% yield as a brown oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.30 (bs, 1H), 7.51 (d, J = 7.3 Hz, 1H), 7.40-7.31 (m, 4H), 7.23-7.14 (m, 4H), 5.41 (s, 2H), 5.15 (s, 1H), 5.05 (s, 1H), 4.81 (s, 2H), 1.85 (s, 3H); \(^1^3\)C NMR (90 MHz, THF-d\(_8\)) \(\delta\) 163.9, 157.1, 141.2, 138.4, 131.1, 128.6, 128.3, 127.9, 127.3, 121.6, 121.4, 121.1, 113.2, 109.9, 89.7, 76.7, 64.9, 19.1; IR (film) 3250, 2926, 1660, 1552, 1475, 1455 cm\(^{-1}\); HRMS (ES) m/z = 344.1263 calcd for C\(_{20}\)H\(_{19}\)NO\(_3\)Na [MNa\(^+\)], found 344.1270.

**Isopropyl 2-(2-methylallyloxy)-1H-indole-3-carboxylate (3.51):** Following general procedure (A) 3.51 (0.191 g, 0.70 mmol) was obtained in 55% yield as a white solid: mp 88-90 °C \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.36 (bs, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.25-7.12 (m, 3H), 5.31-5.28 (m, 1H), 5.19 (s, 1H), 5.06 (s, 1H), 4.83 (s, 2H), 1.88 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); \(^1^3\)C NMR (90 MHz, THF-d\(_8\)) \(\delta\) 163.9, 157.1, 141.2, 138.4, 131.1, 128.6, 128.3, 127.9, 127.3, 121.6, 121.4, 121.1, 113.2, 109.9, 89.7, 76.7, 64.9, 19.1; IR (film) 3250, 2926, 1660, 1552, 1475, 1455 cm\(^{-1}\); HRMS (ES) m/z = 364.1263 calcd for C\(_{22}\)H\(_{21}\)NO\(_3\)Na [MNa\(^+\)], found 364.1270.
1.43 (d, J = 6.2 Hz, 6H); $^{13}$C NMR (90 MHz, THF-d$_8$) δ 163.7, 156.8, 141.4, 130.9, 127.4, 121.4, 121.3, 121.2, 113.0, 110.5, 90.5, 76.8, 65.9, 22.2, 19.1; IR (film) 3227, 2980, 2937, 1656, 1552, 1471, 1374 cm$^{-1}$; HRMS (ES) m/z = 296.1263 calcd for C$_{16}$H$_{19}$NO$_3$Na [MNa]$^+$, found 296.1267.

**tert-Butyl 2-(2-methylallyloxy)-1H-indole-3-carboxylate (3.52):** Following the general procedure (A) 3.52 (0.12 g, 0.418 mmol) was obtained in 34% yield as a pale yellow solid: mp 105-107 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.20 (bs, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.15-7.08 (m, 3H), 5.13 (s, 1H), 5.01 (s, 1H), 4.77 (s, 2H), 1.82 (s, 3H), 1.60 (s, 9H); $^{13}$C NMR (90 MHz, THF-d$_8$) δ 163.8, 156.6, 141.0, 129.9, 127.4, 121.2 (2), 121.1, 113.1, 110.4, 91.6, 78.6, 76.8, 28.6, 19.1; IR (film) 3237, 2976, 1656, 1552, 1459, 1366 cm$^{-1}$; HRMS (ES) m/z = 310.1419 calcd for C$_{17}$H$_{21}$NO$_3$Na [MNa]$^+$, found 310.1611.

**Methyl 2-(2-methylenebutoxy)-1H-indole-3-carboxylate (3.103):** Following the general procedure (A) 3.103 (0.257 g, 0.99 mmol) was obtained in 43% yield as a yellow oil: $^1$H NMR (300 MHz, CDCl$_3$) δ 8.30 (bs, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.26-7.15 (m, 3H), 5.23 (s, 1H), 5.09 (s, 1H), 4.89 (s, 2H), 3.93 (s, 3H), 2.23 (q, J = 7.0 Hz, 2H), 1.13 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (90 MHz, THF-d$_8$) δ 165.1, 157.5, 147.4, 131.5, 127.7, 122.0, 121.9, 121.6, 111.8, 111.1, 90.4, 76.4, 50.4, 26.6, 12.5; IR (film) 3229, 2966,
Representative Procedure (B) for Installation of an Allyl Alcohol to Indole Substrates:

Methyl 2-(allyloxy)-1H-indole-3-carboxylate (3.76): To a flame-dried round-bottomed flask was added 3.95 (0.30 g, 1.71 mmol). After dissolving in CH₂Cl₂ (4 mL) and cooling to 0 °C, 1,4-diazabicyclo[2.2.0]octane (DABCO) (0.108 g, 0.96 mmol) was added followed by recrystallized N-chlorosuccinimide (0.253 g, 1.90 mmol) were added. The resultant solution was stirred at 0 °C for 30 min, followed by addition of allyl alcohol (0.23 mL, 3.42 mmol) and methanesulfonic acid (0.016 mL, 0.24 mmol). This mixture was stirred for 30 min at 0 °C, at which time the reaction mixture was concentrated under vacuum and chromatographed on a base-washed SiC>2 column (1% Et₃N, 24% EtOAc, 75% Hexanes) using 25% EtOAc/Hexanes as the eluent to afford 3.76 (0.224 g, 0.97 mmol) in 57% yield as an off-white oil: mp 80-82 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.21 (bs, 1H), 8.05 (m, 1H), 7.22-7.18 (m, 3H), 6.13-6.05 (m, 1H), 5.49 (d, J = 17.2 Hz, 1H), 5.36 (d, J = 10.4 Hz, 1H), 4.95 (d, J = 5.7 Hz, 2H), 3.94 (s, 3H); ¹³C NMR (90 MHz, THF-d₈) δ 164.7, 157.0, 133.7, 131.0, 127.3, 121.6, 121.5, 121.2, 117.8, 110.7, 90.3, 74.4, 50.0; IR (film) 3229, 2997, 2950, 1668, 1552, 1468, 1328, 1251, 1213 cm⁻¹; HRMS
(ES) \( m/z = 254.0793 \) calcd for \( \text{C}_{13}\text{H}_{13}\text{NO}_3\text{Na} \) [MNa]⁺, found 254.0797. Compound was not stable in solution, and would rearrange while obtaining \(^{13}\text{C} \) NMR.

**Benzyl 2-(allyloxy)-1\(^H\)-indole-3-carboxylate (3.104):** Following the general procedure (B) 3.104 (0.121 g, 0.39 mmol) was obtained in 66% yield as a yellow oil: \(^1\text{H} \) NMR (360 MHz, THF-d\(_8\)) \( \delta \) 10.87 (bs, 1H), 8.07 (m, 1H), 7.53 (d, \( J = 7.3 \) Hz, 2H), 7.37-7.20 (m, 4H), 7.11-7.06 (m, 2H), 6.14-6.04 (m, 1H), 5.45 (dd, \( J = 1.6, 17.2 \) Hz, 1H), 5.39 (s, 2H), 5.24 (dd, \( J = 1.3, 10.5 \) Hz), 4.92 (m, 2H); \(^{13}\text{C} \) NMR (90 MHz, THF-d\(_8\)) \( \delta \) 164.1, 157.2, 138.4, 133.5, 131.2, 128.7, 128.2, 128.0, 127.3, 121.7, 121.6, 121.2, 118.0, 110.8, 90.1, 74.2, 64.9; IR (film) 3229, 3090, 3035, 2950, 2881, 1661, 1552, 1460, 1352, 1259, 1213 cm\(^{-1}\); HRMS (ES) \( m/z = 308.1284 \) calcd for \( \text{C}_{19}\text{H}_{18}\text{NO}_3 \) [MH]**⁺, found 308.1285. Compound was not stable in solution, and would rearrange while obtaining \(^{13}\text{C} \) NMR.

**Isopropyl 2-(allyloxy)-1\(^H\)-indole-3-carboxylate (3.105):** Following the general procedure (B) 3.105 (0.15 g, 0.59 mmol) was obtained in 80% yield as an off-white oil: \(^1\text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.22 (bs, 1H), 8.05 (d, \( J = 7.0 \) Hz, 1H), 7.25-7.19 (m, 3H), 6.18-6.05 (m, 1H), 5.49 (ddd, \( J = 1.4, 2.9, 17.2 \) Hz, 1H), 5.36 (ddd, 1.4, 2.9, 10.4 Hz, 1H), 5.35 (septet, \( J = 6.3 \) Hz, 1H), 4.96 (ddd, \( J = 1.3, 2.7, 5.7 \) Hz, 2H); 1.42 (d, \( J = 6.3 \) Hz, 6H); \(^{13}\text{C} \) NMR (90 MHz, THF-d\(_8\)) \( \delta \) 163.9, 156.9, 133.8, 131.5, 127.4, 121.5 (2),
121.3, 117.7, 110.7, 90.9, 74.4, 66.2, 22.3; IR (film) 3229, 2981, 2935, 1738, 1661, 1552, 1468, 1375, 1244, 1097 cm\(^{-1}\); HRMS (ES) \(m/z = 260.12084\) calcd for C\(_{15}\)H\(_{18}\)N\(_3\) [MH]\(^+\), found 260.1281. Compound was not stable in solution, and would rearrange while obtaining \(^{13}\)C NMR.

tert-Butyl 2-(allyloxy)-1\(H\)-indole-3-carboxylate (3.81): Following the general procedure (A) 3.81 (0.53 g, 1.94 mmol) was obtained in 77% yield as a white solid: mp 124-126 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.36 (bs, 1H), 8.01 (d, \(J = 7.0\) Hz, 1H), 7.25-7.13 (m, 3H), 6.15-6.02 (m, 1H), 5.46 (dd, \(J = 17.2, 1.4\) Hz, 1H), 5.33 (dd, \(J = 10.4, 1.2\) Hz, 1H), 4.92 (m, 2H), 1.66 (s, 9H); \(^{13}\)C NMR (90 MHz, THF-d\(_8\)) \(\delta\) 163.9, 156.7, 134.0, 130.9, 127.4, 121.4 (2), 121.3, 117.7, 110.6, 92.1, 81.6, 74.6, 28.6; IR (film) 3229, 2981, 2881, 1661, 1552, 1468, 1367, 1251, 1174, 1097 cm\(^{-1}\); HRMS (ES) \(m/z = 274.1365\) calcd for C\(_{16}\)H\(_{20}\)NO\(_3\) [MH]\(^+\), found 274.1435. Compound was not stable in solution, and would rearrange while obtaining \(^{13}\)C NMR.

2-(A\(llyloxy\))-N\(_2\),N-dimethyl-1\(H\)-indole-3-carboxamide (3.62): Following the general procedure (A) 3.62 (0.145 g, 0.59 mmol) was obtained in 59% yield as a beige solid: mp °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.85 (bs, 1H), 7.46 (d, \(J = 7.5\) Hz, 1H), 7.15 (d, \(J = 8.0\) Hz, 1H), 7.07 (m, 2H), 5.94 (m, 1H), 5.32 (d, \(J = 17.0,\) Hz, 1H), 5.24 (d, \(J = 10.5\) Hz, 1H), 4.65 (d, \(J = 5.5\) Hz, 2H), 3.11 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 167.2, 150.2, 100
132.5, 129.9, 126.3, 120.9, 120.7, 119.0, 118.6, 110.3, 91.2, 73.1, 38.6; IR (film) 3460, 3182, 3066, 2943, 2765, 1776, 1707, 1591, 1514, 1468, 1429, 1352, 1182 cm⁻¹; HRMS (ES) m/z = 245.1290 calcd for C₁₄H₁₇N₂O₂ [MH]⁺, found 245.1285.

Methyl 2-(2-methylallyloxy)-5-methoxy-1H-indole-3-carboxylate (3.106): Following the general procedure (B) 3.106 (0.03 g, 0.11 mmol) was obtained in 22% yield as an off-white oil: \(^1H\) NMR (300 MHz, CDCl₃) δ 8.44 (bs, 1H), 7.59 (m, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 5.19 (s, 1H), 5.06 (s, 1H), 4.79 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 1.89 (s, 3H); \(^1^C\) NMR (90 MHz, THF-d₈) δ 164.6, 157.1, 156.3, 141.5, 128.2, 125.6, 113.1, 111.2, 110.1, 104.2, 90.2, 76.8, 55.4, 49.9, 19.1; IR (film) 3244, 2950, 1668, 1591, 1552, 1468, 1352, 1274, 1205 cm⁻¹; HRMS (ES) m/z = 298.1056 calcd for C₁₅H₁₇NO₄Na [MNa]⁺, found 298.1066.

Methyl 2-(2-methylallyloxy)-5-bromo-1H-indole-3-carboxylate (3.107): Following the general procedure (B) 3.107 (0.07 g, 0.22 mmol) was obtained in 55% yield as an off-white oil: \(^1H\) NMR (300 MHz, CDCl₃) δ 8.23 (bs, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.26 (m, 1H), 7.09 (d, J = 8.5 Hz, 1H), 5.20 (s, 1H), 5.10 (s, 1H), 4.85 (s, 2H), 3.93 (s, 3H), 1.90 (s, 3H); \(^1^C\) NMR (90 MHz, THF-d₈) δ 164.2, 157.6, 141.1, 134.6, 129.1, 124.3, 123.5, 115.1, 113.4, 112.4, 89.7, 76.8, 50.7, 19.1; IR (film) 3221, 2950, 1668, 1552, 1483, 1352,
1251, 1213 cm\(^{-1}\); HRMS (ES) \(m/z = 346.0055\) calcd for \(C_{14}H_{14}BrNO_{3}\)Na [MNa]\(^+\), found 346.0045.

![Methyl 2-(2-methylallyloxy)-7-methoxy-1H-indole-3-carboxylate](image)

**Methyl 2-(2-methylallyloxy)-7-methoxy-1H-indole-3-carboxylate** (3.108): Following general procedure (B), 3.108 (0.086 g, 0.31 mmol) was obtained in 43% yield as a white resin: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.45\) (bs, 1H), 7.63 (d, \(J = 8.1\) Hz, 1H), 7.13 (t, \(J = 8.0\) Hz, 1H), 6.66 (d, \(J = 7.9\) Hz, 1H), 5.21 (s, 1H), 5.08 (s, 1H), 4.83 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 1.90 (s, 3H); \(^{13}\)C NMR (90 MHz, THF-d\(_8\)) \(\delta 164.0, 156.0, 145.4, 141.1, 127.5, 121.9, 121.3, 113.5, 112.6, 101.9, 90.5, 77.0, 54.6, 49.3, 18.6; IR (film) 3221, 1950, 2842, 1668, 1552, 1475, 1367, 1282, 1220 cm\(^{-1}\); HRMS (ES) \(m/z = 298.1056\) calcd for \(C_{15}H_{17}NO_{3}\)Na [MNa]\(^+\), found 298.1057.

![Methyl 2-(but-2-ynyloxy)-1H-indole-3-carboxylate](image)

**Methyl 2-(but-2-ynyloxy)-1H-indole-3-carboxylate** (3.109): Following the general procedure (A) 3.109 (0.327 g, 1.43 mmol) was obtained in 63% yield as a yellow oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.82\) (bs, 1H), 8.05 (d, \(J = 8.0\) Hz, 1H), 7.22 (m, 3H), 5.01 (q, \(J = 2.5\) Hz, 2H), 3.95 (s, 3H), 1.84 (t, \(J = 2.5\) Hz, 3H); \(^{13}\)C NMR (125 MHz, THF-d\(_8\)) \(\delta 163.5, 155.3, 129.9, 126.0, 120.7, 120.5, 120.3, 109.8, 90.0, 83.5, 73.3, 60.9, 49.0, 1.8; IR (film) 3229, 2997, 2950, 2881, 2757, 2317, 2240, 1668, 1552, 1468, 1344, 1267, 1205 cm\(^{-1}\); HRMS (ES) \(m/z = 244.0974\) calcd for \(C_{14}H_{14}NO_{3}\) [MH]\(^+\), found 244.0963.
Methyl 2-(1-deutero-2-methylenebutoxy)-1H-indole-3-carboxylate (3.96): Following the general procedure (A) 3.96 (0.036 g, 0.14 mmol) was obtained in 17% yield as a yellow resin: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.22 (bs, 1H), 8.04 (d, $J = 7.2$ Hz, 1H), 7.26-7.16 (m, 3H), 5.23 (t, $J = 1.1$ Hz, 1H), 5.09 (s, 1H), 4.86 (s, 1H), 3.91 (s, 3H), 2.23 (q, $J = 7.4$ Hz, 2H), 1.27 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (90 MHz, THF-d$_8$) $\delta$ 164.5, 157.0, 147.0, 131.1, 127.3, 121.5, 121.4, 121.2, 111.5, 110.6, 90.0, 75.8 (t, $J = 22.3$ Hz), 49.9, 26.2, 12.3; IR (film) 3229, 3090, 2935, 2881, 1668, 1570, 1470, 131.1, 127.3, 121.5, 121.4, 121.2, 111.5, 110.6, 90.0, 75.8 (t, $J = 22.3$ Hz), 49.9, 26.2, 12.3; IR (film) 3229, 3090, 2935, 2881, 1668, 1552, 1468, 1328, 1244 cm$^{-1}$; HRMS (ES) $m/z$ = 283.1169 calcd for C$_{15}$H$_{16}$DNO$_3$Na [MNa]$^+$, found 283.1165.

Cu(Ind-box)Cl$_2$ (3.110): To a round-bottomed flask was added CuCl$_2$ (0.06g, 0.45 mmol) and indanol bis(oxazoline) (0.175 g, 0.49 mmol), followed by addition of CH$_2$Cl$_2$ (10 mL). The resulting solution was allowed to stir at room temperature for 1 h, then concentrated under vacuum to give 3.110 (0.29 g, 0.51 mmol) in 100% yield as a green solid.

Pd(BINAP)Cl$_2$ (3.111): To a round-bottomed flask was added PdCl$_2$(MeCN)$_2$ (0.124 g, 0.48 mmol) and R-BINAP (0.300 g, 0.48 mmol), followed by addition of CH$_2$Cl$_2$ (15
The resulting solution was allowed to stir at room temperature for 24 h, then concentrated under vacuum to give 3.111 (0.384 g, 0.48 mmol) in 100% yield as a yellow solid.

\[
\begin{align*}
\text{Pd(}t\text{-BuPHOX)}\text{Cl}_2 (3.112): & \text{ To a round-bottomed flask was added PdCl}_2(\text{MeCN})_2 (0.20} \\
g, 0.52 \text{ mmol}) \text{ and 3.86a (0.133 g, 0.51 mmol), followed by addition of CH}_2\text{Cl}_2 (12 mL). \\
\text{The resulting solution was allowed to stir at room temperature for 24 h, then concentrated} \\
\text{under vacuum to give 3.112 (0.29 g, 0.51 mmol) in 100% yield as a yellow solid.}
\end{align*}
\]

**General Procedure for the Racemic Meerwein-Eschenmoser Claisen Rearrangement:**

3-Allyl-2-oxoindoline-3-carbonitrile (3.26): To a solution of 3.26 (0.015 g, 0.081 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.50 mL) was added SiO\textsubscript{2} (0.02 g, 0.32 mmol). The resulting solution was allowed to stir at room temperature until the starting material was consumed (2 d). The reaction mixture was filtered to remove the SiO\textsubscript{2}, then concentrated under vacuum to afford the rearranged product 3.26 (0.014 g, 0.075 mmol) as a white resin in 93% yield. 

\[ ^1\text{H} \text{NMR (500 MHz, CDCl}_3) \delta 8.70 (bs, 1H), 7.41-7.35 (m, 2H), 7.17 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 5.77-5.69 (m, 1H), 5.24 (d, J = 10.5 Hz, 1H), 5.21 (d, J = 17.2 Hz, 1H), 3.04 (dd, J = 6.4, 13.6 Hz, 1H), 2.82 (dd, J = 8.1, 13.5 Hz, 1H); ^13\text{C} \text{NMR (125} \]
MHz, CDCl₃) δ 172.2, 140.0, 130.4, 128.8, 125.3, 124.7, 123.7, 122.2, 116.4, 110.9, 46.9, 41.1, 22.7; IR (film) 3262, 2922, 2247, 1725, 1621, 1475 cm⁻¹; HRMS (CI): m/z = 199.0791 calcd for C₁₂H₁₀N₂O [MH]⁺, found 199.0866; CSP HPLC (Chiralpak AD, 1.0 mL/min, 95:5 hexanes:i-PrOH): tᵣ(ent-1) = 15.5 min, tᵣ(ent-2) = 18.3 min.

3-(2-Methylallyl)-2-oxoindoline-3-carbonitrile (3.27): Following the general procedure, 3.27 (0.011 g, 0.052 mmol) was obtained as a white resin in 73% yield. ¹H NMR (500 MHz, CDCl₃) δ 8.41 (bs, 1H), 7.34-7.25 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.86 (t, J = 1.5 Hz, 1H), 4.68 (s, 1H), 2.92 (d, J = 13.5 Hz, 1H), 2.79 (d, J = 13.5 Hz, 1H), 1.61 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.0, 140.6, 137.6, 130.2, 125.0, 123.2, 117.9, 117.2, 110.7, 64.4, 46.6, 44.0, 23.4; IR (film) 3250, 2926, 2856, 2227, 1729, 1621, 1475 cm⁻¹; HRMS (CI): m/z = 213.0950 calcd for C₁₂H₁₂N₂O [MH]⁺, found 213.104; CSP HPLC (Chiralpak AD, 1.0 mL/min, 95:5 hexanes:i-PrOH): tᵣ(ent-1) = 13.9 min, tᵣ(ent-2) = 16.1 min.

General Procedure for the Asymmetric Meerwein-Eschenmoser Claisen Rearrangement:

(S)-Methyl 3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.30): To a solution of 3.112 (0.004 g, 0.008 mmol) in CH₂Cl₂ (0.5 mL) was added via cannula a solution of
AgSbF$_6$ (0.005 g, 0.014 mmol) in CH$_2$Cl$_2$ (0.50 mL). The resulting solution was stirred in the absence of light for 3 h, and filtered through a PTFE filter to remove the precipitated AgCl. The resulting clear yellow solution was cooled to 0 °C, followed by addition of 3.31 (0.009 g, 0.038 mmol) in CH$_2$Cl$_2$ (1.0 mL) via cannula. The reaction mixture was stirred at 0 °C until the starting material was completely consumed, as determined by TLC. Filtration through a plug of SiO$_2$ (5 mm x 2 cm) with 25% EtOAc/Hexanes and concentration of the solution under vacuum 3.30 (0.008 g, 0.033 mmol) in 89% yield as a white resin: $[\alpha]_D^\circ$ +79.25 (c 0.40, 89% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.84 (bs, 1H), 7.27-7.26 (m, 2H), 7.05 (t, $J = 7.9$, 1H), 6.94 (d, $J = 7.7$ Hz, 1H), 4.65 (s, 1H), 4.63 (s, 1H), 3.69 (s, 3H), 3.06 (s, 2H), 1.41 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 176.1, 169.6, 141.3, 139.4, 129.1, 128.3, 124.4, 122.6, 115.7, 110.1, 59.9, 53.1, 41.2, 23.6; IR (film) 3250, 2953, 1741, 1702, 1621, 1475 cm$^{-1}$; HRMS (CI) m/z = 245.1052 calcd for C$_{14}$H$_{16}$N0$_3$ [MH]$^+$, found 246.1136; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): $t_R(R) = 16.5$ min, $t_R(S) = 20.3$ min.

(R)-Ethyl 3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.53): Following the general procedure except that 3.38c was employed, 3.53 (0.009 g, 0.033 mmol) was obtained as a white resin in 100% yield. $[\alpha]_D^\circ$ -48.44 (c 0.45, 79% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.93 (bs, 1H), 7.28-7.19 (m, 2H), 7.05 (t, $J = 7.6$ Hz, 1H), 6.89 (d, $J = 7.7$ Hz, 1H), 4.67 (d, $J = 16.6$ Hz, 2H), 4.17 (m, 2H), 3.07 (d, $J = 16.8$ Hz, 1H), 3.03 (d, $J = 16.8$ Hz, 1H), 1.42 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.6,
IR (film) 3250, 2980, 2922, 2853, 1718, 1621, 1475 cm$^{-1}$; HRMS (ES) $m/z = 282.1106$ calcd for C$_{15}$H$_{17}$NO$_3$Na [MNa]$^+$, found 282.1115; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): $t_R(R) = 13.0$ min, $t_R(S) = 20.0$ min.

(R)-Benzyl 3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.54): Following the general procedure except that 3.38c was employed, 3.54 (0.008 g, 0.025 mmol) was obtained as a pale yellow resin in 73% yield. [$\alpha$]$_D^{23}$ = -22.00 (c 0.55, 73% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.25 (bs, 1H), 7.25-7.13 (m, 7H), 7.02 (t, $J$ = 7.6 Hz, 1H), 6.88 (d, $J$ = 7.8 Hz, 1H), 5.12 (s, 2H), 4.66 (s, 1H), 4.62 (s, 1H), 3.07 (d, $J$ = 19.5 Hz, 1H), 3.03 (d, $J$ = 19.5 Hz, 1H), 1.41 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.6, 168.9, 141.3, 139.4, 135.3, 129.1, 128.4, 128.2, 128.1, 127.4, 124.4, 122.6, 115.7, 110.0, 67.3, 60.0, 40.9, 23.7; IR (film) 3242, 2926, 2856, 1718, 1621, 1471 cm$^{-1}$; HRMS (ES) $m/z = 344.1263$ calcd for C$_{20}$H$_{19}$NO$_3$Na [MNa]$^+$, found 344.1264; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): $t_R(R) = 17.8$ min, $t_R(S) = 27.8$ min.

(R)-Isopropyl 3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.55): Following the general procedure except that 3.38c was employed, 3.55 (0.004 g, 0.016 mmol) was obtained as a white resin in 100% yield. [$\alpha$]$_D^{23}$ = -22.00 (c 0.2, 65% ee, CH$_2$Cl$_2$); $^1$H NMR
(500 MHz, CDCl₃) δ 8.22 (bs, 1H), 7.25-7.21 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 5.02-4.97 (m, 1H), 4.65 (s, 1H), 4.62 (s, 1H), 3.04 (d, J = 18.5 Hz, 1H), 3.01 (d, J = 18.5 Hz, 1H), 1.41 (s, 3H), 1.21 (d, J = 6.2 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 175.6, 168.5, 141.2, 139.7, 128.9, 128.6, 124.2, 122.5, 115.5, 109.7, 69.7, 60.1, 40.9, 23.7, 21.4, 21.3; IR (film) 3250, 2984, 1733, 1621, 1475 cm⁻¹; HRMS (ES) m/z = 296.1263 calcd for C₁₆H₁₉NO₃Na [MNa]⁺, found 296.1264; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): tᵣ(R) = 7.7 min, tᵣ(S) = 11.8 min.

(S)-tert-Butyl 3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.56): Following the general procedure except that 3.66 was employed, 3.56 (0.018 g, 0.063 mmol) was obtained in 82% yield as a white resin: [α]²¹D +66.89 (c 0.90, 82% ee, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 9.09 (bs, 1H), 7.23 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 4.61 (s, 2H), 3.04 (d, J = 13.9 Hz, 1H), 2.97 (d, J = 13.9 Hz, 1H), 1.38 (s, 3H), 1.36 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 175.6, 167.9, 141.1, 139.9, 129.0, 128.8, 124.1, 122.4, 115.3, 109.6, 82.5, 60.7, 40.8, 27.7, 23.7; IR (film) 3262, 2980, 2930, 1733, 1621, 1475 cm⁻¹; HRMS (ES) m/z = 310.1419 calcd for C₁₇H₂₁NO₃Na [MNa]⁺, found 310.1416; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): tᵣ(R) = 6.1 min, tᵣ(S) = 9.2 min.
(S)-Methyl 3-(2-methylenebutyl)-2-oxoindoline-3-carboxylate (3.78): Following the general procedure except that 3.86a was employed, 3.78 (0.009 g, 0.03 mmol) was obtained in 82% yield as a white resin: \([\alpha]_D^{23} +59.00 (c 0.45, 92\% \text{ ee, CH}_2\text{Cl}_2); \)\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.12 (bs, 1H), 7.28-7.23 (m, 2H), 7.05 (t, \(J = 7.5\) Hz, 1H), 6.88 (d, \(J = 7.7\) Hz, 1H), 4.66 (t, \(J = 1.4\) Hz, 1H), 4.64 (s, 1H), 3.69 (s, 3H), 3.08 (d, \(J = 16.7\) Hz, 1H), 3.05 (d, \(J = 16.8\) Hz, 1H), 1.68 (q, \(J = 7.4\) Hz, 2H), 0.84 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 176.0, 169.7, 145.0, 141.3, 129.1, 128.3, 124.4, 122.6, 113.2, 110.0, 60.0, 53.1, 39.5, 29.7, 12.3; IR (film) 3275, 2927, 2858, 1715, 1622, 1444, 1236 cm\(^{-1}\); HRMS (CI) \(m/z = 260.1287\) calced for C\(_{15}\)H\(_{18}\)NO\(_3\) [MH]\(^+\), found 259.1208; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): \(t_R(R) = 13.6\) min, \(t_R(S) = 15.8\) min.

(S)-Methyl 3-allyl-2-oxoindoline-3-carboxylate (3.77): Following the general procedure except that 3.86a was employed, 3.77 (0.10 g, 0.043 mmol) was obtained in 100% yield as a white resin: \([\alpha]_D^{23} +51.30 (c 0.50, 83\% \text{ ee, CH}_2\text{Cl}_2); \)\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.20 (bs, 1H), 7.28-7.25 (m, 2H), 7.07 (t, \(J = 7.6\) Hz, 1H), 6.92 (d, \(J = 7.9\) Hz, 1H), 5.49-5.41 (m, 1H), 5.08 (dd, \(J = 1.2, 17.0\) Hz, 1H), 4.97 (d, \(J = 10.1\) Hz, 1H), 3.71 (s, 3H), 3.04 (dd, \(J = 6.7, 13.8\) Hz, 1H), 2.97 (dd, \(J = 7.9, 13.8\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 175.6, 169.3, 141.1, 130.8, 129.1, 128.0, 124.0, 122.8, 120.0, 110.0, 109
59.6, 53.1, 38.4; IR (film) 3252, 3090, 2858, 1715, 1622, 1475, 1437, 1336, 1236 cm\(^{-1}\); HRMS (ES) \(^{m/z}\) = 254.0793 calcd for C\(_{13}\)H\(_{13}\)NO\(_3\)Na [MNa]\(^+\), found 254.0791; CSP HPLC (Chiralpak AD, 1.0 mL/min, 95.5 hexanes:i-PrOH): \(t_R(S) = 18.4\) min, \(t_R(R) = 20.6\) min.

**((S)-Benzy1 3-allyl-2-oxoindoline-3-carboxylate (3.79):** Following the general procedure except that 3.66 was employed, 3.79 (0.008 g, 0.03 mmol) was obtained in 74% yield as a white resin: [\(\alpha\)]\(_D\)\(^{21}\) +51.38 (c 0.40, 72% ee, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.28 (bs, 1H), 7.28-7.22 (m, 5H), 7.17-7.16 (m, 2H), 7.05 (td, \(J = 7.5, 0.9\) Hz, 1H), 6.90 (d, \(J = 7.8\) Hz, 1H), 5.50-5.41 (m, 1H), 5.16 (d, \(J = 15.5\) Hz, 1H), 5.14 (d, \(J = 15.6\) Hz, 1H), 5.08 (dd, \(J = 1.4, 16.9\) Hz, 1H), 4.96 (dd, \(J = 1.7, 10.1\) Hz, 1H), 3.05 (dd, \(J = 6.7, 13.9\) Hz, 1H), 2.99 (dd, \(J = 7.9, 13.9\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 175.3, 168.6, 141.2, 135.3, 130.8, 129.1, 128.4, 128.1, 128.0, 127.4, 124.0, 122.7, 120.0, 110.0, 67.3, 59.7, 38.2; IR (film) 3259, 3066, 2927, 1715, 1622, 1468, 1336 cm\(^{-1}\); HRMS (ES) \(^{m/z}\) = 308.12084 calcd for C\(_{19}\)H\(_{18}\)NO\(_3\) [MH]\(^+\), found 308.1273; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): \(t_R(R) = 20.7\) min, \(t_R(S) = 29.7\) min.

**((S)-Isopropyl 3-allyl-2-oxoindoline-3-carboxylate (3.80):** Following the general procedure except that 3.66 was employed, 3.80 (0.01 g, 0.04 mmol) was obtained in 91%
yield as a white resin: $[\alpha]_D^{20} +44.20$ (c 0.50, 74% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.04 (bs, 1H), 7.25-7.23 (m, 2H), 7.05 (t, $J = 7.6$ Hz, 1H), 6.90 (d, $J = 7.8$ Hz, 1H), 5.50-5.41 (m, 1H), 5.07 (d, $J = 17.0$ Hz, 1H), 5.02 (m, 1H), 5.00 (d, $J = 10.1$ Hz, 1H), 3.01 (dd, $J = 6.7$, 13.8 Hz, 1H), 2.95 (dd, $J = 7.8$, 13.8, 1H), 1.23 (d, $J = 6.3$ Hz, 3H), 1.13 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.5, 168.3, 141.1, 131.0, 128.9, 128.4, 123.9, 122.7, 119.8, 109.8, 69.7, 59.8, 38.3, 21.5, 21.3; IR (film) 3252, 3090, 2981, 2958, 1722, 1622, 1468, 1236 cm$^{-1}$; HRMS (ES) m/z = 282.1208 calcd for C$_{15}$H$_7$NO$_3$Na [MNa]$^+$, found 282.1092; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): $t_R(R) = 11.8$ min, $t_R(S) = 14.9$ min.

(S)-$\text{tert-Butyl}$ 3-allyl-2-oxindoline-3-carboxylate (3.73): Following the general procedure except that 3.69 was employed, 3.73 (0.006 g, 0.02 mmol) was obtained in 60% yield as a white resin: $[\alpha]_D^{20} +106.5$ (c 0.30, 92% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.95 (bs, 1H), 7.26-7.23 (m, 2H), 7.05 (t, $J = 7.6$ Hz, 1H), 6.89 (d, $J = 7.8$ Hz, 1H), 5.50 (m, 1H), 5.06 (d, $J = 17.0$ Hz, 1H), 4.94 (d, $J = 10.1$ Hz, 1H), 2.98-2.90 (m, 2H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.9, 167.7, 141.2, 131.2, 128.8, 128.7, 123.7, 122.6, 119.5, 109.7, 82.5, 60.5, 38.2, 27.7; IR (film) 3252, 3090, 2981, 2927, 1722, 1622, 1475, 1251, 1159 cm$^{-1}$; HRMS (Cl) m/z = 274.1459 calcd for C$_{16}$H$_{20}$NO$_3$ [MH]$^+$, found 274.1362; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): $t_R(R) = 7.2$ min, $t_R(S) = 8.8$ min.
3-allylindolin-2-one (3.61): Following the general racemic procedure 3.61 was obtained as a white resin: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.12 (bs, 1H), 7.23 (m, 2H), 7.00 (dt, $J =$ 0.5, 7.5 Hz, 1H), 6.89 (d, $J =$ 8.0 Hz, 1H), 4.91 (s, 1H), 4.79 (s, 1H), 3.60 (dd, $J =$ 4.5, 9.5 Hz, 1H), 2.83 (dd, $J =$ 4.0, 14.5 Hz, 1H), 2.41 (dd, $J =$ 10.0, 14.0 Hz, 1H), 1.83 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.7, 141.8, 141.1, 129.5, 127.9, 124.9, 122.1, 113.6, 109.5, 43.9, 38.9, 22.2; IR (film) 3213, 3082, 2935, 1707, 1622, 1468, 1336, 1228 cm$^{-1}$; HRMS (ES) $m/z$ = 210.0895 calcd for C$_{12}$H$_{13}$NONa [M+Na]$^+$, found 210.0870.

(S)-Methyl 5-methoxy-3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.87): Following the general procedure except that 3.86a was employed, 3.87 (0.006 g, 0.02 mmol) was obtained in 60% yield as a white resin: $[\alpha]_D^{20}$ $+40.83$ ($c$ 0.30, 91% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.55 (bs, 1H), 6.88 (s, 1H), 6.80 (m, 2H), 4.70 (s, 1H), 4.65 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.05 (d, $J =$ 19.5 Hz, 1H), 3.02 (d, $J =$ 19.4 Hz, 1H), 1.42 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.6, 169.6, 155.9, 139.4, 134.5, 129.5, 115.7, 113.9, 111.3, 110.3, 60.2, 55.8, 53.2, 41.2, 23.7; IR (film) 3259, 2927, 2858, 1715, 1607, 1491, 1444, 1236 cm$^{-1}$; HRMS (ES) $m/z$ = 276.1158 calcd for C$_{15}$H$_{18}$NO$_4$ [MH]$^+$, found 276.1248; CSP HPLC (Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): $t_R(R) = 20.7$ min, $t_R(S) = 23.8$ min.
**Methyl 5-bromo-3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.88):** Following the general procedure except that 3.86a was employed, 3.88 (0.009 g, 0.03 mmol) was obtained in 82% yield as a white resin: $[\alpha]_D^{25} +38.67$ (c 0.45, 87% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.34 (bs, 1H), 7.40 (m, 2H), 6.80 (d, $J = 8.7$ Hz, 1H), 4.70 (s, 1H), 4.63 (s, 1H), 3.72 (s, 3H), 3.05 (d, $J = 19.8$ Hz, 1H), 3.02 (d, $J = 19.8$ Hz, 1H), 1.46 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.3, 168.9, 140.2, 139.0, 132.0, 130.2, 127.7, 116.1, 115.2, 114.4, 59.9, 53.4, 41.2, 23.7; IR (film) 3252, 2958, 2858, 1738, 1614, 1475, 1228 cm$^{-1}$; HRMS (ES) $m/z = 324.0157$ calcd for C$_{14}$H$_{15}$BrNO$_3$ [MH]$^+$, found 324.0240; CSP HPLC (Chiralpak AS, 1.0 mL/min, 92.5:7.5 hexanes:i-PrOH): $t_R(R) = 15.1$ min, $t_R(S) = 25.5$ min.

**Methyl 7-methoxy-3-(2-methylallyl)-2-oxoindoline-3-carboxylate (3.90):** Following the general procedure except that 3.86a was employed, 3.90 (0.009 g, 0.03 mmol) was obtained in 95% yield as a white resin: $[\alpha]_D^{25} +82.78$ (c 0.450, 85% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.65 (bs, 1H), 7.01 (t, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 7.5$ Hz, 1H), 6.84 (d, $J = 8.1$ Hz, 1H), 4.67 (s, 1H), 4.64 (s, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.04 (m, 2H), 1.43 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.7, 169.6, 143.8, 139.5, 130.1, 128.9, 123.1, 116.6, 115.6, 111.3, 60.5, 55.6, 53.1, 41.0, 23.7; IR (film)
(S)-Methyl 3-(buta-2,3-dien-2-yl)-2-oxoindoline-3-carboxylate (3.91): Following the general procedure except that 3.86a was employed, 3.91 (0.004 g, 0.017 mmol) was obtained in 44% yield as a white resin: [α]$_D^{23}$ +84.25 (c 0.20, 39% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.25 (bs, 1H), 7.34 (d, $J=7.5$ Hz, 1H), 7.27 (dt, $J=1.0, 7.5$ Hz, 2H), 7.06 (dt, $J=1.0, 8.0$ Hz, 1H), 6.90 (d, $J=8.0$ Hz, 1H), 4.81 (dq, $J=3.0, 10.5$ Hz, 1H), 4.65 (dq, $J=3.0, 10.5$ Hz, 1H), 3.76 (s, 3H), 1.90 (t, $J=3.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.7, 174.0, 168.2, 140.7, 129.3, 127.4, 126.1, 122.6, 109.8, 97.2, 77.9, 62.3, 53.2, 15.3; IR (film) 3252, 3066, 2958, 2858, 1962, 1738, 1622, 1475, 1437, 1236, 1189 cm$^{-1}$; HRMS (ES) m/z = 244.0950 calcd for C$_{14}$H$_{14}$NO$_3$ [MH]$^+$, found 244.0962; HPLC (Chiralpak AD, 1.0 mL/min, 95:5 hexanes:i-PrOH): $t_R$(ent-1) = 17.7 min, $t_R$(ent-2) = 20.1 min.

(S)-Methyl 3-(2-(deuteromethylene)butyl)-2-oxoindoline-3-carboxylate (3.97): Following the general procedure except that 3.86a was employed, 3.97 (0.008 g, 0.03 mmol) was obtained in 80% yield as a white resin: [α]$_D^{23}$ +43.13 (c 0.40, 92% ee, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.04 (bs, 1H), 7.32-7.24 (m, 2H), 7.05 (t, $J=7.6$ Hz, 1H), 5.52 (t, $J=7.6$ Hz, 1H), 4.25 (s, 3H), 2.34 (s, 3H); IR (film) 3252, 3057, 2926, 2858, 1962, 1738, 1622, 1475, 1437, 1236, 1189 cm$^{-1}$; HRMS (ES) m/z = 244.0950 calcd for C$_{14}$H$_{14}$NO$_3$ [MH]$^+$, found 244.0964; HPLC (Chiralpak AD, 1.0 mL/min, 95:5 hexanes:i-PrOH): $t_R$(ent-1) = 17.7 min, $t_R$(ent-2) = 20.1 min.
Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 4.63 (s, 0.5 H, Z-deutero), 4.62 (s, 0.5 H, E-deutero),
3.70 (s, 3H), 3.07 (d, J = 16.3 Hz, 1H), 3.04 (d, J = 16.2 Hz, 1H), 1.68 (q, J = 7.3 Hz,
2H), 0.84 (t, J = 7.4 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 175.8, 169.9, 145.1, 141.4,
129.3, 128.6, 124.7, 122.8, 113.1 (t, J′CD = 23.6 Hz), 110.1, 60.2, 53.4, 39.7, 29.9, 12.5;
IR (film) 3252, 3090, 2981, 2935, 1715, 1622, 1475, 1375, 1251, 1159 cm−1; HRMS (ES)
m/z = 283.1169 calcd for C15H16DNO3Na [MNa]+, found 283.1173; CSP HPLC
(Chiralpak OD, 1.0 mL/min, 96.5:3.5 hexanes:i-PrOH): tR(R) = 13.6 min, tR(S) = 15.8
min.

Bromosulfonyl derivative of 3.30 (3.72): To a solution of 60% NaH in oil (0.004 g, 0.09
mmol) in THF (1 mL) at 0 °C was added 3.30 (0.011 g, 0.045 mmol). After stirring 5
min, 4-bromobenzene-1-sulfonyl chloride (0.013 g, 0.049 mmol) was added and the
mixture was warmed to rt. After 20 min, H2O was added, and the aqueous layer was
extracted with CH2Cl2, dried over Na2SO4, and concentrated under vacuum to give the
bromosulfonyl derivative as a white solid. 1H NMR (300 MHz, CDCl3) δ 7.94 (m, 3H),
7.68 (d, J = 8.6 Hz, 2H), 7.41 (m, 1H), 7.25 (m, 2H), 4.38 (t, J = 1.5 Hz, 1H), 4.33 (s,
1H), 3.53 (s, 3H), 2.97 (s, 2H).
**N-Camphorsulfonyl derivative of 3.73 (3.75):** To a solution of 60% NaH in oil (0.003 g, 0.13 mmol) in THF (2 mL) at 0 °C was added 3.73 (0.018 g, 0.07 mmol). After stirring 5 min, camphorsulfonyl chloride 3.74 (0.0180 g, 0.07 mmol) was added and the mixture was warmed to rt. After 2 h, H₂O was added, and the aqueous layer was extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated under vacuum to give the camphorsulfonyl derivative in 47% yield as a white solid (0.015 g, 0.03 mmol) which was used without further purification.

The camphorsulfonyl derivative (0.015 g, 0.03 mmol) was treated with a solution of 2,4-dinitrophenylhydrazine (0.26 mL, 0.12 M) in 1:1 H₂SO₄/MeOH. The resulting solution was allowed to stir for 10 min, then cooled to 0 °C, whereupon formation of crystals were observed after 24 h. Instead of obtaining the expected hydrazone, the transesterified methyl ester product was observed. The configuration obtained from the crystal structure was used to establish the absolute stereochemistry of 3.73. The remaining compounds were assigned by analogy. ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, J = 8.3 Hz, 1H), 7.39-7.32 (m, 2H), 7.23 (t, J = 7.5 Hz, 1H), 5.46-5.36 (m, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 3.86 (d, J = 15.0 Hz, 1H), 3.72 (s, 3H), 3.54 (d, J = 14.9 Hz, 1H), 3.06 (m, 2H), 2.50-2.38 (m, 2H), 2.16-2.14 (m, 1H), 2.11-2.04 (m, 1H), 1.98-1.94 (m, 1H), 1.82-1.76 (m, 1H), 1.50-1.44 (m, 1H), 1.16 (s, 3H), 0.91 (s, 3H).
References:


(18) In order to achieve reproducible results, the [Cu(S,S)-box]Cl₂ complex was premade on a larger scale (100-200 mg) to ensure an accurate ratio of copper to ligand (0.92 to 1.0). The copper chloride complex was then treated with AgOTf, AgBF₄, or AgSbF₆, to exchange the counterion on the copper.

(19) In addition, all glassware was base-washed to ensure there was no trace acid to catalyze the rearrangement.


(23) Palladium(II)-BINAP was used at 20 mol%, giving only 15% ee with a 5% standard deviation.


Appendix A: Spectroscopic Data
Figure A1. 500 MHz $^1$H NMR Spectrum of Compound 1.34 in CDCl$_3$
Figure A2. 125 MHz $^{13}$C NMR Spectrum of Compound 1.34 in CDCl$_3$.
Figure A3. IR Spectrum of Compound 1.34
Figure A4. 500 MHz $^1$H NMR Spectrum of Compound 1.35 in CDCl$_3$
Figure A5. 90 MHz $^{13}$C NMR Spectrum of Compound 1.35 in CDCl$_3$
Figure A6. IR Spectrum of Compound 1.35
Figure A7. 500 MHz $^1$H NMR Spectrum of Compound 1.36 in acetone-$d_8$
Figure A8. 125 MHz $^{13}$C NMR Spectrum of Compound 1.36 in CDCl$_3$
Figure A9. IR Spectrum of Compound 1.36
Figure A10. 500 MHz $^1$H NMR Spectrum of Compound 1.33 in CDCl$_3$
Figure A11. 125 MHz $^{13}$C NMR Spectrum of Compound 1.33 in CDCl$_3$
Figure A12. IR Spectrum of Compound 1.33
Figure A13. 500 MHz $^1H$ NMR Spectrum of Compound 1.27 in CDC$_3$
Figure A14. 125 MHz $^{13}$C NMR Spectrum of Compound 1.27 in CDCl$_3$
Figure A15. IR Spectrum of Compound 1.27
Figure A16. 500 MHz 1H NMR Spectrum of Compound 1.46 in CDCl₃
Figure A.17. 125 MHz $^{13}$C NMR Spectrum of Compound 1.46 in CDCl$_3$. 

![125 MHz $^{13}$C NMR Spectrum of Compound 1.46 in CDCl$_3$](image)
Figure A18. IR Spectrum of Compound 1.46
Figure A19. 500 MHz $^1$H NMR Spectrum of Compound 1.37 in CDCl$_3$
Figure A20. 500 MHz $^1$H NMR Spectrum of Compound 1.40 in CDCl$_3$
Figure A21. 125 MHz $^{13}$C NMR Spectrum of Compound 1.40 in CDCl$_3$
Figure A22. IR Spectrum of Compound 1.40
Figure A23. 500 MHz ¹H NMR Spectrum of Compound 1.19 in CDCl₃
Figure A24. 125 MHz $^{13}$C NMR Spectrum of Compound 1.19 in CDCl$_3$. 
Figure A25. IR Spectrum of Compound 1.19
Figure A26. 500 MHz $^1$H NMR Spectrum of Compound 2.61
Figure A27. 125 MHz $^{13}$C NMR Spectrum of Compound 2.61 in CDCl$_3$. 
Figure A28. IR Spectrum of Compound 2.61
Figure A29. 360 MHz $^1$H NMR Spectrum of Compound 2.68 in Acetone-$d_8$
Figure A30. 90 MHz $^{13}$C NMR Spectrum of Compound 2.68 in Acetone-$d_8$
Figure A31. IR Spectrum of Compound 268

[Diagram of IR spectrum with labeled wavenumbers and a structural formula of a compound]
Figure A32. 360 MHz $^1$H NMR Spectrum of Compound 2.69 in Acetone-d$_8$
Figure A33. 90 MHz $^{13}$C NMR Spectrum of Compound 2.69 in Acetone-$d_8$
Figure A34. IR Spectrum of Compound 2.69
Figure A35. 360 MHz H NMR Spectrum of Compound 2.70 in Acetone-d$_8$
Figure A36. 90 MHz $^{13}$C NMR Spectrum of Compound 2.70 in Acetone-d$_8$
Figure A37. IR Spectrum of Compound 2.70
Figure A38. 500 MHz $^1$H NMR Spectrum of Compound 3.42 in CDCl$_3$
Figure A39. 125 MHz $^{13}\text{C}$ NMR Spectrum of Compound 3.42 in CDCl$_3$
Figure A41. 500 MHz $^1$H NMR Spectrum of Compound 3.44 in CDCl$_3$
Figure A42. 125 MHz $^{13}$C NMR Spectrum of Compound 3.44 in CDCl$_3$
Figure A43. IR Spectrum of Compound 3.44
Figure A44. 500 MHz ¹H NMR Spectrum of Compound 3.100 in CDCl₃
Figure A45. 125 MHz $^{13}$C NMR Spectrum of Compound 3.100 in CDCl$_3$
Figure A47. 500 MHz 1H NMR Spectrum of Compound 3.101 in CDCl$_3$
Figure A48. 125 MHz $^{13}$C NMR Spectrum of Compound 3.101 in CDCl$_3$
Figure A49. IR Spectrum of Compound 3.101
Figure A50. 360 MHz $^1$H NMR Spectrum of Compound 3.31 in CDCl$_3$
Figure A51. 90 MHz $^{13}$C NMR Spectrum of Compound 3.31 in THF-$d_8$
Figure A52. IR Spectrum of Compound 3.31
Figure A53. 500 MHz $^1$H NMR Spectrum of Compound 3.24 in CDCl$_3$
Figure A55. IR Spectrum of Compound 3.24
Figure A56. 500 MHz $^1$H NMR Spectrum of Compound 3.25 in CDCl$_3$
Figure A57. 90 MHz $^{13}$C NMR Spectrum of Compound 3.25 in THF-d$_8$
Figure A58. IR Spectrum of Compound 3.25
Figure A59. 500 MHz H NMR Spectrum of Compound 3.49 in CDCl₃
Figure A60. 90 MHz $^{13}$C NMR Spectrum of Compound 3.49 in THF-$d_8$
Figure A61. IR Spectrum of Compound 3.49
Figure A62. 500 MHz $^1$H NMR Spectrum of Compound 3.50 in CDCl$_3$
Figure A63. 90 MHz $^{13}$C NMR Spectrum of Compound 3.50 in THF-d$_8$
Figure A64. IR Spectrum of Compound 3.50
Figure A65. 500 MHz $^1$H NMR Spectrum of Compound 3.51 in CDCl$_3$
Figure A66. 90 MHz $^{13}$C NMR Spectrum of Compound 3.51 in THF-d$_8$
Figure A67. IR Spectrum of Compound 3.51

Wavenumber (cm$^{-1}$)
Figure A68. 500 MHz $^1$H NMR Spectrum of Compound 3.52 in CDCl$_3$. 

Figure A68.
Figure A69. 90 MHz $^{13}$C NMR Spectrum of Compound 3.52 in THF-d$_8$
Figure A70. IR Spectrum of Compound 3.52
Figure A71. 300 MHz $^1$H NMR Spectrum of Compound $3.103$ in CDCl$_3$
Figure A72. 90 MHz $^{13}$C NMR Spectrum of Compound 3.103 in THF-d$_8$
Figure A.73. IR Spectrum of Compound 3.103
Figure A74. 300 MHz $^1$H NMR Spectrum of Compound 3.76 in CDCl$_3$
Figure A75. 90 MHz $^{13}$C NMR Spectrum of Compound 3.75 in THF-d$_8$
Figure A76. IR Spectrum of Compound 3.75
Figure A77. 360 MHz $^1$H NMR Spectrum of Compound 3.104 in THF-d$_8$
Figure A78. 90 MHz $^{13}$C NMR Spectrum of Compound 3.104 in THF-$d_8$
Figure A79. IR Spectrum of Compound 3.104
Figure A80. 300 MHz $^1$H NMR Spectrum of Compound 3.105 in CDCl$_3$
Figure A81. 90 MHz $^{13}\text{C}$ NMR Spectrum of Compound 3.105 in THF-$d_8$. 
Figure A82. IR Spectrum of Compound 3.105
Figure A83. 300 MHz $^1$H NMR Spectrum of Compound 3.81 in CDCl$_3$
Figure A84. 90 MHz $^{13}$C NMR Spectrum of Compound 3.81 in THF-$d_8$
Figure A85. IR Spectrum of Compound 3.81
Figure A86. 300 MHz $^1$H NMR Spectrum of Compound 3.62 in CDCl$_3$
Figure A87. 75 MHz $^{13}$C NMR Spectrum of Compound 3.62 in THF-d$_8$
Figure A88. IR Spectrum of Compound 3.62
Figure A89. 300 MHz $^1$H NMR Spectrum of Compound 3.106 in CDCl$_3$
Figure A90. 90 MHz $^{13}$C NMR Spectrum of Compound 3.106 in THF-d$_8$. 

[Diagram of NMR spectrum with chemical structure formula 3.106]
Figure A91. IR Spectrum of Compound 3.106
Figure A92. 300 MHz $^1$H NMR Spectrum of Compound 3.107 in CDCl$_3$
Figure A93. 90 MHz $^{13}$C NMR Spectrum of Compound 3.107 in THF-d$_8$
Figure A94. IR Spectrum of Compound 3.107
Figure A95. 500 MHz ¹H NMR Spectrum of Compound 3.108 in CDCl₃
Figure A96. 90 MHz $^{13}$C NMR Spectrum of Compound 3.108 in THF-$d_8$
Figure A97. IR Spectrum of Compound 3.108
Figure A98. 500 MHz $^1$H NMR Spectrum of Compound 3.109 in CDCl$_3$
Figure A99. 125 MHz $^{13}$C NMR Spectrum of Compound 3.109 in THF-d$_6$
Figure A100. IR Spectrum of Compound 3.109
Figure A101. 500 MHz $^1$H NMR Spectrum of Compound 3.96 in CDCl$_3$.
Figure A102. 90 MHz $^{13}$C NMR Spectrum of Compound 3.96 in THF-d$_8$
Figure A103. IR Spectrum of Compound 3.96
Figure A104. 500 MHz $^1$H NMR Spectrum of Compound 3.26 in CDCl$_3$
Figure A105. 125 MHz $^{13}$C NMR Spectrum of Compound 3.26 in CDCl$_3$. 

![Chemical Structure](image)
Figure A106. IR Spectrum of Compound 3.26
Figure A107. 500 MHz $^1$H NMR Spectrum of Compound 3.27 in CDCl$_3$
Figure A108. 125 MHz $^{13}$C NMR Spectrum of Compound 3.27 in CDCl$_3$
Figure A109. IR Spectrum of Compound 3.27
Figure A110. 500 MHz $^1$H NMR Spectrum of Compound 3.30 in CDCl$_3$. 

![NMR Spectrum Diagram](image)
Figure A111. 125 MHz $^{13}$C NMR Spectrum of Compound 3.30 in CDCl$_3$
Figure A112. IR Spectrum of Compound 3.30
Figure A113. 500 MHz $^1$H NMR Spectrum of Compound 3.53 in CDCl$_3$
Figure A114. 125 MHz $^{13}$C NMR Spectrum of Compound 3.53 in CDCl$_3$
Figure A115. IR Spectrum of Compound 3.53
Figure A116. 500 MHz ¹H NMR Spectrum of Compound 3.54 in CDCl₃
Figure A117 125 MHz $^{13}$C NMR Spectrum of Compound 3.54 in CDCl$_3$
Figure A118. IR Spectrum of Compound 3.54

[Diagram of IR spectrum with peaks labeled]

239
Figure A119. 500 MHz $^1$H NMR Spectrum of Compound 3.55 in CDCl$_3$.
Figure A120. 125 MHz $^{13}$C NMR Spectrum of Compound 3.55 in CDCl$_3$. 

[Chemical structure diagram]
Figure A121. IR Spectrum of Compound 3.55
Figure A122. 500 MHz $^1$H NMR Spectrum of Compound 3.56 in CDCl$_3$
Figure A123. 125 MHz $^{13}$C NMR Spectrum of Compound 3.56 in CDCl$_3$
Figure A124. IR Spectrum of Compound 3,56
Figure A125. 500 MHz $^1$H NMR Spectrum of Compound 3.78 in CDCl$_3$
Figure A126. 125 MHz $^{13}$C NMR Spectrum of Compound 3.78 in CDCl$_3$
Figure A127. IR Spectrum of Compound 3.78
Figure A128. 500 MHz $^1$H NMR Spectrum of Compound 3.77 in CDCl$_3$.
Figure A129. 125 MHz $^{13}$C NMR Spectrum of Compound 3.77 in CDCl$_3$
Figure A130. IR Spectrum of Compound 3.77
Figure A131. 500 MHz $^1$H NMR Spectrum of Compound 3.79 in CDCl$_3$
Figure A132. 125 MHz $^{13}$C NMR Spectrum of Compound 3.79 in CDCl$_3$. 
Figure A133. IR Spectrum of Compound 3.79
Figure A134. 500 MHz $^1$H NMR Spectrum of Compound 3.80 in CDCl$_3$. 
Figure A135. 125 MHz $^{13}$C NMR Spectrum of Compound 3.80 in CDCl$_3$
Figure A136. IR Spectrum of Compound 3.80
Figure A137. 500 MHz $^1$H NMR Spectrum of Compound 3.73 in CDCl$_3$
Figure A138. 125 MHz $^{13}$C NMR Spectrum of Compound 3.73 in CDCl$_3$
Figure A139. IR Spectrum of Compound 3.73
Figure A1.40. 500 MHz $^1$H NMR Spectrum of Compound 3.61 in CDCl$_3$. 

![NMR Spectrum of Compound 3.61 in CDCl$_3$](image)
Figure A141. 125 MHz $^{13}$C NMR Spectrum of Compound 3.61 in CDCl$_3$. 

[Diagram of Compound 3.61]
Figure A142. IR Spectrum of Compound 3.61
Figure A143. 500 MHz $^1$H NMR Spectrum of Compound 3.87 in CDCl$_3$
Figure A144. 125 MHz $^{13}$C NMR Spectrum of Compound 3.87 in CDCl$_3$.\[\text{\footnotesize MeO.}\]
Figure A145. IR Spectrum of Compound 3.87
Figure A146. 500 MHz $^1$H NMR Spectrum of Compound 3.88 in CDCl$_3$
Figure A147. 125 MHz $^{13}$C NMR Spectrum of Compound 3.88 in CDCl$_3$
Figure A148. IR Spectrum of Compound 3.88
Figure A149. 500 MHz $^1$H NMR Spectrum of Compound 3.90 in CDCl$_3$
Figure A150. 125 MHz $^{13}$C NMR Spectrum of Compound 3.90 in CDCl$_3$. 

![NMR Spectrum Diagram]
Figure A152. 500 MHz $^1$H NMR Spectrum of Compound 3.91 in CDCl$_3$
Figure A153. 125 MHz $^{13}$C NMR Spectrum of Compound 3,91 in CDCl$_3$
Figure A154. IR Spectrum of Compound 3.91
Figure A155. 500 MHz $^1$H NMR Spectrum of Compound 3.97 in CDCl$_3$. 

![500 MHz $^1$H NMR Spectrum of Compound 3.97 in CDCl$_3$](image)
Figure A156. 125 MHz $^{13}$C NMR Spectrum of Compound 3.97 in CDCl$_3$
Figure A157. IR Spectrum of Compound 3.97
Figure A158. 500 MHz $^1$H NMR Spectrum of Compound 3.72 in CDCl$_3$
Figure A159. 500 MHz $^1$H NMR Spectrum of Compound 3.75 in CDCl$_3$
Appendix B

X-ray Structure Determination of Compound 3.72

Compound 3.72, C₂₀H₁₈NSO₅Br, crystallizes in the monoclinic space group P2₁
(systematic absences 0k0: k=odd) with a=7.5156(9)Å, b=15.459(2)Å, c=8.8880(10)Å,
β=94.274(3)°, V=1029.8(2)Å³, Z=2 and d calc =1.497 g/cm³. X-ray intensity data were
collected on a Rigaku Mercury CCD area detector employing graphite-monochromated
Mo-Kα radiation (λ=0.71073 Å) at a temperature of 143K. Preliminary indexing was
performed from a series of twelve 0.5° rotation images with exposures of 30 seconds. A
total of 380 rotation images were collected with a crystal to detector distance of 35 mm, a
2θ swing angle of -14°, rotation widths of 0.5° and exposures of 30 seconds: scan no. 1
was a ϕ-scan from 262.5° to 412.5° at ω = 10° and χ = 20°; scan no. 2 was an ω-scan
from -20° to 20° at χ = -90° and ϕ = 135°. Rotation images were processed using
CrystalClear¹, producing a listing of unaveraged F² and σ(F²) values which were then
passed to the CrystalStructure² program package for further processing and structure
solution on a Dell Pentium III computer. A total of 5598 reflections were measured over
the ranges 5.28 ≤ 2θ ≤ 54.98 °, -9 ≤ h ≤ 7, -20 ≤ k ≤ 14, -10 ≤ l ≤ 11 yielding 3686
281
unique reflections \((R_{int} = 0.0142)\). The intensity data were corrected for Lorentz and polarization effects and for absorption using REQAB\(^3\) (minimum and maximum transmission 0.775, 1.000).

The structure was solved by direct methods (SIR97\(^4\)). Refinement was by full-matrix least squares based on \(F^2\) using SHELXL-97\(^5\). All reflections were used during refinement (\(F^2\)'s that were experimentally negative were replaced by \(F^2 = 0\)). The weighting scheme used was \(w = 1/\left[\sigma^2(F_0^2) + 0.0000P^2 + 0.0000P\right]\) where \(P = (F_0^2 + 2F_c^2)/3\). Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a "riding" model. Refinement converged to \(R_1=0.0243\) and \(wR_2=0.0460\) for 2682 reflections for which \(F > 4\sigma(F)\) and \(R_1=0.0332\), \(wR_2=0.0476\) and \(GOF = 0.721\) for all 3686 unique, non-zero reflections and 256 variables\(^6\). The maximum \(\Delta/\sigma\) in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were +0.380 and -0.515 e Å\(^3\). The Flack absolute structure parameter\(^7\) refined to -0.001(6).

Table B.1 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table B.2. Anisotropic thermal parameters are in Table B.3. Table B.4 and Table B.5 list bond distances and bond angles. Figure B.1 is an ORTEP\(^8\) representation of the molecule with 30% probability thermal ellipsoids displayed.
Figure B.1 ORTEP Drawing of Compound 3.72 with 30% Probability Thermal Ellipsoids.
Table B.1 Summary of Structure Determination of Compound 3.72

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<th>Value</th>
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<tr>
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<td>( \text{P2}_1 ) (#4)</td>
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<td>( Z )</td>
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<td>Cell constants:</td>
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<td>( a )</td>
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</tr>
<tr>
<td>( b )</td>
<td>15.459(2) Å</td>
</tr>
<tr>
<td>( c )</td>
<td>8.8880(10) Å</td>
</tr>
<tr>
<td>( \beta )</td>
<td>94.274(3)°</td>
</tr>
<tr>
<td>( V )</td>
<td>1029.8(2) Å(^3)</td>
</tr>
<tr>
<td>( \mu )</td>
<td>21.28 cm(^{-1})</td>
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<td>Crystal size, mm</td>
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<td>( D_{\text{calc}} )</td>
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<td>( F(000) )</td>
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<td>Radiation:</td>
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<td>No. observed reflections</td>
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<td>No. reflections used in refinement</td>
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<td>No. parameters</td>
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<td>R indices (( F&gt;4\sigma ))</td>
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<td></td>
<td>( wR_2=0.0460 )</td>
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<td>Final Difference Peaks, e/Å(^3)</td>
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<td>Flack absolute structure parameter</td>
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### Table B.2 Refined Positional Parameters for Compound 3.72

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<th>y</th>
<th>z</th>
<th>Ueq, Å²</th>
</tr>
</thead>
<tbody>
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<td>-0.08725(4)</td>
<td>0.68743(2)</td>
<td>-0.03973(3)</td>
<td>0.05001(11)</td>
</tr>
<tr>
<td>C1</td>
<td>0.6127(3)</td>
<td>0.8975(2)</td>
<td>0.3734(3)</td>
<td>0.0216(6)</td>
</tr>
<tr>
<td>C2</td>
<td>0.5866(3)</td>
<td>0.9009(2)</td>
<td>0.5427(2)</td>
<td>0.0236(6)</td>
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<tr>
<td>C3</td>
<td>0.4962(3)</td>
<td>0.9871(2)</td>
<td>0.5592(2)</td>
<td>0.0237(6)</td>
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<tr>
<td>C4</td>
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<td>0.6884(3)</td>
<td>0.0343(7)</td>
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<tr>
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<td>0.4662</td>
<td>1.0002</td>
<td>0.7816</td>
<td>0.046</td>
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<tr>
<td>C5</td>
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<td>0.7645</td>
<td>0.047</td>
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<td>0.5384(3)</td>
<td>0.0337(7)</td>
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<tr>
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<td>1.2019</td>
<td>0.5324</td>
<td>0.045</td>
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<tr>
<td>C7</td>
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<td>0.4062(3)</td>
<td>0.0284(7)</td>
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<tr>
<td>H7</td>
<td>0.3700</td>
<td>1.1348</td>
<td>0.3128</td>
<td>0.038</td>
</tr>
<tr>
<td>C8</td>
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<td>1.0276(2)</td>
<td>0.4201(3)</td>
<td>0.0210(6)</td>
</tr>
<tr>
<td>C9</td>
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<td>0.8292(2)</td>
<td>0.5803(3)</td>
<td>0.0304(7)</td>
</tr>
<tr>
<td>C10</td>
<td>0.2023(4)</td>
<td>0.7498(3)</td>
<td>0.4860(4)</td>
<td>0.0595(10)</td>
</tr>
<tr>
<td>H10a</td>
<td>0.2572</td>
<td>0.6938</td>
<td>0.4827</td>
<td>0.089</td>
</tr>
<tr>
<td>H10b</td>
<td>0.1080</td>
<td>0.7539</td>
<td>0.4073</td>
<td>0.089</td>
</tr>
<tr>
<td>H10c</td>
<td>0.1542</td>
<td>0.7577</td>
<td>0.5821</td>
<td>0.089</td>
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<tr>
<td>C11</td>
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<td>0.8910(2)</td>
<td>0.6401(3)</td>
<td>0.0330(7)</td>
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<tr>
<td>H11a</td>
<td>0.7377</td>
<td>0.8858</td>
<td>0.7450</td>
<td>0.044</td>
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<tr>
<td>H11b</td>
<td>0.8210</td>
<td>0.8378</td>
<td>0.6119</td>
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<td>C12</td>
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<td>0.9651(2)</td>
<td>0.6254(3)</td>
<td>0.0357(8)</td>
</tr>
<tr>
<td>C13</td>
<td>0.9199(5)</td>
<td>1.0222(3)</td>
<td>0.7433(3)</td>
<td>0.0654(12)</td>
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<tr>
<td>H13a</td>
<td>0.9975</td>
<td>1.0686</td>
<td>0.7357</td>
<td>0.087</td>
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<tr>
<td>H13b</td>
<td>0.8611</td>
<td>1.0145</td>
<td>0.8308</td>
<td>0.087</td>
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<td>C14</td>
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<td>0.0561(10)</td>
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Table B.3 Refined Thermal Parameters (U's) for Compound 3.72

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<th>U₂₂</th>
<th>U₃₃</th>
<th>U₁₂</th>
<th>U₁₃</th>
<th>U₁₂</th>
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<tbody>
<tr>
<td>Br1</td>
<td>0.0465(2)</td>
<td>0.0503(2)</td>
<td>0.0511(2)</td>
<td>0.0027(2)</td>
<td>-</td>
<td>-0.0180(2)</td>
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<td>0.01019(12)</td>
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<tr>
<td>C1</td>
<td>0.021(2)</td>
<td>0.022(2)</td>
<td>0.0213(12)</td>
<td>0.0003(12)</td>
<td>-0.0020(10)</td>
<td>-0.0016(13)</td>
</tr>
<tr>
<td>C2</td>
<td>0.027(2)</td>
<td>0.029(2)</td>
<td>0.0160(12)</td>
<td>0.0014(12)</td>
<td>0.0031(10)</td>
<td>0.0015(14)</td>
</tr>
<tr>
<td>C3</td>
<td>0.0215(14)</td>
<td>0.024(2)</td>
<td>0.0253(12)</td>
<td>-0.0013(13)</td>
<td>0.0019(10)</td>
<td>-0.0008(14)</td>
</tr>
</tbody>
</table>
The form of the anisotropic displacement parameter is:
\[ \exp[-2\pi^2(a^2U_{11} h^2+b^2U_{22} k^2+c^2U_{33} l^2+2abU_{12} hl+2acU_{13} kl+2bcU_{23} hl)] \].

Table B.4 Bond Distances in Compound 3.72, Å

<p>| | | | | |</p>
<table>
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</thead>
<tbody>
<tr>
<td>Br1-C18</td>
<td>1.897(3)</td>
<td>C1-O1</td>
<td>1.201(3)</td>
<td>C1-N1</td>
</tr>
<tr>
<td>C1-C2</td>
<td>1.533(3)</td>
<td>C2-C3</td>
<td>1.507(4)</td>
<td>C2-C9</td>
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287
<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
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<tbody>
<tr>
<td>C2-C11 - C3-C4 - C7-C8</td>
<td>1.540(3)</td>
</tr>
<tr>
<td>C4-C5 - C5-C6 - C9-02</td>
<td>1.380(4)</td>
</tr>
<tr>
<td>C7-C8 - C8-N1 - C9-O2</td>
<td>1.367(4)</td>
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<tr>
<td>C9-O2 - C10-O2 - C11-C12</td>
<td>1.346(3)</td>
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<tr>
<td>C12-C13 - C12-C14 - C15-C16</td>
<td>1.375(4)</td>
</tr>
<tr>
<td>C15-C16 - C15-S1 - C17-C18</td>
<td>1.397(4)</td>
</tr>
<tr>
<td>C17-C18 - C18-C19 - S1-O4</td>
<td>1.380(4)</td>
</tr>
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</table>

Table B.5 Bond Angles in Compound 3.72, °

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<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
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<td>O1-C1-N1</td>
<td>125.2(2)</td>
</tr>
<tr>
<td>C3-C2-C9</td>
<td>108.9(2)</td>
</tr>
<tr>
<td>C3-C2-C11</td>
<td>114.2(2)</td>
</tr>
<tr>
<td>C3-C2-C11</td>
<td>119.9(3)</td>
</tr>
<tr>
<td>C3-C2-C11</td>
<td>119.4(3)</td>
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<tr>
<td>C3-C2-C11</td>
<td>117.1(2)</td>
</tr>
<tr>
<td>C3-C2-C11</td>
<td>108.0(2)</td>
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<tr>
<td>O2-C9-C2</td>
<td>110.6(2)</td>
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<tr>
<td>C13-C12-C11</td>
<td>118.9(2)</td>
</tr>
<tr>
<td>C20-C15-S1</td>
<td>120.9(2)</td>
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<tr>
<td>C16-C17-C18</td>
<td>119.2(3)</td>
</tr>
<tr>
<td>C19-C18-Br1</td>
<td>119.8(2)</td>
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<tr>
<td>O4-S1-O5</td>
<td>119.95(11)</td>
</tr>
<tr>
<td>O4-S1-C15</td>
<td>109.21(12)</td>
</tr>
<tr>
<td>C1-N1-C8</td>
<td>110.5(2)</td>
</tr>
<tr>
<td>C9-O2-C10</td>
<td>116.3(2)</td>
</tr>
</tbody>
</table>

Table B.5 Bond Angles in Compound 3.72, °
Compound 3.75, C_{23}H_{27}NSO_{6}, crystallizes in the monoclinic space group P2_{1} (systematic absences 0k0: k=odd) with a=8.7058(10)Å, b=13.9312(2)Å, c=9.1612(10)Å, \( \beta = 94.954(3)^\circ \), \( V = 1106.9(2)Å^3 \), \( Z = 2 \) and \( d_{\text{calc}} = 1.337 \text{ g/cm}^3 \). X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo-K\( \alpha \) radiation (\( \lambda = 0.71073 \text{ Å} \)) at a temperature of 143K. Preliminary indexing was performed from a series of twelve 0.5° rotation images with exposures of 30 seconds. A total of 518 rotation images were collected with a crystal to detector distance of 35 mm, a 2\( \theta \) swing angle of -10°, rotation widths of 0.5° and exposures of 45 seconds: scan no. 1 was a \( \phi \)-scan from 210° to 420° at \( \omega = 10° \) and \( \chi = 20° \); scan no. 2 was an \( \omega \)-scan from -20° to 5° at \( \chi = -90° \) and \( \phi = 45° \); scan no. 3 was an \( \omega \)-scan from -14° to 10° at \( \chi = -90° \) and \( \phi = 0° \). Rotation images were processed using CrystalClear, producing a listing of unaveraged \( F^2 \) and \( \sigma(F^2) \) values which were then passed to the CrystalStructure program package for further processing and structure solution on a Dell Pentium III computer. A total of 7710 reflections were measured over the ranges 5.34 \( \leq 2\theta \leq 50.04° \), -9 \( \leq h \leq 10 \), -14 \( \leq k \leq 16 \), -10 \( \leq l \leq 10 \) yielding 3619 unique reflections \( (R_{\text{int}} = 0.0216) \). The intensity data were corrected for Lorentz and polarization
effects and for absorption using REQAB\(^3\) (minimum and maximum transmission 0.821, 1.000).

The structure was solved by direct methods (SIR97\(^4\)). Refinement was by full-
matrix least squares based on \(F^2\) using SHELXL-97\(^5\). All reflections were used during
refinement (\(F^2\)'s that were experimentally negative were replaced by \(F^2 = 0\)). The
weighting scheme used was \(w=1/[a^2(F_0^2) + 0.0624P^2 + 0.2669P]\) where \(P = (F_0^2 + 2F_c^2)
)/3\). Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined
using a "riding" model. Refinement converged to \(R_1=0.0442\) and \(wR_2=0.1074\) for 3275
reflections for which \(F > 4\sigma(F)\) and \(R_1=0.0495\), \(wR_2=0.1130\) and GOF = 1.050 for all
3619 unique, non-zero reflections and 285 variables\(^6\). The maximum \(\Delta/\sigma\) in the final
cycle of least squares was 0.181 and the two most prominent peaks in the final difference
Fourier were +0.460 and -0.357 e/Å\(^3\).

Table B.6 lists cell information, data collection parameters, and refinement data.
Final positional and equivalent isotropic thermal parameters are given in Table B.7.
Anisotropic thermal parameters are in Table B.8. Table B.9 and Table B.10 list bond
distances and bond angles. Figure B.2 is an ORTEP\(^8\) representation of the molecule with
30% probability thermal ellipsoids displayed.
Figure B.2 ORTEP Drawing of Compound 3.75 with 30% Probability Thermal Ellipsoids
**Table B.6 Summary of Structure Determination of Compound 3.75**

<table>
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<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;27&lt;/sub&gt;NOSO&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
<tr>
<td>Formula weight</td>
<td>445.52</td>
</tr>
<tr>
<td>Crystal class</td>
<td>monoclinic</td>
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<tr>
<td>Space group</td>
<td>P&lt;sub&gt;2&lt;/sub&gt;&lt;sub&gt;1&lt;/sub&gt; (#4)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Cell constants</td>
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</tr>
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<td>a</td>
<td>8.7058(10)Å</td>
</tr>
<tr>
<td>b</td>
<td>13.931(2)Å</td>
</tr>
<tr>
<td>c</td>
<td>9.1612(10)Å</td>
</tr>
<tr>
<td>β</td>
<td>94.954(3)°</td>
</tr>
<tr>
<td>V</td>
<td>1106.9(2)Å³</td>
</tr>
<tr>
<td>μ</td>
<td>1.86 cm&lt;sup&gt;-1&lt;/sup&gt;</td>
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<tr>
<td>crystal size, mm</td>
<td>0.48 x 0.12 x 0.05</td>
</tr>
<tr>
<td>D&lt;sub&gt;calc&lt;/sub&gt;</td>
<td>1.337 g/cm³</td>
</tr>
<tr>
<td>F(000)</td>
<td>472</td>
</tr>
<tr>
<td>Radiation:</td>
<td>Mo-K&lt;sub&gt;a&lt;/sub&gt; (λ=0.71073Å)</td>
</tr>
<tr>
<td>2θ range</td>
<td>5.34 – 50.04°</td>
</tr>
<tr>
<td>hkl collected</td>
<td>-9 ≤ h ≤ 10; -14 ≤ k ≤ 16; -</td>
</tr>
<tr>
<td>No. reflections measured</td>
<td>7710</td>
</tr>
<tr>
<td>No. unique reflections</td>
<td>3619 (R&lt;sub&gt;int&lt;/sub&gt;=0.0216)</td>
</tr>
<tr>
<td>No. observed reflections</td>
<td>3275 (F&gt;4σ)</td>
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<tr>
<td>No. reflections used in refinement</td>
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<tr>
<td>No. parameters</td>
<td>285</td>
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<tr>
<td>R indices (F&gt;4σ)</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=0.0442</td>
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<tr>
<td></td>
<td>wR&lt;sub&gt;2&lt;/sub&gt;=0.1074</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=0.0495</td>
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<td></td>
<td>wR&lt;sub&gt;2&lt;/sub&gt;=0.1130</td>
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<tr>
<td>GOF</td>
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<td>Final Difference Peaks, e/Å³</td>
<td>+0.460, -0.357</td>
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Table B.7 Refined Positional Parameters for Compound 3.75

<table>
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<th>z</th>
<th>Ueq, Å²</th>
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<td>0.2847(4)</td>
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<td>0.4329(3)</td>
<td>0.0441(7)</td>
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<td>0.5300(2)</td>
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<td>0.1541(4)</td>
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<td>0.3757(3)</td>
<td>0.0435(7)</td>
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<td>0.0863(4)</td>
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<td>0.0603(10)</td>
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<td>0.080</td>
</tr>
<tr>
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<td>0.0631(10)</td>
</tr>
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<td>-0.0449</td>
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<td>0.084</td>
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<td>C6</td>
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<td>0.6368(3)</td>
<td>0.1267(4)</td>
<td>0.0551(9)</td>
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<tr>
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<td>0.6580</td>
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<td>0.073</td>
</tr>
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<td>0.0434(7)</td>
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<tr>
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<td>0.0349</td>
<td>0.5059</td>
<td>0.0449</td>
<td>0.058</td>
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<td>0.2559(3)</td>
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<tr>
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<td>0.4073(4)</td>
<td>0.5810(3)</td>
<td>0.5277(4)</td>
<td>0.0533(8)</td>
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\[ U_{eq} = \frac{1}{3}[U_{11}(aa^*2) + U_{22}(bb^*2) + U_{33}(cc^*2) + 2U_{12}aa^*bb^*cos\gamma + 2U_{13}aa^*cc^*cos\beta + 2U_{23}bb^*cc^*cos\alpha] \]

Table B.8 Refined Thermal Parameters (U's) for Compound 3.75

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<th>Atom</th>
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<th>U33</th>
<th>U23</th>
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<td>0.038(2)</td>
<td>0.045(2)</td>
<td>0.0040(14)</td>
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<tr>
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<td>0.043(2)</td>
<td>0.047(2)</td>
<td>-0.0056(14)</td>
<td>0.0016(14)</td>
<td>0.000(2)</td>
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<tr>
<td>C3</td>
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<td>0.034(2)</td>
<td>0.053(2)</td>
<td>-0.0016(14)</td>
<td>0.0035(13)</td>
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<tr>
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<td>0.035(2)</td>
<td>0.090(3)</td>
<td>-0.011(2)</td>
<td>0.001(2)</td>
<td>0.005(2)</td>
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<tr>
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<td>0.032(2)</td>
<td>0.110(3)</td>
<td>0.003(2)</td>
<td>-0.002(2)</td>
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<td>0.040(2)</td>
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<td>-0.006(2)</td>
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<td>C10</td>
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<td>0.082(3)</td>
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<td>-0.004(2)</td>
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<tr>
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<td>0.006(2)</td>
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<tr>
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<td>0.064(2)</td>
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<td>0.007(2)</td>
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<td>0.033(2)</td>
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The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b*c*U_{23}kl+2a*c*U_{13}hl+2a*b*U_{12}hk)]$$.

### Table B.9 Bond Distances in Compound 3.75, Å

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<td>C1-O1</td>
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<tr>
<td>C1-C2</td>
<td>1.532(5)</td>
</tr>
<tr>
<td>C2-C9</td>
<td>1.517(5)</td>
</tr>
<tr>
<td>C2-C3</td>
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<td>C2-C11</td>
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<td>C3-C8</td>
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<td>C4-C5</td>
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<td>C5-C6</td>
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<tr>
<td>C17-C18</td>
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### Table B.10 Bond Angles in Compound 3.75, °

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<td>C8-C3-C2</td>
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<td>Bond</td>
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<tr>
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<td>C18-C21-C15</td>
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<tr>
<td>O5-S1-C14</td>
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</table>

(1) **CrystalClear**: Rigaku Corporation, 1999.

(2) **CrystalStructure**: Crystal Structure Analysis Package, Rigaku Corp. Rigaku/MSC (2002).


(6) \( R_1 = \sum |F_o| - |F_e| / \sum |F_o| \)
\[
\text{wR}_2 = \{ \sum w (F_o^2 - F_e^2)^2 / \sum w(F_o^2)^2 \}^{1/2}
\]
\[
\text{GOF} = \{ \sum w (F_o^2 - F_e^2)^2 / (n - p) \}^{1/2}
\]
where \( n \) = the number of reflections and \( p \) = the number of parameters refined.


Appendix C

Figure C.1 CD Spectra of Bisisonigerone

Figure C.2 CD Spectra of Synthetic Nigerone
Appendix D


Bringmann, G; Gunther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Progress in the Chemistry of Natural Products*, W. Herz; H. Falk; G. W. Kirby; R. E. Moore, Ed; Springer-Verlag Wien: Austria, 2001; 293 pp.


CAVEAT V2.2; P. A. Bartlett, U. C. Berkeley.


Lauri, G., *FUNMAP*.


MacroModel V6.5; W. C. Still, Columbia Univ.


SPARTAN v5.0 (Wavefunction, Inc.; 18401 Von Karman Avenue, Suite 370; Irvine, CA 92612 U.S.A.).


