DEVELOPMENT OF ORGANOCATALYTIC REACTIONS FOR THE ASSEMBLY OF COMPLEX MOLECULES

Chenguang Yu

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DEVELOPMENT OF ORGANOCATALYTIC REACTIONS
FOR THE ASSEMBLY OF COMPLEX MOLECULES

by

CHEN GUANG YU

B.S., Applied Chemistry, Beijing University of Chemical
Technology, 2006

DISSERTATION

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Requirements for the Degree of

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DEVELOPMENT OF ORGANOCATALYTIC REACTIONS FOR THE
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ABSTRACT

Development of efficient organocatalytic reactions for the facile assembly of synthetically and medicinally useful molecules is an important task in modern organic synthesis. Towards this end, my Ph. D. study focuses on the development of novel organocatalytic reactions for the construction of structurally diverse molecular architectures.

A chiral bifunctional amine thiourea as promoter has been developed as an efficient solution to a long standing challenging issue in atropo-enantioselective transesterification of the Bringmann lactones. This organocatalytic approach delivers the first highly enantioselective, high yielding dynamic kinetic resolution process for the preparation of axially chiral biaryl compounds with a broad substrate scope under mild reaction conditions. The higher reaction efficiency attributes to a distinct synergistic activation by
bifunctional amine and thiourea groups from previous reported methods relying on mono activation.

The new reactivity of \( N, O \)-acetals in an aminocatalytic fashion is harnessed for organic synthesis. Unlike widely used strategies requiring the use of acids and/or elevated temperatures, direct replacement of the amine component of the \( N, O \)-acetals by carbon-centered nucleophiles for C-C bond formation is realized under mild reaction conditions. Furthermore, without preformation of the \( N, O \)-acetals, amine catalyzed \textit{in situ} formations of \( N, O \)-acetals are developed. Coupling both reactions into one-pot operation enables to achieve a catalytic process. We demonstrate the employment of simple anilines as promoters for the cyclization-substitution cascade reactions. The process offers an alternative approach to structurally diverse, ‘privileged’ 2-substituted 2\( H \)-chromenes, 1,3-dihydroisobenzofurans and isochromans. The synthetic power of the new process is furthermore shown by its application in the synthesis of natural products and biologically active molecules.

Finally, a chiral amine/Lewis acid synergistically catalyzed cyclization-Michael cascade reaction has also been developed for the construction of chiral \( \gamma,\gamma \)-disubstituted butenolides. More significantly, the binary catalytic system promoted cyclization-Michael-aldol cascade reactions is also applied for the synthesis of (-)-aromdendranediol. The merits of this strategy are not only the employment of simple and cost-effective starting materials but also the enhancement of yields by the synergistic catalysis effect.
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List of Abbreviations

[\alpha]_D  specific rotation at wavelength of sodium D line
Ac  acetyl, acetate
aq.  aqueous
Bn  benzyl
Boc  tert-butyloxycarbonyl
CDCl_3  deuterated chloroform
CHCl_3  chloroform
CH_2Cl_2  methylene chloride
\delta  chemical shift
dr  diastereomeric ratio
DCE  1,2-Dichloroethane
DMF  dimethylformamide
DMSO  dimethyl sulfoxide
ee  enantiomeric excess
equiv.  equivalent
EWG  electron-withdrawing group
EDG  electron-donating group
EtOAc  ethyl acetate
g  gram(s)
h  hour(s)
HPLC  high performance liquid chromatography
Hz  hertz
i-PrOH  iso-propanol
J  coupling constant
LA  Lewis acid
LB  Lewis base
m  meta
MeOH  methanol
mg  milligram(s)
MHz  megahertz
min  minute(s)
 mL  milliter
mmol  millimole
NHC  N-heterocyclic carbene
NMR  nuclear magnetic resonance
o  ortho
p  para
PTC  phase-transfer catalysis
rt  room temperature
cat.  catalyst
TBS  tert-butyldimethylsilyl
TEA  trimethylamine
Tf  trifluoromethanesulfonate
TFA  trifluoroacetic acid
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>μM</td>
<td>micromole</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

1.1 The Development of Organocatalysis

Organocatalysis employs pure small organic molecules without metals to promote organic transformations. The nature of relatively low toxicity, mild reaction conditions and operational simplicity of an organocatalyst makes this catalytic system highly attractive in the practice of synthesis, particularly in chemical and pharmaceutical industry settings. In 1973, Hajos and Parrish reported (S)-proline (3 mol%) catalyzed asymmetric aldol cyclization with 97% enantiomeric excess (Scheme 1.1).\(^1\) However, organocatalysis didn’t received much attention until 2000 when the seminal studies by List and Barbas,\(^2\) and MacMillan, respectively.\(^3\) After more than a decade explosive development, organocatalysis has become the third branch of catalysis, complementary to organometallic and enzymatic catalysis. A variety of organocatalysts such as amines,\(^4\)\(^6\) hydrogen bonding catalysts (for example, thiourea),\(^7\)\(^11\) Brønsted acids,\(^12\)\(^14\) NHCs\(^15\)\(^16\) and phase transfer catalysts\(^17\)\(^19\) have been reported.

Scheme 1.1. (S)-Proline catalyzed asymmetric intramolecular aldol cyclization
1.2 Tertiary Amine Thiourea Bifunctional Organocatalysts

Hydrogen bonding is well known as an indispensable force in bio catalysis. To mimic the catalytic activity of enzymes, many small organic molecules with hydrogen bonding donors have been successfully developed to promote a varieties of asymmetric transformations.\(^7\)\(^-\)\(^9\),\(^20\) Among them are notable tertiary amine thiourea bifunctional organocatalysts. The high efficiency of the bifunctional catalysts arises from the action of tertiary amine and thiourea groups in synergistic cooperative manner. Several efficient bifunctional catalysts have been successfully developed by incorporating both tertiary amine and thiourea motifs to privileged chiral skeletons, such as chiral cyclohexane diamine, cinchona alkaloids and binaphthyl.

**Scheme 1.2.** Takemoto’s catalyst promoted asymmetric Michael addition of malonates to nitrostyrenes

In 2003, Takemoto developed the first tertiary amine thiourea bifunctional organocatalyst 4 demonstrated in promoting enantioselective Michael addition of malonates to nitroolefins in high yields and with enantioselectivities (Scheme 1.2).\(^{21}\) In this protocol, thiourea is designed to activate nitroolefins, while tertiary amine deprotonates
malonates and directs its attack in an enantioselective cooperative manner. Following this
discovery, many enantioselective conjugated additions are also developed using this
bifunctional catalyst.²²-²⁵

Besides conjugate addition, enantioselective cleavage of reactive ester bonds was
also accomplished. In 2005, Berkessel developed dynamic kinetic resolution of azalactones
using ⁴ as catalyst to produce chiral α-amino acids in 69% yield and with 83% ee (Scheme
1.3).²⁶ The reaction was extended to the kinetic resolution of oxazinones to give chiral β-
amino acids ¹⁰ with good enatioselectivities (Scheme 1.4).²¹

**Scheme 1.3.** Amine thiourea ⁴ catalyzed dynamic kinetic resolution of azalactones

![Scheme 1.3](image)

**Scheme 1.4.** Amine thiourea ¹¹ catalyzed kinetic resolution of oxazinones

![Scheme 1.4](image)

Cinchona alkaloid derived thiourea bifunctional catalysts are also proved to be
powerful for asymmetric transformations.¹¹ In 2005, Soós and coworkers designed a
hydroquinine derived thiourea bifunctional catalyst ¹⁴ for the asymmetric Michael addition
of nitromethane to chalcones in 93% yield and with 96% ee (Scheme 1.5).\textsuperscript{27}

**Scheme 1.5.** Soós catalyst promoted Michael addition of nitromethane to chalcone

Chiral axial binaphthyl is also a privilege scaffold in asymmetric transition metal catalysis, such as BINAP\textsuperscript{28} and BINOL.\textsuperscript{29} Binaphthyl derived thiourea bifunctional organocatalysts were developed by Wang and used for asymmetric Morita-Baylis-Hillman reaction in high yields and with high enantioselectivity (Scheme 1.6).\textsuperscript{30} The catalyst 18 also promoted highly enantioselective Michael addition of diketones to nitroolefins using only 1 mol\% catalyst loading.\textsuperscript{31}

**Scheme 1.6.** Wang’s Catalyst Promoted Asymmetric Morita-Baylis-Hillman Reaction

### 1.3 Aminocatalysis

Aminocatalysis uses amines as promoters for organic transformations with aldehydes or ketones. Mechanistically, aminocatalysis starts with the condensation of a
chiral amine catalyst with aldehydes or ketones to \textit{in situ} form a transient enamine or iminium, depending on the existence of a $\alpha,\beta$-carbon-carbon double bond (Scheme 1.7).\textsuperscript{32}

In the absence of a double bond, an electron rich enamine is formed and subsequently reacts with various electrophiles enantioselectively.\textsuperscript{5} Singly Occupied Molecular Orbital (SOMO) catalysis\textsuperscript{33} was also developed by MacMillan based on the single-electron oxidation of the enamines. The resulting radical cations can couple with various weak nucleophiles, which are difficult to realize with previous methods.\textsuperscript{33-38} In the presence of a $\alpha,\beta$-double bond, a formed electron deficient iminium ion can react with various nucleophiles by affording chiral $\beta$-substituted aldehydes/ketones, or participate in Diels-Alder reactions.\textsuperscript{4} Moreover, a transient electron rich enamine resulted from the addition of nucleophiles to iminium can also be trapped with various electrophiles. Based on this chemistry, a number of synthetic efficient cascade reactions have been realized.\textsuperscript{39-41} If a $\gamma$-proton in $\alpha,\beta$-unsaturated aldehydes exists, electron rich dienamines\textsuperscript{42,43} can be potentially formed, which can afford $\gamma$-functionalized aldehydes\textsuperscript{44,45} or participate in respective Diels-Alder\textsuperscript{46} and $[2+2]$\textsuperscript{47} cyclization reaction as an electron rich diene.

\textbf{Scheme 1.7. Aminocatalysis}
1.31 Aminocatalytic Cascade Reactions

Construction of chiral complex molecules from simple starting materials in a minimum steps is highly desirable in organic synthesis. Cascade reactions are one of the most efficient strategies capable of achieving this goal. Accordingly, a great deal of efforts has been devoted to the development of cascaded reactions, especially aminocatalytic cascade reactions. 39,48

In 2000, Barbas developed the first aminocatalytic cascade reaction. In this Robinson annulation, L-proline first condensed with the ketone, generating an electron deficient iminium that reacts with activated methylene. Then, intramolecular aldol condensation was followed by enamine activation, affording tetrahydronaphthalene-1,6(2H,7H)-dione in 49% yield and with 76% ee (Scheme 1.8).49 The most successful and widely used strategy in aminocatalytic cascade reactions is to utilize the interconversion between iminium-enamine and design bifunctional substrates that contain both nucleophilic and electrophilic moieties. In this way, chiral cyclic compounds with different ring sizes and multiple chiral centers can be created. For example, a chiral thiochromenes...
were constructed in high yields with excellent enantioselectivity by Wang through aminocatalytic asymmetric Michael-aldol cascade reaction of $\alpha,\beta$-unsaturated aldehydes and 2-mercaptobenzaldehydes (Scheme 1.9).\textsuperscript{50} An elegant three components triple cascade reaction was also successfully developed by Enders, affording multiple substituted cyclohexanes containing four contiguous chiral centers in moderate yields and with excellent dr and ee (Scheme 1.10).\textsuperscript{51} Impressive in this cascade reaction is the \textit{in situ} formed enamine can selectively reacts with trans-$\beta$-nitrostyrene not $\alpha,\beta$-unsaturated aldehydes, which means that nitrostyrene is more reactive than $\alpha,\beta$-unsaturated aldehydes under the activation of aminocatalyst. The relative reactivity of substrates is the key of this reaction success. Besides enals, alkynals are also viable substrates for the aminocatalytic cascade reactions by creating structurally diverse frameworks.\textsuperscript{52-54} After initial Michael addition of iminium, a novel chiral allenamine intermediate is formed, acting as the nucleophile in a subsequent enantioselective reaction with an electrophile to produce chiral 4$H$-chromene in excellent yields and with excellent enantioselectivity (Scheme 1.11).\textsuperscript{52}

\textbf{Scheme 1.8. Proline catalyzed asymmetric Robinson annulation}
Scheme 1.9. Aminocatalytic asymmetric Michael-Aldol cascade reaction

Scheme 1.10. Aminocatalytic asymmetric three components triple cascade reaction

Scheme 1.11. Aminocatalytic enantioselective Michael-Michael cascade reaction of alkynals

1.32 Combination of Amine and Metal Catalyzed Cascade Reactions

Although great success has been achieved in aminocatalytic cascade reactions, the
expansion of the powerful strategy beyond the current domain is full of challenges due to the limited scope of the amine activation mode. Organometallic catalysis offers a much broader scope of activation of substrates. Hence, merging organometallic catalysis and aminocatalysis may create new organic transformations and dramatically expand the territory of aminocatalysis and much effort has been devoted to this emerging area.\textsuperscript{55-62} The major challenge is the possible incompatibility of aminocatalysts (Lewis base) and transition metal (Lewis acid) catalysts. Therefore, judicious selection of the combination becomes crucial.

\textbf{Scheme 1.12.} \(\alpha\)-Allylation of aldehydes and ketones catalyzed by a combination of pyrrolidine and Pd(PPh\(_3\))\textsubscript{4}

\[\begin{align*}
\text{R = H or alkyl} & \quad \text{R\textsubscript{1} = alkyl} \\
\text{R\textsubscript{1} = H, Ph or alkyl} & \\
\text{Pd(PPh\(_3\))\textsubscript{4}} & \\
\text{DMSO, RT} & \quad \text{yields 65-95\%}
\end{align*}\]

In 2006, Córdova developed the first example of combining aminoa catalyst and metal catalyst, achieving direct \(\alpha\)-allylation of aldehydes and cyclic ketones in good yields (Scheme 1.12).\textsuperscript{63} In this protocol, Pd(PPh\(_3\))\textsubscript{4} activates allyl acetate to generate electron-deficient palladium \(\pi\)-allyl complexes, while pyrrolidine condenses with aldehydes or cyclic ketones to form reactive enamines. It wasn’t until 2012 when an asymmetric version
was developed to give chiral α-allylation products in high yield and with high ee.64

In 2010, Wang developed the first combination of metal catalyst and chiral secondary amine catalyzed asymmetric cascade reaction. In this protocol, a bifunctional molecule containing an activated methylene and a triple bond reacted smoothly with α,β-unsaturated aldehydes under the catalysis of a combination of diphenylprolinol TMS-ether and PdCl2, producing multiple substituted cyclopentenes in good yields and with excellent enantioselectivity (Scheme 1.13).65 At the same time, Córdova66 and Jórgensen67 also reported similar procedures. Based on this strategy, chiral spirocyclic oxindoles,68 dihydrofurans69 and dihydropyrroles70 were also obtained through changing the nucleophilic motif in bifunctional molecules from dimethyl malonate to oxindole, OH and tosyl protected amine groups respectively.

**Scheme 1.13.** Enantioselective Michael-cyclization cascade reactions catalyzed by a combination of diphenylprolinol TMS-ether and PdCl2

![Scheme 1.13](image)

In addition to variation of the electrophilic motifs of bifunctional substrates, allylic acetate were found to be a good electrophilic motif. Therefore, chiral polysubstituted
cyclopentanes and cyclohexanes were prepared in high yield through a novel dynamic catalytic asymmetric Michael/α-allylic alkylation cascade reaction of the newly designed bifunctional substrates and α,β-unsaturated aldehydes mediated by Palladium and chiral amine catalyst (Scheme 1.14).71

Scheme 1.14. Enantioselective Michael-allylation cascade reactions catalyzed by a combination of diphenylprolinol TMS-ether and Pd₂(db)₃/dppe

Promoting cascade reactions by amine and organometallic synergistically catalysis is still in its infancy. Despite the great potential of this powerful binary catalytic system, only limited number of examples have been reported. Toward this end, part of my Ph.D. work is devoted to developing new cascade reactions with the strategy.

1.4 Research Summary

Development of efficient organocatalytic reactions for the facile assemble of synthetically and medicinally useful molecules is a major goal in organic synthesis. Therefore, I will detail my efforts on the development of novel organocatalytic reactions for the construction of structurally diverse molecular architectures. Specifically, Chapter 2 describes dynamic kinetic resolution of biaryl lactones by amine thiourea catalyzed atropo-enantioselective transesterification for the synthesis of axially chiral biaryl compounds.
Chapter 3 focuses on the development of aniline catalyzed cascade reactions by harnessing the new reactivity of $N, O$-acetals in an aminocatalytic fashion. Chapter 4 presents a chiral amine/Lewis acid synergistically catalyzed cyclization-Michael cascade reaction for the construction of chiral $\gamma,\gamma$-disubstituted butenolides.

1.5 References


(69) Lin, S.; Zhao, G.-L.; Deiana, L.; Sun, J.; Zhang, Q.; Leijonmarck, H.; Córdova, A.


Chapter 2

Organocatalytic Dynamic Kinetic Resolution of Biaryl Lactones

2.1 Introduction

Dynamic kinetic resolution (DKR)\textsuperscript{1-3} provides an unrivaled power over traditional kinetic resolution (KR)\textsuperscript{4-6} in asymmetric synthesis, as it offers the capacity of converting both enantiomers of a racemic mixture into an enantioenriched product. Impressive progress has been made for catalytic DKR of compounds contained stereogenic centers.\textsuperscript{7-9} By contrast, there are only a handful of examples reported regarding the synthesis of axially chiral compounds through catalytic DKR approaches despite their prevalence and importance in bioactive molecules\textsuperscript{10,11} and catalysis.\textsuperscript{12-16} The general strategy employs catalytic atroposelective functionalization of configurationally labile biaryls to increase restriction to rotation in biaryl products. Chiral transition metal catalyzed introduction of sterically demanding moiety at ortho-position of freely rotating, rapidly racemizing biaryls has been elegantly realized by the groups of Hayashi, Murai, Stoltz and Virgil, Fernández and Lassaletta, Colobert, and You.\textsuperscript{17-21} However, the seminal work in organocatalytic DKR of racemic biaryls was only recently published by Miller and coworkers with a tripeptide-promoted atroposelective electrophilic ortho-bromination reaction.\textsuperscript{22-35}

DKR of configurationally labile biaryl lactones developed by Bringmann has proved to be a powerful approach to chiral biaryl compounds (Scheme 2.1, Eq. 1\textsuperscript{36}).\textsuperscript{7,10,37} Notably, the chiral products have found broad applications in total synthesis of a number of challenging axially chiral natural products such as korupensamine A and B.\textsuperscript{38}
knipholone,\textsuperscript{39,40} mastigophorene A,\textsuperscript{41} and benanomicin B.\textsuperscript{42} Therefore, optically enriched biaryl products (> 90\% ee) are highly valuable for asymmetric total synthesis. However, achieving highly atropo-enantioselective DKR of the Bringmann’s lactones presents a long-standing challenge in synthesis despite more than 20 years’ effort made by Bringmann and Yamada and others.\textsuperscript{7,10,37} A variety of chiral nucleophilic agents have been explored for atroposelective cleavage of the ester bond to produce enantioenriched configurationally stable chiral biaryl products.\textsuperscript{37} Only chiral oxazaborolidines as hydride transfer reagents for the reduction of the lactones to the corresponding alcohols deliver good enantioselectivities (68-97\% ee) reported by Bringmann in 1992.\textsuperscript{43,44} It is noted that 3.0 equiv of chiral oxazaborolidines were required for effective transformation. In 2008, Yamada and coworkers developed a more efficient catalytic version using a chiral Co(II) catalyst in the presence of modified NaBH\textsubscript{4} as reducing agent obtaining good enantioselectivity (80-93\% ee).\textsuperscript{45} Diastereoselective transesterification of the lactones with alcohols represents a straightforward approach to the chiral biaryls but with limited success so far. Chiral (+)-menthol derived potassium alcoholdate as chiral nucleophile gave the best result with 48\% ee (Scheme 2.1, Eq. 1).\textsuperscript{46} An asymmetric catalytic version using methanol as nucleophile by a chiral BINAP silver complex delivered moderate enantioselectivity (50-84\% ee) (Eq 2).\textsuperscript{47} Clearly, a new catalytic strategy capable of promoting DKR of Bringmann’s lactones with a broad scope and a high level of enantioselectivity (>90\% ee) is urgently needed to streamline the synthesis of the privileged axially chiral biaryls.
Scheme 2.1. Reported asymmetric transesterification of the Bringmann’s lactones

2.2 Research Plan

Bifunctional chiral amine thioureas have demonstrated great versatility and selectivity to facilitate many transformations attributing to their capacity for synergistic dual acid and base activation. The effective activation mode and our experience in this area inspired us to explore them for the DKR of the challenging Bringmann’s lactones (Scheme 2.2). We envisioned that thiourea would activate the strained lactone, while the amine would interact with the hydroxyl group of an alcohol and direct the nucleophilic attack of the activated ester in a cooperative atropo-enantioselective manner. Herein, we wish to disclose the results of the investigation leading to the first example of a metal free quinine-derived thiourea-promoted atropo-enantioselective transesterification of the Bringmann’s lactones. Notably, this protocol is operated under very mild conditions and delivers axially chiral biaryl products in high yields and with excellent enantioselectivities (up to quantitative yields and 99% ee). Moreover, the process shows a broader substrate scope than that of previous studies. A variety of alcohols including benzylic alcohols,
aliphatic alcohols and even phenols perform very well. Moreover, biaryl lactones with a broad range of substituent patterns are successfully transformed to chiral biaryl products.

**Scheme 2.2** Chiral bifunctional amine-thio urea catalyzed transesterification of the Bringmann’s lactones

Our approach: metal free organocatalysis - synergistic activation of both substrates
- high yields and excellent enantioselectivity (up to quantitative yields and 99% ee)
- broad substrate scope for both nucleophiles and electrophiles (35 examples)

![Scheme 2.2: Chiral bifunctional amine-thio urea catalyzed transesterification of the Bringmann’s lactones](image)

**2.3 Results and discussion**

**2.3.1 Optimization of Reaction Conditions**

We commenced our investigation by examining the reaction of biaryl lactone 1a with 4-nitrobenzylic alcohol 2a (Table 2.1). No reaction happened without a catalyst, indicative of a promoter essential for effective transesterification (entry 1). Indeed, Takemoto’s catalyst I was capable of producing desired product 3a in 95% yield and 89% ee within 1h (entry 2). Among the commonly used amine thioureas probed, Soos’s quinine thiourea II proved to be a superior facilitator for this process giving 3a in 98% yield and
with 95% ee in 3h (entry 3). The power of the synergistic activation specifically by a bifunctional amine and thiourea was further demonstrated when no reaction proceeded with either triethylamine or bis(thiourea) catalyst IV (entry 4). Further examining the parameters of solvents (entries 3, and 5-9) and catalyst loading (entries 10-12) revealed the optimal reaction conditions of trifluorotoluene as medium and 5 mol% of II.

**Table 2.1.** Exploration of organocatalyzed atropo-enantioselective transesterification of biaryl lactones

<table>
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<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (%)</th>
<th>Solvent</th>
<th>T (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>CF$_3$Ph</td>
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<td>61</td>
<td>96</td>
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</table>

*a*Unless stated otherwise, see the Experimental Section. *b*Isolated yields. *c*Determined by
chiral HPLC analysis (Chiralcel AS-H).

2.32 Investigation of Substrate Scope

With the optimized condition in hand, the scope of the process was explored (Scheme 2.3). Benzyl alcohols with electron-withdrawing (2a, 2b) or -donating substituents (2c, 2d) gave the desired products in excellent yields and with excellent enantioselectivities (93%-quantitative yields, 91-96% ee). More sterically demanding 9-anthracenemethanol 2e and diaryl substituted methanol 2f were well tolerated. Moreover, heteroaromatic rings including furan 2g, indole 2h, pyridine 2i and quinolone 2j were proved to be valid substrates. Besides benzyl alcohols, simple aliphatic alcohols such as ethanol, butanol, and isopropanol, which gave low enantioselectivity in Yamada’s study, delivered high yielding and highly enantioenriched 3k-m (97, 90 and 90% yields, and 92, 90 and 94% ee, respectively). More acidic trifluoro- 2n and trichloro 2o ethanols reacted much faster (within 0.5 h) but without deteriorating enantioselectivity, presumably as a result of easy deprotonation of OH group by the amine. 2-Methoxyethanol 2p was found to give higher enantioselectivity in shorter time than ethanol (95% ee, 6h vs 92% ee, 36h), which may be ascribed to the oxygen acting as an additional bonding site with the catalyst and the increased acidity of alcohols by inductive effect of oxygen. In contrast, 2-phenoxyethanol 2q gave lower enantioselectivity (90% ee), maybe due to weaker bonding ability of phenoxyl. Excellent yields (95-97%) and enantioselectivity (94-96%) were also achieved for other functionalized alcohols 3-benzyloxy-1-propanol 2r and N-substituted alcohol 2s. It is noted that 1,3-dibenzyloxy-2-propanol 2t with two oxygen substituents further improved enantioselectivity (99% ee) for 3t.
Scheme 2.3 Organocatalytic atropo-enantioselective transesterification of biaryl lactones with alcohols

Unless stated otherwise, see the Experimental Section. Ee value determined by chiral HPLC analysis (Chiralcel AS-H or AD). \(^{b}\)-10 °C. \(^{c}\)2.0 equiv. of alcohol. \(^{d}\)20.0 equiv. of alcohol. \(^{e}\)15 mol% II.

The synthesis of axially chiral phenolic esters from Bringmann’s lactones is more
challenging due to the weaker nucleophilicity of phenols and their vulnerable racemization via reversible lactonization. We found that the chiral phenolic esters could be prepared by using this protocol, but have to balance selectivity and reactivity. Prolonging reaction time could increase yields but caused the racemization of the products. We managed to achieve high to excellent enantioselectivity (90-98% ee) and good yields (50-76%) for phenols bearing electron-neutral (2u), -donating (2v, 2x and 2y) and -withdrawing substituents (2w) when the reaction was performed at –10 °C with controlled short reaction time (Scheme 2.4).

Scheme 2.4. Organocatalytic atropo-enantioselective transesterification of biaryl lactones with phenols

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Unless stated otherwise, see the Experimental Section. ee value determined by chiral HPLC analysis (Chiralcel AD).

After probing the scope and understanding the influence of alcohols on the reaction, we next investigated the tolerance of biaryl lactones (Scheme 2.5). It appears that the variation of substituents on the carbonyl-containing phenyl ring does not show any influence, producing 3z, 3aa, 3ab, 3ac and 3ad in excellent yields and with excellent ee
(92%-quantitative yields, 92-97% ee). Nonetheless, removal of the 2’-methoxyl substituent on the phenolic parts causes dramatic decrease in both yield and ee (3ae, 79%, 62% ee vs 3aa, 97%, 97% ee). It is believed that the methoxyl substituent in biaryl lactone may provide an additional binding site with the catalyst to increase alcohol’s differentiation in attack trajectory. We observed alcohols could affect enantioselectivity. Therefore different alcohols were probed, including 2-methoxyethanol 2p, possessing an additional oxygen atom providing an additional binding site for boosting enantioselectivity, but a similar result was attended for 3af. Pleasingly, 1,3-dibenzyloxyl-2-propanol 2t could give dramatic increase of enantioselectivity (96% ee) and in high yield (84%) for 3ag. Notably, a significant variation of substituents on both aromatic rings including the sensitive 2’-position with the alcohol delivered biaryls 3ah, 3ai, 3aj, and 3ak with high level of enantioselectivity (90-96% ee).

Scheme 2.5. Organocatalytic atropo-enantioselective transesterification of biaryl lactones with alcohols
Unless stated otherwise, see the Experimental Section. ee value determined by chiral HPLC analysis (Chiralcel AS-H or AD). \(^b\)2.0 equiv. of alcohol. \(^c\)10 equiv. of alcohol. \(^d\)15 mol% of III.

**2.33 Synthetic Application**

The protocol can be easily scaled up to a gram scale even with a lower catalyst loading (2 mol%) at a higher concentration (1.0 M) affording 1.167 g of 3a in nearly quantitative yield and excellent ee (95%, Scheme 2.6, Eq. 1). Alcohol 4 can be smoothly attended by LiAlH\(_4\) reduction in 93% yield and without erosion of the optical purity. Furthermore, a useful chiral aminophenol ligand 6\(^{59}\) can be prepared from product 3al via DIBAL-H mediated reduction (Eq. 2). Therefore, the absolute configuration of transesterification products 3 is confirmed by the comparison of the optical rotation of 5 with the reported data.\(^{43}\)
Scheme 2.6. Gram scale synthesis and synthetic elaboration of the transesterification products

2.4 Conclusion

In conclusion, a chiral bifunctional amine thiourea as promoter is developed as a solution to a long standing challenging issue in atropo-enantioselective transesterification of the Bringmann lactones. This organocatalytic approach delivers the first highly enantioselective, high yielding DKR process for the preparation of axially chiral biaryl compounds with a broad substrate scope under mild reaction conditions. The higher reaction efficiency attributes to a distinct synergistic activation mode from previous reported monoactivation methods.

2.5 Experimental Section

General Information:
Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F254 indicator were used for thin-layer chromatography (TLC) analysis. $^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance 300. Chemical shifts in $^1$H NMR spectra are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm) as internal standards. Data for $^1$H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet). Data for $^{13}$C NMR are reported as ppm. $^{13}$C NMR chemical shifts are reported in ppm relative to the central peak of CDCl$_3$ (77.16 ppm) as internal standards.

**General Procedures for the atropo-Enantioselective Esterification:**

**General Procedure for atropo-Enantioselective Transesterification of Biaryl Lactones with Alcohols** (Schemes 2.3 and 2.5, 3a): A mixture of biaryl lactones 1a (0.1 mmol, 31.9 mg), 4-nitrobenzyl alcohol 2a (0.12 mmol, 18.4 mg) and 5 mol% catalyst II (0.05 mmol, 3.0 mg) in 1.0 mL $\alpha,\alpha,\alpha$-trifluoromethanebenzene was stirred for 6h at room temperature. The reaction mixture was directly purified by silica gel chromatography, eluted by hexane/EtOAc = 3:1 to afford the desired product as a white solid (46.7 mg, 99% yield), 96% ee (HPLC Daicel CHIRALCEL AS-H column, hexane/iPrOH=70:30 at 0.5 mL/min, $\lambda$ = 254 nm); $t_{major}$ = 23.09 min, $t_{minor}$ = 31.83 min; $[\alpha]_D^{22.0} = -11.0$ (c = 1.00, MeOH).

**General Procedure for atropo-Enantioselective Transesterification of Biaryl Lactones with Phenols** (Scheme 2.4, 3u): A mixture of biaryl lactones 1a (0.1 mmol, 31.9 mg), phenol 2u (0.12 mmol, 11.3 mg) and 5 mol% catalyst II (0.05 mmol, 3.0 mg) in 1.0 mL
α,α,α-trifluoromethanebenzene was stirred for 1h at -10 °C. The reaction mixture was directly purified by silica gel chromatography, eluted by cold dichloromethane to afford the desired product as a white solid (31 mg, 75% yield), 96% ee (HPLC Daicel CHIRALCEL AD column, hexane/iPrOH=75:25 at 0.5 mL/min, λ = 210 nm): t_{major} = 15.93 min, t_{minor} = 26.88 min, [α]_{D}^{25.0} = +7.9 (c = 1.00, CHCl3)

**General Procedure for Gram Scale Synthesis** (Scheme 2.6, Eq. 1): A mixture of biaryl lactones 1a (2.5 mmol, 798 mg), 4-nitrobenzyl alcohol 2a (3.0 mmol, 459 mg) and 0.02 mol% catalyst II (0.05 mmol, 30 mg) in 2.5 mL α,α,α-trifluoromethanebenzene was stirred for 24h at room temperature. The reaction mixture was directly purified by silica gel chromatography, eluted by hexane/EtOAc= 3:1 to afford the desired product as a white solid (1.167g, 99% yield), 95% ee (HPLC Daicel CHIRALCEL AS-H column, hexane/iPrOH=70:30 at 0.5 mL/min, λ = 254 nm); t_{major} = 23.09 min, t_{minor} = 31.83 min.

4-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-iphenyl]-2-carboxylate (3a): White solid; 99% yield, 96% ee; 1H-NMR (300 MHz, CDCl3) : δ = 8.15 (d, 2H, J = 8.7 Hz), 7.96 (d, 1H, J = 7.5 Hz), 7.52 (d, 1H, J = 7.2 Hz), 7.42 (t, 1H, J = 7.5 Hz), 7.34 (d, 2H, J = 8.4 Hz), 7.07 (d, 1H, J = 8.4 Hz), 6.64 (d, 1H, J = 9.3 Hz), 5.58 (s, 1H), 5.19 (d, 2H, J = 5.1 Hz), 3.85 (s, 3H), 2.06 (s, 3H). 13C NMR (75 MHz, CDCl3, TMS):

![Diagram of 3a](image-url)
166.4, 147.3, 145.5, 143.1, 143.0, 138.1, 1369, 134.2, 129.8, 128.3, 128.1, 128.0, 127.4,
123.3, 122.8, 1145, 110.3, 65.0, 55.8, 19.7. HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 70:30 at 0.5 mL/min, λ = 254 nm): t_{major} = 23.09 min, t_{minor} = 31.83 min,
ee = 96%; [α]D^{22.0} (major) = -11.0 (c = 1.00, MeOH).

2-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3b): White solid; 98% yield, 96% ee; ¹H-NMR (300 MHz, CDCl₃) : δ = 8.09 (dd, 1H, J₁ = 1.2 Hz, J₂ = 7.2 Hz), 7.41-7.62 (m, 5H), 7.07 (d, 1H, J = 8.7 Hz), 6.67 (d, 1H, J = 8.7 Hz), 5.64 (s, 1H), 5.55 (d, 2H, J = 2.1 Hz), 3.87 (s, 3H), 2.08 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 166.1, 147.2, 145.6, 143.3, 138.3, 137.3, 134.3, 133.6, 132.4, 129.8, 129.0, 128.4, 128.3, 128.1, 127.5, 124.9, 122.9, 114.6, 110.5, 63.2, 55.9, 19.8; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 13.66 min, t_{minor} = 24.24 min, ee = 96%; [α]D^{22.3} (major) = -7.0 (c = 1.00, MeOH).

4-Methoxybenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3c): White solid; quantitative yield, 93% ee; ¹H-NMR (300 MHz, CDCl₃) :
\[ \delta = 7.92 \ (d, 1H, J = 7.2 \ Hz), \ 7.48 \ (d, 1H, J = 6.9 \ Hz), \ 7.37 \ (t, 1H, J = 7.5Hz), \ 7.15 \ (d, 1H, J = 8.4 \ Hz), \ 7.07 \ (d, 1H, J = 8.7 \ Hz), \ 6.83 \ (d, 2H, J = 6.9 \ Hz), \ 6.65 \ (d, 1H, J = 8.7 \ Hz), \ 5.54 \ (s, 1H), \ 4.98-5.07 \ (m, 2H), \ 3.86 \ (s, 3H), \ 3.81 \ (s, 3H), \ 2.06 \ (s, 3H). \]  

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3, \ TMS): \ \delta = 166.8, 159.4, 145.6, 143.2, 138.0, 136.9, 133.8, 130.6, 128.2, 128.0, 127.7, 122.9, 114.7, 113.7, 110.4, 66.4, 55.9, 55.3, 19.8; \]  

HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 65:35 at 0.5 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 13.75 \) min, \( t_{\text{minor}} = 30.60 \) min, ee = 93%; \( [\alpha]_D^{25.2} \) (major) = +15.7 (c = 1.00, CHCl3).

**Benzo[d][1,3]dioxol-5-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3d):** White solid; 93% yield, 91% ee; \(^1H\text{-NMR (300 MHz, CDCl}_3) : \ \delta \ 7.92 \ (d, 1H, J = 7.5 \ Hz), \ 7.48 \ (d, 1H, J = 7.5 \ Hz), \ 7.38 \ (t, 1H, J = 7.8 \ Hz), \ 7.08 \ (d, 1H, J = 8.7 \ Hz), \ 6.65-6.71 \ (m, 4H), \ 5.96 \ (s, 2H), \ 5.56 \ (s, 1H), \ 4.98-4.99 \ (m, 2H), \ 3.88 \ (s, 3H), \ 2.05 \ (s, 3H). \]  

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3, \ TMS): \ \delta = 166.8, 147.5, 147.4, 145.6, 143.3, 138.1, 136.9, 133.9, 130.6, 129.5, 128.2, 128.0, 122.9, 122.3, 120.5, 114.8, 110.5, 109.1, 107.9, 101.0, 66.6, 55.9, 19.8; \]  

HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 75:25 at 0.5 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 21.84 \) min, \( t_{\text{minor}} = 35.22 \) min, ee = 91%; \( [\alpha]_D^{25.2} \) (major) = +5.1 (c = 1.00, CDCl3).
**Anthracen-9-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl] -2-carboxylate (3e):** White solid; 98% yield, 90% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta =$ 8.47 (s, 1H), 8.13-8.16 (m, 2H), 8.00-8.04 (m, 3H), 7.35-7.53 (m, 6H), 6.07-6.12 (m, 3H), 5.65 (d, 1H, $J$ = 8.7 Hz), 5.13 (s, 1H), 3.34 (s, 3H), 1.92 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta =$ 167.5, 144.6, 142.5, 138.0, 137.1, 134.0, 131.3, 131.1, 128.8, 128.6, 128.3, 128.0, 127.2, 126.3, 126.0, 125.1, 124.2, 122.1, 114.0, 109.0, 58.9, 55.2, 19.8; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 70:30 at 0.5 mL/min, $\lambda$ = 254 nm): $t_{major}$ = 13.16 min, $t_{minor}$ = 22.26 min, ee = 90%; $[^{[\alpha]}_D]_{23.0}^{23.0}$ (major) = -6.4 (c = 1.00, CHCl$_3$).

**9H-fluoren-9-yl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3f):** White solid; 97% yield, 92% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta =$ 7.98 (d, 1H, $J$ = 7.5 Hz), 7.61 (d, 2H, $J$ = 7.5 Hz), 7.43-7.51 (m, 3H), 7.34-7.41 (m, 3H), 7.20-7.25 (m, 2H), 6.83-6.86 (m, 2H), 6.46 (d, 1H, $J$ = 8.4 Hz), 5.45 (s, 1H), 3.73 (s, 3H), 2.07 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta =$ 167.6, 145.4, 143.2, 142.1, 141.9, 140.9, 140.8, 138.1, 137.3, 134.0, 130.5, 129.1, 129.0, 128.3, 128.0, 127.6, 126.1, 126.0, 122.7,
119.5, 114.5, 110.2, 75.0, 55.8, 19.8; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 90:10 at 0.5 mL/min, λ = 254 nm): t_major = 17.66 min, t_minor = 23.68 min, ee = 92%; [α]D23.4 (major) = +7.2 (c = 1.01, CHCl3).

Furan-2-ylmethyl (R)-6’-bromo-2’-hydroxy-3’-methoxy-6-methyl-[1,1’-biphenyl]-2-carboxylate (3g): White solid; 96% yield, 90% ee; 1H-NMR (300 MHz, CDCl3) : δ = 7.92 (d, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.5 Hz), 7.35-7.40 (m, 2H), 7.11 (d, 1H, J = 8.7 Hz), 6.72 (d, 1H, J = 8.7 Hz), 6.29-6.33 (m, 2H), 5.57 (s, 1H), 5.05 (s, 2H), 3.90 (s, 3H), 2.07 (s, 3H). 13C NMR (75 MHz, CDCl3, TMS): δ = 166.3, 149.4, 145.6, 143.2, 138.1, 137.2, 134.0, 130.1, 128.3, 128.0, 127.5, 122.9, 114.7, 110.5, 110.4, 110.3, 58.4, 55.9, 19.8; HPLC (Daicel CHIRALCEL AD-H column, hexane/iPrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_major = 11.28 min, t_minor = 23.98 min, ee = 90%; [α]D26.1 (major) = +12.2 (c = 1.00, CHCl3).

(1H-indol-2-yl)methyl (R)-6’-bromo-2’-hydroxy-3’-methoxy-6-methyl-[1,1’-biphenyl]-2-carboxylate (3h): White solid; quantitative yield, 91% ee; 1H-NMR (300 MHz, CDCl3) :
δ = 8.25 (s, 1H), 7.89 (d, 1H, J = 7.2 Hz), 7.56 (d, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.2 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.29 (d, 1H, J = 8.4 Hz), 7.19 (dt, 1H, J1 = 1.2 Hz, J2 = 7.8 Hz), 7.09 (dt, 1H, J1 = 1.2 Hz, J2 = 7.8 Hz), 7.04 (d, 1H, J = 8.4 Hz), 6.55 (d, 1H, J = 8.7 Hz), 6.39 (d, 1H, J = 1.2 Hz), 5.55 (s, 1H), 5.17-5.27 (m, 2H), 3.68 (s, 3H), 2.06 (s, 3H). 13C NMR (75 MHz, CDCl3, TMS): δ = 168.1, 145.6, 143.2, 138.1, 136.7, 136.6, 134.1, 132.8, 130.5, 128.0, 127.6, 122.8, 122.4, 120.7, 119.7, 114.6, 111.0, 110.5, 103.2, 60.0, 55.8, 19.8; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 90:10 at 0.5 mL/min, λ = 254 nm): t_major = 50.74 min, t_minor = 39.31 min, ee = 90%; [α]D25.6 (major) = +37.4 (c = 1.00, CHCl3).

Pyridin-3-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3i): White solid; quantitative yield, 90% ee; 1H-NMR (300 MHz, CDCl3): δ = 8.54 (s, 1H), 8.40 (s, 1H), 7.93 (d, 1H, J = 7.5 Hz), 7.48-7.56 (m, 2H), 7.39 (d, 1H, J = 7.5 Hz), 7.21-7.24 (m, 1H), 7.02 (d, 1H, J = 8.7 Hz), 6.62 (d, 1H, J = 8.7 Hz), 5.08 (s, 2H), 3.85 (s, 3H), 2.05 (s, 3H). 13C NMR (75 MHz, CDCl3, TMS): δ = 166.7, 149.5, 149.1, 145.6, 143.2, 137.0, 136.3, 134.1, 130.1, 128.3, 128.0, 127.6, 123.3, 122.8, 114.6, 110.5, 64.0, 55.9, 19.8; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 60:40 at 0.5 mL/min, λ = 254 nm): t_major = 11.98 min, t_minor = 23.77 min, ee = 90%; [α]D23.5 (major) = +11.9 (c = 1.00, CHCl3).
Quinolin-4-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3j): White solid; 97% yield, 93% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta =$ 8.82 (d, 1H, $J$ = 4.2 Hz), 8.14 (d, 1H, $J$ = 8.4 Hz), 8.02 (d, 1H, $J$ = 7.8 Hz), 7.84 (d, 1H, $J$ = 8.4 Hz), 7.73 (t, 1H, $J$ = 7.8 Hz), 7.50-7.58 (m, 2H), 7.41 (t, 1H, $J$ = 7.8 Hz), 7.26-7.27 (m, 1H), 6.78 (d, 1H, $J$ = 8.7 Hz), 6.33 (d, 1H, $J$ = 8.7 Hz), 5.66 (s, 1H), 5.50-5.60 (m, 2H), 3.70 (s, 3H), 2.03 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta =$ 166.6, 149.9, 147.9, 145.3, 143.0, 140.9, 138.3, 137.2, 134.3, 129.9, 129.4, 1285, 128.1, 127.5, 127.0, 126.2, 120.3, 114.4, 110.0, 62.9, 55.7, 19.9; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 60:40 at 0.5 mL/min, $\lambda$ = 254 nm): $t_{\text{major}}$ = 16.27 min, $t_{\text{minor}}$ = 35.66 min, ee = 93%; $[^{[\alpha]}_D^{23.6}]$ (major) = -3.4 (c = 1.00, CHCl$_3$).

Ethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3k): White solid; 97% yield, 92% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta =$ 7.91 (d, 1H, $J$ = 7.8 Hz), 7.49 (d, 1H, $J$ = 7.5 Hz), 7.39 (t, 1H, $J$ = 7.8 Hz), 7.16 (d, 1H, $J$ = 8.7 Hz), 6.78
(d, 1H, \( J = 8.7 \) Hz), 4.10 (q, 2H, \( J = 6.9 \) Hz), 3.92 (s, 3H), 2.08 (s, 3H), 1.07 (t, 3H, \( J = 6.9 \) Hz). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): \( \delta = 166.9, 145.7, 143.4, 138.0, 136.8, 133.7, 130.9, 128.0, 122.9, 114.9, 110.6, 60.6, 56.1, 19.8, 13.7; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 9.72 \) min, \( t_{\text{minor}} = 15.47 \) min, ee = 92%; \([\alpha]D^{25.3}\) (major) = +4.8 (c = 1.00, CHCl\(_3\)).

Butyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3l): White solid; 90% yield, 90% ee; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) : \( \delta = 7.92 \) (dd, 1H, \( J_1 = 0.9 \) Hz, \( J_2 = 7.8 \) Hz), 7.49 (d, 1H, \( J = 6.9 \) Hz), 7.39 (t, 1H, \( J = 7.5 \) Hz), 7.16 (d, 1H, \( J = 8.7 \) Hz), 6.77 (d, 1H, \( J = 8.7 \) Hz), 5.60 (s, 1H), 4.05 (t, 2H, \( J = 6.3 \) Hz), 3.92 (s, 3H), 2.07 (s, 3H), 1.32-1.46 (m, 2H), 1.22-1.29 (m, 2H), 1.22-1.30 (m, 2H), 0.86 (t, 3H, \( J = 7.2 \) Hz). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): \( \delta = 167.1, 145.7, 143.3, 138.0, 136.8, 133.7, 130.9, 128.1, 128.0, 127.9, 122.9, 114.9, 110.5, 64.7, 56.0, 30.4, 19.9, 19.1, 13.7; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 8.93 \) min, \( t_{\text{minor}} = 14.42 \) min, ee = 90%; \([\alpha]D^{25.3}\) (major) = +4.0 (c = 1.00, CHCl\(_3\)).
Isopropyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3m): White solid; 90% yield, 94% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta = 7.89$ (d, 1H, $J = 7.5$ Hz), $7.47$ (d, 1H, $J = 6.9$ Hz), $7.39$ (t, 1H, $J = 7.5$ Hz), $7.16$ (d, 1H, $J = 8.7$ Hz), $6.78$ (d, 1H, $J = 8.7$ Hz), $5.60$ (s, 1H), $4.98$ (septet, 2H, $J = 6.3$ Hz), $3.92$ (s, 3H), $2.07$ (s, 3H), $1.01$-$1.05$ (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.7$, $145.8$, $143.5$, $137.9$, $136.5$, $133.5$, $131.6$, $138.1$, $128.0$, $122.9$, $115.1$, $110.6$, $67.8$, $56.1$, $21.4$, $21.3$, $19.9$; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 90:10 at 0.5 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 14.09$ min, $t_{\text{minor}} = 18.18$ min, ee = 94%; $[\alpha]D^{23.9}$ (major) = -3.2 (c = 1.00, CHCl$_3$).

2,2,2-Trifluoroethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3n): White solid; quantitative yield, 93% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta = 7.98$ (d, 1H, $J = 7.8$ Hz), $7.55$ (d, 1H, $J = 7.5$ Hz), $7.43$ (t, 1H, $J = 7.8$ Hz), $7.18$ (d, 1H, $J = 8.4$ Hz), $6.79$ (d, 1H, $J = 8.7$ Hz), $4.46$ (dq, 2H, $J_1 = 2.1$ Hz, $J_2 = 8.4$ Hz), $3.92$ (s, 3H), $2.09$ (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 165.0$, $145.8$, $143.3$, $138.5$, $137.8$, $134.8$, $128.6$, $128.4$, $128.1$, $127.1$, $123.1$, $122.9$ (q, $J_{C,F} = 275.6$ Hz, CF$_3$), $114.5$, $110.8$, $60.7$
(q, J_C,F = 36.4 Hz, CH2); $^{19}$F (CDCl$_3$) $\delta$ = 72.1. HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 70:30 at 0.5 mL/min, $\lambda$ = 254 nm): $t_{\text{major}}$ = 9.18 min, $t_{\text{minor}}$ = 36.45 min, ee = 93%; $[\alpha]_D^{24.3}$ (major) = +4.4 (c = 1.00, CHCl$_3$). $^{19}$F (282 MHz, CDCl$_3$): $\delta$ -72.1.

![Image of 3o]

2,2,2-Trichloroethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3o): White solid; quantitative yield, 90% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta$ = 8.06 (d, 1H, $J$ = 7.8 Hz), 7.56 (d, 1H, $J$ = 7.5 Hz), 7.44 (t, 1H, $J$ = 7.8 Hz), 7.18 (d, 1H, $J$ = 8.7 Hz), 6.78 (d, 1H, $J$ = 8.7 Hz), 5.65 (s, 1H), 4.73-4.83 (m, 2H), 3.92 (s, 3H), 2.09 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 164.8, 145.8, 143.4, 138.5, 137.8, 134.8, 128.6, 128.2, 127.2, 123.1, 114.6, 110.8, 95.0, 74.5, 56.0, 19.8; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, $\lambda$ = 254 nm): $t_{\text{major}}$ = 9.89 min, $t_{\text{minor}}$ = 25.49 min, ee = 90%; $[\alpha]_D^{25.3}$ (major) = +3.1 (c = 1.01, CHCl$_3$).

![Image of 3p]

2-Methoxyethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3p): White solid; quantitative yield, 95% ee; $^1$H-NMR (300 MHz, CDCl$_3$) :
\[ \delta = 7.95 \ (d, \ 1H, \ J = 7.8 \ Hz), \ 7.49 \ (d, \ 1H, \ J = 7.5 \ Hz), \ 7.39 \ (t, \ 1H, \ J = 7.8 \ Hz), \ 7.17 \ (d, \ 1H, \ J = 8.7 \ Hz), \ 6.78 \ (d, \ 1H, \ J = 8.7 \ Hz), \ 5.63 \ (s, \ 1H), \ 4.22 \ (t, \ 2H, \ J = 4.8 \ Hz), \ 3.92 \ (s, \ 3H), \ 6.78 \ (d, \ 1H, \ J = 8.7 \ Hz), \ 3.43-3.47 \ (m, \ 2H), \ 3.33 \ (s, \ 3H), \ 2.07 \ (s, \ 3H). \]  

\[ ^{13}C \ \text{NMR} \ (75 \ MHz, \ CDCl_3, \ \text{TMS}) : \delta = 166.6, \ 145.8, \ 143.4, \ 138.0, \ 137.1, \ 133.9, \ 130.3, \ 128.2, \ 128.0, \ 127.8, \ 122.9, \ 114.8, \ 110.5, \ 70.2, \ 63.7, \ 58.8, \ 56.0, \ 19.8; \ \text{HPLC} \ (\text{Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, } \lambda = 254 \ nm) : t_{\text{major}} = 10.35 \ \text{min}, \ t_{\text{minor}} = 18.35 \ \text{min}, \ \text{ee} = 95\%; \ [\alpha]_D^{25.9} \text{ (major) } = +4.1 \ (c = 1.00, \ \text{CHCl}_3). \]

2-Phenoxyethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3q): White solid; quantitative yield, 90\% ee; $^{1}H$-NMR (300 MHz, CDCl$_3$) :  
\[ \delta = 7.97 \ (d, \ 1H, \ J = 6.9 \ Hz), \ 7.50 \ (d, \ 1H, \ J = 7.5 \ Hz), \ 7.40 \ (t, \ 1H, \ J = 7.5 \ Hz), \ 7.28-7.33 \ (m, \ 2H), \ 7.09 \ (d, \ 1H, \ J = 8.7 \ Hz), \ 6.96 \ (t, \ 1H, \ J = 7.2 \ Hz), \ 6.85 \ (d, \ 2H, \ J = 8.1 \ Hz), \ 6.64 \ (d, \ 2H, \ J = 8.7 \ Hz), \ 5.61 \ (s, \ 1H), \ 4.41 \ (t, \ 2H, \ J = 4.8 \ Hz), \ 3.89-3.98 \ (m, \ 2H), \ 3.74 \ (s, \ 3H), \ 2.07 \ (s, \ 3H). \]  

$^{13}C$ NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.8, \ 158.5, \ 145.6, \ 143.3, \ 138.0, \ 137.0, \ 134.1, \ 130.2, \ 129.5, \ 129.4, \ 128.5, \ 128.0, \ 122.8, \ 120.9, \ 114.7, \ 114.5, \ 110.4, \ 65.5, \ 63.0, \ 55.8, \ 19.9; \ \text{HPLC} \ (\text{Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, } \lambda = 254 \ nm) : t_{\text{major}} = 11.75 \ \text{min}, \ t_{\text{minor}} = 20.39 \ \text{min}, \ \text{ee} = 90\%; \ [\alpha]_D^{24.6} \text{ (major) } = +9.1 \ (c = 1.01, \ \text{CHCl}_3). \]

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3-(Benzyloxy)propyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3r): White solid; 97% yield, 96% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta = 7.89$ (d, 1H, $J = 7.8$ Hz), 7.49 (d, 1H, $J = 7.2$ Hz), 7.38 (t, 1H, $J = 7.5$ Hz), 7.27-7.34 (m, 5H), 7.15 (d, 1H, $J = 8.7$ Hz), 6.75 (t, 1H, $J = 8.7$ Hz), 5.60 (s, 1H), 4.47 (s, 3H), 4.19 (t, 2H, $J = 6.3$ Hz), 3.89 (s, 3H), 3.43 (t, 2H, $J = 6.3$ Hz), 2.07 (s, 3H), 3.43 (t, 2H, $J = 6.3$ Hz), 3.43 (quint, 2H, $J = 6.3$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.9$, 145.7, 143.3, 138.4, 138.0, 136.8, 133.8, 130.7, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 122.9, 114.9, 110.6, 73.0, 66.8, 62.0, 56.0, 28.9, 19.9; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 10.70$ min, $t_{\text{minor}} = 18.08$ min, ee = 96%; $[\alpha]_D^{25.0}$ (major) = +8.6 (c = 1.00, CHCl$_3$).

3-((Tert-butoxycarbonyl)amino)propyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3s): White solid; 95% yield, 94% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta = 7.88$ (dd, 1H, $J_1 = 0.6$ Hz, $J_2 = 7.5$ Hz), 7.49 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz), 7.39 (t, 1H, $J = 7.5$ Hz), 7.16 (d, 1H, $J = 8.7$ Hz), 6.78 (d, 1H, $J = 8.7$ Hz),
5.91 (s, 1H), 4.65 (s, 1H), 4.10 (t, 2H, J = 6.0 Hz), 3.91 (s, 3H), 3.04 (q, 2H, J = 6.3 Hz), 2.07 (s, 3H), 1.50-1.68 (m, 2H), 1.43 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 167.2, 155.8, 145.9, 143.5, 138.0, 136.8, 133.8, 130.7, 128.0, 122.9, 114.9, 110.7, 79.2, 62.3, 56.1, 37.4, 28.9, 18.4, 19.9; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, λ = 254 nm): tmajor = 8.73 min, tminor = 13.76 min, ee = 94%; [α]D²⁵.⁷ (major) = -7.7 (c = 1.00, CHCl₃).

1,3-Bis(benzyloxy)propan-2-yl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3t): colorless oil; 80% yield, 99% ee; ¹H-NMR (300 MHz, CDCl₃) : δ = 7.94 (dd, 1H, J₁ = 0.9 Hz, J₂ = 7.8 Hz), 7.50 (dd, 1H, J₁ = 0.6 Hz, J₂ = 7.5 Hz), 7.40 (t, 1H, J = 7.5 Hz), 7.26-7.35 (m, 10H), 7.10 (d, 1H, J = 8.7 Hz), 6.69 (d, 1H, J = 8.7 Hz), 5.56 (s, 1H), 5.25 (quint, 1H, J = 5.1 Hz), 4.47-4.52 (m, 4H), 3.83 (s, 3H), 3.43-3.58 (m, 4H), 2.07 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 166.2, 145.8, 143.4, 138.2, 138.0, 136.9, 133.9, 130.7, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 122.9, 114.9, 110.5, 68.5, 68.4, 56.0, 19.9; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 75:25 at 0.5 mL/min, λ = 254 nm): tmajor = 14.43 min, tminor = 25.05 min, ee = 99%; [α]D²⁵.⁶ (major) = +6.5 (c = 1.00, CHCl₃).
Phenyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3u): White solid; 75% yield, 96% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : δ = 8.10 (d, 1H, $J$ = 7.5 Hz), 7.57 (d, 1H, $J$ = 7.5 Hz), 7.47 (t, 1H, $J$ = 7.8 Hz), 7.31 (t, 2H, $J$ = 7.2 Hz), 7.15-7.18 (m, 2H), 6.97 (d, 2H, $J$ = 7.8 Hz), 6.74 (d, 2H, $J$ = 8.7 Hz), 5.67 (s, 1H), 3.88 (s, 3H), 2.13 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 165.3, 150.9, 145.8, 143.4, 138.3, 137.5, 134.4, 130.0, 129.2, 128.5, 128.1, 127.4, 127.4, 123.1, 121.6, 114.7, 110.8, 56.0, 19.9; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 75:25 at 0.5 mL/min, λ = 210 nm): $t_{\text{major}} = 15.93$ min, $t_{\text{minor}} = 26.88$ min, ee = 96%; $[\alpha]_{D}^{25.0}$ (major) = +7.9 (c = 1.00, CHCl$_3$).

4-(Methylthio)phenyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3v): White solid; 60% yield, 93% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : δ = 8.07 (dd, 1H, $J_1$ = 0.9 Hz, $J_2$ = 7.5 Hz), 7.56 (d, 1H, $J$ = 7.5 Hz), 7.46 (t, 1H, $J$ = 7.8 Hz), 7.21 (d, 2H, $J$ = 8.7 Hz), 7.16 (d, 1H, $J$ = 8.7 Hz), 6.90 (d, 2H, $J$ = 8.7 Hz), 6.74 (d, 1H, $J$ = 8.7 Hz), 5.67 (s, 1H), 3.88 (s, 3H), 2.44 (s, 3H), 2.12 (s, 3H). $^{13}$C NMR
(75 MHz, CDCl₃, TMS): δ = 165.3, 148.7, 145.8, 143.4, 138.4, 137.5, 135.3, 134.5, 129.9, 128.5, 128.2, 127.4, 123.1, 122.0, 114.7, 110.8, 56.1, 19.9, 16.6; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 75:25 at 0.5 mL/min, λ = 210 nm): \( t_{\text{major}} = 19.87 \text{ min}, t_{\text{minor}} = 37.23 \text{ min}, \text{ee} = 93\%; [\alpha]_D^{25.0} (\text{major}) = +15.4 \text{ (c = 1.00, CHCl}_3). \)

4-Bromophenyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (3w): White solid; 65% yield, 90% ee; \(^1\)H-NMR (300 MHz, CDCl₃): \( \delta = 8.07 \) (dd, 1H, \( J_1 = 0.9 \text{ Hz}, J_1 = 7.8 \text{ Hz} \)), 7.57 (dd, 1H, \( J_1 = 0.6 \text{ Hz}, J_1 = 7.5 \text{ Hz} \)), 7.48 (d, 1H, \( J = 7.5 \text{ Hz} \)), 7.40-7.44 (m, 2H), 7.16 (d, 1H, \( J = 8.7 \text{ Hz} \)), 6.84-6.87 (m, 2H), 6.75 (d, 1H, \( J = 8.7 \text{ Hz} \)), 5.67 (s, 1H), 3.89 (s, 3H), 2.12 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl₃, TMS): \( \delta = 165.0, 150.0, 145.8, 143.4, 138.5, 137.6, 134.6, 132.3, 129.5, 128.5, 128.2, 127.3, 123.4, 123.0, 118.6, 114.6, 110.8, 56.1, 19.9; \) HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 75:25 at 0.5 mL/min, λ = 210 nm): \( t_{\text{major}} = 17.31 \text{ min}, t_{\text{minor}} = 35.81 \text{ min}, \text{ee} = 90\%; [\alpha]_D^{25.1} (\text{major}) = 13.8 \text{ (c = 1.00, CHCl}_3). \)
3,5-Dimethylphenyl (R)-6’-bromo-2’-hydroxy-3’-methoxy-6-methyl-[1,1’-biphenyl]-2-carboxylate (3x): White solid; 76% yield, 98% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : δ = 8.07 (dd, 1H, $J_1 = 0.6$ Hz, $J_2 = 7.5$ Hz), 7.56 (dd, 1H, $J_1 = 0.6$ Hz, $J_2 = 7.5$ Hz), 7.46 (d, 1H, $J = 7.5$ Hz), 7.16 (t, 1H, $J = 8.7$ Hz), 6.80 (d, 1H, $J = 0.6$ Hz), 6.74 (d, 2H, $J = 8.7$ Hz), 6.58 (s, 2H), 5.66 (s, 1H), 3.88 (s, 3H), 2.26 (s, 6H), 2.12 (s, 3H). 13C NMR (75 MHz, CDCl$_3$, TMS): δ = 165.4, 150.7, 145.8, 143.4, 139.0, 138.3, 137.4, 134.3, 130.2, 128.4, 128.1, 127.5, 127.3, 123.0, 119.1, 114.8, 110.7, 56.0, 21.2, 19.9; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 75:25 at 0.5 mL/min, λ = 210 nm): t$_{\text{major}}$ = 11.68 min, t$_{\text{minor}}$ = 19.69 min, ee = 98%; $[^\alpha]_D^{25.0}$ (major) = +7.0 (c = 1.00, CHCl$_3$).

![3x](image)

o-Tolyl (R)-6’-bromo-2’-hydroxy-3’-methoxy-6-methyl-[1,1’-biphenyl]-2-carboxylate (3y): White solid; 50% yield, 97% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : δ = 8.14 (dd, 1H, $J_1 = 0.6$ Hz, $J_2 = 7.8$ Hz), 7.58 (dd, 1H, $J_1 = 0.6$ Hz, $J_2 = 7.5$ Hz), 7.47 (t, 1H, $J = 7.8$ Hz), 7.40-7.43 (m, 1H), 7.10-7.16 (m, 3H), 6.90 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), 6.72 (t, 1H, $J = 8.7$ Hz), 5.65 (s, 1H), 3.87 (s, 3H), 2.12 (s, 6H). 13C NMR (75 MHz, CDCl$_3$, TMS): δ = 164.8, 149.5, 145.8, 143.4, 138.4, 134.4, 137.8, 134.4, 130.9, 130.5, 129.6, 128.4, 128.1, 126.8, 125.8, 125.2, 123.1, 121.8, 114.6, 110.8, 56.0, 19.9, 16.1; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 70:20 at 0.5 mL/min, λ = 210 nm): t$_{\text{major}}$ = 16.31 min, t$_{\text{minor}}$ = 24.16 min, ee = 97%; $[^\alpha]_D^{25.0}$ (major) = +4.4 (c = 1.00, CHCl$_3$).
4-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-4,6-dimethyl-[1,1'-biphenyl]-2-carboxylate (3z): White solid; quantitative yield, 94% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta$ = 8.14 (d, 2H, $J = 8.7$ Hz), 7.77 (s, 1H), 7.31-7.34 (m, 3H), 7.06 (d, 1H, $J = 8.7$ Hz), 6.63 (d, 1H, $J = 8.7$ Hz), 5.57 (s, 1H), 5.17 (d, 2H, $J = 2.7$ Hz), 3.84 (s, 3H), 2.42 (s, 3H), 2.02 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 166.7, 147.5, 145.6, 143.3, 143.1, 138.0, 135.2, 134.0, 129.8, 128.9, 128.5, 127.6, 123.5, 122.9, 115.0, 110.3, 65.1, 55.9, 21.1, 19.8; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 75:25 at 0.5 mL/min, $\lambda = 254$ nm): $t_{major} = 22.98$ min, $t_{minor} = 36.17$ min, ee = 94%; $\left[\alpha\right]_D^{25.4}$ (major) = +12.6 (c = 1.00, CHCl$_3$).

4-Nitrobenzyl (R)-6'-bromo-6-ethyl-2'-hydroxy-3'-methoxy-[1,1'-biphenyl]-2-carboxylate (3aa): White solid; 97% yield, 97% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta$ = 8.15 (d, 2H, $J = 8.7$ Hz), 7.95 (d, 1H, $J = 7.5$ Hz), 7.57 (d, 1H, $J = 6.9$ Hz), 7.47 (t, 1H, $J = 7.8$ Hz), 7.35 (d, 2H, $J = 8.4$ Hz), 7.06 (d, 1H, $J = 8.7$ Hz), 6.64 (d, 1H, $J = 8.7$ Hz), 5.59
(s, 2H), 5.13-5.23 (m, 2H), 3.85 (s, 3H), 2.37 (q, 2H, \( J = 7.5 \) Hz), 1.08 (t, 3H, \( J = 7.8 \) Hz).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): \( \delta = 166.6, 147.5, 145.5, 143.9, 143.5, 143.1, 136.3, 132.6, 130.0, 128.4, 128.2, 127.2, 123.5, 122.9, 115.2, 110.4, 65.1, 55.9, 26.1, 14.4\).

HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 85:15 at 0.5 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 29.96 \) min, \( t_{\text{minor}} = 55.29 \) min, ee = 97%; \([\alpha]D^{25.2}\) (major) = +5.6 (c = 1.00, CHCl\(_3\)).

4-Nitrobenzyl (R)-6-benzyl-6'-bromo-2'-hydroxy-3'-methoxy-[1,1'-biphenyl]-2-carboxylate (3ab): White solid; 94% yield, 96% ee; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) : \( \delta = 8.14 \) (d, 2H, \( J = 8.4 \) Hz), 7.96 (d, 1H, \( J = 7.2 \) Hz), 7.33-7.45 (m, 4H), 7.14-7.21 (m, 3H), 7.06 (d, 1H, \( J = 8.7 \) Hz), 6.98 (d, 1H, \( J = 6.6 \) Hz), 6.63 (d, 1H, \( J = 8.7 \) Hz), 5.13-5.24 (m, 2H), 3.83 (s, 3H), 3.71 (d, 2H, \( J = 2.1 \) Hz). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): \( \delta = 166.7, 147.5, 145.6, 143.3, 143.1, 138.0, 135.2, 134.0, 129.8, 128.9, 128.5, 127.6, 123.5, 122.9, 115.0, 110.3, 65.1, 55.9, 21.1, 19.8\).

HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 75:25 at 0.5 mL/min, \( \lambda = 254 \) nm): \( t_{\text{major}} = 27.63 \) min, \( t_{\text{minor}} = 57.39 \) min, ee = 95%; \([\alpha]D^{25.5}\) (major) = +19.0 (c = 1.00, CHCl\(_3\)).
4-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-6-isopropyl-3'-methoxy-[1,1'-biphenyl]-2-carboxylate (3ac): White solid; 92% yield, 94% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta = 8.15$ (d, 2H, $J = 8.7$ Hz), 7.92 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.8$ Hz), 7.64 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.8$ Hz), 7.51 (t, 1H, $J = 7.8$ Hz), 7.36 (d, 2H, $J = 8.7$ Hz), 7.06 (d, 1H, $J = 8.7$ Hz), 6.65 (d, 1H, $J = 8.7$ Hz), 5.59 (s, 1H), 5.12-5.23 (m, 2H), 3.85 (s, 3H), 2.58-2.67 (m, 1H), 1.17 (d, 3H, $J = 6.9$ Hz), 1.11 (d, 3H, $J = 6.9$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.7, 148.8, 147.5, 145.5, 143.8, 143.2, 135.3, 130.1, 130.0, 128.6, 128.4, 128.1, 127.1, 123.5, 122.8, 115.5, 110.4, 65.1, 55.9, 30.3, 24.1, 23.6; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 65:35 at 0.5 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 13.33$ min, $t_{\text{minor}} = 31.76$ min, ee = 94%; $[\alpha]_D^{25.1}$ (major) = +4.1 (c = 1.00, CHCl$_3$).

4-Nitrobenzyl (R)-1-(6-bromo-2-hydroxy-3-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (3ad): White solid; quantitative yield, 92% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta = 8.14$ (d, 2H, $J = 8.7$ Hz), 7.88 (d, 1H, $J = 8.1$ Hz), 7.38 (d, 2H, $J = 8.7$ Hz), 7.24 (d, 1H, $J = 8.1$ Hz), 7.06 (d, 1H, $J = 8.7$ Hz), 6.63 (d, 1H, $J = 8.7$ Hz)
Hz), 5.12-5.23 (m, 2H), 3.85 (s, 3H), 2.89 (t, 2H, $J = 5.7$ Hz), 2.29 (t, 2H, $J = 6.0$ Hz), 1.71-1.77 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.4$, 147.5, 145.6, 143.3, 143.1, 143.0, 137.3, 137.0, 129.4, 128.3, 127.6, 126.9, 123.4, 122.9, 114.7, 110.3, 64.9, 55.9, 30.4, 26.8, 22.9, 22.3; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 75:25 at 0.5 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 27.18$ min, $t_{\text{minor}} = 52.71$ min, ee = 92%; $[\alpha]_{D}^{25.6}$ (major) = +19.4 (c = 1.00, CHCl$_3$).

![Image](image.png)

4-Nitrobenzyl (R)-2'-bromo-6-ethyl-6'-hydroxy-[1,1'-biphenyl]-2-carboxylate (3ae):
White solid; 97% yield, 97% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta = 8.16$ (d, 2H, $J = 8.7$ Hz), 7.94 (d, 1H, $J = 7.5$ Hz), 7.61 (d, 1H, $J = 7.2$ Hz), 7.53 (t, 1H, $J = 7.8$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz), 7.14 (d, 1H, $J = 7.8$ Hz), 7.07 (d, 1H, $J = 8.1$ Hz), 6.86 (d, 1H, $J = 8.1$ Hz), 5.18 (s, 2H), 4.61 (s, 1H), 2.33-2.41 (m, 2H), 1.10 (t, 3H, $J = 7.8$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.5$, 153.7, 145.1, 142.7, 134.2, 133.1, 131.4, 129.9, 129.4, 128.6, 128.5, 124.6, 123.8, 123.6, 114.4, 65.5, 26.1, 14.5; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 80:20 at 0.5 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 17.47$ min, $t_{\text{minor}} = 22.42$ min, ee = 62%; $[\alpha]_{D}^{25.1}$ (major) = +4.1 (c = 1.00, CHCl$_3$).
1,3-Bis(benzyloxy)propan-2-yl (R)-2'-bromo-6-ethyl-6'-hydroxy-[1,1'-biphenyl]-2-carboxylate (3ag): colorless oil; 84% yield, 96% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta$ = 7.91 (dd, 1H, $J_1$ = 1.2 Hz, $J_2$ = 7.5 Hz), 7.57 (d, 1H, $J$ = 7.8 Hz), 7.50 (d, 1H, $J$ = 7.8 Hz), 7.26-7.32 (m, 10H), 7.14 (dd, 1H, $J_1$ = 1.2 Hz, $J_2$ = 8.1 Hz), 7.06 (t, 1H, $J$ = 8.1 Hz), 6.81 (dd, 1H, $J_1$ = 0.9 Hz, $J_2$ = 7.8 Hz), 5.20-5.27 (m, 1H), 4.46 (s, 4H), 3.39-3.56 (m, 4H), 2.31-2.40 (m, 2H), 1.09 (t, 3H, $J$ = 7.8 Hz). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 166.5, 154.0, 144.7, 138.0, 134.1, 132.6, 132.1, 129.7, 129.2, 128.6, 128.3, 128.2, 127.6, 124.6, 123.9, 114.7, 73.2, 72.0, 68.6, 68.3, 26.1, 14.5; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 85:15 at 0.5 mL/min, $\lambda$ = 254 nm): t$_{major}$ = 10.88 min, t$_{minor}$ = 15.38 min, ee = 96%; $[^{\alpha}]D^{25.3}$ (major) = -4.5 (c = 1.00, CHCl$_3$).

1,3-Bis(benzyloxy)propan-2-yl (S)-1-(2-hydroxy-4,6-dimethylphenyl)-2-naphthoate (3ah): colorless oil; 56% yield, 90% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : $\delta$ = 7.92-8.04 (m, 4H), 7.58 (dd, 1H, $J_1$ = 1.2 Hz, $J_2$ = 8.1 Hz), 7.43-7.50 (m, 2H), 7.29-7.36(m, 10H), 7.50 (d, 1H, $J$ = 7.8 Hz), 7.26-7.32 (m, 10H), 6.68 (s, 1H), 6.62 (s, 1H), 5.29-5.34 (m, 1H), 4.43-
4.48 (m, 5H), 3.39-3.56 (m, 4H), 2.35 (s, 3H), 1.75 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 167.3, 153.0, 138.6, 138.0, 137.7, 135.1, 134.9, 132.4, 130.0, 128.6, 128.3, 128.1, 128.0, 127.6, 127.3, 126.6, 125.9, 123.0, 122.4, 113.8, 73.1, 72.0, 68.5, 68.4, 21.3, 19.7; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 80:20 at 0.5 mL/min, $\lambda$ = 254 nm): t$_{\text{major}}$ = 10.11 min, t$_{\text{minor}}$ = 13.91 min, ee = 90%; $[\alpha]_{D}^{25.2}$ (major) = +14.6 (c = 1.00, CHCl$_3$).

1,3-Bis(benzyloxy)propan-2-yl (S)-2-(3-bromo-2-hydroxynaphthalen-1-yl)-3,5-dimethylbenzoate (3ai): colorless oil; 71% yield, 96% ee; $^{1}$H-NMR (300 MHz, CDCl$_3$) : $\delta = 7.98$ (s, 1H), 7.77 (s, 1H), 7.62-7.65 (m, 1H), 7.38-7.39 (m, 1H), 7.20-7.34 (m, 11H), 7.13-7.16 (m, 2H), 7.03-7.06 (m, 1H), 5.42 (s, 1H), 5.02 (quint, 1H, 5.4 Hz), 4.37 (s, 2H), 4.18 (s, 2H), 3.23 (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 10.5$ Hz), 3.14 (dd, 1H, $J_1 = 5.7$ Hz, $J_2 = 10.5$ Hz), 3.03 (dd, 1H, $J_1 = 5.4$ Hz, $J_2 = 10.2$ Hz), 2.81 (dd, 1H, $J_1 = 5.7$ Hz, $J_2 = 10.2$ Hz), 2.47 (s, 3H), 1.92 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.9, 146.2, 139.0, 138.4, 138.0, 135.0, 132.6, 132.5, 131.0, 130.8, 129.4, 129.2, 128.3, 128.2, 127.6, 127.4, 127.0, 126.8, 124.4, 124.2, 121.8, 112.2, 73.1, 72.9, 71.6, 68.3, 67.9, 21.1, 19.8; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 97:3 at 0.4 mL/min, $\lambda$ = 254 nm): t$_{\text{major}}$ = 55.96 min, t$_{\text{minor}}$ = 42.98 min, ee = 96%; $[\alpha]_{D}^{25.5}$ (major) = +3.3 (c = 1.00, CHCl$_3$).
1,3-Bis(benzyloxy)propan-2-yl (S)-2-(2-hydroxynaphthalen-1-yl)-3,5-dimethylbenzoate (3aj): colorless oil; 57% yield, 93% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : δ = 7.68-7.74 (m, 3H), 7.38 (s, 1H), 7.11-7.32 (m, 13H), 7.00-7.03 (m, 1H), 5.00 (quint, 1H, 5.4 Hz), 4.26-4.35 (m, 2H), 4.17 (s, 2H), 3.07-3.19 (m, 2H), 2.95-3.00 (m, 1H), 2.77-2.82 (m, 1H), 2.45 (s, 3H), 1.88 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 167.3, 150.1, 139.8, 138.6, 134.9, 133.6, 133.2, 130.0, 129.1, 129.0, 128.9, 128.2, 127.9, 127.5, 127.4, 126.5, 124.0, 123.2, 119.6, 117.6, 73.0, 72.9, 71.7, 68.3, 67.9, 21.1, 19.7; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 85:15 at 0.5 mL/min, λ = 254 nm): t$_{major}$ = 12.13 min, t$_{minor}$ = 17.30 min, ee = 93%; $[\alpha]_{D}^{25.5}$ (major) = -28.9 (c = 1.00, CHCl$_3$).

1,3-Bis(benzyloxy)propan-2-yl (S)-3'-(benzyloxy)-2'-hydroxy-[1,1'-binaphthalene]-2-carboxylate (3ak): white solid; 79% yield, 91% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : δ = 8.16 (d, 1H, J = 8.7 Hz), 8.01 (d, 1H, J = 8.7 Hz), 7.95 (d, 1H, J = 8.1 Hz), 7.10 (d, 1H, J = 8.1 Hz), 7.54 (dt, J$_1$ = 1.2 Hz, J$_2$ = 8.1 Hz), 7.15-7.45 (m, 19H), 7.03-7.08 (m, 1H), 6.94 (d, 1H, J = 8.4 Hz), 5.86 (s, 1H), 5.18-5.27 (m, 2H), 5.10 (quint, 1H, J = 5.4 Hz), 4.30-4.39
(m, 2H), 4.17-4.27 (m, 2H), 3.11-3.29 (m, 3H), 2.94 (dd, $J_1 = 5.7$ Hz, $J_2 = 10.5$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 166.9$, 146.1, 142.9, 138.1, 135.9, 135.4, 135.2, 132.6, 129.7, 129.3, 128.8, 128.5, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 126.8, 126.7, 126.4, 124.7, 124.6, 123.9, 119.0, 106.8, 73.0, 72.9, 71.6, 71.0, 68.4, 68.1; HPLC (Daicel CHIRALCEL IC column, hexane/iPrOH = 70:30 at 0.5 mL/min, $\lambda = 254$ nm): $t_{\text{major}} = 16.80$ min, $t_{\text{minor}} = 19.98$ min, ee = 91%; $[\alpha]_D^{21.7}$ (major) = -21.6 (c = 1.00, CHCl$_3$).

(R)-6-bromo-2'-(hydroxymethyl)-3-methoxy-6'-methyl-[1,1'-biphenyl]-2-ol (4): white solid; 93% yield, 94% ee; $^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.42$ (d, 1H, $J = 7.2$ Hz), 7.37 (t, 1H, $J = 7.5$ Hz), 7.28 (d, 1H, $J = 7.5$ Hz), 7.23 (d, 1H, $J = 8.7$ Hz), 6.80 (d, 1H, $J = 8.7$ Hz), 5.76 (s, 1H), 4.28-4.38 (m, 2H), 3.93 (s, 3H), 2.03 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 146.2$, 143.5, 138.9, 137.1, 134.9, 129.6, 128.7, 126.1, 123.6, 115.4, 111.2, 64.0, 56.1, 19.7; HPLC (Daicel CHIRALCEL AD column, hexane/iPrOH = 85:15 at 0.5 mL/min, $\lambda = 210$ nm): $t_{\text{major}} = 18.62$ min, $t_{\text{minor}} = 26.01$ min, ee = 94%; $[\alpha]_D^{25.3}$ (major) = +17.7 (c = 1.00, CHCl$_3$).
(S)-2-(2-(hydroxymethyl)naphthalen-1-yl)-3,5-dimethylphenol (5): white solid; 95% yield, 90% ee; $^1$H-NMR (300 MHz, CDCl$_3$) : δ = 7.87 (d, 2H, $J = 8.4$ Hz), 7.65 (d, 1H, $J = 8.4$ Hz), 7.46-7.51 (m, 1H), 7.36-7.38 (m, 2H), 6.78 (s, 1H), 6.70 (s, 1H), 6.46 (s, 2H), 2.36 (s, 3H), 1.77 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 153.1, 139.2, 138.0, 137.4, 133.4, 132.5, 131.2, 128.9, 128.2, 126.8, 126.4, 126.2, 125.4, 123.3, 121.0, 114.0, 63.7, 21.3, 19.7; HPLC (Daicel CHIRALCEL AS-H column, hexane/iPrOH = 70:30 at 0.5 mL/min, λ = 254 nm): $t_{\text{major}} = 8.36$ min, $t_{\text{minor}} = 12.01$ min, ee = 90%; $[\alpha]_D^{22}$ (major) = +14.2 (c = 0.51, MeOH).

2.6 References


Chapter 3
Aryl Amine Catalyzed Cascade Reactions

3.1 Anilines Promoted Cyclization-Replacement Cascade Reactions of 2-Hydroxycinnamaldehydes with Various Carbonic Nucleophiles

3.11 Introduction

$N, O$-acetals (also called hemiaminal ethers) are useful building blocks in organic synthesis (Scheme 3.1). They are widely used for the formation of C-C bonds via carbon centered nucleophilic substitution reactions. It is observed that the extrusion of the “O” moiety in $N, O$-acetals is generally favored because of the poorer leaving tendency of “N” and/or higher stability of formed iminium ions (Scheme 3.1). Furthermore, the processes are generally required by a Brønsted or Lewis acid and/or elevated temperature. Although cyclic $N, O$-acetals are also widely used in these processes, still the extrusion of “O” are often seen with “N” embedded in ring structures. Furthermore, to make “O” contained heterocycles, cyclic acetals or hemiacetals are generally used. These precedent studies reflect the challenge in replacement of “N” moiety in $N, O$-acetals by a nucleophile. In addition, $N, O$-acetals are often required to be preformed.

Scheme 3.1. Well studied $N, O$-acetals in "O" involved nucleophilic substitutions reactions

We recently challenged the dogma by developing a new mild approach capable of
direct substitution of “N” component in $N, O$-acetals by carbon nucleophiles. Moreover, we proposed to engineer a method for \textit{in situ} formation of $N, O$-acetal precursors (Scheme 3.2). Therefore, it is expected that the amine shall bestow two fold functions: a leaving group and a promoter for the formation of $N, O$-acetals. The cascade process would produce an unprecedented powerful catalytic approach in $N, O$-acetal involved synthesis.$^{19}$

\textbf{Scheme 3.2.} Proposed amine catalyzed cyclization-“N” involved nucleophilic substitution cascade reaction via an \textit{in situ} formed $N, O$-acetals

\begin{center}
\includegraphics[width=\textwidth]{Scheme3.2.png}
\end{center}

3.12 Research Plan

Our working hypothesis was inspired by our previous study of an iminium ion initiated Michael-Michael cascade reaction that serves as a one-pot protocol for generation of chiral chromanes.$^{20}$ An interesting $N, O$-acetal intermediate 8 is observed in this process by reaction of an \textit{o}-hydroxy-\textit{trans}-cinnamaldehyde 5 with a chiral amine 7 (Scheme 3.3, Eq. 1). Subsequent reaction of the $N, O$-acetal 8 with a \textit{trans}-nitroolefin leads to formation of chromane 6 and concurrent regeneration of the amine catalyst. Analysis of this observation led us to question if the hemiaminal intermediate 8/12 could undergo a direct substitution reaction with nucleophiles. The realization of this process could offer an alternative approach to 2-substituted $2H$-chromenes 11,$^{21,22}$ a class of ‘privileged’ structures
with a broad range of interesting biological activities. They have served as targets for a number of synthetic studies.

**Scheme 3.3.** Amine catalyzed Michael-Michael and proposed cyclization-substitution cascade reactions

Herein we wish to disclose a conceptually novel amine catalyzed formation of $N, O$-acetals from $\alpha, \beta$-unsaturated aldehydes, followed by subsequent substitution by a nucleophile in an efficient catalytic cascade fashion. In this investigation, we uncovered simple aromatic amines that promote cyclization-substitution cascade reactions of $o$-hydroxy trans-cinnamaldehydes 5 with various nucleophiles 9 including indoles, pyrroles, naphthols, phenols and silyl enol ethers (Scheme 3.3, Eq. 2). Notably, it is found that aromatic amines 10 with balanced nucleophilicity and leaving tendency are critical for the cascade processes via *in situ* generated $N, O$-acetals 12. These processes produce structurally diverse 2-substituted 2H-chromenes 11 with high chemo- and regio-selectively. Moreover, the mild reaction conditions enable the process to tolerate a broad range of sensitive functional groups.
3.13 Results and Discussion

3.131 Cyclization-substitution Cascade Reaction of 2-Hydroxylcinnamaldehydes with Electron Rich Arenes

3.131.1 Optimization of Reaction Conditions

As discussed above, the extrusion of the amine from the \(N, O\)-acetal intermediate 8/12 is notoriously difficult. We conceived that an amine with a good leaving tendency might be replaced by a nucleophile. Nonetheless, this property would also need to be balanced by the requirement that the amine serve as a good nucleophile to ensure effective addition to the aldehyde in the route for formation of the iminium ion. We believed that aromatic amines 10 would fulfil the requirements. Accordingly, in the exploratory studies, 2-hydroxylcinnamaldehyde 5a and indole 13a were used as the respective aldehyde and nucleophile reactants in the presence of an aromatic amine 10 (Table 3.1). To our delight, reaction of the these substrates in the presence of aniline (10a) gave rise to formation of the 2-(3-indolyl)chromene 14a, albeit in low yield (26%), along with its regioisomer 15a and an interesting by-product 16a (entry 1). Encouraged by the results, we surveyed other anilines containing various electron donating and withdrawing substituents (entries 1-5). The results show that although 4-fluoroaniline (10b) is superior to 4-methoxyaniline (10c) (entries 2 vs 3) as a catalyst for the double substitution reaction, more electron deficient analogues like 3,4-difluoroaniline (10d) and 4-nitroaniline (10e) are less effective (entries 4 and 5). Increasing steric bulkiness of the aniline, as in 2-methylaniline (10f) and 2,4-dimethylaniline (10g), leads to a deterioration of catalytic potency (entries 6 and 7). It was found that 2-hydroxylaniline 10h serves as an ideal catalyst for the process that generates 14a in modest yield (59%) and selectivity (3.5:1.3:1 14a:15a:16a, entry 8). In contrast, 4-
hydroxylaniline 10k (18% yield, 2.0:0.7:1, entry 11) and 2-methoxylaniline 10l (30%, 1.1:0.6:1, entry 12) are not effective catalysts. Moreover, anilines containing other o-
hydrogen bonding donor groups such as amines 10i and carboxylic acid 10j, and 10m
promote only low yielding processes (entries 9, 10 and 13).

Table 3.1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>Cat</th>
<th>t (h)</th>
<th>% yield</th>
<th>ratio of 14a:15a:16a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>24</td>
<td>26</td>
<td>0.9:0.5:1.0</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>24</td>
<td>34</td>
<td>1.6:0.6:1.0</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>24</td>
<td>11</td>
<td>0.3:0.4:1.0</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>24</td>
<td>12</td>
<td>0.2:0.4:1.0</td>
</tr>
<tr>
<td>5</td>
<td>10e</td>
<td>24</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>10f</td>
<td>24</td>
<td>11</td>
<td>1.2:0.5:1.0</td>
</tr>
<tr>
<td>7</td>
<td>10g</td>
<td>24</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>10h</td>
<td>24</td>
<td>59</td>
<td>3.5:1.3:1.0</td>
</tr>
<tr>
<td>9</td>
<td>10i</td>
<td>24</td>
<td>24</td>
<td>0.8:0.4:1.0</td>
</tr>
<tr>
<td>10</td>
<td>10j</td>
<td>24</td>
<td>28</td>
<td>1.2:0.8:1.0</td>
</tr>
<tr>
<td>11</td>
<td>10k</td>
<td>24</td>
<td>18</td>
<td>2.0:0.7:1.0</td>
</tr>
<tr>
<td>12</td>
<td>10l</td>
<td>24</td>
<td>30</td>
<td>1.1:0.6:1.0</td>
</tr>
<tr>
<td>13</td>
<td>10m</td>
<td>24</td>
<td>49</td>
<td>2.9:0.3:1.0</td>
</tr>
<tr>
<td>14**d</td>
<td>10h</td>
<td>24</td>
<td>63</td>
<td>17.0:1.3:1.0</td>
</tr>
<tr>
<td>15**d,e</td>
<td>10h</td>
<td>24</td>
<td>56</td>
<td>11.0:1.0:1.0</td>
</tr>
<tr>
<td>16**d,f</td>
<td>10h</td>
<td>24</td>
<td>70</td>
<td>12.0:1.0:0.0</td>
</tr>
<tr>
<td>17**d,f,g</td>
<td>10h</td>
<td>22</td>
<td>86</td>
<td>10.0:1.0:0.0</td>
</tr>
</tbody>
</table>
Reaction conditions: unless specified, a mixture of 5a (0.1 mmol), 13a (0.12 mmol), and catalyst (10, 0.01 mmol) in CH₂Cl₂ (0.5 mL) was stirred at rt. \(^b\)Isolated yields. \(^c\)Determined by using \(^1\)H NMR. \(^d\)4Å molecular sieves (MS) added. \(^e\)Ratio of 5a and 13a is 1 : 1.5. \(^f\)Ratio of 5a and 13a is 1.2 : 1. \(^g\)20 mol\% 10h used.

**Table 3.2. Investigation of solvent effect**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>t (h)</th>
<th>Yields (%) (^b)</th>
<th>Ratio (14a:15a:16a)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>24</td>
<td>70</td>
<td>12:1:0</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>48</td>
<td>51</td>
<td>9.3:1:1:1</td>
</tr>
<tr>
<td>3</td>
<td>CHCl₃</td>
<td>36</td>
<td>60</td>
<td>4.5:1:0</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>48</td>
<td>36</td>
<td>3.2:1:1:1</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>EtOAc</td>
<td>72</td>
<td>9</td>
<td>2.1:1.6:1</td>
</tr>
<tr>
<td>7</td>
<td>CH₃CN</td>
<td>72</td>
<td>11</td>
<td>2.1:1:0</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>MeOH</td>
<td>72</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>11(^d)</td>
<td>CH₂Cl₂</td>
<td>72</td>
<td>86</td>
<td>10:1:0</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: unless specified, a mixture of 5a (0.12 mmol), 13a (0.1 mmol), and catalyst (10h, 0.01 mmol) in indicated solvent (0.5 mL) was stirred at rt. \(^b\)Isolated yields. \(^c\)Determined by using \(^1\)H NMR. \(^d\)20 mol\% of 10h was used.

Further studies were carried out accordingly to optimize the reaction of 2-hydroxylcinnamaldehyde 5a with indole 13a promoted by aniline 10h. Unexpectedly, the addition of 4Å molecular sieves (MS) to the reaction mixture leads to a slight increase in
the yield (63%) and a dramatic increase in regioselectivity (17:1.3:1) (entry 14). Furthermore, increasing the ratio of 5a to 13a to 1.2:1 further enhanced the efficiency (70%) and regioselectivity (12:1:0) for formation of adduct 14a (entry 16). Raising the catalyst loading to 20 mol% further improved the yield (86%) while maintaining regioselectivity (10:1.0:0) of the process (entry 17). Of the solvents screened, CH₂Cl₂ was found to be optimal (Table 3.2). Therefore, the optimal reaction conditions for formation of 14a involve the use of 0.12 mmol of 5a (1.2 equiv), 0.1 mmol of 13a (1.0 equiv) and 20 mol% of 10h (0.2 equiv) in 0.5 mL of CH₂Cl₂ with 4Å MS.

3.1312 Investigation of Substrate Scope

An exploratory study was carried out to probe the cyclization-substitution cascade reactions of arene nucleophiles and trans-2-hydroxycinnamaldehyde catalyzed by 2-hydroxyaniline 10h (Scheme 3.4). We first examined potential electronic effects in the trans-2-hydroxycinnamaldehyde reactants using analogues containing electron-neutral (H, 14a), -withdrawing (Cl, 14b) and -donating (Me, 14c) substituents on the aromatic ring. Reactions of these substrates with indole under the optimal condition were found to proceed smoothly to produce corresponding 2H-chromenes 14a-c in high yields (69-90% yields) and with high regioselectivities (8.3:1 to 10:1 r. r.). A variety of electron rich arenes were then explored as potential nucleophiles in this process. The results demonstrate that indoles containing a wide variety of electronically different substituents react with aldehyde 5a under the optimal conditions to generate the corresponding adducts 14e-l. Furthermore, N-methyl indole also serves as a substrate for this reaction, which forms adduct 14m in high yield and with good regioselectivity (78% yield, 5.9:1). N-Methyl
pyrrole undergoes this reaction to generate exclusively the 2-pyrrole adduct \( \textbf{14n} \) in 52% yield. In this case as well as others in which less reactive nucleophiles are employed, tetrahydroquinoline \( \textbf{10m} \) was found to be superior to \( \textbf{10h} \) as a catalyst. In addition to indoles and pyrrole, naphthols and phenols are also applicable for this protocol, as exemplified by the observations that 1-naphthol and 2,3-dimethoxyphenol react smoothly with \( \textbf{5a} \) in the presence of aniline \( \textbf{10m} \) to form \( \textbf{14o} \) (50%) and \( \textbf{14p} \) (51%), respectively.

**Scheme 3.4.** Substrate scope of anilines catalyzed cyclization-substitution cascade reaction of \( \textbf{5} \) with electron-rich arenes \( \textbf{13}^{a} \)
**3.132 Cyclization-substitution Cascade Reaction of 2-hydroxycinnamaldehydes with Silyl Enol Ethers**

**3.1321 Optimization of Reaction Conditions**

To further demonstrate the versatility of the new strategy, reactions employing silyl enol ethers as nucleophiles were explored next. This effort was stimulated by the thought that cyclization-substitution cascade processes of this type would serve as a new method for Csp$^3$-Csp$^3$ bond formation. In advance of these studies, unlike the cases of above electron rich arenes, we were concerned about complications associated with the high reactivity/lability of silyl enol ethers under the conditions employed and the potential lack of regioselectivity of the processes associated with the possible operation of competitive 1,2- and 1,4-addition modes (e.g., 20 and 21) (Scheme 3.5). Finally, we were also concerned about the possible transilylation between the 2-hydroxy moiety of the cinnamaldehyde substrates and the silyl enol ether (e.g., 22), an occurrence that could

\[ ^a \text{Unless specified, see experimental section.} ^b \text{cat. 10m was used.} \]
complicate this process.

Scheme 3.5. Arylamine catalyzed cyclization-substitution cascade reactions of trans-hydroxycinnamaldehydes 5 with silyl enol ethers 17

To explore features of the proposed silyl enol ether addition process, 2-hydroxycinnamaldehyde 5a and the TMS derived silyl enol ether of acetophenone 17a were used as reactants and 2-hydroxyaniline 10h as catalyst. We observed that reaction of these substrates in a respective molar ratio of 1:1.5 under the optimized conditions described above generates the expected chromene 18a in 68% yield and a diastereomeric ratio of 4.3:1 (entry 4, Table 3.3). It is delightful that except for production of a trace amount of the conjugate addition product and acetophenone, this process is not complicated by formation of side products. In an attempt to improve the efficiency of the process, other aryl amine catalysts were explored (Table 3.3). It was found that the simple anilines with electronically different substituents (10a, 10b and 10c) gave similar results as 10h, indicating that ortho-OH doesn’t give the desired synergistic role for this substrates (entries 1-4). When stronger hydrogen bonding donors in the ortho position of anilines were tried
(carboxylic acid, \(10j\); 2-hydroxyl-5-nitroaniline, \(10n\)), lower yields were obtained (26%, 33%, entries 5, 6). Pleasingly, tetrahydroquinoline \(10m\) is an ideal promoter for this reaction, which generates \(18a\) in 82% yield and a 4.7:1 r.r. (entry 7). However, yield is lowered to 74% when the ratio of \(5a\) and \(17a\) is changed to 1:1.2 (entry 8. Encouraged by this results, other secondary aryl amine \(10o-s\) were tested, but no improved result was obtained (entries 9-13).

**Table 3.3. Optimization of reaction conditions\(^a\)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>%yields(^b)</th>
<th>r.r. ((18a:19a))(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(10a)</td>
<td>73</td>
<td>4.0:1</td>
</tr>
<tr>
<td>2</td>
<td>(10b)</td>
<td>68</td>
<td>4.5:1</td>
</tr>
<tr>
<td>3</td>
<td>(10c)</td>
<td>60</td>
<td>4.4:1</td>
</tr>
<tr>
<td>4</td>
<td>(10h)</td>
<td>68</td>
<td>4.3:1</td>
</tr>
<tr>
<td>5</td>
<td>(10j)</td>
<td>26</td>
<td>4.4:1</td>
</tr>
<tr>
<td>6</td>
<td>(10n)</td>
<td>33</td>
<td>4.3:1</td>
</tr>
<tr>
<td>7</td>
<td>(10m)</td>
<td>82</td>
<td>4.7:1</td>
</tr>
<tr>
<td>8(^d)</td>
<td>(10m)</td>
<td>74</td>
<td>5.0:1</td>
</tr>
<tr>
<td>9</td>
<td>(10o)</td>
<td>46</td>
<td>5.3:1</td>
</tr>
<tr>
<td>10</td>
<td>(10p)</td>
<td>73</td>
<td>4.5:1</td>
</tr>
<tr>
<td>11</td>
<td>(10q)</td>
<td>29</td>
<td>4.9:1</td>
</tr>
<tr>
<td>12</td>
<td>(10r)</td>
<td>71</td>
<td>3.8:1</td>
</tr>
<tr>
<td>13</td>
<td>(10s)</td>
<td>39</td>
<td>4.1:1</td>
</tr>
</tbody>
</table>
3.132 Investigation of Substrate Scope

Studies probing the substrate scope of the reaction showed that some 2-hydroxycinnamaldehydes (e.g., 5b, 5d, 5f, and 5v) participate in low yielding reaction with TMS derived silyl enol ether 17a (Scheme 3.6). Analysis of these reactions reveals that transfer of the TMS moiety from 17a to the 2-hydroxy group in the trans-2-hydroxycinnamaldehydes 5 is the major reason for the diminished efficiencies of these reactions. To overcome this problem, the bulkier 2,6-di-tert-butyldimethylsilyl (TBS) ether of acetophenone was employed as the substrate. Indeed, in reactions with this silyl enol ether, the silyl transfer process is less competitive and the yields of the respective chromene forming reactions with 5b, 5d, 5f and 5v increased dramatically (80% vs 60% for 18b, 76% vs 47% for 18d, 86% for vs 68% for 18f and 29% vs 0% for 18v) (Scheme 3.6). Furthermore, the regioselectivities of all reactions of the TBS are significantly improved and the amount of the silyl enol ether reactant can be decreased to 1.1 equiv..

An examination of the TBS-enol ether scope of addition reactions of aldehyde 5a showed that sterically demanding, ortho-substituted acetophenone derived enol ethers only inefficiently participate in this process (e.g., 48% yield for formation of 18l). Nonetheless, both unhindered para- and meta-analogs react to efficiently generate corresponding adducts (e.g., 18h-k). Moreover, TBS-enol ethers of polycyclic aromatic containing methyl ketones, such as that derived from 2-acetylphenanthrene also react with 5a to form adduct (e.g., 80%,
13:1 r.r. 18m) in high yield and regioselectivity. The benzylideneacetone derived TBS-silyl enol ether also reacts to form chromene 18n in 90% yield and 5:1 r.r., as do those arising from heteroaryl methyl ketones like 2-acetylfuran (85%, 18o), 2-acetylthiophen (87%, 18p) and 3-acetylindole (68%, 18q). Non-terminal TBS-enol ethers are also effective substrates, each producing mixtures of diastereomeric chromenes containing two stereogenic centers as exemplified by the conversion of the (E)-TBS-enol ether of butyrophenone to 18r in a 62% yield and with a 4:1 d.r. Similarly, endocyclic TBS-enol ethers of cyclic ketones also react with 5a. For example, the silyl enol ethers of 1-tetralone reacts to form 18s with a high degree of regioselectivity but only modest diastereoselectivity. Similar trends are followed in reactions of the TBS-enol ethers of cyclohexanone and cyclopentanone. Although we originally believed that aldehyde derived silyl enol ethers might be more challenging substrates for this process, we found that the TBS-enol ether of hexanal reacts with 5a to produce the desired product 18v albeit in low yield. It is noteworthy that the TMS-enol ether of hexanal failed to react to generate chromene 18v but the TMS-enol ether of isobutyraldehyde reacts with 5a to form the quaternary carbon containing product 18w in 42% yield and with a 1:0 r. r.. In contrast, the TBS analog of this aldehyde does not undergo this reaction.

**Scheme 3.6.** Arylamine 10m catalyzed cyclization-substitution cascade reaction of cinnamaldehyde derivatives 15 and silyl enol ethers 17a
Unless specified, see experimental section. Isolated yield. The relative stereochemistry was not assigned for this product mixture. Relation configuration is determined by comparison known compounds in ref. 18.

3.133 Asymmetric Cyclization-Substitution Cascade Reaction

Encouraged by the obtained results, asymmetric variant of the cyclization-substitution cascade reaction using chiral aniline as catalyst was also investigated. Devising an efficient chiral aryl amine catalysts is the key point of the success. (S)-(-)-Indoline-2-carboxylic acid and (R)-(+)-1,1’-Binaphthyl-2,2’-diamine are commercially available chiral aryl amines possessing distinct chiral scaffolds. Therefore, we focused on the development of new catalysts derived from their chiral core structures. Many different chiral aryl amines have been prepared and were tested for the asymmetric cascade reaction (table 3.4). (R)-(+)-1,1’-Binaphthyl-2,2’-diamine 10t and its trifluoromethanesulfonate (Tf) protected derivative 10u gave the racemic product (entries 1 and 2). Unfortunately, indoline-2-carboxylic acid 10v didn’t provide any enantioselectivity neither (entry 3).
contrast, (S)-(−)-methyl indoline-2-carboxylic acid 10w produce 14a in 49% yield and 20% ee (entry 4). To further increase enantioselectivity, bulkier (S)-(−)-isopropyl indoline-2-carboxylic acid 10x was also tested, but no improvement was observed (entry 5). Different amides derived from (S)-(−)-Indoline-2-carboxylic acid (10y, 10z) gave racemic 14a. Unexpectedly, methyl phenyl-L-phenylalaninate 10ac didn’t even promote the reaction. Although only a low enantioselectivity was obtained so far, it is promising to achieve high enantioselectivity by devising a proper chiral catalyst, which is undergoing in our lab.

Table 3.4 Asymmetric cyclization-substitution cascade reaction of 2-hydroxycinnamaldehyde 5a and indole 13a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yields %</th>
<th>ee % (14a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10t</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>10u</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>10v</td>
<td>46</td>
<td>-3</td>
</tr>
<tr>
<td>4</td>
<td>10w</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>10x</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>10y</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>10z</td>
<td>73</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>10aa</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>10ab</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>10ac</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*aReaction conditions: unless specified, a mixture of 5a (0.12 mmol), 13a (0.1 mmol), and
a catalyst 10 (0.01 mmol) in CH₂Cl₂ (0.5 mL) was stirred at rt for 24h. ⁶Isolated yield. ⁶determined by HPLC.

### 3.134 Synthetic Applications

As discussed above, chromenes and chromanes scaffolds widely present in a number of natural products and bioactive compounds. The new method we have developed can serve as the powerful tool to construct interestingly substituted members of these heterocyclic families. To demonstrate the synthetic utility of the new protocol, we designed a 2-step route for preparation of the chromene natural product, candenatenin E (25), isolated from the Thai medicinal plant D. candenatensis heartwood (Scheme 3.7).⁴⁷ (E)-4-Hydroxy-3-(3-oxoprop-1-en-1-yl)phenyl pivalate (5h), a readily available starting material, undergoes efficient reaction with 2,3-dimethoxyphenol (23) in the presence of 20 mol% amine catalyst 10m at 40 °C to give the desired product 24 in 54% yield and a 6.8:1 r.r. Racemic candenatenin E (25) is then generated in nearly quantitative yield by simple base promoted saponification of the pivalate ester moiety in 24.

**Scheme 3.7. Two-step synthesis of Candenenine E⁶**
We also used the new method to install a chromene group at the C-3 position of 5-butyl-2-(4-methoxyphenyl)-1H-indole 26. Specifically, reaction of 26 with cinnamaldehyde derivative 5a, catalyzed by aniline 10h produces the potentially bioactive indole-chromene 27 in 68% yield (Scheme 3.8).48

Scheme 3.8. Functionalization of bioactive indole contained compounda

3.135 Mechanistic Study

The studies described above have produced new amine catalyzed cyclization-nucleophilic substitution cascade reactions. These processes, which do not require the use of acid additives or elevated temperatures to activate N, O-acetals in a catalytic manner, take place under mild reaction conditions in high yields and with high degrees of chemoselectivity and regio-selectivity. The key to the success of these processes is the identification of aniline derivatives as catalysts, which have properly balanced nucleophilicities and leaving abilities. The nucleophilicity is essential for the effective reaction with aldehyde to form an iminium ion for the initial cyclization step. However, the good leaving propensity leads to the capacity for the catalyst regeneration. For example, we observed that the more nucleophilic Jørgensen–Hayashi diphenylpyrrolinol TMS catalyst 7 in reaction between cinnamaldehyde 5a and indole (13a) is sufficiently nucleophilic to promote formation of
the iminium intermediate, which then undergoes cyclization to form the N, O-acetal \( \text{8} \) (Scheme 3.9).

However, its poor leaving tendency prevents the subsequent nucleophilic substitution process even with an acid additive (e.g., \( \text{CF}_3\text{CO}_2\text{H} \)).

**Scheme 3.9.** The Results of experiments designed to gain preliminary understanding the mechanism of the cyclization-substitution cascade process

To understand the new aminocatalytic cyclization-substitution process, we carried out more detailed investigation. In this effort, we observed that treatment of aldehyde \( 5\text{a} \)
with a stoichiometric amount of 4-fluoroaniline 10b within 1 h leads to generation of N, O-acetal 28 in quantitative yield (Eq. 1, Scheme 3.9). The N, O-acetal is stable and can be purified and characterized. Moreover, 28 was found to react with indole 13a to form the substitution products 14a and 15a in a combined 61% yield and 3.9:1 r.r. (Eq. 2). Furthermore, preformed hemiacetal 29 does not react with indole 13a under the standard reactions conditions in the presence of 10b, which suggests that the route does not undergo through the hemiacetal (Eq. 3). In addition, we found that trans-cinnamaldehyde 30 does not react with indole 13a in the presence of 10b under the standard reaction conditions. This outcome shows that the cascade process does not takes place via a pathway involving initial addition of indole to the iminium ion formed between the aldehyde and aniline catalyst (Eq. 4). In a similar manner, trans-cinnamaldehyde 30 does not react with tert-butylidimethyl((1-phenylvinyl)oxy)silane 17a in the presence of 10m (Eq. 5).

Scheme 3.10. Proposed catalytic cycle
Based on these experiments, a possible catalytic cycle is proposed (Scheme 3.10). The formation of key $N, O$-acetal 12 from an aniline and trans-2-hydroxycinnamaldehydes 5 is involved. It is noted that two possible pathways exist for the substitution reaction between the $N, O$-acetal 12 and a nucleophile, the first involving direct displacement of the amine by the nucleophile in a concerted process and the second involving stepwise initial loss of the amine followed by addition of the nucleophile to the formed oxonium ion (structure not shown). At the current time, we have no evidence that enables distinction between these two possibilities.

3.14 Conclusion

In the study described above, we developed an unprecedented, aryl amine catalyzed cyclization-substitution cascade reaction for the ‘one-pot’ synthesis of 2-substituted 2$H$-chromenes. Unlike widely used strategies, the protocol employs simple amines as activators for formation of $N, O$-acetals and subsequent direct substitution by nucleophiles under mild conditions without requiring the use of acids or elevated temperatures. Notably, the process takes place in high yields and with high degrees of chemo- and regio-selectivity, and it shows a broad nucleophile substrate scope including indoles, pyroles, phenols and silyl enol ethers. Furthermore, the synthetically value of the new method is demonstrated by its use in a 2-step synthesis of the natural product, candenatenin E, and the facile installation of 2-substituted 2$H$-chromene moiety in biologically active indoles. Importantly, the process developed in this study represents the first example of direct germinal functionalization of aldehydes in a catalytic fashion.
3.2 Cyclization-Substitution Cascade Reactions of Hemiacetals and Various Carbonic Nucleophiles

3.21 Introduction

1,3-Dihydroisobenzofuran and isochromane are privileged scaffolds in pharmaceuticals and natural products with diverse biological activities, such as escitalopram,\textsuperscript{49,50} sonepiprazole,\textsuperscript{51,52} penidicitrinin B\textsuperscript{53} and (-)-Berkelic acid\textsuperscript{54} (Scheme 3.11). Cross Dehydrogenative Coupling (CDC) of 1,3-dihydroisobenzofuran or isochroman with various nucleophiles is a straightforward method for the synthesis of such structures.\textsuperscript{55-57} Liu developed Cross Dehydrogenative Coupling of cyclic ethers and potassium alkynyltrifluoroborates in the presence of trityl ion and GaCl\textsubscript{3}.\textsuperscript{56} A TBHP promoted oxidative cross coupling of isochroman and indoles was also achieved.\textsuperscript{55} The limitation in these protocols is the requirement of a stoichiometric amount of oxidants. Therefore, a mild and efficient method for the synthesis of substituted 1,3-Dihydroisobenzofuran and isochroman is highly desired.

Scheme 3.11. Drugs and natures products containing 1,3-Dihydroisobenzofuran or isochroman
3.22 Research Plan

Recently, we discovered the new reactivity of $N, O$-acetal 12 with the replacement of arylamine by nucleophiles (Scheme 3.12, eq. 1). Hemiacetals 35(c) and its open form-alcohol aldehyde 35(o) can isomerize quickly at room temperature. As expected, a mixture of 35(c) and 35(o) (1:1.8) was obtained by treating phthalide with Dibal-H. We envision that the open form species 35b is trapped by amine to generate a new $N, O$-acetal 36 that will be replaced by various nucleophiles giving 37. This protocol proceeds in mild condition, showing a very broad substrate scope.

Scheme 3.12. Previous and proposed cyclization-substitution cascade reaction
3.23 Results and Discussion

3.231 Optimization of Reaction Condition

To test our hypothesis, 2-(hydroxymethyl)benzaldehyde 35a and indole were used as model substrates in the presence of 20 mol% catalyst and 4Å molecular sieve (Table 3.5). Both 10h and 10m, optimal catalysts in the previous protocol, only provide 37a in 28% and 9% yields respectively (entries 2, 3). Indoline 10p is proved to be a superior catalyst, providing 37a in 51% yield (entry 5). Encouraged by this result, we screened other indoline derivatives (entries 6-10). (S)-Indoline-2-carboxylic acid 10t further improve yield to 71%, which may be attributed to the synergistic effect of carboxylic acid (entry 6). However, only racemic product was obtained although chiral aryl amine catalyst was employed. (S)-Methyl indoline-2-carboxylate 10u without the carboxylic acid provides 54% yield (entry 7). Indoline derived amides (10v and 10w) also offered inferior results (entries 8 and 9). Normal CH2Cl2 gave higher yield (74%) than dry CH2Cl2 (entry 11). However, addition of 10 μL H2O deteriorates yield (20%, entry 12). Decreasing catalyst loading to 10 mol% gave diminished yield (65% yield, entry 13). By studying the reaction mixture, the dimer 38 was found to be a major byproduct. To solve this problem, the ratio of reactants was tuned. Decreasing 35a/13a to 1/1.2 gave lower yield (entry 14). By contrast, increasing 35a/13a to 1.5/1 boosts yield to 90% (entry 15). Solvent screening indicates that CH2Cl2 is the best solvent (table 3.6).
Table 3.5. Optimization of reaction condition$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>catalyst</th>
<th>t (h)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>10h</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>10m</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>10o</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>10p</td>
<td>40</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
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<td>40</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>10v</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>10w</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>10x</td>
<td>40</td>
<td>Trace</td>
</tr>
<tr>
<td>11$^b$</td>
<td>10t</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>12$^c$</td>
<td>10t</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>13$^{bd}$</td>
<td>10t</td>
<td>48</td>
<td>65</td>
</tr>
<tr>
<td>14$^{bf}$</td>
<td>10t</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>15$^{bg}$</td>
<td>10t</td>
<td>48</td>
<td>90</td>
</tr>
</tbody>
</table>

$^a$Unless specified, see experimental section. $^b$Normal CH$_2$Cl$_2$. $^c$Addition of 10μL H$_2$O. $^d$10 mol% catalyst loading. $^{35a/13a} = 1/1.2$. $^{35a/13a} = 1.5/1.$
Table 3.6. Investigation of solvent effect

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>DCE</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>CHCl₃</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>43</td>
</tr>
</tbody>
</table>

*Unless specified, see experimental section.

3.232 Investigation of Substrate Scope

With the optimized condition, the substrate scope is investigated (scheme 3.13). Electronic effects in 2-(hydroxymethyl)benzaldehydes seems very limited. Both electron neutral (35a) and withdrawing substituents (35b, 37c) participated in the reaction smoothly. 2-(1-hydroxyethyl)benzaldehyde 35d with methyl substituent at the other side of hemiacetal proved to be a valid substrate to give 37d in 93% yield and 1.3:1 dr. Besides five member ring, six member ring-isochroman-1-ol 35e with only 2% of open form and 6H-benzo[c]chromen-6-ol 35f were also tolerated to deliver the desired products in 77% and 100% respectively. Indoles with electron neutral (37a), donating (37g and 37h) and withdrawing substituents (37i-37l) are tolerated in this protocol. Notably, Indole-6-carboxaldehyde 13l is also a valid substrate, showing even aldehyde is well tolerated. 2-phenylindole react smoothly, producing 37m in 100% yield in 48h. Allyl 13n and benzyl 13o protected indoles are also proved to be valid substrates. Besides indoles, other electron
rich arenes were also tested. Pyrrole 13p, N-methyl pyrrole 13q, 2-naphthol 13r and 1-naphthol 13s all work well in this protocol. Then, we focused on the formation of C\textsubscript{sp3}-C\textsubscript{sp3} bonds instead of C\textsubscript{sp3}-C\textsubscript{sp2} bonds through the employment of silyl enol ethers as nucleophiles. Acetophenones derived TBS-silyl enol ether showed good tolerance of substituents, such as electron neutral (13t), donating (13u) and withdrawing substituents (13v, 13w). 2-thiophene acetophenone derived TBS-silyl enol ether is a valid substrate, providing 37x in 91% yield in 72h. Both 2-acetylphenanthrene and benzylideneacetone derived silyl enol ethers work well, producing 37y and 37z in 80% and 51% yields respectively.

Scheme 3.13. Arylamine 10t catalyzed cyclization-substitution cascade reaction of 35 and 13
Unless specified, see experimental section.

3.24 Synthetic Application

To prove the significance of this protocol, total synthesis of sonepiprazole was also accomplished (Scheme 3.14). Under the optimized condition, 2-(2-hydroxyethyl)benzaldehyde 35e reacted with 17a, affording 19 in 94% yield. After several reported steps, sonepiprazole can be obtained.58
3.25 Conclusion

In conclusion, an aryl amine catalyzed cyclization-substitution cascade reaction of hemiacetals and various carbonic nucleophiles has been developed through the utilization of the new reactivity of N, O-acetal. This protocol occurred in mild condition, showing a rather broad substrate scope. Indoles, pyrrole, naphthalols and silyl enol ethers are all valid nucleophiles. The total synthesis of sonepiprazole was accomplished.

3.3 Experimental Section

General Information:

Commercially available reagents were used without further purification. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F254 were used for thin-layer chromatography (TLC) analysis. $^1$H and $^{13}$C NMR spectra were recorded on Bruker Advance 500 and 300. Chemical shifts in $^1$H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm) or tetramethylsilane (TMS). Data for $^1$H NMR were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Herts (Hz) and integration.
**General Procedure for Cyclization-Substitution Cascade Reaction of 2-Hydroxy cinnamaldehydes and Electron Rich Arenes (Scheme 3.4):** To a solution of a 2-hydroxycinnamaldehyde 5 (0.12 mmol) in the presence of 20 mol % 10h, and 4Å molecular sieves (100 mg) in anhydrous dichloromethane (0.5 mL) was added an electron rich arene 13 (0.1 mmol). The resulting solution was stirred for a specified time (22-72 h) at room temperature and filtered through a short microcolumn of celite. Concentration of the filtrate gave a residue that was subjected to $^1$H NMR analysis. Isolation of the product was conducted by subjecting the residue to silica gel chromatography.

**General Procedure for Cyclization-Substitution Cascade Reaction of 2-Hydroxy cinnamaldehydes and Silyl Enol Ethers (Scheme 3.6):** To a solution of hydroxycinnamaldehyde 5 (0.1 mmol), 20 mol % 10m, and 4Å molecular sieves (100 mg) in anhydrous dichloromethane (0.5 mL) was added a specified silyl enol ether 17 (0.11 mmol). The resulting solution was stirred for 48 h at room temperature and filtered through a short microcolumn of celite. Concentration of the filtrate in vacuum gave a residue that was subjected to $^1$H NMR analysis. Isolation of the product was conducted by subjecting the residue to silica gel chromatography.

![Image](image.png)

**3-(2H-chromen-2-yl)-1H-indole (14a):** The title compound was prepared according to the
general procedure, as described above in 86% yield and with 10:1 r.r.. $^1$H NMR (300 MHz, CDCl₃, TMS): $\delta =$ 8.06 (s, 1H), 7.83 (d, 1H, $J =$ 7.8 Hz), 7.36 (d, 1H, $J =$ 6.9 Hz), 7.25-7.09 (m, 4H), 7.05 (d, 2H, $J =$ 7.5 Hz), 6.86 (dt, 1H, $JI =$ 0.9 Hz, $J2 =$ 8.1 Hz), 6.75 (d, 1H, $J =$ 7.8 Hz), 6.61 (dd, 1H, $JI =$ 1.2 Hz, $J2 =$ 9.9 Hz), 6.25 (dd, 1H, $JI =$ 1.8 Hz, $J2 =$ 3.3 Hz), 5.97 (dd, 1H, $JI =$ 3.6 Hz, $J2 =$ 9.6 Hz); $^{13}$C NMR (75 MHz, CDCl₃, TMS): $\delta =$ 153.5, 136.7, 129.2, 126.4, 126.1, 124.6, 124.5, 123.9, 122.5, 121.9, 121.0, 120.1, 119.8, 116.4, 115.7, 111.2, 70.4.

![Image of 15a](image1.png)

**3-(4H-chromen-4-yl)-1H-indole (15a):** $^1$H NMR (500 MHz, CDCl₃, TMS): $\delta =$ 7.99 (s, 1H), 7.62 (d, 1H, $J =$ 8.0 Hz), 7.36 (d, 1H, $J =$ 8.0 Hz), 7.16-7.22 (m, 1H), 7.03-7.19 (m, 4H), 6.94 (d, 1H, $J =$ 8.0 Hz), 6.87-6.90 (m, 1H), 6.64 (dd, 1H, $JI =$ 1.5 Hz, $J2 =$ 6.0 Hz), 5.10 (dd, 1H, $JI =$ 3.5 Hz, $J2 =$ 6.0 Hz), 4.99 (m, 1H).

![Image of 14b](image2.png)

**3-(6-Chloro-2H-chromen-2-yl)-1H-indole (14b):** The title compound was prepared according to the general procedure, as described above in 90% yield and with 10:1 r.r.. $^1$H NMR (300 MHz, CDCl₃, TMS): $\delta =$ 8.06 (s, 1H), 7.79 (d, 1H, $J =$ 7.5 Hz), 7.36 (d, 1H, $J =$ 7.8 Hz), 7.14-7.25 (m, 3H), 7.00 (d, 2H, $J =$ 11.4 Hz), 6.65 (d, 1H, $J =$ 8.4 Hz), 6.55 (d,
1H, $J = 9.9$ Hz), 6.23 (s, 1H), 6.01 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 151.9$, 136.7, 128.7, 126.0, 125.7, 125.6, 124.1, 123.5, 123.2, 122.7, 120.2, 119.7, 117.7, 115.1, 111.3, 70.5.

3-(8-Methyl-2H-chromen-2-yl)-1H-indole (14c): The title compound was prepared according to the general procedure, as described above in 69% yield and with 8.3:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.93$ (s, 1H), 7.87 (d, 1H, $J = 7.5$ Hz), 7.31 (d, 1H, $J = 7.5$ Hz), 7.23-7.10 (m, 3H), 6.90 (t, 2H, $J = 7.5$ Hz), 6.74 (t, 1H, $J = 7.5$ Hz), 6.60 (d, 1H, $J = 9.6$ Hz), 6.26 (d, 1H, $J = 3.3$ Hz), 6.99 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.6$ Hz), 2.07 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 151.3$, 136.7, 130.7, 126.3, 125.8, 124.0, 123.9, 123.8, 122.4, 121.6, 120.3, 120.0, 119.8, 115.8, 111.2, 70.0, 15.6.

4-Bromo-3-(2H-chromen-2-yl)-1H-indole (14d): The title compound was prepared according to the general procedure, as described above in 65% yield and with 1.0:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.12$ (s, 1H), 7.34 (d, 1H, $J = 7.5$ Hz), 7.25-7.23 (m, 2H), 6.99-7.09 (m, 3H), 6.90-6.82 (m, 2H), 6.77 (d, 1H, $J = 7.8$ Hz), 6.58 (dd, 1H, $J1 = 0.6$ Hz, $J2 = 9.9$ Hz), 6.02 (dd, 1H, $J1 = 3.9$ Hz, $J2 = 9.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 153.0$, 137.8, 129.2, 126.3, 126.2, 124.9, 124.8, 124.4, 123.9, 123.3, 122.1,
5-Bromo-3-(2H-chromen-2-yl)-1H-indole (14e): The title compound was prepared according to the general procedure, as described above in 48% yield and with 9.5:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.05$ (s, 1H), 7.95 (d, 1H, $J = 1.2$ Hz), 7.28 (dd, 1H, $JI = 1.5$ Hz, $J2 = 7.4$ Hz), 7.18-7.04 (m, 4H), 6.87 (t, 1H, $J = 7.5$ Hz), 6.76 (d, 1H, $J = 7.8$ Hz), 6.61 (dd, 1H, $J1 = 0.9$ Hz, $J2 = 8.7$ Hz), 6.15 (dd, 1H, $JI = 1.2$ Hz, $J2 = 3.0$ Hz), 5.93 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.6$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 153.3$, 135.3, 129.3, 127.8, 126.5, 125.4, 125.1, 124.9, 124.1, 122.4, 121.9, 121.2, 116.4, 115.2, 113.4, 112.7, 70.1.

6-Bromo-3-(2H-chromen-2-yl)-1H-indole (14f): The title compound was prepared according to the general procedure, as described above in 73% yield and with 7.9:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.00$ (s, 1H), 7.66 (d, 1H, $J = 8.4$ Hz), 7.43 (s, 1H), 7.23 (d, 1H, $J = 7.2$ Hz), 7.09-7.03 (m, 3H), 6.86 (t, 1H, $J = 7.5$ Hz), 6.73 (d, 1H, $J = 7.8$ Hz), 6.60 (d, 1H, $J = 9.9$ Hz), 6.17 (s, 1H), 5.92 (dd, 1H, $JI = 3.6$ Hz, $J2 = 9.6$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 153.2$, 137.4, 129.3, 126.5, 125.0, 124.7, 124.5, 124.2, 123.4, 121.8, 121.2, 121.1, 116.3, 115.8, 114.2, 70.2.
5-Chloro-3-(2H-chromen-2-yl)-1H-indole (14g): The title compound was prepared according to the general procedure, as described above in 71% yield and with 7.9:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta =$ 8.06 (s, 1H), 7.79 (d, 1H, $J = 1.8$ Hz), 7.24 (d, 1H, $J = 3.6$ Hz), 7.20 (s, 2H), 7.07-7.04 (m, 2H), 6.89-6.84 (m, 1H), 6.75 (d, 1H, $J = 8.1$ Hz), 6.61 (dd, 1H, $J1 = 1.2$ Hz, $J2 = 9.6$ Hz), 6.16 (dd, 1H, $J1 = 1.5$ Hz, $J2 = 3.3$ Hz), 5.93 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta =$ 153.3, 135.0, 129.3, 127.2, 126.5, 125.8, 125.3, 124.9, 124.2, 122.9, 121.9, 121.2, 119.4, 116.4, 115.3, 112.2, 70.1.

6-Chloro-3-(2H-chromen-2-yl)-1H-indole (14h): The title compound was prepared according to the general procedure, as described above in 74% yield and with 8.1:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta =$ 8.00 (s, 1H), 7.70 (d, 1H, $J = 8.4$ Hz), 7.27 (d, 1H, $J = 1.8$ Hz), 7.12-7.03 (m, 4H), 6.86 (dt, 1H, $J1 = 1.2$ Hz, $J2 = 7.2$ Hz), 6.73 (d, 1H, $J = 7.5$ Hz), 6.60 (dd, 1H, $J1 = 1.2$ Hz, $J2 = 9.6$ Hz), 6.17 (dd, 1H, $J1 = 1.5$ Hz, $J2 = 3.3$ Hz), 5.92 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta =$ 153.3, 137.0, 129.3, 128.4, 126.5, 124.7, 124.5, 124.2, 121.9, 121.2, 120.8, 120.7, 116.3, 115.7, 111.2, 70.2.
3-(2H-chromen-2-yl)-5-fluoro-1H-indole (14i): The title compound was prepared according to the general procedure, as described above in 65% yield and with 7.4:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.02$ (s, 1H), 7.45 (dd, 1H, $J_1$ = 2.4 Hz, $J_2$ = 9.6 Hz), 7.16-7.24 (m, 1H), 7.09-7.04 (m, 2H), 6.91-6.83 (m, 2H), 6.75 (d, 1H, $J = 7.8$ Hz), 6.61 (dd, 1H, $J_1$ = 1.2 Hz, $J_2$ = 9.9 Hz), 6.16 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 3.3 Hz), 5.92 (dd, 1H, $J_1$ = 3.6 Hz, $J_2$ = 9.6 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 158.0$ ($J_{CF} = 233.7$ Hz), 153.3, 133.1, 129.3, 126.5, 125.6, 124.7, 124.2, 121.9, 121.2, 116.3, 115.8, 115.7, 111.9 ($J_{CF} = 9.5$ Hz), 110.9 ($J_{CF} = 26.3$ Hz), 104.9 ($J_{CF} = 23.8$ Hz), 70.3; $^{19}$F NMR (282 Hz, CDCl$_3$): $\delta = -122.1$ Hz.

3-(2H-chromen-2-yl)-5-methoxy-1H-indole (14j): The title compound was prepared according to the general procedure, as described above in 76% yield and with 7.0:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.06$ (s, 1H), 7.82 (d, 1H, $J = 7.5$ Hz), 7.35 (d, 1H, $J = 7.8$ Hz), 7.24-7.12 (m, 3H), 6.95 (d, 1H, $J = 8.4$ Hz), 6.56 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 9.6$ Hz), 6.42 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz), 6.34 (d, 1H, $J = 2.4$ Hz), 5.82 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.6$ Hz), 3.70 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 162.7, 156.7, 138.7, 129.1, 128.1, 126.1, 125.9, 124.5, 123.6, 122.1, 121.8, 117.7, 117.2, 116.7, 113.2,
5-(Benzyloxy)-3-(2H-chromen-2-yl)-1H-indole (14k): The title compound was prepared according to the general procedure, as described above in 80% yield and with 10:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ = 7.85 (s, 1H), 7.44 (d, 2H, $J$ = 6.9 Hz), 7.39-7.28 (m, 4H), 7.15 (d, 1H, $J$ = 8.7 Hz), 7.04 (d, 3H, $J$ = 7.5 Hz), 6.90-6.71 (m, 2H), 6.72 (d, 1H, $J$ = 7.8 Hz), 6.57 (dd, 1H, $J_1$ = 1.5 Hz, $J_2$ = 9.9 Hz), 6.15 (dd, 1H, $J_1$ = 1.8 Hz, $J_2$ = 3.9 Hz), 5.90 (dd, 1H, $J_1$ = 3.6 Hz, $J_2$ = 9.6 Hz), 5.01 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 153.4, 137.5, 131.9, 129.2, 128.4, 127.7, 127.6, 126.4, 124.6, 124.5, 124.3, 122.0, 121.0, 116.4, 115.3, 113.5, 112.0, 103.1, 70.7, 70.6.

3-(2H-chromen-2-yl)-5-methyl-1H-indole (14l): The title compound was prepared according to the general procedure, as described above in 79% yield and with 8.9:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ = 7.89 (s, 1H), 7.59-7.58 (m, 1H), 7.18 (d, 1H, $J$ = 7.8 Hz), 7.00-7.08 (m, 4H), 6.85 (dt, 1H, $J_1$ = 1.2 Hz, $J_2$ = 5.6 Hz), 6.76-6.73 (m, 1H), 6.58 (dd, 1H, $J_1$ = 1.2 Hz, $J_2$ = 9.9 Hz), 6.19 (dd, 1H, $J_1$ = 1.8 Hz, $J_2$ = 3.3 Hz), 6.94 (dd, 1H, $J_1$ = 3.6 Hz, $J_2$ = 9.6 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 153.5, 135.0, 129.3, 129.1, 126.4, 126.3, 124.8, 124.4, 124.2, 124.1, 122.1, 121.0, 119.3, 116.4, 114.8, 110.9,
3-(2H-chromen-2-yl)-1-methyl-1H-indole (14m): The title compound was prepared according to the general procedure, as described above in 78% yield and with 5.9:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.80$ (d, 1H, $J = 7.8$ Hz), 7.29-7.20 (m, 2H), 7.16-7.11 (m, 1H), 7.08-7.02 (m, 3H), 6.84 (t, 1H, $J = 7.5$ Hz), 6.73 (d, 1H, $J = 7.8$ Hz), 6.59 (d, 1H, $J = 9.6$ Hz), 6.22 (dd, 1H, $J_{1} = 1.5$ Hz, $J_{2} = 3.6$ Hz), 5.94 (dd, 1H, $J_{1} = 3.6$ Hz, $J_{2} = 9.6$ Hz), 3.69 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 153.5$, 137.5, 129.1, 128.7, 126.7, 126.4, 124.7, 124.3, 122.0, 119.8, 119.6, 116.4, 113.9, 109.4, 70.3, 32.8. DEPT-135: 129.2, 128.7, 126.4, 124.7, 124.3, 122.0, 120.9, 119.8, 119.6, 116.4, 109.4, 70.3, 32.8.

2-(2H-chromen-2-yl)-1-methyl-1H-pyrrole (14n): The title compound was prepared according to the general procedure, as described above in 52% yield and with 1.0:0 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.07$ (dt, 1H, $J_{1} = 1.5$ Hz, $J_{2} = 7.5$ Hz), 7.02 (dd, 1H, $J_{1} = 1.5$ Hz, $J_{2} = 7.5$ Hz), 6.85 (dt, 1H, $J_{1} = 1.2$ Hz, $J_{2} = 7.2$ Hz), 6.73 (d, 1H, $J = 7.8$ Hz), 6.67 (t, 1H, $J = 2.1$ Hz), 6.61 (d, 1H, $J = 9.6$ Hz), 6.18 (dd, 1H, $J_{1} = 1.5$ Hz, $J_{2} = 3.3$ Hz), 6.03 (t, 1H, $J = 3.0$ Hz), 5.96 (dd, 1H, $J_{1} = 1.5$ Hz, $J_{2} = 3.6$ Hz), 5.89 (dd, 1H, $J_{1} = 3.6$ Hz, $J_{2} = 9.9$ Hz), 3.78 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 152.8$, 130.1, 129.2,
2-(2H-chromen-2-yl)naphthalen-1-ol (14o): The title compound was prepared according to the general procedure, as described above in 50% yield and with 1.0:0 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ = 8.13-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.45-7.41 (m, 3H), 7.28-7.18 (m, 3H), 6.95-6.88 (m, 2H), 6.73 (dd, 1H, $J_1 = 2.1$ Hz, $J_2 = 9.9$ Hz), 6.25 (t, 1H, $J = 2.7$ Hz), 5.91 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 154.8, 148.2, 134.5, 130.0, 128.2, 127.7, 126.5, 126.0, 125.9, 125.2, 124.5, 124.4, 122.9, 121.7, 121.4, 120.5, 116.9, 116.6, 75.8.

4-(2H-chromen-2-yl)-2,3-dimethoxyphenol (14p): The title compound was prepared according to the general procedure, as described above in 51% yield and with 1.0:0 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ = 7.10 (d, 1H, $J = 8.7$ Hz), 6.99 (d, 1H, $J = 6.9$ Hz), 6.78-6.87 (m, 2H), 6.53 (d, 1H, $J = 9.6$ Hz), 6.44 (d, 1H, $J = 8.7$ Hz), 6.25 (s, 1H), 6.08 (s, 1H), 5.80 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.6$ Hz), 3.92 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 146.7, 129.3, 126.5, 124.5, 124.0, 123.9, 123.0, 121.4, 121.0, 119.7, 116.0, 104.2, 103.7, 71.5, 61.0, 55.8.
2-(2H-chromen-2-yl)-1-phenylethan-1-one (18a): The title compound was prepared according to the general procedure, as described above in 80% yield and with 10:1 r.r.. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta = 7.93-7.94\) (m, 2H), 7.54-7.60 (m, 1H), 7.43-7.48 (m, 2H), 7.10 (dt, 1H, \(J_1 = 1.8\) Hz, \(J_2 = 8.1\) Hz), 6.99 (dd, 1H, \(J_1 = 1.8\) Hz, \(J_2 = 7.5\) Hz), 6.88 (dt, 1H, \(J_1 = 1.2\) Hz, \(J_2 = 7.5\) Hz), 6.74 (d, 1H, \(J = 10.8\) Hz), 6.65 (t, 1H, \(J = 9.6\) Hz), 5.86 (dd, 1H, \(J_1 = 3.6\) Hz, \(J_2 = 9.6\) Hz), 5.55-5.58 (m, 1H), 3.61 (dd, 1H, \(J_1 = 6.6\) Hz, \(J_2 = 16.5\) Hz), 3.24 (dd, 1H, \(J_1 = 6.6\) Hz, \(J_2 = 16.5\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): \(\delta = 197.2, 152.7, 136.8, 133.3, 129.3, 128.6, 128.2, 126.5, 125.0, 124.2, 121.5, 121.5, 121.3, 116.2, 71.6, 44.0\).

2-(6-Chloro-2H-chromen-2-yl)-1-phenylethan-1-one (18b): The title compound was prepared according to the general procedure, as described above in 80% yield and with 9.1:1 r.r.. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta = 7.91-7.95\) (m, 2H), 7.55-7.61 (m, 1H), 7.44-7.49 (m, 2H), 7.04 (dd, 1H, \(J_1 = 2.7\) Hz, \(J_2 = 8.7\) Hz), 6.96 (d, 1H, \(J = 2.7\) Hz), 6.65 (d, 1H, \(J = 8.7\) Hz), 6.39 (d, 1H, \(J = 9.6\) Hz), 5.91 (dd, 1H, \(J_1 = 3.9\) Hz, \(J_2 = 9.9\) Hz), 5.54-5.58 (m, 1H), 3.61 (dd, 1H, \(J_1 = 6.6\) Hz, \(J_2 = 16.5\) Hz), 3.23 (dd, 1H, \(J_1 = 6.6\) Hz, \(J_2 = 16.5\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): \(\delta = 196.8, 151.2, 136.7, 133.4, 128.9, 128.7, 128.2, 126.1, 126.0, 123.3 122.8, 117.5, 71.8, 43.8\).
2-(8-Methyl-2H-chromen-2-yl)-1-phenylethan-1-one (18c): The title compound was prepared according to the general procedure, as described above in 97% yield and with 12:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.93$-$7.96$ (m, 2H), 7.54-$7.60$ (m, 1H), 7.42-$7.48$ (m, 2H), 6.96 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.2$ Hz), 6.75-$6.86$ (m, 2H), 6.45 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 9.9$ Hz), 5.85 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 9.6$ Hz), 5.53-$5.58$ (m, 1H), 3.62 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 16.2$ Hz), 2.00 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 197.5$, 150.6, 137.1, 133.3, 130.9, 128.6, 128.3, 125.6, 124.7, 124.6, 124.3, 121.1, 120.7, 72.0, 44.0, 15.2.

2-(7-Bromo-2H-chromen-2-yl)-1-phenylethan-1-one (18d): The title compound was prepared according to the general procedure, as described above in 76% yield and with 12:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.92$-$7.96$ (m, 2H), 7.58-$7.62$ (m, 1H), 7.44-$7.49$ (m, 2H), 7.00 (dd, 1H, $J_1 = 4.8$ Hz, $J_2 = 8.1$ Hz), 6.89 (dd, 1H, $J_1 = 0.3$ Hz, $J_2 = 1.5$ Hz), 6.84 (d, 1H, $J = 8.1$ Hz), 6.40 (d, 1H, $J = 9.9$ Hz), 6.88 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 9.9$ Hz), 5.52-5.57 (m, 1H), 3.60 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 16.5$ Hz), 3.62 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 16.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 196.8$, 153.4, 136.7, 133.5, 128.7, 128.2, 127.5, 125.4, 124.4, 123.5, 121.9, 120.5, 119.6, 72.0, 44.0.
2-(6-Methoxy-2H-chromen-2-yl)-1-phenylethan-1-one (18e): The title compound was prepared according to the general procedure, as described above in 89% yield and with 13:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.93$-$7.95$ (m, 2H), 7.54-$7.69$ (m, 1H), 7.42-$7.48$ (m, 2H), 6.66 (d, 2H, $J = 1.5$ Hz), 6.57 (t, 1H, $J = 1.8$ Hz), 6.42 (dd, 1H, $J1 = 1.5$ Hz, $J2 = 9.9$ Hz), 6.90 (dd, 1H, $J1 = 3.9$ Hz, $J2 = 9.6$ Hz), 5.46-$5.51$ (m, 1H), 3.76 (s, 3H), 3.61 (dd, 1H, $J1 = 6.6$ Hz, $J2 = 16.5$ Hz), 3.22 (dd, 1H, $J1 = 6.6$ Hz, $J2 = 16.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 197.3$, 154.1, 146.5, 1369, 133.3, 128.6, 128.2, 126.1, 124.3, 122.2, 116.8, 114.4, 111.7, 71.5, 55.7, 43.6.

2-(6-Bromo-2H-chromen-2-yl)-1-phenylethan-1-one (18f): The title compound was prepared according to the general procedure, as described above in 86% yield and with 9.1:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.92$-$7.95$ (m, 2H), 7.58 (t, 1H, $J = 7.5$ Hz), 7.46 (t, 1H, $J = 7.5$ Hz), 7.18 (dd, 1H, $J1 = 2.4$ Hz, $J2 = 8.7$ Hz), 7.10 (d, 1H, $J = 2.4$ Hz), 6.60 (d, 1H, $J = 8.4$ Hz), 6.38 (d, 1H, $J = 9.9$ Hz), 5.90 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.9$ Hz), 5.54-$5.58$ (m, 1H), 3.61 (dd, 1H, $J1 = 6.6$ Hz, $J2 = 16.5$ Hz), 3.23 (dd, 1H, $J1 = 6.6$ Hz, $J2 = 16.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 196.8$, 151.8, 136.8, 133.5, 131.8, 129.0, 128.7, 128.7, 126.4, 123.4, 123.3, 118.0, 113.3, 71.8, 43.9.
**2-(5-Bromo-2H-chromen-2-yl)-1-phenylethan-1-one (18g):** The title compound was prepared according to the general procedure, as described above in 86% yield and with 6.4:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.94$ (d, 1H, $J = 8.1$ Hz), 7.58 (t, 1H, $J = 7.2$ Hz), 7.46 (t, 2H, $J = 7.2$ Hz), 7.10 (d, 1H, $J = 7.8$ Hz), 7.95 (t, 1H, $J = 8.1$ Hz), 6.80 (d, 1H, $J = 9.9$ Hz), 6.68 (d, 1H, $J = 7.8$ Hz), 5.97 (dd, 1H, $J1 = 3.0$ Hz, $J2 = 9.0$ Hz), 5.51-5.54 (m, 1H), 3.62 (dd, 1H, $J1 = 6.9$ Hz, $J2 = 16.8$ Hz), 3.22 (dd, 1H, $J1 = 6.3$ Hz, $J2 = 16.8$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 196.8, 153.9, 136.8, 133.5, 129.7, 126.7, 125.4, 123.2, 121.6, 121.5, 115.8, 71.6, 43.7$.

![Chemical Structure 18g](image)

**2-(2H-chromen-2-yl)-1-(p-tolyl)ethan-1-one (18h):** The title compound was prepared according to the general procedure, as described above in 88% yield and with 8.8:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.85$ (d, 1H, $J = 8.1$ Hz), 7.25 (d, 1H, $J = 7.8$ Hz), 7.07-7.12 (m, 1H), 6.98 (d, aH, $J = 7.2$ Hz), 6.87 (dt, 1H, $J1 = 0.9$ Hz, $J2 = 7.5$ Hz), 6.73 (d, 1H, $J = 8.1$ Hz), 6.44 (t, 1H, $J = 9.9$ Hz), 5.85 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.6$ Hz), 5.51-5.56 (m, 1H), 3.60 (dd, 1H, $J1 = 6.6$ Hz, $J2 = 16.2$ Hz), 3.21 (dd, 1H, $J1 = 6.6$ Hz, $J2 = 16.5$ Hz), 2.41 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 196.8, 152.8, 144.2, 134.5, 129.3, 128.4, 126.6, 125.2, 124.2, 121.6, 121.3, 116.3, 71.7, 44.0, 21.6$. 

![Chemical Structure 18h](image)
2-(2H-chromen-2-yl)-1-(4-fluorophenyl)ethan-1-one (18i): The title compound was prepared according to the general procedure, as described above in 78% yield and with 12:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.95$-$7.99$ (m, 2H), 7.07-$7.15$ (m, 3H), 6.99 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), 6.87 (dt, 1H, $J_1 = 0.9$ Hz, $J_2 = 7.5$ Hz), 6.71 (d, 1H, $J = 8.1$ Hz), 6.45 (d, 1H, $J = 9.9$ Hz), 5.42 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 9.6$ Hz), 5.51-5.56 (m, 1H), 3.59 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 16.5$ Hz), 3.19 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 16.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 195.6$, 165.9 (d, $J_{C-F} = 253.6$ Hz), 152.7, 133.5, 131.0 (d, $J_{C-F} = 9.3$ Hz), 129.4, 126.6, 124.9, 124.3, 121.5, 121.4, 116.3, 115.7 (d, $J_{C-F} = 21.8$ Hz), 71.7, 44.0; $^{19}$F NMR (282 MHz, CDCl$_3$), $\delta = 103.1$.

2-(2H-chromen-2-yl)-1-(m-tolyl)ethan-1-one (18j): The title compound was prepared according to the general procedure, as described above in 82% yield and with 12:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.73$-$7.75$ (m, 2H), 7.31-$7.40$ (m, 2H), 6.99 (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.8$ Hz), 6.99 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), 6.99 (dt, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz), 6.73 (d, 1H, $J = 5.1$ Hz), 6.45 (d, 1H, $J = 9.9$ Hz), 5.86 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 9.9$ Hz), 5.53-5.57 (m, 1H), 3.62 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 16.5$ Hz), 3.25 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 16.5$ Hz), 2.40 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 197.4$, 197.0, 165.4, 133.5, 131.0 (d, $J_{C-F} = 9.3$ Hz), 129.4, 126.6, 124.9, 124.3, 121.5, 121.4, 116.3, 115.7 (d, $J_{C-F} = 21.8$ Hz), 71.7, 44.0; $^{19}$F NMR (282 MHz, CDCl$_3$), $\delta = 103.1$. 

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1-(3-Bromophenyl)-2-(2H-chromen-2-yl)ethan-1-one (18k): The title compound was prepared according to the general procedure, as described above in 72% yield and with 19:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.06$ (s, 1H), 7.85 (d, 1H, $J = 7.8$ Hz), 7.69 (d, 1H, $J = 7.8$ Hz), 7.33 (t, 1H, $J = 7.8$ Hz), 7.10 (d, 1H, $J = 7.8$ Hz), 6.99 (d, 1H, $J = 6.3$ Hz), 6.88 (d, 1H, $J = 7.5$ Hz), 6.71 (d, 1H, $J = 8.1$ Hz), 6.45 (d, 1H, $J = 9.9$ Hz), 5.83 (dd, 1H, $J1 = 3.6$ Hz, $J2 = 9.9$ Hz), 5.49-5.55 (m, 1H), 3.58 (dd, 1H, $J1 = 6.9$ Hz, $J2 = 16.5$ Hz), 3.18 (dd, 1H, $J1 = 6.3$ Hz, $J2 = 16.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 195.9, 152.6, 138.7, 136.2, 131.4, 130.2, 129.4, 126.8, 126.6, 124.7, 124.5, 123.0, 121.5, 116.3, 71.6, 44.1.

1-(2-Chlorophenyl)-2-(2H-chromen-2-yl)ethan-1-one (18l): The title compound was prepared according to the general procedure, as described above in 48% yield and with 19:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.49$-7.52 (m, 1H), 7.29-7.42 (m, 3H), 7.08 (dt, 1H, $J1 = 1.5$ Hz, $J2 = 7.8$ Hz), 6.96 (dd, 1H, $J1 = 1.5$ Hz, $J2 = 7.2$ Hz), 6.85 (t, 1H, $J = 7.2$ Hz), 6.69 (d, 1H, $J = 8.1$ Hz), 6.44 (d, 1H, $J = 9.9$ Hz), 5.80 (dd, 1H, $J1 = 3.6$ Hz).
Hz, $J_2 = 9.6$ Hz), 5.47-5.52 (m, 1H), 3.57 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 16.5$ Hz), 3.22 (dd, 1H, $J_1 = 5.4$ Hz, $J_2 = 16.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 200.2$, 152.5, 139.1, 131.9, 130.9, 130.5, 129.4, 129.2, 127.0, 126.6, 124.5, 124.4, 121.4, 121.3, 116.2, 71.6, 48.2.

2-(2H-chromen-2-yl)-1-(phenanthren-2-yl)ethan-1-one (18m): The title compound was prepared according to the general procedure, as described above in 80% yield and with 13:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.68-8.74$ (m, 2H), 8.44 (s, 1H), 8.18-8.21 (m, 1H), 7.91-7.93 (m, 1H), 7.77-7.81 (m, 2H), 7.67-7.70 (m, 2H), 7.11 (t, 1H, $J = 7.5$ Hz), 7.02 (d, 1H, $J = 7.2$ Hz), 6.90 (d, 1H, $J = 7.5$ Hz), 6.74 (d, 1H, $J = 8.1$ Hz), 6.49 (d, 1H, $J = 9.6$ Hz), 5.92 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.6$ Hz), 5.60-5.66 (m, 1H), 3.80 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 16.2$ Hz), 3.37 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 16.2$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 197.0$, 152.8, 134.7, 133.6, 133.1, 131.4, 129.9, 129.7, 129.3, 128.7, 128.0, 127.8, 127.3, 127.0, 126.6, 125.1, 125.0, 124.3, 123.3, 123.2, 121.6, 121.4, 116.4, 71.9, 44.2.

(E)-1-(2H-chromen-2-yl)-4-phenylbut-3-en-2-one (18n): The title compound was prepared according to the general procedure, as described above in 90% yield and with
5.0:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.51$-$7.57$ (m, 3H), $7.39$-$7.41$ (m, 3H),
7.11 (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.8$ Hz), $6.99$ (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), $6.88$ (dt,
1H, $J_1 = 0.9$ Hz, $J_2 = 7.2$ Hz), $6.78$ (d, 1H, $J = 4.5$ Hz), $6.74$ (d, 1H, $J = 3.6$ Hz), $6.45$ (d,
1H, $J = 9.9$ Hz), $5.81$ (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 9.9$ Hz), $5.43$-$5.48$ (m, 1H), $3.32$ (dd, 1H,
$J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz), $2.92$ (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 15.6$ Hz); $^{13}$C NMR (75 MHz,
CDCl$_3$, TMS): $\delta = 197.2$, $152.7$, $143.6$, $134.4$, $130.6$, $129.3$, $129.0$, $128.4$, $126.6$, $126.5$,
$125.0$, $124.3$, $121.6$, $121.4$, $116.3$, $71.8$, $45.9$.

[Chemical structure image]

2-(2H-chromen-2-yl)-1-(furan-2-yl)ethan-1-one (18o): The title compound was
prepared according to the general procedure, as described above in 85% yield and with
5.0:1 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.58$ (dd, 1H, $J_1 = 0.9$ Hz, $J_2 = 1.5$ Hz),
7.18 (dd, 1H, $J_1 = 0.6$ Hz, $J_2 = 3.6$ Hz), $7.08$ (dt, 1H, $J_1 = 1.8$ Hz, $J_2 = 7.8$ Hz), $6.98$ (dd,
1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), $6.87$ (dt, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz), $6.70$ (d, 1H, $J = 8.1$
Hz), $6.53$ (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 3.6$ Hz), $6.45$ (d, 1H, $J = 9.6$ Hz), $5.80$ (dd, 1H, $J_1 =$
$3.6$ Hz, $J_2 = 9.9$ Hz), $5.48$-$5.53$ (m, 1H), $3.48$ (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 15.6$ Hz), $3.03$
(dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 15.6$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 185.9$, $152.7$,
$152.5$, $146.7$, $129.3$, $126.6$, $124.6$, $124.4$, $121.5$, $121.4$, $117.9$, $116.3$, $112.3$, $71.5$, $44.0$.

[Chemical structure image]
2-(2H-chromen-2-yl)-1-(thiophen-2-yl)ethan-1-one (18p): The title compound was prepared according to the general procedure, as described above in 87% yield and with 7.2:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.65$-$7.67$ (m, 2H), 7.00-$7.07$ (m, 2H), 6.97-$7.00$ (m, 1H), 6.87 (t, 1H, $J = 7.5$ Hz), 6.71 (d, 1H, $J = 8.1$ Hz), 6.46 (d, 1H, $J = 9.9$ Hz), 5.83 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.6$ Hz), 5.49-$5.55$ (m, 1H), 3.60 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz), 3.13 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 15.6$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 189.8, 152.6, 144.4, 134.2, 132.6, 129.3, 128.1, 126.6, 124.7, 124.4, 121.5, 121.4, 116.3, 71.7, 44.8.$

![Chemical structure](image)

Tert-butyl 3-(2-(2H-chromen-2-yl)acetyl)-1H-indole-1-carboxylate (18q): The title compound was prepared according to the general procedure, as described above in 68% yield and with 4.6:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.40$-$8.43$ (m, 1H), 8.11-8.15 (m, 2H), 7.36-$7.40$ (m, 2H), 7.10 (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.8$ Hz), 7.00 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), 6.88 (dt, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz), 6.72 (d, 1H, $J = 7.8$ Hz), 6.47 (d, 1H, $J = 9.9$ Hz), 5.86 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 9.9$ Hz), 5.54-$5.60$ (m, 1H), 3.53 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz), 3.11 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 15.6$ Hz), 1.69 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 193.0, 152.7, 149.0, 135.6, 132.7, 129.3, 127.3, 126.6, 125.6, 125.1, 124.5, 124.3, 122.7, 121.6, 121.4, 120.6, 116.3, 115.0, 85.4, 71.8, 45.4, 28.1.$
**18r**

(S)-2-((R)-2H-chromen-2-yl)-1-phenylbutan-1-one (18r): The title compound was prepared according to the general procedure, as described above in 62% yield and with 1.0:0 r.r. and 4.0:1 dr. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.88$ (d, 1H, $J = 7.8$ Hz), 7.52-7.58 (m, 1H), 7.39-7.46 (m, 2H), 6.95-7.00 (m, 2H), 6.81-6.87 (m, 1H), 6.50 (d, 1H, $J = 9.9$ Hz), 6.36 (d, 1H, $J = 7.8$ Hz), 5.85 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 9.9$ Hz), 5.21-5.25 (m, 1H), 3.98-4.03 (m, 1H), 1.66-1.93 (m, 2H), 0.83 (t, 3H, $J = 7.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 202.7$, 152.7, 138.3, 133.0, 129.2, 128.5, 128.3, 126.5, 124.9, 123.1, 121.6, 121.2, 116.3, 76.4, 52.2, 21.2, 11.8.

**18s**

(S)-2-((R)-2H-chromen-2-yl)-3,4-dihydronaphthalen-1(2H)-one (18s): The title compound was prepared according to the general procedure, as described above in 62% yield and with 9.3:1 r.r. and 1.7:1 dr. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.04$ (d, 1H, $J = 7.8$ Hz), 7.41-7.51 (m, 1H), 7.32 (t, 1H, $J = 7.5$ Hz), 7.25 (d, 1H, $J = 6.6$ Hz), 7.07-7.11 (m, 2H), 6.93 (d, 1H, $J = 7.2$ Hz), 6.72-6.89 (m, 2H), 6.43 (d, 1H, $J = 9.9$ Hz), 5.85 (s, 1H), 5.61 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 9.9$ Hz), 3.03-3.14 (m, 3H), 2.39-2.44 (m, 1H), 2.09-2.19 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 197.2$, 154.2, 144.2, 142.1, 133.6, 129.2, 128.8, 127.3, 126.7, 126.6, 125.2, 122.6, 121.0, 115.4, 104.5, 75.0, 53.2, 28.8, 23.8.
(S)-2-((R)-2H-chromen-2-yl)cyclohexan-1-one (28t): The title compound was prepared according to the general procedure, as described above in 87% yield and with 7.4:1 r.r. and 1.1:1 dr. Mixture of two diastereomers. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.04$-$7.12$ (m, 2H), $6.93$ (dt, 2H, $J_1 = 1.8$ Hz, $J_2 = 6.9$ Hz), $6.81$-$6.87$ (m, 2H), $6.70$-$6.79$ (m, 2H), $6.37$-$6.44$ (m, 2H), $5.85$ (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 9.9$ Hz), $5.68$ (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.9$ Hz), $5.68$ (ddd, 1H, $J_1 = 1.5$ Hz, $J_2 = 3.6$ Hz, $J_3 = 7.5$ Hz), $2.87$-$2.91$ (m, 1H), $2.68$-$2.72$ (m, 1H), $2.23$-$2.44$ (m, 7H), $2.03$-$2.09$ (m, 2H), $1.89$-$1.93$ (m, 2H), $1.60$-$1.73$ (m, 7H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 210.8$ (210.6), $153.9$ (153.0), $129.1$, $126.5$ (126.4), $125.4$ (124.7), $123.8$ (123.1), $121.8$ (121.4), $121.1$ (120.9), $116.0$ (115.5), $73.9$ (73.3), $55.9$ (55.4), $42.7$ (42.2), $29.7$ (28.0), $27.7$ (27.5), $24.6$ (24.4).

(S)-2-((R)-2H-chromen-2-yl)cyclopentan-1-one (18u): The title compound was prepared according to the general procedure, as described above in 86% yield and with 7.5:1 r.r. and 1.2:1 dr. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.09$ (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), $6.93$ (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.2$ Hz), $7.09$ (dt, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.2$ Hz), $6.74$ (d, 1H, $J = 7.8$ Hz), $6.47$ (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.8$ Hz), $5.49$ (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.9$ Hz), $5.36$-$5.39$ (m, 1H), $2.70$-$2.72$ (m, 1H), $2.27$-$2.38$ (m, 1H), $1.94$-$2.10$ (m, 4H), $1.77$-
1.83 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 217.9, 153.6, 129.4, 126.5, 125.7, 122.2, 121.4, 121.1, 115.6, 54.5, 38.9, 24.9, 20.6$.

2-(2H-chromen-2-yl)hexanal (18v): The title compound was prepared according to the general procedure, as described above in 29% yield and with 1.0:0 r.r. and 4.0:1 dr. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 9.77$ (d, 1H, $J = 3.3$ Hz), 7.09-7.14 (m, 1H), 6.97 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 5.7$ Hz), 6.86 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 3.3$ Hz), 6.76 (d, 1H, $J = 8.1$ Hz), 6.49 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 9.6$ Hz), 5.73 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 10.2$ Hz), 5.15-5.19 (m, 1H), 2.62-2.30 (m, 1H), 1.30-1.34 (m, 4H), 0.86-0.89 (m, 3H).

(S)-2-((R)-2H-chromen-2-yl)cyclopentan-1-one (18w): The title compound was prepared according to the general procedure, as described above in 42% yield and with 1.0:0 r.r.. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 9.67$ (s, 1H), 7.09 (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 9.0$ Hz), 6.93 (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz), 6.83 (t, 1H, $J = 7.2$ Hz), 6.73 (t, 1H, $J = 8.1$ Hz), 6.52 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 10.2$ Hz), 5.65 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 10.2$ Hz), 5.10 (t, 1H, $J = 2.4$ Hz), 1.19 (s, 3H), 1.14 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 204.4, 153.7, 129.6, 126.6, 126.3, 121.2, 121.0, 120.3, 115.4, 78.9, 51.7, 18.0, 16.9$.  

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2-(4-Hydroxy-2,3-dimethoxyphenyl)-2H-chromen-6-yl pivalate (24): The title compound was prepared according to the general procedure, as described in 54% yield and with 6.8:1 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.07$ (d, 1H, $J = 8.7$ Hz), 6.76 (d, 2H, $J = 1.5$ Hz), 6.73 (d, 1H, $J = 1.5$ Hz), 6.49 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 9.9$ Hz), 6.44 (d, 1H, $J = 9.0$ Hz), 6.25 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 3.6$ Hz), 6.01 (s, 1H), 5.83 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 9.9$ Hz), 3.92 (s, 3H), 3.84 (s, 3H), 1.34 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 177.4$, 152.3, 150.6, 146.7, 144.7, 135.4, 125.4, 123. 4, 123.1, 121.9, 121.7, 119.3, 119.1, 116.5, 103.7, 71.5, 61.0, 55.8, 39.0, 27.1.

2-(4-Hydroxy-2,3-dimethoxyphenyl)-2H-chromen-6-ol (25): The title compound was prepared according to the general procedure, as described in quantitative yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.07$ (d, 1H, $J = 8.7$ Hz), 6.68 (d, 1H, $J = 8.4$ Hz), 6.42-6.58 (m, 4H), 6.17-6.18 (m, 1H), 6.13 (s, 1H), 5.85 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 9.9$ Hz), 3.91 (s, 3H), 3.84 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 152.3$, 149.6, 147.1, 146.8, 135.4, 125.7, 123.9, 123.0, 122.3, 119.3, 116.7, 115.6, 113.0, 103.6, 71.4, 61.0, 55.8.
5-Butyl-3-(2H-chromen-2-yl)-2-(4-methoxyphenyl)-1H-indole (27): The title compound was prepared according to the general procedure, as described above in 68% yield and with 1.0:0 r.r. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.07$ (s, 1H), 7.54-7.58 (m, 3H), 7.12-7.18 (m, 2H), 7.07 (dd, 1H, $J1 = 1.5$ Hz, $J2 = 11.7$ Hz), 6.72-6.79 (m, 6H), 6.67 (d, 1H, $J = 9.6$ Hz), 6.60 (dd, 1H, $J1 = 4.2$ Hz, $J2 = 9.9$ Hz), 5.88 (dd, 1H, $J1 = 4.2$ Hz, $J2 = 9.6$ Hz), 4.37 (d, 1H, $J = 9.6$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 159.8$, 154.6, 137.7, 134.9, 134.4, 129.9, 129.2, 127.8, 126.5, 126.3, 124.9, 124.6, 123.4, 122.2, 121.1, 119.9, 116.2, 114.4, 110.6, 110.5, 71.4, 55.4, 35.8, 34.3, 29.7, 22.4, 14.0.

N-(4-fluorophenyl)-2H-chromen-2-amine (28): The title compound was obtained without purification. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.10-7.18$ (m, 2H), 6.79-6.95 (m, 6H), 6.67 (d, 1H, $J = 9.6$ Hz), 6.02 (dd, 1H, $J1 = 4.2$ Hz, $J2 = 9.9$ Hz), 5.88 (dd, 1H, $J1 = 4.2$ Hz, $J2 = 9.6$ Hz), 4.37 (d, 1H, $J = 9.6$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 157.0$ ($J_{CF} = 235.5$ Hz), 151.7, 140.6, 129.5, 126.8, 126.2, 121.3, 121.0, 120.6, 117.4,
115.8 ($J_{CF} = 8.3$ Hz), 115.6 ($J_{CF} = 6.0$ Hz), 78.8.

**General Procedure for Cyclization-Substitution Cascade Reaction of Hemiacetals and Various Carbonic Nucleophiles (Scheme 3.13):** To a solution of a hemiacetal 35 (0.15 mmol) in the presence of 20 mol % 10t, and 4Å molecular sieves (100 mg) in dichloromethane (0.5 mL) was added a nucleophile 13 or 17 (0.1 mmol). The resulting solution was stirred for a specified time (48-96 h) at room temperature. The reaction mixture was directly purified by silica gel chromatography to afford the desired product.

3-(1,3-Dihydroisobenzofuran-1-yl)-1H-indole (37a): The title compound was prepared according to the general procedure, as described above in 90% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.17$ (s, 1H), 7.29-7.34 (m, 3H), 7.20-7.25(m, 2H), 7.09-7.17 (m, 3H), 6.97-7.02 (m, 1H), 6.53 (s, 1H), 5.20-5.35 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 141.4, 139.7, 136.8, 127.5, 127.4, 126.0, 123.6, 122.4, 122.3, 120.9, 119.9, 119.5, 116.6, 111.2, 19.8, 72.5.
3-(6-Chloro-1,3-dihydroisobenzofuran-1-yl)-1H-indole (37b): The title compound was prepared according to the general procedure, as described above in 89% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta = 8.20\) (s, 1H), 7.26-7.36 (m, 4H), 7.19 (t, 1H, \(J = 7.2\) Hz), 7.06-7.13 (m, 2H), 7.04 (t, 1H, \(J = 7.2\) Hz), 6.49 (s, 1H), 5.16-5.32 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\), TMS): \(\delta = 143.7, 138.2, 136.8, 133.3, 127.9, 125.8, 123.6, 122.7, 122.5, 122.1, 120.1, 119.4, 115.9, 111.3, 79.6, 72.1\).

![37c](image)

3-(5-Bromo-1,3-dihydroisobenzofuran-1-yl)-1H-indole (37c): The title compound was prepared according to the general procedure, as described above in 86% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta = 8.22\) (s, 1H), 7.49 (s, 1H), 7.31-7.38 (m, 2H), 7.19 (d, 1H, \(J = 8.1\) Hz), 7.18 (dt, 1H, \(J1 = 1.2\) Hz, \(J2 = 8.1\) Hz), 7.11 (d, 1H, \(J = 2.4\) Hz), 7.03 (dt, 1H, \(J1 = 0.9\) Hz, \(J2 = 7.2\) Hz), 6.97 (t, 1H, \(J = 7.8\) Hz), 6.46 (s, 1H), 5.21-5.31 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\), TMS): \(\delta = 142.1, 140.6, 136.8, 130.5, 125.8, 124.3, 123.9, 123.7, 122.5, 121.4, 120.0, 119.4, 115.9, 111.3, 79.6, 71.9\).

![37d](image)

3-(3-Methyl-1,3-dihydroisobenzofuran-1-yl)-1H-indole (37d): The title compound was
prepared according to the general procedure, as described above in 93% yield, 1.3:1 dr. $^1$H NMR (300 MHz, CDCl₃, TMS): $\delta = 8.20-8.24$ (m, 1H), 7.24-7.39 (m, 4H), 7.13-7.20 (m, 3H), 6.96-7.07 (m, 2H), 6.44-6.62 (m, 1H), 5.42-5.60 (m, 1H), 1.60-1.68 (m, 3H); $^{13}$C NMR (75 MHz, CDCl₃, TMS): $\delta$ = 144.1(143.9), 142.0 (141.2), 136.9 (136.8), 127.7 (127.6), 127.5 (127.4), 125.9, 124.2(123.5), 122.4 (122.3), 122.2 (122.1), 120.8 (120.7), 119.8 (119.5), 119.7, 116.9 (116.2), 111.3 (111.2), 79.1(78.7), 78.6 (78.5), 22.1 (21.6).

3-(Isochroman-1-yl)-1H-indole (37e): The title compound was prepared according to the general procedure, as described above in 77% yield. $^1$H NMR (300 MHz, CDCl₃, TMS): $\delta = 8.11$ (s, 1H), 7.51 (d, 1H, $J = 7.8$ Hz), 7.34 (d, 1H, $J = 8.1$ Hz), 7.19-7.21 (m, 3H), 7.04-7.11 (m, 2H), 6.97-7.00 (m, 2H), 6.16 (s, 1H), 4.12-4.20 (m, 1H), 3.92-4.00 (m, 1H), 2.89-3.12 (m, 2H).

3-(6H-benzo[c]chromen-6-yl)-1H-indole (37f): The title compound was prepared according to the general procedure, as described above in 100% yield. $^1$H NMR (300 MHz, CDCl₃, TMS): $\delta = 7.92$ (s, 1H), 7.78-7.84 (m, 3H), 7.44 (dt, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz),
7.28-7.32 (m, 1H), 7.13-7.25 (m, 4H), 7.08 (d, 1H, $J = 7.5$ Hz), 7.03 (dt, 1H, $J1 = 1.5$ Hz, $J2 = 7.5$ Hz), 6.96 (dd, 1H, $J1 = 1.2$ Hz, $J2 = 8.1$ Hz); $^{13}$C NMR (75 MHz, CDCl₃, TMS): δ = 153.7, 136.6, 133.8, 130.1, 129.4, 128.3, 127.5, 126.2, 125.9, 124.9, 123.0, 122.9, 122.4, 122.0, 121.8, 120.3, 120.0, 118.1, 115.2, 111.2, 73.7.

3-(1,3-Dihydroisobenzofuran-1-yl)-5-methyl-1H-indole (37g): The title compound was prepared according to the general procedure, as described above in 84% yield. $^1$H NMR (300 MHz, CDCl₃, TMS): δ = 7.82 (s, 1H), 7.24-7.29 (m, 2H), 7.16-7.18 (m, 2H), 7.01 (d, 1H, $J = 8.4$ Hz), 6.51-6.52 (m, 1H), 4.82 (s, 1H).

3-(1,3-Dihydroisobenzofuran-1-yl)-5-methoxy-1H-indole (37h): The title compound was prepared according to the general procedure, as described above in 99% yield. $^1$H NMR (300 MHz, CDCl₃, TMS): δ = 8.02 (s, 1H), 7.31 (d, 2H, $J = 13.2$ Hz), 7.12-7.17 (m, 2H), 6.83 (dd, 1H, $J1 = 2.4$ Hz, $J2 = 8.7$ Hz), 6.69 (d, 1H, $J = 2.4$ Hz), 6.53 (s, 1H), 5.20-5.34 (m, 2H), 3.70 (s, 3H) $^{13}$C NMR (75 MHz, CDCl₃, TMS): δ = 154.2, 141.3, 139.8, 132.0, 127.6, 127.6, 127.4, 126.7, 124.2, 122.5, 120.9, 116.5, 112.6, 111.9, 101.4, 79.8, 72.5, 55.7.
3-(1,3-Dihydroisobenzofuran-1-yl)-1H-indole-5-carbonitrile (37i): The title compound was prepared according to the general procedure, as described above in 96% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.44$ (s, 1H), 7.35-7.39 (m, 3H), 7.24-7.29 (m, 1H), 7.21 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 8.7$ Hz), 7.07-7.11 (m, 2H), 6.97 (d, 1H, $J = 3.6$ Hz), 6.47 (s, 1H), 5.21-5.36 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 140.8$, 139.4, 135.4, 127.8, 127.7, 127.5, 125.1, 124.8, 122.2, 122.0, 121.0, 116.0, 113.1, 112.7, 79.5, 72.4.

Ethyl 3-(1,3-dihydroisobenzofuran-1-yl)-1H-indole-5-carboxylate (37j): The title compound was prepared according to the general procedure, as described above in 65% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.44$ (s, 1H), 8.16 (s, 1H), 7.89 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 8.7$ Hz), 7.32-7.35 (m, 3H), 7.13-7.16 (m, 2H), 6.57 (s, 1H), 5.21-5.36 (m, 2H), 3.88 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 168.0$, 141.0, 19.6, 139.4, 127.8, 127.4, 125.8, 124.4, 123.8, 122.5, 122.2, 122.1, 121.1, 118.5, 110.9, 79.3, 72.6, 51.8.
6-Chloro-3-(1,3-dihydroisobenzofuran-1-yl)-1H-indole (37k): The title compound was prepared according to the general procedure, as described above in 83% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.16$ (s, 1H), 7.32-7.33 (m, 3H), 7.23-7.27 (m, 1H), 7.17 (d, 1H, $J = 2.4$ Hz), 7.11 (t, 2H, $J = 7.8$ Hz), 6.97 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 8.4$ Hz), 6.48 (s, 1H), 5.14-5.53 (m, 2H).

3-(1,3-Dihydroisobenzofuran-1-yl)-1H-indole-6-carbaldehyde (37l): The title compound was prepared according to the general procedure, as described above in 50% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 9.97$ (s, 1H), 8.92 (s, 1H), 7.84 (s, 1H), 7.53 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 8.4$ Hz), 7.33-7.36 (m, 4H), 7.23-7.28 (m, 1H), 7.14 (d, 1H, $J = 7.5$ Hz), 6.53 (s, 1H), 5.22-5.37 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 192.6$, 140.9, 139.5, 136.4, 131.3, 131.1, 128.1, 127.8, 127.6, 122.2, 121.2, 121.1, 119.8, 117.4, 114.1, 79.4, 72.6.
3-(1,3-Dihydroisobenzofuran-1-yl)-2-phenyl-1H-indole (37m): The title compound was prepared according to the general procedure, as described above in 100% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.28$ (s, 1H), 7.68-7.72 (m, 2H), 7.42-7.52 (m, 3H), 7.36 (d, 2H, $J = 6.6$ Hz), 7.32 (s, 1H), 7.22(dt, 1H, $J1 = 1.8$ Hz, $J2 = 7.5$ Hz), 7.12(dt, 1H, $J1 = 0.9$ Hz, $J2 = 8.1$ Hz), 7.04 (d, 1H, $J = 7.2$ Hz), 6.89 (dt, 1H, $J1 = 0.9$ Hz, $J2 = 7.2$ Hz), 6.75 (d, 1H, $J = 7.8$ Hz), 6.58 (s, 1H), 5.24-5.44 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ 141.4, 139.7, 138.2, 136.2, 132.2, 128.9, 128.8, 128.3, 127.5, 127.5, 127.4, 127.2, 122.5, 122.3, 120.9, 120.2, 120.0, 112.0, 110.9, 79.5, 72.6.

1-Allyl-3-(1,3-dihydroisobenzofuran-1-yl)-1H-indole (37n): The title compound was prepared according to the general procedure, as described above in 60% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.35-7.36$ (m, 2H), 7.15-7.33 (m, 5H), 7.11 (s, 1H), 7.04 (dt, 1H, $J1 = 0.9$ Hz, $J2 = 7.2$ Hz), 6.56 (s, 1H), 5.96-6.02 (m, 1H), 5.12-5.37 (m, 4H), 4.70-4.72 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ 141.5, 139.7, 137.1, 133.2, 127.5, 127.3, 127.1, 126.8, 122.4, 121.9, 120.9, 119.7, 119.6, 117.5, 115.5, 109.7, 79.7, 72.4, 48.8.
1-Benzyl-3-(1,3-dihydroisobenzofuran-1-yl)-1H-indole (37o): The title compound was prepared according to the general procedure, as described above in 69% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.23-7.35$ (m, 8H), 7.13-7.18 (m, 5H), 7.02 (dt, 1H, $J_1 = 0.9$ Hz, $J_2 = 7.2$ Hz), 6.55 (s, 1H), 5.26-5.33 (m, 2H), 5.21-5.22 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ 141.5, 139.7, 137.3, 137.2, 133.9, 128.7, 127.6, 127.5, 127.4, 126.8, 125.8, 122.4, 122.1, 120.9, 119.8, 119.7, 115.8, 109.9, 79.8, 72.4, 50.1.

2-(1,3-Dihydroisobenzofuran-1-yl)-1H-pyrrole (37p): The title compound was prepared according to the general procedure, as described above in 50% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.21$ (s, 1H), 7.26-7.53 (m, 3H), 7.18 (d, 1H, $J = 7.5$ Hz), 6.75 (s, 1H), 6.18-6.26 (m, 3H), 5.01-5.23 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 140.1, 139.6, 131.2, 127.9, 127.5, 122.5, 121.0, 118.6, 108.4, 107.6, 79.6, 72.3.$
2-(1,3-Dihydroisobenzofuran-1-yl)-1-methyl-1H-pyrrole (37q): The title compound was prepared according to the general procedure, as described above in 54% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.27-7.34$ (m, 3H), 7.20 (d, 1H, $J = 6.6$ Hz), 6.64 (s, 1H), 6.31 (s, 1H), 6.04 (t, 1H, $J = 2.7$ Hz), 5.94 (s, 1H), 5.10-5.21 (m, 2H), 3.55 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 139.9, 139.7, 131.4, 127.8, 127.3, 124.2, 122.7, 120.9, 109.4, 106.5, 78.8, 72.1, 34.1$.

![37r](image)

1-(1,3-Dihydroisobenzofuran-1-yl)naphthalen-2-ol (37r): The title compound was prepared according to the general procedure, as described above in 82% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 9.33$ (s, 1H), 7.89 (d, 1H, $J = 8.7$ Hz), 7.84 (d, 1H, $J = 7.8$ Hz), 7.75 (d, 1H, $J = 9.0$ Hz), 7.54 (dt, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz), 7.28-7.42 (m, 3H), 7.09-7.15 (m, 3H), 6.95 (d, 1H, $J = 7.8$ Hz), 5.26-5.46 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 154.6, 140.6, 138.0, 131.9, 130.0, 128.9, 128.8, 128.1, 127.9, 126.9, 123.0, 122.2, 121.4, 120.9, 120.0, 113.6, 83.6, 72.2$.

![37s](image)

2-(1,3-Dihydroisobenzofuran-1-yl)naphthalen-1-ol (37s): The title compound was
prepared according to the general procedure, as described above in 56% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.87$ (s, 1H), 8.22-8.24 (m, 1H), 7.78-7.81 (m, 1H), 7.39-7.51 (m, 3H), 7.24-7.33 (m, 3H), 7.15 (d, 1H, $J = 7.2$ Hz), 6.48 (s, 1H), 5.27-5.42 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 151.5$, 140.5, 137.9, 134.2, 128.0, 127.8, 127.3, 126.5, 125.5, 125.2, 124.8, 122.2, 122.1, 121.0, 119.2, 116.5, 86.7, 72.5.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (37t): The title compound was prepared according to the general procedure, as described above in 85% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.98$-8.01 (m, 2H), 7.55-7.60 (m, 1H), 7.44-7.49 (m, 2H), 7.27-7.30 (m, 4H), 5.89-5.93 (m, 1H), 5.07-519 (m, 2H), 3.55 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 16.5$ Hz), 3.35 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 16.8$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 197.8$, 141.4, 139.2, 137.0, 133.2, 128.6, 128.2, 127.7, 127.4, 121.5, 121.0, 80.1, 72.6, 45.6.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(m-tolyl)ethan-1-one (37u): The title compound was prepared according to the general procedure, as described above in 84% yield. $^1$H
NMR (300 MHz, CDCl₃, TMS): δ = 7.78-7.81 (m, 2H), 7.35-7.38 (m, 2H), 7.23-7.31 (m, 4H), 5.89-5.93 (m, 1H), 5.07-5.19 (m, 2H), 3.54 (dd, 1H, \(J₁ = 7.2 \text{ Hz}, J₂ = 16.5 \text{ Hz}\)), 3.34 (dd, 1H, \(J₁ = 8.1 \text{ Hz}, J₂ = 16.5 \text{ Hz}\)), 2.41 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 198.0, 141.5, 139.2, 138.4, 137.1, 134.0, 128.7, 128.4, 127.7, 127.4, 125.5, 121.5, 121.0, 80.1, 72.6, 45.6, 21.3.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(4-fluorophenyl)ethan-1-one (37v): The title compound was prepared according to the general procedure, as described above in 71% yield. ¹H NMR (300 MHz, CDCl₃, TMS): δ = 8.00-8.04 (m, 2H), 7.25-7.32 (m, 2H), 7.10-7.16 (m, 2H), 5.06-5.18 (m, 2H), 5.06-5.18 (m, 2H), 3.51 (dd, 1H, \(J₁ = 7.5 \text{ Hz}, J₂ = 16.5 \text{ Hz}\)), 3.31 (dd, 1H, \(J₁ = 5.1 \text{ Hz}, J₂ = 16.5 \text{ Hz}\)); ¹³C NMR (75 MHz, CDCl₃, TMS): δ = 196.2, 164.1, 141.2, 139.2, 133.6, 131.0, 130.9, 127.8, 127.4, 121.4, 121.0, 115.8, 115.5, 80.1, 72.6, 45.5.

1-(2-Chlorophenyl)-2-(1,3-dihydroisobenzofuran-1-yl)ethan-1-one (37w): The title compound was prepared according to the general procedure, as described above in 91%
yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ = 7.53-7.56 (m, 1H), 7.36-7.42 (m, 2H), 7.21-7.34 (m, 5H), 5.84 (t, 1H, $J = 6.3$ Hz), 5.08-5.10 (m, 2H), 3.45 (d, 2H, $J = 6.3$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 200.7, 140.9, 139.1, 131.9, 131.0, 130.4, 129.4, 127.8, 127.4, 126.9, 121.3, 121.0, 80.1, 72.6, 49.8.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(thiophen-2-yl)ethan-1-one (37x): The title compound was prepared according to the general procedure, as described above in 91% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ = 7.73 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 3.9$ Hz), 7.66 (dd, 1H, $J_1 = 1.2$ Hz, $J_2 = 3.9$ Hz), 7.23-7.31 (m, 4H), 7.13 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 5.1$ Hz), 5.85-5.89 (m, 1H), 5.07-5.19 (m, 2H), 3.46 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 15.9$ Hz), 3.27 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 15.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 190.5, 144.5, 141.1, 139.1, 134.0, 132.5, 128.1, 127.8, 127.4, 121.4, 121.0, 80.3, 72.6, 46.3.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(phenanthren-2-yl)ethan-1-one (37y): The title compound was prepared according to the general procedure, as described above in 80% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ = 8.70 (t, 2H, $J = 8.1$ Hz), 8.50 (d, 1H, $J = 2.1$
Hz), 8.23 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 8.7$ Hz), 7.89-7.92 (m, 1H), 7.78 (s, 2H), 7.65-7.70 (m, 2H), 7.32-7.33 (m, 3H), 7.28-7.30 (m, 1H), 5.99-6.03 (m, 1H), 5.11-5.20 (m, 2H), 3.72 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 16.8$ Hz), 3.50 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 16.8$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 197.6, 141.4, 139.2, 134.7, 133.4, 132.9, 131.3, 129.7, 129.6, 128.6, 127.8, 127.7, 127.4, 127.2, 127.0, 125.1, 123.3, 123.1, 121.5, 121.0, 80.2, 72.6, 45.7.

![37z](image)

(E)-1-(1,3-dihydroisobenzofuran-1-yl)-4-phenylbut-3-en-2-one (37z): The title compound was prepared according to the general procedure, as described above in 51% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ = 7.53-7.62 (m, 3H), 7.39-7.41 (m, 3H), 7.22-7.31 (m, 4H), 6.82 (d, 1H, $J = 15.9$ Hz), 5.79-5.83 (m, 1H), 5.07-5.20 (m, 2H), 3.22 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 15.9$ Hz), 3.09 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 15.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 197.8, 143.4, 141.3, 139.2, 134.4, 130.6, 128.9, 128.4, 127.8, 127.4, 126.5, 121.4, 121.0, 80.2, 72.6, 47.5.

![39](image)

2-(Isochroman-1-yl)-1-phenylethan-1-one (39): The title compound was prepared according to the general procedure, as described above in 94% yield. $^1$H NMR (300 MHz,
CDCl$_3$, TMS): $\delta$ = 8.02 (d, 2H, $J$ = 7.2 Hz), 7.56 (d, 1H, $J$ = 7.2 Hz), 7.47 (t, 2H, $J$ = 7.2 Hz), 7.11-7.22 (m, 4H), 5.51 (d, 1H, $J$ = 5.7 Hz), 4.06-4.15 (m, 1H), 3.77-3.86 (m, 1H), 3.62 (dd, 1H, $J_1 = 8.7$ Hz, $J_2 = 16.2$ Hz), 3.33 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 16.2$ Hz), 2.97-3.08 (m, 1H), 2.62-2.75 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta$ = 198.2, 137.6, 137.3, 134.0, 133.1, 129.1, 128.6, 128.3, 126.6, 126.3, 124.6, 72.7, 63.5, 45.5, 28.9.

3.4 References

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Chapter 4

Enantioselective Cyclization-Michael Addition Cascade Reaction by a Binary Catalytic System

4.1 Introduction

The $\gamma$, $\gamma$-disubstituted butenolides are widely distributed in biologically active natural products.$^{1-4}$ Accordingly, considerable efforts have been made on the construction of the challenging quaternary stereogenic carbon center.$^{5-11}$ In 2003, MacMillan and coworkers found that chiral $\gamma$, $\gamma$-disubstituted butenolide could be obtained through Michael addition of silyloxy furans to $\alpha$, $\beta$-unsaturated aldehydes using imidazolidinone as catalyst.$^{12}$ In 2009, Buchwald and coworkers found that a palladium complex catalyzed $\gamma$-arylation of $\gamma$-substituted butenolides, yielding achiral $\gamma$, $\gamma$-disubstituted butenolides.$^5$ Later, the construction of chiral $\gamma$, $\gamma$-disubstituted butenolides were developed by Chen and coworkers through the asymmetric allylic alkylation of $\gamma$-substituted butenolides with Morita-Baylis-Hillman carbonates catalyzed by (DHDQ)$_2$PYR.$^6$ Thiourea-amine bifunctional organocatalysts also successfully catalyzed asymmetric Michael addition of $\gamma$-substituted butenolides to (E)-oxazolidinone enoates$^{11}$ and nitroolefins$^{10}$ respectively. Asymmetric Michael addition of $\gamma$-butenolide to $\alpha$, $\beta$-unsaturated aldehydes was also developed by Alexakis by using chiral secondary amine as catalyst.$^9$
4.2 Research Plan

Lewis acid-catalyzed cyclization of readily available alkynoic acids has been reported for the synthesis of $\gamma$-substituted butenolides.\textsuperscript{13,14} We envision that if we could couple the \textit{in situ} formation of the $\gamma$-substituted butenolides from Lewis acid-catalyzed cyclization of alkynoic acids with the aminocatalytic Michael addition of $\gamma$-substituted butenolides to $\alpha, \beta$-unsaturated aldehydes, the process would be more economic and less time-consuming due to no extra steps for the preparation and purification needed (Scheme 4.1). The hypothesis looks simple on paper, but the major challenges to implement this strategy are: 1) the incompatibility of Lewis acid and aminocatalyst; 2) the interference of basic aminocatalyst and alkynoic acids for the cyclization of alkynoic acids.

\textbf{Scheme 4.1.} Organocatalytic and transition metal catalyzed ‘one-pot’ synthesis of chiral $\gamma,\gamma$-disubstituted butenolides
4.3 Results and Discussion

4.31 Optimization of Reaction Condition

To test our hypothesis, the first step cyclization of 3-pentynoic acid 4a was evaluated by screening different metal salts (Table 4.1). Both PdCl2 and Cu(OTf)2 failed to promote the reaction (entries 1 and 2). Pleasingly, AuCl could promote the reaction albeit in low conversion (30%, entry 3). Encouraged by this result, a stronger Gold(I) Lewis acid (Ph3PAuOTf) was tested and a higher reactivity was observed, yielding 2a in 90% conversion (entry 4). AgNO3 was proved to be a superior catalyst and gave 2a in 100% conversion (entry 5).

Table 4.1. Metal-catalyzed cyclization of 3-pentynoic acid

<table>
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<tr>
<th>Entry</th>
<th>Metal salts</th>
<th>Conversion (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>PdCl2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>AuCl</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Ph3PAuCl + AgOTf</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>AgNO3</td>
<td>100</td>
</tr>
</tbody>
</table>

The reaction was run with 4a (0.1 mmol) and metal salt (0.01 mmol) in 1 mL CH2Cl2 at room temperature for 24 h. Determined by 1H-NMR.

Combination of AgNO3 and different aminocatalysts was tested next for the cyclization-Michael addition cascade reaction (entries 1-7, Table 4.2). Pleasingly, the combination of diphenylprolinol TMS-ether 5a and AgNO3 catalyzed the cascade reaction to afford the desired product in high yield and with excellent enantioselectivity and

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moderate diastereoselectivity (92% yield, 96% ee, 83% ee, and 2.3:1 dr, entry 1). The bulkier aminocatalyst-diphenylprolinol TBDMS-ether 5b gave higher ee, similar dr but more sluggish reaction rate (entry 2). Electron withdrawing substituent on the catalyst’s aryl groups 5c renders the catalyst less active (entry 3). Secondary amine hydrochloride salts 5d and 5g totally inhibited the reaction and even no intermediate 2a was observed (entries 4 and 7). This indicates that the acidic additive inhibits the AgNO3 catalyzed cyclization of 3-pentynoic acid. The catalyst 5a was selected as the organocatalyst for the further optimization by comprising the stereoselectivity and reactivity. Next, different silver salts were screened with 5a as the organocatalyst. It turned out that all silver salts can work with catalyst 5a and gave excellent enantioselectivity but varied in yields and diastereoselectivity (entries 8-12). Silver salts with non-coordinating anions such as AgBF4, AgCN, AgOTf and AgSbF4 gave lower yields (entries 8, 9, 11 and 12). AgOAc gave 100% yield but lower dr 1.8:1 (entry 10). Different solvents were screened with 5a as organocatalyst and AgNO3 as metal catalyst, and PhCF3 was proved to be the optimal solvent (entries 13-19).
Table 4.2. Combinations of an aminocatalyst and a metal salt-catalyzed cyclization-Michael cascade reaction between cinnamaldehyde and 3-pentyenoic acid$^a$

![Chemical Structures](insert:chemical_structures.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Metal</th>
<th>Solvent</th>
<th>Yield (%)$^b$</th>
<th>dr$^c$</th>
<th>ee$^{d,e}$</th>
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<tr>
<td>1</td>
<td>5a</td>
<td>AgNO$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>92</td>
<td>2.3:1</td>
<td>96, 83</td>
</tr>
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<td>2</td>
<td>5b</td>
<td>AgNO$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>62</td>
<td>2.0:1</td>
<td>98, 90</td>
</tr>
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<td>3</td>
<td>5c</td>
<td>AgNO$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>30</td>
<td>N.D.</td>
<td>N.D.</td>
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<td>CH$_2$Cl$_2$</td>
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<td>AgNO$_3$</td>
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<td>40</td>
<td>1.3:1</td>
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<td>-</td>
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<td>5a</td>
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<td>2.3:1</td>
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<td>80</td>
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<td>&gt;99, 86</td>
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<td>5a</td>
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<td>DCE</td>
<td>64</td>
<td>2.2:1</td>
<td>N.D.</td>
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<td>Hexane</td>
<td>57</td>
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<td>5a</td>
<td>AgNO$_3$</td>
<td>CH$_2$CN</td>
<td>83</td>
<td>1.9:1</td>
<td>99, 89</td>
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<td>17</td>
<td>5a</td>
<td>AgNO$_3$</td>
<td>Toluene</td>
<td>74</td>
<td>2.8:1</td>
<td>99, 86</td>
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<td>5a</td>
<td>AgNO$_3$</td>
<td>CF$_3$-Ph</td>
<td><strong>97</strong></td>
<td><strong>3.2:1</strong></td>
<td><strong>98, 88</strong></td>
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<td>5a</td>
<td>AgNO$_3$</td>
<td>m-xylene</td>
<td>87</td>
<td>2.3:1</td>
<td>97, 83</td>
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</table>

$^a$The reaction was run with 1a (0.1 mmol), 4a (0.1 mmol), amine catalyst 5 (0.02 mmol) and a metal salt (0.01 mmol) in 1 mL indicated solvent at room temperature for 24h.

$^b$Isolated yield. $^c$Determined by $^1$H-NMR. $^d$Determined by HPLC. $^e$The absolute structure is determined based on the reference 15. N.R.: no reaction. N.D.: not determined.
4.32 Investigation of Substrate Scope

With the optimal condition in hand, the generality of this binary catalytic system-catalyzed cyclization-Michael cascade reaction was then evaluated. A variety of aromatic and aliphatic \( \alpha, \beta \)-unsaturated aldehydes were tolerated in the reaction (entries 1-15, Table 4.3). It seemed that the electronic property and steric hindrance had little effect on the enantioselectivity but much influence on the diastereoselectivity and yield. The aromatic \( \alpha, \beta \)-unsaturated aldehydes with electron-withdrawing substituents (entries 2-4 and 8-10) facilitated the reaction and gave excellent yields, while electron-donating substituents (entries 5-7 and 11) usually gave lower yields. The electronic nature of the para-substitution of cinnamaldehydes usually has little effect on the diastereoselectivity, but the exception is that the para-methoxy-substituted cinnamaldehyde gave the reversed diastereoisomer (entry 6). Ortho-substituted cinnamaldehyde gave low and even reversed dr, which may be ascribed to the larger steric hinderance (entries 10 and 11). Heteroaromatic \( \alpha, \beta \)-unsaturated aldehyde also participated in the reaction smoothly and gave the desired product in 70% yield, 2.1:1 dr and 95%, 77% ee (entry 13). Aliphatic \( \alpha, \beta \)-unsaturated aldehydes couldn’t engage in the reaction under the standard condition, but the combination of diphenylprolinol TMS-ether and Ph\(_3\)PAuOTf could successfully facilitate the reaction in high yields and with excellent ee and much higher diastereoselectivity (entries 14 and 15). Besides pent-3-ynoic acid 4a, hex-3-ynoic acid 4b also participated in the reaction, offering the desired product in 80% yield, 2.0:1 dr and 92%, 88% ee (entry 16).
Table 4.3. A combination of an amine catalyst I and AgNO₃-catalyzed cyclization-Michael cascade reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>t (h)</th>
<th>Yield (%)ᵃ</th>
<th>dr</th>
<th>ee (%)ᵈ</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>24</td>
<td>97</td>
<td>3.2:1</td>
<td>98, 88</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl-Ph</td>
<td>Me</td>
<td>24</td>
<td>96</td>
<td>2.6:1</td>
<td>98, 88</td>
</tr>
<tr>
<td>3</td>
<td>4-NO₂-Ph</td>
<td>Me</td>
<td>24</td>
<td>97</td>
<td>2.0:1</td>
<td>96, 87</td>
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<tr>
<td>4</td>
<td>4-CN-Ph</td>
<td>Me</td>
<td>24</td>
<td>98</td>
<td>2.6:1</td>
<td>94, 87</td>
</tr>
<tr>
<td>5</td>
<td>4-Me-Ph</td>
<td>Me</td>
<td>24</td>
<td>89</td>
<td>2.3:1</td>
<td>99, N.D.</td>
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<tr>
<td>6</td>
<td>4-MeO-Ph</td>
<td>Me</td>
<td>48</td>
<td>72</td>
<td>1:1.6</td>
<td>79, 94</td>
</tr>
<tr>
<td>7</td>
<td>3-Me-Ph</td>
<td>Me</td>
<td>48</td>
<td>79</td>
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<td>98, 89</td>
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<tr>
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<td>3-F-Ph</td>
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<td>24</td>
<td>81</td>
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<td>3-AcO-Ph</td>
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<td>100</td>
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<td>94, 88</td>
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<td>2-Cl-Ph</td>
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<td>90</td>
<td>1.1:1</td>
<td>93, 96</td>
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<tr>
<td>11</td>
<td>2-Me-Ph</td>
<td>Me</td>
<td>48</td>
<td>88</td>
<td>1:1.3</td>
<td>99, 87(99, 92)</td>
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<td>12</td>
<td>1-naphthyl</td>
<td>Me</td>
<td>48</td>
<td>91</td>
<td>2.2:1</td>
<td>98, 87</td>
</tr>
<tr>
<td>13</td>
<td>2-Furyl</td>
<td>Me</td>
<td>48</td>
<td>70</td>
<td>2.1:1</td>
<td>95, 77</td>
</tr>
<tr>
<td>14</td>
<td>Et</td>
<td>Me</td>
<td>48</td>
<td>85</td>
<td>5.7:1</td>
<td>96, N.D.</td>
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<tr>
<td>15</td>
<td>n-Pr</td>
<td>Me</td>
<td>48</td>
<td>78</td>
<td>9.1:1</td>
<td>96, 94</td>
</tr>
<tr>
<td>16</td>
<td>Ph</td>
<td>Et</td>
<td>24</td>
<td>80</td>
<td>2.0:1</td>
<td>92, 88</td>
</tr>
</tbody>
</table>

ᵃThe reaction was run with I (0.1 mmol), 4 (0.1 mmol), 5a (0.02 mmol) and AgNO₃ (0.01 mmol) in 1 mL PhCF₃ at room temperature. ᵇIsolated yield. ᶜDetermined by ¹H-NMR. ᵈDetermined by HPLC. ⁵The reaction was run with I (0.3 mmol), 4 (0.1 mmol), 5a (0.02 mmol), AuCl (0.05 mmol) and AgOTf (0.05 mmol) in 1 mL PhCF₃ at room temperature.

4.4 Synthetic Application

Since the products contain a double bond and an aldehyde motif, it is easy to construct more complex natural-product-like or drug-like molecules through simple manipulations. For example, a chiral fused bicyclic molecule 7 was prepared in 78% yield
and with 98% ee by a simple Bu₃SnH-mediated intramolecular reductive radical conjugate addition of 3a and subsequently oxidation of the generated alcohol by PCC (Scheme 4.2).

**Scheme 4.2.** The transformation of the product 3a

To further elucidate the significance of this powerful binary catalytic system, the chiral compound 9 was successfully synthesized in 62% yield, 6.2:1 dr and 91% ee through the combination of diphenylprolinol TMS-ether and Ph₃PAuOTf-catalyzed cyclization-Michael-Aldol triple-cascade reaction, which is a key intermediate in the total synthesis of (-)-aromdendranediol (Scheme 4.3).

**Scheme 4.3.** The binary catalytic system promoted cyclization-Michael-Aldol cascade reaction
4.5 Mechanism Study

Regarding the reaction mechanism, it is proposed that an alkynoic acid is catalyzed by AgNO₃ or Ph₃PAuOTf to form a γ-substituted butenolide that attacks the iminium ion derived from the in situ condensation of an α, β-unsaturated aldehyde and a chiral aminocatalyst. To better understand the reaction mechanism, the proposed intermediate 8a directly reacted with cinnamaldehyde 7a only using diphenylprolinol TMS-ether I as the catalyst otherwise under the standard reaction condition, but surprisingly the reaction occurred with lower yield and dr (Scheme 15, a). This indicates that the synergistic effect between aminocatalyst and Lewis acid is in play. It was found that 15a can’t react with cinnamaldehyde using I as the catalyst otherwise under the standard condition (Scheme 15, b). However, under the same condition, 8a can be isomerized to 15a in 10% conversion in 24 h (Scheme 15, c). The addition of AgNO₃ to this condition totally inhibited the isomerization even in prolonged reaction time (48 h) (Scheme 15, d). This proves the synergistic effect of this binary catalytic system, which inhibits the side reaction and improves reaction yield. The reason for the enhancement of diastereoselectivity is still unclear so far. It was also found that the presence of secondary amine facilitated the silver-catalyzed cyclization (10h vs 16h for the completion of the cyclization reaction).

Scheme 4.4. Mechanism study

\[
\begin{align*}
\text{Ph} & \text{CHO} \\
\text{7a} & \text{Ph} \text{CF}_3 \\
\text{73\% yield} & \text{1.4:1 dr} \\
\text{96\%, 78\% ee}
\end{align*}
\]
4.6 Conclusion

In conclusion, a powerful binary catalytic system consisting diphenylprolinol TMS-ether I and AgNO₃ or Ph₃PAuOTf has been developed for the cyclization-Michael and the cyclization-Michael-Aldol cascade reactions. The merits of this strategy are not only the employment of simpler and less expensive starting materials but also the enhancement of yields due to the synergistic effect.

4.7 Experimental Section

General Procedure for the Enatioselective Cyclization-Michael Cascade Reaction of Alkynoic Acids and Aromatic α,β-unsaturated Aldehydes: A mixture of aromatic α,β-unsaturated aldehydes 1 (0.1 mmol), alkynoic acids 4 (0.1 mmol), the catalyst 5a (6.5 mg, 0.02 mmol) and AgNO₃(1.7 mg, 0.01 mmol) in PhCF₃ (1 mL) was stirred at room temperature for the indicated time. The reaction mixture was quickly filtered over a short
pad of silica gel (ethyl ether). The solvent was removed under reduced pressure and the residue was added 1 mL CH₂Cl₂ and ethyl 2-(triphenylphosphoranylidene)acetate (0.1 mmol). After 12h, the reaction mixture was directly purified by silica gel chromatography to afford the desired product as yellowish oil.

**General Procedure for the Enatioselective Cyclization-Michael Cascade Reaction of Alkynoic Acids and Aliphatic α,β-unsaturated Aldehydes:** A mixture of Ph₃PAuCl (5.0 mg, 0.01 mmol) and AgOTf (2.6 mg, 0.01 mmol) in PhCF₃ (1 mL) was stirred at room temperature for 5 minutes. Then, alkynoic acid 4 (0.2 mmol) and aliphatic α,β-unsaturated aldehydes 1 (0.6 mmol) were added and continued to stir for another 48 hours. The reaction mixture was quickly filtered over a short pad of silica gel (ethyl ether). The solvent was removed under reduced pressure and the residue was added 1 mL CH₂Cl₂ and ethyl 2-(triphenylphosphoranylidene)acetate (0.1 mmol). After 12h, the reaction mixture was directly purified by silica gel chromatography to afford the desired product as yellowish oil. The absolute configuration of the products is determined through the comparison of the NMR data and the specific rotation of 3a [α]D²⁷ = +133.7 (c = 1.0, CHCl₃) with what were reported in the previous literature.¹ The diastereomeric ratio (dr) was determined by ¹H NMR of the first step reaction mixture based on the integration of the proton of H-C-CO₂ in the butenolide ring of the products and enantiomeric excess (ee) was determined by HPLC (Daicel Chiralcel AS-H column or Daicel Chirapak IC column, λ = 210 nm).
(S,E)-ethyl 5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-phenylpent-2-enoate (6a) (Table 4.3, entry 1): The title compound was prepared according to the general procedure, as described above in 97% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta =$ 7.21-7.33 (m, 4H), 7.11-7.14 (m, 2H), 6.62 (dt, 1H, $J_1 = 7.2$ Hz, $J_2 = 22.8$ Hz), 5.94 (d, 1H, $J = 5.7$ Hz), 4.08 (q, 2H, $J = 7.2$ Hz), 3.16 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 11.4$ Hz), 2.55-2.72 (m, 2H), 1.43 (s, 3H), 1.21 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta =$ 172.1, 166.1, 158.6, 145.6, 137.5, 128.9, 128.7, 127.8, 123.3, 121.3, 90.1, 60.2, 52.3, 31.8, 23.7, 14.1; HPLC (Daicel Chirapak IC column, hexane/iPrOH=80:20 at 0.5 mL/min, $\lambda =$ 210 nm): Retention time: For the major diastereoisomers, $t_{\text{minor}} =$ 114.16 min, $t_{\text{major}} =$ 155.00 min, ee = 98%; For the minor diastereoisomers, $t_{\text{major}} =$ 87.73 min, $t_{\text{minor}} =$ 94.86 min, ee = 88%; dr = 3.2:1; $[\alpha]_D^{29} =$ +133.8 (c = 1.0, CHCl$_3$).

(S,E)-ethyl-5-(4-chlorophenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6b) (Table 4.3, entry 2): The title compound was prepared according to the general procedure, as described above in 96% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta =$ 7.27-7.30 (m, 3H), 7.05-7.08 (m, 2H), 6.59 (dt, 1H, $J_1 = 7.2$ Hz, $J_2 = 15.3$ Hz), 5.93 (d, 1H, $J = 5.7$ Hz), 5.94 (d, 1H, $J = 15.6$ Hz), 4.10 (q, 2H, $J = 7.2$ Hz), 3.13 (dd, 1H, $J_1 = 3.9$ Hz).
Hz, $J_2 = 11.4$ Hz), 2.53-2.78 (m, 2H), 1.45 (s, 3H), 1.22 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 171.9$, 165.9, 158.5, 145.0, 136.0, 133.7, 130.0, 129.1, 123.6, 121.5, 89.7, 60.3, 51.6, 31.8, 23.5, 14.1; HPLC (Daicel Chirapak IC column, hexane/iPrOH=80:20 at 0.5 mL/min, $\lambda = 210$ nm): Retention time: For the major diastereoisomers, $t_{\text{minor}} = 88.83$ min, $t_{\text{major}} = 109.02$ min, ee = 98%; For the minor diastereoisomers $t_{\text{major}} = 68.57$ min, $t_{\text{minor}} = 79.03$ min, ee = 88%; $\text{dr} = 2.6:1$; $[\alpha]_D^{29} = +163.3$ (c = 1.0, CHCl$_3$).

(S,E)-ethyl-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-(4-nitrophenyl)pent-2-enoate (6c (Table 4.3, entry 3): The title compound was prepared according to the general procedure, as described above in 97% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 8.17$ (d, 2H, $J = 8.7$ Hz), 7.38-7.50 (m, 1H), 7.27-7.33 (m, 2H), 6.51-6.62 (m, 1H), 5.90 (d, 1H, $J = 5.7$ Hz), 5.71-5.76 (m, 1H), 4.09 (q, 2H, $J = 6.9$ Hz), 3.27 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 11.7$ Hz), 2.58-2.92 (m, 2H), 1.52 (s, 3H), 1.21 (t, 3H, $J = 6.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 171.4$, 165.7, 158.3, 147.5, 145.1, 144.1, 129.6, 124.0, 124.2, 124.0, 121.6, 89.0, 60.4, 51.9, 31.9, 23.3, 14.1; HPLC (Daicel Chirapak IC column, hexane/iPrOH=80:20 at 0.5 mL/min, $\lambda = 210$ nm): Retention time: For the major diastereoisomers, $t_{\text{major}} = 206.12$ min, $t_{\text{minor}} = 287.38$ min, ee = 96%; For the minor diastereoisomers, $t_{\text{major}} = 155.38$ min, $t_{\text{minor}} = 247.43$ min, ee = 92%; $\text{dr} = 2.0:1$; $[\alpha]_D^{29} = +140.5$ (c = 1.0, CHCl$_3$).
(S,E)-ethyl-5-(4-cyanophenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6c) (Table 4.3, entry 4): The title compound was prepared according to the general procedure, as described above in 98% yield. $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta = 7.61$ (d, 2H, $J = 8.0$ Hz), 7.24-7.26 (m, 3H), 6.59 (dt, 1H, $J_1 = 7.5$ Hz, $J_2 = 15.5$ Hz), 5.90 (d, 1H, $J = 6.0$ Hz), 5.72 (d, 1H, $J = 15.5$ Hz), 4.09 (q, 2H, $J = 7.0$ Hz), 3.20 (dd, 1H, $J_1 = 4.0$ Hz, $J_2 = 11.5$ Hz), 2.82-2.86 (m, 1H), 2.63-2.69 (m, 1H), 1.50 (s, 3H), 1.22 (t, 3H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$, TMS): $\delta =$ 171.5, 165.8, 158.3, 144.3, 143.0, 132.6, 129.5, 124.0, 121.6, 118.2, 112.0, 89.1, 60.4, 52.1, 31.7, 23.3, 14.1; HPLC (Daicel Chirapak IC column, hexane/iPrOH=75:25 at 0.5 mL/min, $\lambda = 210$ nm): Retention time: for the major diastereoisomers, $t_{\text{major}} = 191.78$ min, $t_{\text{minor}} = 266.61$ min, ee = 94%; for the minor diastereoisomers, $t_{\text{major}} = 150.27$ min, $t_{\text{minor}} = 216.85$ min, ee = 87%; dr = 2.6:1; $[\alpha]_D^{29} = +158.1$ (c = 1.0, CHCl$_3$).

((S,E)-ethyl-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-(p-tolyl)pent-2-enoate (6d) (Table 4.3, entry 5): The title compound was prepared according to the general procedure, as described above in 89% yield. $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta =$ 7.32
(d, 1H, J = 5.5 Hz), 7.10-7.14 (m, 3H), 7.00 (d, 1H, J = 8.0 Hz), 6.59 (dt, 1H, J1 = 7.0 Hz, J2 = 15.5 Hz), 5.95 (d, 1H, J = 5.5 Hz), 5.72 (d, 1H, J = 15.5 Hz), 4.08 (q, 2H, J = 7.0 Hz), 3.12 (dd, 1H, J1 = 3.5 Hz, J2 = 12 Hz), 2.66-2.70 (m, 2H), 2.48-2.55 (m, 2H), 2.3 (s, 3H), 1.4 (s, 3H), 1.21 (t, 3H, J = 7.0 Hz); 13C NMR (125 MHz, CDCl3, TMS): δ = 172.2, 166.1, 158.7, 145.8, 137.5, 134.4, 129.5, 128.6, 123.1, 121.3, 90.3, 60.2, 51.9, 31.8, 23.7, 21.0, 14.2; HPLC (Daicel Chirapak IC column, hexane/iPrOH=90:10 at 0.5 mL/min, λ = 210 nm): Retention time: 275.28 min, 377.98 min, ee = 99%, dr = 2.3:1; [α]D29 = +83.5 (c = 1.0, CHCl3).

(S,E)-ethyl-5-(4-methoxyphenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6e) (Table 4.3, entry 6): The title compound was prepared according to the general procedure, as described above in 72% yield. 1H NMR (500 MHz, CDCl3, TMS): δ = 7.30 (d, 1H, J = 5.5 Hz), 7.03 (d, 1H, J = 8.5 Hz), 6.82-6.86 (m, 2H), 6.61 (dt, 1H, J1 = 7.0 Hz, J2 = 15.5 Hz), 5.94 (d, 1H, J = 5.5 Hz), 5.70 (m, 1H), 4.08 (q, 2H, J = 7.0 Hz), 3.79 (s, 3H), 3.11 (dd, 1H, J1 = 3.5 Hz, J2 = 11.5 Hz), 2.50-2.70 (m, 2H), 1.4 (s, 3H), 1.21 (t, 3H, J = 7.0 Hz); 13C NMR (125 MHz, CDCl3, TMS): δ = 166.1, 160.5, 158.8, 145.8, 145.7, 130.3, 129.7, 123.2, 121.3, 114.2, 90.4, 60.2, 55.2, 51.4, 31.9, 23.6, 14.2; HPLC (Daicel Chirapak IC column, hexane/iPrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, tminor = 149.22 min, tmajor = 202.19 min, ee = 94%; for the minor diastereoisomers, tmajor = 122.50 min, tminor = 134.24 min, ee = 79%; dr = 1.6:1;
[\alpha]D^{29} = +84.2 (c = 1.0, CHCl₃).

(S,E)-ethyl-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-(m-tolyl)pent-2-enoate

(6f) (Table 4.3, entry 7): The title compound was prepared according to the general procedure, as described above in 79% yield. ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.33 (d, 1H, J = 5.5 Hz), 7.19 (t, 1H, J = 7.5 Hz), 7.06 (d, 1H, J = 7.5 Hz), 6.92 (s, 2H), 6.62 (dt, 1H, J₁ = 7.0 Hz, J₂ = 15.5 Hz), 5.96 (d, 1H, J = 5.5 Hz), 5.73 (d, 1H, J = 15.5 Hz), 4.09 (q, 2H, J = 7.0 Hz), 3.11 (dd, 1H, J₁ = 3.5 Hz, J₂ = 11.0 Hz), 2.65-2.71 (m, 2H), 2.49-2.56 (m, 2H), 2.33 (s, 3H), 1.41 (s, 3H), 1.21 (t, 3H, J = 7.0 Hz); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 158.6, 145.8, 138.5, 137.4, 129.5, 128.7, 128.6, 123.1, 121.3, 90.2, 60.2, 52.2, 31.8, 23.8, 21.5, 14.1; HPLC (Daicel Chirapak IC column, hexane/iPrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, tₘᵢₙᵒᵣₙ = 102.54 min, tₘᵃᵢⱼᵒᵣₙ = 132.95 min, ee = 98%; for the minor diastereoisomers, tₘᵃᵢⱼᵒᵣₙ = 77.24 min, tₘᵢₙᵒᵣₙ = 89.89 min, ee = 89%; dr = 2.5:1; [\alpha]D^{29} = +115.6 (c = 1.0, CHCl₃).

(S,E)-ethyl-5-(3-fluorophenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate

(6g)
(S,E)-ethyl-5-(3-acetoxyphenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6h) (Table 4.3, entry 9): The title compound was prepared according to the general procedure, as described above in 100% yield. $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta =$ 7.84 (d, 1H, $J =$ 7.5 Hz), 7.72 (s, 1H), 7.43 (t, 1H, $J =$ 7.5 Hz), 7.30-7.37 (m, 2H), 6.58 (dt, 1H, $J_1 =$ 7.0 Hz, $J_2 =$ 15.5 Hz), 5.91 (d, 1H, $J =$ 6.0 Hz), 5.73 (d, 1H, $J =$ 15.5 Hz), 4.07 (q, 2H, $J =$ 7.5 Hz), 3.22 (dd, 1H, $J_1 =$ 3.5 Hz, $J_2 =$ 11.5 Hz), 2.75-2.80 (m, 2H), 2.60 (s, 3H), 1.46 (s, 3H), 1.20 (t, 3H, $J =$ 7.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$, TMS): $\delta =$ 197.7, 171.8, 165.9, 158.6, 145.0, 138.3, 137.5, 133.3, 129.2, 128.2, 128.1, 123.6, 121.5,
89.6, 60.3, 52.0, 31.8, 26.7, 23.4, 14.1; HPLC (Daicel Chiralcel AS-H column, hexane/iPrOH=90:10 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomer, 182.25 min (major), 210.47 min (minor), ee = 94%; HPLC (Daicel Chirapak IC column, hexane/iPrOH=70:30 at 0.5 mL/min, λ = 210 nm): Retention time: for the minor diastereoisomer, 104.83 min (major), 139.69 min (minor), ee = 88%; dr = 2.6:1; [α]D29 = +87.3 (c = 1.0, CHCl3).

(S,E)-ethyl-5-(2-chlorophenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6i) (Table 4.3, entry 10): The title compound was prepared according to the general procedure, as described above in 90% yield. 1H NMR (500 MHz, CDCl3, TMS): δ = 7.38-7.55 (m, 2H), 7.29-7.34 (m, 1H), 7.16-7.24 (m, 2H), 6.56-6.66 (m, 1H), 5.65-6.14 (m, 2H), 4.09 (q, 2H, J = 6.5 Hz), 3.80-3.94 (m, 1H), 2.50-2.92 (m, 2H), 1.29 (s, 3H), 1.45 (s, 3H), 1.21 (t, 3H, J = 7.0 Hz); 13C NMR (125 MHz, CDCl3, TMS): δ = 172.2, 172.1, 166.0, 165.9, 160.4, 158.8, 145.1, 144.7, 135.6 135.2, 135.1, 129.8, 129.7, 129.6, 128.8, 127.5, 127.4, 123.5, 121.2, 120.9, 90.2, 89.8, 60.2, 45.6, 45.5, 32.7, 32.0, 23.0, 22.2, 14.1 (the mixture of two diastereoisomers); HPLC (Daicel Chiralcel AS-H column, hexane/iPrOH=90:10 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, tminor = 2.04 min, tmajor = 53.48 min, ee = 93%; for the minor diastereoisomers, tminor = 62.31 min, tmajor = 82.31 min, ee = 96%; dr = 1.1:1; [α]D29 = +82.6 (c = 1.0, CHCl3).
(S,E)-ethyl 5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-(o-tolyl)pent-2-enoate (6j) (Table 4.3, entry 11): The title compound was prepared according to the general procedure, as described above in 88% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.37-7.40$ (m, 1H), 7.29 (d, 1H, $J = 5.7$ Hz), 7.15-7.17 (m, 2H), 6.57 (dt, 1H, $J1 = 7.2$ Hz, $J2 = 15.3$ Hz), 6.08 (d, 1H, $J = 5.7$ Hz), 5.71 (dt, 1H, $J1 = 1.5$ Hz, $J2 = 15.6$ Hz), 4.09 (q, 2H, $J = 7.2$ Hz), 3.31 (t, 1H, $J = 7.5$ Hz), 2.64 (dt, 1H, $J1 = 0.9$ Hz, $J2 = 7.2$ Hz), 2.26 (s, 3H), 1.35 (s, 3H), 1.21 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 172.2$, 166.1, 160.5, 145.4, 130.7, 127.7, 127.4, 126.6, 123.3, 121.1, 90.7, 60.2, 46.1, 33.4, 21.7, 20.5, 14.1; HPLC (Daicel Chiralcel AS-H column, hexane/iPrOH=90:10 at 0.5 mL/min, $\lambda = 210$ nm): Retention time: For the major diastereoisomer, $t_{\text{minor}} = 57.44$ min, $t_{\text{major}} = 86.73$ min, ee = 99%; For the minor diastereoisomer, $t_{\text{major}} = 89.15$ min, $t_{\text{minor}} = 112.79$ min, ee = 92%; $d_r = 1:1.3$, $[\alpha]_D^{29} = +79.7$ (c = 1.0, CHCl$_3$).

(S,E)-ethyl-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-(naphthalen-1-yl)pent-2-enoate (6k) (Table 4.3, entry 12): The title compound was prepared according to the general procedure, as described above in 91% yield. $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta$
= 7.79-7.83 (m, 3H), 7.59 (s, 1H), 7.49-7.50 (m, 2H), 7.37 (d, 1H, \(J = 5.5\) Hz), 7.26 (d, 1H, \(J = 5.5\) Hz), 6.64 (dt, 1H, \(J1 = 7.5\) Hz, \(J2 = 15.5\) Hz), 5.93 (d, 1H, \(J = 5.5\) Hz), 5.75 (d, 1H, \(J = 15.5\) Hz), 4.04 (q, 2H, \(J = 7.0\) Hz), 3.34 (dd, 1H, \(J1 = 3.5\) Hz, \(J2 = 11.5\) Hz), 2.66-2.83 (m, 2H), 1.47 (s, 3H), 1.17 (t, 3H, \(J = 7.5\) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), TMS): \(\delta = 172.1, 166.0, 158.6, 145.5, 135.0, 133.3, 132.8, 128.7, 128.0, 127.8, 126.4, 126.2, 126.0, 123.4, 121.4, 90.2, 60.2, 52.4, 31.8, 23.9, 14.1; \)HPLC (Daicel Chirapak IC column, hexane/iPrOH=90:10 at 0.5 mL/min, \(\lambda = 210\) nm): Retention time: For the major diastereoisomers, \(t_{major} = 354.86\) min, \(t_{minor} = 496.32\) min, \(ee = 98%\); For the minor diastereoisomer, \(t_{major} = 283.274\) min, \(t_{minor} = 303.04\) min, \(ee = 87%\); \(dr = 2.2:1; [\alpha]D^{29} = +119.4 (c = 1.0, CHCl\(_3\)).

(S,E)-ethyl-5-(furan-2-yl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6l) (Table 4.3, entry 13): The title compound was prepared according to the general procedure, as described above in 70% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta = 7.50\) (d, 1H, \(J = 5.7\) Hz), 7.32-7.36 (m, 1H), 6.60-6.70 (m, 1H), 6.31 (dd, 1H, \(J1 = 1.8\) Hz, \(J2 = 3.3\) Hz), 6.18 (d, 1H, \(J = 3.3\) Hz), 6.05 (d, 1H, \(J = 5.7\) Hz), 5.70 (dt, 1H, \(J1 = 1.2\) Hz, \(J2 = 15.6\) Hz), 4.09 (q, 2H, \(J = 7.1\) Hz), 3.30 (dd, 1H, \(J1 = 3.9\) Hz, \(J2 = 11.4\) Hz), 2.31-2.53 (m, 2H), 1.39 (s, 3H), 1.23 (t, 1H, \(J = 7.2\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): \(\delta = 172.0, 166.1, 158.7, 151.2, 144.8, 142.3, 123.4, 121.4, 110.5, 109.3, 89.4, 60.2, 45.9, 30.5, 23.7, 14.2; \)HPLC (Daicel Chiralcel AS-H column, hexane/iPrOH=90:10 at 0.5
mL/min, $\lambda = 210$ nm): Retention time: For the major diastereoisomer, $t_{\text{minor}} = 64.41$ min, $t_{\text{major}} = 71.68$ min, ee = 95%; For the minor diastereoisomer, $t_{\text{major}} = 84.20$ min, $t_{\text{minor}} = 122.82$ min, ee = 77%, dr = 2.1:1; $[\alpha]_D^{29} = +79.4$ (c = 1.0, CHCl$_3$).

(R,E)-ethyl-5-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)hept-2-enoate (6m) (Table 4.3, entry 14): The title compound was prepared according to the general procedure, as described above in 85% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.39$ (d, 1H, $J = 5.7$ Hz), 6.88 (dt, 1H, $J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz), $\delta = 6.04$ (d, 1H, $J = 5.7$ Hz), 5.82 (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 15.3$ Hz), 4.18 (q, 2H, $J = 7.2$ Hz), 2.13-2.37 (m, 2H), 1.76-1.84 (m, 1H), 1.52-1.63 (m, 1H), 1.46 (s, 3H), 1.23-1.38 (m, 4H), 0.94 (t, 3H, $J = 7.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 172.1, 166.2, 159.4, 147.0, 122.9, 121.2, 91.3, 60.3, 46.8, 31.9, 22.8, 22.4, 14.2, 12.4$; HPLC (Daicel Chirapak IC column, hexane/iPrOH=80:20 at 0.5 mL/min, $\lambda = 210$ nm): Retention time: For the major diastereoisomer, $t_{\text{minor}} = 110.48$ min, $t_{\text{major}} = 128.28$, ee = 96%, dr = 5.7:1; $[\alpha]_D^{29} = +25.8$ (c = 1.0, CHCl$_3$).

(R,E)-ethyl 5-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)oct-2-enoate (6n) (Table 4.3, entry 15): The title compound was prepared according to the general procedure, as
described above in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 7.39$ (d, 1H, $J = 5.7$ Hz), 6.88 (dt, 1H, $J_1 = 7.5$ Hz, $J_2 = 15.6$ Hz), 6.04 (d, 1H, $J = 5.7$ Hz), 5.80 (dt, 1H, $J_1 = 1.5$ Hz, $J_2 = 15.6$ Hz), 4.17 (q, 2H, $J = 7.2$ Hz), 2.11-2.33 (m, 2H), 1.45 (s, 3H), 1.19-1.41 (m, 7H), 0.87 (t, 3H, $J = 6.9$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta =$172.1, 166.2, 159.4, 147.1, 122.8, 121.2, 91.2, 60.3, 45.1, 32.5, 32.2, 22.3, 21.2, 14.2, 14.1; HPLC (Daicell Chirapak IC column, hexane/iPrOH=80:20 at 0.5 mL/min, $\lambda = 210$ nm): For the major diastereoisomers $t_{\text{minor}} = 103.33$ min, $t_{\text{major}} = 118.39$ min, ee = 96%; For the minor diastereoisomers $t_{\text{major}} = 68.54$ min, $t_{\text{minor}} = 72.83$ min, ee = 94%; $\text{dr} = 9.1:1$; $[^\alpha]D^{29} = +42.3$ (c = 1.0, CHCl$_3$).

(S,E)-ethyl 5-((R)-2-ethyl-5-oxo-2,5-dihydrofuran-2-yl)-5-phenylpent-2-enoate (6o) (Table 4.3, entry 16): The title compound was prepared according to the general procedure, as described above in 80% yield. $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta = 7.31$ (t, 2H, $J = 7.5$ Hz), 7.23-7.27 (m, 2H), $\delta = 7.12$ (t, 2H, $J = 7.5$ Hz), 6.61 (dt, 1H, $J_1 = 7.0$ Hz, $J_2 = 16.0$ Hz), 6.01 (d, 2H, $J = 5.5$ Hz), 5.71 (t, 2H, $J = 16.0$ Hz), 4.08 (q, 2H, $J = 7.0$ Hz), 3.21 (dt, 1H, $J_1 = 3.5$ Hz, $J_2 = 11.5$ Hz), 2.51-2.72 (m, 2H), 1.91-1.96 (m, 2H), 1.62-1.70 (m, 2H), 1.21 (t, 3H, $J = 7.5$ Hz), 0.78 (t, 3H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$, TMS): $\delta =$ 172.4, 166.1, 157.2, 145.7, 137.6, 128.9, 128.8, 127.8, 123.2, 122.4, 92.9, 60.2, 51.2, 31.9, 28.7, 14.1, 7.50; HPLC (Daicell Chiralcel AS-H column, hexane/iPrOH=90:10 at 0.5 mL/min, $\lambda = 210$ nm): (Daicell Chirapak IC column, hexane/iPrOH=95:5 at 0.5 mL/min, $\lambda$
= 210 nm): For the major diastereoisomers $t_{\text{minor}} = 566.18 \text{ min}$, $t_{\text{major}} = 675.96 \text{ min}$, ee = 92%; For the minor diastereoisomers $t_{\text{major}} = 355.13 \text{ min}$, $t_{\text{minor}} = 390.47 \text{ min}$, ee = 88%; dr = 2.0:1; $[\alpha]_D^{29} = +93.8 \ (c = 1.0, \text{CHCl}_3)$.

The Procedure for the Preparation of (3aS, 6S, 6aS)-6a-methyl-6-phenyltetrahydro-2H-cyclopenta[b]furan-2,4(5H)-dione (7): A mixture of 3a (23mg, 0.1 mmol), AIBN (0.3 mmol) and Bu$_3$SnH (1.7mg, 0.01 mmol) in benzene (1 mL) was stirred at 80 oC for 2h. The reaction mixture was quickly filtered over a short pad of silica gel (ethyl ether). The solvent was removed under reduced pressure and the residue was dissolved in 1.5 mL CH$_2$Cl$_2$. Then, 0.3 mmol of pyridinium chlorochromate (PCC) and 61.3 mg of silica were added. After 3h, the reaction mixture was directly purified by silica gel chromatography to afford the desired product as colorless solid. The compound was prepared according to the procedure, as described above in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ = 7.31-7.39 (m, 3H), 7.11-7.14 (m, 2H), 3.75 (q, 1H, $J$ = 4.2 Hz), 2.72-3.03 (m, 5H), 1.20 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 215.9, 173.9, 139.1, 129.0, 127.8, 127.6, 93.2, 51.7, 49.1, 43.7, 32.5, 22.4; HPLC (Daicel Chiralcel AD-H column, hexane/iPrOH = 80:20 at 0.5 mL/min, λ = 210 nm): $t_{\text{minor}} = 16.39 \text{ min}$, $t_{\text{major}} = 21.77 \text{ min}$, ee = 98%; $[\alpha]_D^{29} = +32.3 \ (c = 1.0, \text{CHCl}_3)$. 
The Procedure of Preparation for the Preparation of (E)-6-oxohept-2-enal (13): A mixture of crotonaldehyde (6 mmol), 5-Hexen-2-one (2 mmol) and Grubbs catalyst II (8.5 mg, 0.01 mmol) in CH$_2$Cl$_2$ (4 mL) was stirred under N$_2$ atmosphere at room temperature for 10h. Then, Grubbs catalyst II (8.5 mg, 0.01 mmol) was added into the reaction mixture again. The solvent was removed under reduced pressure and the residue was directly purified by silica gel chromatography to afford the desired product as the brown liquid.

The compound was prepared according to the procedure, as described above in 96% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ = 9.46 (d, 1H, $J = 7.8$ Hz), 6.83 (dt, 1H, $J_1 = 6.3$ Hz, $J_2 = 15.9$ Hz), 2.54-2.68 (m, 4H), 2.16 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): δ = 206.4, 193.7, 156.5, 133.1, 41.1, 29.8, 26.3.

The Procedure of Preparation for the Preparation of (1S,2R,5R)-2-hydroxy-2-methyl-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)cyclopentanecarbaldehyde (9): A mixture of Ph$_3$PAuCl (5.0 mg, 0.01 mmol) and AgOTf (2.6 mg, 0.01 mmol) in PhCF$_3$ (1 mL) was stirred at room temperature for 5 minutes. Then, alkynoic acid 4a (0.2 mmol), (E)-6-oxohept-2-enal 8 (0.4 mmol), and the catalyst 5a (12.4 mg, 0.04 mmol) were added
and continued to stir for another 48 hours. The reaction mixture was directly purified by silica gel chromatography to afford the desired product as yellowish brown oil.

The compound was prepared according to the procedure, as described above in 50% yield. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta = 9.86$ (d, 1H, $J = 1.8$ Hz), 7.35 (d, 1H, $J = 5.7$ Hz), 6.11 (d, 1H, $J = 5.7$ Hz), 3.05-3.13 (m, 1H), 2.61 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 8.7$ Hz), 1.90-2.03 (m, 1H), 1.83 (s, 1H), 1.67-1.71 (2H), 1.52 (s, 3H), 1.39 (s, 3H), 1.29-1.33 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, TMS): $\delta = 206.4$, 193.7, 156.5, 133.1, 41.1, 29.8, 26.3. The diastereomeric ratio (dr) was determined by $^1$H NMR of crude reaction mixture based on the integration of the proton of CO-H $H_{\text{major}} = 9.86$ (doublet) Vs $H_{\text{minor}} = 9.82$ (doublet). The absolute configuration of 14 was determined by the comparison with the data in previous paper.$^1$ HPLC (Daicel Chirapak IC column, hexane/iPrOH = 75:25 at 0.5 mL/min, $\lambda = 210$ nm): $t_{\text{minor}} = 46.78$ min, $t_{\text{major}} = 45.11$ min, ee = 91%; $[^\alpha]_D^{29} = -11.7$ (c = 1.0, CHCl$_3$).

4.8. References


(2) Rodríguez, A. D. Tetrahedron 1995, 51, 4571.


