CHAPTER 2

CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-Substituted Chiral Phthalides and its Application to the Synthesis of (-)-Matteucen C and Butylphthalide
Section I: CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: a Facile Entry to 3-Substituted Chiral Phthalides

2.1.1 Introduction

Chiral phthalides [isobenzofuran-1(3H)-ones] comprising of 5-membered lactones are found in a large number of plant products displaying broad and potent biological activities.¹ Some representative examples are shown in Fig. 1. 3-Butylphthalide (1), a component in the Chinese folk medicine extracted from celery seed oil,²a is in phase II clinical trials in China and potentially can be used for the treatment of stroke.²b Moreover, it is employed for seasoning and flavoring purposes, shows anticonvulsant action,²c increases the duration of anesthesia,²d and exhibits cerebral antiischemic action.²e

![Chemical structures](image)

**Fig. 1:** Some of the examples of chiral phthalides
Fuscinarin (2) is a potent human CCR5 antagonist, used effectively for blocking HIV entry into host cells.\(^3\) (-)-Hydrastine (3) is active at the opioid receptor.\(^4\) In addition, it possesses antipaclitaxel-resistant human ovarian cancer activity through c-Jun kinases-mediated apoptosis and is in phase I clinical trials.\(^5\) Both Virgatolide A (4) and (-)-Alcyopterosin E (5) show cytotoxic activity against HeLa cells.\(^6\) Due to the biological importance of 3-substituted phthalides 1-5 (Fig. 1), their molecular architectures have become a platform for new synthetic methodology development.\(^7\)

### 2.1.2 Review of Literature

Literature search revealed that there are various methods available for the synthesis of 3-substituted phthalide derivatives, which are described below.

**Noyori’s approach (1990)\(^8\)**

Noyori et al. have described the synthesis of chiral phthalide ((S)-3-methyl isobenzo furan-1(3H)-one) 8 via asymmetric hydrogenation of ethyl o-acetylenzoate 6 in ethanol with 0.4 mol% of the (S)-BINAP(7)-Ru catalyst at 100 atm H\(_2\) pressure in 97% ee and 97% yield (Scheme 1).

\[
\begin{align*}
\text{CO}_2\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{(6)} & \quad \text{(8)} \\
\text{(97% ee)} & \quad \text{(S)-BINAP (7)}
\end{align*}
\]

**Scheme 1:** (i) Ru(OOC\text{CH}_3)\text{H}_2[(S)-\text{BINAP}] (0.4 mol%), H\(_2\) (100 atm), EtOH, 0.5N HCl, 35 °C, 165 h, 97%.

**Butsugan’s approach (1992)\(^9\)**

Butsugan et al. have reported the synthesis of optically active 3-ethyl- and 3-n-butylphthalides using enantioselective addition of dialkylzinc reagents. Thus, o-phthalaldehyde 9 was subjected to asymmetric addition of dialkyl reagents, catalyzed
by chiral 1,2-disubstituted ferrocenyl amino alcohol 12, followed by oxidation of the resulting lactols 10a-b to provide phthalides 11a-b in 88-89% ee (Scheme 2).

![Scheme 2:](image)

**Scheme 2:** (i) (-)-DFPE (12) (5 mol%), 25 °C, 1-3 h, (ii) Ag₂O, 0 °C.

**Lin’s approach (2002)**

Ni-catalyzed tandem homo addition of o-bromoaldehydes 13a-b via *in situ* cyclization was developed in presence of (S)-BINAP (7) and Zn that provided optically pure phthalides 14a-b in good yields with moderate enantiomeric excess (Scheme 3).

![Scheme 3:](image)

**Scheme 3:** (i) NiCl₂(PPh₃)₂ (0.2 equiv). (S)-BINAP (7), Zn, toluene, 90 °C.
Mori’s approach (2003)\(^{11}\)

Mori et al. have used Sharpless asymmetric dihydroxylation as the key reaction. Thus, commercially available methyl 3,4,5-trihydroxybenzoate 15 was benzylated completely and subjected to bromination with NBS to afford bromo compound 16 in 96\% yield. The bromo compound 16 was subjected to Miyaura-Suzuki coupling with (E)-1-octeneboronic acid to give olefin 17. Asymmetric dihydroxylation of olefin 17 with AD-mix-β proceeded to furnish phthalide 18 in 54\% yield with 45\% ee (Scheme 4).

\[
\text{Scheme 4: (i) (a) BnBr, K}_2\text{CO}_3, 96\%; (b) NBS, DMF, 96\%; (ii) (E)-CH}_3(CH)_2CH=CHB(OH)\text{, Pd(PPh}_3)_4, K}_2\text{CO}_3, C}_6\text{H}_6\text{EtOH (5:1), 71\%; (iii) AD-mix-β, CH}_3\text{SO}_2\text{NH}_2, \text{tert-BuOH:H}_2\text{O (1:1), 54\%.}
\]

Tanaka’s approach (2004)\(^{12}\)

Tanaka et al. have described the enantioselective synthesis of axially chiral phthalides by the cationic [Rh\(^{1}\)(H\(_8\)-BINAP)] complex-catalyzed alkyne cyclotrimerization. The reaction of aryl-substituted 1,6-diyne 19a-d with terminal monoyne 20 in the presence of the cationic complex [Rh\(^{1}\)(H\(_8\)-BINAP)] provided axially chiral phthalides 21a-d in high yields with moderate enantioselectivity (Scheme 5).
Scheme 5: (i) 5% [Rh{[(S)-H\textsubscript{8}-BINAP}]BF\textsubscript{4} (1 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 3 h.

Same authors have developed a cationic rhodium(I)/Solphys (24) complex-catalyzed asymmetric one-pot transesterification followed by [2+2+2] cycloaddition of 1,6-diyne esters 22a-f with tertiary propargylic alcohols 23a-f leading to enantioenriched tricyclic 3,3-disubstituted phthalides 25a-f in good yields (66-87%) with moderate enantioselectivity (Scheme 6).

Scheme 6: (i) 5% [Rh(cod)\textsubscript{2}]BF\textsubscript{4}/(R)-Solphys (24) (1 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 1-3 h.

Vaccher’s approach (2005)\textsuperscript{13}

Vaccher et al. have reported the synthesis of 3-benzoyloxy methylisobenzofuranone 30 using Sharpless asymmetric dihydroxylation as the key step. Thus, phthalaldehyde 26 was firstly protected using propane-1,3-diol to give the benzaldehyde derivative.
27, which was subjected to Wittig reaction to afford the styrene derivative 28. Asymmetric dihydroxylation using AD-mix-β gave diol, which was selectively protected with benzoyl chloride to afford compound 29 with a free secondary hydroxyl group. Removal of the acetal from 29 in acidic medium gave benzo[c]furan 30, which was converted to phthalide 31 in 50% yield using RuCl₃-NaIO₄ combination as oxidant (Scheme 7).

**Scheme 7:** (i) p-TSA, propan-1,3-diol, toluene, 5 h, 82%; (ii) tert-BuOK, CH₃(C₆H₅)₃PBr, toluene, 3 h, 78%; (iii) (a) AD-mix-β, tert-BuOH: H₂O (1:1), 12 h, 72%; (b) BzCl, (C₆H₅)₃N, toluene, 5 h, 78%; (iv) p-TSA, acetone, H₂O, 1 h, 82%; (v) NaIO₄, RuCl₃, CH₃CN, EtOAc, H₂O, 50%.

**Cheng’s approach (2007)**

Cheng et al. have reported Co-bidentate phosphine complex-catalyzed synthesis of phthalides 34a-f. Thus, methyl 2-iodobenzoates 32 underwent cyclization reactions with various aromatic aldehydes 33a–f in the presence of [CoI₂(dppe)] (5 mol%) and Zn powder in dry THF at 75 °C for 24 h to give the corresponding phthalide derivatives 34a-f in 89-94% yields with 70-98% ee (Scheme 8).
Xu’s approach (2009)

Xu et al. have reported a new diamine ligand 37 for asymmetric transfer hydrogenation (ATH) to synthesize 3-substituted phthalides. The reductive cyclization of 2-acylaryl carboxylates 35a-f via the new [RuCl₂(p-cymene)]₂/37-catalyzed ATH and subsequent in situ lactonization under aqueous conditions proceeded to give a variety of 3-substituted phthalides 36a-f in high yields (93-97%) with high ee (98-99%) (Scheme 9).
Dong’s approach (2009)\textsuperscript{16}

Dong \textit{et al.} have employed [Rh(cod)Cl]$_2$-catalyzed hydroacylation of ketones 38\textit{a}-\textit{f} in presence of duanphos 40 (10 mol%), and AgNO$_3$ (10 mol%) to give chiral phthalides 39\textit{a}-\textit{f} in 81-94\% yields with 92-98\% ee (\textbf{Scheme 10}).

\begin{equation}
\begin{array}{c}
\text{R} \quad \text{CHO} \\
\text{CH}_2\text{C}=\text{O} \\
\text{R}_1
\end{array}
\xrightarrow{i}
\begin{array}{c}
\text{R} \quad \text{CHO} \\
\text{CH}_2\text{C}=\text{O} \\
\text{R}_1
\end{array}
\end{equation}

\textbf{Scheme 10}: (i) [Rh(cod)Cl]$_2$ (10 mol%), Duanphos (40) (10 mol%), AgNO$_3$ (10 mol%), toluene, 90 °C, 3-3.5 h.

Wang’s approach (2010)\textsuperscript{17}

Wang \textit{et al.} have described the synthesis of chiral phthalides 43\textit{a}-\textit{e} by employing organocatalytic asymmetric aldol-lactonization as the key reaction.

\begin{equation}
\begin{array}{c}
\text{R} \quad \text{CHO} \\
\text{CH}_2\text{C}=\text{O} \\
\text{R}_1
\end{array}
\xrightarrow{i}
\begin{array}{c}
\text{R} \quad \text{CHO} \\
\text{CH}_2\text{C}=\text{O} \\
\text{R}_1
\end{array}
\end{equation}

\textbf{Scheme 11}: (i) (a) L-prolinamide alcohol 44 (2.5 mol%), PhCO$_2$H (2.5 mol%), -40 °C, 12-24 h; (b) K$_2$CO$_3$, acetone:methanol (10:1), 15 min.
Thus, 2-formylbenzoic esters 41a-e and ketone 42 were subjected to aldol reaction using \( L \)-prolinamide alcohol 44 as catalyst and \( \text{PhCO}_2\text{H} \) as an additive to give 3-substituted phthalides 43a-e in 77-91% yield with 74-97% ee (Scheme 11).

**Gotor’s approach (2012)**

Gotor et al. have described Baker’s yeast-catalyzed bioreduction of 2-acetylbenzo nitriles 45a-e followed by aqueous HCl that provided access to enantiopure (S)-3-methylphthalides 46a-e in moderate to excellent yields (42-99%) with >98% ee (Scheme 12).

\[
\begin{align*}
\text{45a-e} & \quad \text{46a-e} \\
& \quad (>98\% \text{ ee}) \\
& \quad \text{i}
\end{align*}
\]

**Scheme 12:** (i) (a) Baker’s yeast, glucose, \( \text{H}_2\text{O} \), 25 °C, 16-72 h; (b) \( \text{HCl} \) 1M, 25 °C, 48 h.

### 2.1.3 Present Work

#### 2.1.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of 3-substituted phthalides employ either chiral auxiliaries or expensive organometallic reagents in stoichiometric amounts and often lack in broad substrate scope and higher reaction stereoselectivity; only a few are atom economical. In this context, a more practical and efficient synthesis of functionalized 3-substituted phthalide derivatives is highly desirable. In this section, we present a single-step oxidative cyclization of cyanocinnamates and styrenic substrates that affords 3-substituted phthalides in high yields via synergetic acceleration of CN and osmate ester groups present in proximity.
positions. Since the method involves asymmetric dihydroxylation (ADH) as the key chiral inducing reaction, a brief account of ADH is described below.

2.1.3.2 Asymmetric Dihydroxylation (ADH)

In recent years, much attention has been focused on the catalytic asymmetric synthesis. It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).\(^{19}\) Among all these reactions, Sharpless catalytic Asymmetric Dihydroxylation (ADH) is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active \textit{vicinal-syn}-diols from activated as well as unactivated olefins.\(^{20}\) In 1936, Criegee \textit{et al.}\(^{21}\) found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerated the rate of reaction considerably. A major breakthrough had occurred in the field of asymmetric oxidation when Sharpless \textit{et al.}\(^{20b}\) demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO\(_4\)-mediated asymmetric oxidation of olefins.

\[
\text{Ligand Acceleration} = \frac{\text{Saturation rate with ligand}}{\text{Rate without ligand}}
\]

\textbf{Scheme 13:} Mechanism of OsO\(_4\)-catalyzed dihydroxylation of olefin
Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, namely dihydroquinidine (DHQD) and dihydroquinine (DHQ) (Scheme 13).  

To improve the %ee of the chiral diol, the second catalytic cycle of ADH should be avoided and this was achieved by employing the K₃Fe(CN)₆ as reoxidant and using biphasic conditions (Fig. 2).

![Catalytic cycle for ADH using K₃Fe(CN)₆ as co-oxidant](image_url)

**Fig. 2:** Catalytic cycle for ADH using K₃Fe(CN)₆ as co-oxidant

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) reoxidized and recycled into the catalytic cycle. Further improvement in the ADH was realized by the addition of methyl sulfonamide (MeSO₂NH₂) to the
reaction mixture. It also helps to accelerate the hydrolysis, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di-tri- and tetra-substituted olefins at 0 °C, which improved the selectivity as well as enantiomeric excess.

In order to develop the asymmetric version of the Os-catalyzed ADH reaction, Sharpless and coworkers screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the bis-DHQ or DHQD ethers of phthalazine-1,4-diol have proven to be the best for obtaining high enantioselective diols.\(^{23}\) (Fig. 3).

**Fig. 3:** Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.\(^ {24}\) Sharpless et al.\(^ {20}\) have shown that the facial selectivity for both ligands (DHQ)\(_2\)PHAL and (DHQD)\(_2\)PHAL is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model (Fig. 4) in which olefin with the constraints will be attacked either from the top (i.e. \(\beta\)) face in the presence of
dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

![Diagram showing enantioselectivity mnemonic scheme](image)

**Fig. 4:** Enantioselectivity mnemonic scheme

### 2.1.4 Results and Discussion

Recently, Sudalai *et al.* have developed a novel protocol of ADH process followed by Co-catalyzed “one-pot” reductive cyclization (CoCl₂-NaBH₄) of nitro cyclic sulfites 47a-f that led to the construction of 3-substituted tetrahydroquinolin-3-ols 48a-f (Scheme 14).²⁵

![Scheme 14](image)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48a</td>
<td>H</td>
<td>H</td>
<td>81%</td>
</tr>
<tr>
<td>48b</td>
<td>OMe</td>
<td>OMe</td>
<td>78%</td>
</tr>
<tr>
<td>48c</td>
<td>OCH₂O</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>48d</td>
<td>OBN</td>
<td>OMe</td>
<td>83%</td>
</tr>
<tr>
<td>48e</td>
<td>OBN</td>
<td>OBN</td>
<td>85%</td>
</tr>
<tr>
<td>48f</td>
<td>Ocyclopentyl</td>
<td>OMe</td>
<td>82%</td>
</tr>
</tbody>
</table>

**Scheme 14:** (i) CoCl₂·6H₂O (1 mol%), NaBH₄ (4 equiv), EtOH, 0 to 25 °C.

In analogy with this, we reasoned that subjecting cyano cyclic sulfites to the same reaction conditions should afford synthetically useful benzazepines.²⁶ In order to synthesize cyano cyclic sulfite, we visualized a strategy in which cyano diol 52 could
serve as a starting material to cyano cyclic sulfite. Accordingly, o-cyanobenzaldehyde 49 was subjected to Wittig olefination to afford \((E)-\alpha,\beta\)-unsaturated ester 50a in 88% yield (Scheme 15). The formation of cinnamate ester 50a was confirmed from its \(^1\)H NMR spectrum, which showed two doublets at \(\delta 6.60\) (d, \(J = 16\) Hz, 1H) and 7.96 (d, \(J = 16\) Hz, 1H) confirming the presence of \(\alpha\)- and \(\beta\)-CH olefin protons of -CH=CHCO\(_2\)Et. This was further ascertained by the presence of characteristic carbon signals at \(\delta 122.9\) and 139.0 corresponding to \(\alpha\)- and \(\beta\)-carbon signal of olefinic ester -CH=CHCO\(_2\)Et in its \(^{13}\)C NMR spectrum (Fig. 5).

Fig. 5: \(^1\)H and \(^{13}\)C NMR spectra of o-cyanocinnamate 50a
In order to validate our hypothesis, ethyl 2-cyanocinnamate 50a was subjected to Sharpless asymmetric dihydroxylation using (DHQ$_2$)$_2$PHAL as the chiral ligand, with THF as co-solvent for better solubility. Surprisingly, the reaction took altogether a different course to give the cyclized chiral phthalide 51a exclusively with 99% ee in a single step, instead of the expected cyano diol 52 (Scheme 15). This unexpected transformation is characterized by high rate, excellent yield and enantioselectivity, which is attributed to coordination assistance provided by the neighboring CN group to osmate ester, leading to faster hydrolysis of osmate ester in the catalytic cycle. Incidentally, the rate of ADH process for electron-deficient o- substituted cinnamates is generally reported to be sluggish (48 h to 7 days) giving products invariably with moderate enantioselectivity (88% ee).

\[
\text{49} \quad \xrightarrow{\text{i}} \quad \text{50a} \quad \xrightarrow{\text{ii}} \quad \text{51a, 99\% ee}
\]

**Scheme 15:** (i) Ph$_3$P=CHCO$_2$Et, benzene, reflux, 12 h, 88%; (ii) K$_2$[OsO$_2$(OH)$_2$] (0.1 mol%), (DHQ)$_2$PHAL (0.5 mol%), K$_3$Fe(CN)$_6$ (3 equiv), K$_2$CO$_3$ (3 equiv), tert-BuOH:THF:H$_2$O (1:1:2), 25 °C, 7 h.

The formation of chiral phthalide 51a was confirmed by the presence of a doublet of doublet at δ 4.66 (dd, $J = 2.1, 5.8$ Hz) integrating for one methine proton (-CH-OH) and a doublet at δ 5.79 (d, $J = 2.1$ Hz, 1H) integrating for benzylic proton (-CH-O-CO-) in its $^1$H NMR spectrum. It was further substantiated by the carbon signals displaying at δ 70.3 and 80.3 in its $^{13}$C NMR spectrum, corresponding to carbons
attached to hydroxyl and lactone groups respectively (Fig. 6). The IR spectrum of phthalide 51a displayed two strong absorption bands at 1720 and 1768 cm⁻¹ due to the presence of ester and γ-lactone carbonyl groups respectively.

![Fig. 6: ¹H and ¹³C NMR spectra of phthalide 51a](image)

Further, the formation of chiral phthalide 51a was confirmed by COSY and mass spectra (Fig. 7).
Fig. 7: COSY and mass spectra of phthalide 51a

The enantiomeric excess (99% ee) of chiral phthalide 51a was determined from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 12.16 (99.65%) and 13.80 (0.35%) (Fig. 8).
Encouraged by the result, we became interested in the scope of the reaction by subjecting other o-cyanoalkenes 50b-z. o-Cyanoalkenes 50b-z were prepared in 76-84% yield, in a single step, starting from the corresponding o-bromo alkene derivatives 52b-z via Rosenmund-von Braun reaction with CuCN (3 equiv) and DMF as solvent at 150 °C (Scheme 16). o-Bromo alkene derivatives 52b-z were in turn prepared in high yields via Wittig or Julia olefination of the respective benzaldehydes by following the literature procedures.28

![HPLC chromatogram of phtalide 51a](image.png)

**Fig. 8:** HPLC chromatogram of phtalide 51a

<table>
<thead>
<tr>
<th>No</th>
<th>Ret. Time (min)</th>
<th>Height (µ AU)</th>
<th>Area (µ AU* min)</th>
<th>Rel. Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.16</td>
<td>28495.075</td>
<td>14410.126</td>
<td>99.65</td>
<td>n. a.</td>
<td>BMB</td>
</tr>
<tr>
<td>2</td>
<td>13.80</td>
<td>189.662</td>
<td>50.523</td>
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<td>n. a.</td>
<td>BMB</td>
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</table>
When subjected to Os-catalyzed asymmetric dihydroxylation (ADH) using (DHQD)$_2$PHAL as the chiral ligand, o-cyano $\alpha,\beta$-unsaturated esters 50b-l gave the corresponding chiral phthalide derivatives 51b-l in 92-95% yields with excellent enantioselectivities (98-99% ee). Results of such studies are presented in Table 1. As can be seen, in every case, the reaction proceeded rapidly within 7 h giving the desired phthalides 51b-l in excellent yields and ees (up to 99%) at ambient conditions. For instance, substrates having halogen (entry i), highly electron-rich (entry f) or electron-deficient (entry j) groups on the aromatic nucleus including 2-naphthyl system (entry l) underwent this oxidative cyclization smoothly affording the corresponding phthalides 51b-l with excellent yields in one step.

Subsequently, we extended our study to include other styrene derivatives 50m-z bearing different functionalities on the aromatic nucleus as well as on the $\beta$-position of the styrene derivative side chain ($R^3$) (Table 2). It was again found that this ADH process displayed a wide substrate scope tolerating alkyl, aryl, alkoxy, fluoro or tosyl groups. Excellent yields of phthalide derivatives 51m-z (93-95%) and enantioselectivities (97-99%ee) were indeed realized in all the cases studied. The stereochemistry of the cyclized products was assigned according to the previously established absolute configuration of phthalides as well as in accordance with ADH rules.$^{29}$
Table 1: CN-assisted Os-catalyzed oxidative cyclization of cyano ethyl cinnamates

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>yield (%)(^a)</th>
<th>ee (%)(^b)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>b</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>c</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>94</td>
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</tr>
<tr>
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<tr>
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<td>H</td>
<td>95</td>
<td>98</td>
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</tr>
<tr>
<td>l</td>
<td>(E)-ethyl 3-(1-cyanonaphthalen-2-yl)acrylate</td>
<td>94</td>
<td>98</td>
<td></td>
<td></td>
</tr>
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</table>

\(^a\) Isolated yield after column chromatographic purification. \(^b\) ee determined by chiral HPLC analysis. \(^c\) ee determined by Mosher’s ester analysis for entries h, i & l.
Table 2: CN-assisted Os-catalyzed oxidative cyclization of cyano styrene derivatives

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>yield (%)</th>
<th>ee (%)</th>
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</thead>
<tbody>
<tr>
<td>m</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
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</tr>
<tr>
<td>n</td>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>95</td>
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<td>o</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>p</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
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*a* Isolated yield after column chromatographic purification. *b* ee determined by chiral HPLC analysis. *c* ee determined by Mosher’s ester analysis for entries t, u, w-z. *d* reaction completed in 3 h for m-v.

The formation of phthalide derivatives 51m-z were confirmed by ¹H and ¹³C NMR spectroscopy. For example: The formation of phthalide 51m was confirmed by the
appearance of typical signals at δ 3.90 (d, J = 11.8 Hz, 1H), 4.14 (d, J = 11.8 Hz, 1H) and 5.54-5.59 (m, 1H) due to diastereotopic methylene protons and benzylic proton respectively, in its ¹H NMR spectrum. Further, its ¹³C NMR spectrum showed characteristic signals at δ 61.7, 81.5 and 170.6 corresponding to carbons attached to oxygen atoms and carbonyl carbon of lactone respectively (Fig. 9). Its IR spectrum displayed a strong absorption at 1756 cm⁻¹ indicating the presence of lactone carbonyl group.

**Fig. 9**: ¹H and ¹³C NMR spectra of phthalide 51m
The enantiomeric excess of chiral phthalides 51m-z was determined by chiral HPLC analysis and also by Mosher’s ester analysis. For example: The enantiomeric excess of chiral phthalide 51n was determined as 99% from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 1 mL/min) retention time 27.19 min (99.36%) and 39.72 min (0.64%) (Fig. 10).

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Fig. 10: HPLC chromatogram of phthalide 51n

The higher reactivity of cyano substituted cinnamates and styrenes 50a-z were substantiated by carrying out several competitive experiments involving 1:1 molar
equivalents of aromatic substrates with or without cyano substitution; the results of which are presented in Table 3. The results clearly showed that cyano substituted substrates reacted almost 10-12 times faster than the one without cyano substitution, giving excellent yields of phthalides (92-94%).

Table 3: Competitive experiments

<table>
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<th>entry</th>
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<tr>
<td>1</td>
<td>50a + ethyl cinnamate</td>
<td>51a</td>
<td>92</td>
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<tr>
<td>2</td>
<td>50e + 3,5-dimethoxyethyl cinnamate</td>
<td>51e</td>
<td>93</td>
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<td>3</td>
<td>50m + styrene</td>
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<tr>
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</tr>
<tr>
<td>5</td>
<td>50r + 3,4,5-trimethoxystyrene</td>
<td>51r</td>
<td>92</td>
</tr>
</tbody>
</table>

a1:1 molar equivalents of aromatics substrates with and without cyano substitution (1 mmol each) AD-mix-β (0.5 mol%), tert-BuOH:THF:H₂O (0.5: 0.5:1), 25 °C, 3 h for entries 3-5 and 7 h for entries 1 and 2. bIsolated yields after column chromatographic purification. c5-8 % of 1, 2-diol from the corresponding substrates without cyano substitution was indeed isolated.

In order to account for the mechanistic course of the reaction, the following experiments (Scheme 17) were conducted: (i) AD-mix-β of substrates 54 & 55 for 36 h gave the corresponding cyanodiols 56 & 57 respectively, indicating that both CN and C=C groups must be positioned in proximity for CN coordination assistance to take place; (ii) asymmetric aminohydroxylation of 50a gave the expected amino alcohol 58 (64%) with no phthalide formation, suggesting that coordination of CN onto imino osmate ester is thermodynamically less favorable, due to its reduced Lewis acid character; (iii) in addition, imino intermediates 59a-b were indeed isolated in 20% yield during the AD-mix-β of substrates 50a and 50 w.
This study clearly excludes the hydrolysis of CN to \( \text{CO}_2\text{H} \) followed by cyclization route, (iv) addition of benzonitrile as an external source of CN-assistance resulted in no rate enhancement for the ADH process.

**Scheme 18:** Mechanism of CN-assisted Os-catalyzed oxidative cyclization

On the basis of these results, a mechanistic model is presented in species A in which a synergism involving co-ordination of CN to Os(VI) and concurrent attack of osmate ester onto electropositive carbon of CN is shown that probably helps to accelerate the hydrolysis of osmate ester. These results indicate the 5-exo-dig type cyclization\(^\text{32}\) to
afford iminoesters 59a-b, which finally lead to the formation of phthalides 51a or 51w (Scheme 18). The formation of iminoester 59b was clearly demonstrated by IR data of the nonsubstituted imidate C=NH band (at 1687 cm$^{-1}$) and the phthalide (51w) C=O band (at 1752 cm$^{-1}$) (Fig. 11).

Fig. 11: IR spectra of iminoester 59b and phthalide 51w
2.1.5 Conclusion
A novel CN-assisted oxidative cyclization for the synthesis of a wide variety of 3-substituted phthalides and their structural analogues via ADH process of cyano cinnamates and styrene derivatives has been demonstrated. This reaction is highly practical in the sense that the products were obtained in excellent yields and optical purities (97-99% ee) and shows broad substrate scope and good functional group tolerance. The synergism shown by CN and osmate groups in proximity helps to enhance the rate of this reaction. We believe that this oxidative intramolecular cyclization ADH strategy should find wide applications in the total synthesis of other bioactive phthalide frameworks.

2.1.6 Experimental Section

Typical experimental procedure for the preparation of (E)-Ethyl 3-(2-cyano phenyl)acrylate (50a)
To a stirred solution of 2-cyanobenzaldehyde 49 (2 g, 7.9 mmol) in benzene (40 mL), Ph₃P=CHCO₂Et (3.1 g, 8.6 mmol) was added. It was then refluxed for 12 h under N₂ atmosphere. After the completion of reaction, benzene was distilled out to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and pet. ether:EtOAC (90:10) as eluent] afforded the cyano cinnamate 50a (1.4 g).

Yield: 88%, colorless solid; mp: 60-62 °C; IR (CHCl₃, cm⁻¹): υₛₐₚₓ 765, 784, 1031, 1184, 1318, 1447, 1480, 1594, 1640, 1712, 2225, 2938, 2983; ¹H NMR (200 MHz, CDCl₃): δ 1.36 (t, J = 7.3 Hz, 3H), 4.31 (q, J = 7.3 Hz, 2H), 6.60 (d, J = 16 Hz, 1H), 7.47 (td, J = 1.4, 7.5 Hz, 1H), 7.62 (td, J = 1.4, 7.5 Hz, 1H), 7.70-7.76 (m, 2H), 7.96 (d, J = 16 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 14.1, 60.7, 112.5, 116.8, 122.9, 126.8, 129.9, 132.8, 133.3, 137.1, 139.1, 165.4; Analysis: C₁₂H₁₁NO₂ requires C, 71.63; H, 5.51; N, 6.96; found: C, 71.59; H, 5.56; N, 6.93%
Typical experimental procedure for the preparation of (S)-Ethyl 2-((R)-1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51a)

A 50 mL RB flask was charged with K$_3$Fe(CN)$_6$ (1 g, 3 mmol), K$_2$CO$_3$ (414 mg, 3 mmol), tert-BuOH (2.5 mL), THF (2.5 mL) and H$_2$O (5 mL) and stirred for 10 min. Subsequently, (DHQD)$_2$PHAL (8 mg, 1 mol%) and K$_2$OsO$_4$·2H$_2$O (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, (E)-ethyl 3-(2-cyanophenyl)acrylate (50a) (200 mg, 1 mmol) was added and allowed to stir for 7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] gave 51a (221 mg).

**Yield:** 94%; colorless solid; **mp:** 146-148 ºC; [α]$_{D}^{25}$ -95.65 (c 1.24, CHCl$_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 12.16 (99.65%) and 13.80 (0.35%); **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 762, 856, 968, 1027, 1068, 1078, 1210, 1298, 1349, 1467, 1611, 1652, 1702, 1768, 2924, 3014, 3440; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.29 (t, $J = 7.1$ Hz, 3H), 3.16 (d, $J = 5.7$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 4.66 (dd, $J = 2.1$, 5.8 Hz, 1H), 5.79 (d, $J = 2.1$ Hz, 1H), 7.57 (t, $J = 7.0$ Hz, 2H), 7.68-7.75 (m, 1H), 7.90-7.93 (m, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 13.7, 62.3, 70.3, 80.3, 122.0, 125.3, 126.4, 129.3, 134.0, 145.7, 169.8, 170.7; **HRMS** (ESI) $m/z$ calcd for C$_{12}$H$_{12}$O$_5$ [M + Na]$^+$: 259.1357, found: 259.1352; **Analysis:** C$_{12}$H$_{12}$O$_5$ requires C, 61.01; H, 5.12; found: C, 60.96; H, 5.07%.
General experimental procedure for the preparation of o-cyanoalkenes (50b-z)

o-Bromo alkenes 52b-z (1 mmol) were taken in dry DMF (10 mL) and CuCN (3 mmol) was added and the mixture refluxed under N₂ for 18 h (monitored by TLC). It was then cooled to 25 °C, and then diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] to give o-cyanoalkenes 50b-z in 76-84% yield.

(E)-Ethyl 3-(2-cyano-5-methoxyphenyl)acrylate (50b)

Yield: 86%, colorless solid; mp: 130-132 °C; IR (CHCl₃, cm⁻¹): νmax 728, 868, 1026, 1256, 1490, 1594, 1607, 1640, 1712, 2228, 2853, 2923 3023; ¹H NMR (200 MHz, CDCl₃): δ 1.36 (t, J = 7 Hz, 3H), 3.90 (s, 3H), 4.29 (q, J = 7 Hz, 2H), 6.56 (d, J = 16 Hz, 1H), 6.97 (dd, J = 2.5, 8.7 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 16 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 14.2, 55.6, 60.8, 104.6, 112.1, 116.0, 117.3, 123.1, 135.0, 139.4, 162.7, 165.5; Analysis: C₁₃H₁₃NO₃ requires C, 67.52; H, 5.67; N, 6.06; found: C, 67.49; H, 5.61; N, 6.01%.

(E)-Ethyl 3-(2-cyano-4,5-dimethoxyphenyl)acrylate (50c)

Yield: 87%, colorless solid; mp: 159-161 °C; IR (CHCl₃, cm⁻¹): νmax 761, 848, 1094, 1149, 1204, 1326, 1462, 1571, 1594, 1709, 2222, 2984, 3018; ¹H NMR (200 MHz, CDCl₃): δ 1.36 (t, J = 7.3 Hz, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.29 (q, J = 7.3 Hz, 2H), 6.47 (d, J = 16 Hz, 1H), 7.07 (s, 1H), 7.11 (s, 1H), 7.89 (d, J = 16 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 14.2, 55.9, 56.2, 60.7, 105.2, 108.2, 114.2, 117.1, 120.7, 131.5, 139.2, 150.5, 152.6, 165.8; Analysis: C₁₄H₁₅NO₄ requires C, 64.36; H, 5.79; N, 5.36; found: C, 64.32; H, 5.71; N, 5.34%.
(E)-Ethyl 3-(2-cyano-3,4-dimethoxyphenyl)acrylate (50d)

**Yield:** 88%, colorless solid; **mp:** 145-147 °C; **IR** (CHCl₃, cm⁻¹): v_max 758, 894, 1078, 1138, 1208, 1318, 1326, 1462, 1571, 1594, 1608, 1710, 2222, 2984, 3018; **¹H NMR** (200 MHz, CDCl₃): δ 1.35 (t, J = 7.0 Hz, 3H), 3.93 (s, 3H), 4.03 (s, 3H), 4.27 (q, J = 7.0 Hz, 2H), 6.48 (d, J = 16 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 16 Hz, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 14.3, 56.1, 60.6, 61.6, 107.9, 114.1, 116.4, 120.7, 122.9, 129.7, 139.2, 152.1, 153.5, 165.9; **Analysis:** C₁₄H₁₅NO₄ requires C, 64.36; H, 5.79; N, 5.36; found: C, 64.34; H, 5.71; N, 5.32%.

(E)-Ethyl 3-(2-cyano-3,5-dimethoxyphenyl)acrylate (50e)

**Yield:** 87%, colorless solid; **mp:** 119-122 °C; **IR** (CHCl₃, cm⁻¹): v_max 734, 876, 1069, 1128, 1208, 1326, 1478, 1568, 1594, 1608, 1712, 2228, 2958, 3082; **¹H NMR** (200 MHz, CDCl₃): δ 1.36 (t, J = 7.1 Hz, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 4.29 (q, J = 7.1 Hz, 2H), 6.47 (d, J = 2.1 Hz, 1H), 6.55 (d, J = 16 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 16 Hz, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 14.3, 55.7, 56.1, 60.8, 94.9, 96.1 99.4, 103.4, 114.8, 123.3, 139.6, 140.1, 163.4, 163.9, 165.6; **Analysis:** C₁₄H₁₅NO₄ requires C, 64.36; H, 5.79; N, 5.36; found: C, 64.32; H, 5.71; N, 5.34%.

(E)-Ethyl 3-(2-cyano-3,4,5-trimethoxyphenyl)acrylate (50f)

**Yield:** 88%, colorless solid; **mp:** 150-152 °C; **IR** (CHCl₃, cm⁻¹): v_max 669, 703, 749, 940, 1260, 1311, 1573, 1607, 1640, 1708, 2210, 2979, 3016; **¹H NMR** (200 MHz, CDCl₃): δ 1.36 (t, J = 7.1 Hz, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 4.06 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.50 (d, J = 16 Hz, 1H), 6.91 (s, 1H), 7.84 (d, J = 16 Hz, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 14.3, 55.8, 60.3, 109.1, 115.4, 117.0, 118.5, 126.2, 142.5, 148.5, 151.1, 161.2; **Analysis:** C₁₅H₁₇NO₅ requires C, 61.85; H, 5.88; N, 4.81; found: C, 61.82; H, 5.79; N, 4.75%.
5-((E)-2-(Ethoxycarbonyl)vinyl)-4-cyano-2-methoxyphenyl 4-methylbenzene sulfonate (50g)

Yield: 87%, colorless solid; mp: 150-151 °C; IR (CHCl₃, cm⁻¹): v_max 742, 865, 1030, 1128, 1232, 1318, 1329, 1478, 1571, 1594, 1608, 1708, 2225, 2982, 3025; ¹H NMR (200 MHz, CDCl₃): δ 1.35 (t, J = 6.9 Hz, 3H), 2.48 (s, 3H), 3.73 (s, 3H), 4.30 (q, J = 6.9 Hz, 2H), 6.54 (d, J = 16 Hz, 1H), 7.09 (s, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.39 (s, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 16 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 14.2, 21.7, 56.0, 61.0, 104.5, 110.3, 116.0, 123.8, 128.3, 129.7, 132.6, 137.9, 138.4, 139.1, 145.8, 155.6, 165.2; Analysis: C₂₀H₁₉NO₆S requires C, 59.84; H, 4.77; N, 3.49; found: C, 59.78; H, 4.69; N, 3.42%.

(E)-Ethyl 3-(5-(benzoyloxy)-2-cyano-4-methoxyphenyl)acrylate (50h)

Yield: 86%, colorless solid; mp: 146-148 °C; IR (CHCl₃, cm⁻¹): v_max 738, 825, 1031, 1098, 1234, 1334, 1380, 1467, 1568, 1575, 1608, 1710, 2228, 2982, 3034; ¹H NMR (200 MHz, CDCl₃): δ 1.35 (t, J = 7.2 Hz, 3H), 3.93 (s, 3H), 4.28 (q, J = 7.3 Hz, 2H), 5.20 (s, 2H), 6.34 (d, J = 15.4 Hz, 1H), 7.08 (s, 2H), 7.34-7.43 (m, 5H), 7.84 (d, J = 15.4 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 14.3, 56.2, 60.8, 71.0, 105.5, 110.5, 114.7, 117.2, 120.9, 127.3, 128.8, 131.5, 135.4, 139.3, 151.1, 151.8, 165.9; Analysis: C₂₀H₁₉NO₄ requires C, 71.20; H, 5.68; N, 4.15; found: C, 71.14; H, 5.61; N, 4.09%.

(E)-Ethyl 3-(2-cyano-5-fluorophenyl)acrylate (50i)

Yield: 85%, colorless solid; mp: 72-74 °C; IR (CHCl₃, cm⁻¹): v_max 756, 828, 866, 981, 1030, 1186, 1226, 1276, 1325, 1370, 1480, 1574, 1603, 1640, 1693, 2984, 3012; ¹H NMR (200 MHz, CDCl₃): δ 1.36 (t, J = 7.2 Hz, 3H), 4.31 (q, J = 7.2 Hz, 2H), 6.58 (d, J = 15.9 Hz, 1H), 7.19 (td, J = 2.8, 8.4 Hz, 1H), 7.41 (dd, J = 2.6, 9.1 Hz, 1H), 7.74 (dd, J = 5.4, 8.4 Hz, 1H), 7.91 (d, J = 15.9 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 14.1, 60.9, 108.8, 133.9 (d, J = 23.6 Hz), 116.0, 117.6 (d, J = 23.6 Hz), 124.2, 135.7
(d, $J = 9.8$ Hz), 140.2 (d, $J = 8.8$ Hz), 164.5 (d, $J = 257.7$ Hz), 164.9; **Analysis:** C$_{12}$H$_{10}$FNO$_2$ requires C, 65.75; H, 4.60; N, 6.39; found: C, 65.68; H, 4.56; N, 6.36%.

**(E)-Ethyl 3-(2-cyano-5-nitrophenyl)acrylate (50j)**

**Yield:** 87%, colorless solid; **mp:** 105-107 ºC; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 739, 830, 968, 1032, 1106, 1346, 1540, 1708, 2233, 2980, 3087; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.38 (t, $J = 7.0$ Hz, 3H), 4.33 (q, $J = 7.0$ Hz, 2H), 6.78 (d, $J = 15.8$ Hz, 1H), 7.95 (d, $J = 2.0$ Hz, 1H), 7.98 (d, $J = 15.8$ Hz, 1H), 8.33 (dd, $J = 2.0$, 8.4 Hz, 1H) 8.59 (d, $J = 2.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 14.2, 61.3, 115.2, 117.8, 121.7, 124.1, 125.9, 134.7, 136.9, 139.5, 150.2, 164.8; **Analysis:** C$_{12}$H$_{10}$N$_2$O$_4$ requires C, 58.54; H, 4.09; N, 11.38; found: C, 58.48; H, 4.02; N, 11.31%.

**(E)-Ethyl 3-(5-cyano- benzo[d][1,3]dioxol-6-yl)acrylate (50k)**

**Yield:** 86%, colorless solid; **mp:** 148-149 ºC; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 728, 878, 1042, 1134, 1256, 1366, 1382, 1478, 1568, 1594, 1608, 1712, 2218, 2958, 3082; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.35 (t, $J = 7$ Hz, 3H), 4.28 (q, $J = 7$ Hz, 2H), 6.12 (s, 2H), 6.41 (d, $J = 15.8$ Hz, 1H), 7.05 (s, 1H), 7.13 (s, 1H), 7.90 (d, $J = 15.8$ Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 14.3, 60.8, 102.8, 105.9, 106.8, 111.8, 116.9, 121.4, 133.9, 138.9, 149.2, 151.9, 165.7; **Analysis:** C$_{13}$H$_{11}$NO$_4$ requires C, 63.67; H, 4.52; N, 5.71; found: C, 63.59; H, 4.48; N, 5.65%.

**(E)-Ethyl 3-(1-cyanonaphthalen-2-yl)acrylate (50l)**

**Yield:** 88%, colorless solid; **mp:** 118-119 ºC; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 784, 865, 989, 1030, 1106, 1210, 1275, 1291, 1319, 1368, 1573, 1607, 1712, 2218, 2978, 3084; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.35 (t, $J = 7.0$ Hz, 3H), 4.32 (q, $J = 7.0$ Hz, 2H), 6.68 (d, $J = 16$ Hz, 1H), 7.59-7.78 (m, 3H), 7.90 (d, $J = 7.7$ Hz, 1H), 8.04 (d, $J = 8.7$ Hz, 1H), 8.19 (d, $J = 16$ Hz, 1H), 8.28 (d, $J = 8.7$ Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 14.2, 60.8, 110.8, 115.5, 122.1, 123.5, 125.8, 128.3, 129.1, 132.5, 132.9, 137.0, 139.5,
165.5; **Analysis:** \( \text{C}_16\text{H}_{13}\text{NO}_2 \) requires C, 76.48; H, 5.21; N, 5.57; found: C, 76.42; H, 5.19; N, 5.52%.

**2-Vinylbenzonitrile (50m)**

**Yield:** 86%, colorless gum; **IR** (CHCl\(_3\), cm\(^{-1}\)): \( \nu_{\text{max}} \) 752, 839, 962, 1014, 1072, 1118, 1202, 1308, 1347, 1368, 1444, 1573, 1607, 1625, 1675, 2215, 2889, 2923, 3012; \(^1\text{H}\) **NMR** (200 MHz, CDCl\(_3\)): \( \delta \) 5.54 (d, \( J = 10.6 \text{ Hz} \), 1H), 5.95 (d, \( J = 17.8 \text{ Hz} \), 1H), 7.08 (dd, \( J = 10.6, 17.8 \text{ Hz} \), 1H), 7.34 (td, \( J = 1.2, 7.5 \text{ Hz} \), 1H), 7.51-7.70 (m, 3H); \(^{13}\text{C}\) **NMR** (50 MHz, CDCl\(_3\)): \( \delta \) 111.0, 117.4, 118.7, 125.2, 127.8, 132.5, 132.7, 140.4; **Analysis:** \( \text{C}_9\text{H}_7\text{N} \) requires C, 83.69; H, 5.46; N, 10.84; found: C, 83.62; H, 5.41; N, 10.78%.

**4-Methoxy-2-vinylbenzonitrile (50n)**

**Yield:** 84%, colorless gum, **IR** (CHCl\(_3\), cm\(^{-1}\)): \( \nu_{\text{max}} \) 752, 839, 1030, 1083, 1119, 1256, 1308, 1347, 1368, 1456, 1573, 1607, 1625, 1668, 2208, 2923, 3081; \(^1\text{H}\) **NMR** (200 MHz, CDCl\(_3\)): \( \delta \) 3.88 (s, 3H), 5.53 (d, \( J = 11.1 \text{ Hz} \), 1H), 5.92 (d, \( J = 17.7 \text{ Hz} \), 1H), 6.85 (dd, \( J = 2.3, 8.5 \text{ Hz} \), 1H), 7.03 (dd, \( J = 11.1, 17.7 \text{ Hz} \), 1H), 7.11 (s, 1H), 7.55 (d, \( J = 8.5 \text{ Hz} \), 1H); \(^{13}\text{C}\) **NMR** (50 MHz, CDCl\(_3\)): \( \delta \) 55.4, 103.2, 110.4, 114.1, 117.9, 118.7, 132.9, 134.4, 142.5, 162.7; **Analysis:** \( \text{C}_{10}\text{H}_{9}\text{NO} \) requires C, 75.45; H, 5.70; N, 8.80; found: C, 75.41; H, 5.67; N, 8.73%.

**4,5-Dimethoxy-2-vinylbenzonitrile (50o)**

**Yield:** 88%, colorless solid; **mp:** 106-107 °C; **IR** (CHCl\(_3\), cm\(^{-1}\)): \( \nu_{\text{max}} \) 752, 839, 936, 1031, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2210, 2923, 3052; \(^1\text{H}\) **NMR** (200 MHz, CDCl\(_3\)): \( \delta \) 3.91 (s, 3H), 3.97 (s, 3H), 5.45 (d, \( J = 11.0 \text{ Hz} \), 1H), 5.80 (d, \( J = 17.2 \text{ Hz} \), 1H), 6.94-7.08 (m, 3H); \(^{13}\text{C}\) **NMR** (50 MHz, CDCl\(_3\)): \( \delta \) 55.7, 55.9, 102.7, 106.9, 113.5, 116.5, 117.7, 132.5, 134.9, 148.7, 152.5;
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Analysis: $C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40; found: C, 69.75; H, 5.75; N, 7.39%.

2,3-Dimethoxy-6-vinylbenzonitrile (50p)

Yield: 86%, colorless solid; mp: 108-110 °C; IR (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 748, 840, 936, 1028, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2202, 2981, 3029; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.88 (s, 3H), 3.90 (s, 3H), 5.53 (d, $J = 10.9$ Hz, 1H), 5.90 (d, $J = 17.3$ Hz, 1H), 6.37 (d, $J = 2.2$ Hz, 1H), 6.69 (d, $J = 2.2$ Hz, 1H), 7.01 (dd, $J = 10.9$, 17.3 Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 56.1, 61.5, 106.7, 114.7, 116.7, 120.8, 132.4, 133.4, 151.5, 151.7; Analysis: $C_{11}H_{11}NO_2$ requires C, 69.75; H, 5.75; N, 7.39%.

2,4-Dimethoxy-6-vinylbenzonitrile (50q)

Yield: 83%, colorless solid; mp: 76-79 °C; IR (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 724, 867, 968, 1030, 1086, 1119, 1259, 1308, 1386, 1389, 1456, 1578, 1612, 1636, 1656, 2212, 2985, 3029; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.86 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 5.40 (d, $J = 10.8$ Hz, 1H), 5.79 (d, $J = 17.6$ Hz, 1H), 6.94 (d, $J = 17.6$ Hz, 1H), 7.07 (d, $J = 8.5$ Hz, 1H), 7.32 (d, $J = 8.5$ Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 55.5, 55.9, 93.6, 97.5, 101.7, 115.5, 118.9, 133.1, 143.4, 163.0, 163.8; Analysis: $C_{11}H_{11}NO_2$ requires C, 69.75; H, 5.75; N, 7.39%.

2,3,4-Trimethoxy-6-vinylbenzonitrile (50r)

Yield: 87%, colorless solid; mp: 102-103 °C; IR (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 771, 867, 1051, 1105, 1204, 1238, 1257, 1580, 1609, 1753, 2228, 2979, 3013; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.86 (s, 3H), 3.96 (s, 3H), 4.04 (s, 3H), 5.48 (d, $J = 11.2$ Hz, 1H), 5.83 (d, $J = 17.3$ Hz, 1H), 6.85 (s, 1H), 6.97 (dd, $J = 11.2$, 17.3 Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 55.9, 60.8, 61.5, 98.7, 103.4, 114.8, 117.8, 132.6, 137.2, 141.1, 155.4,
157.2; **Analysis:** C\textsubscript{12}H\textsubscript{13}NO\textsubscript{3} requires C, 65.74; H, 5.98; N, 6.39; found: C, 65.72; H, 5.91; N, 6.37%.

4-Cyano-2-methoxy-5-vinylphenyl 4-methylbenzenesulfonate (50s)

**Yield:** 82%, colorless solid; **mp:** 149-150 °C; **IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 746, 845, 938, 1034, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2220, 2978, 3075; \(^1\text{H NMR}\) (200 MHz, CDCl\textsubscript{3}): \( \delta \) 2.48 (s, 3H), 3.74 (s, 3H), 5.57 (d, \( J = 10.9 \) Hz, 1H), 5.86 (d, \( J = 17.6 \) Hz, 1H), 6.93-7.08 (m, 2H), 7.28 (s, 1H), 7.35 (d, \( J = 8.0 \) Hz, 2H), 7.77 (d, \( J = 8.2 \) Hz, 2H); \(^{13}\text{C NMR}\) (50 MHz, CDCl\textsubscript{3}): \( \delta \) 21.7, 55.8, 102.9, 108.9, 116.6, 119.7, 127.7, 128.5, 129.6, 132.3, 132.7, 137.7, 141.4, 145.6, 155.5; **Analysis:** C\textsubscript{17}H\textsubscript{15}NO\textsubscript{4}S requires C, 61.99; H, 4.59; N, 4.25; found: C, 61.89; H, 4.53; N, 4.23%.

4-(Benzyloxy)-5-methoxy-2-vinylbenzonitrile (50t)

**Yield:** 84%, colorless solid; **mp:** 111-113 °C; **IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 747, 858, 934, 1028, 1065, 1119, 1232, 1308, 1394, 1389, 1456, 1574, 1612, 1631, 1656, 2220, 2988, 3086; \(^1\text{H NMR}\) (200 MHz, CDCl\textsubscript{3}): \( \delta \) 3.90 (s, 3H), 5.21 (s, 2H), 5.39 (d, \( J = 11.1 \) Hz, 1H), 5.66 (d, \( J = 17.4 \) Hz, 1H), 6.89-7.04 (m, 2H), 7.10 (s, 1H), 7.32-7.47 (m, 5H); \(^{13}\text{C NMR}\) (50 MHz, CDCl\textsubscript{3}): \( \delta \) 56.0, 70.8, 103.1, 109.2, 114.0, 116.6, 117.8, 127.2, 128.2, 128.6, 132.6, 134.9, 135.7, 149.3, 151.8; **Analysis:** C\textsubscript{17}H\textsubscript{15}NO\textsubscript{2} requires C, 76.96; H, 5.70; N, 5.28; found: C, 76.91; H, 5.67; N, 5.27%.

4-Flouro-2-vinylbenzonitrile (50u)

**Yield:** 86%, colorless solid; **mp:** 105-107 °C; **IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 752, 839, 962, 1014, 1072, 1118, 1202, 1308, 1347, 1368, 1444, 1573, 1607, 1625, 1675, 2853, 2923, 3012; \(^1\text{H NMR}\) (500 MHz, CDCl\textsubscript{3}): \( \delta \) 5.62 (d, \( J = 11.0 \) Hz, 1H), 5.96 (d, \( J = 17.3 \) Hz, 1H), 7.02-7.08 (m, 2H), 7.34 (dd, \( J = 2.2, 9.4 \) Hz, 1H), 7.64 (dd, \( J = 5.5, 8.5 \) Hz, 1H); \(^{13}\text{C NMR}\) (50 MHz, CDCl\textsubscript{3}): \( \delta \) 107.6, 112.6 (d, \( J = 23.7 \) Hz), 115.8 (d, \( J = 13.0 \) Hz).
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23.7 Hz), 116.8, 120.2, 132.2, 143.8 (d, J = 9.5 Hz), 165.1 (d, J = 243.8 Hz);

**Analysis:** C₉H₆FN requires C, 73.46; H, 4.11; N, 9.52; found: C, 73.44; H, 4.08; N, 9.49%.

6-Vinylbenzo[d][1,3]dioxole-5-carbonitrile (50ν)

**Yield:** 88%, colorless solid; **mp:** 88-91 ºC; **IR** (CHCl₃, cm⁻¹): v_max 756, 868, 930, 1038, 1162, 1263, 1359, 1486, 1505, 1604, 1615, 2219, 2916, 3018; **¹H NMR** (200 MHz, CDCl₃): δ 5.44 (d, J = 11.1 Hz, 1H), 5.77 (d, J = 17.3 Hz, 1H), 6.07 (s, 2H), 6.95-7.04 (m, 2H), 7.09 (s, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 102.3, 104.0, 104.8, 110.9, 117.2, 117.7, 132.5, 137.5, 147.4, 151.8; **Analysis:** C₁₀H₇NO₂ requires C, 69.34; H, 4.07; N, 8.09; found: C, 69.34; H, 4.02; N, 7.99%.

2-((E)-Pent-1-ethyl)benzonitrile (50w)

**Yield:** 87%, colorless solid; **mp:** 126-128 ºC; **IR** (CHCl₃, cm⁻¹): v_max 756, 857, 974, 1037, 1095, 1184, 1202, 1216, 1251, 1275, 1291, 1319, 1347, 1368, 1393, 1444, 1477, 1573, 1607, 1640, 1716, 2219, 2984, 3023; **¹H NMR** (200 MHz, CDCl₃): δ 0.98 (t, J = 7.3 Hz, 3H), 1.45-1.63 (m, 2H), 2.22-2.33 (m, 2H), 6.43 (dt, J = 15.3, 6.8 Hz, 1H), 6.74 (d, J = 15.3 Hz, 1H), 7.25 (dd, J = 15.3, 1.4 Hz, 1H), 7.45-7.62 (m, 3H); **¹³C NMR** (50 MHz, CDCl₃): δ 13.7, 22.2, 35.2, 110.5, 117.9, 125.2, 126.0, 126.8, 132.5, 132.7, 136.4, 141.1; **Analysis:** C₁₂H₁₃N requires C, 84.17; H, 7.65; N, 8.18; found: C, 84.14; H, 7.61; N, 8.15%.

4,5-Dimethoxy-2-((E)-3-tert-butyldimethylsilyloxyprop-1-ethyl)benzonitrile (50x)

**Yield:** 85%, colorless gum; **IR** (CHCl₃, cm⁻¹): v_max 748, 876, 932, 1032, 1098, 1276, 1339, 1486, 1505, 1604, 1615, 2220, 2989, 3054; **¹H NMR** (200 MHz, CDCl₃): δ 0.12 (s, 6H), 0.94 (s, 9H), 3.88 (s, 3H), 3.94 (s, 3H), 4.39 (dd, J = 1.7, 4.7 Hz, 2H), 6.27-6.39 (m, 1H), 6.89 (d, J = 15.5 Hz, 1H), 6.98 (s, 1H), 7.00 (s, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ -5.3, 18.3, 25.9, 55.8, 55.9, 63.3, 102.6, 107.4, 113.7, 117.9, 124.9,
132.4, 134.8, 148.4, 152.5; **Analysis:** C\textsubscript{18}H\textsubscript{27}NO\textsubscript{3}Si requires C, 64.83; H, 8.16; N, 4.20; found: C, 64.79; H, 8.09; N, 4.13%.

4,5-Dimethoxy-2-styrylbenzonitrile (50y)

**Yield:** 83%, colorless solid; **mp:** 158-159 °C; **IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 696, 761, 1149, 1204, 1326, 1462, 1571, 1594, 2215, 2984, 3023; **\(^1\)H NMR** (200 MHz, CDCl\textsubscript{3}): \( \delta \) 3.91 (s, 3H), 4.01 (s, 3H), 7.01-7.17 (m, 3H), 7.26-7.42 (m, 4H), 7.54 (d, \( J = 6.9 \) Hz, 2H); **\(^{13}\)C NMR** (50 MHz, CDCl\textsubscript{3}): \( \delta \) 55.9, 102.9, 106.8, 113.6, 118.0, 123.8, 126.7, 128.6, 128.7, 128.8, 131.2, 134.9, 136.1, 148.5, 152.6; **Analysis:** C\textsubscript{17}H\textsubscript{15}NO\textsubscript{2} requires C, 76.96; H, 5.70; N, 5.28; found: C, 76.89; H, 5.57; N, 5.19%.

2,3,4-Trimethoxy-6-((E)-oct-1-enyl)benzonitrile (50z)

**Yield:** 86%, colorless solid; **mp:** 172-174 °C; **IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 694, 755, 878, 969, 989, 1097, 1216, 1271, 1452, 1464, 1513, 1600, 2220, 2970, 3025, 3059; **\(^1\)H NMR** (200 MHz, CDCl\textsubscript{3}): \( \delta \) 0.87-0.93 (m, 3H), 1.26-1.46 (m, 8H), 2.21-2.31 (m, 2H), 3.85 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.23-6.36 (m, 1H), 6.63 (d, \( J = 15.6 \) Hz, 1H), 6.78 (s, 1H); **\(^{13}\)C NMR** (50 MHz, CDCl\textsubscript{3}): \( \delta \) 14.1, 22.6, 28.9, 29.0, 31.6, 33.1, 56.0, 61.1, 61.6, 98.3, 103.3, 115.4, 125.8, 135.9, 138.1, 140.5, 155.6, 157.2; **Analysis:** C\textsubscript{18}H\textsubscript{25}NO\textsubscript{3} requires C, 71.26; H, 8.31; N, 4.62; found: C, 71.22; H, 8.28; N, 4.58%.

(E)-Ethyl 3-(3-cyanophenyl)acrylate (54)

**Yield:** 93%; colorless solid; **mp:** 62-65 °C; **IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 710, 765, 977, 1032, 1185, 1278, 1318, 1447, 1480, 1640, 1712, 2225, 2938, 2983; **\(^1\)H NMR** (200 MHz, CDCl\textsubscript{3}): \( \delta \) 1.35 (d, \( J = 7 \) Hz, 3H), 4.28 (d, \( J = 7 \) Hz, 2H), 6.48 (d, \( J = 16.1 \) Hz, 1H), 7.48-7.80 (m, 5H); **\(^{13}\)C NMR** (50 MHz, CDCl\textsubscript{3}): \( \delta \) 14.1, 60.5, 113.2, 117.8, 120.8, 129.6, 131.1, 131.6, 132.8, 135.5, 141.5, 165.7; **Analysis:** C\textsubscript{12}H\textsubscript{11}NO\textsubscript{2} requires C, 71.63; H, 5.51; N, 6.96; found: C, 71.59; H, 5.45; N, 6.85%.
(E)-Ethyl 3-(4-cyanophenyl)acrylate (55)

Yield: 93%; colorless solid; mp: 68-70 °C; IR (CHCl₃, cm⁻¹): υ_max 730, 795, 955, 1065, 1194, 1268, 1375, 1445, 1495, 1652, 1721, 2226, 2983; ¹H NMR (200 MHz, CDCl₃): δ 1.35 (d, J = 7.1 Hz, 3H), 4.28 (d, J = 7.1 Hz, 2H), 6.51 (d, J = 15.8 Hz, 1H), 7.59-7.71 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 14.1, 60.6, 113.2, 117.9, 121.6, 128.2, 132.4, 138.5, 141.8, 165.7; Analysis: C₁₂H₁₁NO₂ requires C, 71.63; H, 5.51; N, 6.96; found: C, 71.58; H, 5.48; N, 6.88%.

General experimental procedure for the preparation of chiral phthalides (51b-z)

A 50 mL RB flask was charged with K₃Fe(CN)₆ (3 mmol), K₂CO₃ (3 mmol), tert-BuOH (2.5 mL), THF (2.5 mL) and H₂O (5 mL) and stirred for 10 min. Subsequently, (DHQD)₂PHAL (1 mol%) and K₂OsO₄·2H₂O (0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, o-cyanoalkenes 50b-z (1 mmol) was added and allowed to stir for 3-7 h at 25 °C. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 °C. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] gave phthalides 51b-z in 92-95% yield.

(S)-Ethyl 2-((R)-1,3-dihydro-5-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxylacetate (51b)

Yield: 95%; colorless solid; mp: 121-122 °C; [α]D<sub>25</sub> -94.49 (c 1.15, CHCl₃); 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 1 mL/min) retention time 25.80 min (99.55%) and 30.33 min (0.45%); IR (CHCl₃, cm⁻¹): υ_max 724, 876, 1031, 1084, 1191, 1212, 1278, 1295, 1357, 1398, 1445, 1486, 1578, 1607, 1721, 1765, 2984, 3023, 3415; ¹H NMR (200 MHz, CDCl₃): δ 1.29 (t, J = 7.2 Hz,
3H), 3.14 (br s, 3H), 3.91 (s, 3H), 4.29 (q, \( J = 7.2 \) Hz, 2H), 4.63 (d, \( J = 1.7 \) Hz, 1H), 5.69 (d, \( J = 2.2 \) Hz, 1H), 6.96 (d, \( J = 2.1 \) Hz, 1H), 7.05 (dd, \( J = 2.1, 8.6 \) Hz, 1H), 7.80 (d, \( J = 8.6 \) Hz, 1H); \(^{13}\text{C NMR} (50 \text{ MHz, CDCl}_3): \delta 14.0, 55.7, 62.6, 70.5, 79.6, 106.0, 116.9, 118.9, 127.0, 148.5, 164.7, 169.5, 170.8; \text{Analysis}: \text{C}_{13}\text{H}_{14}\text{O}_6 \text{requires C, 58.64}; H, 5.30; \text{found}: C, 58.62; H, 5.19%.

(S)-Ethyl 2-((R)-1,3-dihydro-5,6-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxylacetate (51c)

\textbf{Yield}: 94%; colorless solid; \textbf{mp}: 144-146 °C; \([\alpha]^{\text{D}}_{25} -95.12 \text{ (c 1.12, CHCl}_3); 99\% \text{ ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 23.18 min (99.36\%) and 27.60 min (0.64\%); IR (CHCl}_3, \text{ cm}^{-1}): \nu_{\text{max}} 758, 945, 1125, 1507, 1722, 1764, 2925, 3010, 3341; \text{^1H NMR (200 MHz, CDCl}_3): \delta 1.30 (t, \( J = 7.2 \) Hz, 3H), 3.20 (d, \( J = 6.2 \) Hz, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 4.29 (q, \( J = 7.2 \) Hz, 2H), 4.62 (dd, \( J = 2.4, 6.1 \) Hz, 1H), 5.66 (d, \( J = 2.2 \) Hz, 1H), 6.93 (s, 1H), 7.27 (s, 1H); \text{^{13}C NMR (50 MHz, DMSO-d}_6): \delta 14.3, 56.1, 56.3, 61.1, 70.1, 81.1, 105.2, 105.7, 118.2, 141.6, 150.4, 154.7, 170.2, 171.3; \text{Analysis}: \text{C}_{14}\text{H}_{16}\text{O}_7 \text{requires C, 64.36}; H, 5.79; N, 5.36; \text{found}: C, 64.32; H, 5.71; N, 5.34%.

(S)-Ethyl 2-((R)-1,3-dihydro-6,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (41d)

\textbf{Yield}: 94\%, colorless solid; \textbf{mp}: 110-112 °C; \([\alpha]^{\text{D}}_{25} -95.28 \text{ (c 1.0, CHCl}_3); 99\% \text{ ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 23.90 min (99.44\%) and 27.87 min (0.56\%); IR (CHCl}_3, \text{ cm}^{-1}): \nu_{\text{max}} 762, 946, 1132, 1298, 1518, 1728, 1764, 2985, 3034, 3425; \text{^1H NMR (200 MHz, CDCl}_3): \delta 1.30 (t, \( J = 7.1 \) Hz, 3H), 3.19 (br s, 1H), 3.91 (s, 3H), 4.10 (s, 3H), 4.29 (q, \( J = 7.1 \) Hz, 2H), 4.57 (s, 1H), 5.65 (d, \( J = 2.0 \) Hz, 1H), 7.13 (d, \( J = 8.1 \) Hz, 1H), 7.23 (d, \( J = 8.1 \) Hz, 1H); \text{^{13}C NMR (50 MHz, CDCl}_3): \delta 14.0, 56.6, 62.2, 62.6, 70.7, 79.0,
116.4, 118.7, 119.2, 138.5, 148.3, 152.9, 167.2, 170.9; **Analysis:** C_{14}H_{16}O_{7} requires C, 64.36; H, 5.79; found: C, 64.34; H, 5.71%.

**(S)-Ethyl 2-((R)-1,3-dihydro-5,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51e)**

**Yield:** 94%, colorless solid; **mp:** 154-156 °C; [α]^{D}_{25} -96.29 (c 1.15, CHCl₃); 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 18.37 min (99.60%) and 21.74 min (0.40%); **IR** (CHCl₃, cm⁻¹): υ_{max} 746, 985, 1130, 1287, 1514, 1723, 1762, 2954, 3085, 3414; **¹H NMR** (200 MHz, CDCl₃): δ 1.32 (t, J = 7.2 Hz, 3H), 3.37 (br s, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.30 (q, J = 7.2 Hz, 2H), 4.61 (s, 1H), 5.67 (s, 1H), 6.47 (s, 1H), 6.59 (s, 1H); **¹³C NMR** (50 MHz, CD₃OD): δ 14.5, 56.5, 56.8, 62.9, 71.9, 82.1, 99.8, 100.2, 108.0, 153.0, 160.9, 168.9, 170.6, 172.4; **Analysis:** C_{14}H_{16}O_{7} requires C, 64.36; H, 5.79; found: C, 64.34; H, 5.76%.

**(S)-Ethyl 2-((R)-1,3-dihydro-5,6,7-trimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51f)**

**Yield:** 92%, colorless solid; **mp:** 111-112 °C; [α]^{D}_{25} -94.65 (c 1.23, CHCl₃); **IR** (CHCl₃, cm⁻¹): υ_{max} 1012, 1094, 1140, 1254, 1350, 1475, 1602, 1765, 2954, 3085, 3408 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 1.31 (t, J = 7.2 Hz, 3H), 3.09 (s,1H), 3.86 (s, 3H), 3.96 (s, 3H), 4.13 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 4.58 (d, J = 2.1 Hz, 1H), 5.58 (d, J = 2.1 Hz, 1H), 6.70 (s, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 13.9, 56.3, 61.1, 62.0, 62.4, 79.1, 99.5, 111.0, 141.9, 143.5, 152.1, 159.6, 167.3, 176.7; **Analysis:** C_{15}H_{18}O_{8} requires C, 55.21; H, 5.56; found: C, 55.18; H, 5.53%.

**(S)-Ethyl 2-((R)-5-(p-toluenesulfonyloxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51g)**

**Yield:** 93%, colorless solid; **mp:** 107-108 °C; [α]^{D}_{25} -94.89 (c 1.15, CHCl₃); **IR** (CHCl₃, cm⁻¹): υ_{max} 768, 819, 1025, 1050, 1120, 1180, 1190, 1330, 1374, 1494, 1614, 1767, 2924, 3012, 3371; **¹H NMR** (200 MHz, CDCl₃): δ 1.27 (t, J = 7.2 Hz, 3H), 2.48
(S)-Ethyl 2-((R)-5-(benzyl oxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51h)

**Yield:** 94%, colorless solid; **mp:** 138-140 °C; [α]_D^{25} = -96.04 (c 1.21, CHCl₃); **IR** (CHCl₃, cm⁻¹): v_{max} 738, 856, 1025, 1078, 1130, 1184, 1195, 1336, 1395, 1494, 1645, 1765, 2942, 3035, 3413; **¹H NMR** (200 MHz, CDCl₃): δ 1.28 (t, J = 7.0 Hz, 3H), 3.04 (d, J = 5.9 Hz, 1H), 3.94 (s, 3H), 4.27 (q, J = 7.0 Hz, 2H), 4.55 (dd, J = 2.5, 5.9 Hz, 1H), 5.22 (d, J = 3.5 Hz, 2H), 5.61 (d, J = 2.0 Hz, 1H), 6.94 (s, 1H), 7.26 (s, 1H), 7.29-7.45 (m, 5H); **¹³C NMR** (50 MHz, DMSO-d₆): δ 13.7, 55.7, 61.4, 70.3, 70.6, 79.9, 105.2, 105.8, 118.5, 127.0, 127.8, 128.2, 135.3, 139.9, 150.7, 153.5, 169.6, 170.4; **Analysis:** C₂₀H₂₉O₇ requires C, 64.51; H, 5.41; found: C, 64.39; H, 5.36%.

(S)-Ethyl 2-((R)-5-fluoro-1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (50i)

**Yield:** 94%, colorless solid; **mp:** 108-109 °C; [α]_D^{25} = -95.41 (c 1.15, CHCl₃); **IR** (CHCl₃, cm⁻¹): v_{max} 756, 891, 1052, 1097, 1130, 1190, 1325, 1374, 1485, 1629, 1765, 2928, 3015, 3351; **¹H NMR** (200 MHz, CDCl₃): δ 1.30 (t, J = 7.2 Hz, 3H), 3.17 (d, J = 6.7 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 4.62 (dd, J = 2.2, 5.8 Hz, 1H), 5.74 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.91 (dd, J = 5.8, 8.3 Hz, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 13.9, 62.2, 70.2, 79.7, 109.5 (d, J = 24.6 Hz), 117.6 (d, J = 24.6 Hz), 122.7, 127.7, 148.6 (d, J = 10.3 Hz), 166.3 (d, J = 256.3 Hz), 168.5, 170.5; **Analysis:** C₁₂H₁₁FO₅ requires C, 56.70; H, 4.36; found: C, 56.67; H 4.33%.
(S)-Ethyl 2-((R)-1,3-dihydro-5-nitro-1-oxoisobenzofuran-3-yl)-2-hydroxy acetate (51j)

**Yield:** 93%, colorless solid; **mp:** 146-148 ºC; $[\alpha]^{D}_{25}$ -95.28 (c 1.0, CHCl$_3$); **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 738, 829, 967, 1037, 1106, 1346, 1540, 1740, 1779, 2853, 2918, 3009, 3444; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.35 (t, $J = 7.2$ Hz, 3H), 3.21 (d, $J = 6.1$ Hz, 1H), 4.36 (q, $J = 7.2$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 1H), 5.90 (s, 1H), 8.09 (d, $J = 8.2$ Hz, 1H), 8.42-8.46 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 14.1, 63.2, 70.1, 80.1, 117.8, 125.3, 127.0, 131.8, 146.8, 151.7, 167.3, 170.2; **Analysis:** C$_{12}$H$_{11}$NO$_7$ requires C, 51.25; H, 3.94; N, 4.98; found: C, 51.24; H, 3.85; N, 4.93%.

(S)-Ethyl 2-((R)-5-1,3-dihydro-5,6-dioxomethyl-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51k)

**Yield:** 95%, colorless solid; **mp:** 150-153 ºC; $[\alpha]^{D}_{25}$ -95.74 (c 1.0, CHCl$_3$); **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 786, 891, 1015, 1054, 1122, 1183, 1196, 1356, 1395, 1489, 1618, 1755, 2942, 3021, 3410; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.31 (t, $J = 7.1$ Hz, 3H), 3.10 (br s, 1H), 4.30 (qd, $J = 1.4$, 7.1 Hz, 2H), 4.56 (s, 1H), 5.62 (d, $J = 2.1$ Hz, 1H), 6.14 (dd, $J = 1.4$, 4.4 Hz, 2H), 6.89 (s, 1H), 7.20 (s, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 14.0, 62.6, 70.4, 79.6, 101.8, 102.7, 104.2, 120.4, 142.2, 149.6, 153.7, 169.2, 170.8; **Analysis:** C$_{13}$H$_{12}$O$_7$ requires C, 55.72; H, 4.32; found: C, 55.65; H, 4.29%.

(S)-Ethyl 2-((R)-1,3-dihydro-1-oxonaphtho[2, 1-c]furan-3-yl)-2-hydroxyacetate (51l)

**Yield:** 94%, colorless solid; **mp:** 107-109 ºC; $[\alpha]^{D}_{25}$ -95.69 (c 1.15, CHCl$_3$); **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 784, 865, 989, 1010, 1106, 1210, 1275, 1291, 1319, 1368, 1573, 1607, 1750, 2978, 3084, 3457; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.28 (t, $J = 7.4$ Hz, 3H), 3.14 (d, $J = 6.0$ Hz, 1H), 4.31 (q, $J = 7.4$ Hz, 2H), 4.74 (dd, $J = 2.1$, 6.0 Hz, 1H), 5.85 (d, $J = 2.1$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 1H), 7.63-7.78 (m, 2H), 7.97 (d, $J = 8.5$ Hz, 1H), 8.16 (d, $J = 8.5$ Hz, 1H) 8.97 (d, $J = 8.5$ Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$+ CD$_3$OD): $\delta$ 13.2, 61.4, 69.8, 80.3, 118.1, 118.6, 120.2, 122.4, 126.7, 128.0,
128.3, 133.0, 135.2, 147.6, 170.3; **Analysis:** C_{16}H_{14}O_{5} requires C, 67.13; H, 4.93; found: C, 67.11; H, 4.89%.

**(R)-3-(Hydroxymethyl)isobenzofuran-1(3H)-one (51m)**

**Yield:** 95%, colorless solid; **mp:** 101-104 °C; [α]_{D}^{25} 78.12 (c 1.23, CHCl_{3}); 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 8.03 (99.36%) and 9.24 (0.64%); **IR** (CHCl_{3}, cm^{-1}): υ_{max} 744, 847, 968, 1025, 1067, 1089, 1211, 1288, 1349, 1467, 1607, 1640, 1756, 2924, 3012, 3440; {^1}H NMR (200 MHz, CDCl_{3}): 2.61 (s, 1H), 3.90 (d, J = 11.8 Hz, 1H), 4.14 (d, J = 11.8 Hz, 1H), 5.54-5.59 (m, 1H), 7.55 (t, J = 7.7 Hz, 2H), 7.70 (td, J = 1.1, 7.4 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H); {^{13}}C NMR (50 MHz, CDCl_{3}+CD_{3}OD): δ 61.7, 81.5, 121.6, 124.2, 125.6, 128.4, 133.3, 146.7, 170.6; **Analysis:** C_{9}H_{8}O_{3} requires C, 65.85; H, 4.91; found: C, 65.83; H, 4.85%.

**(R)-3-(Hydroxymethyl)-5-methoxyisobenzofuran-1(3H)-one (51n)**

**Yield:** 95%, colorless solid; **mp:** 137-140 °C; [α]_{D}^{25} 78.36 (c 1.12, CHCl_{3}); 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 1 mL/min) retention time 27.19 min (99.36%) and 39.72 min (0.64%); **IR** (CHCl_{3}, cm^{-1}): υ_{max} 728, 868, 1026, 1256, 1490, 1607, 1640, 1749, 2853, 2923, 3440; {^1}H NMR (200 MHz, CDCl_{3}): δ 2.31 (br s, 1H), 3.84-3.91 (m, 4H), 4.06-4.14 (m, 1H), 5.46 (t, J = 5.3 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 2.0, 8.6 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H); {^{13}}C NMR (50 MHz, CDCl_{3}+CD_{3}OD): δ 54.8, 62.1, 81.0, 105.5, 116.3, 117.7, 126.0, 149.8, 164.5, 170.8; **Analysis:** C_{10}H_{10}O_{4} requires C, 61.85; H, 5.19; found: C, 61.79; H, 5.12%.

**(R)-3-(Hydroxymethyl)-5,6-dimethoxyisobenzofuran-1(3H)-one (51o)**

**Yield:** 93%, colorless solid; **mp:** 165-167 °C; [α]_{D}^{25} 77.89 (c 1, CHCl_{3}); 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min)
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retention time 23.18 min (99.36%) and 27.60 min (0.64%); IR (CHCl₃, cm⁻¹): \( \nu_{\text{max}} \)
698, 828, 956, 1027, 1056, 1225, 1266, 1309, 1335, 1474, 1508, 1612, 1752, 2922,
3023, 3358; \(^1\)H NMR (200 MHz, CDCl₃): \( \delta \) 2.71 (t, \( J = 6.4 \) Hz, 1H), 3.81-3.90 (m, 
1H), 3.93 (s, 3H), 3.99 (s, 3H), 4.04-4.15 (m, 1H), 5.42-5.47 (m, 1H), 6.93 (s, 1H),
7.25 (s, 1H); \(^{13}\)C NMR (50 MHz, DMSO-d₆): \( \delta \) 56.1, 56.3, 62.4, 81.6, 105.0, 105.8,
117.9, 142.4, 150.3, 154.6, 170.5; Analysis: \( \text{C}_{11}\text{H}_{12}\text{O}_5 \) requires C, 58.93; H, 5.39;
found: C, 58.85; H, 5.37%.

(R)-3-(Hydroxymethyl)-6,7-dimethoxyisobenzofuran-1(3H)-one (51p)

Yield: 94%, colorless solid; mp: 85-88 °C; \([\alpha]_{\text{D}}^{25} -78.21 \) (c 1, CHCl₃); 99% ee from 
chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention 
time 18.35 min (99.35%) and 20.85 min (0.56%); IR (CHCl₃, cm⁻¹): \( \nu_{\text{max}} \)
698, 798, 956, 1030, 1067, 1220, 1328, 1339, 1458, 1605, 1745, 2976, 3012, 3457; \(^1\)H NMR 
(200 MHz, CDCl₃): \( \delta \) 2.24 (br s, 1H), 3.79-3.85 (m, 1H), 3.90 (s, 3H), 3.95 (s, 3H),
4.03-4.09 (m, 1H), 5.35-5.39 (m, 1H), 6.42 (s, 1H), 6.48(s, 1H); \(^{13}\)C NMR (50 MHz, 
CDCl₃): \( \delta \) 56.6, 62.0, 63.7, 80.7, 116.8, 118.4, 119.4, 139.6, 148.0, 152.5, 168.2;
Analysis: \( \text{C}_{11}\text{H}_{12}\text{O}_5 \) requires C, 58.93; H, 5.39; found: C, 58.83; H, 5.36%.

(R)-3-(Hydroxymethyl)-5,7-dimethoxyisobenzofuran-1(3H)-one (51q)

Yield: 94%, colorless solid; mp: 152-153 °C; \([\alpha]_{\text{D}}^{25} -78.1 \) (c 1, CHCl₃); 99% ee from 
chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention 
time 18.27 min (99.36%) and 20.40 min (0.64%); IR (CHCl₃, cm⁻¹): \( \nu_{\text{max}} \)
695, 765, 950, 1030, 1058, 1232, 1331, 1365, 1463, 1615, 1751, 2982, 3010, 3443; \(^1\)H NMR 
(200 MHz, CDCl₃): \( \delta \) 2.53 (br s, 1H), 3.77-3.88 (m, 3H), 3.91 (s, 3H), 3.99-4.04 (m, 
3H), 4.10 (s, 1H), 5.40-5.45 (m, 1H), 7.09 (dd, \( J = 8.4, 8.2 \) Hz, 1H), 7.22 (d, \( J = 8.2 
Hz, 1H); \(^{13}\)C NMR (50 MHz, CDCl₃): \( \delta \) 54.6, 54.9, 62.2, 80.4, 97.6, 98.2, 105.8,
151.7, 158.9, 166.6, 168.9; **Analysis:** C_{11}H_{12}O_{5} requires C, 58.93; H, 5.39; found: C, 58.89; H, 5.37%.

(\textit{R})-3-(Hydroxymethyl)-5,6,7-trimethoxyisobenzofuran-1(3H)-one (51r)

**Yield:** 93%, colorless solid; **mp:** 178-180 °C; [\alpha]_{D}^{25} = -78.05 (c 1.15, CHCl₃); **IR** (CHCl₃, cm⁻¹): \nu_{max} 1014, 1097, 1254, 1345, 1483, 1600, 1754, 2947, 3017, 3444; **\textit{1}H NMR** (200 MHz, CDCl₃): \delta 2.62 (br s, 1H), 3.84-3.90 (m, 4H), 3.96 (s, 3H), 4.03-4.09 (m, 1H), 4.13 (s, 3H), 5.35-5.39 (m, 1H), 6.69 (s, 1H); **\textit{13}C NMR** (50 MHz, CDCl₃+CD₃OD): \delta 56.3, 61.1, 62.0, 63.7, 80.6, 99.9, 110.6, 141.8, 144.8, 152.1, 159.7, 168.3; **Analysis:** C_{12}H_{14}O₆ requires C, 56.09; H, 5.55; found: C, 56.05; H, 5.53%.

(\textit{R})-1,3-Dihydro-1-(hydroxymethyl)-5-methoxy-3-oxoisobenzofuran-6-yl 4-methylbenzenesulfonate (51s)

**Yield:** 95%, colorless solid; **mp:** 152-154 °C; [\alpha]_{D}^{25} = -77.79 (c 1.18, CHCl₃); **IR** (CHCl₃, cm⁻¹): \nu_{max} 734, 849, 973, 103, 1053, 1178, 1345, 1372, 1494, 1614, 1755, 2919, 3018, 3437; **\textit{1}H NMR** (200 MHz, CDCl₃): \delta 2.24 (br s, 1H), 2.48 (s, 3H), 3.80 (s, 3H), 3.92 (dd, J = 4.6, 12.3 Hz, 1H), 4.03 (dd, J = 4.7, 12.3 Hz, 1H), 5.44 (t, J = 4.6 Hz, 1H), 6.97 (s, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.48 (s, 1H), 7.78 (d, J = 8.2 Hz, 2H); **\textit{13}C NMR** (50 MHz, CDCl₃+CD₃OD): \delta 20.0, 55.0, 61.4, 80.9, 105.3, 117.4, 119.3, 127.6, 128.8, 131.9, 138.9, 145.1, 147.7, 156.6, 169.5; **Analysis:** C_{17}H_{16}O_{7}S requires C, 56.04; H, 4.43; found: C, 55.97; H, 4.37%.

(\textit{R})-5-(Benzyloxy)-3-(hydroxymethyl)-6-methoxyisobenzofuran-1(3H)-one (51t)

**Yield:** 94%, colorless solid; **mp:** 126-128 °C; [\alpha]_{D}^{25} = -78.22 (c 1.10, CHCl₃); **IR** (CHCl₃, cm⁻¹): \nu_{max} 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385; **\textit{1}H NMR** (200 MHz, CDCl₃): \delta 2.31 (br s, 1H), 3.75-3.85 (m, 1H), 3.92 (s, 3H), 3.98-4.06 (m, 1H), 5.22 (s, 2H), 5.36-5.41 (m, 1H), 6.92 (s, 1H), 7.28 (s, 1H), 7.32-7.45 (m, 5H); **\textit{13}C NMR** (50 MHz, CDCl₃): \delta 56.2, 64.1,
71.1, 81.0, 105.4, 106.6, 118.6, 127.3, 128.3, 128.7, 135.6, 140.9, 151.2, 154.0, 170.5;

**Analysis:** C_{17}H_{16}O_{5} requires C, 67.99; H, 5.37; found: C, 67.91; H, 5.35%.

(R)-5-Fluoro-3-(hydroxymethyl)isobenzofuran-1(3H)-one (51u)

**Yield:** 93%, colorless gum; [α] D^{25} -77.21 (c 1.2, CHCl_{3}); **IR** (CHCl_{3}, cm^{-1}): \nu_{max} 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385; **^1H NMR** (500 MHz, CDCl_{3}): \delta 2.87 (br s, 1H), 3.93 (dd, \(J = 4.0, 12.5\) Hz, 1H), 4.11 (dd, \(J = 4.0, 12.5\) Hz, 1H), 5.51-5.53 (t, \(J = 4.0\) Hz, 1H), 7.21-7.27 (m, 2H), 7.88-7.91 (m, 1H); **^13C NMR** (50 MHz, CDCl_{3}): \delta 63.4, 80.9, 109.7 (d, \(J = 24.6\) Hz), 117.7 (d, \(J = 24.6\) Hz), 122.6, 128.2 (d, \(J = 9.4\) Hz), 149.7 (d, \(J = 9.4\) Hz), 167.3 (d, \(J = 398.5\) Hz), 167.9; **Analysis:** C_{9}H_{7}FO_{3} requires C, 59.35; H, 3.87; found: C, 73.44, H, 4.08%.

(R)-3-(Hydroxymethyl)-5,6-dioxomethylisobenzofuran-1(3H)-one (51v)

**Yield:** 94%, colorless solid; **mp:** 144-145 °C; [α] D^{25} -78.11 (c 1.2, CHCl_{3}); **IR** (CHCl_{3}, cm^{-1}): \nu_{max} 698, 852, 957, 1024, 1067, 1232, 1286, 1319, 1343, 1484, 1582, 1612, 1766, 2942, 3054, 3389; **^1H NMR** (200 MHz, CDCl_{3}): \delta 2.40 (br s, 1H), 3.84 (dd, \(J = 4.0, 12.4\) Hz, 1H), 4.06 (dd, \(J = 4.0, 12.4\) Hz, 1H), 5.41 (m, 1H), 6.13 (d, \(J = 2.3\) Hz, 2H), 6.87 (s, 1H), 7.20 (s, 1H); **^13C NMR** (50 MHz, DMSO-d_{6}): \delta 62.1, 81.3, 102.8, 103.3, 119.7, 144.5, 149.0, 153.2, 169.6; **Analysis:** C_{10}H_{8}O_{5} requires C, 57.70; H, 3.87; found: C, 57.68; H, 3.85%.

(R)-3-((R)-1-Hydroxybutyl)isobenzofuran-1(3H)-one (51w)

**Yield:** 93%; colorless solid; **mp:** 103-109 °C; [α] D^{25} -76.89 (c 1, CHCl_{3}); **IR** (CHCl_{3}, cm^{-1}): \nu_{max} 694, 728, 1080, 1212, 1287, 1467, 1618, 1752, 2873, 2959, 3433; **^1H NMR** (200 MHz, CDCl_{3}): \delta 0.93 (t, \(J = 6.8\) Hz, 3H), 1.44-1.72 (m, 4H), 1.97 (br s, 1H), 3.99 (br s, 1H), 5.40 (d, \(J = 3.6\) Hz, 1H), 7.51-7.57 (m, 2H), 7.65-7.73 (m, 1H), 7.87-7.92 (m, 1H); **^13C NMR** (50 MHz, CDCl_{3}): \delta 13.9, 18.8, 34.9, 71.9, 83.2, 122.4,
125.6, 126.6, 129.2, 134.0, 147.2, 170.5; **Analysis**: C_{12}H_{14}O_{3} requires C, 69.88; H, 6.84; found: C, 69.82; H, 6.81%.

**(R)-3-((R)-1-Hydroxy-2-tertiarybutyldimethylsilyl ethyl)-5,6-dimethoxyisobenzofuran-1(3H)-one (51x)**

**Yield**: 94%, colorless solid; **mp**: 166-168 °C; [α]_{D}^{25} = -79.24 (c 1.1, CHCl_{3}); **IR** (CHCl_{3}, cm^{-1}): υ_{max} 775, 837, 1060, 1137, 1471, 1503, 1740, 2855, 2926, 3406; **^{1}H NMR** (200 MHz, CDCl_{3}): δ 0.08 (d, J = 5.4 Hz, 6H), 0.90 (s, 9H), 2.30 (d, J = 5.5 Hz, 1H), 3.62-3.82 (m, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.05-4.12 (m, 1H), 5.51 (d, J = 3.4 Hz, 1H), 6.98 (s, 1H), 7.28 (s, 1H); **^{13}C NMR** (50 MHz, CDCl_{3}): δ -5.0, -4.5, 17.8, 25.5, 56.2, 63.1, 73.3, 80.1, 104.2, 106.0, 118.9, 141.5, 150.6, 154.6, 170.6; **Analysis**: C_{18}H_{28}O_{8}Si requires C, 58.67; H, 7.66; found: C, 58.65; H, 7.56%.

**(R)-3-(Hydroxy(phenyl)methyl)-5,6-dimethoxyisobenzofuran-1(3H)-one (51y)**

**Yield**: 94%, colorless solid; **mp**: 113-115 °C; [α]_{D}^{25} = -79.23 (c 1.15, CHCl_{3}); **IR** (CHCl_{3}, cm^{-1}): υ_{max} 756, 857, 974, 1026, 1064, 1158, 1216, 1334, 1604, 1743, 2858, 2928, 3430; **^{1}H NMR** (200 MHz, CDCl_{3}): δ 3.05 (br s, 1H), 3.64 (s, 3H), 3.90 (s, 3H), 4.69 (d, J = 7.4 Hz, 1H), 5.47 (d, J = 7.4 Hz, 1H), 5.85 (s, 1H), 7.20 (s, 1H), 7.34-7.41 (m, 5H); **^{13}C NMR** (50 MHz, CDCl_{3}+CD_{3}OD): δ 54.7, 74.3, 83.0, 104.3, 117.4, 126.6, 127.4, 138.1, 140.6, 149.8, 153.5, 170.6; **Analysis**: C_{19}H_{16}O_{5} requires C, 67.99; H, 5.37; found: C, 67.92; H, 5.29%.

**(R)-3-((R)-1-Hydroxyheptyl)-5,6,7-trimethoxyisobenzofuran-1(3H)-one (51z)**

**Yield**: 92%, colorless solid; **mp**: 113-115 °C; [α]_{D}^{25} = -78.36 (c 1.08, CHCl_{3}); **IR** (CHCl_{3}, cm^{-1}): υ_{max} 796, 1089, 1130, 1254, 1326, 1465, 1543, 1749, 2898, 2974, 3988 cm^{-1}; **^{1}H NMR** (200 MHz, CDCl_{3}): δ 0.87-0.93 (m, 3H), 1.26-1.37 (m, 8H), 1.64-1.78 (m, 2H), 3.87 (s, 3H), 3.94-3.96 (m, 4H), 4.13 (s, 3H), 5.23 (d, J = 3.0 Hz, 1H), 6.68 (s, 1H); **^{13}C NMR** (50 MHz, CDCl_{3}): δ 14.0, 22.5, 25.7, 29.1, 31.7, 32.8, 56.3, 61.2
Chiral Phthalides

Chapter II

(2S, 3R)-Ethyl 3-(3-cyanophenyl)-2,3-dihydroxypropanoate (56)

Yield: 93%; colorless gum; [α]D25 -36.06 (c 1.2, CHCl3); IR (CHCl3, cm⁻¹): υmax 680, 725, 954, 1057, 1118, 1214, 1291, 1734, 2229, 2985, 3443; 1H NMR (200 MHz, CDCl3): δ 1.30 (d, J = 7.1 Hz, 3H), 3.26 (d, J = 7.5 Hz, 1H), 3.43 (d, J = 5.8 Hz, 1H), 4.24-4.34 (m, 3H), 5.02 (dd, J = 2.3, 7.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.57-7.67 (m, 2H), 7.72 (s, 1H); 13C NMR (50 MHz, CDCl3): δ 14.1, 62.3, 73.5, 74.5, 112.2, 118.6, 129.0, 130.2, 130.9, 131.3, 141.9, 172.3; Analysis: C12H13NO4 requires C, 61.27; H, 5.57; N, 5.95; found: C, 61.27; H, 5.57; N, 5.95.

Benzyl(1R,2S)-2-(ethoxycarbonyl)-1-(2-cyanophenyl)-2-hydroxyethylcarbamate (58)

Sodium hydroxide (60 mg, 1.5 mmol) was dissolved in water (4 mL), and 0.5 mL of this NaOH solution was transferred to a small vial containing K2OsO2(OH)4 (0.02 mmol for 4 mol %) for later use. To the remainder of the NaOH solution were added the carbamate (1.55 mmol) and n-PrOH (2 mL). The mixture was stirred for 2-3 min and placed in a water bath before tert-butylhypochlorite (175 µL, 1.52 mmol) was slowly added with vigorous stirring. Then, the resulting solution was sequentially...
treated with a solution of \((\text{DHQD})_2\text{PHAL}\) (0.025 mmol for 5 mol \%) in \(n\)-PrOH (1 mL), the \(\alpha\)-cyano ethylcinnamate (0.50 mmol), the previously prepared solution of \(\text{K}_2\text{OsO}_2(\text{OH})_4\), and \(n\)-PrOH (1 mL). The reaction mixture was monitored by TLC to establish completion, quenched by the addition of saturated aqueous sodium sulfite (4 mL) while being cooled in an ice-water bath, and stirred for an additional 30 min. The separated aqueous phase was extracted with EtOAc (3 X 5 mL), and the combined organic extracts were washed with water (3 mL) followed by brine (5 mL), dried over anhyd.Na\(_2\)SO\(_4\), and concentrated under reduced pressure to give the crude products which were purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (60:40) as an eluent] to give product \(58\) in 64\% yield with dr 6:1.

**Yield:** 64\%; colorless gum; \([\alpha]_D^{25} -36.06\) (c 1.1, CHCl\(_3\)); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 756, 857, 974, 1037, 1095, 1184, 1202, 1275, 1291, 1319, 1347, 1368, 1393, 1477, 1573, 1607, 1640, 1716, 2219, 2984, 3023, 3415; **\(^1\)H NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 1.28 (t, \(J = 7.1\) Hz, 3H), 3.34 (d, \(J = 7.5\) Hz, 1H), 4.29 (q, \(J = 7.1\) Hz, 2H), 4.50 (s, 1H), 5.06 (dd, \(J = 2.3, 7.5\) Hz, 1H), 5.62 (d, \(J = 8.9\) Hz, 1H), 5.85 (d, \(J = 8.9\) Hz, 1H), 7.32-7.36 (m, 5H), 7.39-7.56 (m, 3H), 7.66-7.77 (m, 1H); **\(^{13}\)C NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 14.2, 55.3, 60.3, 62.8, 72.5, 111.1, 117.0, 122.0, 128.4, 132.8, 133.2, 142.9, 145.8, 155.3, 172.0; **Analysis:** \(\text{C}_{12}\text{H}_{13}\text{NO}_4\) requires C, 61.27; H, 5.57; N, 5.95; found: C, 61.26; H, 5.54; N, 5.89.
Section II:

First Enantioselective Synthesis of (-)-Matteucen C and Facile Synthesis of antilschemic Stroke Drug, 3-Butylphthalide

2.2.1 Introduction

3-Alkylated phthalide frameworks are present in a large number of natural products and biologically active compounds. In recent years such chiral phthalide systems have attracted considerable attention as they play a pivotal role in modern drug discovery. Among them (-)-matteucen C (62) and 3-butylphthalide (1) are of particular interest due to their biological activities. Matteuccia orientalis (HOOK.) TREV (Onocleaceae), mainly distributed in Southern China, is a Chinese medicinal herb used for the treatment of hemostatics and relieving ostalgia. Search for new bioactive constituents from the rhizomes of this plant led to the isolation of new isocoumarin derivatives, such as matteucen A (60), racemic-matteucen B (61) and new phthalide derivative, (-)-matteucen C (62) (Fig. 12).
Worldwide ischemic stroke is the second leading cause of human morbidity and mortality. Currently, ischemic stroke approximately causes loss of 5 million people each year, and the mortality rate of stroke is increasing. Studies have suggested that the pathogenesis of ischemic stroke is attributed to the interaction of multiple factors, including genetic high risk, thrombosis, and chronic inflammatory diseases such as hypertension, diabetes, and etc. During the process of ischemic stroke, the platelet aggregation related thrombosis limits sufficient blood flow in the special region of the brain and leads to ischemic inflammation and brain damage. Although few drugs are available for the intervention of ischemic stroke, the efficacy of these drugs are not satisfactory and need to be used in combinations with other active drugs. For centuries in China, seeds of *Apium graveolens Linn*, Chinese celery have been employed against ischemic stroke and 3-butylphtalide (1) has been reported as the active ingredient in the seed oil of *Apium graveolens Linn* celery. 3-Butylphtalide (1) (Fig. 12), was approved as antiischemic drug by the State Food and Drug Administration (SFDA) of China in 2002. It intervents ischemic stroke through multiple mechanism for example, by improving energy metabolism, reducing oxidative damage, improving micro circulation in arterioles, decreasing neuronal apoptosis, improving mitochondrial function and inhibiting inflammation. Moreover, it showed promising preclinical potential as a multi-target drug for the prevention and treatment of Alzheimer’s disease and vascular dementia. It is noteworthy that Alzheimer’s disease is the most common form of senile dementia, characterized by progressive memory loss and vascular dementia, the second most common cause of dementia especially in the Asian population. Currently, there is no specific drug available to prevent or cure vascular dementia.
2.2.2 Review of Literature

Literature search revealed that there is no report available for the synthesis of (-)-matteucen C (62), where as there are six reports for the synthesis of 3-butylphthalide. A short description of all the six methods are presented below.

Takahashi’s approach (1991)\textsuperscript{45}

Takahashi et al. have utilized valine-based chiral auxiliary for the introduction of chirality in 3-butylphthalide (1) synthesis. Thus, chiral oxazolidine 64 was prepared by condensation of phthalaldehyde 24 with (S)-N-methyl valinol 63 in 56% yield (dr = 93:7). Diastereoselective addition of dibutylcupriolithium onto oxazolidine 64 followed by subsequent hydrolysis under acidic condition afforded lactol 65 in 85% ee. Further, oxidation of lactol 65 with PCC gave 3-butylphthalide (1) (Scheme 19).

\begin{equation}
\begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
+ \begin{array}{c}
\text{N} \\
\text{OH}
\end{array}
\xrightarrow{i}
\begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
\xrightarrow{\text{ii - iii}}
\begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
\xrightarrow{\text{iv}}
\begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
\xrightarrow{\text{ii - iii}}
\begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
\end{equation}

**Scheme 19:** (i) anhyd. Na\textsubscript{2}SO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 16 h, 56%; (ii) (\textsuperscript{6}Bu)\textsubscript{2}CuLi, Et\textsubscript{2}Zn, \textsuperscript{9}BuMgCl, THF, -50 °C, 24 h; (iii) p-TSA, THF:H\textsubscript{2}O (5:1), reflux, 1 h, 86% (over 2 steps); (iv) PCC, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 30 min, 41%.
Soai’s approach (1991)\textsuperscript{46}

Soai et al. have described the synthesis of 3-butylphthalide (1) using enantioselective addition of dibutylzinc reagent as key step. Thus, \( o \)-bromobenzaldehyde 66 was subjected to asymmetric addition of dibutylzinc reagent catalyzed by chiral N,N-dibutynorephedrine (67) to give alcohol 68 in 94% yield and 90% ee. Treatment of alcohol 68 with \( n \)-BuLi followed by quenching with DMF afforded lactol 65 in 82% yield, which was finally transformed to 3-butylphthalide (1) using Ag\(_2\)O oxidation (Scheme 20).

Scheme 20: (i) (1S, 2R)-DBNE (67), \( n \)-Bu\(_2\)Zn, hexane, 25 °C, 17 h, 94%; (ii) \( n \)-BuLi, DMF, 82%; (iii) Ag\(_2\)O, 25 °C, 76%.

Matsui’s approach (1993)\textsuperscript{47}

Matsui et al. have commenced their synthesis from commercially available benzoyl chloride 69. The chiral benzamide 71 was obtained in 90% yield by treating benzoyl chloride 69 with chiral amine 70. \textit{ortho}-Lithiation of chiral benzamide 71 followed by diastereoselective addition onto \( n \)-pentanal afforded alcohol 72 in 57% yield (dr = 90:10). Finally, cyclization under acidic condition provided 3-butylphthalide (1) (Scheme 21).
Kitayama's approach (2002)\textsuperscript{48}

Kitayama have reported the synthesis of 3-butyolphthalide (1) by employing enzymatic reduction as the key reaction. Methyl 2-pentanoyl benzoate (74) was prepared from phthalic anhydride 73 by reacting with dibutylcadmium, followed by esterification in acidic methanol. Methyl 2-pentanoylbenzoate (74) was subjected to enzymatic reduction with \textit{Pseudomonas putida} ATCC to give 3-butyolphthalide (1) in 80% yield and 99% ee (Scheme 22).

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme22.png}
\caption{Scheme 22: (i) CdCl\textsubscript{2}, n-BuBr, Mg, THF, reflux, 30 min, 64%; (ii) 97\% H\textsubscript{2}SO\textsubscript{4}, CH\textsubscript{3}OH, reflux, 30 min, 64\%; (iii) \textit{Pseudomonas putida} ATCC 12633, H\textsubscript{2}O, 0 °C, 24 h, 80\%.
\end{figure}
\end{center}
Kosaka’s approach (2002)\textsuperscript{49}

Kosaka et al. have utilized camphorsultam dichlorophthalic acid (76) for enantio-resolution of racemic alcohol as key step in 3-butylphthalide (1) synthesis. Thus, racemic alcohol 75 was esterified with chiral auxiliary 76 to give diastereomeric mixture of esters, which were separated by HPLC to provide optically pure ester 77 in 49\% yield. Enantiopure diol 78 was obtained by treating ester 77 with methanolic KOH. Selective oxidation of primary alcohol in 78 followed by lactol formation in a single step was achieved with Ir catalyst 79 to afford 3-butylphthalide (1) in 99\% ee (Scheme 23).

\[ \text{OH} \quad \text{C}_4\text{H}_9 \quad \text{OTBDPS} \quad + \quad \text{X}_c\text{-H} \quad \overset{i}{\rightarrow} \quad \text{OH} \quad \text{C}_4\text{H}_9 \quad \text{OTBDPS} \quad \overset{\text{ii}}{\rightarrow} \]

\[ \text{OH} \quad \text{C}_4\text{H}_9 \quad \text{OH} \quad \overset{\text{iii}}{\rightarrow} \quad \text{3-Butylphthalide} \]

\[ X_c\text{-H} = \]

\[ \text{76} \]

\[ \text{HN} \quad \text{Ir} \quad \text{O} \quad \text{79} \]

\textbf{Scheme 23:} (i) DCC, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 18 h, HPLC separation, 49\%; (ii) KOH, CH\textsubscript{3}OH, 16 h, 99\%; (iii) Ir catalyst 79, acetone, 25 °C to 50 °C, 48 h, 84\%.

List’s approach (2010)\textsuperscript{50}

List et al. have achieved the synthesis of 3-butylphthalide (1) by employing kinetic resolution as the key reaction. These authors have developed a new spirocyclic
phosphoric acid catalyst [(S)-STRIP (81)], for kinetic resolution of homoaldol 80 to afford chiral alcohol 82 in 34% yield and 95% ee. Jones oxidation of chiral alcohol 82 provided access to 3-butylphthalide (1) in 85% yield (Scheme 24).

![Scheme 24: (i) (S)-STRIP (81), CH₂Cl₂, 4 A° MS, 25 °C, 6 h, 34%; (ii) CrO₃, conc. H₂SO₄, acetone:water (3:1), 0 °C, 1 h, 85%.](image)

### 2.2.3 Present Work

#### 2.2.3.1 Objective

Even though few methods have been reported for the synthesis of 3-butylphthalide (1), they suffer from certain limitations such as use of chiral auxiliary, expensive and exotic reagents, low overall yields, etc. In this context, a more practical method for the synthesis of 3-butylphthalide (1) is highly desirable. In Section I of this Chapter, we have described an elegant method for the synthesis of 3-substituted chiral phthalide derivatives 51a-z. In continuation of the work on Os-catalyzed oxidative cyclization of o-cyano alkenes, a short synthesis of two natural products namely (-)-matteucen C (62) and 3-butylphthalide (1) is described in this section. 51
Retrosynthetic analysis of (-)-matteucen C (62) reveals that α-cyanostilbene derivative (85) could serve as the key intermediate for the oxidative cyclization leading to the synthesis of (-)-matteucen C (62). α-Cyanostilbene derivative (85) can in turn be obtained from α-bromobenzaldehyde (83) (Fig. 13).

Similarly, we envisaged that 3-butylphthalide (1) could be obtained by means of Barton-McCombie deoxygenation of phthalide 51w. The required phthalide 51w could be prepared by means of oxidative cyclization of α-cyanostyrene 50w. The α-cyanostyrene 50w could in turn be obtained from α-bromobenzaldehyde (66) (Fig. 14).

**Fig. 13**: Retrosynthetic analysis of (-)-matteucen C (62)

**Fig. 14**: Retrosynthetic analysis of 3-butylphthalide (1)
2.2.4 Results and Discussion

(a) First Enantioselective Synthesis of (-)-Matteucen C (62)

The complete synthetic sequence for (-)-matteucen C (62), wherein Os-catalyzed CN-assisted oxidative cyclization of o-cyanostilbene derivative (85) constitutes a key step for the introduction of chirality, is presented in Scheme 25.

Accordingly, the synthesis of (-)-matteucen C (62) was undertaken starting from o-bromobenzaldehyde derivative 83, which on subjecting to Wittig olefination \([\text{PhCH}_2\text{Ph}_3\text{P}^\text{T}, n-\text{BuLi}, \text{THF}]\) gave \((E)\)-o-bromostilbene derivative 84 in 82% yield. Two doublets at \(\delta\ 6.99\ (d, J = 16.1\ \text{Hz}, 1\text{H})\) and 7.52 (d, \(J = 16.1\ \text{Hz}, 1\text{H}\) integrating for one proton each in the \(^1\text{H}\) NMR spectrum of 84 accounted for olefinic protons. It was further supported by the typical olefinic carbon signals at \(\delta\ 127.9\) and 128.6 in its \(^{13}\text{C}\) NMR spectrum (Fig. 15).
Fig. 15: $^1$H and $^{13}$C NMR spectra of o-bromostilbene derivative 84

o-Bromostilbene derivative 84 was then converted to o-cyanostilbene derivative 85 using Rosenmund-von Braun reaction [CuCN, DMF, reflux, 83%]. The formation of the o-cyanostilbene derivative 85 was confirmed by the appearance of CN carbon at $\delta$ 115.7 in its $^{13}$C NMR spectrum. Its IR spectrum displayed a sharp CN stretching vibrational frequency at 2216 cm$^{-1}$ (Fig. 16).
Fig. 16: $^{13}$C NMR and IR spectra of o-cyanostilbene derivative 85

o-Cyanostilbene derivative 85 was then subjected to CN-assisted one-pot oxidative cyclization using AD-mix-$\beta$ process to give chiral phthalide 86 in 93% yield and 99% ee. The $^1$H, $^{13}$C NMR and IR spectra of 86 confirmed the formation of phthalide (Fig. 17). Thus, the methine protons attached to lactone moiety and hydroxyl group resonated at $\delta$ 4.77 (d, $J = 6.4$ Hz, 1H) and 5.45 (d, $J = 6.4$ Hz, 1H) respectively in its $^1$H NMR spectrum. It was further substantiated by the appearance of carbonyl carbon [-($\text{C}=\text{O})$-O-] signal at $\delta$ 169.8 in its $^{13}$C NMR spectrum. Its IR spectrum also exhibited a characteristic lactone carbonyl absorption band at 1752 cm$^{-1}$. 

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### Table 1: HPLC Analysis of Phthalide 86

<table>
<thead>
<tr>
<th>No</th>
<th>Ret. Time (min)</th>
<th>Height (µ AU)</th>
<th>Area (µ AU² min)</th>
<th>Rel. Area (%)</th>
<th>Amount (%)</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.27</td>
<td>40895.238</td>
<td>30456.124</td>
<td>99.36</td>
<td>n. a.</td>
<td>BMB</td>
</tr>
<tr>
<td>2</td>
<td>20.40</td>
<td>2196.930</td>
<td>195.138</td>
<td>0.64</td>
<td>n. a.</td>
<td>BMB</td>
</tr>
</tbody>
</table>

**Fig. 17:** $^1$H, $^{13}$C NMR spectra and HPLC chromatogram of phthalide 86
The enantiomeric excess of chiral phthalide 86 was determined to be 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 18.27 min (99.36%) and 20.40 min (0.64%) (Fig. 17).

Finally, demethylation of chiral phthalide 66 was achieved with BBr$_3$ in CH$_2$Cl$_2$ that afforded (-)-matteucen C (62) in 69% yield with 99% ee. The optical rotation of the target molecule was found to be $[\alpha]^{D}_{25}$ -54.16 (c 1.0, CH$_3$OH). The formation of (-)-matteucen C (62) was confirmed by the appearance of two doublets at $\delta$ 4.94 (t, $J$ = 4.8 Hz, 1H) and 5.45 (d, $J$ = 4.0 Hz, 1H) in its $^1$H NMR spectrum corresponding to the methine protons attached to benzylic hydroxyl group and lactone moiety respectively (Fig. 18). The corresponding methine carbons resonated at $\delta$ 72.6 and 81.7 in its $^{13}$C NMR spectrum. The spectral data of (-)-matteucen C (62) were in complete agreement with the reported values.$^{34}$

![Fig. 18: $^1$H NMR spectrum of (-)-matteucen C (62)](image_url)
(b) Facile Enantioselective Synthesis of 3-Butylphthalide (1)

The synthetic scheme for 3-butylphthalide (1), wherein Os-catalyzed CN-assisted oxidative cyclization of o-cyanostyrene 50w constitutes a key step for the introduction of chirality, is shown in Scheme 26.

Scheme 26: (i) NaHMDS, THF, -78 °C to 25 °C, 14 h, 82%; (ii) CuCN (3.5 equiv), dry DMF, reflux, 14 h, 87%; (iii) AD-mix-β, tert-BuOH:THF:H2O (0.5:0.5:1), 25 °C, 7 h, 93%; (iv) (a) 1,1-thiocarbonyldiimidazole, DMAP (10 mol%), CH2Cl2, 18 h; (b) AIBN (10 mol%), Bu3SnH, toluene, reflux, 15 min, 86%.

The present synthesis of 3-butylphthalide (1) commenced from commercially available o-bromobenzaldehyde (66), which on subjecting to Julia-Kocienski olefination52 with butyl sulfone 87 gave (E)-2-bromoalkene 52w in 82% yield. The formation of (E)-2-bromoalkene 52w was confirmed from its 1H NMR spectrum, which showed a doublet at δ 6.69 (d, J = 15.6 Hz, 1H) and a triplet of doublet at δ 6.15 (td, J = 6.9, 15.6 Hz, 1H) corresponding to trans-olefinic protons of alkene 52w; it was further confirmed by its 13C NMR spectrum, which displayed typical carbon signals at δ 127.4 and 128.8 corresponding to olefinic carbons (Fig. 19).
(E)-2-Bromoalkene 52w was then converted to o-cyanoalkene derivative 50w using Rosenmund-von Braun reaction [CuCN, DMF, reflux, 87%]. Its $^1$H NMR spectrum showed characteristic doublet at $\delta$ 6.74 (d, $J = 15.3$ Hz, 1H) and a triplet of doublet at $\delta$ 6.43 (dt, $J = 6.8, 15.3$ Hz, 1H), corresponding to trans-olefinic protons of alkene 50w. Its $^{13}$C NMR spectrum showed a characteristic carbon signal for CN carbon at $\delta$ 117.9 confirming the formation of o-cyanoalkene 50w (Fig. 20). Its IR spectrum displayed a sharp CN stretching vibrational frequency at 2219 cm$^{-1}$. 

Fig. 19: $^1$H and $^{13}$C NMR spectra of (E)-2-bromoalkene 52w
o-Cyanoalkene 50w was then subjected to CN-assisted one-pot oxidative cyclization using AD-mix-β process to give chiral phthalide 51w in 93% yield and 97% ee. The $^1$H, $^{13}$C NMR and IR spectra of 51w confirmed the formation of phthalide 51w (Fig. 21). The methine proton attached to lactone moiety resonated at δ 5.40 (d, $J = 3.6$ Hz, 1H) in its $^1$H NMR spectrum. It was further substantiated by the appearance of carbonyl carbon [-(C=O)-O-] signal at δ 170.5 in its $^{13}$C NMR spectrum. Its IR spectrum exhibited a characteristic lactone carbonyl absorption band at 1752 cm$^{-1}$.
Fig. 21. $^1$H, $^{13}$C NMR and IR spectra of phthalide 51w
The optical purity of chiral phthalide 51w was determined to be 97% ee from $^1$H NMR analysis of the corresponding Mosher’s ester 88 (Fig. 22) (see experimental section for details).

![1H NMR spectrum of Mosher’s ester 88](image)

**Fig. 22:** $^1$H NMR spectrum of Mosher’s ester 88

Finally, Barton-McCombie protocol$^{53}$ was utilized for deoxygenation of alcohol 51w, in a two-step reaction sequence: (i) xanthate formation of alcohol 51w (1,1-thiocarbonyldiimidazole, DMAP); (ii) followed by reduction of formed xanthate (Bu$_3$SnH, AIBN) afforded 3-butylphthalalde (1) in 86% yield. The $^1$H NMR spectrum of 3-butylphthalalde (1) showed typical proton signals at $\delta$ 5.46 (dd, $J = 4.3, 7.9$ Hz, 1H), 1.68-1.86 (m, 1H) and 1.97-2.07 (m, 1H) corresponding to the methine proton attached to lactone moiety and homobenzylic protons respectively. Its $^{13}$C NMR spectrum showed a characteristic carbonyl resonance of lactone [-$(C=O)-O-]$ at $\delta$ 170.3 (Fig. 23). The ee of 3-butylphthalalde (1) was found to be 97% based on comparison of its optical rotation with the reported value $[[\alpha]^D_{25} -67.0 (c$ 1.15,
CHCl₃); lit.⁴⁹ [α]D²⁵ -64.7 (c 1.06, CHCl₃). The spectral data of 3-butylphthalide (1) were in complete agreement with the reported values.⁴⁶-⁵¹

Fig. 23: ¹H and ¹³C NMR spectra of 3-butylphthalide (1)

2.2.5 Conclusion

A short and an efficient enantioselective synthesis of (-)-mateuucen C (62) and 3-butylphthalide (1) has been achieved in four linear steps (44 % overall yield, 99% ee and 57% overall yield, 97% ee respectively). Synthesis of (-)-mateuucen C (62) was achieved for the first time, thereby confirming its structural and stereochemical
assignments. The CN-assisted one-pot oxidative cyclization of o-cyanoalkene derivatives 85 and 50w was used as the key reaction, which proceeded to give high enantioselectivity.

2.2.6 Experimental Section

(E)-2-Bromo-1, 5-dimethoxy-3-styrylbenzene (84)

To a stirred solution of benzyltriphenylphosphonium iodide (2.1 g, 4.5 mmol) in THF was added n-butyllithium in hexane (2.8 mL, 4.5 mmol). The solution was stirred for 30 min at 0 °C followed by the addition of 2-bromobenzaldehyde (83) (1 g, 4.1 mmol) in THF dropwise via syringe at the same temperature and the reaction mixture was allowed to stir for 90 min at 25 °C (monitored by TLC). It was then cooled to 0 °C, diluted with sat. NH₄Cl (25 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (90:10) as an eluent] affording (E)-2-bromostyrene derivative 84 (1.12 g) as a gum.

Yield: 86%; colorless gum; IR (CHCl₃, cm⁻¹): υmax 669, 769, 1216, 1384, 1468, 1580, 2098, 3020; ¹H NMR (200 MHz, CDCl₃): δ 3.86 (s, 3H), 3.89 (s, 3H), 6.42 (d, J = 2.7 Hz, 1H), 6.99 (d, J = 16.1 Hz, 1H), 7.26-7.40 (m, 3H), 7.52 (d, J = 16.1 Hz, 1H), 7.53-7.55 (m, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 55.3, 56.1, 98.9, 102.4, 105.1, 126.8, 127.9, 128.0, 128.6, 131.5, 136.9, 138.5, 156.7, 159.4; Analysis: C₁₆H₁₅BrO₂ requires C, 60.21; H, 4.74; found: C, 60.08; H, 4.59%.
2, 4-Dimethoxy-6-styrylbenzonitrile (85)

$\alpha$-Bromostilbene derivative 84 (1 g, 3.1 mmol) was taken up in dry DMF (10 mL) and CuCN (0.83 g, 9.3 mmol) was added and the mixture refluxed under N$_2$ for 18 h (monitored by TLC). The reaction mixture was then cooled to 25 °C and then diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na$_2$SO$_4$ and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] to give $\alpha$-cyanostilbene derivative 85 (0.7 g).

**Yield:** 83%; colorless solid; **mp:** 147-148 °C; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 694, 831, 953, 1045, 1073, 1150, 1203, 1326, 1460, 1570, 1595, 2216; $^1$H **NMR** (400 MHz, CDCl$_3$): $\delta$ 3.90 (s, 6H), 6.34 (d, $J = 2.3$ Hz, 1H), 6.80 (d, $J = 2.3$ Hz, 1H), 7.20 (d, $J = 16.4$ Hz, 1H), 7.26-7.30 (m, 1H), 7.32-7.38 (m, 3H), 7.55 (d, $J = 7.4$ Hz, 2H); $^{13}$C **NMR** (100 MHz, CDCl$_3$): $\delta$ 55.6, 56.0, 94.1, 97.4, 101.4, 115.7, 124.4, 127.2, 128.8, 133.5, 136.1, 143.4, 163.2, 163.9; **Analysis:** C$_{17}$H$_{15}$NO$_2$ requires C, 76.96; H, 5.70; N, 5.28; found: C, 76.92; H, 5.68; N, 5.24%.

(R)-3-((R)-Hydroxy(phenyl)methyl)-5,7-dimethoxyisobenzofuran-1-(3H)-one (86)

A 50 mL RB flask was charged with K$_3$Fe(CN)$_6$ (1 g, 3 mmol), K$_2$CO$_3$ (414 mg, 3 mmol), tert-BuOH (2.5 mL), THF (2.5 mL) and H$_2$O (5 mL) and stirred for 10 min. Subsequently, (DHQD)$_2$PHAL (8 mg, 1 mol%) and K$_2$OsO$_4\cdot$2H$_2$O (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, $\alpha$-cyanostilbene derivative 85 (265 mg, 1 mmol) was added and allowed to stir for 7 h at 25 °C. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 °C. The organic layer was separated, aqueous layer extracted

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with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] gave 86 (221 mg).

**Yield:** 93%; colorless solid; **mp:** 170-172 °C; \( [\alpha]^{25}D - 77.56 \) (c 1.15, CHCl₃); 99% ee from chiral HPLC analysis (Chiracel OJ-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 18.27 min (99.36%) and 20.40 min (0.64%); IR (CHCl₃, cm⁻¹): \( \nu_{\text{max}} \) 698, 759, 1041, 1336, 1461, 1625, 1754, 2981, 3018, 3444; \(^1\)H NMR (500 MHz, CD₃OD): \( \delta \) 3.61 (s, 3H), 3.84 (s, 3H), 4.77 (d, \( J = 6.4 \) Hz, 1H), 5.45 (d, \( J = 6.4 \) Hz, 1H), 5.78 (d, \( J = 1.7 \) Hz, 1H), 6.35 (d, \( J = 1.7 \) Hz, 1H), 7.29-7.32 (m, 5H); \(^1\)C NMR (125 MHz, CDCl₃+CD₃OD): \( \delta \) 56.1, 76.0, 83.9, 99.9, 102.9, 107.6, 128.2, 128.8, 129.0, 139.2, 152.0, 159.9, 167.1, 169.8; HRMS (ESI) m/z calcld for C₁₇H₁₆O₅ [M + Na]⁺: 323.0890, found: 323.0850; **Analysis:** C₁₇H₁₆O₅ requires C, 67.99; H, 5.37; found: C, 67.85; H, 5.29%.

**(-)-5, 7-Dihydroxy-3-((R)-hydroxy(phenyl)methyl)isobenzofuran-1(3H)-one:** [(-)-Matteucen C] (62)

To a solution of phthalide 86 (0.17 mmol, 50 mg) in CH₂Cl₂ (5 mL) at -78 °C was added BBr₃ (1.36 mL, 1.36 mmol, 1 M in CH₂Cl₂) over 10 min. The reaction mixture was allowed to warm to 25 °C and then stirred for 24 h. It was quenched with sat. aq. NaHCO₃ (5 mL). The aqueous layer washed with CH₂Cl₂ and extracted with ethyl acetate (3 x10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhyd. Na₂SO₄. After concentration, the crude product was purified by silica gel column chromatography to give 62 (31 mg).

**Yield:** 68%; colorless powder; **mp:** 135-147 °C; \( [\alpha]^{25}D - 54.16 \) (c 1.0, CH₃OH); IR (CHCl₃, cm⁻¹): \( \nu_{\text{max}} \) 691, 710, 1169, 1615, 1684, 1725, 3364; \(^1\)H NMR (500 MHz,
DMSO-\(d_6\)): \(\delta\) 4.94 (t, \(J = 4.8\) Hz, 1H), 5.44 (d, \(J = 4.0\) Hz, 1H), 5.73 (d, \(J = 4.8\) Hz, 1H), 6.23 (d, \(J = 1.8\) Hz, 1H), 6.25 (d, \(J = 1.8\) Hz, 1H), 7.27-7.36 (m, 5H), 10.30 (s, 1H), 10.33 (s, 1H); \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta\) 72.6, 81.7, 101.1, 102.3, 104.2, 126.9, 127.3, 127.6, 140.7, 151.5, 157.6, 163.9, 167.7; Analysis: C\(_{15}\)H\(_{12}\)O\(_5\) requires C, 66.17; H, 4.44; found: C, 66.09; H, 4.39%.

\((E)-1\)-Bromo-2-(pent-1-enyl)benzene (52w)

To a stirred solution of sulfone \(87\) (1 g, 3.78 mmol) in dry THF (20 mL) at -78 °C under N\(_2\) atmosphere was added drop-wise NaHMDS (4.15 mL, 4.15 mmol), the mixture was stirred for 30 min followed by addition of neat \(o\)-bromobenzaldehyde (66) (0.3 mL, 5.6 mmol). After being stirred for 3 h at -78 °C, the mixture was allowed to warm slowly to 25 °C and stirred for 10 h, finally quenched with H\(_2\)O. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic extracts were dried over anhyd. Na\(_2\)SO\(_4\) and concentrated under reduced pressure to get the crude alkene, which was purified by column chromatography on silica gel with pet. ether:EtOAc (95:5) to give pure \((E)-o\)-bromoalkene 52w (0.700 g, 82%).

**Yield:** 82%; colorless oil; IR (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 671, 757, 929, 1025, 1216, 1435, 1465, 1588, 1647, 2870, 2929; \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 0.97 (t, \(J = 7.3\) Hz, 3H), 1.47-1.54 (m, 2H), 2.18-2.29 (m, 2H), 6.15 (td, \(J = 6.9, 15.6\) Hz, 1H), 6.69 (d, \(J = 15.6, 1H\)), 7.04 (dt, \(J = 1.8, 7.6\) Hz, 1H), 7.22 (t, \(J = 7.6\) Hz, 1H), 7.44-7.53 (m, 2H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 13.7, 22.2, 35.2, 123.4,126.8, 127.4, 128.1, 128.8, 132.8, 134.1, 137.7; Analysis for C\(_{11}\)H\(_{13}\)Br requires: C, 58.69; H, 5.82%; found: C, 58.47; H, 5.69%.

\((E)-2-\text{(Pent-1-en-1-yl)benzonitrile (50w)}\)

\(o\)-Bromoalkene 52w (0.7 g, 3.1 mmol) was taken up in dry DMF (10 mL) and CuCN (0.83 g, 9.3 mmol) was added and the mixture refluxed under N\(_2\) for 14 h (monitored
by TLC). The reaction mixture was then cooled to 25 °C and then diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to get the crude o-cyanoalkene, which was purified by column chromatography on silica gel with pet. ether:EtOAc (80:20) to give pure o-cyanoalkene 50w (0.461 g, 87%).

**Yield:** 87%, colorless solid; **mp:** 126-128 °C; **IR** (CHCl₃, cm⁻¹): νmax 756, 857, 974, 1037, 1095, 1184, 1202, 1216, 1251, 1275, 1291, 1319, 1347, 1368, 1393, 1444, 1477, 1573, 1607, 1640, 1716, 2219, 2984, 3023; **¹H NMR** (200 MHz, CDCl₃): δ 0.98 (t, J = 7.3 Hz, 3H), 1.48-1.60 (m, 2H), 2.22-2.33 (m, 2H), 6.43 (dt, J = 6.8, 15.3 Hz, 1H), 6.74 (d, J = 15.3 Hz, 1H), 7.25 (dd, J = 15.3, 1.4 Hz, 1H), 7.45-7.62 (m, 3H); **¹³C NMR** (50 MHz, CDCl₃): δ 13.7, 22.2, 35.2, 110.5, 117.9, 125.2, 126.0, 126.8, 132.5, 132.7, 136.4, 141.1; **Analysis:** C₁₂H₁₃N requires C, 84.17; H, 7.65; N, 8.18; found: C, 84.14; H, 7.61; N, 8.15%.

**(R)-3-((R)-1-Hydroxybutyl)isobenzofuran-1(3H)-one (51w)**

A 50 mL RB flask was charged with K₃Fe(CN)₆ (1 g, 3 mmol), K₂CO₃ (414 mg, 3 mmol), tert-BuOH (2.5 mL), THF (2.5 mL) and H₂O (5 mL) and stirred for 10 min. Subsequently, (DHQD)₂PHAL (8 mg, 1 mol%) and K₂OsO₄·2H₂O (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, o-cyanoalkene 50w (172 mg, 1 mmol) was added and allowed to stir for 7 h at 25 °C. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 °C. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to yield the crude
product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (75:25) as an eluent] gave phthalide 51w (0.191 g, 93%).

**Yield:** 93%; colorless solid; **mp:** 103-109 ºC; [α]D 25 -76.89 (c 1, CHCl3); 97% ee by Mosher’s ester analysis; **IR** (CHCl3, cm−1): νmax 694, 728, 1080, 1212, 1287, 1467, 1618, 1752, 2873, 2959, 3433; **1H NMR** (200 MHz, CDCl3): δ 0.93 (t, J = 6.8 Hz, 3H), 1.44-1.72 (m, 4H), 1.97 (br s, 1H), 3.99 (br s, 1H), 5.40 (d, J = 3.6 Hz, 1H), 7.51-7.57 (m, 2H), 7.65-7.73 (m, 1H), 7.87-7.92 (m, 1H); **13C NMR** (50 MHz, CDCl3): δ 13.9, 18.8, 34.9, 71.9, 83.2, 122.4, 125.6, 126.6, 129.2, 134.0, 147.2, 170.5; **Analysis:** C12H14O3 requires C, 69.88; H, 6.84; found: C, 69.82; H 6.81%.

**Mosher’s ester of (R)-3-((R)-1-Hydroxybutyl)isobenzofuran-1(3H)-one (88)**

A two-neck 10 mL flask with septum was charged with (38 mg, 0.18 mmol) N,N’-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH2Cl2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 ºC for 10 min and a solution of alcohol 51w (34 mg, 0.16 mmol) in CH2Cl2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (R)-α-methoxy-α-trifluoromethylphenyl acetic acid (42 mg, 0.176 mmol) in CH2Cl2 (2 mL). The reaction mixture was then stirred at 0 ºC for additional one hour and then at room temperature for overnight. The reaction mixture was then diluted with CH2Cl2 (50 mL), washed with saturated NaHCO3 solution (50 mL), dried over anhyd. Na2SO4 and then concentrated under reduced pressure to get Mosher’s ester 88 (53 mg, 80%) as a thick syrup.

**Yield:** 80%; [α]D 25 -42.5 (c 0.4, CHCl3); **IR** (CHCl3, cm−1): νmax 650, 737, 1016, 1154, 1243, 1410, 1496, 1644, 1754, 2255, 2851, 2930, 2951,3069, 3156; **1H NMR** (400 MHz, CDCl3): δ 0.93 (t, J = 6.8 Hz, 3H), 1.26-1.41 (m, 2H), 1.73-1.85 (m, 2H), 3.16 (s, 3H), 5.56 (d, J = 3.6 Hz, 1H), 5.63-5.71 (m, 1H), 7.17-7.35 (m, 5H), 7.46-7.52 (m,
2H), 7.67 (td, J = 1.13, 7.4 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.1, 19.3, 33.8, 37.5, 49.9, 80.1, 92.8 (d, J = 36.3 Hz), 123.8 (d, J = 271.4 Hz), 125.8, 127.5, 128.1, 129.1, 131.9, 137.2, 148.1, 165.2, 170.6; **Analysis:**

$\text{C}_{23}\text{H}_{23}\text{F}_{3}\text{O}_{4}$ requires C, 65.71; H, 5.51; found: C, 65.62; H, 5.34%.

**S-3-Butylisobenzofuran-1(3H)-one: [3-Butylphthalide] (1)**

Under a nitrogen atmosphere, 1,1-thiocarbonyldiimidazole (233 mg, 1.818 mmol) was added to a solution of 51w (250 mg, 1.212 mmol) and DMAP (22 mg, 0.121 mmol) in CH$_2$Cl$_2$ (10 mL). After stirring for 18 h at room temperature, solvent was removed *in vacuo*. To this were added AIBN (20 mg, 0.121 mmol) and tributyltin hydride (1.6 ml, 6.06 mmol) in toluene (15 mL) and the mixture was refluxed for 15 min. It was then diluted with ethyl acetate and successively washed with water and brine. The organic layer was dried with anhyd. Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was chromatographed twice on silica gel (pet. ether:EtOAc 80:20) to give butylphthalide (163 mg, 86%).

**Yield:** 86%; colourless oil; [α]$^D_{25}$ -67.0 (c 1.15, CHCl$_3$); lit.$^{49}$ [α]$^D_{25}$ -64.7 (c 1.06, CHCl$_3$); **IR** (CHCl$_3$): 780, 1346, 1465, 1526, 1716, 2932 cm$^{-1}$; **$^1$H NMR** (200 MHz, CDCl$_3$): δ 0.88-0.95 (m, 3H), 1.32-1.53 (m, 4H), 1.68-1.86 (m, 1H), 1.97-2.07 (m, 1H), 5.46 (dd, J = 4.3, 7.9 Hz, 1H), 7.42 (dd, J = 1.13, 7.6 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.66 (td, J = 1.13, 7.4 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$): δ 13.8, 22.5, 26.9, 34.4, 81.3, 121.8, 125.5, 128.9, 133.9, 150.1, 170.3; **Analysis:**

$\text{C}_{12}\text{H}_{14}\text{O}_{2}$ requires C, 75.76; H, 7.42; found: C, 75.72; H, 7.39%.
2.2.7 References


(-)-Matteucen C and 3-Butylphthalide


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