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DEVELOPMENT OF ORGANOCATALYTIC REACTIONS FOR THE ASSEMBLY OF COMPLEX MOLECULES

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by

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

DISSERTATION

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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 *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 *γ,γ*-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
δ	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

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
μM	micromole

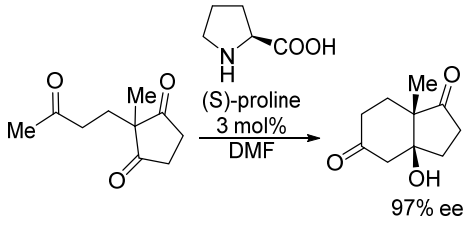
Chapter 1

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.

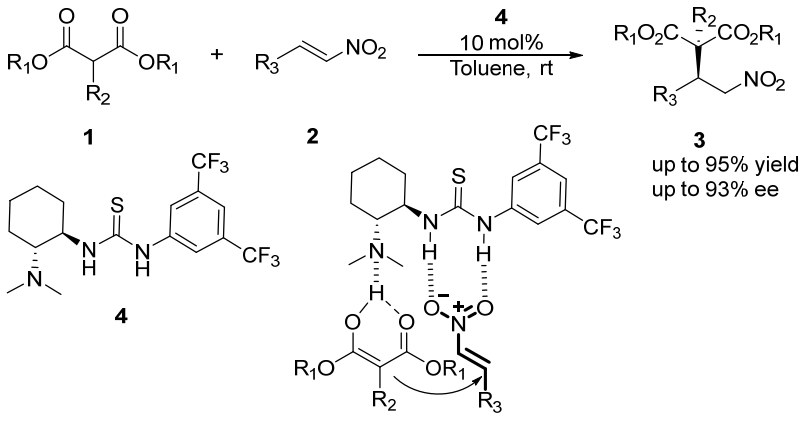
Scheme 1.1. (*S*)-Proline catalyzed asymmetric intramolecular aldol cyclization



1.2 Tertiary Amine Thiourea Bifunctional Organocatalysts

Hydrogen bonding is well known as an indispensable force in biocatalysis. 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

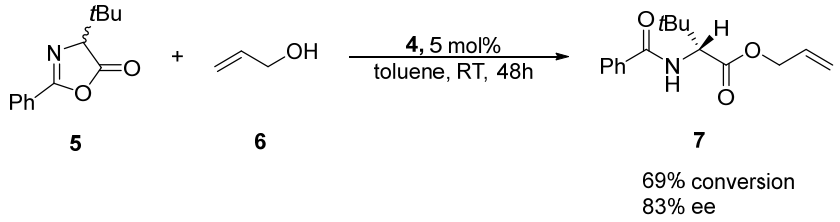


In 2003, Takemoto developed the first tertiary amine thiourea bifunctional organocatalyst **4** demonstrated in promoting enantioselective Michael addition of malonates to nitroolefins in high yields and with enantioselectivities (Scheme 1.2).[21] In this protocol, thiourea is designed to activate nitroolefins, while tertiary amine deprotonates

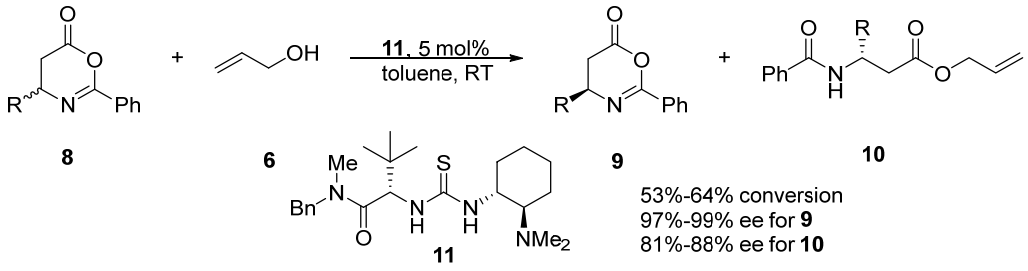
malonates and directs its attack in an enantioselective cooperative manner. Following this discovery, many enantioselective conjugated additions are also developed using this bifunctional catalyst.[22-25]

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



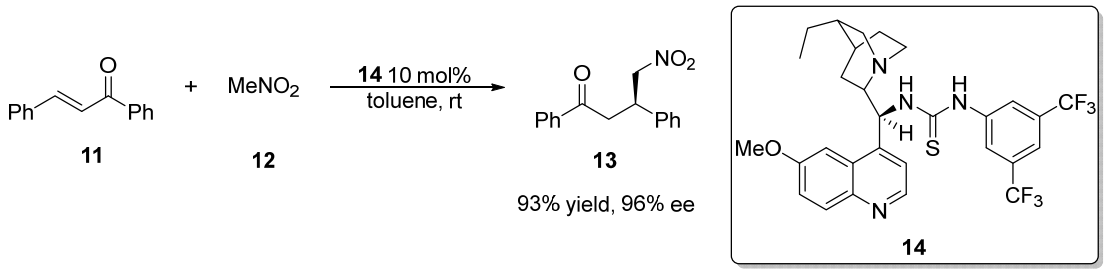
Scheme 1.4. Amine thiourea **11** catalyzed kinetic resolution of oxazinones



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

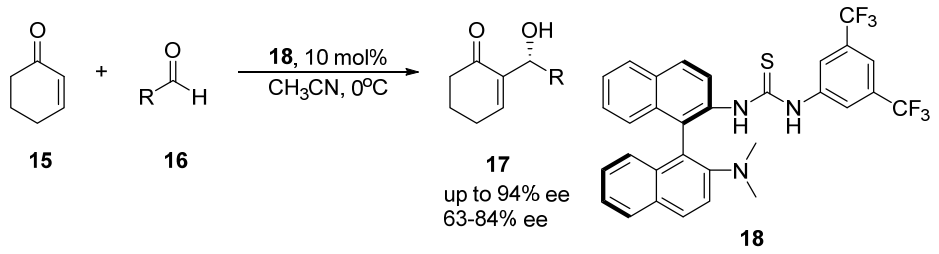
of nitromethane to chalcones in 93% yield and with 96% ee (Scheme 1.5).[27]

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[28] and BINOL.[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).[30] The catalyst **18** also promoted highly enantioselective Michael addition of diketones to nitroolefins using only 1 mol% catalyst loading.[31]

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

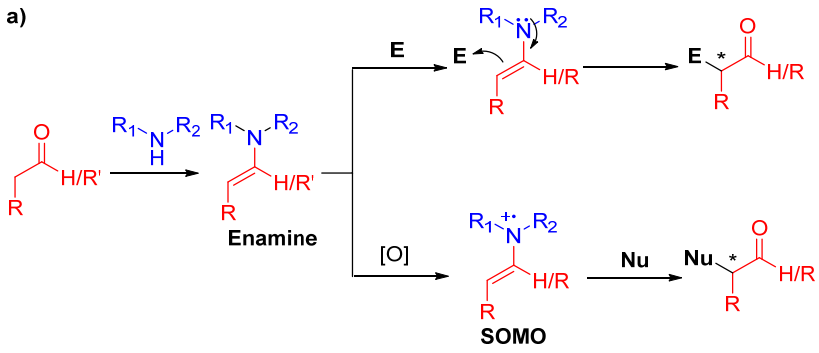


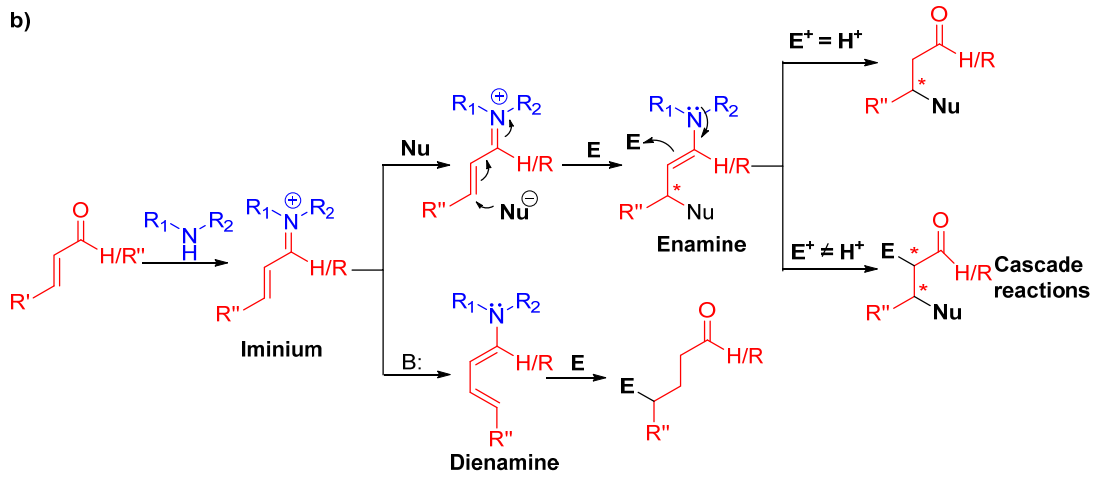
1.3 Aminocatalysis

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 *in situ* form a transient enamine or iminium, depending on the existence of a *α,β*-carbon-carbon double bond (Scheme 1.7).[32] In the absence of a double bond, an electron rich enamine is formed and subsequently reacts with various electrophiles enantioselectively.[5] Singly Occupied Molecular Orbital (**SOMO**) catalysis[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.[33-38] In the presence of a *α,β*-double bond, a formed electron deficient iminium ion can react with various nucleophiles by affording chiral *β*-substituted aldehydes/ketones, or participate in Diels-Alder reactions.[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.[39-41] If a *γ*-proton in *α,β*-unsaturated aldehydes exists, electron rich dienamines[42,43] can be potentially formed, which can afford *γ*-functionalized aldehydes[44,45] or participate in respective Diels-Alder[46] and [2+2][47] cyclization reaction as an electron rich diene.

Scheme 1.7. Aminocatalysis





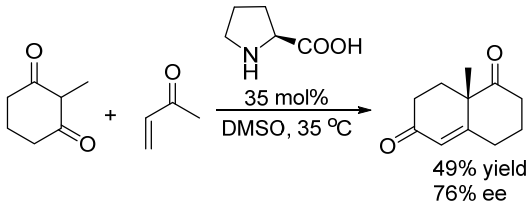
1.31 Aminocatalytic Cascade Reactions

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]

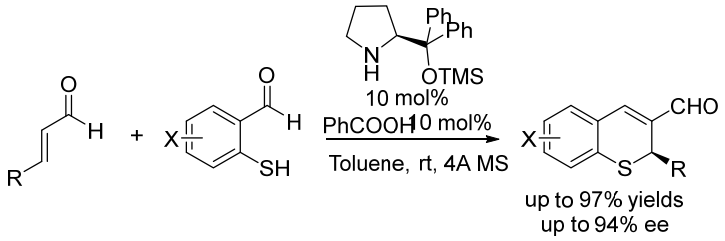
In 2000, Barbas developed the first aminocatalytic cascade reaction. In this Robinson annulation, L-proline first condensed with the ketone, generating an electron deficient iminium that reacts with activated methylene. Then, intramolecular aldol condensation was followed by enamine activation, affording tetrahydronaphthalene-1,6(2*H*,7*H*)-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 *α,β*-unsaturated aldehydes and 2-mercaptobenzaldehydes (Scheme 1.9).[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).[51] Impressive in this cascade reaction is the *in situ* formed enamine can selectively reacts with trans-*β*-nitrostyrene not *α,β*-unsaturated aldehydes, which means that nitrostyrene is more reactive than *α,β*-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.[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).[52]

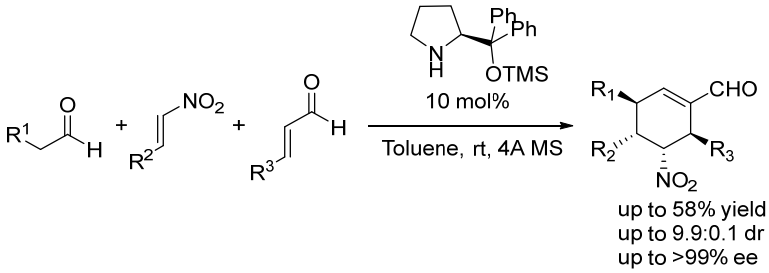
Scheme 1.8. Proline catalyzed asymmetric Robinson annulation



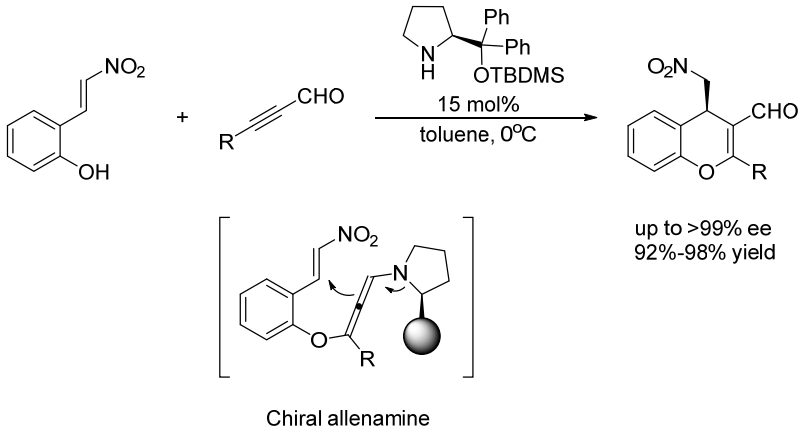
Scheme 1.9. Aminocatalytic asymmetric Michael-Aldol cascade reaction



Scheme 1.10. Aminocatalytic asymmetric three components triple cascade reaction



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

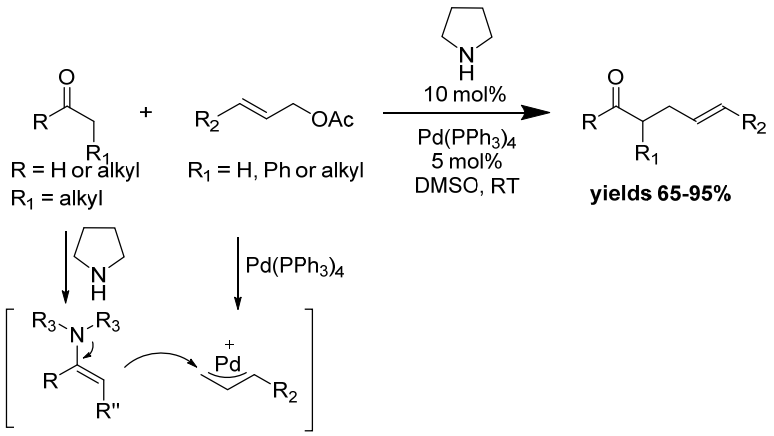


1.32 Combination of Amine and Metal Catalyzed Cascade Reactions

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.[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.

Scheme 1.12. α-Allylation of aldehydes and ketones catalyzed by a combination of pyrrolidine and $Pd(PPh_3)_4$

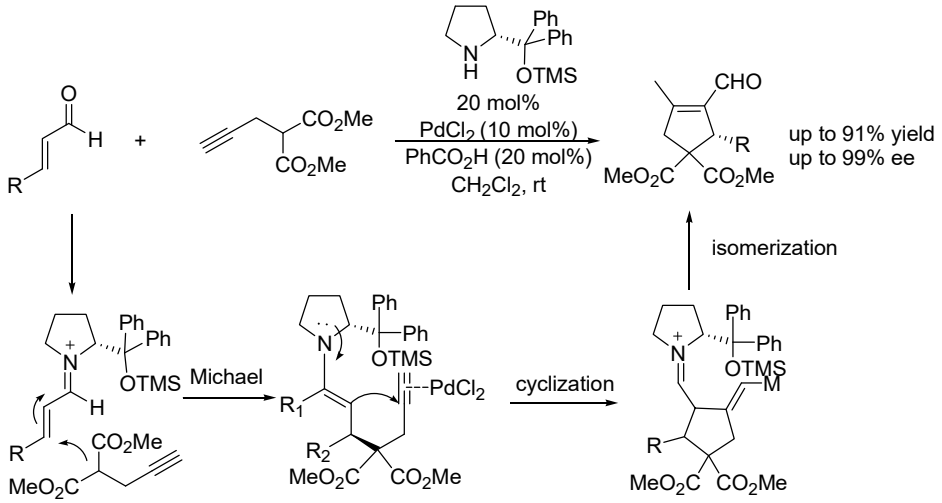


In 2006, Córdova developed the first example of combining aminoatalyst and metal catalyst, achieving direct *α*-allylation of aldehydes and cyclic ketones in good yields (Scheme 1.12).[63] In this protocol, $Pd(PPh_3)_4$ activates allyl acetate to generate electron-deficient palladium π-allyl complexes, 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 $PdCl_2$, producing multiple substituted cyclopentenes in good yields and with excellent enantioselecitivity (Scheme 1.13).[65] At the same time, Córdova[66] and Jórgensen[67] also reported similar procedures. Based on this strategy, chiral spirocyclic oxindoles,[68] dihydrofurans[69] and dihydropyrroles[70] were also obtained through changing the nucleophilic motif in bifunctional molecules from dimethyl malonate to oxindole, OH and tosyl protected amine groups respectively.

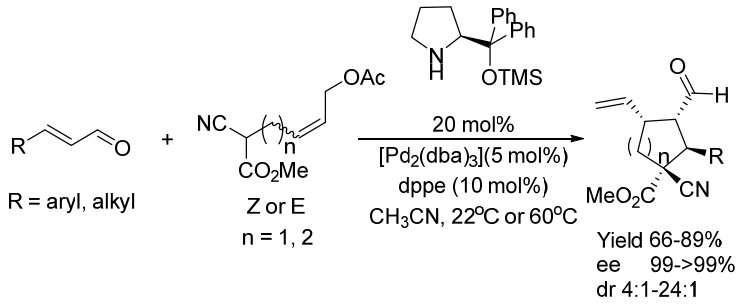
Scheme 1.13. Enantioselective Michael-cyclization cascade reactions catalyzed by a combination of diphenylprolinol TMS-ether and $PdCl_2$



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 $Pd_2(dba)_3$/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 γ,γ-disubstituted butenolides.

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Chapter 2

Organocatalytic Dynamic Kinetic Resolution of Biaryl Lactones

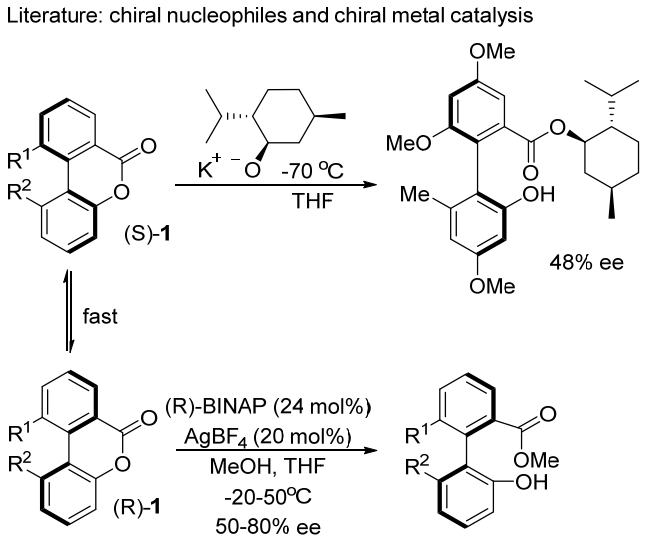
2.1 Introduction

Dynamic kinetic resolution (DKR)[1-3] provides an unrivaled power over traditional kinetic resolution (KR)[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.[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[10,11] and catalysis.[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.[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.[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[36]).[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,[38]

knipholone,[39,40] mastigophorene A,[41] and benanomicin B.[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.[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.[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.[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 $NaBH_4$ as reducing agent obtaining good enantioselectivity (80-93% ee).[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 alcoholate as chiral nucleophile gave the best result with 48% ee (Scheme 2.1, Eq. 1).[46] An asymmetric catalytic version using methanol as nucleophile by a chiral BINAP silver complex delivered moderate enantioselectivity (50-84% ee) (Eq 2).[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

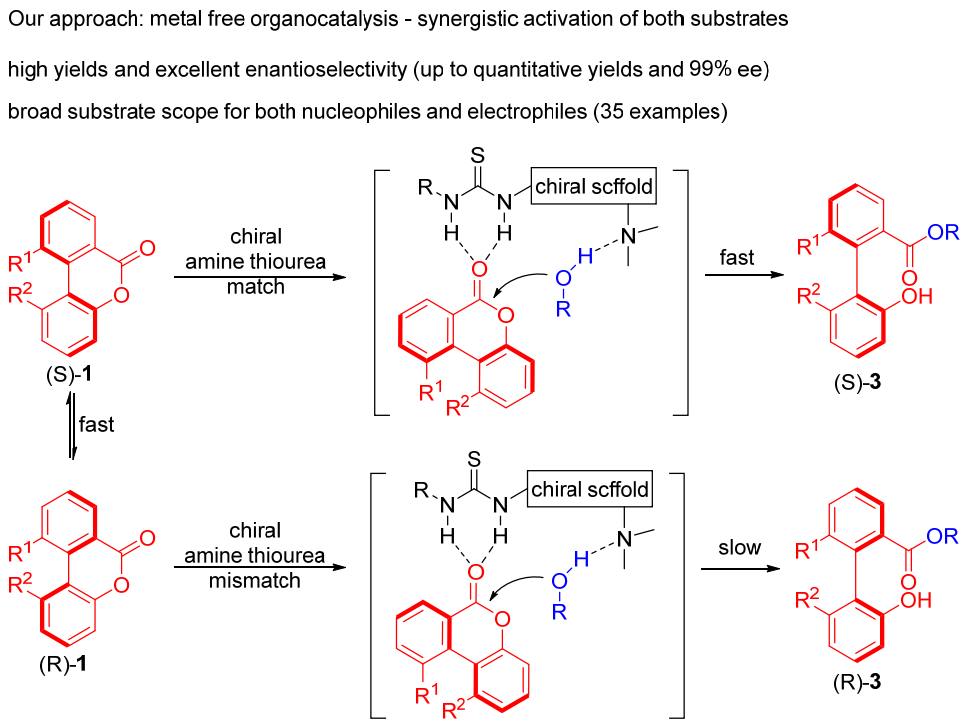


2.2 Research Plan

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.[48-51] The effective activation mode and our experience in this area[52-58] 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-thiourea catalyzed transesterification of the Bringmann's lactones



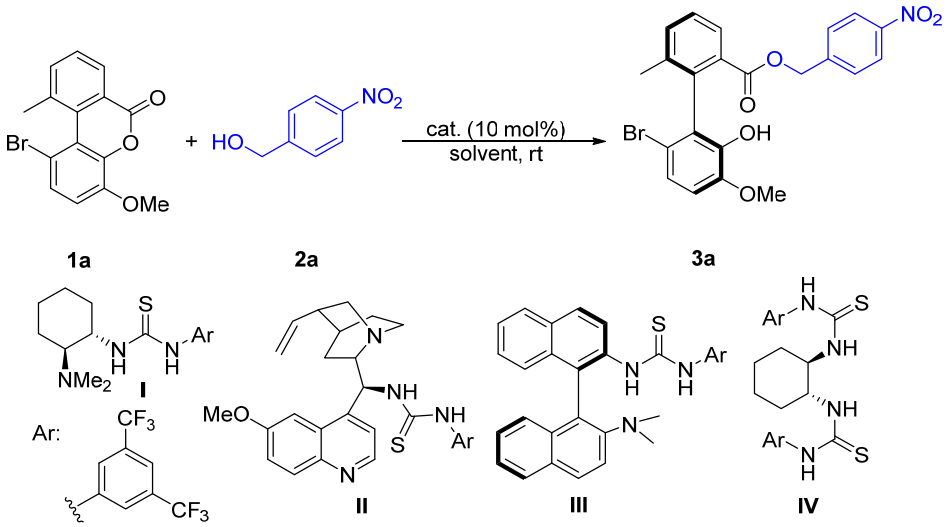
2.3 Results and discussion

2.31 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[a]



Entry	Catalyst	Loading (%)	Solvent	T (h)	Yield (%)[b]	ee (%)[c]
1	none	0	DCM	12	0	-
2	**I**	10	DCM	2	95	89
3	**II**	10	DCM	3	98	95
4	**III**	10	DCM	24	24	31
5	**IV**	10	DCM	24	0	-
6	**III**	10	Toluene	1.5	99	93
7	**III**	10	CF_3Ph	0.5	98	95
8	**III**	10	$CHCl_3$	1.5	99	94
9	**III**	10	Xylene	1.5	91	94
10	**III**	5	CF_3Ph	6	99	96
11	**III**	3	CF_3Ph	12	99	96
12	**III**	1	CF_3Ph	72	61	96

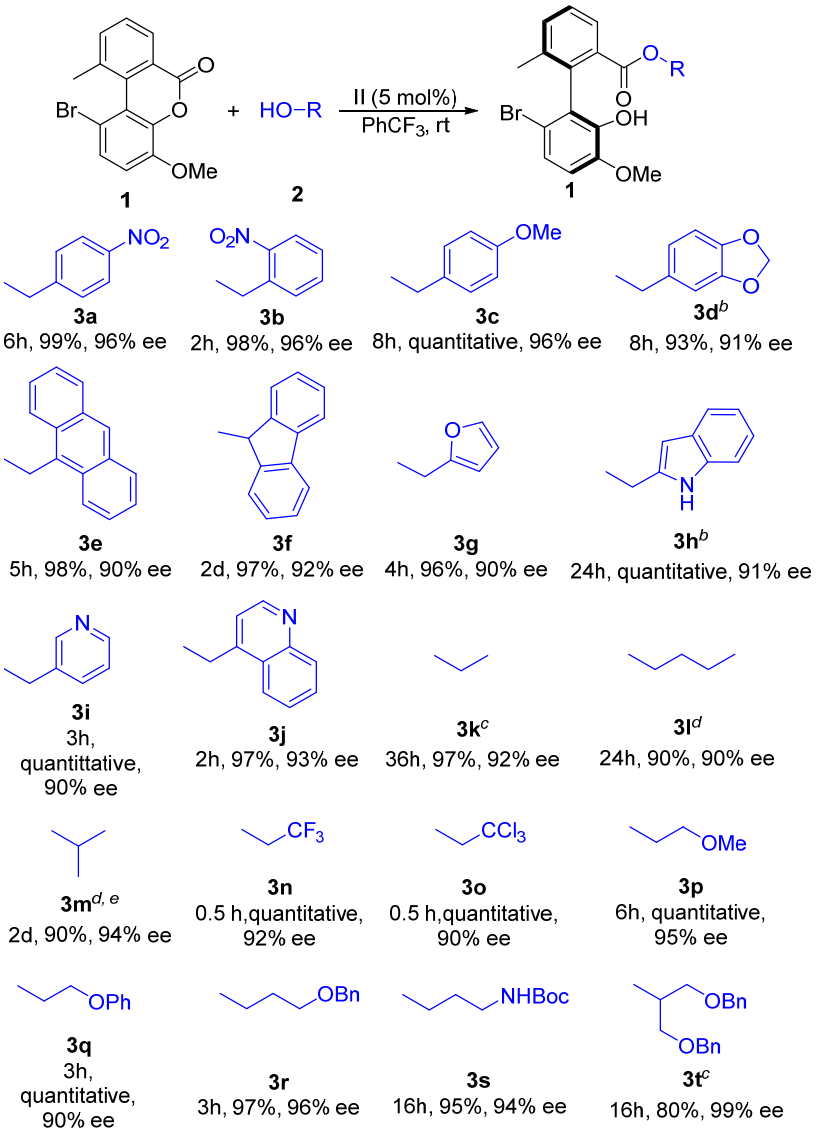
[a]Unless stated otherwise, see the Experimental Section. [b]Isolated yields. [c]Determined by

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-dibenzyloxyl-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

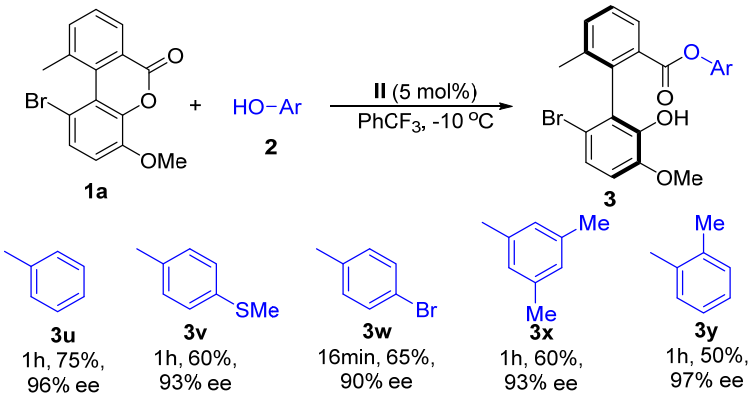


[a]Unless stated otherwise, see the Experimental Section. Ee value determined by chiral HPLC analysis (Chiralcel AS-H or AD). [b]-10 °C. [c]2.0 equiv. of alcohol. [d]20.0 equiv. of alcohol. [e]15 mol% **II**.

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

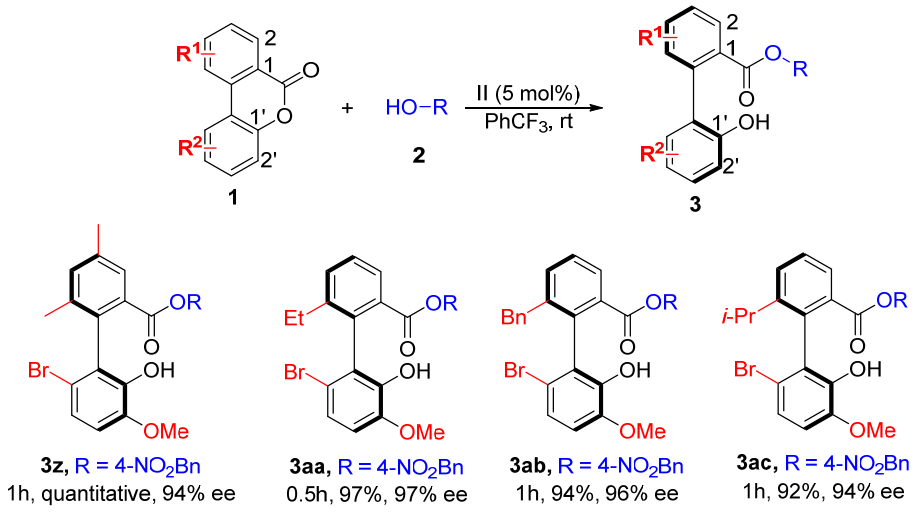


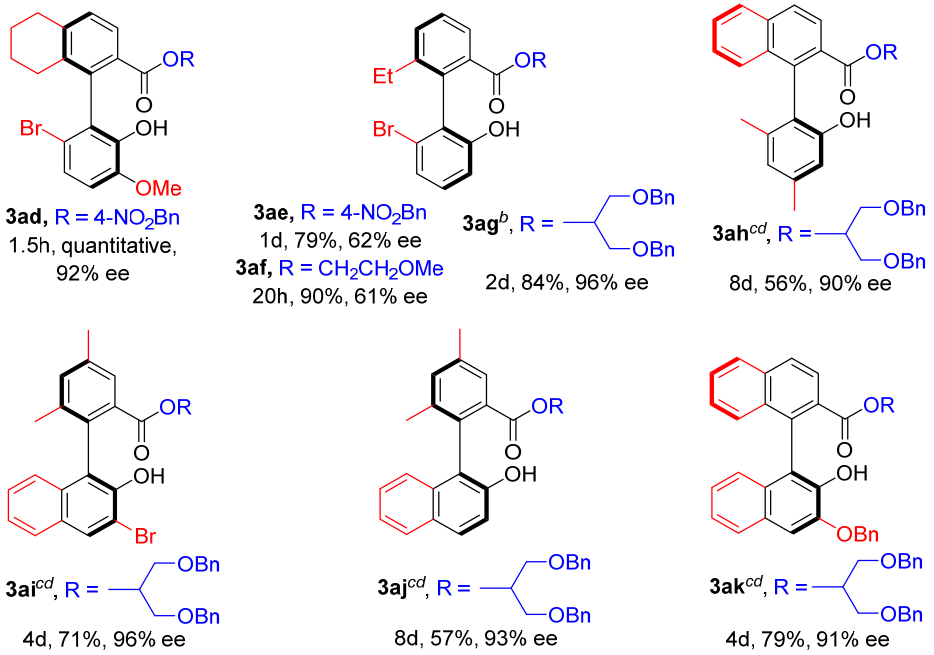
[a]Unless stated otherwise, see the Experimental Section. ee value determined by chiral HPLC analysis (Chiralcel AD).

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



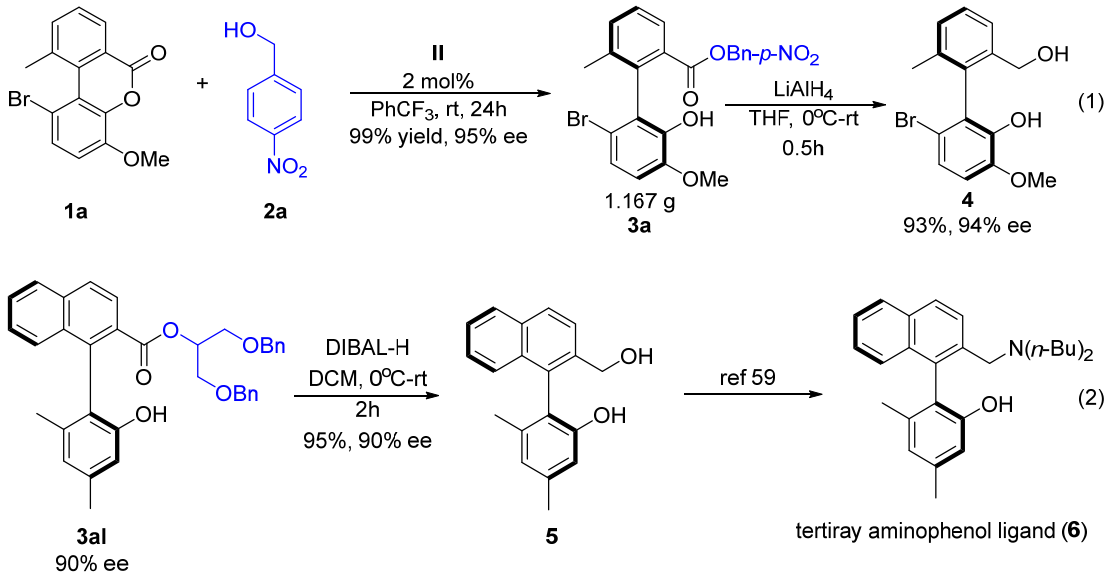


[a]Unless stated otherwise, see the Experimental Section. ee value determined by chiral HPLC analysis (Chiralcel AS-H or AD). [b]2.0 equiv. of alcohol. [c]10 equiv. of alcohol. [d]15 mol% of **III**.

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 transesterificaiton 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 F_{254} 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.

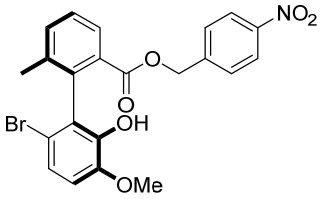
General Procedures for the *atropo*-Enantioselective Esterification:

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 α,α,α-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/*i*PrOH=70:30 at 0.5 mL/min, λ = 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/*i*PrOH=75:25 at 0.5 mL/min, λ = 210 nm): t_{major} = 15.93 min, t_{minor} = 26.88 min,; $[\alpha]_D^{25.0}$ = +7.9 (c = 1.00, $CHCl_3$)

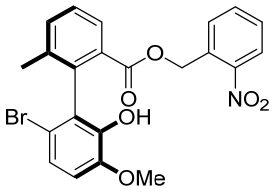
General Procedure for Gram Scale Synthesis (Scheme 2.6, Eq. 1**):** A mixture of biaryl lactones **1a** (2.5 mmol, 798 mg), 4-nitrobenzyl alcohol **2a** (3.0 mmol, 459 mg) and 0.02 mol% catalyst **II** (0.05 mmol, 30 mg) in 2.5 mL α,α,α-trifluoromethanebenzene was stirred for 24h at room temperature. 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/*i*PrOH=70:30 at 0.5 mL/min, λ = 254 nm); t_{major} = 23.09 min, t_{minor} = 31.83 min.



3a

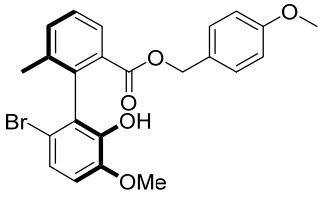
4-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-iphenyl]-2-carb-oxylate (**3a**): White solid; 99% yield, 96% ee; 1H-NMR (300 MHz, CDCl3) : δ = 8.15 (d, 2H, *J* = 8.7 Hz), 7.96 (d, 1H, *J* = 7.5 Hz), 7.52 (d, 1H, *J* = 7.2 Hz), 7.42 (t, 1H, *J* = 7.5 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.07 (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). ^{13}C NMR (75 MHz, $CDCl_3$, TMS):

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/*i*PrOH = 70:30 at 0.5 mL/min, λ = 254 nm): t_{major} = 23.09 min, t_{minor} = 31.83 min, ee = 96%; $[\alpha]_D^{22.0}$ (major) = -11.0 (c = 1.00, MeOH).



3b

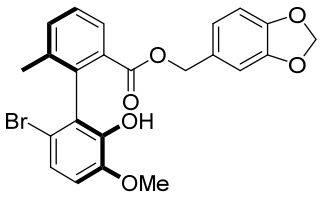
2-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carb-oxylate (**3b**): White solid; 98% yield, 96% ee; ^{1}H-NMR (300 MHz, CDCl3) : δ = 8.09 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.2 Hz), 7.41-7.62 (m, 5H), 7.07 (d, 1H, J = 8.7 Hz), 6.67 (d, 1H, J = 8.7 Hz), 5.64 (s, 1H), 5.55 (d, 2H, J = 2.1 Hz), 3.87 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 13.66 min, t_{minor} = 24.24 min, ee = 96%; $[\alpha]_D^{22.3}$ (major) = -7.0 (c = 1.00, MeOH).



3c

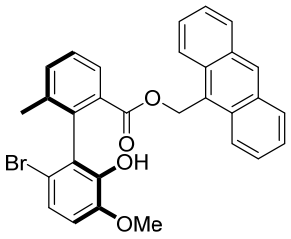
4-Methoxybenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3c**): White solid; quantitative yield, 93% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) :

δ = 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 NMR (75 MHz, $CDCl_3$, TMS): δ = 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 13.75 min, t_{minor} = 30.60 min, ee = 93%; $[\alpha]_D^{25.2}$ (major) = +15.7 (c = 1.00, $CHCl_3$).



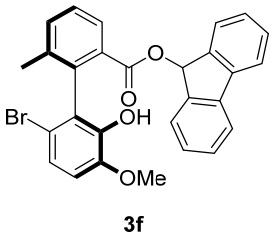
3d

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; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 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 NMR (75 MHz, $CDCl_3$, TMS): δ = 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 254 nm): t_{major} = 21.84 min, t_{minor} = 35.22 min, ee = 91%; $[\alpha]_D^{25.2}$ (major) = +5.1 (c = 1.00, $CDCl_3$).



3e

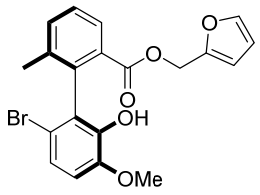
Anthracen-9-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl] -2-carboxylate (**3e**): White solid; 98% yield, 90% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.47 (s, 1H), 8.13-8.16 (m, 2H), 8.00-8.04 (m, 3H), 7.35-7.53 (m, 6H), 6.07-6.12 (m, 3H), 5.65 (d, 1H, *J* = 8.7 Hz), 5.13 (s, 1H), 3.34 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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/*i*PrOH = 70:30 at 0.5 mL/min, λ = 254 nm): t_{major} = 13.16 min, t_{minor} = 22.26 min, ee = 90%; $[\alpha]_D^{23.0}$ (major) = -6.4 (c = 1.00, $CHCl_3$).



3f

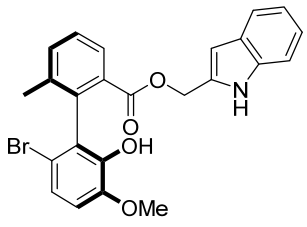
9H-fluoren-9-yl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3f**): White solid; 97% yield, 92% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.98 (d, 1H, *J* = 7.5 Hz), 7.61 (d, 2H, *J* = 7.5 Hz), 7.43-7.51 (m, 3H), 7.34-7.41 (m, 3H), 7.20-7.25 (m, 2H), 6.83-6.86 (m, 2H), 6.46 (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): δ = 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/*i*PrOH = 90:10 at 0.5 mL/min, λ = 254 nm): t_{major} = 17.66 min, t_{minor} = 23.68 min, ee = 92%; $[\alpha]_D^{23.4}$ (major) = +7.2 (c = 1.01, $CHCl_3$).



3g

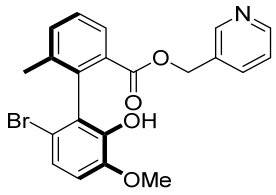
Furan-2-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3g**): White solid; 96% yield, 90% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.92 (d, 1H, *J* = 7.8 Hz), 7.49 (d, 1H, *J* = 7.5 Hz), 7.35-7.40 (m, 2H), 7.11 (d, 1H, *J* = 8.7 Hz), 6.72 (d, 1H, *J* = 8.7 Hz), 6.29-6.33 (m, 2H), 5.57 (s, 1H), 5.05 (s, 2H), 3.90 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 11.28 min, t_{minor} = 23.98 min, ee = 90%; $[\alpha]_D^{26.1}$ (major) = +12.2 (c = 1.00, $CHCl_3$).



3h

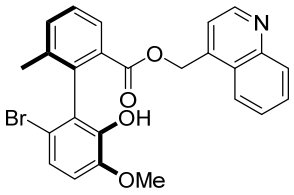
(1H-indol-2-yl)methyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3h**): White solid; quantitative yield, 91% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) :

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, J_1 = 1.2 Hz, J_2 = 7.8 Hz), 7.09 (dt, 1H, J_1 = 1.2 Hz, J_2 = 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). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 168.1, 145.6, 143.3, 138.1, 136.7, 136.6, 134.1, 132.8, 130.5, 128.1, 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/*i*PrOH = 90:10 at 0.5 mL/min, λ = 254 nm): t_{major} = 50.74 min, t_{minor} = 39.31 min, ee = 90%; $[\alpha]_D^{25.6}$ (major) = +37.4 (c = 1.00, $CHCl_3$).



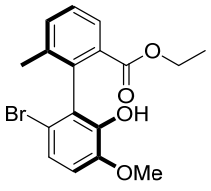
3i

Pyridin-3-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3i**): White solid; quantitative yield, 90% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : 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). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 166.7, 149.5, 149.1, 145.6, 143.3, 138.2, 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/*i*PrOH = 60:40 at 0.5 mL/min, λ = 254 nm): t_{major} = 11.98 min, t_{minor} = 23.77 min, ee = 90%; $[\alpha]_D^{23.5}$ (major) = +11.9 (c = 1.00, $CHCl_3$).



3j

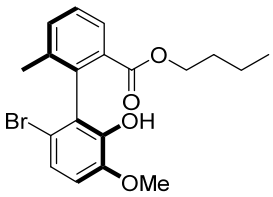
Quinolin-4-ylmethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3j**): White solid; 97% yield, 93% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.82 (d, 1H, *J* = 4.2 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), 8.02 (d, 1H, *J* = 7.8 Hz), 7.84 (d, 1H, *J* = 8.4 Hz), 7.73 (t, 1H, *J* = 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): δ = 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/*i*PrOH = 60:40 at 0.5 mL/min, λ = 254 nm): t_{major} = 16.27 min, t_{minor} = 35.66 min, ee = 93%; $[\alpha]_D^{23.6}$ (major) = -3.4 (c = 1.00, $CHCl_3$).



3k

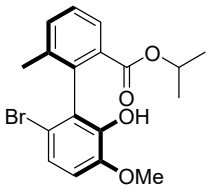
Ethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3k**): White solid; 97% yield, 92% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.91 (d, 1H, *J* = 7.8 Hz), 7.49 (d, 1H, *J* = 7.5 Hz), 7.39 (t, 1H, *J* = 7.8 Hz), 7.16 (d, 1H, *J* = 8.7 Hz), 6.78

(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): δ = 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 9.72 min, t_{minor} = 15.47 min, ee = 92%; $[\alpha]_D^{25.3}$ (major) = +4.8 (c = 1.00, $CHCl_3$).



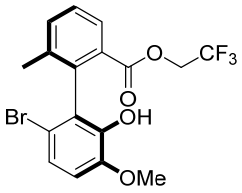
3l

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, $CDCl_3$) : δ = 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): δ = 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 8.93 min, t_{minor} = 14.42 min, ee = 90%; $[\alpha]_D^{25.3}$ (major) = +4.0 (c = 1.00, $CHCl_3$).



3m

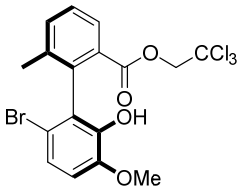
Isopropyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3m**): White solid; 90% yield, 94% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.89 (d, 1H, *J* = 7.5 Hz), 7.47 (d, 1H, *J* = 6.9 Hz), 7.39 (t, 1H, *J* = 7.5 Hz), 7.16 (d, 1H, *J* = 8.7 Hz), 6.78 (d, 1H, *J* = 8.7 Hz), 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): δ = 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/*i*PrOH = 90:10 at 0.5 mL/min, λ = 254 nm): t_{major} = 14.09 min, t_{minor} = 18.18 min, ee = 94%; $[\alpha]_D^{23.9}$ (major) = -3.2 (c = 1.00, $CHCl_3$).



3n

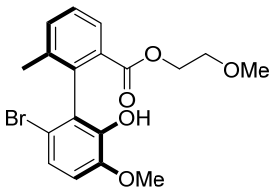
2,2,2-Trifluoroethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3n**): White solid; quantitative yield, 93% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.98 (d, 1H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.5 Hz), 7.43 (t, 1H, *J* = 7.8 Hz), 7.18 (d, 1H, *J* = 8.4 Hz), 6.79 (d, 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): δ = 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, CH_2); ^{19}F ($CDCl_3$) δ = 72.1. HPLC (Daicel CHIRALCEL AD column, hexane/*i*PrOH = 70:30 at 0.5 mL/min, λ = 254 nm): t_{major} = 9.18 min, t_{minor} = 36.45 min, ee = 93%; $[\alpha]_D^{24.3}$ (major) = +4.4 (c = 1.00, $CHCl_3$). ^{19}F (282 MHz, $CDCl_3$): δ -72.1.



3o

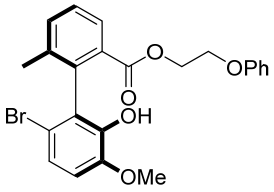
2,2,2-Trichloroethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3o**): White solid; quantitative yield, 90% ee; ^1H-NMR (300 MHz, $CDCl_3$) : δ = 8.06 (d, 1H, *J* = 7.8 Hz), 7.56 (d, 1H, *J* = 7.5 Hz), 7.44 (t, 1H, *J* = 7.8 Hz), 7.18 (d, 1H, *J* = 8.7 Hz), 6.78 (d, 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): δ = 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 9.89 min, t_{minor} = 25.49 min, ee = 90%; $[\alpha]_D^{25.3}$ (major) = +3.1 (c = 1.01, $CHCl_3$).



3p

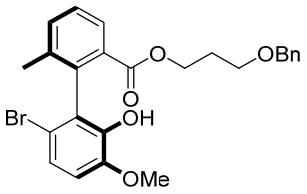
2-Methoxyethyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3p**): White solid; quantitative yield, 95% ee; ^1H-NMR (300 MHz, $CDCl_3$) :

δ = 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 NMR (75 MHz, $CDCl_3$, TMS): δ = 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; HPLC (Daicel CHIRALCEL AD column, hexane/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 10.35 min, t_{minor} = 18.35 min, ee = 95%; $[\alpha]_D^{25.9}$ (major) = +4.1 (c = 1.00, $CHCl_3$).



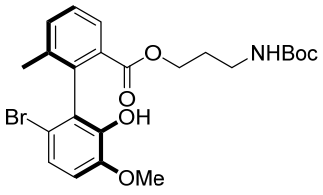
3q

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, $CDCl_3$) : δ = 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): δ = 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; HPLC (Daicel CHIRALCEL AD column, hexane/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 11.75 min, t_{minor} = 20.39 min, ee = 90%; $[\alpha]_D^{24.6}$ (major) = +9.1 (c = 1.01, $CHCl_3$).



3r

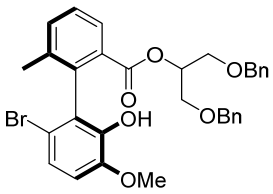
3-(Benzyloxy)propyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3r**): White solid; 97% yield, 96% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.89 (d, 1H, *J* = 7.8 Hz), 7.49 (d, 1H, *J* = 7.2 Hz), 7.38 (t, 1H, *J* = 7.5 Hz), 7.27-7.34 (m, 5H), 7.15 (d, 1H, *J* = 8.7 Hz), 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): δ = 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 10.70 min, t_{minor} = 18.08 min, ee = 96%; $[\alpha]_D^{25.0}$ (major) = +8.6 (c = 1.00, $CHCl_3$).



3s

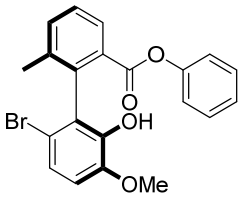
3-((Tert-butoxycarbonyl)amino)propyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3s**): White solid; 95% yield, 94% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.88 (dd, 1H, J_1 = 0.6 Hz, J_2 = 7.5 Hz), 7.49 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.5 Hz), 7.39 (t, 1H, *J* = 7.5 Hz), 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). ^{13}C NMR (75 MHz, $CDCl_3$, 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 8.73 min, t_{minor} = 13.76 min, ee = 94%; $[\alpha]_D^{25.7}$ (major) = -7.7 (c = 1.00, $CHCl_3$).



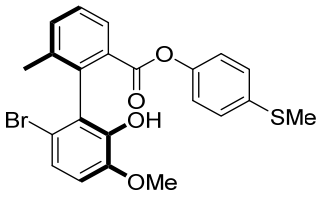
3t

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; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.94 (dd, 1H, J_1 = 0.9 Hz, J_2 = 7.8 Hz), 7.50 (dd, 1H, J_1 = 0.6 Hz, J_2 = 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). ^{13}C NMR (75 MHz, $CDCl_3$, 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 254 nm): t_{major} = 14.43 min, t_{minor} = 25.05 min, ee = 99%; $[\alpha]_D^{25.6}$ (major) = +6.5 (c = 1.00, $CHCl_3$).



3u

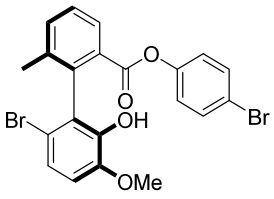
Phenyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3u**): White solid; 75% yield, 96% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.10 (d, 1H, *J* = 7.5 Hz), 7.57 (d, 1H, *J* = 7.5 Hz), 7.47 (t, 1H, *J* = 7.8 Hz), 7.31 (t, 2H, *J* = 7.2 Hz), 7.15-7.18 (m, 2H), 6.97 (d, 2H, *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, 125.5, 123.1, 121.6, 114.7, 110.8, 56.0, 19.9; HPLC (Daicel CHIRALCEL AD column, hexane/*i*PrOH = 75:25 at 0.5 mL/min, λ = 210 nm): t_{major} = 15.93 min, t_{minor} = 26.88 min, ee = 96%; $[\alpha]_D^{25.0}$ (major) = +7.9 (c = 1.00, $CHCl_3$).



3v

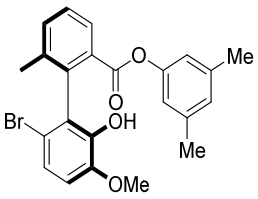
4-(Methylthio)phenyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylate (**3v**): White solid; 60% yield, 93% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.07 (dd, 1H, J_1 = 0.9 Hz, J_2 = 7.5 Hz), 7.56 (d, 1H, *J* = 7.5 Hz), 7.46 (t, 1H, *J* = 7.8 Hz), 7.21 (d, 2H, *J* = 8.7 Hz), 7.16 (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, $CDCl_3$, 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 210 nm): t_{major} = 19.87 min, t_{minor} = 37.23 min, ee = 93%; $[\alpha]_D^{25.0}$ (major) = +15.4 (c = 1.00, $CHCl_3$).



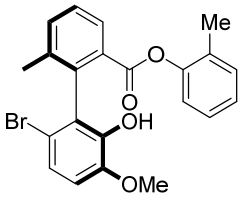
3w

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, $CDCl_3$) : δ = 8.07 (dd, 1H, J_1 = 0.9 Hz, J_1 = 7.8 Hz), 7.57 (dd, 1H, J_1 = 0.6 Hz, J_1 = 7.5 Hz), 7.48 (d, 1H, J = 7.5 Hz), 7.40-7.44 (m, 2H), 7.16 (d, 1H, J = 8.7 Hz), 6.84-6.87 (m, 2H), 6.75 (d, 1H, J = 8.7 Hz), 5.67 (s, 1H), 3.89 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 210 nm): t_{major} = 17.31 min, t_{minor} = 35.81 min, ee = 90%; $[\alpha]_D^{25.1}$ (major) = 13.8 (c = 1.00, $CHCl_3$).



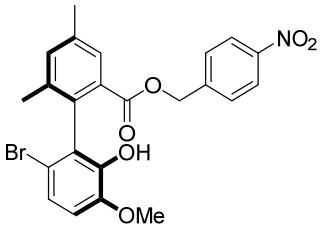
3x

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_1 = 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). ^{13}C 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 210 nm): t_{major} = 11.68 min, t_{minor} = 19.69 min, ee = 98%; $[\alpha]_D^{25.0}$ (major) = +7.0 (c = 1.00, $CHCl_3$).



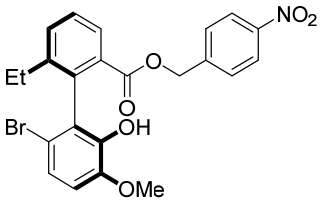
3y

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). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 164.8, 149.5, 145.8, 143.4, 138.4, 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/*i*PrOH = 70:20 at 0.5 mL/min, λ = 210 nm): t_{major} = 16.31 min, t_{minor} = 24.16 min, ee = 97%; $[\alpha]_D^{25.0}$ (major) = +4.4 (c = 1.00, $CHCl_3$).



3z

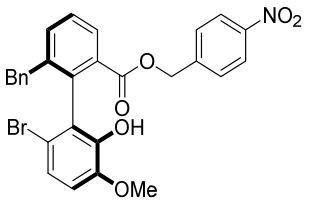
4-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-3'-methoxy-4,6-dimethyl-[1,1'-biphenyl]-2-carboxylate (**3z**): White solid; quantitative yield, 94% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.14 (d, 2H, *J* = 8.7 Hz), 7.77 (s, 1H), 7.31-7.34 (m, 3H), 7.06 (d, 1H, *J* = 8.7 Hz), 6.63 (d, 1H, *J* = 8.7 Hz), 5.57 (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): δ = 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 254 nm): t_{major} = 22.98 min, t_{minor} = 36.17 min, ee = 94%; $[\alpha]_D^{25.4}$ (major) = +12.6 (c = 1.00, $CHCl_3$).



3aa

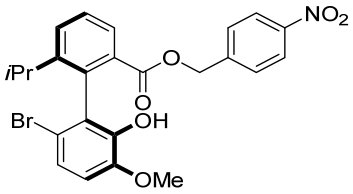
4-Nitrobenzyl (R)-6'-bromo-6-ethyl-2'-hydroxy-3'-methoxy-[1,1'-biphenyl]-2-carboxylate (**3aa**): White solid; 97% yield, 97% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.15 (d, 2H, *J* = 8.7 Hz), 7.95 (d, 1H, *J* = 7.5 Hz), 7.57 (d, 1H, *J* = 6.9 Hz), 7.47 (t, 1H, *J* = 7.8 Hz), 7.35 (d, 2H, *J* = 8.4 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): δ = 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/*i*PrOH = 85:15 at 0.5 mL/min, λ = 254 nm): t_{major} = 29.96 min, t_{minor} = 55.29 min, ee = 97%; $[\alpha]_D^{25.2}$ (major) = +5.6 (c = 1.00, $CHCl_3$).



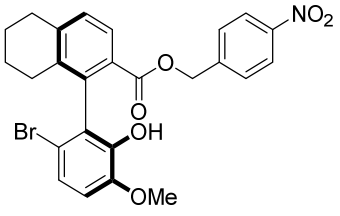
3ab

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, $CDCl_3$) : δ = 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): δ = 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 254 nm): t_{major} = 27.63 min, t_{minor} = 57.39 min, ee = 95%; $[\alpha]_D^{25.5}$ (major) = +19.0 (c = 1.00, $CHCl_3$).



3ac

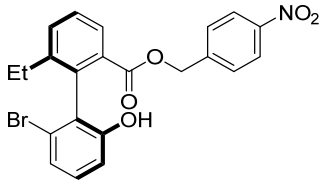
4-Nitrobenzyl (R)-6'-bromo-2'-hydroxy-6-isopropyl-3'-methoxy-[1,1'-biphenyl]-2-carboxylate (**3ac**): White solid; 92% yield, 94% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.15 (d, 2H, *J* = 8.7 Hz), 7.92 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.8 Hz), 7.64 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.8 Hz), 7.51 (t, 1H, *J* = 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): δ = 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/*i*PrOH = 65:35 at 0.5 mL/min, λ = 254 nm): t_{major} = 13.33 min, t_{minor} = 31.76 min, ee = 94%; $[\alpha]_D^{25.1}$ (major) = +4.1 (c = 1.00, $CHCl_3$).



3ad

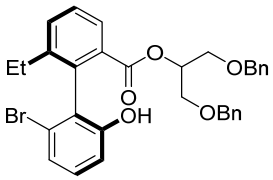
4-Nitrobenzyl (R)-1-(6-bromo-2-hydroxy-3-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (**3ad**): White solid; quantitative yield, 92% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.14 (d, 2H, *J* = 8.7 Hz), 7.88 (d, 1H, *J* = 8.1 Hz), 7.38 (d, 2H, *J* = 8.7 Hz), 7.24 (d, 1H, *J* = 8.1 Hz), 7.06 (d, 1H, *J* = 8.7 Hz), 6.63 (d, 1H, *J* = 8.7

Hz), 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): δ = 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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 254 nm): t_{major} = 27.18 min, t_{minor} = 52.71 min, ee = 92%; $[\alpha]_D^{25.6}$ (major) = +19.4 (c = 1.00, $CHCl_3$).



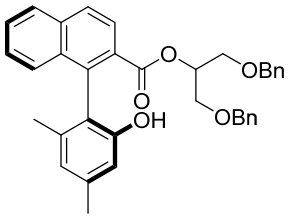
3ae

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, $CDCl_3$) : δ = 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): δ = 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/*i*PrOH = 80:20 at 0.5 mL/min, λ = 254 nm): t_{major} = 17.47 min, t_{minor} = 22.42 min, ee = 62%; $[\alpha]_D^{25.1}$ (major) = +4.1 (c = 1.00, $CHCl_3$).



3ag

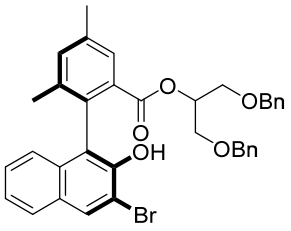
1,3-Bis(benzyloxy)propan-2-yl (R)-2'-bromo-6-ethyl-6'-hydroxy-[1,1'-biphenyl]-2-carboxylate (**3ag**): colorless oil; 84% yield, 96% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.91 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.5 Hz), 7.57 (d, 1H, J = 7.8 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.26-7.32 (m, 10H), 7.14 (dd, 1H, 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): δ = 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/*i*PrOH = 85:15 at 0.5 mL/min, λ = 254 nm): t_{major} = 10.88 min, t_{minor} = 15.38 min, ee = 96%; $[\alpha]_D^{25.3}$ (major) = -4.5 (c = 1.00, $CHCl_3$).



3ah

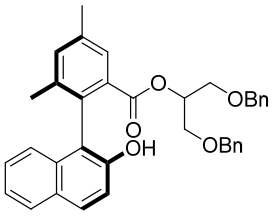
1,3-Bis(benzyloxy)propan-2-yl (S)-1-(2-hydroxy-4,6-dimethylphenyl)-2-naphthoate (**3ah**): colorless oil; 56% yield, 90% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.92-8.04 (m, 4H), 7.58 (dd, 1H, J_1 = 1.2 Hz, J_2 = 8.1 Hz), 7.43-7.50 (m, 2H), 7.29-7.36(m, 10H), 7.50 (d, 1H, J = 7.8 Hz), 7.26-7.32 (m, 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): δ = 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/*i*PrOH = 80:20 at 0.5 mL/min, λ = 254 nm): t_{major} = 10.11 min, t_{minor} = 13.91 min, ee = 90%; $[\alpha]_D^{25.2}$ (major) = +14.6 (c = 1.00, $CHCl_3$).



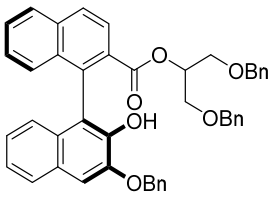
3ai

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, $CDCl_3$) : δ = 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): δ = 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/*i*PrOH = 97:3 at 0.4 mL/min, λ = 254 nm): t_{major} = 55.96 min, t_{minor} = 42.98 min, ee = 96%; $[\alpha]_D^{25.5}$ (major) = +3.3 (c = 1.00, $CHCl_3$).



3aj

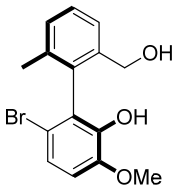
1,3-Bis(benzyloxy)propan-2-yl (S)-2-(2-hydroxynaphthalen-1-yl)-3,5-dimethylbenzoate (**3aj**): colorless oil; 57% yield, 93% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 7.68-7.74 (m, 3H), 7.38 (s, 1H), 7.11-7.32 (m, 13H), 7.00-7.03 (m, 1H), 5.00 (quint, 1H, 5.4 Hz), 4.26-4.35 (m, 2H), 4.17 (s, 2H), 3.07-3.19 (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/*i*PrOH = 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, $CHCl_3$).



3ak

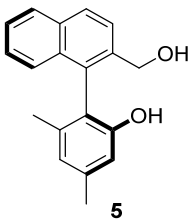
1,3-Bis(benzyloxy)propan-2-yl (S)-3'-(benzyloxy)-2'-hydroxy-[1,1'-binaphthalene]-2-carboxylate (**3ak**): white solid; 79% yield, 91% ee; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ = 8.16 (d, 1H, *J* = 8.7 Hz), 8.01 (d, 1H, *J* = 8.7 Hz), 7.95 (d, 1H, *J* = 8.1 Hz), 7.10 (d, 1H, *J* = 8.1 Hz), 7.54 (dt, J_1 = 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): δ = 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/*i*PrOH = 70:30 at 0.5 mL/min, λ = 254 nm): t_{major} = 16.80 min, t_{minor} = 19.98 min, ee = 91%; $[\alpha]_D^{21.7}$ (major) = -21.6 (c = 1.00, $CHCl_3$).



4

(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, $CDCl_3$) : δ = 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): δ = 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/*i*PrOH = 85:15 at 0.5 mL/min, λ = 210 nm): t_{major} = 18.62 min, t_{minor} = 26.01 min, ee = 94%; $[\alpha]_D^{25.3}$ (major) = +17.7 (c = 1.00, $CHCl_3$).



5

(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), 4.46 (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/*i*PrOH = 70:30 at 0.5 mL/min, λ = 254 nm): t_{major} = 8.36 min, t_{minor} = 12.01 min, ee = 90%; $[\alpha]_D^{22}$ (major) = +14.2 (c = 0.51, MeOH).

2.6 References

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Chapter 3

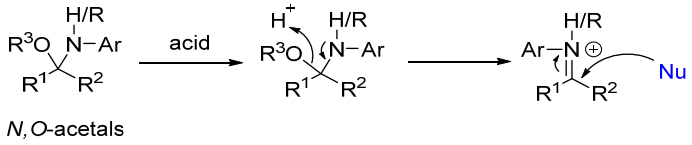
Aryl Amine Catalyzed Cascade Reactions

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).[1-3] 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).[4-7] 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.[8-12] Furthermore, to make "O" contained heterocycles, cyclic acetals or hemiacetals are generally used.[13-18] 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

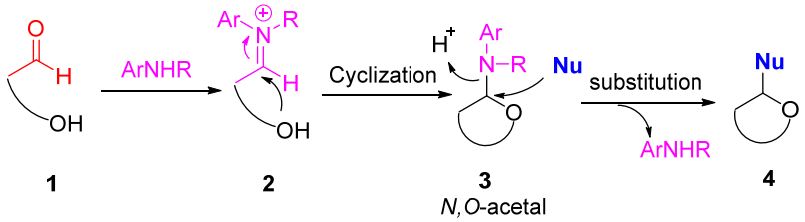


N, O-acetals

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 *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]

Scheme 3.2. Proposed amine catalyzed cyclization-"N" involved nucleophilic substitution cascade reaction via an *in situ* formed *N, O*-acetals

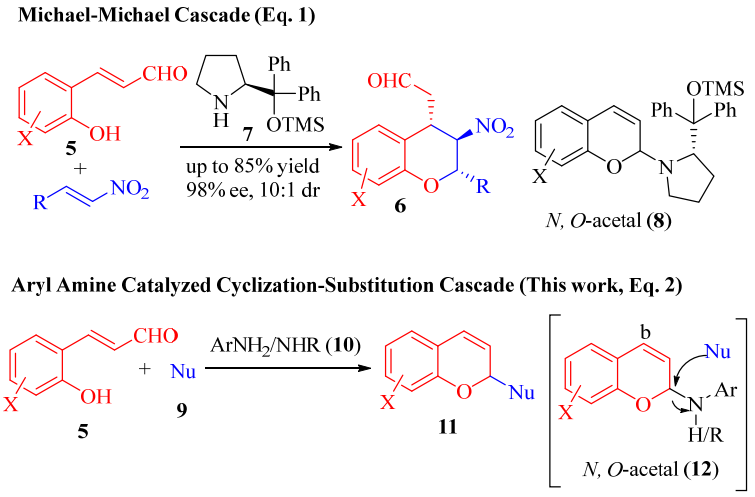


3.12 Research Plan

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 *o*-hydroxy-*trans*-cinnamaldehyde **5** with a chiral amine **7** (Scheme 3.3, Eq. 1). Subsequent reaction of the *N, O*-acetal **8** with a *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 2*H*-chromenes **11**,[21,22] a class of 'privileged' structures

with a broad range of interesting biological activities.[23-25] They have served as targets for a number of synthetic studies.[20-22,26-46]

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 *α*, *β*-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 2*H*-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

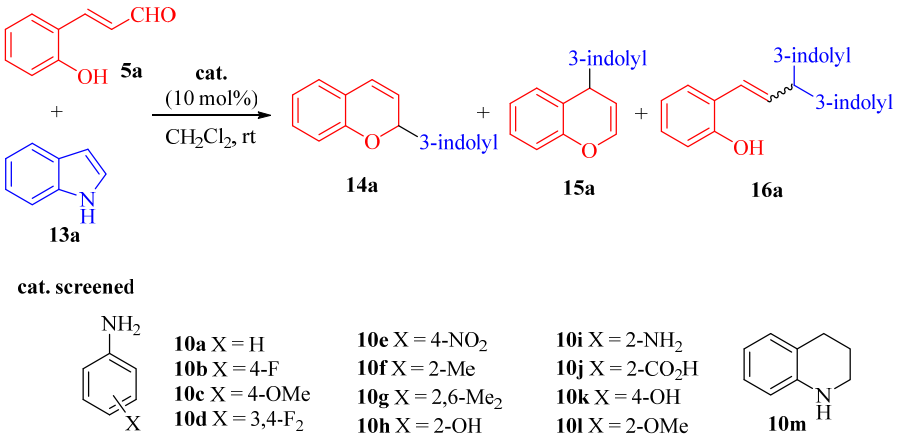
3.131 Cyclization-substitution Cascade Reaction of 2-Hydroxylcinnamaldehydes with Electron Rich Arenes

3.1311 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-methoxylaniline (**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).

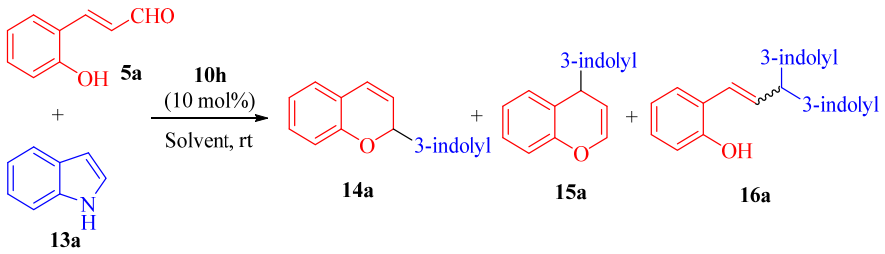
Table 3.1. Optimization of reaction conditions[a]



entry	Cat	t (h)	% yield[b]	ratio of **14a:15a:16a**[c]
1	**10a**	24	26	0.9:0.5:1.0
2	**10b**	24	34	1.6:0.6:1.0
3	**10c**	24	11	0.3:0.4:1.0
4	**10d**	24	12	0.2:0.4:1.0
5	**10e**	24	0	-
6	**10f**	24	11	1.2:0.5:1.0
7	**10g**	24	<5	-
8	**10h**	24	59	3.5:1.3:1.0
9	**10i**	24	24	0.8:0.4:1.0
10	**10j**	24	28	1.2:0.8:1.0
11	**10k**	24	18	2.0:0.7:1.0
12	**10l**	24	30	1.1:0.6:1.0
13	**10m**	24	49	2.9:0.3:1.0
14[d]	**10h**	24	63	17.0:1.3:1.0
15[d,e]	**10h**	24	56	11.0:1.0:1.0
16[d,f]	**10h**	24	70	12.0:1.0:0.0
17[d,f,g]	**10h**	22	86	10.0:1.0:0.0

[a]Reaction conditions: unless specified, a mixture of **5a** (0.1 mmol), **13a** (0.12 mmol), and catalyst (**10**, 0.01 mmol) in CH_2Cl_2 (0.5 mL) was stirred at rt. [b]Isolated yields. [c]Determined by using ^1H 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[a]



Entry	Solvent	t (h)	Yields (%)[b]	Ratio (**14a**:**15a**:**16a**)[c]
1	CH_2Cl_2	24	70	12:1:0
2	DCE	48	51	9.3:1.1:1
3	$CHCl_3$	36	60	4.5:1:0
4	Toluene	48	36	3.2:1.1:1
5	THF	72	0	-
6	EtOAc	72	9	2.1:1.6:1
7	CH_3CN	72	11	2.1:1:0
8	DMF	72	0	-
9	DMSO	72	0	-
10	MeOH	72	0	-
11[d]	CH_2Cl_2	72	86	10:1:0

[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 ^1H 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

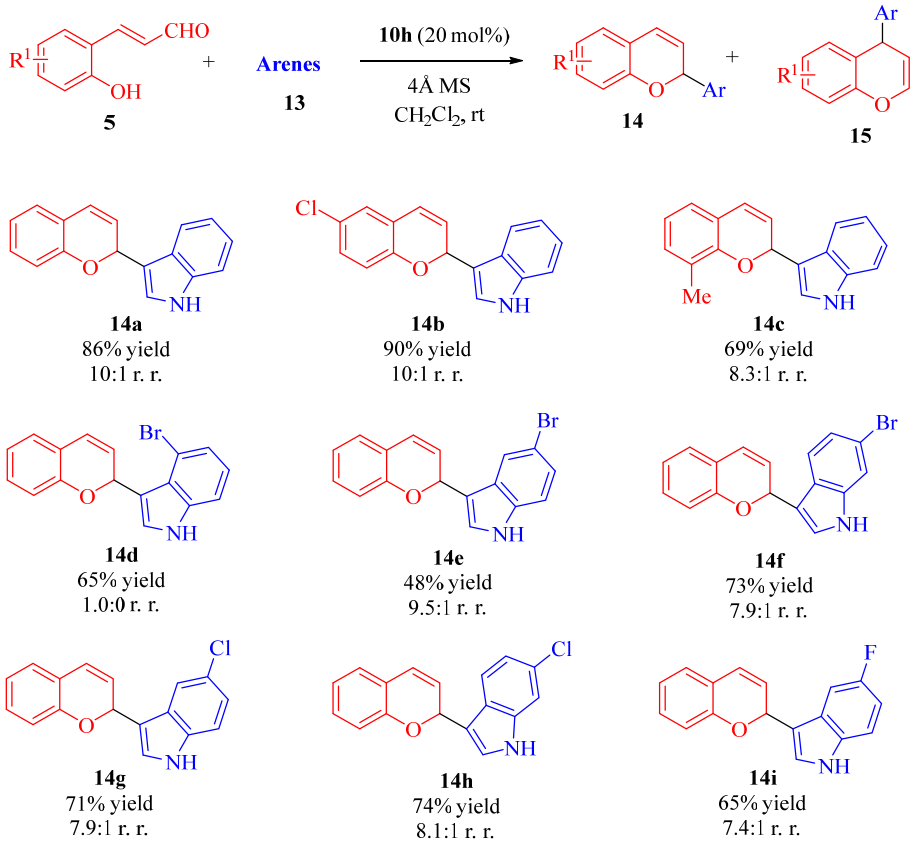
the yield (63%) and a dramatic increase in regioselectivity (17:1.3:1) (entry 14). Furthermore, increasing the ratio of **5a** to **13a** to 1.2:1 further enhanced the efficiency (70%) and regioselectivity (12:1:0) for formation of adduct **14a** (entry 16). Raising the catalyst loading to 20 mol% further improved the yield (86%) while maintaining regioselectivity (10:1.0:0) of the process (entry 17). Of the solvents screened, CH_2Cl_2 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 CH_2Cl_2 with 4Å MS.

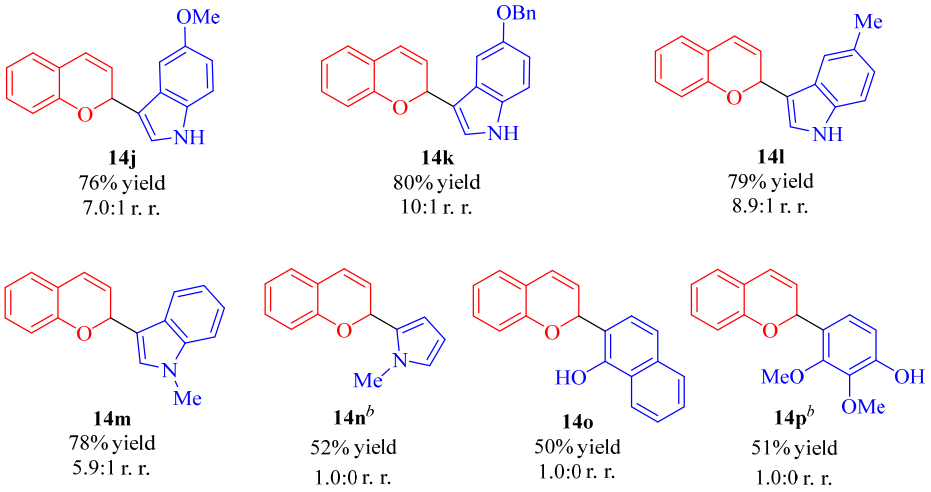
3.1312 Investigation of Substrate Scope

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 2*H*-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 **14n** in 52% yield. In this case as well as others in which less reactive nucleophiles are employed, tetrahydroquinoline **10m** was found to be superior to **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-dimethoxylphenol react smoothly with **5a** in the presence of aniline **10m** to form **14o** (50%) and **14p** (51%), respectively.

Scheme 3.4. Substrate scope of anilines catalyzed cyclization-substitution cascade reaction of **5** with electron-rich arenes **13**[a]





[a]Unless specified, see experimental section. [b]cat. **10m** was used.

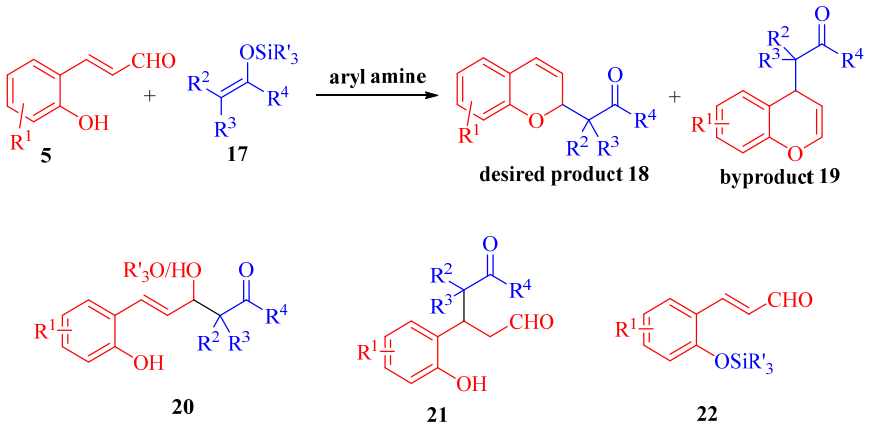
3.132 Cyclization-substitution Cascade Reaction of 2-hydroxylcinnamaldehydes with Silyl Enol Ethers

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

complicate this process.

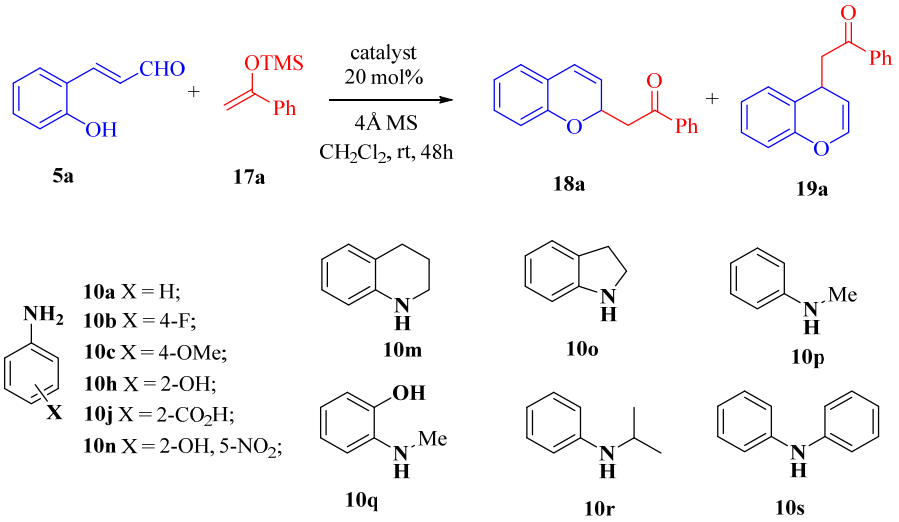
Scheme 3.5. Arylamine catalyzed cyclization-substitution cascade reactions of *trans*-hydroxycinnamaldehydes 5 with silyl enol ethers 17



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 delighting 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 similiar results as **10h**, indicating that *orth*-OH dosen't give the desired synergistic role for this substrates (entries 1-4). When strogner 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 10**o-s** were tested, but no improved result was obtained (entries 9-13).

Table 3.3. Optimization of reaction conditions[a]



Entry	Catalyst	%yields[b]	r.r. (**18a**:**19a**)[c]
1	**10a**	73	4.0:1
2	**10b**	68	4.5:1
3	**10c**	60	4.4:1
4	**10h**	68	4.3:1
5	**10j**	26	4.4:1
6	**10n**	33	4.3:1
7	**10m**	82	4.7:1
8[d]	**10m**	74	5.0:1
9	**10o**	46	5.3:1
10	**10p**	73	4.5:1
11	**10q**	29	4.9:1
12	**10r**	71	3.8:1
13	**10s**	39	4.1:1

[a]Reaction conditions: unless specified, a mixture of **5a** (0.1 mmol), **17a** (0.15 mmol), and a catalyst **10** (0.02 mmol) in CH_2Cl_2 (0.5 mL) was stirred at rt for 48h. [b]Isolated yields. [c]Determined by ^{1}H-NMR. [d]The ratio of **5a** to **17a** is 1:1.2.

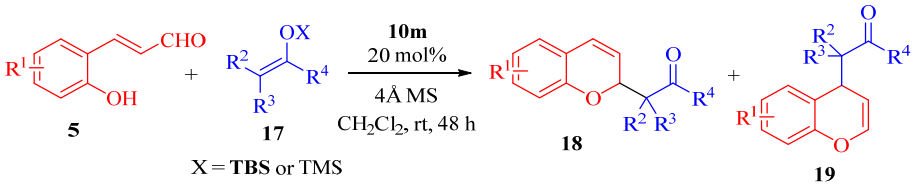
3.1322 Investigation of Substrate Scope

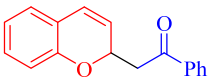
Studies probing the substrate scope of the reaction showed that some 2-hydroxycinnamaldehydes (e. g., **5b**, **5d**, **5f** and **5v**) participate in low yielding reaction with TMS derived silyl enol ether **17a** (Scheme 3.6). Analysis of these reactions reveals that transfer of the TMS moiety from **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 *t*-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 diastereomeic 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 regioselecitivity 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.

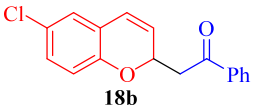
Scheme 3.6. Arylamine **10m** catalyzed cyclization-substitution cascade reaction of cinnamaldehyde derivatives **15** and silyl enol ethers **17**[a]





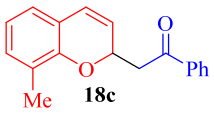
18a

X = TBS	X = TMS
80% yield	82% yield
10.1:1 r.r.	4.7:1 r.r.



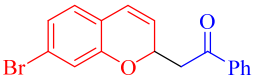
18b

X = TBS	X = TMS
80% yield	60% yield
9.1:1 r.r.	4.4:1 r.r.



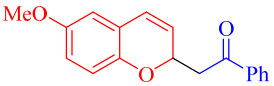
18c

X = TBS	X = TMS
97% yield	99% yield
12:1 r.r.	2.8:1 r.r.



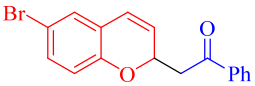
18d

X = TBS	X = TMS
76% yield	47% yield
12:1 r.r.	5.8:1 r.r.



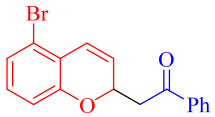
18e

X = TBS	**X = TMS**
89% yield	92% yield
13:1 r.r.	4.8:1 r.r.



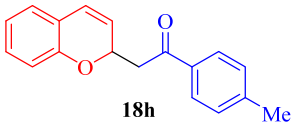
18f

X = TBS	X = TMS
86% yield	68% yield
9.1:1 r.r.	4.8:1 r.r.

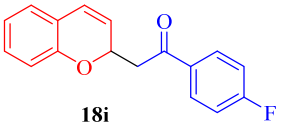


18g

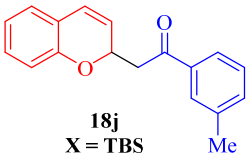
X = TBS	X = TMS
73% yield	80% yield
6.4:1 r.r.	1.9:1 r.r.



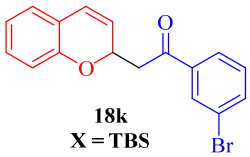
18h
X = TBS
88% yield
8.8:1 r.r.



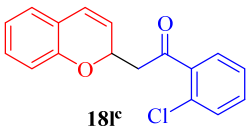
18i
X = TBS
78 % yield
12:1 r.r.



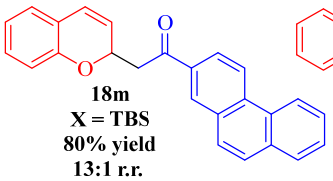
18j
X = TBS
82% yield
12:1 r.r.



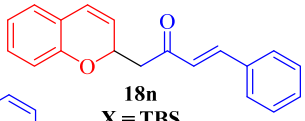
18k
X = TBS
72% yield
19:1 r.r.



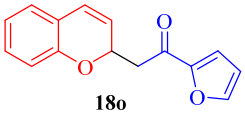
18l[c]
X = TBS
48% yield
19:1 r.r.



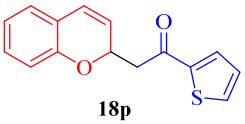
18m
X = TBS
80% yield
13:1 r.r.



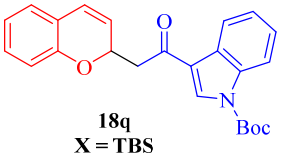
18n
X = TBS
90% yield
5:1 r.r.



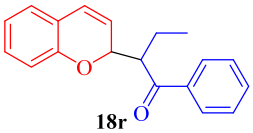
18o
X = TBS
85% yield
5.1:1 r.r.



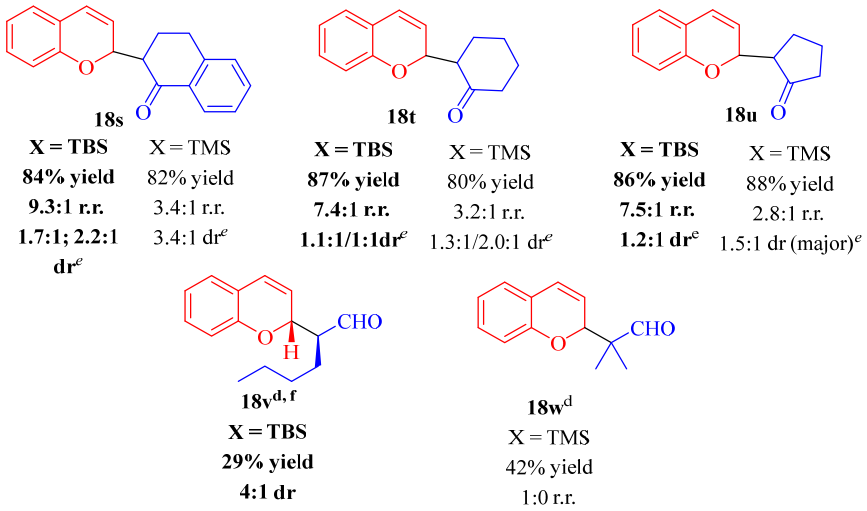
18p
X = TBS
87% yield
7.2:1 r.r.



18q
X = TBS
68% yield
4.6:1 r.r.



18r
X = TBS
62% yield
1:0 r. r.
4:1 dr[e]



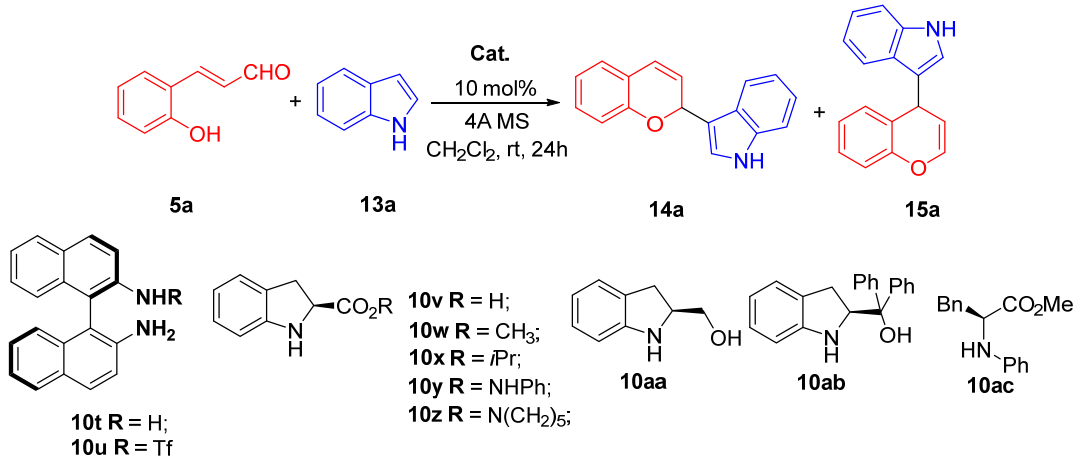
[a]Unless specified, see experimental section. [b]Isolated yield. [c]72 h. [d]96 h. [e]The relative stereochemistry was not assigned for this product mixture. [f]Relation configuration is determined by comparison known compounds in ref. 18.

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). By

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-hydroxylcinnamaldehyde **5a** and indole **13a**[a]



Entry	Catalyst	Yields %[b]	ee % (**14a**)[c]
1	**10t**	58	0
2	**10u**	55	3
3	**10v**	46	-3
4	**10w**	49	20
5	**10x**	57	18
6	**10y**	55	2
7	**10z**	73	2
8	**10aa**	43	0
9	**10ab**	48	1
10	**10ac**	0	-

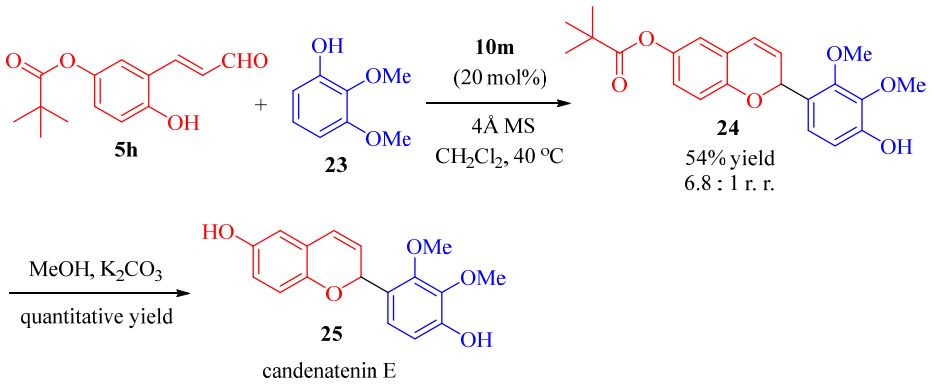
[a]Reaction conditions: unless specified, a mixture of **5a** (0.12 mmol), **13a** (0.1 mmol), and

a catalyst **10** (0.01 mmol) in CH_2Cl_2 (0.5 mL) was stirred at rt for 24h. [b]Isolated yield. [c]determined by HPLC.

3.134 Synthetic Applications

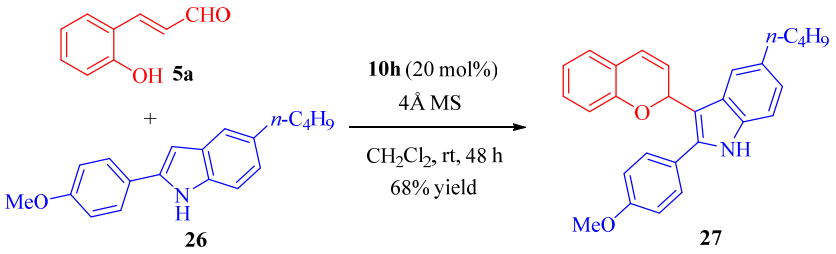
As discussed above, chromenes and chromanes scaffolds widely present in a number of natural products and bioactive compounds. The new method we have developed can serve as the powerful tool to construct interestingly substituted members of these heterocyclic families. To demonstrate the synthetic utility 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 Candenatenine E[a]



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 compound[a]

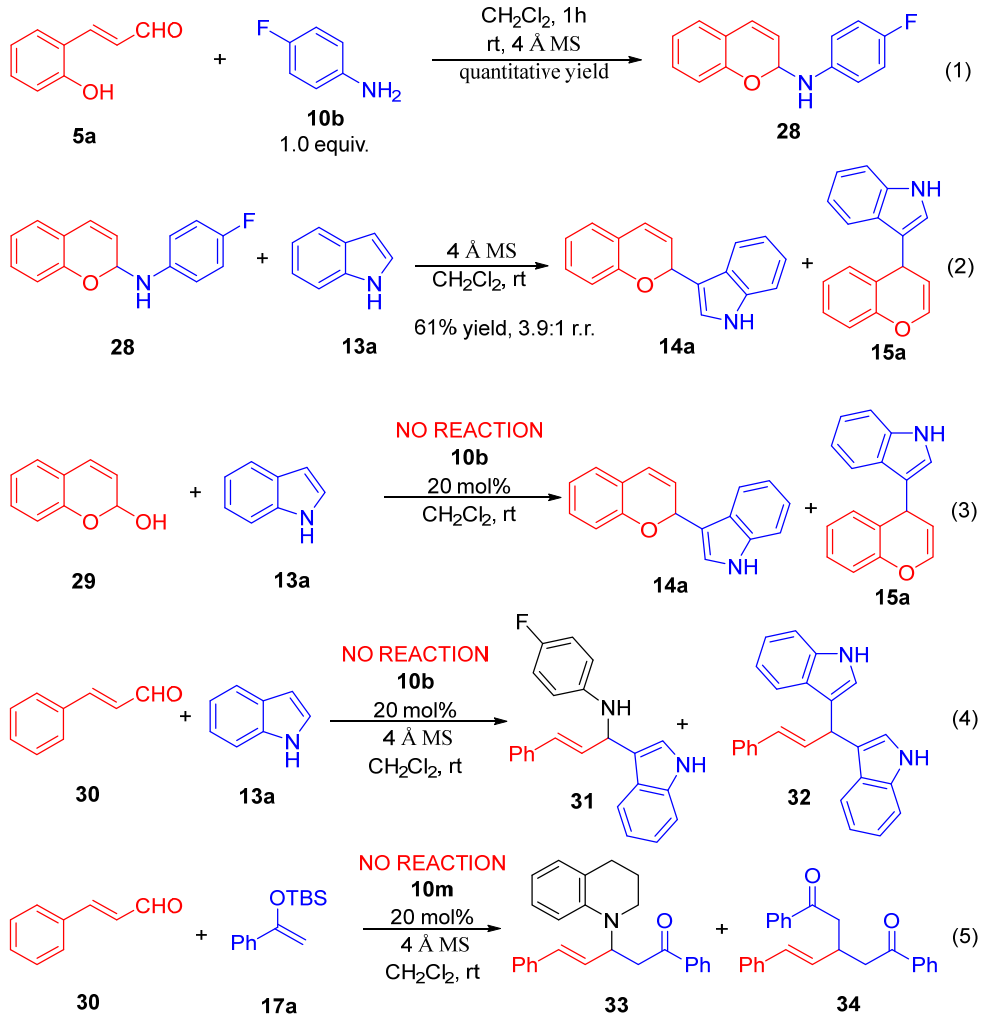


3.135 Mechanistic Study

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 chemo- 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 **8** (Scheme 3.9).[20] However, its poor leaving tendency prevents the subsequent nucleophilic substitution process even with an acid additive (e.g., CF_3CO_2H).

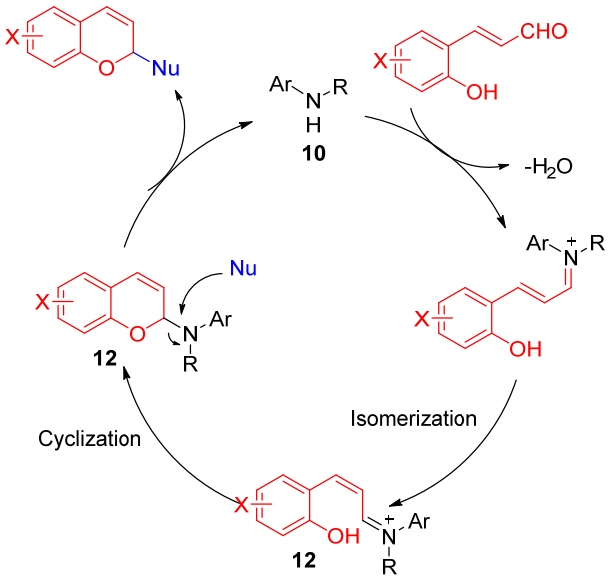
Scheme 3.9. The Results of experiments designed to gain preliminary understanding the mechanism of the cyclization-substitution cascade process



To understand the new aminocatalytic cyclization-substitution process, we carried out more detailed investigation. In this effort, we observed that treatment of aldehyde **5a**

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-butyldimethyl((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

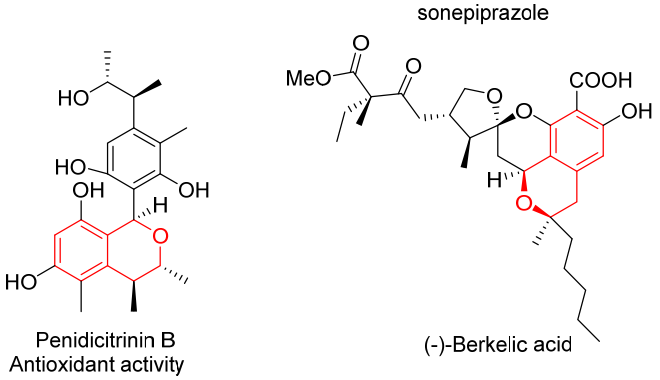
In the study described above, we developed an unprecedented, aryl amine catalyzed cyclization-substitution cascade reaction for the 'one-pot' synthesis of 2-substituted 2*H*-chromenes. Unlike widely used strategies, the protocol employs simple amines as activators for formation of *N, O*-acetals and 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.

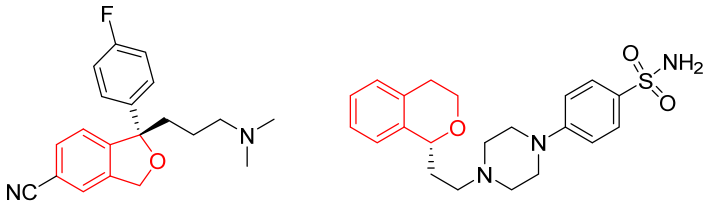
3.2 Cyclization-Substitution Cascade Reactions of Hemiacetals and Various Carbonic Nucleophiles

3.21 Introduction

1,3-Dihydroisobenzofuran and isochromane are privileged scaffolds in pharmaceuticals and natural products with diverse biological activities, such as escitalopram,[49,50] sonepiprazole,[51,52] penidicitrinin B[53] and (-)-Berkelic acid[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.[55-57] Liu developed Cross Dehydrogenative Coupling of cyclic ethers and potassium alkynyltrifluoroborates in the presence of trityl ion and $GaCl_3$.[56] A TBHP promoted oxidative cross coupling of isochroman and indoles was also achieved.[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



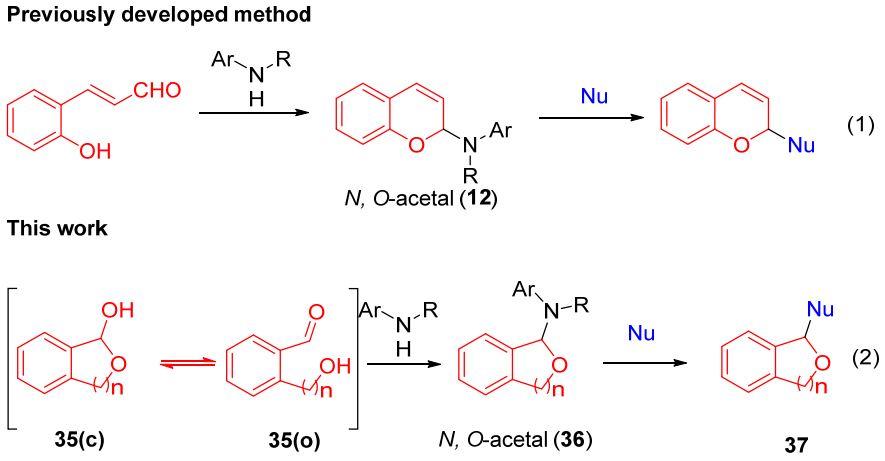


Escitalopram
Antidepress and mood stab.

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). Hemiacetal **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

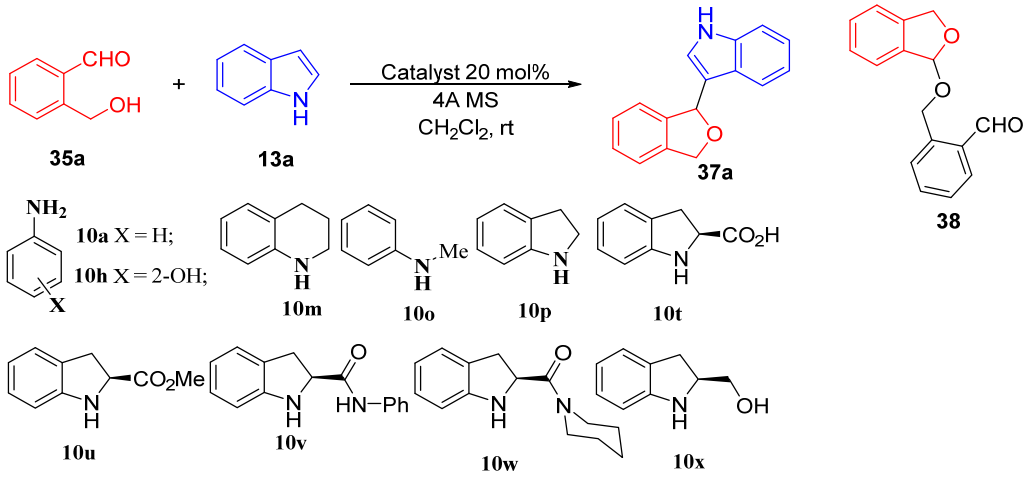


3.23 Results and Discussion

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 CH_2Cl_2 gave higher yield (74%) than dry CH_2Cl_2 (entry 11). However, addition of 10 μL H_2O 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 CH_2Cl_2 is the best solvent (table 3.6).

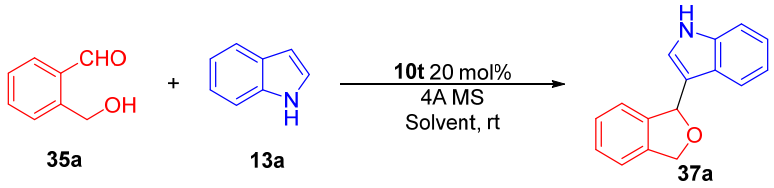
Table 3.5. Optimization of reaction condition[a]



Entry	catalyst	t (h)	Yields (%)
1	**10a**	40	43
2	**10h**	40	28
3	**10m**	40	9
4	**10o**	40	25
5	**10p**	40	51
6	**10t**	40	71
7	**10u**	40	54
8	**10v**	40	35
9	**10w**	40	13
10	**10x**	40	Trace
11[b]	**10t**	40	74
12[c]	**10t**	40	20
13[bd]	**10t**	48	65
14[bf]	**10t**	48	67
15[bg]	**10t**	48	90

[a]Unless specified, see experimental section. [b]Normal CH_2Cl_2. [c]Addition of 10μL H_2O. [d]10 mol% catalyst loading. [f]**35a**/**13a** = 1/1.2. [g]**35a**/**13a** = 1.5/1.

Table 3.6. Investigation of solvent effect[a]



Entry	Solvent	Yields (%)
1	MeOH	5
2	CH_3CN	10
3	THF	15
4	DCE	51
5	$CHCl_3$	43
6	CH_2Cl_2	74
7	Toluene	43

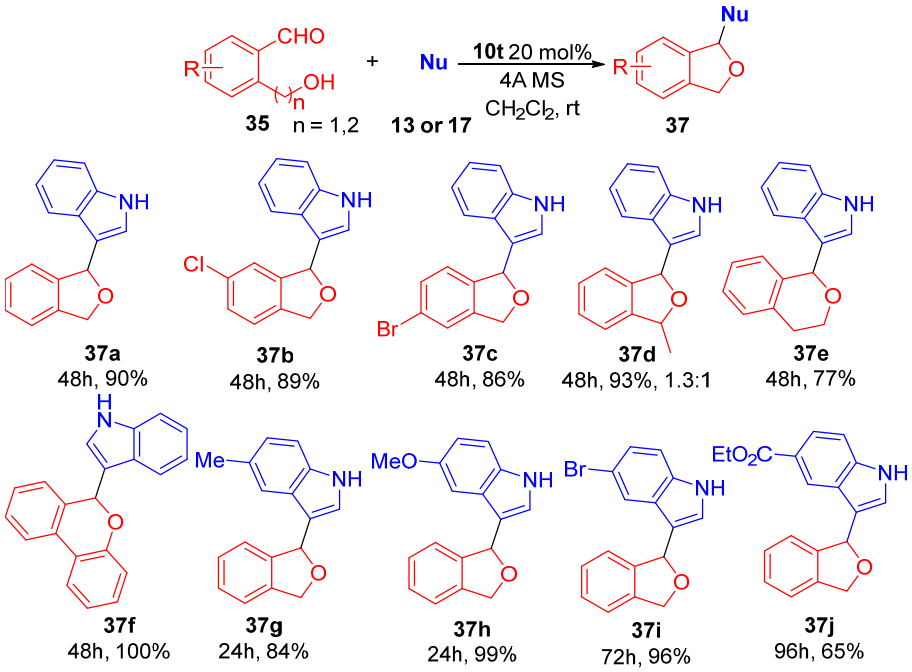
[a]Unless specified, see experimental section.

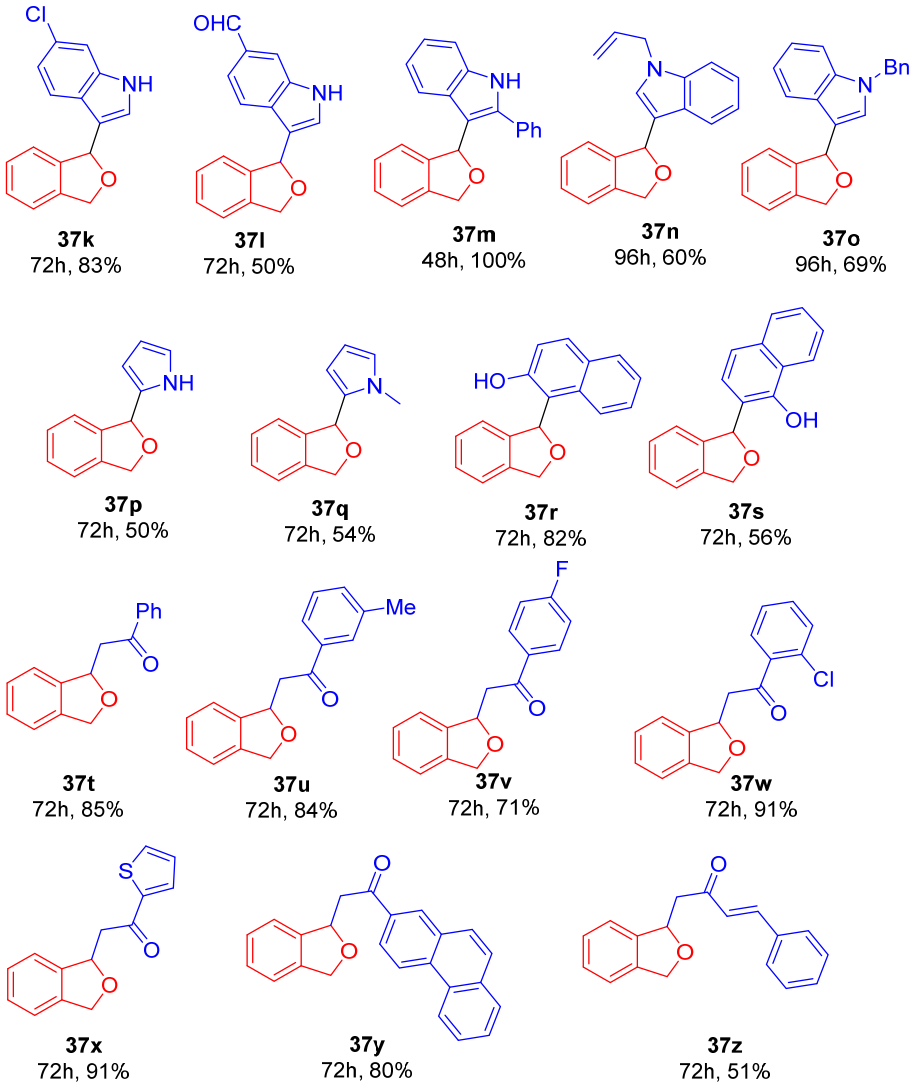
3.232 Investigation of Substrate Scope

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 6*H*-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_{sp3}-C_{sp3} bonds instead of C_{sp3}-C_{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**[a]



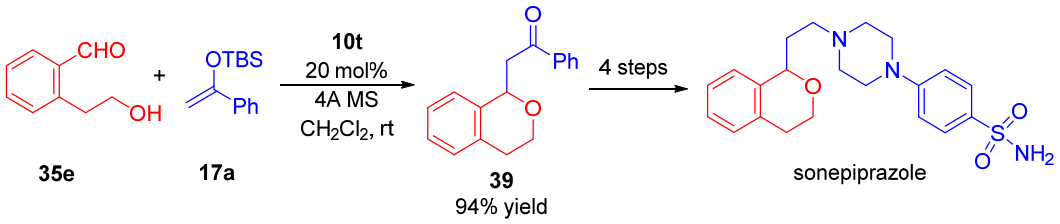


[a]Unless specified, see experimental section.

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]

Scheme 3.14. Total synthesis of sonepiprazole



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.

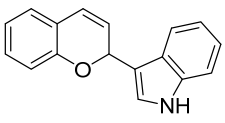
3.3 Experimental Section

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 F_{254} 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.

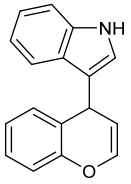
General Procedure for Cyclization-Substitution Cascade Reaction of 2-Hydroxy cinnamaldehydes and Silyl Enol Ethers (Scheme 3.6): To a solution of hydroxycinnamaldehyde **5** (0.1 mmol), 20 mol % **10m**, and 4Å molecular sieves (100 mg) in anhydrous dichloromethane (0.5 mL) was added a specified silyl 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.



14a

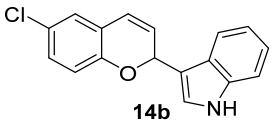
3-(2H-chromen-2-yl)-1H-indole (14a): The title compound was prepared according to the

general procedure, as described above in 86% yield and with 10:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 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, *J1* = 0.9 Hz, *J2* = 8.1 Hz), 6.75 (d, 1H, *J* = 7.8 Hz), 6.61 (dd, 1H, *J1* = 1.2 Hz, *J2* = 9.9 Hz), 6.25 (dd, 1H, *J1* = 1.8 Hz, *J2* = 3.3 Hz), 5.97 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



15a

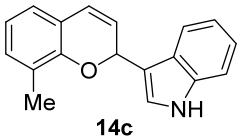
3-(4H-chromen-4-yl)-1H-indole (15a): ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.99 (s, 1H), 7.62 (d, 1H, *J* = 8.0 Hz), 7.36 (d, 1H, *J* = 8.0 Hz), 7.16-7.22 (m, 1H), 7.03-7.19 (m, 4H), 6.94 (d, 1H, *J* = 8.0 Hz), 6.87-6.90 (m, 1H), 6.64 (dd, 1H, *J1* = 1.5 Hz, *J2* = 6.0 Hz), 5.10 (dd, 1H, *J1* = 3.5 Hz, *J2* = 6.0 Hz), 4.99 (m, 1H).



14b

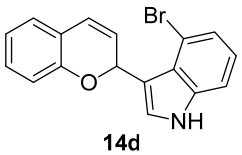
3-(6-Chloro-2H-chromen-2-yl)-1H-indole (14b): The title compound was prepared according to the general procedure, as described above in 90% yield and with 10:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.06 (s, 1H), 7.79 (d, 1H, *J* = 7.5 Hz), 7.36 (d, 1H, *J* = 7.8 Hz), 7.14-7.25 (m, 3H), 7.00 (d, 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): δ = 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.



14c

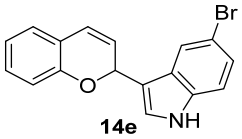
3-(8-Methyl-2H-chromen-2-yl)-1H-indole (14c): The title compound was prepared according to the general procedure, as described above in 69% yield and with 8.3:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.93 (s, 1H), 7.87 (d, 1H, *J* = 7.5 Hz), 7.31 (d, 1H, *J* = 7.5 Hz), 7.23-7.10 (m, 3H), 6.90 (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): δ = 151.3, 136.7, 130.7, 126.3, 125.8, 1250, 124.1, 123.9, 123.8, 122.4, 121.6, 120.3, 120.0, 119.8, 115.8, 111.2, 70.0, 15.6**.**



14d

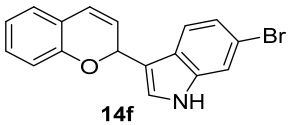
4-Bromo-3-(2H-chromen-2-yl)-1H-indole (14d): The title compound was prepared according to the general procedure, as described above in 65% yield and with 1.0:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.12 (s, 1H), 7.34 (d, 1H, *J* = 7.5 Hz), 7.25-7.23 (m, 2H), 6.99-7.09 (m, 3H), 6.90-6.82 (m, 2H), 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): δ = 153.0, 137.8, 129.2, 126.3, 126.2, 124.9, 124.8, 124.4, 123.9, 123.3, 122.1,

121.0, 116.7, 115.9, 114.0, 110.6, 68.7.



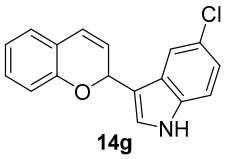
14e

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): δ = 8.05 (s, 1H), 7.95 (d, 1H, *J* = 1.2 Hz), 7.28 (dd, 1H, *J1* = 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, *J1* = 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): δ = 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.



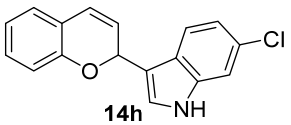
14f

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): δ = 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, *J1* = 3.6 Hz, *J2* = 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



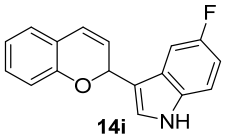
14g

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): δ = 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): δ = 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.



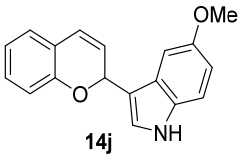
14h

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): δ = 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): δ = 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.



14i

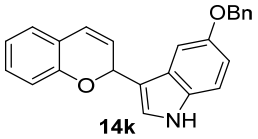
3-(2H-chromen-2-yl)-5-fluoro-1H-indole (14i): The title compound was prepared according to the general procedure, as described above in 65% yield and with 7.4:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.02 (s, 1H), 7.45 (dd, 1H, *J1* = 2.4 Hz, *J2* = 9.6 Hz), 7.16-7.24 (m, 1H), 7.09-7.04 (m, 2H), 6.91-6.83 (m, 2H), 6.75 (d, 1H, *J* = 7.8 Hz), 6.61 (dd, 1H, *J1* = 1.2 Hz, *J2* = 9.9 Hz), 6.16 (dd, 1H, *J1* = 1.5 Hz, *J2* = 3.3 Hz), 5.92 (dd, 1H, *J1* =3.6 Hz, *J2* = 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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, $CDCl_3$): δ = -122.1 Hz.



14j

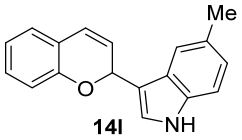
3-(2H-chromen-2-yl)-5-methoxy-1H-indole (14j): The title compound was prepared according to the general procedure, as described above in 76% yield and with 7.0:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.06 (s, 1H), 7.82 (d, 1H, *J* = 7.5 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 7.24-7.12 (m, 3H), 6.95 (d, 1H, *J* = 8.4 Hz), 6.56 (dd, 1H, *J1* = 1.2 Hz, *J2* = 9.6 Hz), 6.42 (dd, 1H, *J1* = 2.4 Hz, *J2* = 8.4 Hz), 6.34 (d, 1H, *J* = 2.4 Hz), 5.82 (dd, 1H, *J1* = 3.3 Hz, *J2* = 9.6 Hz), 3.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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,

109.1, 104.0, 72.6, 57.2.



14k

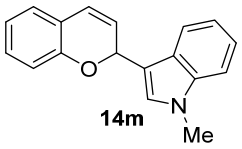
5-(Benzyloxy)-3-(2H-chromen-2-yl)-1H-indole (14k): The title compound was prepared according to the general procedure, as described above in 80% yield and with 10:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.85 (s, 1H), 744 (d, 2H, *J* = 6.9 Hz), 7.39-7.28 (m, 4H), 7.15 (d, 1H, *J* = 8.7 Hz), 7.04 (d, 3H, *J* = 7.5 Hz), 6.90-6.71 (m, 2H), 6.72 (d, 1H, *J* = 7.8 Hz), 6.57 (dd, 1H, *J1* = 1.5 Hz, *J2* = 9.9 Hz), 6.15 (dd, 1H, *J1* = 1.8 Hz, *J2* = 3.9 Hz), 5.90 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.6 Hz), 5.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



14l

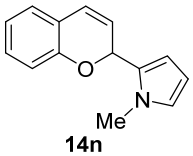
3-(2H-chromen-2-yl)-5-methyl-1H-indole (14l): The title compound was prepared according to the general procedure, as described above in 79% yield and with 8.9:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.89 (s, 1H), 7.59-7.58 (m, 1H), 7.18 (d, 1H, *J* = 7.8 Hz), 7.00-7.08 (m, 4H), 6.85 (dt, 1H, *J1* = 1.2 Hz, *J2* = 5.6 Hz), 6.76-6.73 (m, 1H), 6.58 (dd, 1H, *J1* = 1.2 Hz, *J2* = 9.9 Hz), 6.19 (dd, 1H, *J1* = 1.8 Hz, *J2* = 3.3 Hz), 6.94 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.6 Hz),; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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,

70.4, 21.5.



14m

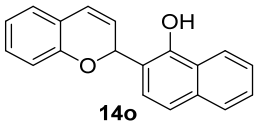
3-(2H-chromen-2-yl)-1-methyl-1H-indole (14m): The title compound was prepared according to the general procedure, as described above in 78% yield and with 5.9:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.80 (d, 1H, *J* = 7.8 Hz), 7.29-7.20 (m, 2H), 7.16-7.11 (m, 1H), 7.08-7.02 (m, 3H), 6.84 (t, 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, *J1* = 1.5 Hz, *J2* = 3.6 Hz), 5.94 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.6 Hz), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 153.5, 137.5, 129.1, 128.7, 126.6, 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.



14n

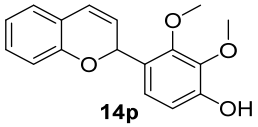
2-(2H-chromen-2-yl)-1-methyl-1H-pyrrole (14n): The title compound was prepared according to the general procedure, as described above in 52% yield and with 1.0:0 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.07 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 7.02 (dd, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.85 (dt, 1H, *J1* = 1.2 Hz, *J2* = 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, *J1* = 1.5 Hz, *J2* = 3.3 Hz), 6.03 (t, 1H, *J* = 3.0 Hz), 5.96 (dd, 1H, *J1* = 1.5 Hz, *J2* = 3.6 Hz), 5.89 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 152.8, 130.1, 129.2,

126.6, 125.3, 124.4, 122.7, 121.7, 121.2, 116.2, 110.2, 106.7, 69.0, 34.2.



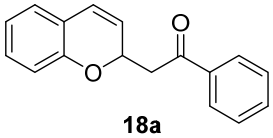
14o

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, *J1* = 2.1 Hz, *J2* = 9.9 Hz), 6.25 (t, 1H, *J* = 2.7 Hz), 5.91 (dd, 1H, *J1* = 3.3 Hz, *J2* = 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.



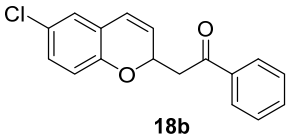
14p

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, CDCl3, 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, *J1* = 3.3 Hz, *J2* = 9.6 Hz), 3.92 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, CDCl3, 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.



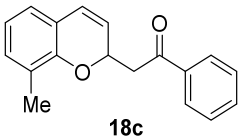
18a

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, CDCl3, TMS): δ = 7.93-7.94 (m, 2H), 7.54-7.60 (m, 1H), 7.43-7.48 (m, 2H), 7.10 (dt, 1H, *J1* = 1.8 Hz, *J2* = 8.1 Hz), 6.99 (dd, 1H, *J1* = 1.8 Hz, *J2* = 7.5 Hz), 6.88 (dt, 1H, *J1* = 1.2 Hz, *J2* = 7.5 Hz), 6.74 (d, 1H, *J* = 10.8 Hz), 6.65 (t, 1H, *J* = 9.6 Hz), 5.86 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.6 Hz), 5.55-5.58 (m, 1H), 3.61 (dd, 1H, *J1* = 9.6 Hz, *J2* = 16.5 Hz), 3.24 (dd, 1H, J1 = 6.6 Hz, J2 = 16.5 Hz); ^{13}C NMR (75 MHz, CDCl3, TMS): δ = 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.



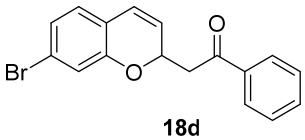
18b

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): δ = 7.91-7.95 (m, 2H), 7.55-7.61 (m, 1H), 7.44-7.49 (m, 2H), 7.04 (dd, 1H, *J1* = 2.7 Hz, *J2* = 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, *J1* = 3.9 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): δ = 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.



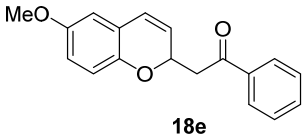
18c

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): δ = 7.93-7.96 (m, 2H), 7.54-7.60 (m, 1H), 7.42-7.48 (m, 2H), 6.96 (dd, 1H, *J1* = 1.2 Hz, *J2* = 7.2 Hz), 6.75-6.86 (m, 2H), 6.45 (dd, 1H, *J1* = 1.5 Hz, *J2* = 9.9 Hz), 5.85 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.6 Hz), 5.53-5.58 (m, 1H), 3.62 (dd, 1H, *J1* = 7.2 Hz, *J2* = 16.2 Hz), 3.19 (dd, 1H, J1 = 6.0 Hz, J2 = 16.2 Hz), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



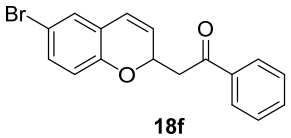
18d

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): δ = 7.92-7.96 (m, 2H), 7.58-7.62 (m, 1H), 7.44-7.49 (m, 2H), 7.00 (dd, 1H, *J1* = 4.8 Hz, *J2* = 8.1 Hz), 6.89 (dd, 1H, *J1* = 0.3 Hz, *J2* = 1.5 Hz), 6.84 (d, 1H, *J* = 8.1 Hz), 6.40 (d, 1H, *J* = 9.9 Hz), 6.88 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 5.52-5.57 (m, 1H), 3.60 (dd, 1H, *J1* = 6.6 Hz, *J2* = 16.5 Hz), 3.62 (dd, 1H, *J1* = 6.6 Hz, *J2* = 16.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



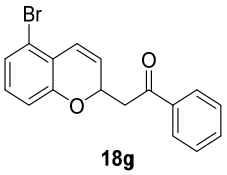
18e

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): δ = 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): δ = 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.



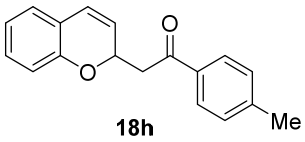
18f

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): δ = 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): δ = 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.



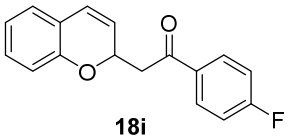
18g

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): δ = 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), 3.23 (dd, 1H, *J1* = 6.3 Hz, *J2* = 16.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



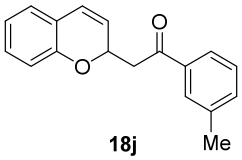
18h

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): δ = 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): δ = 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.



18i

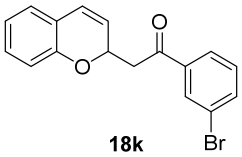
2-(2H-chromen-2-yl)-1-(4-fluorophenyl)ethan-1-one (18i): The title compound was prepared according to the general procedure, as described above in 78% yield and with 12:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.95-7.99 (m, 2H), 7.07-7.15 (m, 3H), 6.99 (dd, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.87 (dt, 1H, *J1* = 0.9 Hz, *J2* = 7.5 Hz), 6.71 (d, 1H, *J* = 8.1 Hz), 6.45 (d, 1H, *J* = 9.9 Hz), 5.42 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.6 Hz), 5.51-5.56 (m, 1H), 3.59 (dd, 1H, *J1* = 6.9 Hz, *J2* = 16.5 Hz), 3.19 (dd, 1H, *J1* = 6.3 Hz, *J2* = 16.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 195.6, 165.9 (d, $J_{C\text{-}F}$ = 253.6 Hz), 152.7, 133.5, 131.0 (d, $J_{C\text{-}F}$ = 9.3 Hz), 129.4, 126,6, 124.9, 124.3, 121.5, 121.4, 116.3, 115.7 (d, $J_{C\text{-}F}$ = 21.8 Hz), 71.7, 44.0; ^{19}F NMR (282 MHz, CDCl3), δ =103.1.



18j

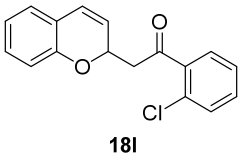
2-(2H-chromen-2-yl)-1-(m-tolyl)ethan-1-one (18j): The title compound was prepared according to the general procedure, as described above in 82% yield and with 12:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.73-7.75 (m, 2H), 7.31-7.40 (m, 2H), 6.99 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.8 Hz), 6.99 (dd, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.99 (dt, 1H, *J1* = 1.2 Hz, *J2* = 7.5 Hz), 6.73 (d, 1H, *J* = 5.1 Hz), 6.45 (d, 1H, *J* = 9.9 Hz), 5.86 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 5.53-5.57 (m, 1H), 3.62 (dd, 1H, *J1* = 6.6 Hz, *J2* = 16.5 Hz), 3.25 (dd, 1H, *J1* = 6.6 Hz, *J2* = 16.5 Hz), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 197.4,

152.7, 138.4, 136.9, 134.1, 129.3, 128.8, 128.5, 126.6, 125.5, 125.1, 124.2, 121.6, 121.3, 116.3, 71.7, 44.1, 21.3.



18k

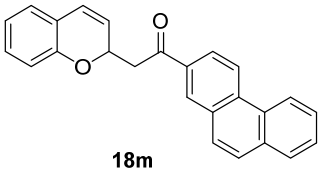
1-(3-Bromophenyl)-2-(2H-chromen-2-yl)ethan-1-one (18k): The title compound was prepared according to the general procedure, as described above in 72% yield and with 19:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.06 (s, 1H), 7.85 (d, 1H, *J* = 7.8 Hz), 7.69 (d, 1H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 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): δ = 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.



18l

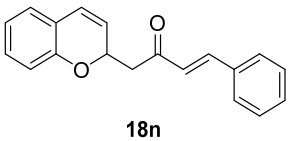
1-(2-Chlorophenyl)-2-(2H-chromen-2-yl)ethan-1-one (18l): The title compound was prepared according to the general procedure, as described above in 48% yield and with 19:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.49-7.52 (m, 1H), 7.29-7.42 (m, 3H), 7.08 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.8 Hz), 6.96 (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, *J2* = 9.6 Hz), 5.47-5.52 (m, 1H), 3.57 (dd, 1H, *J1* = 7.8 Hz, *J2* = 16.5 Hz), 3.22 (dd, 1H, *J1* = 5.4 Hz, *J2* = 16.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



18m

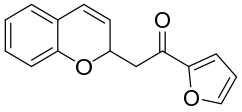
2-(2H-chromen-2-yl)-1-(phenanthren-2-yl)ethan-1-one (18m): The title compound was prepared according to the general procedure, as described above in 80% yield and with 13:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.68-8.74 (m, 2H), 8.44 (s, 1H), 8.18-8.21 (m, 1H), 7.91-7.93 (m, 1H), 7.77-7.81 (m, 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, *J1* = 3.3 Hz, *J2* = 9.6 Hz), 5.60-5.66 (m, 1H), 3.80 (dd, 1H, *J1* = 6.9 Hz, *J2* = 16.2 Hz), 3.37 (dd, 1H, *J1* = 6.3 Hz, *J2* = 16.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



18n

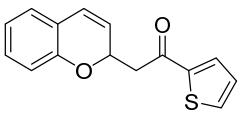
(E)-1-(2H-chromen-2-yl)-4-phenylbut-3-en-2-one (18n): The title compound was prepared according to the general procedure, as described above in 90% yield and with

5.0.1:1 r.r.. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.51-7.57 (m, 3H), 7.39-7.41 (m, 3H), 7.11 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.8 Hz), 6.99 (dd, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.88 (dt, 1H, *J1* = 0.9 Hz, *J2* = 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, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 5.43-5.48 (m, 1H), 3.32 (dd, 1H, *J1* = 7.2 Hz, *J2* = 15.6 Hz), 2.92 (dd, 1H, *J1* = 6.0 Hz, *J2* = 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



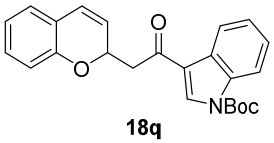
18o

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): δ = 7.58 (dd, 1H, *J1* = 0.9 Hz, *J2* = 1.5 Hz), 7.18 (dd, 1H, *J1* = 0.6 Hz, *J2* = 3.6 Hz), 7.08 (dt, 1H, *J1* = 1.8 Hz, *J2* = 7.8 Hz), 6.98 (dd, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.87 (dt, 1H, *J1* = 1.2 Hz, *J2* = 7.5 Hz), 6.70 (d, 1H, *J* = 8.1 Hz), 6.53 (dd, 1H, *J1* = 1.8 Hz, *J2* = 3.6 Hz), 6.45 (d, 1H, *J* = 9.6 Hz), 5.80 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 5.48-5.53 (m, 1H), 3.48 (dd, 1H, *J1* = 7.5 Hz, *J2* = 15.6 Hz), 3.03 (dd, 1H, *J1* = 6.0 Hz, *J2* = 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



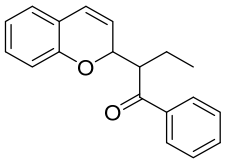
18p

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): δ = 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, *J1* = 3.3 Hz, *J2* = 9.6 Hz), 5.49-5.55 (m, 1H), 3.60 (dd, 1H, *J1* = 7.2 Hz, *J2* = 15.6 Hz), 3.13 (dd, 1H, *J1* = 6.0 Hz, *J2* = 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



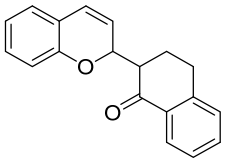
18q

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): δ = 8.40-8.43 (m, 1H), 8.11-8.15 (m, 2H), 7.36-7.40 (m, 2H), 7.10 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.8 Hz), 7.00 (dd, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.88 (dt, 1H, *J1* = 1.2 Hz, *J2* = 7.5 Hz), 6.72 (d, 1H, *J* = 7.8 Hz), 6.47 (d, 1H, *J* = 9.9 Hz), 5.86 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 5.54-5.60 (m, 1H), 3.53 (dd, 1H, *J1* = 7.2 Hz, *J2* = 15.6 Hz), 3.11 (dd, 1H, *J1* = 6.0 Hz, *J2* = 15.6 Hz), 1.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



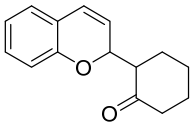
18r

(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): δ = 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, *J1* = 4.2 Hz, *J2* = 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): δ = 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.



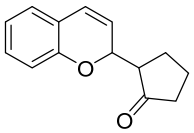
18s

(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): δ = 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, *J1* = 3.0 Hz, *J2* = 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): δ = 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.



18t

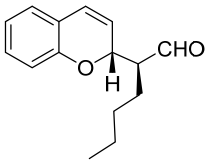
(S)-2-((R)-2H-chromen-2-yl)cyclohexan-1-one (28t): The title compound was prepared according to the general procedure, as described above in 87% yield and with 7.4:1 r.r. and 1.1:1 dr. Mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.04-7.12 (m, 2H), 6.93 (dt, 2H, *J1* = 1.8 Hz, *J2* = 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, *J1* = 3.9 Hz, *J2* = 9.9 Hz), 5.68 (dd, 1H, *J1* = 3.3 Hz, *J2* = 9.9 Hz), 5.46-5.49 (m, 1H), 5.68 (ddd, 1H, *J1* = 1.5 Hz, *J2* = 3.6 Hz, *J3* = 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): δ = 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).



18u

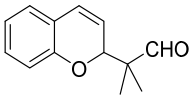
(S)-2-((R)-2H-chromen-2-yl)cyclopentan-1-one (18u): The title compound was prepared according to the general procedure, as described above in 86% yield and with 7.5:1 r.r. and 1.2:1 dr. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.09 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.93 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.2 Hz), 7.09 (dt, 1H, *J1* = 1.2 Hz, *J2* = 7.2 Hz), 6.74 (d, 1H, *J* = 7.8 Hz), 6.47 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.8 Hz), 5.49 (dd, 1H, *J1* = 3.3 Hz, *J2* = 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): δ = 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.



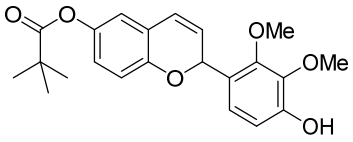
18v

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): δ = 9.77 (d, 1H, *J* = 3.3 Hz), 7.09-7.14 (m, 1H), 6.97 (dd, 1H, *J1* = 1.8 Hz, *J2* = 5.7 Hz), 6.86 (dd, 1H, *J1* = 1.2 Hz, *J2* = 3.3 Hz), 6.76 (d, 1H, *J* = 8.1 Hz), 6.49 (dd, 1H, *J1* = 1.2 Hz, *J2* = 9.6 Hz), 5.73 (dd, 1H, *J1* = 3.6 Hz, *J2* = 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).



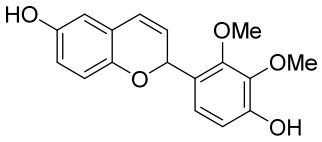
18w

(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): δ = 9.67 (s, 1H), 7.09 (dt, 1H, *J1* = 1.5 Hz, *J2* = 9.0 Hz), 6.93 (dt, 1H, *J1* = 1.5 Hz, *J2* = 7.5 Hz), 6.83 (t, 1H, *J* = 7.2 Hz), 6.73 (t, 1H, *J* = 8.1 Hz), 6.52 (dd, 1H, *J1* = 1.5 Hz, *J2* = 10.2 Hz), 5.65 (dd, 1H, *J1* = 3.0 Hz, *J2* = 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): δ = 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.



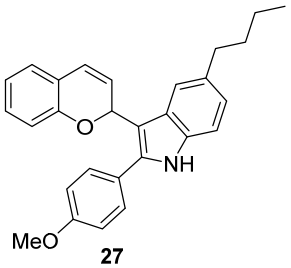
24

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): δ = 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, *J1* = 1.8 Hz, *J2* = 9.9 Hz), 6.44 (d, 1H, *J* = 9.0 Hz), 6.25 (dd, 1H, *J1* = 1.8 Hz, *J2* = 3.6 Hz), 6.01 (s, 1H), 5.83 (dd, 1H, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 3.92 (s, 3H), 3.84 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



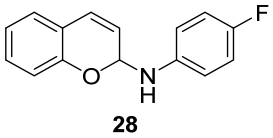
25

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): δ = 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, *J1* = 3.6 Hz, *J2* = 9.9 Hz), 3.91 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 152.3, 149.6, 147.1, 146.8, 135.5, 125.7, 123.9, 123.0, 122.3, 119.3, 116.7, 115.6, 113.0, 103.6, 71.4, 61.0, 55.8.



27

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): δ = 8.07 (s, 1H), 7.54-7.58 (m, 3H), 7.29 (d, 1H, *J* = 8.4 Hz), 7.12-7.18 (m, 2H), 7.07 (dd, 1H, *J1* = 1.5 Hz, *J2* = 11.7 Hz), 6.98-7.03 (m, 2H), 6.94 (dd, 1H, *J1* = 0.9 Hz, *J2* = 7.5 Hz), 6.93 (d, 1H, *J* = 7.8 Hz), 6.60 (dd, 1H, *J1* = 2.4 Hz, *J2* = 9.6 Hz), 6.19 (t, 1H, *J* = 2.7 Hz), 5.91 (dd, 1H, *J1* = 2.7 Hz, *J2* = 9.6 Hz), 3.85 (s, 3H), 2.65 (t, 1H, *J* = 7.5 Hz), 1.53-1.63 (m, 1H), 1.30-1.37 (m, 3H), 0.91 (t, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.

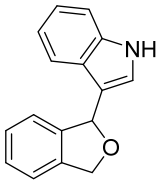


28

N-(4-fluorophenyl)-2H-chromen-2-amine (28): The title compound was obtained without purification. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 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): δ = 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,

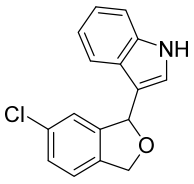
115.8 (J_{CF} = 8.3 Hz), 115.6 (J_{CF} = 6.0 Hz), 78.8.

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.



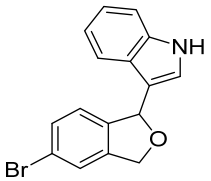
37a

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): δ = 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): δ = 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.



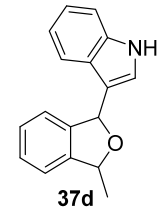
37b

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): δ = 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): δ = 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

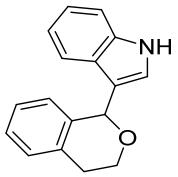
3-(5-Bromo-1,3-dihydroisobenzofuran-1-yl)-1H-indole (37c): The title compound was prepared according to the general procedure, as described above in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.22 (s, 1H), 7.49 (s, 1H), 7.31-7.38 (m, 2H), 7.19 (d, 1H, *J* = 8.1 Hz), 7.18 (dt, 1H, *J1* = 1.2 Hz, *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): δ = 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
48h, 93%, 1.3:1

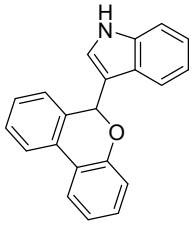
3-(3-Methyl-1,3-dihydroisobenzofuran-1-yl)-1H-indole (37d): The title compound was

prepared according to the general procedure, as described above in 93% yield, 1.3:1 dr. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 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, $CDCl_3$, TMS): δ = 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).



37e

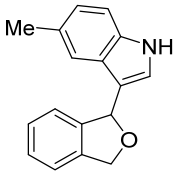
3-(Isochroman-1-yl)-1H-indole (37e): The title compound was prepared according to the general procedure, as described above in 77% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.11 (s, 1H), 7.51 (d, 1H, *J* = 7.8 Hz), 7.34 (d, 1H, *J* = 8.1 Hz), 7.19-7.21 (m, 3H), 7.04-7.11 (m, 2H), 6.97-7.00 (m, 2H), 6.16 (s, 1H), 4.12-4.20 (m, 1H), 3.92-4.00 (m, 1H), 2.89-3.12 (m, 2H).



37f

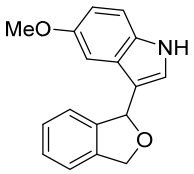
3-(6H-benzo[c]chromen-6-yl)-1H-indole (37f): The title compound was prepared according to the general procedure, as described above in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.92 (s, 1H), 7.78-7.84 (m, 3H), 7.44 (dt, 1H, *J1* = 1.2 Hz, *J2* = 7.5 Hz),

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, $CDCl_3$, 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.



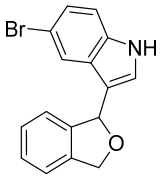
37g

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, $CDCl_3$, 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).



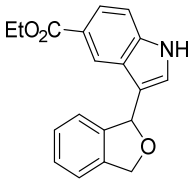
37h

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, $CDCl_3$, 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, $CDCl_3$, 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.



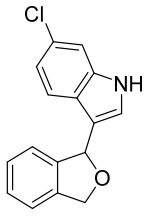
37i

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): δ = 8.44 (s, 1H), 7.35-7.39 (m, 3H), 7.24-7.29 (m, 1H), 7.21 (dd, 1H, *J1* = 2.4 Hz, *J2* = 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): δ = 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.



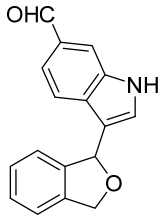
37j

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): δ = 8.44 (s, 1H), 8.16 (s, 1H), 7.89 (dd, 1H, *J1* = 1.5 Hz, *J2* = 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): δ = 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.



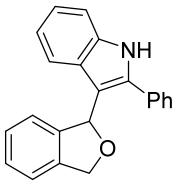
37k

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): δ = 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, *J1* = 1.8 Hz, *J2* = 8.4 Hz), 6.48 (s, 1H), 5.14-5.5.33 (m, 2H).



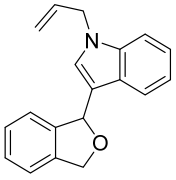
37l

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): δ = 9.97 (s, 1H), 8.92 (s, 1H), 7.84 (s, 1H), 7.53 (dd, 1H, *J1* = 1.2 Hz, *J2* = 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): δ = 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.



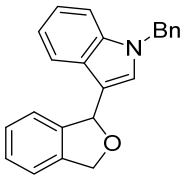
37m

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): δ = 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): δ 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.



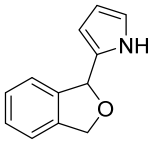
37n

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): δ = 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): δ 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.



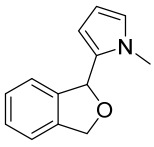
37o

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): δ = 7.23-7.35 (m, 8H), 7.13-7.18 (m, 5H), 7.02 (dt, 1H, *J1* = 0.9 Hz, *J2* = 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): δ 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.



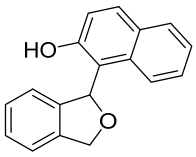
37p

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): δ = 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): δ = 140.1, 139.6, 131.2, 127.9, 127.5, 122.5, 121.0, 118.6, 108.4, 107.6, 79.6, 72.3.



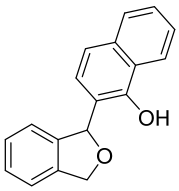
37q

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): δ = 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): δ = 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

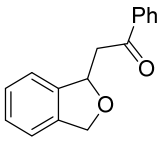
1-(1,3-Dihydroisobenzofuran-1-yl)naphthalen-2-ol (37r): The title compound was prepared according to the general procedure, as described above in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.33 (s, 1H), 7.89 (d, 1H, *J* = 8.7 Hz), 7.84 (d, 1H, *J* = 7.8 Hz), 7.75 (d, 1H, *J* = 9.0 Hz), 7.54 (dt, 1H, *J1* = 1.2 Hz, *J2* = 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): δ = 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

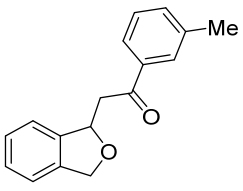
2-(1,3-Dihydroisobenzofuran-1-yl)naphthalen-1-ol (37s): The title compound was

prepared according to the general procedure, as described above in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 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): δ = 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.



37t

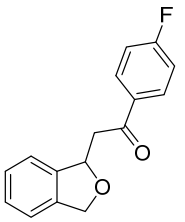
2-(1,3-Dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (37t): The title compound was prepared according to the general procedure, as described above in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.98-8.01 (m, 2H), 7.55-7.60 (m, 1H), 7.44-7.49 (m, 2H), 7.27-7.30 (m, 4H), 5.89-5.93 (m, 1H), 5.07-519 (m, 2H), 3.55 (dd, 1H, *J1* = 7.2 Hz, *J2* = 16.5 Hz), 3.35 (dd, 1H, *J1* = 8.1 Hz, *J2* = 16.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



37u

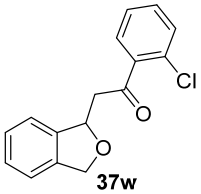
2-(1,3-Dihydroisobenzofuran-1-yl)-1-(m-tolyl)ethan-1-one (37u): The title compound was prepared according to the general procedure, as described above in 84% yield. ^{1}H

NMR (300 MHz, $CDCl_3$, 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 Hz, *J2* = 16.5 Hz), 3.34 (dd, 1H, *J1* = 8.1 Hz, *J2* = 16.5 Hz), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 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.



37v

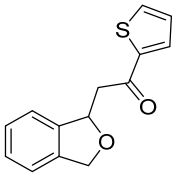
2-(1,3-Dihydroisobenzofuran-1-yl)-1-(4-fluorophenyl)ethan-1-one (37v): The title compound was prepared according to the general procedure, as described above in 71% yield. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.00-8.04 (m, 2H), 7.25-7.32 (m, 2H), 7.10-7.16 (m, 2H), 5.06-5.18 (m, 2H), 5.06-5.18 (m, 2H), 3.51 (dd, 1H, J_1 = 7.5 Hz, J_2 = 16.5 Hz), 3.31 (dd, 1H, J_1 = 5.1 Hz, J_2 = 16.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 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.



37w

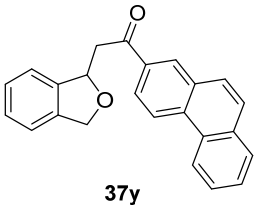
1-(2-Chlorophenyl)-2-(1,3-dihydroisobenzofuran-1-yl)ethan-1-one (37w): The title compound was prepared according to the general procedure, as described above in 91%

yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 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): δ = 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.



37x

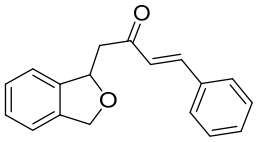
2-(1,3-Dihydroisobenzofuran-1-yl)-1-(thiophen-2-yl)ethan-1-one (37x): The title compound was prepared according to the general procedure, as described above in 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.73 (dd, 1H, *J1* = 1.2 Hz, *J2* = 3.9 Hz), 7.66 (dd, 1H, *J1* = 1.2 Hz, *J2* = 3.9 Hz), 7.23-7.31 (m, 4H), 7.13 (dd, 1H, *J1* = 3.9 Hz, *J2* = 5.1 Hz), 5.85-5.89 (m, 1H), 5.07-5.19 (m, 2H), 3.46 (dd, 1H, *J1* = 7.5 Hz, *J2* = 15.9 Hz), 3.27 (dd, 1H, *J1* = 7.8 Hz, *J2* = 15.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.



37y

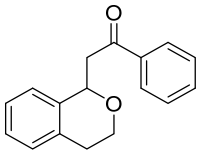
2-(1,3-Dihydroisobenzofuran-1-yl)-1-(phenanthren-2-yl)ethan-1-one (37y): The title compound was prepared according to the general procedure, as described above in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.70 (t, 2H, *J* = 8.1 Hz), 8.50 (d, 1H, *J* = 2.1

Hz), 8.23 (dd, 1H, *J1* = 1.8 Hz, *J2* = 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, *J1* = 7.5 Hz, *J2* = 16.8 Hz), 3.50 (dd, 1H, *J1* = 5.1 Hz, *J2* = 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

(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, *J1* = 7.5 Hz, *J2* = 15.9 Hz), 3.09 (dd, 1H, *J1* = 7.8 Hz, *J2* = 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

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): δ = 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, *J1* = 8.7 Hz, *J2* = 16.2 Hz), 3.33 (dd, 1H, *J1* = 3.6 Hz, *J2* = 16.2 Hz), 2.97-3.08 (m, 1H), 2.62-2.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 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.

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Chapter 4

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

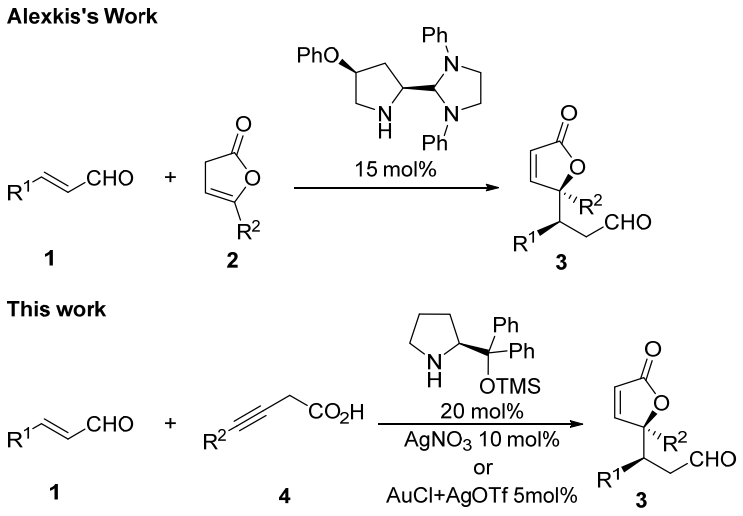
4.1 Introduction

The *γ, γ*-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 *γ, γ*-disubstituted butenolide could be obtained through Michael addition of silyloxy furans to *α, β*-unsaturated aldehydes using imidazolidinone as catalyst.[12] In 2009, Buchwald and coworkers found that a palladium complex catalyzed *γ*-arylation of *γ*-substituted butenolides, yielding achiral γ, γ-disubstituted butenolides.[5] Later, the construction of chiral γ, γ-disubstituted butenolides were developed by Chen and coworkers through the asymmetric allylic alkylation of γ-substituted butenolides with Morita-Baylis-Hillman carbonates catalyzed by $(DHDQ)_2PYR$.[6] Thiourea-amine bifunctional organocatalysts also successfully catalyzed asymmetric Michael addition of γ-substituted butenolides to (*E*)-oxazolidinone enoates[11] and nitroolefins[10] respectively. Asymmetric Michael addition of *γ*-butenolide to α, β-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 *γ*-substituted butenolides.[13,14] We envision that if we could couple the *in situ* formation of the *γ*-substituted butenolides from Lewis acid-catalyzed cyclization of alkynoic acids with the aminocatalytic Michael addition of γ-substituted butenolides to α, β-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.

Scheme 4.1. Organocatalytic and transition metal catalyzed 'one-pot' synthesis of chiral *γ,γ*-disubstituted butenolides

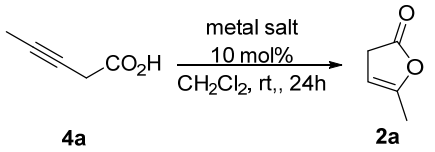


4.3 Results and Discussion

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 $PdCl_2$ 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 ($Ph_3PAuOTf$) was tested and a higher reactivity was observed, yielding **2a** in 90% conversion (entry 4). $AgNO_3$ 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[a]



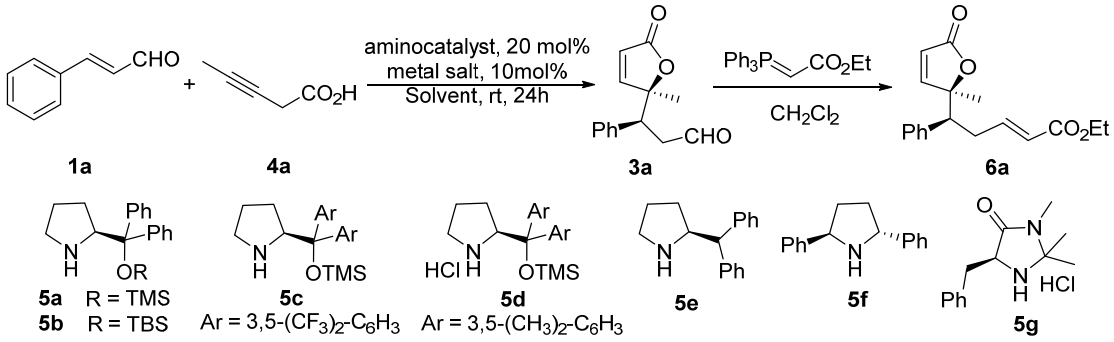
Entry	Metal salts	Conversion (%)[b]
1	$PdCl_2$	0
2	$Cu(OTf)_2$	0
3	AuCl	30
4	Ph_3PAuCl + AgOTf	90
5	$AgNO_3$	100

[a]The reaction was run with **4a** (0.1 mmol) and metal salt (0.01 mmol) in 1 mL CH_2Cl_2 at room temperature for 24 h. [b]Determined by ^{1}H-NMR.

Combination of $AgNO_3$ 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 $AgNO_3$ catalyzed the cascade reaction to afford the desired product in high yield and with excellent enantioselectivity and

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 $AgNO_3$ 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 siliver 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 $AgBF_4$, AgCN, AgOTf and $AgSbF_4$ 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 $AgNO_3$ as metal catalyst, and $PhCF_3$ 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-pentynoic acid[a]



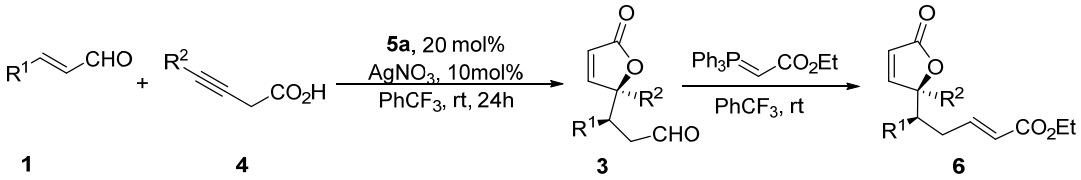
Entry	Amine	Metal	Solvent	Yield (%)[b]	dr[c]	ee[d,e]
1	**5a**	$AgNO_3$	CH_2Cl_2	92	2.3:1	96, 83
2	**5b**	$AgNO_3$	CH_2Cl_2	62	2.0:1	98, 90
3	**5c**	$AgNO_3$	CH_2Cl_2	30	N.D.	N.D.
4	**5d**	$AgNO_3$	CH_2Cl_2	N.R.	-	-
5	**5e**	$AgNO_3$	CH_2Cl_2	86	1.6:1	-79, -57
6	**5f**	$AgNO_3$	CH_2Cl_2	40	1.3:1	-13, 39
7	**5g**	$AgNO_3$	CH_2Cl_2	N.R.	-	-
8	**5a**	$AgBF_4$	CH_2Cl_2	62	2.1:1	96, 88
9	**5a**	AgCN	CH_2Cl_2	58	2.3:1	95, 83
10	**5a**	AgOAc	CH_2Cl_2	100	1.8:1	95, 63
11	**5a**	$AgSbF_4$	CH_2Cl_2	77	1.5:1	96, 88
12	**5a**	AgOTf	CH_2Cl_2	80	1.8:1	>99, 86
13	**5a**	$AgNO_3$	DCE	64	2.2:1	N.D.
14	**5a**	$AgNO_3$	MeOH	78	1.4:1	76, 40
15	**5a**	$AgNO_3$	Hexane	57	2.0:1	97, 78
16	**5a**	$AgNO_3$	CH_3CN	83	1.9:1	99, 89
17	**5a**	$AgNO_3$	Toluene	74	2.8:1	99, 86
18	**5a**	**$AgNO_3$**	**CF_3-Ph**	**97**	**3.2:1**	**98, 88**
19	**5a**	$AgNO_3$	m-xylene	87	2.3:1	97, 83

[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 *α, β*-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 *α, β*-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). Hetero-aromatic α, β-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 *α,β*-unsaturated aldehydes couldn't engage in the reaction under the standard condition, but the combination of diphenylprolinol TMS-ether and $Ph_3PAuOTf$ 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 $AgNO_3$-catalyzed cyclization-Michael cascade reaction[a]



1 **4** **3** **6**

Entry	R^1	R^2	t (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	Me	24	97	3.2:1	98, 88
2	4-Cl-Ph	Me	24	96	2.6:1	98, 88
3	4-NO_2-Ph	Me	24	97	2.0:1	96, 87
4	4-CN-Ph	Me	24	98	2.6:1	94, 87
5	4-Me-Ph	Me	24	89	2.3:1	99, N.D.
6	4-MeO-Ph	Me	48	72	1:1.6	79, 94
7	3-Me-Ph	Me	48	79	2.5:1	98, 89
8	3-F-Ph	Me	24	81	2.6:1	98, 89
9	3-AcO-Ph	Me	24	100	2.1:1	94, 88
10	2-Cl-Ph	Me	24	90	1.1:1	93, 96
11	2-Me-Ph	Me	48	88	1:1.3	99, 87(99, 92)
12	1-naphthyl	Me	48	91	2.2:1	98, 87
13	2-Furyl	Me	24	70	2.1:1	95, 77
14[e]	Et	Me	48	85	5.7:1	96, N.D.
15[e]	*n*-Pr	Me	48	78	9.1:1	96, 94
16	Ph	Et	24	80	2.0:1	92, 88

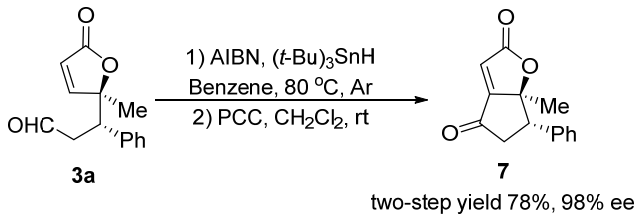
[a]The reaction was run with **1** (0.1 mmol), **4** (0.1 mmol), **5a** (0.02 mmol) and $AgNO_3$ (0.01 mmol) in 1 mL $PhCF_3$ at room temperature. [b]Isolated yield. [c]Determined by ^{1}H-NMR. [d]Determined by HPLC. [e]The reaction was run with **1** (0.3 mmol), **4** (0.1 mmol), **5a** (0.02 mmol), AuCl (0.05 mmol) and AgOTf (0.05 mmol) in 1 mL $PhCF_3$ 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

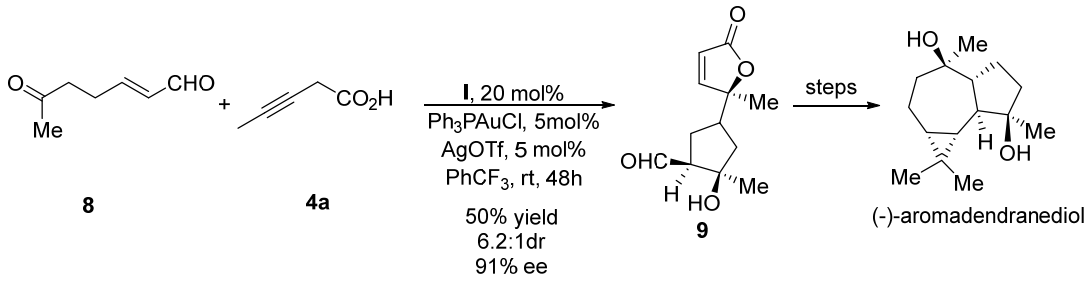
and with 98% ee by a simple Bu_3SnH-mediated intramolecular reductive radical conjugate addition of **3a** and subsequently oxidation of the generated alcohol by PCC (Scheme 4.2).

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 $Ph_3PAuOTf$-catalyzed cyclization-Michael-Aldol triple-cascade reaction, which is a key intermediate in the total synthesis of (-)-aromdendranediol (Scheme 4.3).

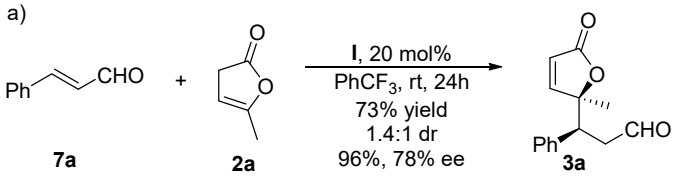
Scheme 4.3. The binary catalytic system promoted cyclization-Michael-Aldol cascade reaction

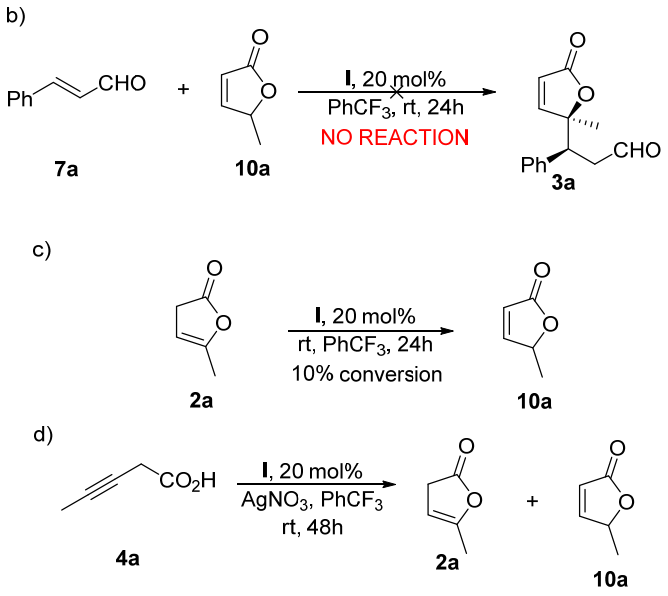


4.5 Mechanism Study

Regarding the reaction mechanism, it is proposed that an alkynoic acid is catalyzed by $AgNO_3$ or $Ph_3PAuOTf$ 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 aminocatayst 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 $AgNO_3$ 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





4.6 Conclusion

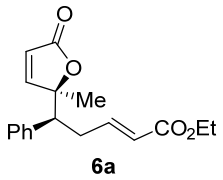
In conclusion, a powerful binary catalytic system consisting diphenylprolinol TMS-ether **I** and $AgNO_3$ or $Ph_3PAuOTf$ has been developed for the cyclization-Michael and the cyclization-Michael-Aldol cascade reactions. The merits of this strategy are not only the employment of simpler and less expensive starting materials but also the enhancement of yields due to the synergistic effect.

4.7 Experimantal 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 $AgNO_3$(1.7mg, 0.01 mmol) in $PhCF_3$ (1 mL) was stirred at room temperature for the indicated time. The reaction mixture was quickly filtered over a short

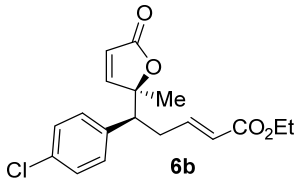
pad of silica gel (ethyl ether). The solvent was removed under reduced pressure and the residue was added 1 mL CH_2Cl_2 and ethyl 2-(triphenylphosphoranylidene)acetate (0.1 mmol). After 12h, the reaction mixture was directly purified by silica gel chromatography to afford the desired product as yellowish oil.

General Procedure for the Enatioselective Cyclization-Michael Cascade Reaction of Alkynoic Acids and Aliphatic *α,β*-unsaturated Aldehydes: A mixture of Ph_3PAuCl (5.0 mg, 0.01 mmol) and AgOTf (2.6mg, 0.01 mmol) in $PhCF_3$ (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 CH_2Cl_2 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** $[\alpha]_D^{27}$ = +133.7 (c = 1.0, $CHCl_3$) 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-CO_2 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).



6a

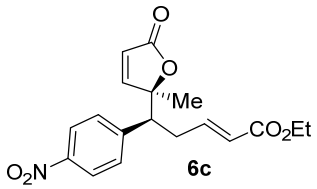
(S,E)-ethyl 5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-phenylpent-2-enoate (6a) (Table 4.3, entry 1): The title compound was prepared according to the general procedure, as described above in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.21-7.33 (m, 4H), 7.11-7.14 (m, 2H), 6.62 (dt, 1H, *J1* = 7.2 Hz, *J2* = 22.8 Hz), 5.94 (d, 1H, *J* = 5.7 Hz), 4.08 (q, 2H, *J* = 7.2 Hz), 3.16 (dd, 1H, *J1* = 3.9 Hz, *J2* = 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): δ = 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/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: For the major diastereoisomers, t_{minor} = 114.16 min, t_{major} = 155.00 min, ee = 98%; For the minor diastereoisomers, t_{major} = 87.73 min, t_{minor} = 94.86 min, ee = 88%; dr = 3.2:1; $[\alpha]_D^{29}$ = +133.8 (c = 1.0, $CHCl_3$).



6b

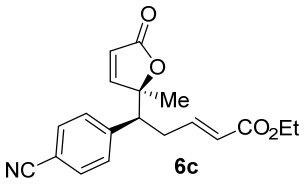
(S,E)-ethyl-5-(4-chlorophenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6b) (Table 4.3, entry 2): The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.27-7.30 (m, 3H), 7.05-7.08 (m, 2H), 6.59 (dt, 1H, *J1* = 7.2 Hz, *J2* = 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, *J1* = 3.9

Hz, *J2* = 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): δ = 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/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: For the major diastereoisomers, t_{minor} = 88.83 min, t_{major} = 109.02 min, ee = 98%; For the minor diastereoisomers t_{major} = 68.57 min, t_{minor} = 79.03 min, ee = 88%; dr = 2.6:1; $[\alpha]_D^{29}$ = +163.3 (c = 1.0, $CHCl_3$).



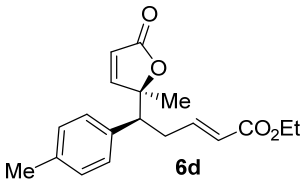
6c

(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): δ = 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, *J1* = 3.9 Hz, *J2* = 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): δ = 171.4, 165.7, 158.3, 147.5, 145.1, 144.1, 129.6, 124.2, 124.0, 121.6, 89.0, 60.4, 51.9, 31.9, 23.3, 14.1; HPLC (Daicel Chirapak IC column, hexane/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: For the major diastereoisomers, t_{major} = 206.12 min, t_{minor} = 287.38 min, ee = 96%; For the minor diastereoisomers, t_{major} = 155.38 min, t_{minor} = 247.43 min, ee = 92%; dr = 2.0:1; $[\alpha]_D^{29}$ = +140.5 (c = 1.0, $CHCl_3$).



6c

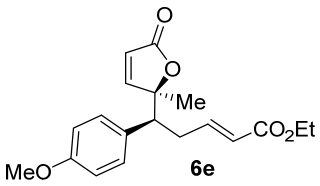
(S,E)-ethyl-5-(4-cyanophenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6c) (Table 4.3, entry 4): The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.61 (d, 2H, J = 8.0 Hz), 7.24-7.26 (m, 3H), 6.59 (dt, 1H, *J1* = 7.5 Hz, *J2* = 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, *J1* = 4.0 Hz, *J2* = 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): δ = 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/*i*PrOH=75:25 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, t_{major} = 191.78 min, t_{minor} = 266.61 min, ee = 94%; for the minor diastereoisomers, t_{major} = 150.27 min, t_{minor} = 216.85 min, ee = 87%; dr = 2.6:1; $[\alpha]_D^{29}$ = +158.1 (c = 1.0, $CHCl_3$).



6d

((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): δ = 7.32

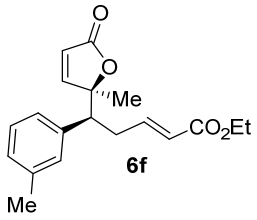
(d, 1H, *J* = 5.5 Hz), 7.10-7.14 (m, 3H), 7.00 (d, 1H, *J* = 8.0 Hz), 6.59 (dt, 1H, *J1* = 7.0 Hz, *J2* = 15.5 Hz), 5.95 (d, 1H, *J* = 5.5 Hz), 5.72 (d, 1H, *J* = 15.5 Hz), 4.08 (q, 2H, *J* = 7.0 Hz), 3.12 (dd, 1H, *J1* = 3.5 Hz, *J2* = 12 Hz), 2.66-2.70 (m, 2H), 2.48-2.55 (m, 2H), 2.3 (s, 3H), 1.4 (s, 3H), 1.21 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 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/*i*PrOH=90:10 at 0.5 mL/min, λ = 210 nm): Retention time: 275.28 min, 377.98 min, ee = 99%, dr = 2.3:1; $[\alpha]_D^{29}$ = +83.5 (c = 1.0, $CHCl_3$).



6e

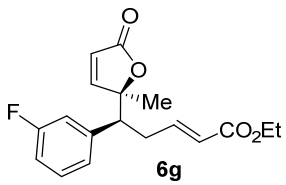
(S,E)-ethyl-5-(4-methoxyphenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6e) (Table 4.3, entry 6): The title compound was prepared according to the general procedure, as described above in 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.30 (d, 1H, *J* = 5.5 Hz), 7.03 (d, 1H, *J* = 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); ^{13}C NMR (125 MHz, $CDCl_3$, 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/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, t_{minor} = 149.22 min, t_{major} = 202.19 min, ee = 94%; for the minor diastereoisomers, t_{major} = 122.50 min, t_{minor} = 134.24 min, ee = 79%; dr = 1.6:1;

$[\alpha]_D^{29}$ = +84.2 (c = 1.0, $CHCl_3$).



6f

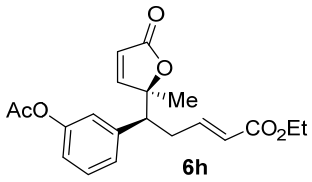
(S,E)-ethyl-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-(m-tolyl)pent-2-enoate (6f) (Table 4.3, entry 7): The title compound was prepared according to the general procedure, as described above in 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.33 (d, 1H, *J* = 5.5 Hz), 7.19 (t, 1H, *J* = 7.5 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); ^{13}C NMR (125 MHz, $CDCl_3$, 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/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, t_{minor} = 102.54 min, t_{major} = 132.95 min, ee = 98%; for the minor diastereoisomers, t_{major} = 77.24 min, t_{minor} = 89.89 min, ee = 89%; dr = 2.5:1; $[\alpha]_D^{29}$ = +115.6 (c = 1.0, $CHCl_3$).



6g

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

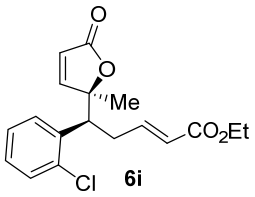
enoate (6g) (Table 4.3, entry 8): The title compound was prepared according to the general procedure, as described above in 81% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.27-7.33 (m, 2H), 6.92-6.99 (m, 2H), 6.83 (d, 1H, *J* = 10 Hz), 6.60 (dt, 1H, *J1* = 7.5 Hz, *J2* = 15.5 Hz), 5.95 (d, 1H, *J* = 5.5 Hz), 5.73 (d, 1H, *J* = 15.5 Hz), 4.09 (q, 2H, *J* = 7.0 Hz), 3.15 (dd, 1H, *J1* = 3.5 Hz, *J2* = 11.5 Hz), 2.71-2.76 (m, 2H), 2.51-2.58 (m, 2H), 1.45 (s, 3H), 1.22 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 171.8, 166.0, 158.3, 145.0, 140.1, 130.5, 130.4, 124.4, 123.6, 121.5, 115.7, 115.6, 115.0, 114.8, 89.6, 60.3, 52.0, 31.8, 23.6, 14.1; HPLC (Daicel Chirapak IC column, hexane/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, t_{minor} = 97.52 min, t_{major} = 122.43 min, ee = 98%; for the minor diastereoisomers, t_{major} = 66.73 min, t_{minor} = 84.03 min, ee = 89%; dr = 2.6:1; $[\alpha]_D^{29}$ = +90.8 (c = 1.0, $CHCl_3$).



6h

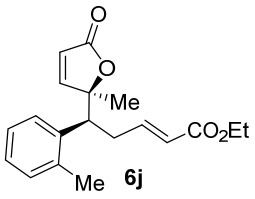
(S,E)-ethyl-5-(3-acetoxyphenyl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6h) (Table 4.3, entry 9): The title compound was prepared according to the general procedure, as described above in 100% yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.84 (d, 1H, *J* = 7.5 Hz), 7.72 (s, 1H), 7.43 (t, 1H, *J* = 7.5 Hz), 7.30-7.37 (m, 2H), 6.58 (dt, 1H, *J1* = 7.0 Hz, *J2* = 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, *J1* = 3.5 Hz, *J2* = 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): δ = 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/ *i*PrOH=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/*i*PrOH=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; $[\alpha]_D^{29}$ = +87.3 (c = 1.0, $CHCl_3$).



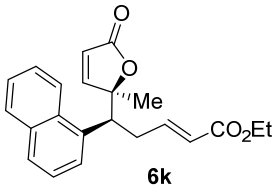
6i

(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. ^{1}H NMR (500 MHz, $CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$, 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/*i*PrOH=90:10 at 0.5 mL/min, λ = 210 nm): Retention time: for the major diastereoisomers, t_{minor} = 2.04 min, t_{major} = 53.48 min, ee = 93%; for the minor diastereoisomers, t_{minor} = 62.31 min, t_{major} = 82.31 min, ee = 96%; dr = 1.1:1; $[\alpha]_D^{29}$ = +82.6 (c = 1.0, $CHCl_3$).



6j

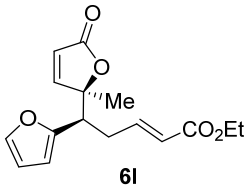
(S,E)-ethyl 5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-5-(o-tolyl)pent-2-enoate (6j) (Table 4.3, entry 11): The title compound was prepared according to the general procedure, as described above in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.37-7.40 (m, 1H), 7.29 (d, 1H, *J* = 5.7 Hz), 7.15-7.17 (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): δ = 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/*i*PrOH=90:10 at 0.5 mL/min, λ = 210 nm): Retention time: For the major diastereoisomer, t_{minor} = 57.44 min, t_{major} = 86.73 min, ee = 99%; For the minor diastereoisomer, t_{major} = 89.15 min, t_{minor} = 112.79 min, ee = 92%; dr = 1:1.3, $[\alpha]_D^{29}$ = +79.7 (c = 1.0, $CHCl_3$).



6k

(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): δ

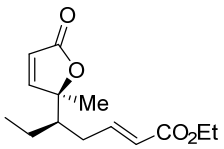
= 7.79-7.83 (m, 3H), 7.59 (s, 1H), 7.49-7.50 (m, 2H), 7.37 (d, 1H, *J* = 5.5 Hz), 7.26 (d, 1H, *J* = 5.5 Hz), 6.64 (dt, 1H, *J1* = 7.5 Hz, *J2* = 15.5 Hz), 5.93 (d, 1H, *J* = 5.5 Hz), 5.75 (d, 1H, *J* = 15.5 Hz), 4.04 (q, 2H, *J* = 7.0 Hz), 3.34 (dd, 1H, *J1* = 3.5 Hz, *J2* = 11.5 Hz), 2.66-2.83 (m, 2H), 1.47 (s, 3H), 1.17 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 172.1, 166.0, 158.6, 145.5, 135.0, 133.3, 132.8, 128.7, 128.0, 127.8, 127.7, 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/*i*PrOH=90:10 at 0.5 mL/min, λ = 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, $CHCl_3$).



6l

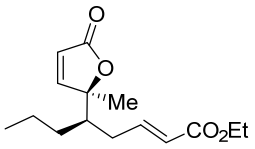
(S,E)-ethyl-5-(furan-2-yl)-5-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pent-2-enoate (6l) (Table 4.3, entry 13): The title compound was prepared according to the general procedure, as described above in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.50 (d, 1H, *J* = 5.7 Hz), 7.32-7.36 (m, 1H), 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): δ = 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/*i*PrOH=90:10 at 0.5

mL/min, λ = 210 nm): Retention time: For the major diastereoisomer, t_{minor} = 64.41 min, t_{major} = 71.68 min, ee = 95%; For the minor diastereoisomer, t_{major} = 84.20 min, t_{minor} = 122.82 min, ee = 77%, dr = 2.1:1; $[\alpha]_D^{29}$ = +79.4 (c = 1.0, $CHCl_3$).



6m

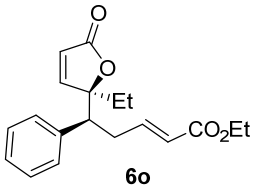
(R,E)-ethyl-5-((S)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)hept-2-enoate (6m) (Table 4.3, entry 14): The title compound was prepared according to the general procedure, as described above in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.39 (d, 1H, *J* = 5.7 Hz), 6.88 (dt, 1H, *J1* = 7.2 Hz, *J2* = 15.6 Hz), δ = 6.04 (d, 1H, *J* = 5.7 Hz), 5.82 (dt, 1H, *J1* = 1.5 Hz, *J2* = 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): δ = 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/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): Retention time: For the major diastereoisomer, t_{minor} = 110.48 min, t_{major} = 128.28, ee = 96%, dr = 5.7:1; $[\alpha]_D^{29}$ = +25.8 (c = 1.0, $CHCl_3$).



6n

(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

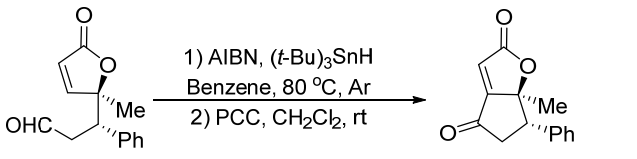
described above in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.39 (d, 1H, *J* = 5.7 Hz), 6.88 (dt, 1H, *J1* = 7.5 Hz, *J2* = 15.6 Hz), 6.04 (d, 1H, *J* = 5.7 Hz), 5.80 (dt, 1H, *J1* = 1.5 Hz, *J2* = 15.6 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 2.11-2.33 (m, 2H), 1.45 (s, 3H), 1.19-1.41 (m, 7H), 0.87 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ =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 (Daicel Chirapak IC column, hexane/*i*PrOH=80:20 at 0.5 mL/min, λ = 210 nm): For the major diastereoisomers t_{minor} = 103.33 min, t_{major} = 118.39 min, ee = 96%; For the minor diastereoisomers t_{major} = 68.54 min, t_{minor} = 72.83 min, ee = 94%; dr = 9.1:1; $[\alpha]_D^{29}$ = +42.3 (c = 1.0, $CHCl_3$).



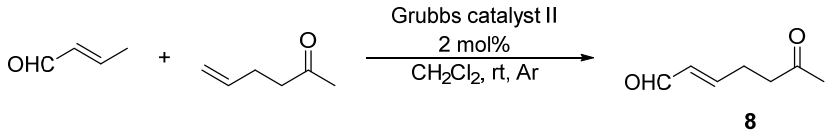
6o

(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): δ = 7.31 (t, 2H, *J* = 7.5 Hz), 7.23-7.27 (m, 2H), δ = 7.12 (t, 2H, *J* = 7.5 Hz), 6.61 (dt, 1H, *J1* = 7.0 Hz, *J2* = 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, *J1* = 3.5 Hz, *J2* = 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): δ = 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 (Daicel Chiralcel AS-H column, hexane/*i*PrOH=90:10 at 0.5 mL/min, λ = 210 nm): (Daicel Chirapak IC column, hexane/*i*PrOH=95:5 at 0.5 mL/min, λ

= 210 nm): For the major diastereoisomers t_{minor} = 566.18 min, t_{major} = 675.96 min, ee = 92%; For the minor diastereoisomers t_{major} = 355.13 min, t_{minor} = 390.47 min, ee = 88%;dr = 2.0:1; $[\alpha]_D^{29}$ = +93.8 (c = 1.0, $CHCl_3$).

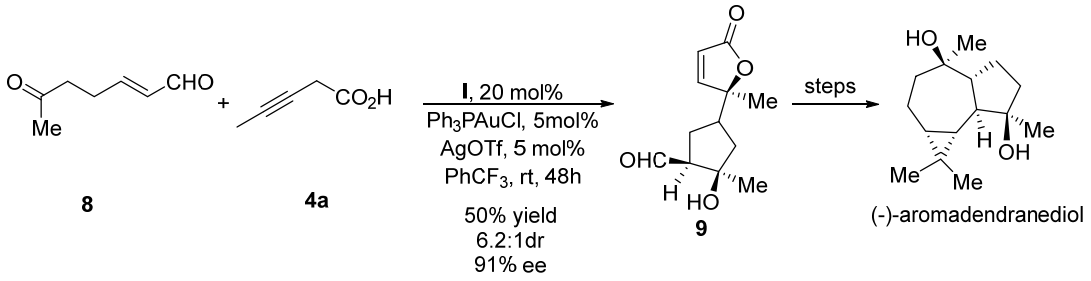


The Procedure for the Preparation of (3aS, 6S, 6aS)-6a-methyl-6-phenyltetrahydro-2H-cyclopenta[b]furan-2,4(5H)-dione (7): A mixture of **3a** (23mg, 0.1 mmol), AIBN (0.3 mmol) and Bu_3SnH (1.7mg, 0.01 mmol) in benzene (1 mL) was stirred at 80 °C for 2h. The reaction mixture was quickly filtered over 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_2Cl_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/*i*PrOH = 80:20 at 0.5 mL/min, λ = 210 nm): t_{minor} = 16.39 min, t_{major} = 21.77 min, ee = 98%; $[\alpha]_D^{29}$ = +32.3 (c = 1.0, $CHCl_3$).



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_2Cl_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, *J1* = 6.3 Hz, *J2* = 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_3PAuCl (5.0 mg, 0.01 mmol) and AgOTf (2.6mg, 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): δ = 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, *J1* = 1.8 Hz, *J2* = 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): δ = 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_{major} = 9.86 (doublet) Vs H_{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/*i*PrOH = 75:25 at 0.5 mL/min, λ = 210 nm): t_{minor} = 46.78 min, t_{major} = 45.11 min, ee = 91%; $[\alpha]_D^{29}$ = -11.7 (c = 1.0, $CHCl_3$).

4.8. References

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