CHAPTER 3

Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

3.1 INTRODUCTION

The construction of all-carbon quaternary stereocenters remains one of the most challenging problems in asymmetric catalysis and has been an area of great interest in our laboratories. Over the past several years, significant effort from many research groups has been directed toward the enantioselective synthesis of 3,3-disubstituted oxindoles and derivatives thereof, given the prevalence of this structural motif in biologically active molecules and their interesting molecular architectures (Figure 3.1). Although a number of catalytic enantioselective approaches to this motif have been developed (Heck reaction, cyanoamidation, cycloadditions, arylation, alkylation, acyl migration, Claisen rearrangement, aldol, Mannich, and conjugate addition reactions), we

1 This work was performed in collaboration with Drs. Xiaoqing Han, Shyam Krishnan, and Scott Virgil.
pursued an alternative tactic. In all of the reported systems that rely on stereoselective functionalization of an existing oxindole, this oxindole unit serves as a nucleophile. In contrast, we present herein an unusual strategy for the enantioselective synthesis of substituted oxindoles with C(3) quaternary stereocenters that employs the oxindole moiety as the electrophilic partner in a facile and rapid coupling to malonate nucleophiles.

Figure 3.1. Naturally occurring 3,3-disubstituted oxindoles and indolines bearing all-carbon quaternary stereocenters

3.2 DEVELOPMENT OF CATALYTIC ENANTIOSELECTIVE ALKYLATION

3.2.1 Background and Initial Results

Despite an early report from Hinman and Bauman in 1964, the use of 3-haloxindoles as electrophiles in substitution chemistry has been limited. Although the addition of carbon-based π- and heteroatom-nucleophiles to the C(3) position of oxindoles has been reported, no enantioselective methods exist. We recently reported
the base-promoted addition of malonate esters to 3-halooxindoles by the in situ formation of a putative \( o \)-azaxylylene (Scheme 3.1a).\textsuperscript{21} In light of these results and our general interest in stereoablative reactions,\textsuperscript{22} we sought to develop a catalytic enantioselective system (Scheme 3.1b).\textsuperscript{23} We hypothesized that a Lewis acid could facilitate the base-mediated reaction by lowering the \( pK_a \) of the N–H proton of the halooxindole and/or the C\( _\alpha \)–H proton of the malonate. Through either pathway, complexation by a chiral Lewis acid could potentially lead to asymmetric induction.

Scheme 3.1  (a) Base-mediated addition of malonates to halooxindoles via a reactive \( o \)-azaxylylene intermediate.  (b) Proposed Lewis acid-catalyzed enantioselective alkylation of 3-halooxindoles.  Only the malonate activation pathway is shown.

We reasoned that the key to implementing a catalytic enantioselective system would be to identify a base that would not promote competitive background reactions in the absence of a catalyst. In our initial experiments, we found that exposure of racemic bromooxindole (\( \pm \))-76 to \( N,N \)-diisopropylethylamine (\( i \)-Pr\(_2\)NEt) and dimethyl malonate in the absence of a Lewis acid did not result in formation of adduct 77.\textsuperscript{24} Encouraged by
this finding, we then surveyed a variety of chiral Lewis acids (e.g., CuII, MgII, LaIII, and NiII complexes) that could potentially promote the asymmetric alkylation (Table 3.1). We found that several chiral Lewis acids could promote alkylation; however, only copper afforded adduct 77 with promising enantiomeric excess (Table 3.1, Entry 1). We also surveyed a variety of bases for the asymmetric alkylation of racemic bromooxindole (±)-76 (Table 3.2) and found that i-Pr2NEt provided desired adduct 77 with the best yield and ee. Alkyl amines, such as N-methyl-dicyclohexylamine, afforded adduct 77 with ee’s comparable to that observed with i-Pr2NEt albeit in diminished yields (Table 3.2, Entries 5, 8, and 10). Ultimately, the combination of copper(II) triflate and (S)-Ph-BOX (78) gave the most promising result, producing 77 in 63% yield and 77% ee (Table 3.3, entry 1).25,26 Related bis(oxazoline) ligands 79-82 resulted in diminished yields and enantioselectivities (Table 3.3, entries 2-5). Given the strong electronic preference observed in related Lewis acid catalyzed processes, we investigated the effect of less coordinating counterions.27 Although imparting only a moderate influence on chemical yield, a more pronounced counterion effect was observed with enantioselectivity. For example, using the hexafluoroantimonate (SbF6−) complex produced malonate adduct 77 in 72% yield and 84% ee in less than 10 min (Table 3.3, entry 9). Ultimately, we found that employing the preformed [Cu(78)] (SbF6)2 catalyst at low temperature (i.e., −40 °C) in the presence of 3Å molecular sieves28 produced oxindole 77 in 77% yield and 88% ee (Table 3.4, entry 1).
Table 3.1 Lewis acid metal screen for enantioselective malonate alkylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal Salt</th>
<th>Yield [%]b</th>
<th>ee [%]c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂</td>
<td>63</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>Mg(OTf)₂</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>3*</td>
<td>La(OTf)₃</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂</td>
<td>59</td>
<td>25</td>
</tr>
</tbody>
</table>

* a. Performed with (-)-Ph-BOX.  b. Isolated yield.  c. Measured by chiral HPLC.

Table 3.2 Base optimization for enantioselective malonate alkylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield [%]b</th>
<th>ee [%]c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1*</td>
<td>Pyridine</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2*</td>
<td>2,6-di-tert-butylpyridine</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3*</td>
<td>N-Methylmorpholine</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4*</td>
<td>DMAP</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>N-Methyl-dicyclohexylamine</td>
<td>46</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Cs₂CO₃</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>

* a. No product observed.  b. Isolated yield.  c. Measured by chiral HPLC.
### Table 3.3 Ligand screen for enantioselective malonate alkylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Ligand</th>
<th>Yield[0]%</th>
<th>ee[0]%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTf</td>
<td>78</td>
<td>63</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>OTf</td>
<td>79</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>OTf</td>
<td>ent-80</td>
<td>24</td>
<td>-42</td>
</tr>
<tr>
<td>4</td>
<td>OTf</td>
<td>81</td>
<td>37</td>
<td>-64</td>
</tr>
<tr>
<td>5</td>
<td>OTf</td>
<td>82</td>
<td>49</td>
<td>13</td>
</tr>
<tr>
<td>6[a]</td>
<td>PF6</td>
<td>78</td>
<td>65</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>NTf2</td>
<td>78</td>
<td>65</td>
<td>79</td>
</tr>
<tr>
<td>8[a]</td>
<td>BF4</td>
<td>78</td>
<td>61</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>SbF6</td>
<td>78</td>
<td>72</td>
<td>84</td>
</tr>
</tbody>
</table>

[a] Performed at –78 → 23 °C. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. [d] The catalyst was generated by in situ metathesis of [Cu(OTf)Cl] with the corresponding AgX salt.

---

### 3.2.2 Substrate Scope

On examining the scope of the transformation, we found that malonate esters could be alkylationed with various 3-alkyl and 3-aryl halooxindoles in good yields and high enantioselectivities (Tables 3.4 and 3.5).[^29] Methyl, ethyl, and benzyl malonates were each added to bromide (±)-76, via the putative o-azaxylylene, with similar levels of selectivity and yield (Table 3.4, entries 1-3). Silyl ethers (entries 1-4 and 6), benzoate esters (entry 5), and phthalimides (entries 8-10) were all tolerated as substituents on the alkyl chain at C(3). Additionally, substituted alkyl chains of various lengths led to alkylation products in high enantioselectivities (entries 1 and 6). Finally, substitution of
the bromooxindole core at C(5) with a methoxy group produced the malonate addition product in 51% yield and 91% ee (entry 10).

Table 3.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>Temp[°C]</th>
<th>Yield [a] [%]</th>
<th>ee [b] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–40</td>
<td>77</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>i-Pr²NEt</td>
<td>3ÅMS</td>
<td>CH₂Cl₂</td>
<td>72 h</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>OTIPS</td>
<td>R² = Me</td>
<td>–40</td>
<td>77</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>OTIPS</td>
<td>R² = Bn</td>
<td>–40</td>
<td>78</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OBz</td>
<td>R² = Me</td>
<td>–40</td>
<td>77</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OTIPS</td>
<td>R² = Me</td>
<td>–20</td>
<td>47</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OTIPS</td>
<td>R² = Me</td>
<td>–40</td>
<td>44</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>R² = Me</td>
<td>–20</td>
<td>42</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>OMe</td>
<td>R² = Me</td>
<td>–20</td>
<td>51</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>R² = Me</td>
<td>–20</td>
<td>63</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

[a] Yield of isolated product. [b] Determined by chiral-phase HPLC.

In addition to reactions with bromooxindoles, dimethyl malonate reacted smoothly with racemic 3-aryl chlorooxindoles to produce the C(3)-malonate adducts in good yields and enantioselectivities (Table 3.5). In these reactions, Et₃N proved to be a better base than i-Pr₂NEt in terms of both yield and enantioselectivity. Products with phenyl (entry 1), bromophenyl (entry 3), 3,5-dimethylphenyl (entry 4), and naphthyl substitution at C(3) (entry 5) were stereoselectively formed by this method. Additionally, methoxy substituents on the oxindole framework at C(5) were well tolerated (entry 2).
### Table 3.5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>Temp(°C)</th>
<th>Yield[a] [%]</th>
<th>ee[b] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>H</td>
<td>-20</td>
<td>76</td>
<td>-76[c]</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>OMe</td>
<td>-20</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>0</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>-40</td>
<td>69</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>0</td>
<td>74</td>
<td>74</td>
</tr>
</tbody>
</table>

[a] Yield of isolated product.  [b] Determined by chiral-phase HPLC.  [c] (R)-Ph-BOX was employed as the ligand.

### 3.2.3 Applications to Natural Product Scaffolds

We proceeded to apply this new method for the enantioselective generation of C(3)-quaternary oxindoles to the synthesis of natural product scaffolds. To construct the pyrrolidinylspirooxindole core prevalent in a large family of biologically active alkaloids, we began with malonate adduct 83 (Table 3.4, entry 9), which could be recrystallized to 99% ee (Scheme 3.2). Oxindole malonate 83 was converted to phthalimidoester 84 by Krapcho decarboxylation.³⁰ Cleavage of phthalimide 84 with hydrazine resulted in rapid formation of spirocyclic bis(lactam) 85. Double alkylation of oxindole 85 produced...
bis(p-bromobenzyl)lactam \(86\), a crystalline compound amenable to single crystal x-ray analysis, which allowed for its determination of absolute configuration.\(^{31}\)

Scheme 3.2

In addition to spirocyclic motifs, fused pyrrolidinoindolines are also a key moiety found in many natural products. To access this family, quaternary C(3)-aryl oxindole malonate adduct \(87\) was subjected to Krapcho decarboxylation and \(N\)-alkylation to give methyl ester \(88\) (Scheme 3.3). Finally, ester \(88\) was converted to \(N\)-methyl amide \(89\) and reduced with LiAlH\(_4\) to provide lactam \(90\), which contains the pyrrolidinoindoline core.

Scheme 3.3
3.3 CONCLUSION

In summary, we have discovered a unique copper-catalyzed enantioselective synthesis of C(3)-quaternary oxindoles. This stereoablative transformation most likely involves the in situ formation of a highly reactive o-azaxylylene from C(3)-halooxindoles followed by enantioselective malonate addition. Finally, we have demonstrated that our method is useful for the rapid and stereoselective construction of biologically active core structures. Mechanistic studies and further synthetic applications of our method are underway.
3.4 EXPERIMENTAL SECTION

3.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, anisaldehyde, or ceric ammonium molybdate staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm and flow rate of 1 mL/min, unless otherwise stated. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and a Varian Mercury 300 spectrometer (at 300 MHz and 75 MHz, respectively) and are reported relative to Me$_4$Si (δ 0.0). Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for $^{13}$C NMR spectra are reported in terms of chemical shift relative to Me$_4$Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm$^{-1}$). High resolution mass spectra were either obtained from the Caltech Mass Spectral Facility or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric
pressure chemical ionization (APCI) or mixed (MM) ionization mode. Optical rotations were measured on either a Jasco P-1010 using a 50 mm path-length cell or Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Melting points were determined using a Thomas capillary melting point apparatus and the values reported are uncorrected. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.
3.4.2 General Synthesis of 3-Alkyl Bromooxindoles From Corresponding 3-Alkyl Indoles.

3-bromo-3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (76).

3-(2-((triisopropylsilyloxy)ethyl)-1H-indole (2.0 g, 6.3 mmol, 1.0 equiv) was dissolved in a mixture of THF (63 mL), t-BuOH (63 mL), and H₂O (1.3 mL). The solution was cooled to 0–5 °C and solid N-bromosuccinimide (1.6 g, 8.9 mmol, 1.4 equiv) was added in small portions over 60 minutes. The reaction mixture was then allowed to warm to ambient temperature and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO₂, 6% EtOAc in hexanes→10% EtOAc in hexanes) to afford bromooxindole 76 as an off-white solid (791 mg, 30% yield) and oxindole 91 as a colorless oil (712 mg, 34% yield).

3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (91): Rₜ = 0.30 (SiO₂, 25% EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.31 (br s, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.20 (tt, J = 8.0, 1.0 Hz, 1H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 3.92 (m, 2H), 3.66 (app. t, J = 6.5 Hz, 1H), 2.25 (m, 1H), 2.07 (m, 1H), 1.04 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 180.5, 141.5, 129.7, 127.8, 124.6, 122.2, 109.6, 60.1, 42.8, 33.7, 18.1, 12.1; IR (neat film, NaCl) 3215, 2941, 2863, 1711, 1620, 1471, 1109, 747 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₉H₂₃NO₂Si[M+H]⁺: 334.2202, found 334.2202.
Oxindole 91 could be brominated to give bromooxindole 76 as follows: To a solution of oxindole 91 (485 mg, 1.5 mmol, 1.0 equiv) in THF (15 mL) that had been pre-cooled to –78 ºC was added a freshly prepared solution of LiHMDS (536 mg, 3.2 mmol, 2.2 equiv) in THF (4 mL) dropwise. The reaction mixture was then maintained at –78 ºC for 30 minutes, and then transferred via cannula to a solution of NBS (518 mg, 2.9 mmol, 2.0 equiv) in THF (10 mL) that had been pre-cooled to –78 ºC and wrapped in aluminum foil to exclude light. The reaction mixture was allowed to warm to –40 ºC and maintained at this temperature for 2 hours. The reaction mixture was then poured into saturated aqueous NH₄Cl (60 mL). 1 M aqueous Na₂S₂O₃ (40 mL) was then added, and the mixture was stirred for 10 minutes to reduce any excess NBS. The mixture was then extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure to afford a pale yellow solid. Purification by column chromatography (SiO₂, 10% EtOAc in hexanes) afforded bromooxindole 76 as a pale yellow solid (468 mg, 78% yield). Rᶠ = 0.35 (SiO₂, 25% EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 9.56 (s, 1H), 7.37 (dd, J = 7.5, 0.5 Hz, 1H), 7.26 (app. t, J = 5.0 Hz, 1H), 7.07 (app. dt, J = 7.5, 1.0 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 3.62 (m, 2H), 2.89 (m, 1H), 2.61 (m, 1H), 0.91 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 177.4, 140.2, 130.1, 129.7, 124.8, 123.0, 111.0, 60.1, 55.8, 41.7, 17.8, 11.9; IR (neat film, NaCl) 3202, 2946, 2866, 1725, 1619, 1474, 1115 cm⁻¹; HMRS (FAB+) m/z calc’d for C₁₉H₃₁BrNO₂Si [M+H]⁺: 412.1307, found 412.1290.

1-methyl-3-(2-(((triisopropylsilyl)oxy)ethyl)-1H-indole (92).
To NaH (53 mg, 60%, 1.3 mmol, 1.2 equiv) in DMF (1 mL) was added a solution of 3-(2-(triisopropylsilyloxy)ethyl)-1H-indole (350 mg, 1.1 mmol, 1.0 equiv) in DMF (4 mL) at ambient temperature. The solution was stirred for 20 min and then MeI (103 μL, 1.7 mmol, 1.5 equiv) was added dropwise. The solution was stirred for an additional 30 min at ambient temperature. Water (5 mL) and brine (5 mL) were added, and the mixture was extracted with a mixture of hexanes/EtOAc (1:2) (2 x 15 mL). The combined extracts were dried with MgSO₄ prior to concentration. The residue obtained was purified by column chromatography (SiO₂, 2% EtOAc in hexanes) to afford 1-methyl-3-(2-(triisopropylsilyloxy)ethyl)-1H-indole as a pale yellow viscous oil (303 mg, 83% yield). Rᵣ = 0.66 (22% EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.23 (td, J = 7.2, 1.2 Hz, 1H), 7.11 (ddd, J = 6.9, 6.6, 1.2 Hz, 1H), 6.91 (s, 1H), 3.94 (t, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.04 (t, J = 7.2 Hz, 2H), 1.15-1.05 (comp. m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 137.0, 128.2, 127.1, 121.5, 119.1, 118.8, 111.6, 109.2, 64.5, 32.7, 29.2, 18.2, 12.2; IR (neat film, NaCl) 3056, 2942, 2865, 1616, 1470, 1382, 1328, 1248, 1100, 1069, 1013, 918, 883 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₀H₃₃NSi [M]+: 331.2331, found 331.2320.

1-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (93).

Prepared according to the procedure used for oxindole 91 using N-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 2% EtOAc in hexanes→5% EtOAc in hexanes). Isolated as a colorless viscous oil. 43% yield. Rᵣ = 0.41 (17% EtOAc in
3-bromo-1-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (94).

Prepared according to the procedure used for bromooxindole 76 using N-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 2% EtOAc in hexanes→5% EtOAc in hexanes). Isolated as a pale yellow viscous oil. 28% yield. \( R_f = 0.56 \) (17% EtOAc in hexanes); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.39 (dd, \( J = 7.5, 1.2 \) Hz, 1H), 7.31 (td, \( J = 7.8, 1.2 \) Hz, 1H), 7.08 (td, \( J = 7.5, 1.2 \) Hz, 1H), 6.80 (d, \( J = 7.8 \) Hz, 1H), 3.67-3.54 (m, 2H), 3.21 (s, 3H), 2.84 (ddd, \( J = 14.1, 7.2, 6.6 \) Hz, 1H), 2.60 (ddd, \( J = 13.8, 5.4, 4.5 \) Hz, 1H), 0.91 (s, 21H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 174.2, 142.7, 130.1, 129.7, 124.8, 123.1, 108.8, 60.3, 55.3, 41.8, 26.8, 17.9, 11.9; IR (neat film, NaCl) 2943, 2891, 2866, 1732, 1614, 1494, 1471, 1422, 1372, 1344, 1244, 1137, 1104, 1071, 1018, 958 cm\(^{-1}\); HRMS (FAB+) \textit{m/z} calc’d for \( C_{20}H_{33}NO_2Si^{81}Br [M]^+ \): 428.1443, found 428.1447.
3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1H-indole (95).

To a solution of tryptophol (1.1 g, 6.6 mmol, 1.0 equiv) and imidazole (1.0 g, 14.6 mmol, 2.2 equiv) in DMF (25 mL) was added TIPSCl (1.9 mL, 7.3 mmol, 1.1 equiv) dropwise at ambient temperature. The reaction solution was stirred for 18 hours. Saturated aqueous NaHCO₃ (50 mL) was added and the mixture was extracted with EtOAc (2 x 50 mL). The combined extracts were dried with MgSO₄ prior to concentration. The residue obtained was purified by column chromatography (SiO₂, 9% EtOAc in hexanes) to afford 3-(2-((tert-butyldiphenylsilyloxy)ethyl)-1H-indole as a yellow viscous oil (2.60 g, 98% yield). \( R_f = 0.60 \) (22% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 7.89 \) (br s, 1H), \( 7.67 \) (dd, \( J = 7.5, 1.5 \) Hz, 4H), \( 7.44-7.40 \) (m, 3H), \( 7.38-7.32 \) (m, 5H), \( 7.18 \) (td, \( J = 7.5, 1.0 \) Hz, 1H), \( 7.06 \) (td, \( J = 7.5, 1.0 \) Hz, 1H), \( 7.00 \) (d, \( J = 2.5 \) Hz, 1H), \( 3.95 \) (t, \( J = 7.5 \) Hz, 2H), \( 3.05 \) (t, \( J = 7.5 \) Hz, 2H), \( 1.08 \) (s, 9H); \(^1\)C NMR (125 MHz, CDCl₃) \( \delta 135.7, 134.1, 129.7, 127.8, 127.7, 122.3, 122.0, 119.3, 119.0, 113.1, 111.1, 64.6, 28.8, 27.0, 19.3.

3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)indolin-2-one (96).

Prepared according to the procedure used for oxindole 91 using N-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 57% yield. \( R_f = 0.30 \) (22% EtOAc in
hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.08 (br s, 1H), 7.66 (dt, $J = 6.5$, 1.5 Hz, 2H), 7.52 (dt, $J = 6.5$, 1.5 Hz, 2H), 7.44-7.36 (comp. m, 4H), 7.33 (tt, $J = 7.5$, 1.0 Hz, 2H), 7.22 (tt, $J = 8.0$, 1.0 Hz, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 6.98 (td, $J = 7.5$, 1.0 Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 1H), 3.86 (ddd, $J = 12.5$, 7.0, 5.5 Hz, 1H), 3.78 (dt, $J = 10.5$, 6.0 Hz, 1H), 3.69 (t, $J = 7.5$ Hz, 1H), 2.27 (dq, $J = 14.0$, 6.0 Hz, 1H), 2.19-2.12 (m, 1H), 1.01 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 180.3, 141.6, 135.8, 135.6, 133.6 (2 C), 129.8, 129.7, 129.4, 127.9, 127.8 (2 C), 124.7, 122.3, 109.7, 60.6, 42.9, 32.9, 26.9, 19.2; IR (neat film, NaCl) 3198, 3071, 2956, 2930, 2889, 2857, 1709, 1621, 1472, 1428, 1390, 1335, 1307, 1235, 1111, 1073, 953 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{26}$H$_{30}$NO$_2$Si [M+H]$^+$: 416.2046, found 416.2033.

\[
\text{3-bromo-3-((tert-butyldiphenylsilyl)oxy)ethyl} \text{indolin-2-one (97).}
\]

Prepared according to the procedure used for bromooxindole 76 using N-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO$_2$, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 13% yield. $R_f = 0.46$ (22% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.48 (br s, 1H), 7.50 (dt, $J = 6.5$, 1.5 Hz, 2H), 7.41 (tt, $J = 7.5$, 1.5 Hz, 1H), 7.37-7.30 (comp. m, 5H), 7.28-7.23 (comp. m, 4 H), 7.10 (td, $J = 8.0$, 1.0 Hz, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 3.54-3.46 (m, 2H), 3.01 (ddd, $J = 15.5$, 9.0, 6.5 Hz, 1H), 2.60 (dt, $J = 14.0$, 4.0 Hz, 1H), 0.92 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 176.4, 140.1, 135.7, 135.4, 133.1, 132.9, 130.3, 129.9, 129.7, 129.7, 127.8, 127.7, 125.2, 123.2, 110.8, 60.7, 55.4, 41.2, 26.6, 19.0; IR (neat film, NaCl) 3209, 3175, 3107, 2930, 2879, 2857, 1731, 1614, 1470, 1427, 1388, 1332, 1195, 1107, 1084,
824, 758, 748 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{26}\)H\(_{29}\)NO\(_2\)Si\(^{81}\)Br \([\text{M+H}]^+\): 496.1118, found 496.1130.

3-(4-((triisopropylsilyl)oxy)butyl)-1H-indole (98).

To a solution of indole-3-butyric acid (1.5 g, 7.4 mmol, 1.0 equiv) in THF (20 mL) at 0 °C was added a solution of LAH (5.5 mL, 11 mmol, 2.0 M in THF, 1.5 equiv) dropwise. The reaction mixture was then allowed to warm to ambient temperature and stirred for 6 hours. Water (2 mL), 10 % aqueous NaOH (2 mL), and water (6 mL) were added in succession, and the mixture was stirred at ambient temperature for additional 30 min, filtered through Celite, concentrated under vacuum to get indole-3-butanol as a pale yellow viscous oil (1.40 g). The crude product was used for the next step without further purification.

To a solution of the above crude alcohol (1.4 g, 7.4 mmol) and imidazole (1.1 g, 16 mmol, 2.2 equiv) in DMF (20 mL) was added TIPSCl (1.7 mL, 8.1 mmol, 1.1 equiv) dropwise at ambient temperature. The reaction solution was stirred for 18 hours. Saturated aqueous NaHCO\(_3\) (30 mL) was added and the mixture was extracted with EtOAc (4 x 30 mL). The combined extracts were dried with MgSO\(_4\) prior to concentration. The residue obtained was purified by column chromatography (SiO\(_2\), 5% EtOAc in hexanes) to afford 3-(4-(triisopropylsilyloxy)butyl)-1H-indole as a pale yellow viscous oil (2.50 g, 98% yield). \(R_f = 0.45\) (22% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.90 (br s, 1H), 7.62 (dd, \(J = 7.5, 1.0\) Hz, 1H), 7.35 (dt, \(J = 8.0, 1.0\) Hz, 1H),
7.19 (td, \( J = 7.5, 1.0 \text{ Hz, 1H} \)), 7.11 (td, \( J = 7.5, 1.0 \text{ Hz, 1H} \)), 6.98 (t, \( J = 1.0 \text{ Hz, 1H} \)),
3.74 (t, \( J = 6.5 \text{ Hz, 2H} \)), 2.79 (t, \( J = 7.5 \text{ Hz, 2H} \)), 1.84-1.78 (m, 2H), 1.70-1.64 (m, 2H),
1.14-1.01 (comp. m, 21H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 136.5, 127.8, 121.9, 121.2,
119.2 (2 C), 117.1, 111.1, 63.5, 33.1, 26.5, 25.1, 18.2, 12.2; IR (neat film, NaCl) 3420, 3057, 2941, 1458, 1420, 1382, 1351, 1336, 1246, 1228, 1105, 1070, 1012, 995,
969, 882, 796, 739 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{21}\)H\(_{35}\)NOSi [M+H]\(^+\): 345.2488, found 345.2483.

\[
\begin{align*}
\text{3-(4-((triisopropylsilyl)oxy)butyl)indolin-2-one (99).} \\
\text{Prepared according to the procedure used for oxindole 91 using N-bromosuccinimide} \\
(1.0 \text{ equiv}). \text{ Purified by flash chromatography (SiO} \_2, 9\% \text{ EtOAc in hexanes} \rightarrow 17\% \text{ }
\text{EtOAc in hexanes). Isolated as a white solid. 15\% yield. \( R_f = 0.11 \) (29\% EtOAc in hexanes); \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.80 (br s, 1H), 7.24 (d, \( J = 7.0 \text{ Hz, 1H} \)), 7.20 (t, \( J = 7.0 \text{ Hz, 1H} \)), 7.01 (td, \( J = 7.5, 1.0 \text{ Hz, 1H} \)), 6.90 (d, \( J = 7.5 \text{ Hz, 1H} \)), 3.70-3.61 (m, 2H), 3.48 (t, \( J = 6.5 \text{ Hz, 1H} \)), 2.07-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.61-1.53 (m, 2H),
1.52-1.43 (m, 2H), 1.09-0.97 (m, 21H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 180.8, 141.7,
129.9, 127.9, 124.4, 122.4, 109.8, 63.2, 46.2, 33.0, 30.6, 22.4, 18.1, 12.1; IR (neat film, NaCl) 3209, 3091, 2942, 2892, 2866, 1711, 1621, 1486, 1472, 1383, 1338, 1233, 1106,
1070, 1015, 996, 883 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{21}\)H\(_{36}\)NO\(_2\)Si [M+H]\(^+\): 362.2515, found 362.2498.
\]
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

3-bromo-3-(4-((triisopropylsilyl)oxy)butyl)indolin-2-one (100).

Prepared according to the procedure used for bromooxindole 76 using N-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a pale yellow viscous oil. 15% yield. R_f = 0.34 (22% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 9.03 (br s, 1H), 7.37 (d, J = 7.0 Hz, 1H), 7.26 (td, J = 7.0, 1.0 Hz, 1H), 7.08 (td, J = 7.5, 0.5 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.65-3.56 (m, 2H), 2.42 (t, J = 8.0 Hz, 2H), 1.56-1.47 (m, 2H), 1.31-1.22 (m, 2H), 1.04-0.93 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 177.0, 139.8, 130.5, 130.1, 124.9, 123.5, 110.8, 62.8, 56.9, 39.4, 32.6, 22.1, 18.1, 12.1; IR (neat film, NaCl) 3239, 2943, 2865, 2732, 1619, 1472, 1383, 1331, 1246, 1208, 1180, 1112, 1069, 1014, 996, 882, 749 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₁H₃₅NO₂Si₈Br [M+H]^+: 442.1600, found 442.1583.

2-(1H-indol-3-yl)ethyl benzoate (101).

To a solution of benzoic acid (0.97 g, 7.9 mmol, 1.0 equiv) and EDCI (1.7 g, 8.7 mmol, 1.1 equiv) in CH₂Cl₂ (15 mL) was added DMAP (0.11 g, 0.87 mmol, 0.11 equiv) and tryptophol (1.5 g, 8.7 mmol, 1.1 equiv) at 23 ºC. The reaction mixture was stir at 23 ºC for 14 hours. Saturated aqueous NaHCO₃ solution (30 mL) was added and the mixture was extracted with CH₂Cl₂ (2 x 30 mL). The combined extracts were dried with MgSO₄
prior to concentration. Purification by flash chromatography (SiO₂, 9% EtOAc in hexanes→17% EtOAc in hexanes) afforded 2-(1H-indol-3-yl)ethyl benzoate as a yellow solid (1.05 g, 50% yield).²¹ \(^1\)H NMR (300 MHz, CDCl₃) δ 8.09-8.03 (comp. m, 3H), 7.72-7.69 (m, 1H), 7.57 (tt, \(J = 7.5, 1.2\) Hz, 1H), 7.48-7.41 (comp. m, 2H), 7.40-7.37 (m, 1H), 7.23 (td, \(J = 6.9, 1.5\) Hz, 1H), 7.17 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.11 (d, \(J = 2.4\) Hz, 1H), 4.63 (t, \(J = 7.5\) Hz, 2H), 3.26 (td, \(J = 6.9, 0.9\) Hz, 2H); \(^1\)C NMR (75 MHz, CDCl₃) δ 166.8, 136.3, 133.1, 130.5, 129.7, 128.5, 127.6, 122.3, 122.2, 119.6, 118.9, 112.2, 111.3, 65.2, 25.0.

\[\text{2-(2-oxoindolin-3-yl)ethyl benzoate (102).}\]

Prepared according to the procedure used for oxindole 91 using \(N\)-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 5% EtOAc in hexanes→25% EtOAc in hexanes). Isolated as a white solid. 47% yield. \(R_f = 0.21\) (33% EtOAc in hexanes); \(^1\)H NMR (300 MHz, CDCl₃) δ 8.99 (br s, 1H), 7.96-7.92 (comp. m, 2H), 7.50 (t, \(J = 7.2\) Hz, 1H), 7.39 (t, \(J = 7.8\) Hz, 2H), 7.27 (d, \(J = 7.5\) Hz, 1H), 7.20 (t, \(J = 7.5\) Hz, 1H), 7.02 (td, \(J = 7.5, 0.9\) Hz, 1H), 6.89 (d, \(J = 7.8\) Hz, 1H), 4.52 (dt, \(J = 11.4, 7.2\) Hz, 1H), 4.41 (dt, \(J = 11.1, 6.8\) Hz, 1H), 3.66 (t, \(J = 6.0\) Hz, 1H), 2.48 (q, \(J = 6.3\) Hz, 2H); \(^1\)C NMR (75 MHz, CDCl₃) δ 181.1, 166.5, 141.6, 133.1, 130.1, 129.7, 128.6, 128.4, 128.3, 124.4, 122.6, 110.2, 61.8, 43.4, 29.2; IR (neat film, NaCl) 3207, 3059, 2961, 1715, 1620, 1471, 1452, 1335, 1314, 1272, 1176, 1116, 1070, 1026 cm⁻¹; HRMS (FAB+) \(m/z\) calc’d for \(\text{C}_{17}\text{H}_{16}\text{NO}_{3} [\text{M+H}]^+: 282.1130\), found 282.1126.
2-(3-bromo-2-oxoindolin-3-yl)ethyl benzoate (103).

Prepared according to the procedure used for bromooxindole 76 using N-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO$_2$, 5% EtOAc in hexanes→25% EtOAc in hexanes). Isolated as a pale yellow solid. 23% yield. $R_f = 0.48$ (33% EtOAc in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.64 (br s, 1H), 7.86-7.81 (comp. m, 2H), 7.48 (td, $J = 7.8$, 1.2 Hz, 1H), 7.42 (d, $J = 7.8$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.25 (td, $J = 7.5$, 1.6 Hz, 1H), 7.07 (td, $J = 7.5$, 1.2 Hz, 1H), 6.85 (t, $J = 7.1$, 1H), 4.34 (dt, $J = 11.7$, 5.7 Hz, 1H), 4.16 (ddd, $J = 11.4$, 8.1, 4.8 Hz, 1H), 3.06 (ddd, $J = 14.4$, 8.4, 6.0 Hz, 1H), 2.89 (dt, $J = 14.4$, 5.4 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 176.4, 166.2, 139.8, 133.3, 130.6, 129.6, 129.6, 129.5, 128.4, 125.0, 123.7, 111.2, 61.4, 54.5, 38.2; IR (neat film, NaCl) 3256, 3090, 3064, 3033, 2961, 1723, 1619, 1602, 1473, 1451, 1329, 1316, 1273, 1192, 1114, 1071, 1028, 752 cm$^{-1}$; HRMS (FAB+) m/z calc’d for C$_{17}$H$_{13}$N$_2$O$_2$ $^{81}$Br [M+H]$^+$: 360.0296, found 360.0287.

2-(2-(2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (104).

Prepared from N-phthalimidotryptamine according to the procedure used for oxindole 91. 54% yield. $R_f = 0.12$ (SiO$_2$, 50% EtOAc in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.82 (bs, 1H), 7.75 (m, 2H), 7.66 (m, 2H), 7.29 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 7.7$ Hz, 1H), 6.87 (t, $J = 7.7$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 3.97 (m, 1H), 3.80 (m, 1H), 3.53 (t, $J = 6.0$ Hz, 1H), 2.51 (m, 1H), 2.32 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.7,
168.2, 141.3, 133.9, 132.1, 128.6, 128.0, 124.1, 123.2, 122.4, 109.7, 43.9, 35.2, 28.5;
IR (Neat film, NaCl) 3271, 1772, 1711, 1621, 1471, 1398, 1220, 1022, 718 cm\(^{-1}\); HRMS
(FAB+) \(m/z\) calc’d for C\(_{18}\)H\(_{15}\)N\(_2\)O\(_3\) [M+H]\(^+\): 307.1083, found 307.1076.

\[\text{NPhth} \quad 105\]

2-(2-(3-bromo-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (105).

Prepared from N-phthalimidotryptamine according to the procedure used for bromooxindole 76. 9% yield. \(R_f = 0.31\) (SiO\(_2\), 50% EtOAc in hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.71 (s, 1H), 7.71 (m, 2H), 7.62 (m, 2H), 7.28 (m, 1H), 7.06 (m, 1H), 6.80 (m, 2H), 3.81 (m, 1H), 3.65 (m, 1H), 3.01 (m, 1H), 2.86 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.5, 167.8, 139.8, 134.0, 131.8, 130.2, 129.5, 124.4, 123.2, 123.1, 111.1, 54.2, 36.5, 34.6; IR (Neat film, NaCl) 3256, 1711, 1615, 1471, 1398, 1184, 716 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{18}\)H\(_{14}\)BrN\(_2\)O\(_3\) [M+H]\(^+\) 385.0188, found 385.0178.

\[\text{NPhth} \quad 106\]

2-((2-oxoindolin-3-yl)methyl)isoindoline-1,3-dione (106).

Prepared from N-(indol-3-yl)methyl]phthalimide according to the procedure used for oxindole 91 using N-bromosuccinimide (1.0 equiv).\(^{33}\) Purified by flash chromatography (SiO\(_2\), 25% EtOAc in hexanes→50% EtOAc in hexanes; then 9% EtOAc in DCM). Isolated as a pale yellow solid with 35% (w/w) of succinimide. 23% yield (corrected for succinimide). \(R_f = 0.17\) (9% EtOAc in DCM); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.15 (br s, 1H), 7.90-7.86 (m, 2H), 7.76-7.71 (m, 2H), 7.22 (td, \(J = 7.5, 1.0\) Hz, 1H), 7.19 (d, \(J = 7.0\) Hz, 1H), 6.99 (td, \(J = 7.5, 1.0\) Hz, 1H), 6.87 (d, \(J = 8.0\) Hz, 1H), 4.20 (dd, \(J = 14.0, 9.0\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 175.9, 153.5, 138.1, 133.6, 133.5, 130.9, 129.4, 126.8, 116.2, 53.8, 45.8, 36.3, 34.1; IR (Neat film, NaCl) 3280, 1700, 1605, 1492, 1396, 1220, 1020, 716 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{18}\)H\(_{16}\)N\(_2\)O\(_3\) [M+H]\(^+\) 385.0188, found 385.0178.
Hz, 1H), 4.14 (dd, J = 14.0, 6.0 Hz, 1H), 3.99 (dd, J = 9.0, 6.0 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.5, 168.3, 141.6, 134.2, 132.1, 128.8, 126.6, 124.6, 123.7, 122.6, 110.1, 43.5, 38.2; HRMS (FAB+) $m/z$ calc’d for C$_{17}$H$_{13}$N$_2$O$_3$ [M+H]$^+$: 293.0926, found 293.0915.

2-((3-bromo-2-oxoindolin-3-yl)methyl)isoindoline-1,3-dione (107). Prepared from N-(indol-3-yl)methyl]phthalimide according to the procedure used for bromooxindole 76 using N-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO$_2$, 25% EtOAc in hexanes→50% EtOAc in hexanes, then 9% EtOAc in DCM). Isolated as a white solid. 22% yield. R$_f$ = 0.30 (9% EtOAc in DCM); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.13 (br s, 1H), 7.76–7.72 (comp. m, 2H), 7.68–7.64 (comp. m, 2H), 7.47 (d, J = 7.5 Hz, 1H), 7.20 (td, J = 8.0, 1.5 Hz, 1H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 4.64 (ABq, J = 14.5 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.6, 167.4, 140.3, 134.4, 131.5, 130.9, 127.4, 126.3, 123.8, 123.3, 110.8, 53.7, 43.9; IR (neat film, NaCl) 3268, 1778, 1734, 1719, 1617, 1472, 1389, 1335, 1192, 1142, 986, 967, 876 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{17}$H$_{12}$N$_2$O$_3$Br [M+H]$^+$: 371.0031, found 371.0044.

2-((5-methoxy-1H-indol-3-yl)methyl)isoindoline-1,3-dione (108).

CH$_3$I (0.89 mL, 14 mmol, 5.0 equiv) was added to a solution of 5-methoxy-gramine (0.58 g, 2.8 mmol, 1.0 equiv) in THF (25 mL) at 0 ºC over 30 min. After stirring of the reaction mixture at ambient temperature for 1 hour, the solvent was removed in vacuo.
The residue was heated with potassium phthalimide (0.53 g, 2.8 mmol, 1 equiv) at 140 °C for 6 hours. Upon cooling to ambient temperature, the reaction mixture was then diluted with water (20 mL) and brine (20 mL) and then extracted with EtOAc (3 x 50 mL). The organic layers were collected and dried with MgSO₄. Purification by column chromatography (SiO₂, 33% EtOAc in hexanes) afforded \(N\)-(5-methoxy-indol-3-yl)methyl]phthalimide as a yellow solid (441 mg, 51% yield). \(R_f = 0.23\) (33% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 8.06 (br s, 1H), 7.81-7.78 (comp. m, 2H), 7.67-7.64 (comp. m, 2H), 7.44 (d, \(J = 2.5\) Hz, 1H), 7.38 (d, \(J = 2.5\) Hz, 1H), 7.22 (dd, \(J = 9.0, 0.5\) Hz, 1H), 6.85 (dd, \(J = 8.5, 2.5\) Hz, 1H), 4.99 (s, 2H), 3.91 (s, 3H); \(^1\)C NMR (125 MHz, CDCl₃) \(\delta\) 168.4, 154.5, 133.9, 132.4, 131.1, 127.1, 125.9, 123.3, 113.0, 111.9, 111.3, 101.0, 55.9, 32.8; IR (neat film, NaCl) 3401, 2938, 1767, 1708, 1488, 1432, 1394, 1334, 1216, 1178, 1056 cm⁻¹; HRMS (FAB+) \(m/z\) calc’d for \(C_{18}H_{14}N_2O_3\) [M⁺]: 306.1005, found 306.1007.

\(\text{2-((5-methoxy-2-oxoindolin-3-yl)methyl)}\text{isoindoline-1,3-dione (109).}\)

Prepared according to the procedure similar to that used to synthesize oxindole 91 using \(N\)-bromosuccinimide (1.6 equiv). Purified by column chromatography (SiO₂, 9% EtOAc in \(\text{CH}_2\text{Cl}_2 \rightarrow 17%\) EtOAc in \(\text{CH}_2\text{Cl}_2\)). Isolated as a white solid. 33% yield. \(R_f = 0.06\) (9% EtOAc in DCM); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 7.89-7.85 (comp. m, 2H), 7.75-7.7.71 (comp. m, 2H), 7.73 (bs, 1H), 6.80 (s, 1H), 6.77 (d, \(J = 8.0\) Hz, 1H), 6.74 (dd, \(J = 8.5, 2.0\) Hz, 1H), 4.19 (dd, \(J = 14.0, 9.5\) Hz, 1H), 4.12 (dd, \(J = 14.0, 7.0\) Hz, 1H), 3.95 (dd, \(J = 9.0, 7.0\) Hz, 1H), 3.72 (s, 3H); \(^1\)C NMR (125 MHz, CDCl₃) \(\delta\) 176.9, 168.3,
2-((3-bromo-5-methoxy-2-oxindolin-3-yl)methyl)isoindoline-1,3-dione (110).

Prepared according to the procedure similar to that used to synthesize bromooxindole 76 using N-bromosuccinimide (1.6 equiv). Purified by column chromatography (SiO₂, 9% EtOAc in DCM) and then recrystallized from DCM. Isolated as a yellow solid. 78% yield. 

\[
\begin{align*}
\text{R}_f &= 0.18 \text{ (9% EtOAc in DCM)}; \quad ^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta 7.78-7.74 \text{ (comp. m, 2H), 7.69-7.65 \text{ (comp. m, 2H), 7.61 \text{ (br s, 1H), 7.07, (d, } J = 2.5 \text{ Hz, 1H), 6.75 (dd, } J = 7.5, 2.5 \text{ Hz, 1H), 6.70 (d, } J = 7.5, 1H), 4.62 (ABq, } J = 15.0 \text{ Hz, 2H), 3.77 (s, 3H));} \\
\text{^{13}C NMR (125 MHz, CDCl}_3\text{)} \delta 174.2, 167.4, 156.1, 134.4, 133.3, 131.6, 128.3, 123.8, 117.1, 111.9, 111.2, 56.0, 53.9, 43.9; \quad \text{IR (neat film, NaCl) 3271, 2997, 1777, 1721, 1492, 1389, 1299, 1205, 719 cm}^{-1}; \quad \text{HRMS (FAB+) m/z calc’d for C}_{18}\text{H}_{14}\text{N}_2\text{O}_4\text{Br} [M+H]^+: 401.0137,} \\
\text{found 401.0142.}
\end{align*}
\]

3.4.3 General Synthesis of 3-Aryl Haloxindoles from Isatin

3-chloro-3-phenylindolin-2-one (113).

To a solution of isatin (111, 1.0 g, 6.8 mmol, 1.0 equiv) in THF (60 mL) cooled to –40 °C was added PhMgBr (3 M in Et₂O, 5.7 mL, 17 mmol, 2.5 equiv). The reaction mixture
was allowed to warm to ambient temperature. After 6 hours, 1 N hydrochloric acid (30 mL) was added dropwise to quench the reaction, and the phases were separated. The aqueous phase was extracted with ether (2 x 50 mL), dried with sodium sulfate and concentrated to afford 112 as a yellow solid in 99% yield. No further purification was necessary. \( R_f = 0.18 \) (20% EtOAc in DCM); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 7.39-7.37 (comp. m, 2H), 7.33-7.26 (comp. m, 4H), 7.17 (d, \( J = 7.5 \) Hz, 1H), 7.06 (ddd, \( J = 8.5, 8.5, 1.0 \) Hz, 1H), 6.97 (d, \( J = 7.8 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) \( \delta \) 181.8, 143.2, 142.2, 135.0, 130.8, 129.4, 129.1, 126.8, 126.2, 124.2, 111.5, 79.5; IR (neat film, NaCl) 3312, 1711, 1473, 1183 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{14}\)H\(_{11}\)O\(_2\)N [M\(^+\)] 225.0790, found 255.0796.

To a cooled (0 °C) solution of hydroxyoxindole 112 (322 mg, 1.4 mmol, 1.0 equiv) and pyridine (1.2 mL, 14 mmol, 3.0 equiv) in THF (10 mL) in flask equipped with a stirbar was added thionyl chloride (520 \( \mu \)L, 850 mg, 5.0 equiv) in a dropwise manner. The solution was stirred at 0 °C for one hour or until complete by TLC. Water (60 mL) then added and the mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (1 x 100 mL), and then dried with MgSO\(_4\) prior to concentration. Purification by flash chromatography (SiO\(_2\), 10% EtOAc in hexanes) afforded chlorooxindole 113 as a white powder (83% yield). \( R_f = 0.27 \) (25% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.20 (bs, 1H), 7.56-7.54 (comp. m, 2H), 7.39-7.32 (comp. m, 5H), 7.14 (ddd, \( J = 7.6, 7.6, 0.9 \) Hz, 1H), 6.97 (d, \( J = 7.8 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 175.2, 139.9, 136.5, 131.0, 130.6, 129.1, 128.7, 127.6, 126.5, 123.9, 110.8, 66.8; IR (neat film, NaCl) 3247, 1729, 1619, 1472, 1322, 1211 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{14}\)H\(_{11}\)ONCl [M+H\(^+\)]: 244.0529, found 244.0539.
3-(4-bromophenyl)-3-hydroxyindolin-2-one (114).

Prepared according to the procedure used for hydroxyoxindole 112. Purified by flash chromatography (SiO$_2$, 50% EtOAc in hexanes). Isolated as a white powder. 80% yield. R$_f$ = 0.33 (50% EtOAc in hexanes); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.38 (app. d, $J$ = 8.5 Hz, 2H), 7.23-7.19 (comp. m, 3H), 7.08 (d, $J$ = 7.3 Hz, 1H), 6.96 (dd, $J$ = 7.6, 7.6 Hz, 1H), 6.88 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 179.9, 141.9, 140.2, 133.2, 131.2, 129.8, 127.6, 124.9, 123.0, 121.7, 110.3, 77.8; IR (neat film, NaCl) 3234, 1718, 1621, 1472, 1184 cm$^{-1}$; HRMS (EI$^+$) $m/z$ calc’d for C$_{14}$H$_{10}$BrNO$_2$ [M]$^+$: 302.9895, found 302.9896.

3-(4-bromophenyl)-3-chloroindolin-2-one (115).

Prepared according to the procedure used for chlorooxindole 113. Purified by flash chromatography (SiO$_2$, 20% EtOAc in hexanes). Isolated as a white solid. 63% yield. R$_f$ = 0.67 (50% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.59 (s, 1H), 7.49 (app. d, $J$ = 8.8 Hz, 2H), 7.42 (app. d, $J$ = 8.8 Hz, 2H), 7.53 (app. t, $J$ = 6.1 Hz, 2H), 7.16 (dd, $J$ = 7.6, 7.6 Hz, 1H), 6.98 (d, $J$ = 7.5 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.2, 140.0, 135.6, 131.9, 130.9, 130.4, 129.4, 127.6, 126.3, 124.0, 111.2, 66.2; IR (neat film, NaCl) 3247, 1728, 1619, 1472, 1395, 1322, 1211, 1011 cm$^{-1}$; HRMS (EI$^+$) $m/z$ calc’d for C$_{14}$H$_{19}$ONCl$^+$Br [M]$^+$: 322.9536, found 322.9521.
3-(3,5-dimethylphenyl)-3-hydroxyindolin-2-one (116).

Prepared according to the procedure used for hydroxyoxindole 112. Purified by flash chromatography (SiO$_2$, 20% EtOAc in DCM). Isolated as a pale yellow solid. 46% yield. $R_f = 0.50$ (50% EtOAc in hexanes); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.29 (ddd, $J = 7.8, 7.8, 1.2$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.04 (ddd, $J = 7.6, 7.6, 1.0$ Hz, 1H), 6.98-6.96 (comp. m, 3H), 6.92 (s, 1H), 2.26 (s, 6H); $^{13}$C NMR (125 MHz, MeOD) $\delta$ 182.0, 143.2, 142.0, 139.2, 135.3, 130.8, 130.6, 126.2, 124.5, 124.2, 111.5, 79.5, 21.6; IR (neat film, NaCl) 3270, 1720, 1620, 1472, 1186, 1109 cm$^{-1}$; MS (EI$^+$) $m/z$ calc’d for C$_{16}$H$_{15}$O$_2$N [M$^+$]: 253.1103, found 253.1112.

3-chloro-3-(3,5-dimethylphenyl)indolin-2-one (117).

Prepared according to the procedure used for chlorooxindole 113. Purified by flash chromatography (SiO$_2$, 20% EtOAc in hexanes). Isolated as a light yellow solid. 85% yield. $R_f = 0.40$ (25% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36-7.30 (comp. m, 2H), 7.14-7.11 (comp. m, 3H), 6.98-6.97 (comp. m, 2H), 2.30 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.7, 140.0, 138.4, 136.2, 131.5, 130.9, 130.4, 126.3, 125.2, 123.8, 110.9, 67.0, 21.5; IR (neat film, NaCl) 3247, 1729, 1619, 1473, 1192 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{16}$H$_{15}$ClNO [M+H]$^+$: 272.0842, found 272.0847.
3-hydroxy-3-(naphthalen-2-yl)indolin-2-one (118).

Prepared according to the procedure used for hydroxyoxindole 112. Purified by flash chromatography (SiO₂, 50% EtOAc in hexanes). Isolated as a yellow solid. 86% yield. Rₚ = 0.46 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CD₃OD) δ 7.84 (d, J = 1.5 Hz, 1H), 7.73-7.71 (comp. m, 2H), 7.69 (d, J = 8.5 Hz, 1H), 7.38-7.36 (comp. m, 2H), 7.31 (dd, J = 8.8, 2.0 Hz, 1H), 7.22 (ddd, J = 7.8, 1.2 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.96 (dd, J = 8.0, 8.0 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H); ¹³C NMR (125 MHz, CD₃OD) δ 181.5, 143.2, 139.3, 134.8, 134.5, 134.5, 130.8, 129.2, 129.0, 128.6, 127.3, 127.2, 126.2, 125.6, 124.7, 124.1, 111.5, 79.5; IR (Neat Film, NaCl) 3235, 1727, 1711, 1619, 1471, 1339, 1180, 1109, 1074, 893, 929, 859, 811, 754, 740 cm⁻¹; HRMS (EI⁺) m/z calc’d for C₁₈H₁₃O₂N [M⁺]: 275.0946, found 275.0936.

3-chloro-3-(naphthalen-2-yl)indolin-2-one (119).

Prepared according to the procedure used for chlorooxindole 113. Purified by flash chromatography (SiO₂, 0% EtOAc in hexanes→40% EtOAc in hexanes). Isolated as a pale yellow solid. 67% yield. Rₚ = 0.30 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CD₃OD) δ 7.83 (s, 1H), 7.72-7.68 (comp. m, 3H), 7.38 (comp. m, 2H), 7.29 (dd, J = 8.5,
1.7 Hz, 1H), 7.22 (dd, \(J = 7.8, 7.8\) Hz, 1H), 7.11 (d, \(J = 7.6\) Hz, 1H), 6.96 (dd, \(J = 7.6, 7.6\) Hz, 1H), 6.91 (d, \(J = 7.8\) Hz, 1H); \(^{13}\)C NMR (125 MHz, MeOD) \(\delta\) 180.4, 142.0, 138.2, 133.6, 133.4, 133.3, 129.6, 128.0, 127.9, 127.4, 126.1, 126.0, 125.0, 124.4, 123.5, 122.9, 110.3, 78.4; IR (neat film, NaCl) 3261, 1726, 1679, 1622, 1474, 1342, 1268, 1180, 1126, 1111, 933, 894, 810, 752 cm\(^{-1}\); HRMS (EI\(^{+}\)) \(m/z\) calc’d for C\(_{18}\)H\(_{12}\)ONCl [M]\(^{+}\): 293.0607, found 293.0604.

**3-hydroxy-5-methoxy-3-phenylindolin-2-one (120).**

Prepared according to the procedure used for hydroxyoxindole 112. Purified by flash chromatography (SiO\(_2\), 20% EtOAc in hexanes→50% EtOAc in hexanes). Isolated as a pale pink solid. 86% yield. \(R_f = 0.25\) (50% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 7.39-7.36 (comp. m, 2H), 7.34-7.26 (comp. m, 3H), 6.91-6.85 (comp. m, 2H), 6.78 (d, \(J = 1.4\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) \(\delta\) 181.7, 157.8, 142.0, 136.1, 129.3, 129.0, 126.7, 115.6, 112.6, 111.9, 79.8, 56.2; IR (neat film, NaCl) 3271, 1708, 1489, 1203, 1026, 758, 733 cm\(^{-1}\); HRMS (EI\(^{+}\)) \(m/z\) calc’d for C\(_{15}\)H\(_{13}\)NO\(_3\) [M]\(^{+}\): 255.0895, found 255.0891.

**3-chloro-5-methoxy-3-phenylindolin-2-one (121).** Prepared according to the procedure used for chlorooxindole 113. Purified by flash chromatography (SiO\(_2\), 20% EtOAc in hexanes). Isolated as a white powder. 66% yield. \(R_f = 0.70\) (50% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.20 (s, 1H), 7.56 (comp. m, 2H), 7.40-7.26 (comp. m,
3H), 6.95 (app. s, 1H), 6.90-6.86 (comp. m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.4, 156.8, 136.6, 133.2, 132.2, 129.2, 128.9, 127.6, 116.0, 112.6, 111.5, 67.2, 56.0; IR (neat film, NaCl) 3206, 2961, 1726, 1613, 1492, 1440, 1300, 1206, 1146, 1104, 1031, 959, 846, 814, 750, 734, 695 cm$^{-1}$; MS (FAB$^+$) $m/z$ calc’d for C$_{15}$H$_{12}$ClNO$_2$ [M]$^+$: 273.0556, found 273.0557.

3-butyl-3-hydroxyindolin-2-one (122).

Prepared according to the procedure used for hydroxyoxindole 112. Purified by flash chromatography (SiO$_2$, 33% EtOAc in hexanes $\rightarrow$ 50% EtOAc in hexanes) and recrystallized from EtOAc and hexanes. Isolated as a white solid. 29% yield. R$_f$ = 0.47 (33% EtOAc in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.82 (br s, 1H), 7.37 (dd, $J$ = 7.2, 0.6 Hz, 1H), 7.27 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.09 (td, $J$ = 7.5, 1.2 Hz, 1H), 6.88 (d, $J$ = 7.8 Hz, 1H), 2.76 (s, 1H), 1.99-1.90 (comp. m, 2H), 1.31-1.16 (comp. m, 3H), 1.12-1.04 (comp. m, 1H), 0.82 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 181.0, 140.6, 130.7, 129.7, 124.4, 123.3, 110.5, 77.2, 38.4, 25.3, 22.9, 13.9; IR (neat film, NaCl) 3401, 3189, 2951, 2934, 2860, 1718, 1624, 1474, 1400, 1338, 1234, 1194, 1103, 1083, 1059, 1010, 961, 774, 748 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{12}$H$_{15}$NO$_2$ [M+H]$^+$: 205.1103, found 205.1109.

3-bromo-3-butylindolin-2-one (123).
To cooled solution (0 °C) of 3-butyl-3-hydroxyindolin-2-one (188 mg, 0.916 mmol, 1.0 equiv) and pyridine (0.89 mL, 0.99 mmol, 12 equiv) in THF (8 mL) in a flask equipped with a stir bar was added a solution of POBr$_3$ (1.0 g, 3.7 mg, 4.0 equiv) in THF (2 mL) in a dropwise manner. The reaction solution was stirred at 0 °C for 20 min. Water (20 mL) then added and the mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were dried with MgSO$_4$ prior to concentration. Purification by flash chromatography (SiO$_2$, 10% EtOAc in hexanes) afforded 3-bromo-3-butylindolin-2-one as a pale yellow viscous oil (31% yield). $R_f = 0.48$ (33% EtOAc in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) δ 9.45 (br s, 1H), 7.38 (dd, $J = 7.2, 0.6$ Hz, 1H), 7.27 (td, $J = 7.5, 1.2$ Hz, 1H), 7.09 (td, $J = 7.8, 1.2$ Hz, 1H), 6.98 (d, $J = 7.1$ Hz, 1H), 2.47-2.32 (comp. m, 2H), 1.37-1.00 (comp. m, 4H), 0.83 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.3, 139.9, 130.6, 130.1, 124.8, 123.5, 111.0, 57.1, 39.3, 27.6, 22.6, 13.9; IR (neat film, NaCl) 3247, 2957, 2930, 2872, 1722, 1618, 1472, 1381, 1331, 1223, 1193, 1139, 1118, 1102, 1018, 863, 837 cm$^{-1}$; HRMS (FAB+) m/z calcd. for C$_{12}$H$_{15}$BrNO [M+H]+$^+$: 268.0337, found 268.0328.

### 3.4.4 Synthesis of [Cu((R)-Ph-BOX)(SbF$_6$)$_2$]

(R)-Ph-BOX (190 mg, 0.58 mmol, 1.0 equiv) was stirred in the presence of copper(II) chloride (82 mg, 0.61 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (8 mL) for 24 hours at ambient temperature in a glovebox. The reaction mixture was then filtered through Celite, and the
green solution was concentrated under reduced pressure to afford [Cu((R)-Ph-BOX)Cl$_2$] as a light green powder (272 mg, >99% yield).

A 25 mL reaction flask equipped with a magnetic stir bar was charged with [Cu((R)-PhBOX)Cl$_2$] (103 mg, 0.22 mmol, 1.0 equiv) and silver hexafluoroantimonate (150 mg, 2.0 equiv) in a glovebox. The flask was wrapped with aluminum foil to prevent exposure to light, and CH$_2$Cl$_2$ (11 mL) was added. The flask was capped and the reaction mixture stirred in the glovebox for 14 hours, then filtered through a pad of Celite. The dark green filtrate was concentrated under reduced pressure to afford [Cu((R)-PhBOX)(SbF$_6$)$_2$] as a dark green powder (174 mg, 92% yield).

3.4.5 General Procedure for Enantioselective Malonate Alkylation

A 1 dram vial equipped with a stirbar was charged with [Cu((R)-PhBOX)(SbF$_6$)$_2$] (17.4 mg, 0.02 mmol, 0.2 equiv) and 3ÅMS (32.3 mg) in the glovebox. After the reaction vial was removed from the glove box, DCM (0.25 mL of 0.5 mL added, 0.2 M solution) was added, and the mixture was allowed to stir for 15 minutes. Upon cooling to reaction temperature, malonate (34.3 uL, 0.3 mmol, 3.0 equiv) followed by halooxindole (0.1 mmol, 1.0 equiv) were dissolved in the remaining DCM and were added via syringe to give a dark blue-green solution. Base (0.2 mmol, 2.0 equiv) was then added to give a dark brown solution. Upon completion of reaction, saturated aqueous ammonium
chloride solution (2 mL) was added. Upon extraction with DCM (3 x 2 mL), the combined organic layers were dried with sodium sulfate and purified as stated.

Malonate Adduct 77 (Table 3.4, Entry 1).

Purified by flash chromatography (SiO₂, 5% acetonitrile in benzene). Isolated as a white solid. 77% yield. R_f = 0.53 (17% acetonitrile in benzene); ¹H NMR (300 MHz, CDCl₃) δ 7.54 (m, 2H), 7.21 (td, J = 7.7, 1.0 Hz, 1H), 7.01 (td, J = 7.6, 1.0 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 4.17 (s, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 3.51 (m, 1H), 3.35 (m, 1H), 3.25 (m, 2H), 0.93 (s, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 179.3, 168.0, 167.1, 141.4, 129.4, 128.6, 125.4, 109.5, 58.9, 57.1, 52.5, 52.5, 50.9, 38.5, 17.9, 11.9; IR (neat film, NaCl) 3251, 2941, 2863, 1747, 1721, 1687, 1471, 1321, 1197, 1114 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₄H₃₈NO₆Si [M+H]+:464.2468, found 464.2468; [α]D ²⁵ –28.6 (c 0.43, CH₂Cl₂, 88% ee).

Malonate Adduct 124 (Table 3.4, Entry 2).

Purified by flash chromatography (SiO₂, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 73% yield. R_f = 0.24 (33% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.80 (br s, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.20 (td, J = 8.0, 1.0 Hz, 1H), 7.00 (td, J = 7.5, 1.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 4.29-4.23 (m, 2H), 4.14 (s, 1H), 4.00-3.89 (m, 2H), 3.52 (ddd, J = 12.0, 8.0, 7.0 Hz, 1H), 3.36 (ddd, J = 13.5, 8.5,
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Haloindoles

5.0 Hz, 1H), 2.32-2.21 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H), 0.99 (t, J = 7.0 Hz, 3H), 0.93 (s, 21H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.5, 167.8, 166.9, 141.6, 129.7, 128.7, 125.9, 122.7, 109.5, 61.8 (2C), 59.1, 57.6, 51.0, 38.9, 18.1, 14.2, 13.8, 12.1; IR (neat film, NaCl) 3218, 2942, 2866, 1731, 1716, 1621, 1472, 1197 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{26}$H$_{42}$NO$_6$Si [M+H]$^+$: 492.2781, found 492.2774; [\(\alpha\)]$_D$$^{25}$ -16.4 (c 0.78, CH$_2$Cl$_2$, 84% ee).

Malonate Adduct 125 (Table 3.4, Entry 3).

Purified by flash chromatography (SiO$_2$, 7% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 78% yield. $R_f$ = 0.25 (33% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.80 (br s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.33-7.23 (comp. m, 8H), 7.16 (td, J = 7.5, 1.0 Hz, 1H), 7.07 (dd, J = 8.0, 1.5 Hz, 2H), 6.94 (td, J = 7.5, 0.5 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 5.20 (ABq, J = 17.0 Hz, 2H), 4.91 (ABq, J = 18.5 Hz, 2H), 4.27 (s, 1H), 3.50 (dt, J = 9.5, 6.0 Hz, 1H), 3.50 (ddd, J = 10.0, 8.5, 5.0 Hz, 1H), 2.33-2.22 (m, 2H), 0.92 (s, 21H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.3, 167.5, 166.6, 141.5, 135.2, 135.1, 129.4, 128.8, 128.7, 128.6, 128.43, 128.39, 125.7, 122.7, 109.8, 67.7, 67.5, 59.1, 57.6, 51.1, 38.9, 18.1, 12.1; IR (neat film, NaCl) 3251, 2941, 2863, 1747, 1721, 1687, 1471, 1321, 1197, 1114 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{26}$H$_{42}$NO$_6$Si [M+H]$^+$: 464.2468, found 464.2468; [\(\alpha\)]$_D$$^{25}$ -17.7 (c 0.71, CH$_2$Cl$_2$, 88% ee).

Malonate Adduct 126 (Table 3.4, Entry 4).
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

Purified by flash chromatography (SiO₂, 5% acetonitrile in benzene). Isolated as a white solid. 78% yield. \( R_f = 0.48 \) (17% acetonitrile in benzene); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 7.56 \) (br s, 1 H), 7.51 (dd, \( J = 8.0, 1.5 \) Hz, 2H), 7.42-7.39 (comp. m, 3H), 7.38-7.35 (comp. m, 2H), 7.33-7.28 (comp. m, 4H), 7.21 (td, \( J = 7.5, 1.5 \) Hz, 1H), 6.98 (td, \( J = 7.5, 1.0 \) Hz, 1H), 6.80 (d, \( J = 7.5 \) Hz, 1H), 4.13 (s, 1H), 3.73 (s, 3H), 3.51 (s, 3H), 3.46 (ddd, \( J = 14.0, 7.5, 6.5 \) Hz, 1H), 3.34 (ddd, \( J = 12.0, 7.5, 4.5 \) Hz, 1H), 2.38 (dt, \( J = 13.5, 8.0 \) Hz, 1H), 2.25 (ddd, \( J = 13.5, 6.5, 4.5 \) Hz, 1H), 0.94 (s, 9H); \(^13\)C NMR (125 MHz, CDCl₃) \( \delta 179.1, 168.1, 167.1, 141.5, 135.6, 135.5, 133.5, 133.4, 129.7, 129.6, 129.1, 128.6, 127.7 \) (2 C), 125.6, 122.6, 109.6, 59.8, 57.5, 52.7, 52.6, 51.0, 38.2, 26.8, 19.1; IR (neat film, NaCl) 3369, 3071, 2953, 2930, 2857, 1736, 1717, 1620, 1472, 1429, 1325, 1237, 1198, 1156, 1112, 1088, 1022, 823, 740 cm⁻¹; HRMS (FAB+) \( m/z \) calc’d for \( \text{C}_{31}\text{H}_{36}\text{NO}_6\text{Si} \) [M+H]+: 546.2312, found 546.2320; \([\alpha]_{D}^{25} = -17.3 \) (c 0.94, CH₂Cl₂, 88% ee).

Malonate Adduct 127 (Table 3.4, Entry 6).

Purified by flash chromatography (SiO₂, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 47% yield. \( R_f = 0.16 \) (22% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 7.80 \) (br s, 1H), 7.53 (d, \( J = 7.5 \) Hz, 1H), 7.20 (td, \( J = 7.5, 1.0 \) Hz, 1H), 7.01 (td, \( J = 7.5, 1.0 \) Hz, 1H), 6.84 (d, \( J = 7.5 \) Hz, 1H), 4.15 (s, 1H), 3.79 (s, 3H), 3.56-3.46 (comp. m, 2H), 3.51 (s, 3H), 1.96-1.89 (comp. m, 2H), 1.46-1.31 (comp. m, 2H), 1.18-1.08 (comp. m, 1H), 1.02-0.88 (comp. m, 21H); \(^13\)C NMR (125 MHz, CDCl₃) \( \delta 179.6, 168.2, 167.3, 141.5, 129.9, 128.5, 125.2, 122.8, 109.4, 63.0, 57.2, 52.9, 52.8, 52.7, 36.4, 33.0, 20.0, 18.1, 12.1; IR (neat film, NaCl) 3248, 2944, 2866, 1736,
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

1716, 1620, 1472, 1436, 1326, 1225, 1155, 1109, 1058, 995, 883, 752 cm⁻¹; HRMS (FAB+) m/z calc’d for C_{26}H_{42}NO_{6}Si [M+H]⁺: 492.2781, found 492.2775; [α]_{D}^{25} = -6.3 (c 0.58, CH₂Cl₂, 86% ee).

Malonate Adduct 128 (Table 3.4, Entry 5).

Purified by flash chromatography (SiO₂, 9% acetonitrile in benzene). Isolated as a white solid. 51% yield. R₂ = 0.13 (33% EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.23 (br s, 1H), 7.85 (dd, J = 8.1, 1.2 Hz, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.51 (tt, J = 7.5, 1.2 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.19 (td, J = 7.5, 1.2 Hz, 1H), 7.01 (td, J = 7.8, 1.2 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 4.19 (s, 1H), 4.08 (comp. m, 2H), 3.78 (s, 3H), 3.51 (s, 3H), 2.53 (t, J = 6.6 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 179.2, 167.8, 166.9, 166.2, 141.6, 133.0, 129.9, 129.7, 130.1, 128.8, 128.3, 125.5, 122.9, 110.1, 60.7, 57.3, 52.8, 52.7, 51.2, 34.6; IR (neat film, NaCl) 3307, 2955, 1723, 1620, 1473, 1452, 1436, 1318, 1274, 1199, 1158, 1117, 1026, 756, 714 cm⁻¹; HRMS (FAB+) m/z calc’d for C_{22}H_{22}NO_{7} [M+H]⁺: 412.1396, found 412.1392; [α]_{D}^{25} = -52.5 (c 1.40, CH₂Cl₂, 83% ee).

Malonate Adduct 129 (Table 3.4, Entry 7).

Purified by flash chromatography (SiO₂, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a pale yellow solid. 47% yield. R₂ = 0.22 (33% EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.11 (br s, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.22
(td, $J = 7.8, 2.0$ Hz, 1H), 7.02 (td, $J = 7.5, 1.5$ Hz, 1H), 6.87 (d, $J = 7.8$ Hz, 1H), 4.15 (s, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 1.93-1.87 (comp. m, 2H), 1.22-1.04 (comp. m, 3H), 0.81-0.72 (comp. m with a triplet at $\delta 0.75$, $J = 7.5$ Hz, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 179.9, 168.2, 167.3, 141.6, 130.1, 128.5, 125.2, 122.7, 109.5, 57.3, 52.8, 52.7, 52.6, 36.2, 25.5, 22.8, 13.9; IR (neat film, NaCl) 3249, 2956, 2930, 2862, 1736, 1716, 1620, 1486, 1472, 1436, 1327, 1292, 1230, 1198, 1157, 1057, 1022, 755 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{17}$H$_{22}$NO$_5$ [M+H]$^+$: 320.1498, found 320.1512; $[\alpha]_D^{25}$ –10.6 (c 1.46, CH$_2$Cl$_2$, 84% ee).

![Malonated Adduct 130](image)

**Malonated Adduct 130 (Table 3.4, Entry 10).**

Purified by flash chromatography (SiO$_2$, 17% acetone in hexanes). Isolated as a white solid. 63% yield. $R_f = 0.22$ (33% acetone in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.07 (br s, 1H), 7.73-7.70 (comp. m, 2H), 7.66-7.63 (comp. m, 2H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.07 (td, $J = 7.5, 1.0$ Hz, 1H), 6.88 (td, $J = 7.5, 1.0$ Hz, 1H), 6.84 (d, $J = 7.5$ Hz, 1H), 4.18 (s, 1H), 3.82 (s, 3H), 3.56 (t, $J = 7.5$ Hz, 2H), 3.50 (s, 3H), 2.52 (dt, $J = 13.5, 8.0$ Hz, 1H), 2.35 (quintet, $J = 7.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 178.5, 167.9, 167.8, 166.9, 141.4, 133.9, 132.1, 128.9, 128.8, 125.4, 123.2, 122.9, 110.0, 57.0, 52.9, 52.7, 51.3, 33.6, 33.5; IR (neat film, NaCl) 3261, 3034, 2935, 2935, 1755, 1724, 1698, 1473, 1398, 1347, 1272, 1153, 1060, 719 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{23}$H$_{21}$N$_2$O$_7$ [M+H]$^+$: 437.1349, found 437.1342; $[\alpha]_D^{25}$ –4.4 (c 0.56, MeOH, 94% ee).
Malonate Adduct 131 (Table 3.4, Entry 8).

Purified by flash chromatography (SiO$_2$, 5% acetonitrile in benzene→25% acetonitrile in benzene). Isolated as a white solid. 42% yield. $R_f = 0.48$ (17% acetonitrile in benzene); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.79 (br s, 1H), 7.70-7.74 (m, 2H), 7.18 (td, $J = 7.5, 1.5$ Hz, 1H), 7.00 (td, $J = 8.0, 1.0$ Hz, 1H), 6.81 (d, $J = 7.5$ Hz, 1H), 4.62 (d, $J = 14.5$ Hz, 1H), 4.30 (s, 1 H), 4.15 (d, $J = 14.5$ Hz, 1H), 3.90 (s, 3H), 3.50 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 177.2, 168.1, 168.0, 167.3, 141.2, 134.2, 131.8, 129.3, 127.8, 126.5, 123.6, 122.7, 109.9, 54.7, 53.0, 52.9, 52.4, 41.3; IR (neat film, NaCl) 3340, 2954, 2924, 2853, 1776, 1732, 1718, 1618, 1472, 1434, 1394, 1354, 1316, 1295, 1225, 1197, 1158, 1001, 905 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{22}$H$_{19}$N$_2$O$_7$ [M]$^+$: 423.1192, found 423.1203; [$\alpha$]$_D^{25}$ –3.3 (c 0.55, CH$_2$Cl$_2$, 81% ee).

Malonate Adduct 83 (Table 3.4, Entry 9).

Purified by flash chromatography (SiO$_2$, 33% EtOAc in hexanes→50% EtOAc in hexanes; then 9% acetonitrile in benzene→17% acetonitrile in benzene). Isolated as a white solid. 42% yield. $R_f = 0.22$ (17% acetonitrile in benzene); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.89-7.76 (m, 2H), 7.69-7.66 (m, 2H), 7.48 (br s, 1H), 7.41 (d, $J = 2.0$ Hz, 1H), 6.75-6.71 (comp. m, 2H), 4.62 (d, $J = 14.5$ Hz, 1H), 4.30 (s, 1 H), 4.10 (d, $J = 14.5$ Hz,
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.52 (s, 3H); $^1$H NMR (125 MHz, CDCl$_3$) $\delta$ 177.1, 168.1, 168.0, 167.2, 155.7, 134.6, 134.1, 131.8, 129.1, 123.6, 114.6, 113.2, 110.4, 55.9, 54.6, 53.0, 52.9, 52.8, 41.3; IR (neat film, NaCl) 3350, 3003, 2954, 2840, 1776, 1722, 1602, 1488, 1468, 1435, 1394, 1331, 1301, 1265, 1206, 1160, 1051, 1032, 1004, 909, 815, 720 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{23}$H$_{21}$N$_2$O$_8$ [M+H]$^+$: 453.1298, found 453.1319; $[\alpha]_D^{25}$ –2.3 (c 1.10, CHCl$_3$, 95% ee).

Malonate Adduct 87 (Table 3.5, Entry 1).

Purified by flash chromatography (SiO$_2$, 10% acetonitrile in toluene→15% acetonitrile in toluene). Isolated as a pale yellow solid. 76% yield. $R_f$ = 0.22 (33% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.08 (bs, 1H), 7.71 (d, $J$ = 7.6 Hz, 1H), 7.25-7.16 (comp. m, 5H), 7.06 (ddd, $J$ = 7.6, 7.6, 0.9 Hz, 1H), 6.84 (d, $J$ = 7.8 Hz, 1H), 4.85 (s, 1H), 3.50 (s, 3H), 3.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 178.7, 167.8, 167.3, 141.8, 137.3, 129.2, 128.7, 128.4, 128.0, 127.1, 122.8, 110.1, 58.5, 56.7, 52.7, 52.6; IR (neat film, NaCl) 3254, 2954, 1734, 1620, 1473, 1436, 1325, 1156, 1039, 912, 733 cm$^{-1}$; HRMS (FAB) $m/z$ calc’d for C$_{19}$H$_{18}$NO$_5$ [M+H]$^+$: 340.1185, found 340.1183; $[\alpha]_D^{25}$ –66.6 (c 1.12, CH$_2$Cl$_2$, 76% ee).

Malonate Adduct 132 (Table 3.5, Entry 3).
Purified by flash chromatography (SiO$_2$, toluene → 20% acetonitrile in toluene).

Isolated as a 74% yield. Isolated as a pale yellow oil. 84% yield. R$_f$ = 0.45 (20% acetonitrile in toluene); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.38 (app. d, J = 8.5 Hz, 2H), 7.33 (dd, J = 8.8, 8.8 Hz, 1H), 7.20 (app. d, J = 6.8 Hz, 2H), 7.15 (dd, J = 7.8, 7.8 Hz, 1H), 6.93 (d, J = 7.6 Hz), 4.85 (s, 1H), 3.61 (s, 3H), 3.43 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.0, 167.7, 167.2, 141.6, 136.5, 131.9, 129.6, 129.0, 128.4, 128.2, 123.2, 122.6, 110.2, 58.5, 56.3, 52.9, 52.8; IR (neat film, NaCl) 3307, 1736, 1619, 1472, 1435, 1323, 1158 cm$^{-1}$; HRMS (EI$^+$) m/z calc’d for C$_{19}$H$_{16}$O$_5$NBr [M]+: 417.0212, found 417.0219; [α]$_D^{25}$ +175.0 (c 1.52, CH$_2$Cl$_2$, 81% ee).

Malonate Adduct 133 (Table 3.5, Entry 4).

Purified by flash chromatography (SiO$_2$, toluene → 10% acetonitrile in toluene).

Isolated as a yellow oil. 69% yield. R$_f$ = 0.25 (15% acetonitrile in toluene); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.24 (bs, 1H), 7.95 (d, J = 7.1 Hz, 1H), 7.29 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.12 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.87-6.85 (comp. m, 3H), 4.90 (s, 1H), 3.60 (s, 3H), 3.38 (s, 3H), 2.21 (s, 6H); $^{13}$C NMR (500 MHz, CDCl$_3$) δ 178.9, 167.9, 167.5, 141.8, 138.1, 137.3, 129.8, 129.1, 129.0, 128.3, 124.7, 122.8, 110.0, 58.4, 56.7, 52.6, 52.5, 21.6; IR (neat film, NaCl) 3248, 2956, 1737, 1718, 1618, 1473, 1324, 1199, 1155 cm$^{-1}$; HRMS (FAB) m/z calc’d for C$_{21}$H$_{22}$NO$_5$ [M+H]$^+$: 368.1498, found 368.1507; [α]$_D^{25}$ +181.7 (c 0.84, CH$_2$Cl$_2$, 84% ee).
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

Malonate Adduct 134 (Table 3.5, Entry 5).

Purified by flash chromatography (SiO$_2$, toluene→20% acetonitrile in toluene). Isolated as a light yellow solid. 74% yield. R$_f$ = 0.65 (50% EtOAc in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.06 (d, J = 7.8 Hz, 1H), 8.01 (s, 1H), 7.77-7.76 (comp. m, 2H), 7.70-7.68 (comp. m, 1H), 7.23 (bs, 1H), 7.58 (dd, J = 8.5, 2.0 Hz, 1H), 7.45-7.39 (comp. m, 2H), 7.33 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.19 (ddd, J = 7.8, 7.8, 1.0 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 5.05 (s, 1H), 3.52 (s, 3H), 3.42 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.6, 167.9, 167.5, 141.9, 134.8, 133.3, 133.0, 129.4, 128.8, 128.6, 128.5, 127.7, 126.8, 126.6, 126.4, 124.6, 123.1, 110.2, 58.5, 56.9, 52.8, 52.7; IR (neat film, NaCl) 3256, 3059, 2953, 1732, 1619, 1597, 1472, 1435, 1323, 1294, 1198, 1157, 1037, 912, 732, 648 cm$^{-1}$; HRMS (FAB$^+$) m/z calc’d for C$_{23}$H$_{20}$O$_5$N $[M+H]^+$: 390.1341, found 390.1354; $\left[\alpha\right]_{D}^{25}$ +171.8 (c 1.20, CH$_2$Cl$_2$, 74% ee).

Malonate Adduct 135 (Table 3.5, Entry 2).

Purified by flash chromatography (SiO$_2$, toluene → 10% acetonitrile in toluene). Isolated as an orange solid. 82% yield. R$_f$ = 0.23 (15% acetonitrile in toluene); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.90 (s, 1H), 7.6 (app. s, 1H), 7.24-7.23 (app. d, J = 6.6 Hz, 2H), 7.20-6.74 (comp. m, 5H), 4.92 (s, 1H), 3.83 (s, 3H), 3.57 (s, 3H), 3.45 (s, 3H); $^{13}$C NMR
(125 MHz, CDCl$_3$) δ 178.3, 167.8, 167.3, 156.0, 137.3, 135.0, 130.0, 128.7, 128.0, 127.0, 114.9, 114.4, 110.3, 58.4, 57.1, 56.0, 52.7, 52.6; IR (neat film, NaCl) 3271, 2953, 1733, 1600, 1487, 1437, 1301, 1266, 1207, 1156, 1058, 1033 cm$^{-1}$; HRMS (FAB$^+$) m/z calc’d for C$_{20}$H$_{19}$O$_6$N$[^{M}]^+$: 369.1212, found 369.1204; [α]$_{D}^{25}$ +168.1 (c 1.09, CH$_2$Cl$_2$, 84% ee).
### 3.4.6 Chiral HPLC Assay conditions

**Table 3.6**

<table>
<thead>
<tr>
<th>Malonate Adduct</th>
<th>Conditions</th>
<th>Time</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Malonate Adduct" /></td>
<td>5% IPA/Hexanes</td>
<td>28.9 min (major)</td>
<td>88%</td>
</tr>
<tr>
<td><img src="image2" alt="Malonate Adduct" /></td>
<td>5% IPA/Hexanes</td>
<td>35.3 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Malonate Adduct" /></td>
<td>4% EtOH/Hexanes</td>
<td>16.4 min (major)</td>
<td>84%</td>
</tr>
<tr>
<td><img src="image4" alt="Malonate Adduct" /></td>
<td>4% EtOH/Hexanes</td>
<td>19.0 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Malonate Adduct" /></td>
<td>4% EtOH/Hexanes</td>
<td>24.4 min (major)</td>
<td>88%</td>
</tr>
<tr>
<td><img src="image6" alt="Malonate Adduct" /></td>
<td>4% EtOH/Hexanes</td>
<td>28.1 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image7" alt="Malonate Adduct" /></td>
<td>10% IPA/Hexanes</td>
<td>16.8 min (major)</td>
<td>88%</td>
</tr>
<tr>
<td><img src="image8" alt="Malonate Adduct" /></td>
<td>10% IPA/Hexanes</td>
<td>24.4 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image9" alt="Malonate Adduct" /></td>
<td>5% IPA/Hexanes</td>
<td>17.7 min (major)</td>
<td>86%</td>
</tr>
<tr>
<td><img src="image10" alt="Malonate Adduct" /></td>
<td>5% IPA/Hexanes</td>
<td>41.9 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image11" alt="Malonate Adduct" /></td>
<td>20% IPA/Hexanes</td>
<td>19.9 min (major)</td>
<td>83%</td>
</tr>
<tr>
<td><img src="image12" alt="Malonate Adduct" /></td>
<td>20% IPA/Hexanes</td>
<td>33.1 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image13" alt="Malonate Adduct" /></td>
<td>10% IPA/Hexanes</td>
<td>19.5 min (major)</td>
<td>84%</td>
</tr>
<tr>
<td><img src="image14" alt="Malonate Adduct" /></td>
<td>10% IPA/Hexanes</td>
<td>24.4 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image15" alt="Malonate Adduct" /></td>
<td>80% EtOH/Hexanes</td>
<td>17.2 min (major)</td>
<td>94%</td>
</tr>
<tr>
<td><img src="image16" alt="Malonate Adduct" /></td>
<td>80% EtOH/Hexanes</td>
<td>22.8 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image17" alt="Malonate Adduct" /></td>
<td>80% EtOH/Hexanes</td>
<td>18.6 min (major)</td>
<td>81%</td>
</tr>
<tr>
<td><img src="image18" alt="Malonate Adduct" /></td>
<td>80% EtOH/Hexanes</td>
<td>26.0 min (minor)</td>
<td></td>
</tr>
<tr>
<td><img src="image19" alt="Malonate Adduct" /></td>
<td>80% EtOH/Hexanes</td>
<td>21.7 min (major)</td>
<td>91%</td>
</tr>
<tr>
<td><img src="image20" alt="Malonate Adduct" /></td>
<td>80% EtOH/Hexanes</td>
<td>35.4 min (minor)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.7

<table>
<thead>
<tr>
<th>Malonate Adduct</th>
<th>Conditions</th>
<th>Time</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>20% IPA/Hexanes</td>
<td>7.6 min (major)</td>
<td>76%</td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>19.5 min (minor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>15% IPA/Hexanes</td>
<td>26.1 min (major)</td>
<td>–81%</td>
</tr>
<tr>
<td><img src="image4" alt="Structure" /></td>
<td>37.5 min (minor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Structure" /></td>
<td>15% IPA/Hexanes</td>
<td>14.1 min (major)</td>
<td>–84%</td>
</tr>
<tr>
<td><img src="image6" alt="Structure" /></td>
<td>34.5 min (minor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image7" alt="Structure" /></td>
<td>20% IPA/Hexanes</td>
<td>29.2 min (major)</td>
<td>–74%</td>
</tr>
<tr>
<td><img src="image8" alt="Structure" /></td>
<td>41.2 min (minor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image9" alt="Structure" /></td>
<td>15% IPA/Hexanes</td>
<td>21.4 min (major)</td>
<td>–84%</td>
</tr>
<tr>
<td><img src="image10" alt="Structure" /></td>
<td>40.5 min (minor)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.4.7 Synthesis of Pyrrolidinone-spirooxindoles

Phthalimidoester 84 (Scheme 3.2).

To a round bottom flask equipped with a stirbar, malonate adduct (99% ee, 115 mg, 0.25 mmol, 1 equiv) and sodium chloride (30 mg, 0.51 mmol, 2 equiv) were dissolved in water (23 μL, 1.3 mmol, 5 equiv) and DMSO (5 mL). The reaction flask was then
heated to 150 °C for 5 hours. Upon cooling to ambient temperature, the reaction mixture was then diluted with water (5 mL) and brine (5 mL) and then extracted with EtOAc (3 x 20 mL). The organic layers were collected and dried with MgSO₄. Purification by column chromatography (SiO₂, 9% acetonitrile in benzene→17% acetonitrile in benzene) afforded phthalimidoester 84 as a pale yellow solid (57.5 mg, 58% yield). Rᵢ = 0.09 (17% acetonitrile in benzene);¹H NMR (500 MHz, CDCl₃) δ 7.82 (dd, J = 5.0, 3.0 Hz, 2H), 7.71 (dd, J = 5.0, 3.0 Hz, 2H), 7.54 (br s, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 6.74 (dd, J = 9.0, 2.5 Hz, 1H), 4.00 (ABq, J = 14.0 Hz, 2H), 3.74 (s, 3H), 3.51 (s, 3H), 3.15 (ABq, J = 17.0 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 178.4, 170.2, 168.2, 155.7, 134.5, 134.3, 131.9, 130.8, 123.7, 113.7, 110.9, 110.5, 55.9, 51.9, 50.4, 43.1, 38.6; IR (neat film, NaCl) 3306, 2997, 2952, 2838, 1776, 1719, 1604, 1490, 1468, 1437, 1395, 1363, 1302, 1207, 1140, 1027, 928, 908, 812 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₁H₁₉N₂O₆ [M+H]⁺: 395.1243, found 395.1243; [α]D¹⁸.⁰ +26.1 (c 1.00, CH₂Cl₂).

Spirocyclic Oxindole 85 (Scheme 3.2). To a solution of phthalimidoester 84 (13 mg, 0.032 mmol, 1 equiv) in EtOH (3 mL) was added H₂NNH₂•H₂O (16 μL, 0.32, 10 equiv) at 23 °C. The reaction flask was then heated to 95 °C for 13 hours. Upon cooling to ambient temperature, reaction mixture was filtered through a short plug of celite and concentrated. Purification by preparative TLC (SiO₂, 9% MeOH in DCM) afforded spirocyclic oxindole 85 as a white solid (6.5 mg, 88% yield). Rᵢ = 0.36 (9% MeOH in
DCM); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.82 (br s, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 6.83 (d, $J = 7.5$ Hz, 1H), 6.80 (dd, $J = 7.5, 2.0$ Hz, 1H), 5.98 (bs, 1H), 3.87 (d, $J = 9.5$ Hz, 1H), 3.79 (s, 3H), 3.59 (dd, $J = 9.5, 0.5$ Hz, 1H), 2.98 (d, $J = 16.5$ Hz, 1H), 2.50 (d, $J = 17.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 179.0, 175.3, 156.7, 134.9, 132.9, 113.8, 110.7, 109.6, 56.1, 51.0, 50.4, 40.4; IR (neat film, NaCl) 3231, 2956, 2925, 2847, 1699, 1494, 1439, 1306, 1207, 1179, 1033 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{13}$H$_{13}$N$_2$O$_3$ [M+H]$^+$: 233.0926, found 233.0918; $[\alpha]_{D}^{23.0} +43.5$ (c 0.65, MeOH).

**Bis(p-Br-benzyl)lactam 86 (Scheme 3.2).** To a cooled (0 °C) mixture of NaH (3.4 mg, 60 %, 0.84 mmol, 3.0 equiv) in THF (1 mL) was added a solution of spirocyclic oxindole 85 (6.5 mg, 0.028 mmol, 1.0 equiv) in THF (2.0 mL) in a dropwise manner via syringe. The flask containing the oxindole was rinsed with THF (1 mL) and this solution was also added dropwise via syringe at 0 °C. The reaction was allowed to stir for 30 minutes at 23 °C before the addition of 4-bromobenzyl bromide (21 mg, 0.84 mmol, 3.0 equiv). After stirring for 14 hours at 23 °C, the reaction was quenched with brine (3 mL) and extracted with CH$_2$Cl$_2$ (3 x 5 mL). The organic layers were collected and dried with MgSO$_4$. Purification by column chromatography (SiO$_2$, 25% EtOAc in CH$_2$Cl$_2$) afforded bis(p-Br-benzyl)lactam 86 as a white solid (10.1 mg, 67% yield). Mp: 214.5-216 °C from CH$_2$Cl$_2$/hexanes; $R_f = 0.66$ (50% EtOAc in CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 (dt, $J = 8.5, 2.5$ Hz, 2H), 7.43 (dt, $J = 9.0, 2.5$ Hz, 2H), 7.22 (dt, $J = 8.5, 2.5$ Hz, 2H), 7.11 (dt, $J = 8.5, 2.5$ Hz, 2H), 6.71-6.68 (comp. m, 2H), 6.60 (d, $J = 9.5$ Hz, 1H), 4.80
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

(ABq, \( J = 16.0 \) Hz, 2H), 4.66 (d, \( J = 14.5 \) Hz, 1H), 4.41 (d, \( J = 15.0 \) Hz, 1H), 3.74 (d, \( J = 9.5 \) Hz, 1H), 3.69 (s, 3 H), 3.31 (d, \( J = 9.5 \) Hz, 1H), 3.12 (d, \( J = 17.0 \) Hz, 1H), 2.63 (d, \( J = 17.0 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 177.4, 171.7, 156.9, 135.0, 134.9, 134.6, 134.4, 132.2, 130.2, 129.1, 122.1, 122.0, 113.5, 110.0, 109.4, 105.1, 55.9, 55.3, 47.1, 46.5, 43.7, 41.7; IR (neat film, NaCl) 2930, 1700, 1601, 1488, 1435, 1406, 1366, 1294, 1200, 1177, 1071, 1034, 1012, 798 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{26}\)H\(_{23}\)N\(_2\)O\(_3\)Br\(^{81}\)Br [M+H]+: 571.0055, found 571.0048; \( [\alpha]_{D}^{25.0} \) –46.7 (c 0.39, CH\(_2\)Cl\(_2\)).

### 3.4.8 Synthesis of Other Pyrrolidinone-spirooxindole: Further Confirmation of Absolute Stereochemistry

(R)-1-benzyl-5-methoxy-1'-methylspiro[indoline-3,3'-pyrrolidine]-2,5'-dione (138).

To a solution of phthalimidoester 83\(^{38}\) (56 mg, 0.14 mmol, 1.0 equiv) in THF (2 mL) was added a solution of KO\(_t\)-Bu (19 mg, 0.17 mmol, 1.2 equiv) in THF (1 mL) was added in a dropwise manner via syringe at 23 °C. The reaction was allowed to stir for 20 minutes before the addition of BnBr (51 \( \mu \)L, 0.43 mmol, 3.0 equiv) via syringe. After stirring for 3 hours at 23 °C, the reaction was quenched with saturated brine solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined and dried with MgSO\(_4\). Purification by column chromatography (SiO\(_2\), 33% EtOAc in hexanes→50% EtOAc in hexanes) afforded 136 as a pale yellow solid (45.5 mg, 66% yield). \( R_f = 0.50 \) (50% EtOAc in hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.86-7.82 (m, 2H), 7.73-7.69 (m, 2H), 7.43 (d, \( J = 7.5 \) Hz, 2H), 7.32 (t, \( J = 7.5 \) Hz, 2H), 7.25 (tt, \( J = 7.5, 2.0 \) Hz, 1H),
6.86 (d, J = 2.0 Hz, 1H), 6.65 (dd, J = 8.5, 2.0 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.93
(ABq, J = 16.0 Hz, 2H), 4.02 (ABq, J = 14.0 Hz, 2H), 3.70 (s, 3H), 3.45 (s, 3H), 3.20
(ABq, J = 17.0 Hz, 2H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 176.8, 170.1, 168.2, 155.8,
136.1, 135.8, 134.3, 131.9, 130.5, 128.8, 127.6 (2 C), 123.7, 113.3, 110.8, 110.0, 55.9,
51.9, 50.0, 44.5, 43.3, 38.7; IR (neat film, NaCl) 2951, 2930, 2858, 1776, 1717, 1717, 1602,
1496, 1456, 1435, 1394, 1333, 1298, 1206, 1178, 1144, 1077, 1029 cm\(^{-1}\); HRMS (FAB+) m/z calc’d for C\(_{28}\)H\(_{25}\)N\(_2\)O\(_6\) [M+H]\(^+\): 485.1713, found 485.1707; \([\alpha]_D\)\(^{19.0}\) = -17.7 (c 1.00, CH\(_2\)Cl\(_2\)).

To a solution of benzylated 136 (46 mg, 0.094 mmol, 1.0 equiv) in EtOH (5 mL) was added H\(_2\)NNH\(_2\)•H\(_2\)O (46 \(\mu\)L, 0.94, 10 equiv) at 23 °C. The reaction flask was then heated to 95 °C for 18 hours. Upon cooling to ambient temperature, reaction mixture was filtered though a short plug of Celite and concentrated. Purification by column chromatography (SiO\(_2\), 2% MeOH in DCM→3% MeOH in DCM) afforded spirocyclic lactam 137 as a white solid (26 mg, 87% yield). \(R_f = 0.59\) (9% MeOH in DCM); \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.34-7.31 (comp. m, 2H), 7.29-7.25 (comp. m, 3H), 6.99 (d, J = 2.5 Hz, 1H), 6.72 (dd, J = 7.5, 2.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.35 (br s, 1H),
4.90 (s, 2H), 3.92 (d, J = 9.0 Hz, 1H), 3.76 (s, 3H), 3.50 (d, J = 9.5 Hz, 1H), 3.03 (d, J =
16.5 Hz, 1H), 2.51 (d, J = 16.5 Hz, 1H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 177.2, 175.6,
156.8, 135.6, 135.2, 134.5, 129.0, 128.0, 127.4, 113.4, 110.1, 109.6, 56.0, 51.2, 50.0,
44.3, 40.6; IR (neat film, NaCl) 3271, 2925, 1705, 1602, 1496, 1455, 1436, 1368, 1298,
1200, 1178, 1032 cm\(^{-1}\); HRMS (ESI–APCI) m/z calc’d for C\(_{19}\)H\(_{18}\)N\(_2\)O\(_3\) [M+H]\(^+\): 323.1390, found 323.1393; \([\alpha]_D\)\(^{23.0}\) = +64.7 (c 0.50, CH\(_2\)Cl\(_2\)).
To a mixture of NaH (9.9 mg, 60 %, 0.248 mmol, 3 equiv) in THF (0.5 mL) at 23 °C was added a solution of spirocyclic lactam 137 (24.7 mg, 0.0825 mmol, 1 equiv) in THF (2.0 mL) in a dropwise manner via syringe. The flask containing the spirocyclic lactam was rinsed with THF (2 x 1 mL), and the solution was also added dropwise via syringe at 23 °C. The reaction was allowed to stir for 30 minutes before the addition of MeI (16 μL, 0.25 mmol, 3.0 equiv) via syringe. After stirring for 14 hours at 23 °C, the reaction was quenched with water (30 μL) and concentrated under reduced pressure. Purification by column chromatography (SiO₂, 55% EtOAc in CH₂Cl₂) afforded 138 as a white solid (20 mg, 79% yield). Mp: 146.0-147.5 °C; Rｆ = 0.18 (33% EtOAc in CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.32 (td, J = 7.5, 1.5 Hz, 2H), 7.28-7.24 (comp. m, 3H), 6.87 (d, J = 3.0 Hz, 1H), 6.71 (dd, J = 7.5, 3.0 Hz, 1H), 6.65 (d, J = 7.5 Hz, 1H), 4.89 (ABq, J = 16.0 Hz, 2H), 3.88 (d, J = 9.5 Hz, 1H), 3.74 (s, 3H), 3.45 (d, J = 9.5 Hz, 1H), 3.07 (dd, J = 17.0, 0.5 Hz, 1H), 2.99 (s, 3H), 2.58 (d, J = 17.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 177.7, 171.9, 156.8, 135.6, 135.3, 134.9, 129.0, 127.9, 127.4, 113.1, 110.1, 109.5, 58.1, 56.0, 47.2, 44.3, 41.6, 29.0; IR (neat film, NaCl) 3033, 2929, 2879, 2837, 1704, 1602, 1496, 1456, 1436, 1368, 1298, 1200, 1178, 1033, 977 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₀H₂₁N₂O₃ [M+H]⁺: 337.1552, found 337.1567; [α]_D^{22.0} +37.3 (c 1.00, CH₂Cl₂)

### 3.4.9 Synthesis of Fused Indolinopyrrolidinone

![Synthesis of Fused Indolinopyrrolidinone](image)

(S)-methyl 2-(1-methyl-2-oxo-3-phenylindolin-3-yl)acetate (88).
A round bottom flask equipped with a stirbar was charged with malonate adduct 87 (50 mg, 0.14 mmol, 1.0 equiv), lithium chloride (116 mg, 0.27 mmol, 2.0 equiv), water (12 μL, 0.68 mmol, 5.0 equiv), and DMSO (2 mL). The reaction flask was then heated at 150 °C for 12 hours. Upon cooling to ambient temperature, reaction mixture was diluted with water (10 mL) and then extracted with EtOAc (5 x 5 mL). The organic layers were collected and dried with MgSO₄. Purification by flash chromatography (SiO₂, 50% EtOAc in hexanes) afforded 139 as a colorless oil (62% yield). Rᵥ = 0.41 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.87 (br s, 1H), 7.31-7.21 (comp. m, 7H), 7.04 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 6.92 (dd, J = 7.8, 0.5 Hz, 1H), 3.54 (d, J = 16.1 Hz, 1H), 3.44 (s, 3H), 3.26 (d, J = 16.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 180.2, 170.3, 141.8, 139.1, 131.8, 128.9, 128.8, 127.8, 126.7, 124.9, 122.6, 110.3, 53.9, 51.9, 41.7; IR (neat film, NaCl) 3248, 1721, 1619, 1472, 1203 cm⁻¹; HRMS (FAB⁺) m/z calc’d for C₁₇H₁₆NO₃ [M+H]⁺ 282.1130, found 282.1138.

To a cooled (0 °C) solution of methyl ester 139 (14.3 mg, 0.051 mmol, 1.0 equiv) in THF (5mL) was added a freshly prepared stock solution of KOr-Bu (6.8 mg, 0.061 mmol, 1.2 equiv) in THF in a dropwise manner via syringe. The reaction was allowed to stir for 15 minutes before addition of MeI (9.5 μL, 0.15 mmol, 3.0 equiv) via syringe. After stirring for one hour at 0 °C, the reaction was quenched with saturated brine (2 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were collected and dried with MgSO₄. Purification by column chromatography (SiO₂, 20 % EtOAc in hexanes) afforded methyl ester 88 as a light yellow oil (68% yield. 56% yield over two steps). Rᵥ = 0.57 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.24 (comp. m, 7H), 7.11 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 3.55 (d, J = 16.4 Hz, 1H),
Fused Indolinopyrroloidinone 90.

A freshly prepared stock solution of trimethylaluminum amine complex was prepared by adding trimethylaluminum (0.5 mL, 2 M in toluene) to a mixture of methyl amine hydrochloride (67.5 mg, 1 mmol) in toluene (4.5 mL) at 0 °C and allowing to warm to ambient temperature. After the methane evolution had ceased (about 1 hour), the aluminum amine complex solution (0.9 mL, 0.18 mmol, 3.0 equiv) was added to a solution of methyl ester 88 (18 mg, 0.061 mmol, 1 equiv) in toluene (2 mL) at ambient temperature, and the reaction mixture was immediately heated to 50 °C. The reaction was maintained at 50 °C for five days, where an additional freshly prepared trimethylaluminum amine complex (0.9 mL, 0.18 mmol, 3 equiv) was added after initial 72 hours. Reaction was then cooled to room temperature and quenched with aqueous solution of saturated Rochelle’s salt (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried with MgSO₄. Purification by flash chromatography (SiO₂, 10% toluene in acetonitrile) afforded amide 89 isolated as a white solid (71% yield). \( R_f = 0.62 \) (10% toluene in acetonitrile); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.36-7.24 (comp. m, 7H), 7.10 (ddd, \( J = 7.3, 7.3, 1.0 \) Hz, 1H), 6.90 (d, \( J = 7.6 \) Hz, 1H),
6.17 (br s, 1H), 3.38 (d, $J = 15.4$ Hz, 1H), 3.28 (s, 3H), 3.03 (d, $J = 15.4$ Hz, 1H),
2.59 (d, $J = 4.9$, 3H), $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.0, 169.3, 143.6, 139.4, 132.0, 128.9, 128.7, 127.7, 126.6, 124.6, 123.0, 108.7, 54.3, 44.2, 26.8, 26.4; IR (neat film, NaCl) 3326, 2933, 1711, 1653, 1615, 1495, 1470, 1375, 1349 cm$^{-1}$; HRMS (FAB$^+$) $m/z$ calc’d for C$_{18}$H$_{19}$O$_2$N$_2$ [M+H]$^+$: 295.1447, found 295.1436.

To a cooled (0 °C) solution of methyl amide 89 (5.0 mg, 0.017 mmol, 1.0 equiv) in THF was added a solution of lithium aluminum hydride (2.0 M in hexanes, 12 equiv) in a dropwise fashion via syringe. The reaction was stirred for 1 hour and then quenched with brine solution. Following extraction with EtOAc (3 x 10 mL), the organic layers were collected and dried with MgSO$_4$. Purification by flash chromatography (SiO$_2$, 50% EtOAc in hexanes) afforded fused tricycle 90 as a white solid (92% yield). $R_f = 0.24$ (50% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33-7.30 (comp. m, 2H), 7.26-7.18 (comp. m, 4H), 7.05 (d, $J = 7.3$ Hz, 1H), 6.79 (ddd, $J = 7.6$, 7.6, 1.0 Hz, 1H), 6.55 (d, $J = 7.8$ Hz, 1H), 4.96 (s, 1H), 3.26 (d, $J = 17.3$ Hz, 1H), 3.11 (d, $J = 17.3$ Hz, 1H), 3.10 (s, 3H), 2.98 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.0, 149.6, 144.5, 134.0, 129.3, 129.0, 127.3, 126.2, 125.0, 119.2, 108.1, 93.2, 53.9, 44.5, 35.4, 28.8; IR (neat film, NaCl) 3054, 2925, 1692, 1606, 1494 cm$^{-1}$; HRMS (FAB$^+$) $m/z$ calc’d for C$_{18}$H$_{19}$ON$_2$ [M+H]$^+$: 279.1497, found 279.1509.
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Haloindoles

3.5 NOTES AND REFERENCES FOR TEXT


(4) For selected recent examples, see: (a) Overman, L. E.; Rosen, M. D. Angew. Chem. Int. Ed. 2000, 39, 4596–4599. (b) Lerchner, A.; Carreira, E. M. J. Am.
Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles


Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles


(24) See the Experimental Section for details.


(26) For an example of bis(oxazoline)-mediated MeLi additions to electrophiles and an excellent discussion of the use of bisoxazolines in general, see: Denmark, S. D.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878.


(28) Exposure of racemic bromooxindole (±)-**76** to preformed [Cu(78)] (SbF₆)₂ in the presence of i-Pr₂NEt at −40°C without molecular sieves gave malonate adduct **77** in 68% yield and 86% ee.
(29) Consistent with our proposal of an \( o \)-azaxylylene intermediate, exposure of \( N \)-methyl bromooxindole \( 94 \) to our reaction conditions (see Table 3.4) failed to give a detectable amount of the malonate adduct.


(31) The absolute configuration depicted for all products in Tables 3.4 and 3.5 is derived by analogy from the X-ray analysis of \( 86 \).


(36) For compounds in Table 3.4 Entries 8–10, the bromooxindole was added in one portion as a solid due to low solubility in \( \text{CH}_2\text{Cl}_2 \).

(37) Malonate adduct \( 83 \) was recrystallized to 99% ee from \( \text{CH}_2\text{Cl}_2 \)-hexanes (3.5:1).

(38) Malonate adduct \( 83 \) was recrystallized to 97% ee from \( \text{CH}_2\text{Cl}_2 \)-hexanes (3.5:1).