ABSTRACT

The thesis entitled “Enantioselective Synthesis of Bioactive Molecules via Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and CuCN-Mediated Annulations in C-C, C-O Bond Formation” is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to develop useful synthetic methodologies. **Chapter 1** describes the cobalt-catalyzed hydrolytic kinetic resolution of alkoxy epoxides and their application in the asymmetric synthesis of (S,S)-reboxetine, (-)-chloramphenicol and (+)-thiamphenicol. **Chapter 2** deals with the CoCl₂-catalyzed reductive cyclization of nitro cyclic sulphites using NaBH₄ to give the corresponding tetrahydroquinolin-3-ol and its application in the asymmetric synthesis of anachelin H chromophore and 1-[(S)-3-(dimethylamino)-3,4- dihydro-6,7-dimethoxyquinolin-1-(2H)-yl]propan-1-one (S-903). **Chapter 3** presents the synthesis of 3-substituted chiral phthalides using CN-assisted oxidative cyclization of cyano cinnamates and styrene derivatives and its application in the synthesis of (-)-Matteucen C, isocoumarins and alkylidene phthalides. **Chapter 4** describes the CuCN-mediated “one-pot” route to 1-amino-2-naphthalene carboxylic acid derivatives, 3-substituted phthalides and its application in the enantioslective synthesis of Colletotrialide.

**CHAPTER 1**

Cobalt-catalyzed Hydrolytic Kinetic Resolution of Alkoxy Epoxides: A Short Enantioselective Synthesis of (S,S)-Reboxetine, (-)-Chloramphenicol and (+)-Thiamphenicol

Jacobsen’s Hydrolytic Kinetic Resolution (HKR) has emerged as an effective method for obtaining chiral epoxides and 1,2-diols in a highly enantioenriched forms.¹ These compounds are important intermediates in the synthesis of various bioactive molecules.² In view of easy availability of chiral ligands and the simplicity of the reaction conditions with water being used as the nucleophile, HKR is being used extensively for providing several chiral building blocks in the synthesis of biologically active compounds.³ This chapter deals with the development of a novel method in which HKR of two stereocenters in alkoxy epoxides catalyzed by chiral Co(III)(salen)OAc complex can
produce chiral alkoxy epoxides and alkoxy diols. This method is also applied in the asymmetric synthesis of (S,S)-Reboxetine, (-)-Chloramphenicol and (+)-Thiamphenicol. This chapter is divided into three sections.

Section I: Cobalt-catalyzed Hydrolytic Kinetic Resolution of Alkoxy Epoxides

For the first time, HKR of racemic *syn*-* or *anti-* alkoxy epoxide derivatives was carried out. In this strategy, the relative stereochemistry between the alkoxy and the epoxide functions is established prior to the HKR step and thus a single asymmetric reaction is employed to form compounds with two asymmetric centres.\(^4\)

**Table 1:** Co-catalyzed HKR of *syn*-alkoxy epoxides

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Alkoxy epoxide (±)-1a-k</th>
<th>Alkoxy Epoxide 2a-k</th>
<th>Alkoxy Diol 3a-k</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>R X</td>
<td>yield (%)(^a) ee (%)(^b)</td>
<td>yield (%)(^a) ee (%)(^b,c)</td>
</tr>
<tr>
<td>a</td>
<td>H OMe</td>
<td>48 97</td>
<td>47 98</td>
</tr>
<tr>
<td>b</td>
<td>OMe OMe</td>
<td>47 98</td>
<td>46 97</td>
</tr>
<tr>
<td>c</td>
<td>Me OMe</td>
<td>44 97</td>
<td>45 98</td>
</tr>
<tr>
<td>d</td>
<td>Br OMe</td>
<td>45 97</td>
<td>42 98</td>
</tr>
<tr>
<td>e</td>
<td>SMe OMe</td>
<td>47 98</td>
<td>46 97</td>
</tr>
<tr>
<td>f</td>
<td>H OBn</td>
<td>45 98</td>
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<td>g</td>
<td>OMe OBn</td>
<td>49 96</td>
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<td>h</td>
<td>Me OBn</td>
<td>48 96</td>
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<tr>
<td>i</td>
<td>Cl OBn</td>
<td>45 95</td>
<td>42 98</td>
</tr>
<tr>
<td>j</td>
<td>Br OBn</td>
<td>44 98</td>
<td>47 98</td>
</tr>
<tr>
<td>k</td>
<td>SMe OBn</td>
<td>48 96</td>
<td>47 97</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after column chromatographic purification. \(^b\) ee determined by chiral HPLC. \(^c\) ee determined by Mosher’s ester analysis.

The racemic *syn*-* and *anti-* alkoxy epoxides, the substrates for HKR, were efficiently prepared in highly diastereoselective manner\(^5\) from the corresponding (*E*)- and (*Z*)-allylic alcohols respectively, involving essentially a two-step reaction sequence of NBS-
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bromination in the presence of MeOH or BnOH, as the case may be, followed by treatment with base to form the corresponding racemic epoxides. In this section, we have described a flexible, novel method that employs HKR of racemic alkoxy epoxides to generate two stereocentres of high optical purities in a single step. Thus, when HKR of racemic syn-alkoxy epoxides 1a-k was performed with (R,R)-Co(III)(salen)OAc complex (0.5 mol%) and H₂O (0.48 equiv.), the corresponding chiral epoxides 2a-k and diols 3a-k were isolated in high yields and optical purity (Table 1). Similarly, anti-alkoxy epoxides 4a-b when subjected to (S,S)-Co(III)(salen)OAc-catalyzed HKR, produced chiral anti-alkoxy epoxides 5a-b and corresponding diols 6a-b with high enantio purity (Table 2).

Table 1: Enantioselective Synthesis of (S,S)-Reboxetine

Reboxetine, 2-[α-(2-ethoxyphenoxy) phenylmethyl]morpholine 7 is a specific norepinephrine reuptake inhibitor (NRI) widely studied for its pharmacological properties. In this section, we describe a concise enantioselective synthesis of (S,S)-reboxetine 7 using two stereocentered HKR of alkoxy epoxide. Our synthesis of (S,S)-reboxetine 7 started with the benzyloxy bromination of cinnamyl alcohol 8 using NBS and BnOH to give benzyloxy bromoalcohol 9 in 85% yield. Benzyloxy bromoalcohol 9 on treatment with NaOH powder, in THF afforded racemic syn-benzyloxy epoxide 1a in
88% yield, which was then subjected to HKR using \((R,R)\)-Co(III)(salen)OAc to furnish the chiral benzyloxy epoxide 2a in 45% chemical yield and 98% ee along with the corresponding benzyloxy diol 3a in 44% yield and 98% ee.

\[
\begin{align*}
\text{8} & \xrightarrow{i} \text{9} \\
\text{(±)-1a \((2SR, 3SR)\)} & \xrightarrow{iii} \text{3a}\quad 44\% \text{ yield} \quad 98\% \text{ ee} \\
\text{11} & \xrightarrow{v} \text{10} \\
\text{12 \(R = Bn\)} & \xrightarrow{vii} \text{13 \(R = H\)} \\
\text{14 \(R = Boc\)} & \xrightarrow{ix} \text{7 \(R = H\)} \\
\end{align*}
\]

Scheme 1: (i) NBS, BnOH, CH\(_3\)CN, 25 °C, 3 h, 85%; (ii) NaOH powder, THF, 25 °C, 2 h, 88%; (iii) \((R,R)\)-Co(III)(salen)OAc (1 mol%), THF, H\(_2\)O (0.48 equiv.), 0 °C, 12 h; (iv) 30% NH\(_4\)OH, MeOH, 25 °C, 12 h, 83%; (v) (a) ClCH\(_2\)COCl, Et\(_3\)N, CH\(_2\)Cl\(_2\), -10 °C; (b) KO'Bu, t-BuOH, 3 h, , 72% ; (vi) (a) Red-Al, dry toluene, 25 °C, then 2N NaOH; (b) (Boc)\(_2\)O, Et\(_3\)N, CH\(_2\)Cl\(_2\), 0 °C, 1 h, 85%; (vii) 10% Pd/C, H\(_2\) (1 atm), MeOH, 25 °C, 12 h, 92%; (viii) (a) CBr\(_4\), PPh\(_3\), imid., CH\(_2\)Cl\(_2\), 25 °C, 2 h; (b) 2-ethoxyphenol, NaH, DMF, 3 h, 72%; (ix) TFA, CH\(_2\)Cl\(_2\), 0 °C, 1 h, 96%.
Both chiral benzyloxy epoxide 2a and azido diol 3a could be readily separated by column chromatographic purification. Regiospecific opening of epoxide 2a with 30% NH₄OH gave amino alcohol 10 in 83% yield, which was condensed with chloroacetyl chloride under basic conditions to afford imide 11 in 72% yield. Imide 11 was reduced to the morpholine derivative in situ which was protected as carbamate 12 in 85% yield using (Boc)₂O. Deprotection of benzyl group in 12 gave the alcohol 13 in 88% yield. The transformation of 13 to (S,S)-reboxetine 7 in 98% ee was achieved in 2-steps (i) conversion of alcohol to bromo derivative followed by nucleophilic displacement with sodium salt of o-ethoxy phenol affording N-Boc protected reboxetine 14 (ii) deprotection of N-Boc with trifluoroacetic acid (Scheme 1).

**Section III: Enantioselective Synthesis of (-)-Chloramphenicol and (+)-Thiamphenicol**

(-)-Chloramphenicol 15 and (+)-thiamphenicol 20 are broad-spectrum antibiotics with a range of biological activities.⁶ While chloramphenicol 15 is active only in its D-threo configuration and is especially effective in the treatment of typhus, dysentery and ocular bacterial infections,⁷ (+)-thiamphenicol 20, a synthetic analogue of chloramphenicol 15, is bacteriostatic for both gram-positive and gram-negative aerobes and for some anaerobes.⁸ In this section, we describe the application of two stereocentered HKR for the stereoselective synthesis of (-)-chloramphenicol 15 and (+)-thiamphenicol 20. Racemic syn-benzyloxy epoxide 1a was subjected to HKR using (R,R)-Co(III)(salen)OAc to furnish the required chiral benzyloxy diol 3a in 44% chemical yield and 98% ee. Selective protection of primary alcohol in diol 3a was achieved using Bu₂SnO and benzyl bromide in 82% yield. Alcohol 16 was then subjected to Appel reaction condition to give anti-benzyloxybromo compound 17, nucleophilic displacement of bromide in 17 to azide 18 was achieved in 80% yield. Deprotection of benzyl ethers and reduction of azide proceeded smoothly under catalytic hydrogenation of 18 followed by acylation with Ac₂O gave triacetate 19. The synthesis of (-)-chloramphenicol (15) was completed by sequences of reactions such as nitration, acid mediated hydrolysis and N-acylation with 76% yield over three steps with 98%ee (Scheme 2).
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The same strategy was extended to the synthesis of (+)-thiamphenicol 20. Our synthesis started with the benzyloxy bromination of 4-(methylthio)cinnamyl alcohol 21 using NBS and BnOH to give benzyloxy bromoalcohol 22 in 84% yield. Racemic syn-benzyloxy epoxide 1f was obtained in 86% yield by subjecting benzyloxy bromoalcohol 22 with NaOH powder in THF, which was then subjected to HKR using (R,R)-Co(III)(salen)OAc to furnish the chiral benzyloxy epoxide 2f in 48% chemical yield and 96% ee along with the corresponding benzyloxy diol 3f in 47% yield and 97% ee. Selective protection of primary alcohol in diol 3f was achieved using Bu₂SnO and benzyl bromide in 82%. Alcohol 23 was then subjected to Appel reaction condition to give anti-benzyloxybromo compound 24, nucleophilic displacement of bromo in 24 to azide 25 was achieved with 78% yield. Deprotection of benzyl ethers and reduction of azide proceeded smoothly under catalytic hydrogenation of 25, followed by acylation with AC₂O gave triacetate 19.

Scheme 2: (i) (R,R)-Co(III)(salen)OAc (1mol%), THF, H₂O (0.48 equiv.), 0 °C, 12 h; (ii) Bu₂SnO, toluene, reflux, 12 h, then BnBr, TBAB, reflux, 20h, 82%; (iii) CBr₄, imid., PPh₃, CH₂Cl₂, 0 °C, 3h, 76%; (iv) NaN₃, DMF, 60 °C, 12h, 80%; (v) (a) 20% Pd(OH)₂/C, MeOH, H₂ (1atm), 25 °C, 12h; (b) Ac₂O, DMAP, pyridine, 94% (for 2 steps); (vi) (a) conc. HNO₃-conc. H₂SO₄, -20°C to 25°C; 1.5 h; (b) aq. 5% HCl, 90 °C; (c) Cl₂CHCO₂Me, 90 °C, 1h, 76% (for 3 steps).
Oxidation of 26 with mCPBA converted the methylsulfanyl group into methyl sulfonyl group which was then subjected to the known reaction sequences such as acid mediated hydrolysis and N-acylation with 78% yield over three steps with 97%ee (Scheme 3).

Scheme 3: (i) NBS, BnOH, CH₃CN, 25 °C, 3 h, 84%; (ii) NaOH powder, THF, 25 °C, 2 h, 86%; (iii) (R,R)-Co(III)(salen)OAc (1 mol%), THF, H₂O (0.48 equiv.), 0 °C, 12 h; (iv) Bu₂SnO, toluene, reflux, 12 h. then BnBr, TBAB, reflux, 18 h, 84%; (v) CBr₄, imidazole, Ph₃P, CH₂Cl₂, 0 °C, 4 h, 76%; (vi) NaN₃, DMF, 60 °C, 12 h, 78%; (vii) (a) 10% Pd/C, MeOH, H₂ (1 atm), 25 °C, 12 h; (b) Ac₂O, DMAP, pyridine, 94%; (viii) (a) mCPBA, CH₂Cl₂; (b) aq. 5% HCl, 90 °C; (c) Cl₂CHCO₂Me, 90 °C, 1 h, 78% (for 3 steps).

CHAPTER 2
Asymmetric Synthesis of Tetrahydroquinolin-3-ols, Anachelin H Chromophore and 1-((S)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-yl)propan-1-one
CoCl₂–NaBH₄ combination is one of the most effective reducing systems, capable of selectively reducing a variety of functional groups including alkene, N₃, CN, etc. when
present alone. This chapter deals with development of a novel method for the synthesis of tetrahydroquinolin-3-ols $31\text{a}-e$ via CoCl$_2$-catalyzed reductive cyclization of cyclic sulphonates followed by its application in the synthesis of anachelin H chromophore and 1-[(S)-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2$H$)-yl]propan-1-one (S-903). This chapter is divided into three sections.

**Section I: A New Route to the Synthesis of (R)-Tetrahydroquinolin-3-ols via CoCl$_2$-catalyzed Reductive Cyclization of Cyclic Sulphonates with NaBH$_4$**

Substituted tetrahydroquinolines display a wide range of physiological activities such as analgesic, antiarrhythmic, cardiovascular, immuno-suppresive, antitumor, antiallergenic, anticonvulsant antifertility and NMDA antagonist activities. This section describes a novel methodology for the synthesis of substituted tetrahydroquinolin-3-ols $31\text{a}-f$ via CoCl$_2$-catalyzed one-pot reduction of cyclic sulphonates $30\text{a}-f$ using NaBH$_4$ as reducing agent.

\[
\text{Scheme 4:} \quad (i) \text{OsO}_4 (0.5 \text{ mol}\%), (\text{DHQ})_2\text{-PHAL} (1 \text{ mol}\%), \text{K}_3\text{Fe(CN)}_6 (3 \text{ equiv.}), \text{K}_2\text{CO}_3 (3 \text{ equiv.}), \text{MeSO}_2\text{NH}_2 (1 \text{ equiv.}), \text{t}-\text{BuOH}:\text{H}_2\text{O} (1:1), 25 ^\circ\text{C}, 24 \text{ h}, 80-95\%; (ii) \text{conc. HNO}_3,\text{CH}_2\text{Cl}_2, 1 \text{ h}, 25 ^\circ\text{C}, 70-81\%; (iii) \text{SOCl}_2,\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2, 0 ^\circ\text{C}, 91-95\%; (iv) \text{CoCl}_2\cdot6\text{H}_2\text{O} (1 \text{ mol}\%), \text{NaBH}_4 (4 \text{ equiv.}), \text{EtOH}, 0 -25 ^\circ\text{C}.
\]

$\alpha,\beta$-Unsaturated esters $27\text{b}-f$, prepared readily from Wittig olefination of the corresponding benzaldehydes, were subjected to Os-catalyzed asymmetric dihydroxylation (ADH) using (DHQ)$_2$-PHAL as ligand to give the corresponding $\alpha$-diols.
28b-f, which on nitration using conc. HNO₃ in CH₂Cl₂ at 25 ºC gave the nitro derivatives 29b-f in high yields. Nitrodiols 29a-f were then smoothly converted into the corresponding cyclic sulphites 30b-f (SOCl₂, Et₃N in CH₂Cl₂) in excellent yields. These cyclic sulphites 30a-f, when subjected to CoCl₂-catalyzed reduction with NaBH₄, the corresponding tetrahydroquinoline derivatives 31a-f were obtained in 78-83% yields. In this reaction, we observed the reduction of multifunctional groups and cyclization, all occurring in a single step (Scheme 4).

Section II: Asymmetric Formal Synthesis of Anachelin H Chromophore

Anachelin H intermediate 32, a secondary metabolite recently isolated from cyanobacterium *Anabaena cylindrica*, which serves as a ligand for iron (siderophores) mediating iron uptake.¹¹a,b In this section, we describe a short formal synthesis of anachelin H chromophore 32, by employing CoCl₂-catalyzed one-pot reductive cyclization of the corresponding cyclic sulphite 30b as the key step (Scheme 5).

![Scheme 5](image)

Catalytic one-pot reduction of cyclic sulphite 30b using CoCl₂·6H₂O (1 mol%) and NaBH₄ (5 equiv.), gave the tetrahydroquinoline derivative 31b in 78% yield and 95% ee. Selective amine protection in 31b was achieved with TsCl to give amide 33 in 82% yield. Chiral amido alcohol 33 was then mesylated (MsCl, Et₃N in CH₂Cl₂) to give 34 and
Abstract

Subsequent displacement of the mesylate with azide anion (NaN₃, DMF) gave azide 35. Finally, azide 35 was subjected to reduction with sodium amalgam in NaH₂PO₄ whereby reduction of both azide and tosylate functions took place efficiently to afford the known intermediate (S)-3-aminotetrahydroquinoline 36 in 76% yield and 95% ee. The conversion of (S)-3-aminotetrahydroquinoline 36 to anachelin H chromophore 32¹¹c has been reported in the literature.

Section III: Asymmetric Synthesis of 1-[(S)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2H)-yl]propan-1-one

Asymmetric synthesis of 1-[(S)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2H)-yl]propan-1-one (37), a positive inotropic agent,¹² is described in this section.

Scheme 6: (i) CoCl₂·6H₂O (1 mol%), NaBH₄, EtOH, 0-25 °C, 78%; (ii) (CH₃CH₂CO)₂O, Et₃N, CH₂Cl₂, 0 °C, 91%; (iii) MsCl, Et₃N, CH₂Cl₂, 0 °C, 10 min; (iv) NaN₃, DMF, 80 °C, 12 h, 91%; (v) H₂ (1 atm) 10% Pd/C, MeOH, 25 °C, 12 h; (vi) HCHO (40 % aq. solution), HCO₂H, 80 °C, 3 h, 73%.

Tetrahydroquinolinol 31b, prepared by the CoCl₂-catalyzed reduction of the corresponding cyclic sulphite 30b, was treated with propionic anhydride to give amido alcohol 38 in 93% yield and 95.5% ee. Alcohol 38 on mesylation (MsCl, Et₃N in CH₂Cl₂) followed by its displacement with azide (NaN₃ in DMF) gave azide 40 in 91% yield.
Finally, azide 40 was reduced to amine 41 \([\text{H}_2 (1 \text{ atm}), 10\% \text{ Pd/C}]\). The \(N, N'\)-dimethylation of amine 41 was achieved by its treatment with formic acid and formaldehyde solution under reflux condition to afford 37 in 73\% yield and 94\% ee (Scheme 6).

CHAPTER 3
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, Isocoumarins and Alkylidenephthalides

Sharpless asymmetric dihydroxylation (ADH) is one of the most effective methods for the preparation of chiral diols, which are important intermediates for the synthesis of various bioactive compounds. This chapter deals with development of a novel method for the synthesis of chiral phthalides (43a-z) via CN-assisted oxidative cyclization of cyano cinnamates followed by its application to the synthesis of (-)-matteucen C, isocoumarins and alkylidenephthalides. This chapter is divided into three sections.

Section I: CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-Substituted Chiral Phthalides

Chiral phthalides [isobenzofuran-1(3\text{H})-ones] comprising of 5-membered lactones are found in a large number of plant products displaying broad and potent biological activities such as anticonvulsant, anesthesia, antiischemic, antiHIV, anticancer and antibiotics.\(^{13}\) The Sharpless’ asymmetric dihydroxylation (AD) of alkenes has emerged as a most reliable method for the preparation of chiral 1,2-diols, widely found in bioactive compounds and pharmaceuticals. Ligand acceleration is central to the efficiency and selectivity of AD catalytic process.\(^{14}\) In this section, we describe a single-step oxidative cyclization of cyanocinnamates and styrene substrates that affords 3-substituted phthalides in high yields via synergetic acceleration of CN and osmate ester groups present in proximity positions. From the course of our study on the construction of 3-substituted tetrahydroquinolin-3-ols via AD process and Co-catalyzed “one-pot” reductive cyclization (\(\text{CoCl}_2-\text{NaBH}_4\)) of nitro cyclic sulfites, we reasoned that subjecting cyano cyclic sulfites to the same reaction conditions should afford synthetically useful benzazepines. To our surprise, when ethyl 2-cyanocinnamate 42a was subjected to a typical AD-mix-\(\beta\) process for 7 h, with THF as co-solvent for better solubility, the
corresponding chiral phthalide $43a$ was obtained exclusively in 99%ee. Encouraged by this result, we examined the scope of the reaction with other cyano cinnamate esters and styrene derivatives $42b-z$. In every case, the reaction proceeded rapidly in 3 to 7 h giving the desired phthalides $43b-z$ in excellent yields and ees (up to 99%). For instance, substrates having halogen, highly electron-rich or electron-deficient substituents on the aromatic ring including 2-naphthyl nuclear system underwent this oxidative cyclization smoothly affording the corresponding phthalides in excellent yields (Scheme 7).

Scheme 7: (i) AD-mix-β, MeSO$_2$NH$_2$, t-BuOH:THF:H$_2$O (0.5:0.5:1), 25 °C, 3 to 7 h.

Section II: First Enantioselective Synthesis of (-)-Matteucen C

Matteucen C (44), isolated from Chinese medicinal herb, is used in the treatment of hemostatics and relieving ostalgia. This section illustrates a practical, first enantioselective synthesis of (-)-matteucen C 44, by employing CN-assisted oxidative cyclization of the corresponding $o$-cyano styrene derivative 47 as the key step. Our approach to the synthesis of (-)-matteucen C 44 commenced with 2-bromo-3,5-dimethoxybenzaldehyde 45, which was subjected to Wittig reaction to afford trans-stilbene 46 in 82% yield. Rosenmund-von Braun reaction was carried out for conversion of bromo stilbene 46 to cyano stilbene 47 using CuCN under reflux condition in DMF. Cyano stilbene 47 was then subjected to AD-mix-β process to give chiral phthalide 48 in 93% yield and 99%ee via CN-assisted “one-pot” oxidative cyclization. Finally, demethylation of chiral phthalide 48 with BBr$_3$ in CH$_2$Cl$_2$ gave (-)-matteucen C in 69% yield and 99% ee (Scheme 8). Thus, an efficient enantioselective synthesis of (-)-matteucen C has been achieved for the first time, confirming its structural and stereochemical assignments using CN-assisted one-pot oxidative cyclization.
SECTION III: A Novel Approach to Isocoumarins and Alkylidenephthalides

Isocoumarins are important secondary metabolites obtained from various fungi and possess a wide range of biological activities.\(^{16}\) The alkylidenephthalides have antispasmodic, herbicidal, and insecticidal activities.\(^ {17}\) In view of the biological activity and synthetic utility as intermediates, we have developed a novel route to synthesize these compounds at ambient conditions using PPh\(_3\) and DEAD. We observed that hydroxyphthalides 49, on treatment with DEAD (1.5 equiv.) and PPh\(_3\) (1.5 equiv.) gave isocoumarins 50 in 84-95% yields. In the case of both electron-donating as well as electron withdrawing substituents on aromatic ring of hydroxyphthalides gave the corresponding isocoumarins in one-pot with excellent yields (Scheme 9).
During the course of our investigation on synthesis of isocoumarins, we observed that simple variation in hydroxyl phthalides 51, led to the formation of biologically active alkylidene phthalides 52 in one-pot up to 92% yield. This transformation holds good for both electron-donating as well as electron withdrawing substituents on aromatic ring of hydroxyphthalides 51 (Scheme 10).

\[
\begin{align*}
\text{Scheme 10:} & \quad (i) \text{PPh}_3 (1.5 \text{ equiv.}), \text{DEAD (1.5 equiv.)}, \text{THF}, \\
& \quad 25 \, ^\circ\text{C}, \, 5 \, \text{h.}
\end{align*}
\]

**CHAPTER 4**

**CuCN-Mediated “One-pot” Route to 1-Amino-2-naphthalenecarboxylic acid Derivatives and 3-Substituted Phthalides: Enantioslective Synthesis of Colletotrialide**

Copper(I) cyanide (CuCN) is a versatile reagent employed in many organic transformations. For example (i) aryl nitriles can be prepared by the cyanation of aryl halides with an excess of CuCN in polar high-boiling solvent such as DMF, nitrobenzene, or pyridine at reflux temperature (Rosenmund-von Braun Reaction) (ii) in the regioselective and stereoselective allylation and conjugate additions (iii) in the palladium coupling of α-lithio amines and aryl iodides. This chapter deals with development of a novel “one-pot” route to 1-amino-2-naphthalenecarboxylic acid derivatives 54 from the corresponding bromo derivatives 53 and 3-substituted phthalides 56 from the corresponding bromo alcohols 55 via CuCN-mediated cascade and tandem reactions respectively. Also included is its application to the enantioselective synthesis of colletotrialide. This chapter is divided into three sections.
Abstract

Section I: CuCN-Mediated “One-pot” Cascade Route to 1-Amino-2-naphthalenecarboxylic Acid Derivatives

1-Amino-2-naphthalenecarboxylic acid derivatives 54 are the key intermediates of dyes and pigments useful in peptide synthesis.18 There are very few methods available in the literature for the direct synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives. Moreover, known methods involve multiple-step sequences and also the process requires consumption of large quantities of hazardous chemicals with longer reaction time constituting less efficiency and narrow substrate scope. During the course of our investigation on Rosenmund-von Braun Reaction (Br – CN exchange) of 53 with CuCN, we observed an annulation strategy to 1-amino-2-naphthalenecarboxylic acid derivatives 54. This prompted us to explore the effectiveness of this “cascade” reaction using CuCN. We thus found that several 1-(2-bromo-phenyl) but-2-ene derivatives 53 when treated with CuCN (3.5 equiv.) in DMF at reflux condition, produced the corresponding 1-amino-2-naphthalenecarboxylic acid derivatives 54 in 78-86% yields (Scheme 11).

\[
\begin{align*}
\text{R} &= \text{H, alkyl, alkoxy, halo, NO}_2, \text{CN, etc.} \\
\text{up to 86% yield} \\
\text{9 examples}
\end{align*}
\]

**Scheme 11:** (i) CuCN (3.5 equiv.), DMF, 150 °C, 12 h.

SECTION II: CuCN-Mediated “One-pot” Synthesis of 3-Substituted Phthalides

Phthalides are versatile building blocks for the synthesis of biologically active compounds and have been proven to be useful in the treatment of circulatory and heart diseases.16 In particular, 3-substituted phthalides are useful intermediates for the synthesis of tri- and tetracyclic natural products, such as anthracycline antibiotics.17 Therefore, significant effort has been focused on synthesizing these organic frameworks. However, known methods involve multiple step sequences and require consumption of large quantities of costly chemicals with narrow substrate scope. During the course of our
investigation on Rosenmund-von Braun Reaction using CuCN, we observed that one-pot conversion of \(o\)-bromobenzyl alcohol derivatives 55 to 3-substituted phthalides 56 (CuCN (3.5 equiv.), DMF, reflux) (Scheme 12) took place. Thus, several \(o\)-bromobenzyl alcohol derivatives 55 with electron-donating as well as electron withdrawing substituents on aromatic ring underwent “one-pot” tandem cyclization and 3-substituted phthalides 56 were produced in high yields.

Scheme 12: (i) CuCN (3.5 equiv.), DMF, 150 °C, 10 h.

Section III: Enantioselective Synthesis of Colletotrialide

Recently a new phthalide, colletotrialide 57 was isolated from the endophytic fungus Colletotrichum sp. 2 which exhibited cytotoxic activity toward the HepG2 cell line.\(^{19}\) This section describes the enantioselective synthesis of colletotrialide 57 via “one-pot” tandem cyclization of \(o\)-bromobenzyl alcohol derivatives 65.

Our complete synthetic sequence for colletotrialide 57, commencing from the precursor aldehyde 58, is shown in Scheme 14. Aldehyde 58 was subjected to Brown allylation using (+)-Ipc2B(allyl)borane at -78 ºC to afford homoallylic alcohol 59 in 89% yield and 95% ee, which was protected as its silyl ether 60 in 96% yield. Regioselective hydroboration and oxidation of olefin 60 resulted in primary alcohol 61 in 84% yield. Aromatic electrophilic bromination of alcohol 61 (NBS, \(\text{CH}_2\text{Cl}_2\)) provided brominated alcohol 62 in 94% yield, which was further converted to the desired ketone 64 in three-step sequence: (i) the primary alcohol function in 62 was oxidized (IBX, DMSO) to provide the corresponding aldehyde 63; (ii) subsequent \(n\)-propyl Grignard addition yielded the corresponding secondary alcohol; (iii) secondary alcohol was oxidized to give ketone 64 using Swern oxidation ((COCl)\(_2\), \(\text{Et}_3\text{N}\), \(\text{CH}_2\text{Cl}_2\)). Deprotection of the silyl group in 64 (TBAF, THF) provided alcohol 65 with 88% yield. Alcohol 65 was subjected
to one-pot tandem cyclization to afford chiral phthalide 66 in 86% yield. Finally selective deprotection of mono methyl ether (AlCl₃) furnished colletotrialide 57 in 74% yield (Scheme 14).

Scheme 13: (i) (+)-Ipc₂B(allyl)borane, Et₂O, -78 °C, 1 h then 1N NaOH, 30% H₂O₂, 89%, 95% ee; (ii) TBDPSCl, Et₃N, DMF, 25 °C, 8 h, 96%; (iii) BH₃.DMS, THF, 25 °C, 2 h then 1N NaOH, 30% H₂O₂, 84%; (iv) NBS, CH₂Cl₂, 25 °C, 2 h, 94%; (v) IBX, DMSO, 25 °C, 2 h, 93%; (vi) (a) C₃H₇Mgl, Et₂O, 25 °C, 3 h; (b) (COCl)₂, Et₃N, CH₂Cl₂, -78 °C, 1 h, 92%; (vii) TBAF, THF, 25 °C, 10 h, 88%; (viii) CuCN (3.5 equiv.), DMF, reflux, 12 h, 86%; (ix) AlCl₃, C₂H₅SH, CH₂Cl₂, 74%.

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Abstract