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DEVELOPMENT OF NOVEL EFFICIENT ORGANOCATALYTIC REACTIONS FOR THE CONSTRUCTION OF COMPLEX MOLECULAR ARCHITECTURES

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DISSERTATION

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DEDICATION

To

My Parents, Yufeng Song and Guisong Liu

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ABSTRACT

Facile construction of synthetically and medicinally significant optically active molecular architectures from simple and readily available materials via catalytic enantioselective cascade processes is the cental goal in organic synthesis. Toward this end, my Ph. D. work focuses on the development of novel organocatalytic asymmetric cascade reactions and their application in the synthesis of versatile molecular structures.

A novel amine catalyzed decarboxylative enantioselective Diels–Alder reaction between aldehydes and readily available coumarin-3-carboxylic acids as dienophiles via dienamine catalysis has been realized. Notably, the decarboxylation facilitates the release of the catalyst in the Diels–Alder reaction adducts and achieves high reaction efficiency in terms of reaction time, yield and enantio- and diastereo-selectivity. Furthermore, the Diels–Alder adducts are smoothly transformed into optically active bridged tricyclic benzopyrans by a novel but unexpected 'one-pot' protocol of $LiAlH_4$ or $NaBH_4$ mediated reduction and subsequent acid (workup) catalyzed highly stereoselective cyclization. Moreover, the decarboxylative strategy is applied to the efficient 'one-pot' synthesis of aromatized xanthones by pyrrolidine catalyzed Diels–Alder reactions of enals and subsequent oxidation reaction using DDQ.

In addition, we have designed and implemented an unprecedented amine-catalyzed [4+1] annulation reaction. The notable features of the process include a new conjugate addition-protonation-conjugate addition cascade sequence by employing readily available ynals and *N*-protected-2-aminophenols as reactants. The mild reaction protocol allows for a broad spectrum of ynals and 2-aminophenols to engage in the cascade sequence with high efficiency. Synthetically and biologically important benzoxazoles are created in one-pot operation.

Finally, intermolecular enantioselective desymmetrization of *p*-quinols by urea catalyst mediated sulfa-Michael addition reactions has been developed to furnish the corresponding products in good yields and moderate to good enantioselectivities as single diastereomers.

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List of Schemes

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List of Abbrevations

$[\alpha]_D$	Specific Rotation at Wavelength of Sodium D Line
Ac	Acetyl
aq.	Aqueous
Ar	Aromatic
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
bp	Boilong Point
t-Bu	*t*-Butyl
Bz	Benzoyl
c	Concentration
Cbz	Benzyloxycarbonyl
$CDCl_3$	Deuterated Chloroform
δ	Chemical Shift
DCE	Dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
D_2O	Deuterated Water
EDG	Electron Donating Group
ee	Enantiomeric Excess
eq.	equivalent

EtOAc	Ethyl Acetate
EWG	Electron Withdrawing Group
g	Gram
h	Hour
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
J	Coupling Constant
λ	Wavelength
LUMO	Lowest Unoccupied Molecular Orbital
m-	Meta-
Me	Methyl
MeCN	Acetonitrile
Mg	Magnesium
mg	Milligram
min.	Minute
mL	Milliliter
mp	Melting Point
Ms-	Methanesulfonyl
NMR	Nuclear Magnetic Resonance
o-	Ortho

p-	Para-
Ph	Phenyl
PG	Protecting Group
ppm	Parts per Million
i-PrOH	Isopropyl Alcohol
rt	Room Temperature
TB(DM)S	*tert*-Butyldimethylsilyl
TBME	*tert*-Butylmethylether
TEA	Triethylamine
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
μL	Microliter

Chapter 1

Development of Organocatalysis

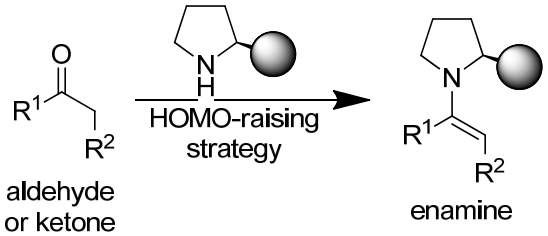
1.1 Introduction to Chiral Amine Catalysis

Organocatalysis has become an important and widely applied synthetic strategy after ten years of rapid development.[1] In this context, chiral secondary amine[2] catalyzed enantioselective reactions via enamine[3] or iminium[4] mode have conceptualized the field. Chiral primary amine catalytic model,[5] phase transfer catalytic model,[6] chiral Brønsted base catalytic model,[7] chiral Brønsted acid catalytic model,[8] H-bonding catalytic model,[9] and nucleophilic heterocyclic carbene catalytic model[10] have been also developed soon after. In relation to my studies, chiral secondary amine catalysis and chiral thiourea catalysis are introduced in detail in this chapter.

1.1.1 Enamine Catalysis

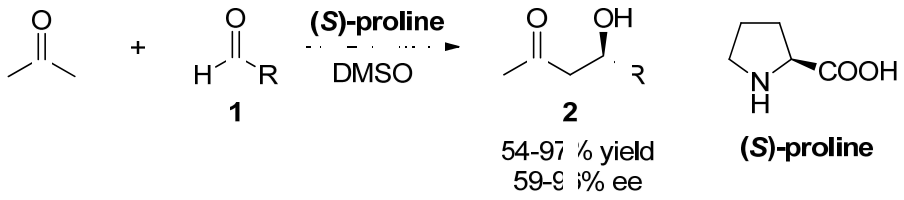
Enamine activated aldehydes or ketones are generally suitable nucleophiles which can be applied in the α-functionalization of aldehydes or ketones via a HOMO-raising strategy (Scheme 1.1).[3]

Scheme 1.1 Enamine formation



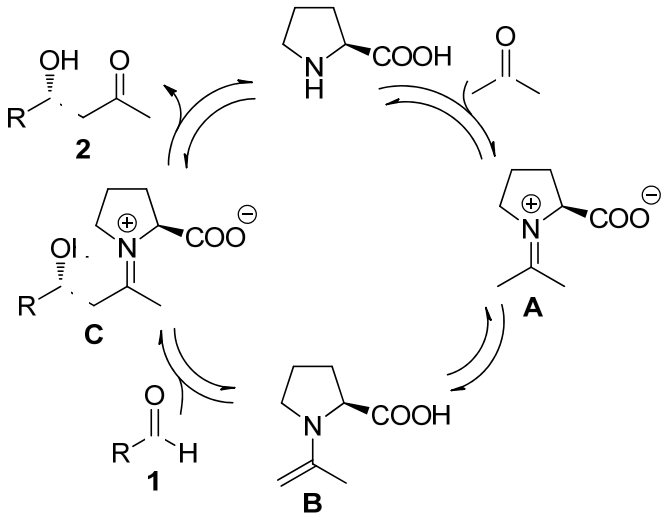
Inspired by the study that calss I aldolases mediate aldolization via enamine mechanism, Benjamin List and co-workers developed proline catalyzed asymmetric aldol reaction between acetone and a variety of aldehydes for the first time (Scheme 1.2).[11]

Scheme 1.2 (*S*)-proline catalyzed asymmetric aldolization



The mechanism of (*S*)-proline catalyzed asymmetric aldol reaction is shown in scheme 1.3. Iminium **A**, produced from dehydration between (*S*)-proline and acetone, is in equilibrium with enamine **B**. The nucleophilic enamine **B** can attack aldehyde **1** enantioselectively to afford intermediate **C**. (*S*)-proline is regenerated upon hydrolysis of **C** and aldol product **2** is released at the same time.

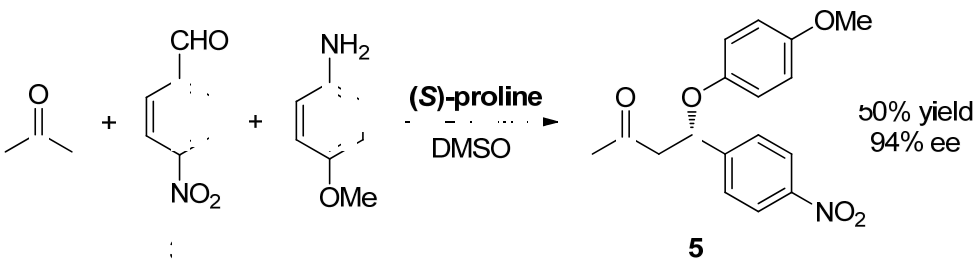
Scheme 1.3 Mechanism of (*S*)-proline catalyzed asymmetric aldolization



The emamine catalysis can be extended to various kinds of reactions by replacing the electrophile **1** according to the mechanism of asymmetric aldolization via enamine

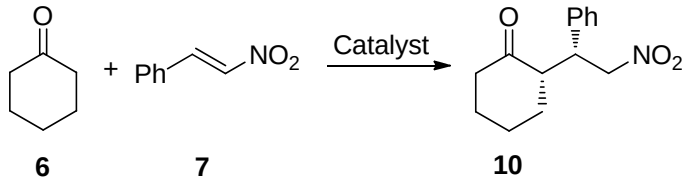
catalysis (Scheme 1.3). For example, *in-situ* prepared imine was exposed to enamine **B** to produce Mannich product **5** in 50% yield and 94% ee (Scheme 1.4).[12]

Scheme 1.4 (*S*)-proline catalyzed asymmetric Mannich reaction.



List and co-workers also developed the first proline catalyzed Michael addition reaction between ketone **6** and nitroolefin **7** to give Michael product **10** in good yields and dr but only low ee (Table 1.1, entry 1).[13]

Table 1.1 Michael addition reactions mediated by different catalysts

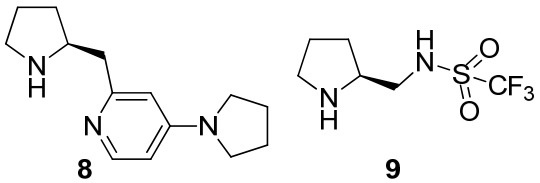


entry	catalyst	solvent	yield (%)[a]	dr[b]	ee (%)[c]
1	(*S*)-proline	DMSO	94	>20:1	23
2[d]	**8**	$CHCl_3$	95	>20:1	99
3	**9**	*i*-PrOH	96	>20:1	97

[a] Isolated yields. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] 2,4-dinitrobenzenesulfonic acid as additive.

The enantioselectivity of the Michael addition reaction was improved by utilizing respective chiral pyrrolidine-pyridine conjugate base catalyst[14] or pyrrolidine sulfonamide (Figure 1.1)[15] in 2004 (Table 1.1, entry 2 and 3).

Figure 1.1 Secondary amine catalysts **8** and **9**



Other electrophiles involved α-functionalization reactions of carbonyl compounds via enamine catalysis were also developed to furnish the corresponding products in good yields and enantioselectivities.[3]

1.1.2 Diels–Alder Reactions via Enamine Catalysis

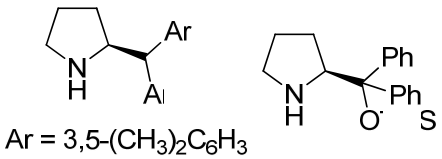
More importantly, chiral amine catalysis can be applied in the cascade processes for rapid synthesis of valuable optically active building blocks from readily available starting materials. Especially, the enamines produced from carbonyl compounds and chiral amine catalysts can participate in all kinds of Diels–Alder reactions designed for the facile construction of cyclic structures.

1.1.2.1 Inverse-Electron-Demanding [4+2] Reactions

It is envisioned that chiral enamines can participate in asymmetric hetero-Diels–Alder reactions with β,γ-unsaturated α-ketoesters as electron-rich dienophiles. Jørgensen and co-workers found that the proposed organocatalytic inverse-electron-demanding hetero-Diels–Alder reaction was feasible to furnish the desired products **13** in good yields

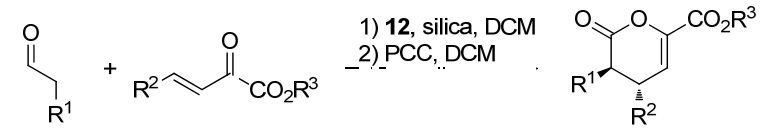
and enantioselectivities as single diastereomers after oxidation (Scheme 1.5).[16] It is noteworthy that silica is used for the regeneration of catalyst **12**.

Figure 1.2 Chiral catalysts **12** and **15**



15

Scheme 1.5 Organocatalytic hetero-Diels–Alder reaction



11

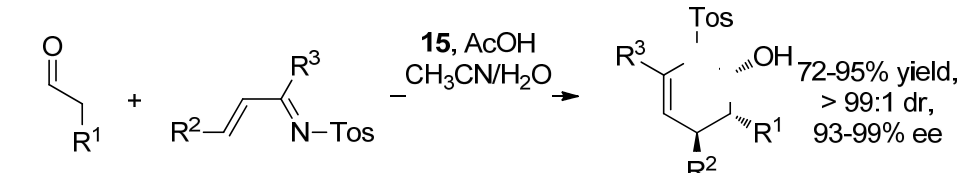
R^1 = alkyl R^2 = alkyl or aryl
R^3 = Me or Et

13

62-93% yield,
> 100:1 dr,
80-94% ee

Inspired by Jørgensen's ingenious design of oxy-Diels–Alder reactions between enamines and β,γ-unsaturated α-ketoesters, Chen and co-workers developed highly stereoselective inverse-electron-demand aza-Diels–Alder reactions of *N*-sulfonyl-1-aza-1,3-butadienes and enamines to furnish the chiral piperidine derivatives **16** in good yields, diastereoselectivities and enantioselectivities (Scheme 1.6).[17]

Scheme 1.6 Aza-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes



R^1 = alkyl

14

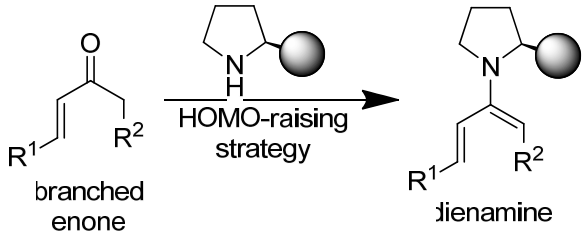
R^2, R^3 = alkyl or aryl

16

1.1.2.2 [4+2] Reactions with Enamine-Activated Dienes

Contrary to the inverse-electron-demanding Diels–Alder reactions employing enamine as dienophiles, Diels–Alder reactions of chiral 2-amino-1,3-dienes (Scheme 1.7), *in situ* generated from *α,β*-unsaturated ketones and chiral amine catalysts have also been developed.[18]

Scheme 1.7 Dienamine formation from branched enones



High enantioselectivity for the Diels–Alder product was not achieved until 5-dimethyl thiazolidinium-4-carboxylate (DMTC) was utilized to catalyze the domino Knoevenagel/Diels–Alder reactions in 2003.[19]

Scheme 1.8 Organocatalytic three-component Diels–Alder reaction

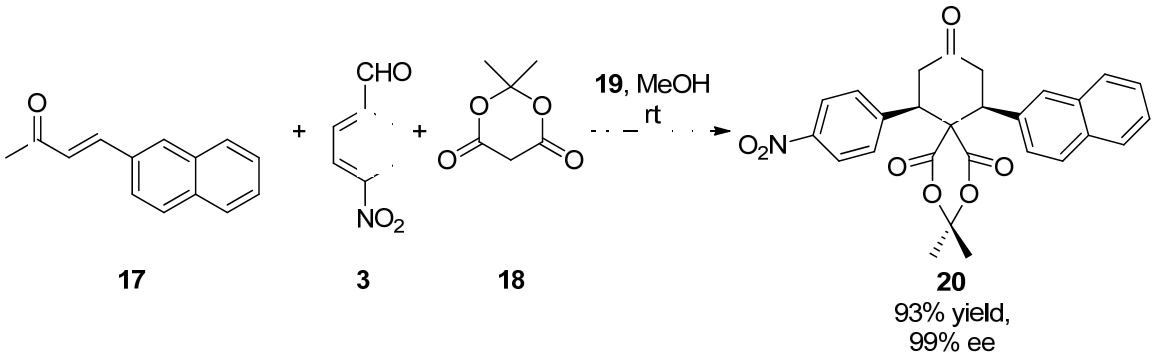
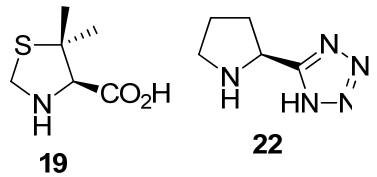


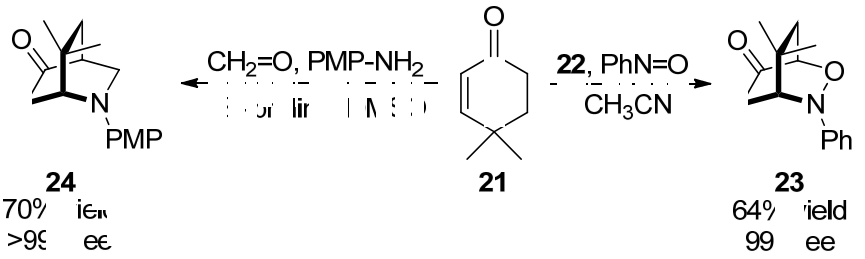
Figure 1.3 Organocatalysts **19** and **22**



Highly substituted spiro[5,5]undecane-1,5,9-trione **20** was produced from enone **17**, aldehydes **3**, and 2,2-dimethyl-1,3-dioxane-4,6-dione **18** in 93% yield and 99% ee as a single diastereomer (Scheme 1.8).

The strategy was extended to hetero-Diels–Alder reactions of enamine produced from enone **21** with *O*-nitroso[20] or in situ prepared imine[21] to produce enantiopure Diels–Alder adducts in moderate yields (Scheme 1.9).

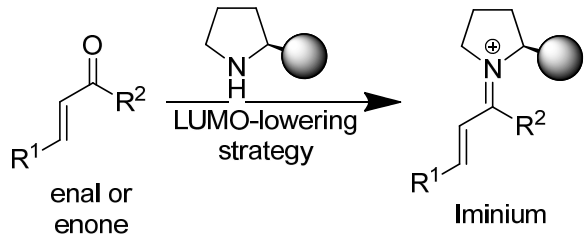
Scheme 1.9 Hetero-Diels–Alder reactions via enamine catalysis



1.1.3 Iminium Catalysis

α,β-Unsaturated aldehydes or ketones can be activated by forming iminium ions with a chiral amine catalyst (Scheme 1.10). Correspondingly, iminium activated enals or enones are considered as electrophiles which can be utilized in the β-functionalization of enals or enones through a LUMO-lowering model. Compared to the corresponding α,β-unsaturated aldehydes or ketones, the iminium ions are more prone to a nucleophilic attack.

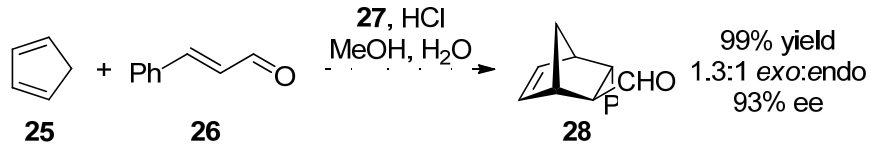
Scheme 1.10 Iminium formation



1.1.3.1 Iminium-Activated Diels–Alder Reactions

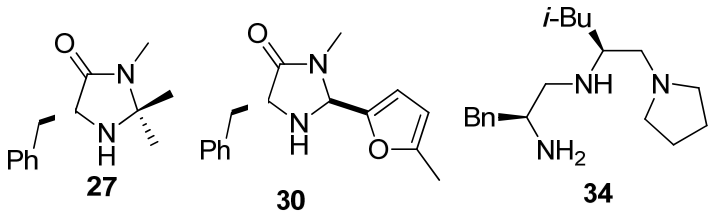
The asymmetric iminium catalysis can be traced back to 1993.[22] However, a more general platform for Diels–Alder reaction via iminium catalysis was established by MacMillan and co-workers in 2000 (Scheme 1.11).[23]

Scheme 1.11 Diels–Alder reaction via iminium catalysis



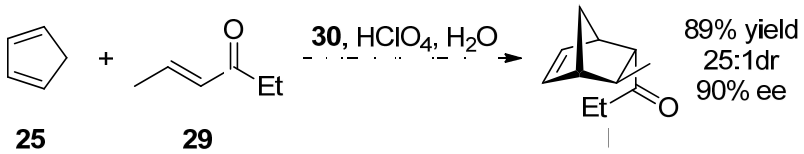
Diels–Alder products were obtained from various dienes and α,β-unsaturated aldehydes in good yields and enantioselectivities. Low diastereoselectivities were observed for the Diels–Alder reaction employing cyclopentadiene. The diastereoselectivities were greatly improved when cyclopentadiene was replaced with other dienes.

Figure 1.4 Organocatalysts **27**, **30** and **34**



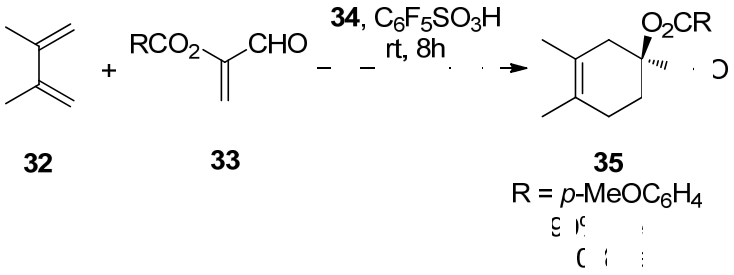
MacMillan and co-workers were surprised to find that racemic cycloaddition adduct was obtained when α,β-unsaturated aldehyde was replaced with α,β-unsaturated ketone.[24] Upon optimizing reaction condition, 2-(5-methylfuryl)-derived imidazolidinone **30** was identified as an effective promoter for the Diels–Alder reactions of α,β-unsaturated ketone **29** to afford the desired product **31** in 89% yield, 25:1 dr and 90% ee (Scheme 1.12).

Scheme 1.12 Diels–Alder reactions of α,β-unsaturated ketone



Although great results had been achieved in secondary amine mediated Diels–Alder reactions, it was found that α-substituted acroleins were difficult to be activated by secondary amines. However, primary amine catalyst **34** was effective for promoting the asymmetric Diels–Alder reaction between α-substituted acrolein and diene to produce the desired product **35** in 99% yield and 90% ee (Scheme 1.13).[25]

Scheme 1.13 Diels–Alder reaction of α-substituted acrolein



1.1.3.2 Iminium-Activated Sequential [4+2] Reactions

Different from the concerted asymmetric Diels–Alder reactions leading to chiral cyclohexene structures, sequential [4+2] reactions of α, β-unsaturated aldehydes affording benzene-fused cyclic building blocks have also been reported.

Initially, 2-mercaptobenzaldehyde **36** was employed to react with enal **26** to afford thiochromene **38** in 85% yield and 94% ee (Scheme 1.14).[26]

Scheme 1.14 Cascade Michael-aldol reaction

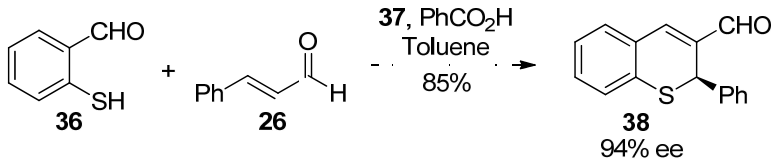
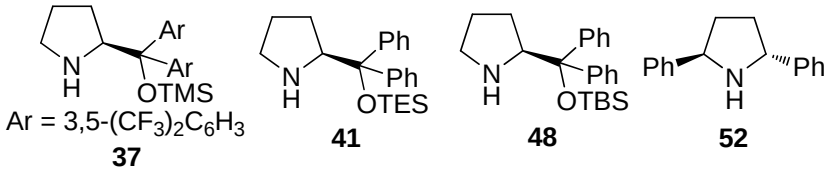
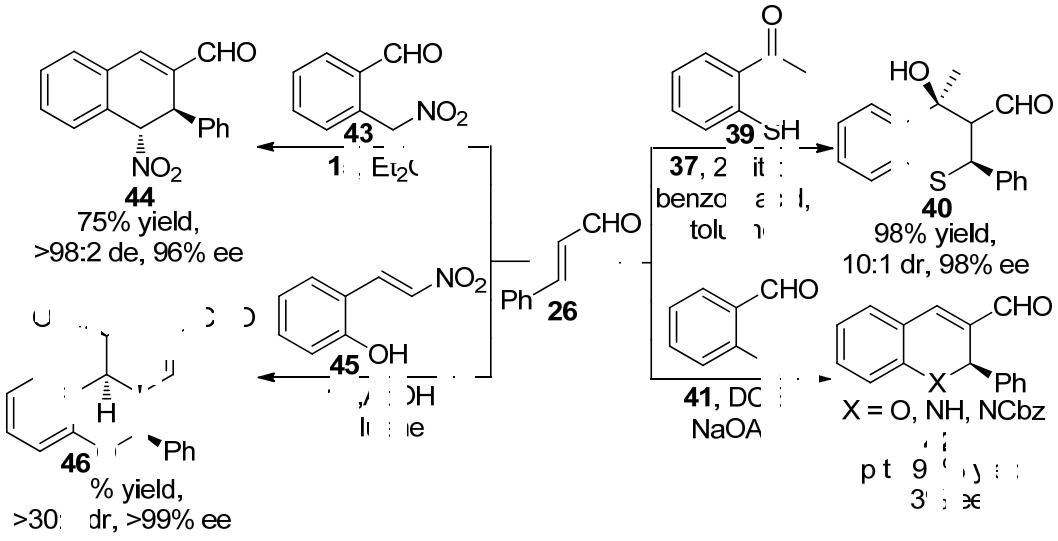


Figure 1.5 Organoatalysts



The extension of this strategy was soon realized by replacing 2-mercaptobenzaldehyde **36** to 2-mercaptoacetophenone,[27] salicylaldehydes,[28] 2-amino benzaldehydes,[29] 2-(nitromethyl)benzaldehyde,[30] 2-((*E*)-2-nitrovinyl)phenol[31] for the sequential [4+2] reaction to furnish the desired products in moderate to good yields with high enantio- and diastereoselectivities as shown in scheme 1.15.

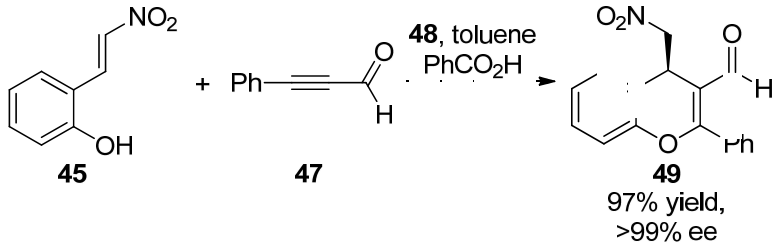
Scheme 1.15 Expansion of [4+2] reactions of enals



It is noteworthy that an additional Michal-aldol condensation occurs after the [4+2] reaction between **26** and 2-((*E*)-2-nitrovinyl)phenol **45** via iminium catalysis to produce complex structure **46** with excellent results (Scheme 1.15).[31]

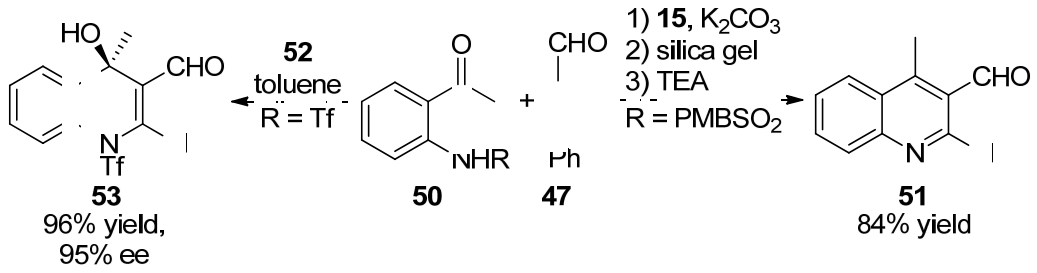
2-((*E*)-2-Nitrovinyl)phenol **45** was also found to engage in a sequential [4+2] reaction with alkynal **47** via iminium catalysis efficiently (Scheme 1.16).[32] The process proceeded smoothly to produce synthetically and biologically significant chiral 4*H*-chromene **49** in high yield (97%) and with excellent enantioselectivity (>99%).

Scheme 1.16 Oxa-Michael-Michael reaction of alkynalsw



Quinolines **51** and chiral 1,4-dihydroquinolines **53** were obtained from the sequential [4+2] reactions of protected 2-amino acetophenones **50** and alkynals **47** divergently by the choice of different protecting groups in **50** (Scheme 1.17).[33]

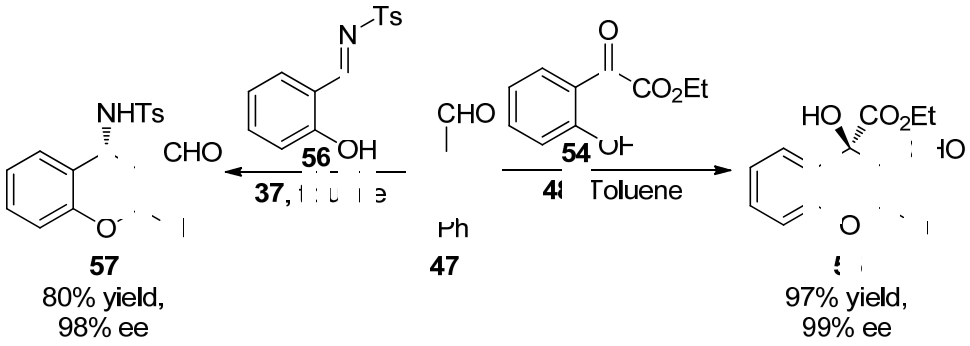
Scheme 1.17 Aza-Michael-aldol reactions



The sequential [4+2] reactions of alkynal **47** were extended to (2-hydroxy-phenyl)-2-oxoacetates **54**[34] and salicylimines **56**[35] to produce optically active 4*H*-chromenes **55**

with a quaternary chiral center and 4-amino-4*H*-chromenes **57** respectively (Scheme 1.18).

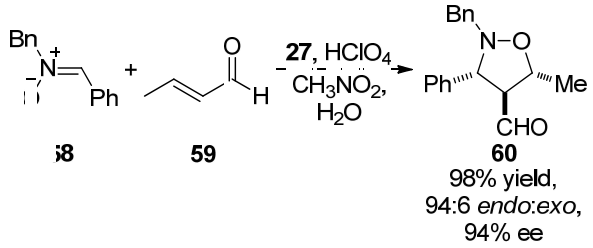
Scheme 18 Other [4+2] ractions of alkynal **47**



1.1.3.3 Iminium-Activated [3+2] Reactions

Iminium-activated [3+2] cycloaddition reactions leading to five-membered ring architectures have also been initially developed by MacMillan and co-workers by simply replacing diene in the previously reported Diels–Alder reaction[23] to nitrone **58** to provide isoxazolidine **60** in 98% yield, 94:6 dr and 94% ee (Scheme 1.19) in 2000.[36] Highly chemo- and enantioselective organocatalytic three-component reaction of enals with *in situ* generated nitrones from *N*-arylhydroxylamines and aldehydes was reported.[37]

Scheme 1.19 [3+2] cycloaddition of nitrone **58**



Similarly, polysubstituted pyrrolidines can also be prepared from [3+2] cycloaddition reactions of azomethine ylides through MacMillan's LUMO-lowering

strategy by iminium activation. The [3+2] reaction between azomethine ylide **61** and enal **26** proceeds smoothly to furnish stereoisomerically pure highly functionalized polysubstituted pyrrolidine **63** in good yield with complete regioselectivity and excellent diastereo- and enantioselectivity (Scheme 1.20).[38]

Scheme 1.20 [3+2] cycloaddition of azomethyne ylide

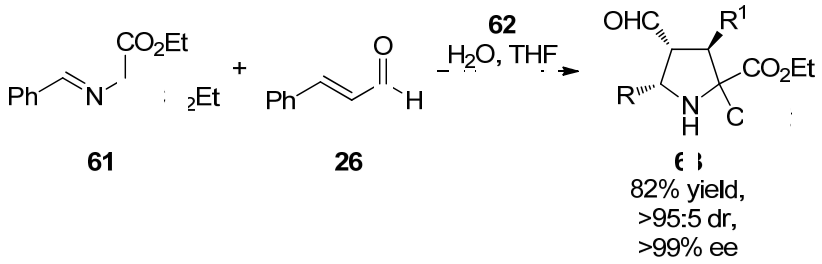
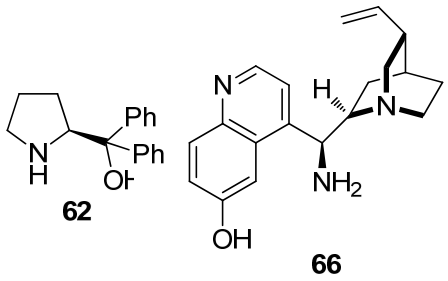
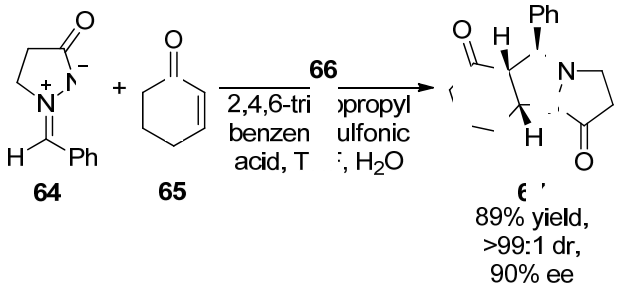


Figure 1.6 Catalysts



Extension of iminium-activated [3+2] cycloadditions to azomethine imines with α,β-unsaturated aldehydes[39] and cyclic enones[40] has been realized by Chen and co-workers.

Scheme 1.21 1,3-dipolar cycloaddition of azomethine imine

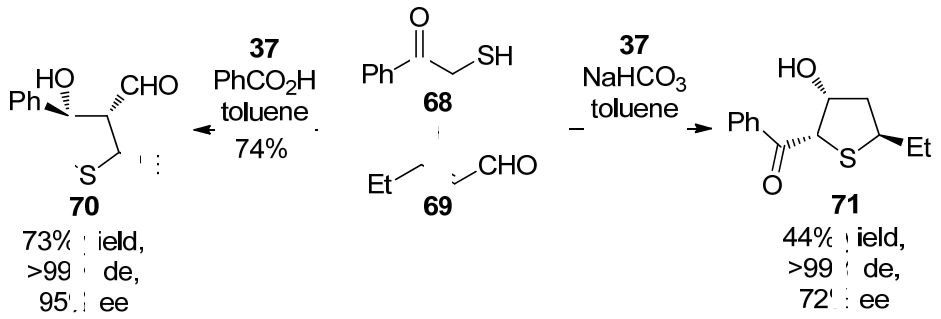


Notably, the multifunctional cinchona alkaloid derived primary amine catalyst was found to promote the [3+2] cycloaddition reaction of azomethine imine **64** and enone **65** efficiently to give tricyclic compound **67** in 89% yield and 90% ee (Scheme 1.21).

1.1.3.4 Iminium-Activated Sequential [3+2] Reactions

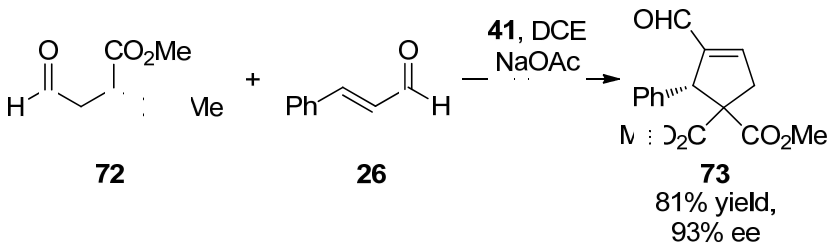
Similar to enantioselective sequential [4+2] cascade reactions employing reactants bearing 1,4-nucleophilic-electrophilic sites, sequential [3+2] reactions of reactants with 1,3-nucleophilic-electrophilic sites have been implemented to furnish five-membered ring structures.

Scheme 1.22 [3+2] Reactions of 2-mercapto-1-phenylethanone



The first highly enantioselective sequential [3+2] reaction between 2-mercapto-1-phenylethanone **68** and enal **69** was reported to produce highly functionalized tetrahydrothiophenes **70** or **71** depending on the additives used (Scheme 1.22).[41]

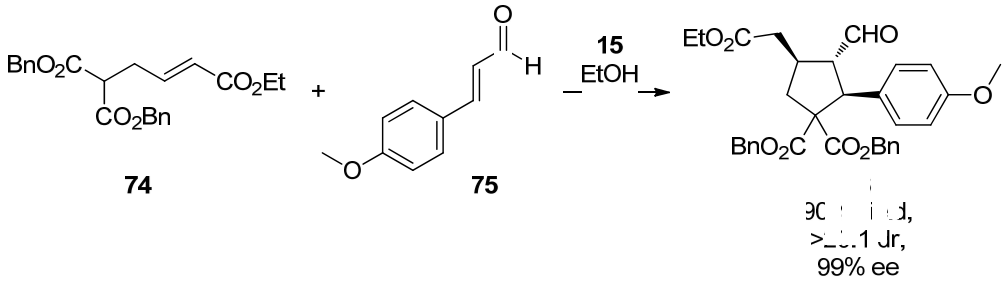
Scheme 1.23 Cascade Michael-aldol reactions



As a continuation of our cascade reactions, we identified that aldehyde **72** bearing a malonate unit was suitable reactant with compatible 1,3-nucleophilic and electrophilic functionalities for [3+2] reactions (Scheme 1.23).[42]

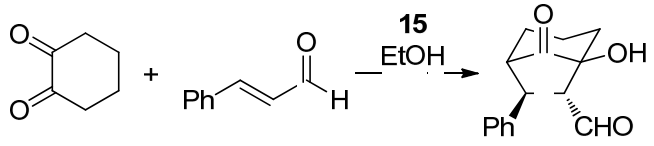
It was proposed that undesirable side reactions could be minimized by using bulky and enolizable malonates and organocatalyst **41**. The assumption was proved to be feasible by the sequential [3+2] reaction between enal **26** and aldehyde **72** to produce the desired product **73** in 81% yield and 93% ee.

Scheme 1.24 Cascade double Michael addition reactions



In addition the [3+2] reaction employing aldehyde **72** through Michael-aldol sequence, a novel [3+2] cascade reaction of α,β-unsaturated ester **74** with enal **75** via Michael-Michael sequence was also conducted (Scheme 1.24). The advantage of the novel system is that the [3+2] adduct with three stereogenic centers can be formed. The desired tetrasubstituted cyclopentane **76** was obtained.[43]

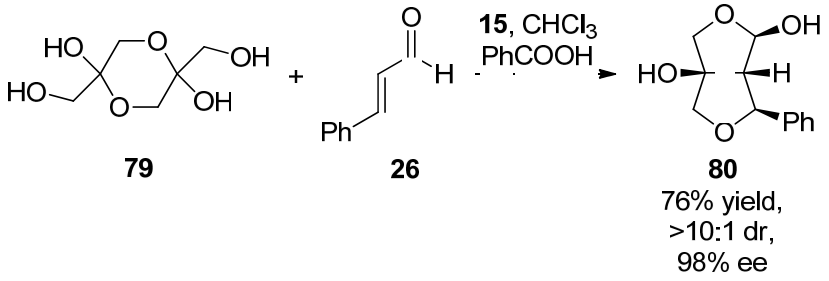
Scheme 1.25 Enantioselective domino Michael/aldol reaction



The similar strategy was applied to [3+2] cascade reaction between 1,2-cyclohexadione **77** and the α,β-unsaturated aldehyde **26** to provide the bicyclic molecule **78** in 77% yield and 96% ee (Scheme 1.25).[44]

Interestingly, alcohol dihydroxyacetone dimer **79** can also be utilized in the [3+2] reaction of α,β-unsaturated aldehyde **26** and an additional hemiacetalization to provide hexahydrofuro[3,4-*c*]furane **80** in excellent yield and with diastereo- and enantioselectivity (Scheme 1.26).[45]

Scheme 1.26 One-step synthesis of hexahydrofuro[3,4-c]furane



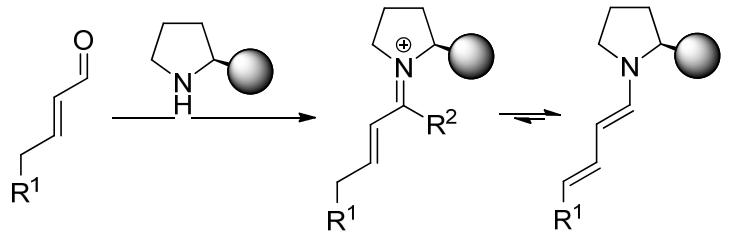
79 **26** **80**

76% yield,
>10:1 dr,
98% ee

1.1.4 Dienamine Catalysis

Jørgensen and co-workers unexpectedly found that more than 50% of **37** was present in the form of dienamine rather than iminium when it was mixed with 2-pentenal **69** in C_6D_6 (Scheme 1.27).[46]

Scheme 1.27 Dienamine formation from enals



enal Iminium dienamine

LUMO-lowering strategy

HOMO-raising strategy

In fact, the expected iminium could not be detected in the same experiment by using ^{1}H NMR. Different from the dienamine produced from branched enones for α- and β-functionalization, the dienamine produced from enals can be used to achieve the goal of γ-functionalization.

1.1.4.1 γ-Functionalization via Dienamine Catalysis

The resulting dienamine formed from 2-pentenal **69** and catalyst **37** was then exposed to electrophilic diethyl azodicarboxylate **81**.[46] The electronic property of electrophilic enal **58** was inverted to act as a nucleophile for the reaction with diethyl azodicarboxylate **81** to afford adduct **82** in moderate yield and ee (Scheme 1.28).

Scheme 1.28 γ-Amination of α,β-unsaturated aldehyde

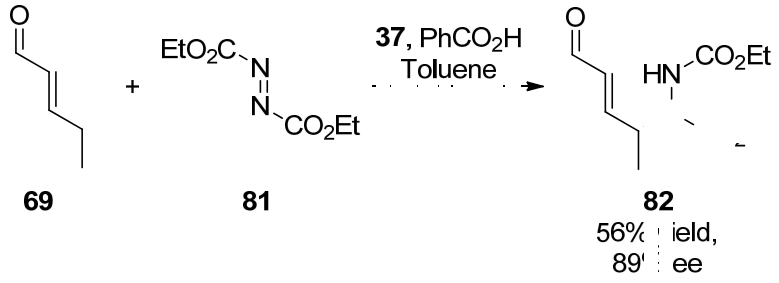
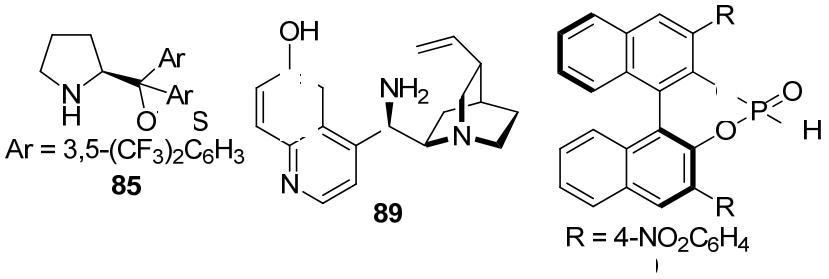


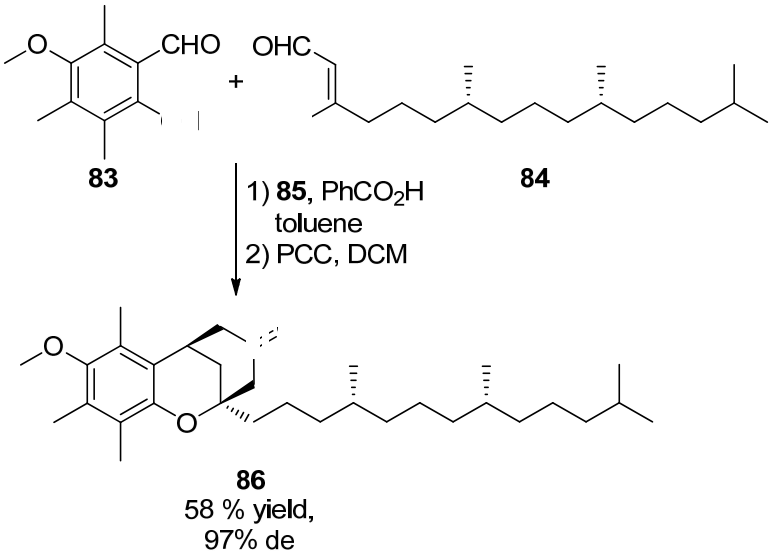
Figure 1.7 Catalysts



Aldol reaction of dienamine was also conducted in an aldol-oxo-Michael-hemiacetlization-oxidation sequence to produce valuable building block **86** in 58% yield

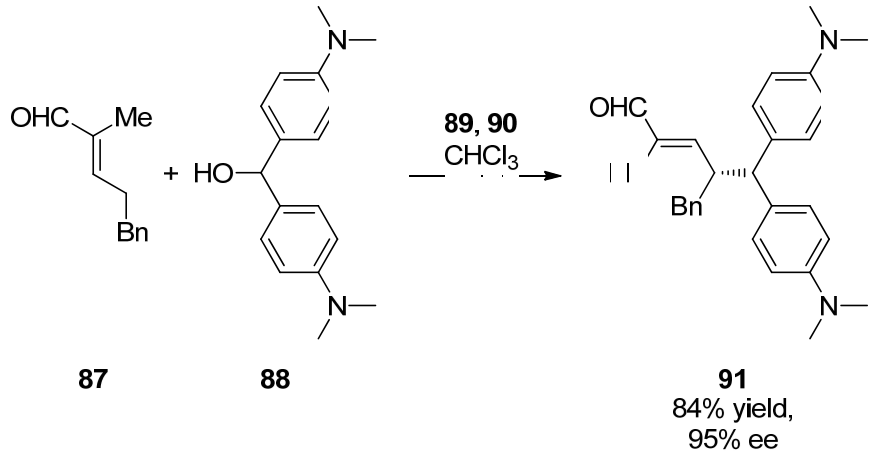
and 97% de (Scheme 1.29).[47] The resulting adduct **86** was then applied to the synthesis of α-tocopherol.

Scheme 1.29 Synthesis of **86** via dienamine catalysis



The relative low yields observed for the γ-functionalization of enals may be attributed to the competing reactions for α-functionalization of enals. It is assumed that the regioselectivity of the reaction can be improved by blocking the α-position of enals.

Scheme 1.30 γ-Functionalization of α-branched enal



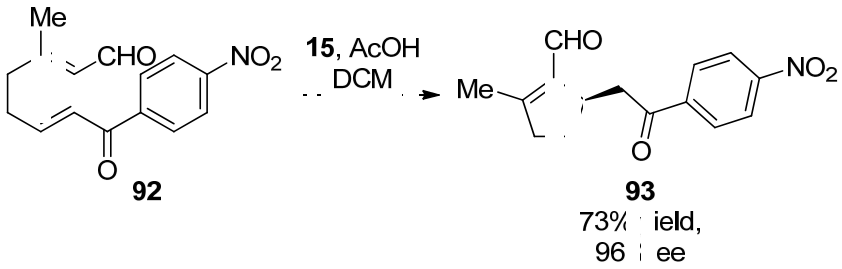
The assumption was proved to be feasible by employing α-branched enal **87** for the dienamine mediated reaction with **88** through an S_N1 pathway to furnish adduct **91** in 84% yield and 95% ee (Scheme 1.30).[48]

The same research group extended the strategy to the reactions of β-substituted cyclohexenone derivatives with nitroalkenes[49] and α-keto esters[50].

1.1.4.2 α-Functionalization via Dienamine Catalysis

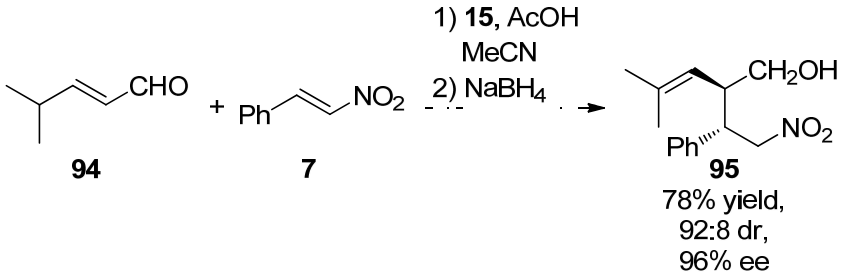
Similarly, α-functionalization of α,β-unsaturated aldehydes can be selectively realized by blocking the γ-position of the enals with an additional substituent. An intramolecular Rauhut-Currier reaction was designed with γ-disubstituted enal **92** to give product **93** in 73% yield and 96% ee (Scheme 1.31).[51]

Scheme 1.31 Intramolecular Rauhut-Currier reaction



It is controversial to conclude that the selective attack from α-position is attributed to the blocking of γ-position of enal **92**. The prevention of attack from γ-position may also result from the high transition-state energy for the formation of four-membered ring. The controversy was excluded by the intermolecular reaction between γ-disubstituted enal **94** and nitroolefin **7** via dienamine catalysis (Scheme 1.32).[52] Furthermore, dienamine-activated selective α-alkylation of enals was also developed.[53]

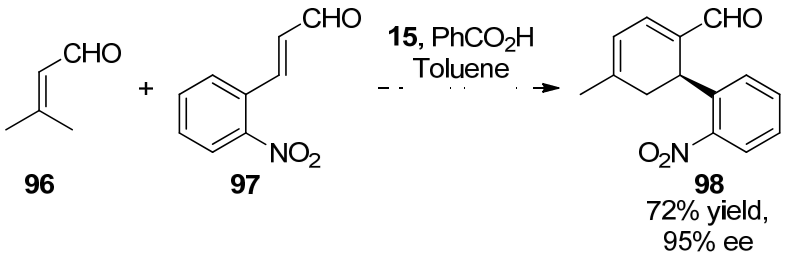
Scheme 1.32 Intermolecular Michael reaction via dienamine catalysis



1.1.4.3 Diels–Alder Reactions

It is soon realized that the dienamines produced from enals can also be applied as dienes for Diels–Alder reactions through similar strategy as dienamines formed from branched enones as discussed previously. Hong and co-workers reported that Diels–Alder reaction between 3-methylbut-2-enal **96** and α,β-unsaturated aldehyde **97** can be achieved to afford [4+2] adduct **98** in 72% yield and 95% ee (Scheme 1.33).[54]

Scheme 1.33 Diels–Alder reaction via dienamine catalysis



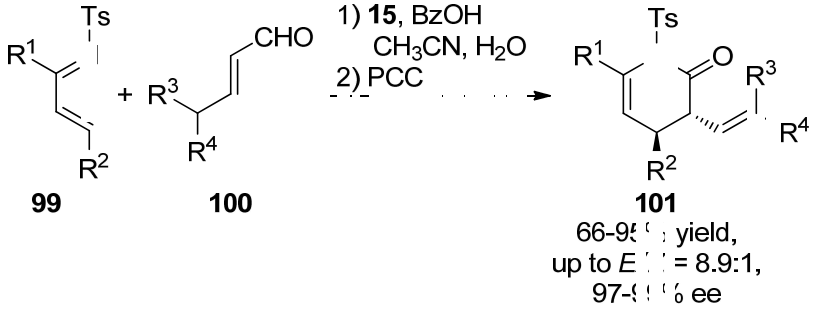
Intramolecular Diels–Alder reactions between dienamine unit and α,β-unsaturated aldehyde unit were also investigated to prepare bicyclic structures.[55] In addition, reactive quinones were utilized as dienophiles in the Diels–Alder reactions with dienamines.[56]

1.1.4.4 Inverse-Electron-Demanding Diels–Alder Reactions

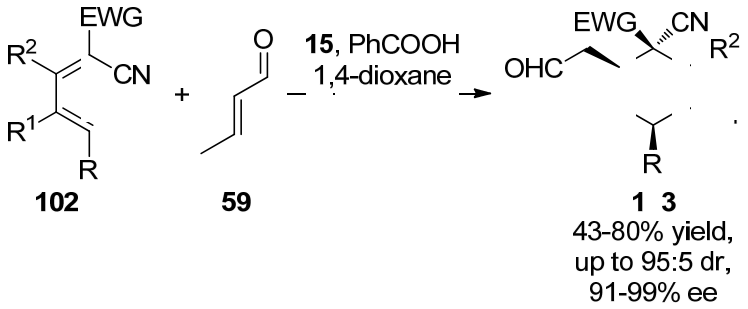
Electron-rich dienamine can also be employed as dienophiles in inverse-electron-demanding Diels–Alder reactions when it is exposed to suitable electron-deficient dienes.

Chen and co-workers found that inverse-electron-demanding aza-Diels–Alder reactions of electron-deficient *N*-sulfonyl 1-aza-1,3-butadienes with aliphatic α,β-unsaturated aldehydes proceeded smoothly with exclusive α regioselectivity. Chiral piperidine derivatives bearing several functional groups were constructed with moderate to good yields (66-95%), moderate *E/Z* ratios and excellent enantioselectivities (97-99% ee) (Scheme 1.34).[57]

Scheme 1.34 Inverse-electron-demanding aza-Diels–Alder reactions



Scheme 1.35 All-carbon-based Diels–Alder reaction



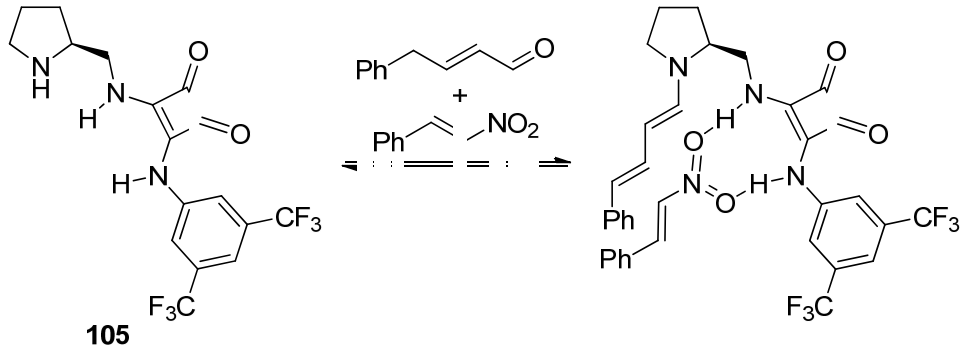
It is proposed that the regioselectivity of enals in the inverse-electron-demanding Diels–Alder reactions can be inverted by employing γ-unsubstituted crotonaldehyde. Indeed, β,γ-selectivity was observed when the strategy was extended to all-carbon-based asymmetric inverse-electron-demand Diels–Alder reactions with crotonaldehyde.

Cyclohexene derivatives with substantial substitution diversity were obtained with high diastereo- and enantioselectivities (up to 99% ee, d.r. up to 95:5) (Scheme 1.35).[58]

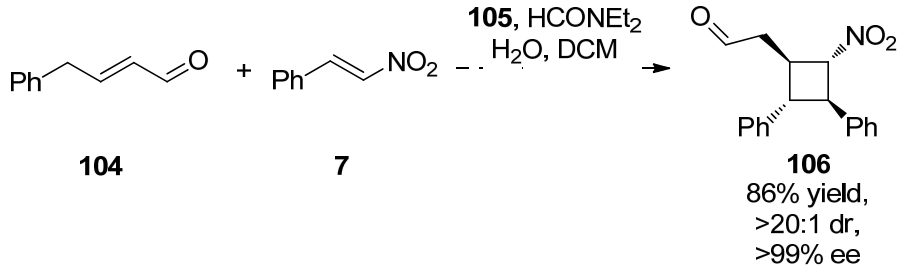
1.1.4.5 [2+2] Reactions

It was conceived that β,γ-selectivity can also be achieved with γ-substituted enals by utilizing appropriate bifunctional catalyst in dienamine catalysis.[59] Bifunctional catalyst **105** activates enal with secondary amine unit and nitroolefin **7** with H-bonding unit simultaneously. It is believed that the substrates are positioned within a suitable distance for β,γ-selectivity from the computational studies (Scheme 1.36).

Scheme 1.36 Association of enal and nitroolefin with catalyst **105**

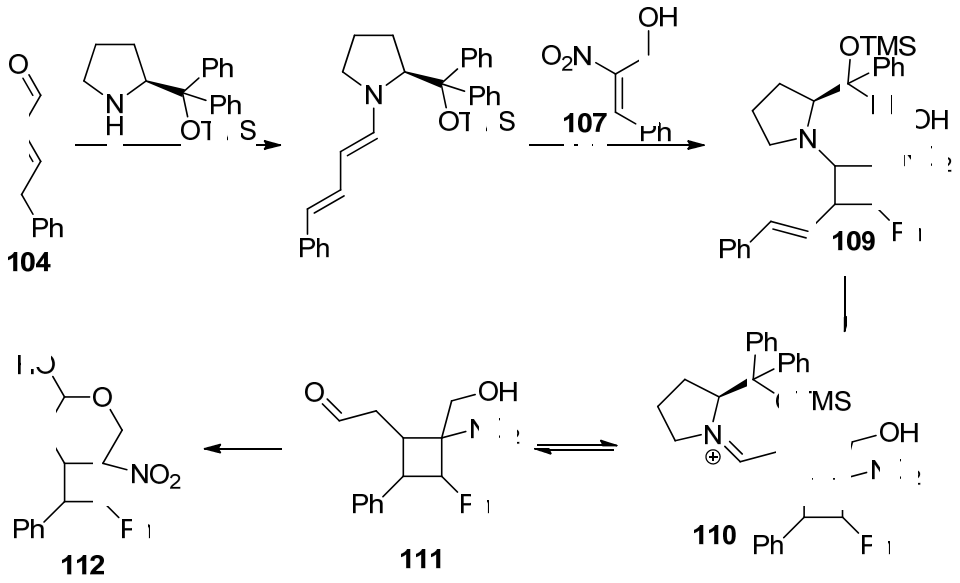


Scheme 1.37 [2+2] cycloaddition reaction via dienamine catalysis



The desired [2+2] cycloaddition product **106** was obtained in 86% yield, >20:1 dr and >99% ee (Scheme 1.37). It is noteworthy that $HCONEt_2$ was added to improve the solubility of the catalyst and H_2O was added to accelerate the reaction.

Scheme 1.38 Design of **15**-catalyzed [2+2] cycloaddition reaction



An alternative strategy for the β,γ-selectivity with simple secondary amine catalysts was also developed by favorable formation of hemiacetals to stabilize the desired [2+2] adducts (Scheme 1.38).[60] Special α-branched nitroolefin **107** was utilized to produce intermediates **109** and **110** resulting from α- and β,γ-selectivity respectively. It is assumed that intermediate **109** will be transformed to **110** for the formation of stable hemiacetal **112**. The cycloadduct **112** was obtained in 86% yield and 91% ee as expected under dienamine with catalyst **15** and H-bonding catalysis with **108** (Scheme 1.39).

Scheme 1.39 [2+2] Cycloaddition reaction of α-branched nitroolefin

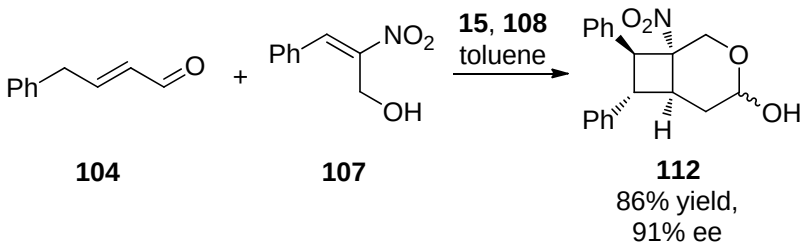
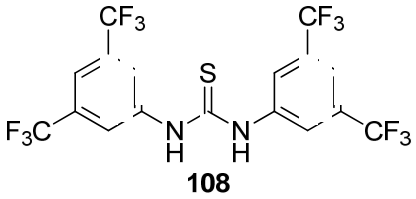


Figure 1.8 Catalyst **108**

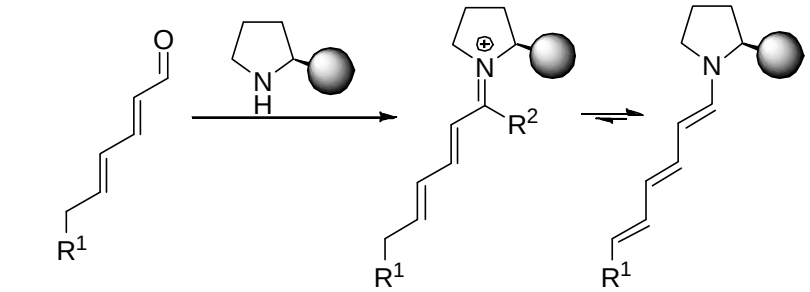


108

1.1.5 Trienamine Catalysis

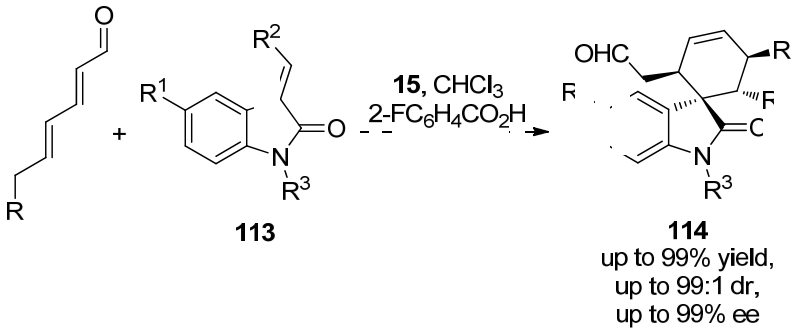
Naturally, extension of the enals in the dienamine catalysis to 2,4-hexadienals will provide an access to trienamines which can be used as reactive dienes for Diels–Alder reactions (Scheme 1.40).

Scheme 1.40 Dienamine formation from enals



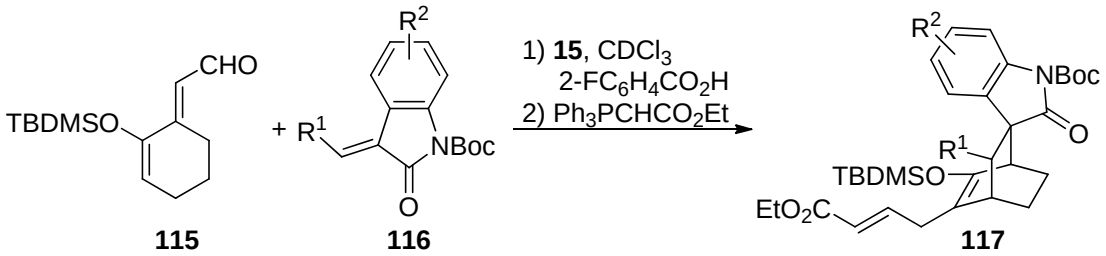
Chen and Jøgensen applied the strategy to the reaction with nitroolefins,[61] (*Z*)-olefinic azlactones,[62] 3-olefinic oxindoles,[63] olefinic cyanoacetates.[63] Spirocyclic products **114** can be prepared from the Diels–Alder reactions of trienamines and 3-olefinic oxindoles in excellent results (Scheme 1.41).[63] Indole-2,3-quinodimethane strategy was also applied in the Diels–Alder reactions via trienamine catalysis.[64] Besides, it was found that trienamine could also be prepared from 2,4-dienones.[65]

Scheme 1.41 Diels–Alder reactions of 3-olefinic oxindole



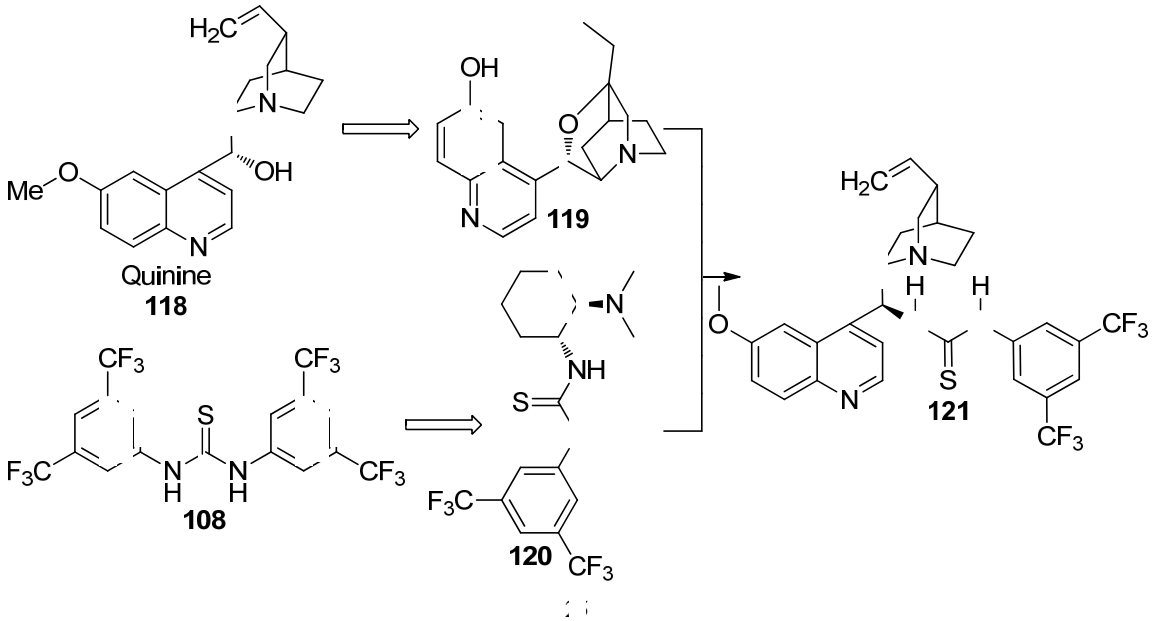
More importantly, reactions of cross-trienamines and 3-olefinic oxindoles for the formation bridged bicyclic adducts **117** were also introduced (Scheme 1.42).[66]

Scheme 1.42 Diels–Alder reactions of cross-trienamines



1.2 Chiral Thiourea Catalysis

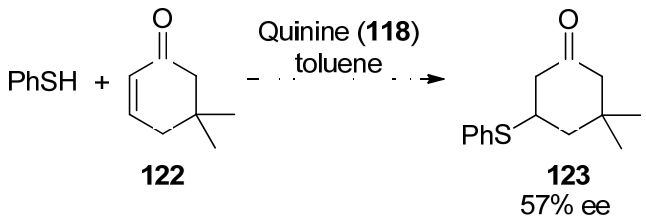
Scheme 1.43 Development of chiral thiourea catalysts



Chiral thiourea catalysts, especially cinchona alkaloid-derived thiourea catalysts have been widely utilized to mediate various transformations to furnish optically active building blocks. It has been proved that cost effective cinchona alkaloid-derived thiourea catalysts are efficient bifunctional catalysts for a number classes of reactions. The development of the catalysts can be traced back to 30 years ago (Scheme 1.43).

As early as 1981, it was found that sulfa-Michael addition reaction between PhSH and enone **122** proceeded smoothly to give product **123** in 57% ee (Scheme 1.44).[67]

Scheme 1.44 Quinine promoted sulfa-Michael addition reaction



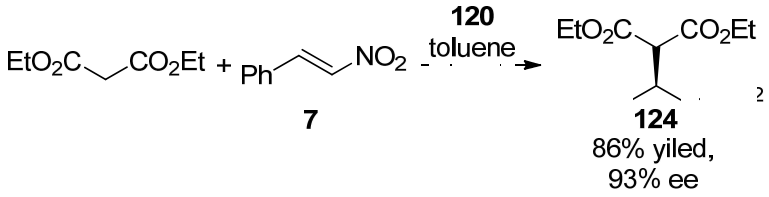
Quinine was considered to be bifunctional catalyst which activated PhSH with tertiary amine unit and enone **122** with OH group through H-bonding simultaneously. It was also assumed that the enantioselectivity could be improved by providing bifunctional catalyst with more basic unit and stronger H-bonding donating ability.

It is well known that OH group on aromatic ring is more acidic than corresponding secondary alcohols. Thus, the phenolic OH group can be acted as stronger H-bonding donor. A novel bifunctional catalyst **119** was prepared by 6′-demethylation of cinchona alkaloid-derivative. Excellent enentioselectivities were observed in **119**-mediated asymmetric Baylis-Hillman reactions.[68]

Thiourea **108** was identified as efficient H-bonding donor in Diels–Alder reactions.[69] Therefore, 3,5-$(CF_3)_2$-C_6H_3 attached thiourea unit was connected to chiral

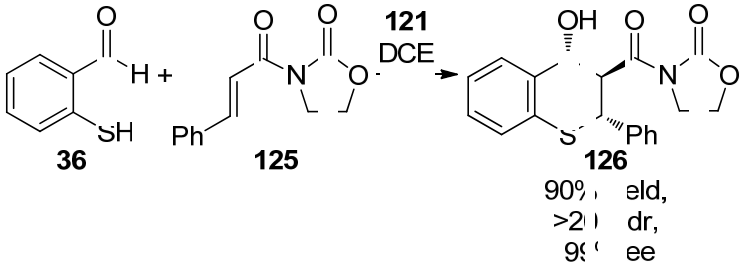
scaffold soon afterwards. In 2003, chiral thiourea catalyst **120** was first employed as functional catalyst for Michael addition reaction between diethyl malonate and nitroolefin **7** to produce adduct **124** in 86% yield and 93% ee (Scheme 1.45).[70]

Scheme 1.45 Chiral thiourea **120** catalyzed Michael addition reaction



Superior cinchona alkaloid-derived thiourea catalysts bearing more basic unit and rigid conformation were also developed in 2005.[71] The inexpensive catalysts have been proved to be efficient in numerous kinds of reactions. It is worth noting that chiral thiourea catalyst **121** was employed in the cascade reaction between 2-mercaptobenzaldehyde **36** and α,β-unsaturated oxazolidinone **125** to give cyclic product **126** with excellent results (Scheme 1.46).[72]

Scheme 1.46 Chiral thiourea **121** catalyzed Michael-aldol reactions



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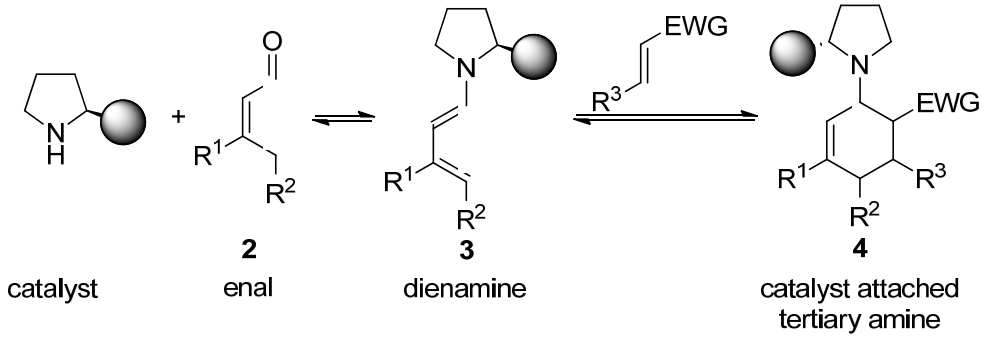
Chapter 2

Enantioselective Decarboxylative Diels–Alder reactions

2.1 Background

While impressive progress has been made in the Diels–Alder reactions employing dienamines as dienes as discussed in Chapter 1, the scope of the strategy is still limited. In these processes, it has to realy on utilizing reactive dienophiles bearing α-proton and strong withdrawing groups to achieve the goal of catalyst regeneration. Otherwise, Diels–Alder reaction between dienamine **3** and dienophile can only provide catalyst 'trapped' tertiary amine intermediate **4** (Scheme 2.1). Intermediate **4** may decompose to produce enal **2** through a retro-Diels–Alder sequence or be separated as a stable compound.

Scheme 2.1 Challenge in Diels–Alder reaction via dienamine catalysis



Rawal and co-workers applied secondary amine tethered diene **5** to hetero-Diels–Alder reactions with aldehydes **6**.[1] Although the secondary amine could be removed by the addition of acetal chloride, one equivalent of secondary amine was still needed (Scheme 2.2).

Scheme 2.2 Hetero-Diels–Alder reaction of dienamine

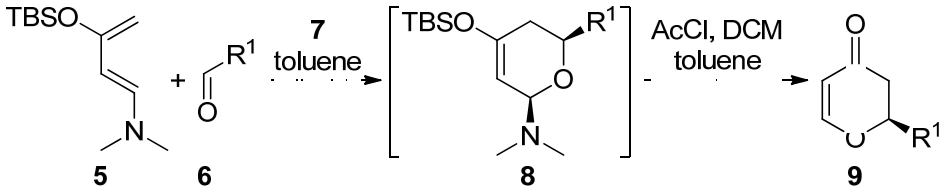
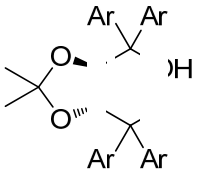
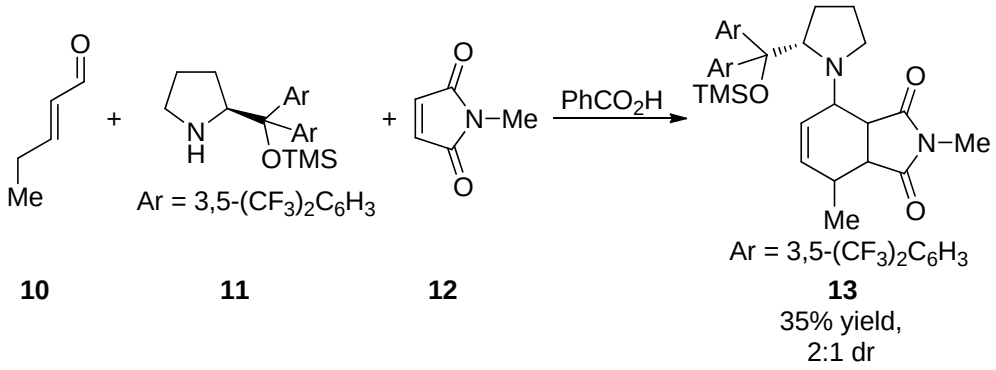


Figure 2.1 Catalyst **7**



Jørgensen and co-workers separated the catalyst attached Diels–Alder intermediate **13** in 35% yield with 2:1 dr in 2006 (Scheme 2.3).[2] It was found that elimination of the catalyst **11** from the tertiary amine was difficult.

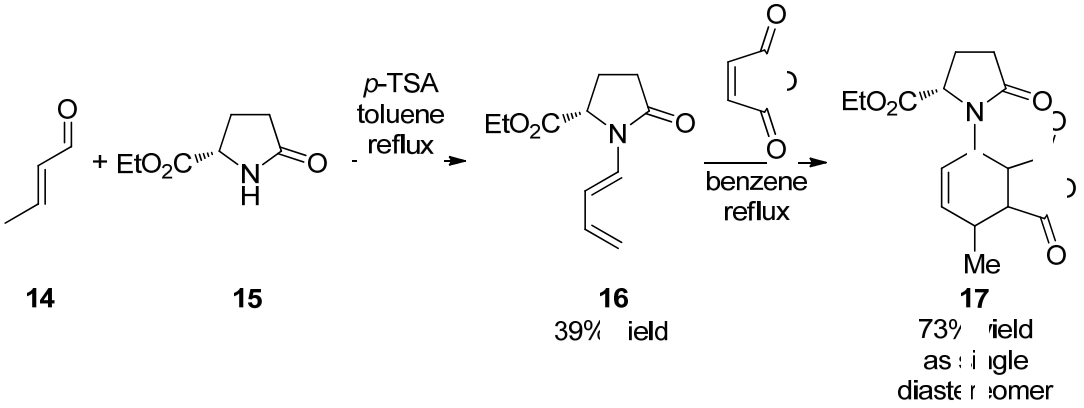
Scheme 2.3 Preparetion of intermediate **13**



Formation of catalyst attached Diels–Alder intermediate was confirmed by Beller and co-workers in the asymmetric Diels–Alder reaction between chiral *N*-dienyl lactam **16** and maleic anhydride to give chiral lactam attached product **17** in 73% yield (Scheme 2.4).[3] Besides, reactive dienophiles are necessary in the Diels–Alder reactions with dienamines. For example, control experiment of employing coumarin as dienophile in the

Diels–Alder reactions with dienamines was unsuccessful. Thus, the scope of Diels–Alder reactions via dienamine catalysis is rather limited.

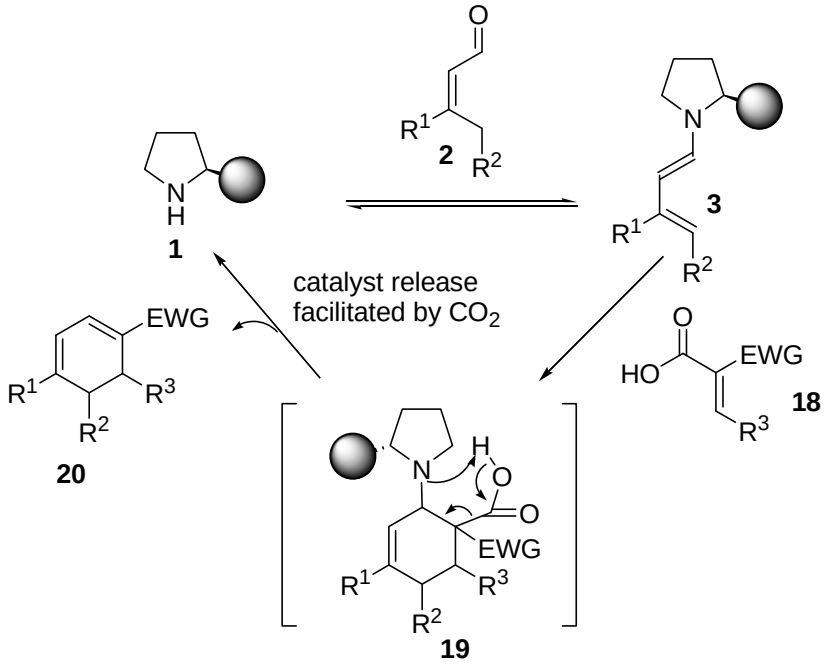
Scheme 2.4 Diels–Alder reaction of chiral *N*-dienyl lactam



2.2 Research Design

In view of the challenges, a novel catalytic enantioselective Diels–Alder reaction of readily available coumarin-3-carboxylic acids with aldehydes is designed (Scheme 2.5).[4] The carboxylic moiety not only enhances the reactivitity of coumarins as dienophiles, but also facilitates the release of the amine catalyst.[5] Different from the reported studies in aminocatalytic Diels–Alder reactions where the dienophiles contain prerequisite α-hydrogen, essential for the release of the amine catalyst,[6] a novel catalyst release mode via a decarboxylation is uncovered. Importantly, the decarboxylation assisted release of the catalyst enables the Diels–Alder reaction to proceed efficiently (short reaction times and high yields) under mild reaction conditions, and highly enantio- and diastereo-selectively.

Scheme 2.5 Design of decarboxylative Diels–Alder reactions

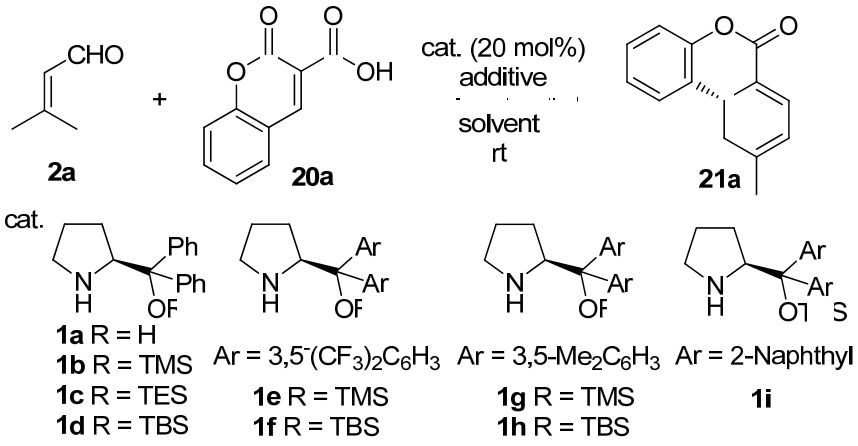


Diels–Alder reactions between *in-situ* formed dienamine **3** and various dienophiles lead to catalyst attached tertiary amine adducts. Regeneration of the catalyst is prevented due to the difficulty in eliminating the catalyst from tertiary amine structure. Although the release of catalyst was realized by employing special dienophiles bearing strong electron-withdrawn group and *α*-proton, the efficiency of the reaction was generally low. We envisioned that the release of the catalyst can be facilitated by utilizing dienophile **18** bearing *α*-carboxylic acid group (Scheme 2.5). Elimination of the catalyst from tertiary amine **19** could be facilitated by decarboxylation. In addition, substrate scope of the reaction can be expanded greatly by using temporarily activated weak dienophiles.

2.3 Optimization of Reaction Conditions

Diels–Alder reaction of 3-methyl-2-butenal **2a** with coumarin-3-carboxylic acid **20a** was selected as the model reaction (Table 2.1).

Table 2.1 Optimization of Reaction Conditions.[a]



Entry	Cat.	Additive	Solvent	t (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	none	DCE	10	81	19
2	**1b**	none	DCE	0.5	97	54
3	**1c**	none	DCE	0.5	94	74
4	**1d**	none	DCE	1	95	81
5	**1e**	none	DCE	2/3	92	10
6	**1f**	none	DCE	3	87	0
7	**1g**	none	DCE	3	94	61
8	**1h**	none	DCE	10	85	89
9	**1i**	none	DCE	10	96	92
10	**1i**	none	toluene	4	94	39
11[d]	**1i**	none	TME	4	90	29
12	**1i**	none	THF	4	91	40
13	**1i**	none	EtOAc	4	85	54
14	**1i**	none	CH_3CN	4	81	69
15	**1i**	none	DMSO	6	80	76
16	**1i**	none	CH_2Cl_2	7	97	88
17	**1i**	none	$CHCl_3$	7	95	94
18	**1i**	none	MeOH	7	79	87
19	**1i**	$PhCO_2H$	$CHCl_3$	10	91	91
20	**1i**	AcOH	$CHCl_3$	10	90	90
21	**1i**	DIPEA	$CHCl_3$	10	81	86
22	**1i**	2,6-lutidine	$CHCl_3$	10	83	91
23[e]	**1i**	none	$CHCl_3$	24	89	92

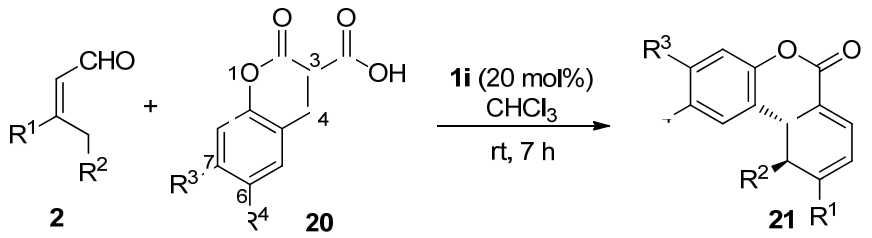
[a] Conditions: unless specified, see Experimental Section. [b] Isolated yields. [c] Determined by chiral HPLC. [d] TME = *tert*-butyl methyl ether [e] 0 °C.

The model reaction between 3-methyl-2-butenal **2a** and coumarin-3-carboxylic acid **20a** in the presence of chiral amine **1a** in dichloroethane (DCE) at rt was carried out. To our delight, the process took place regioselectively to give the desired product **21a** in 81% yield but with poor enantioselectivity (entry 1). The catalyst was facilely released via the designed decarboxylation and a quick process (10 h) was observed. Encouraged by the outcomes, we screened more chiral amine promoters (Table 1). It was found that the catalyst played significant roles in governing reaction efficiency and enantioselectivity. The TMS catalyst **1b**[10] was more efficient for promoting the Diels–Alder reaction by affording 97% yield of **21a** in just 30 min with 54% ee (entry 2). More bulky diarylprolinol silyl catalysts (e.g., **1c**: TES and **1d**: TBS, entries 3-4) further enhanced the enantioselectivity of the product formed. Nonetheless, we were surprised to find that ee values of **21a** decreased dramatically when more hindered catalysts **1e** and **1f** bearing CF_3 groups on the aromatic ring were employed (entries 5 and 6). We speculated that the decrease of ee values might be attributed to the strong electron-withdrawing properties of CF_3 groups. The assumption was verified by the studies of the catalysts **1g** and **1h**, where the CF_3 moiety was replaced by methyl group (entries 7 and 8). Among the catalysts probed, catalyst **1i** was proved to be the best. In this case, 96% yield of **21a** with 92% ee in 10 h was achieved (entry 9). In addition to catalysts, solvents were also critical to the enantioselectivity of the reaction. In general, non-polar solvents such as toluene, TME, and THF led to low ee values (entries 10-12), while slightly improved ones were observed with polar EtOAc, CH_3CN, DMSO and MeOH (entries 13-15 and 18). Chlorinated solvents CH_2Cl_2 and $CHCl_3$ were good choice for the reaction (entries

16 and 17). Acidic or basic additives were detrimental (entries 19-22). Finally, no benefit was gained when the reaction was conducted at a decreased temperature (entry 23).

2.4 Expansion of Substrate Scope

Table 2.2 Scope of **IX** Catalyzed Diels–Alder Reactions.[a]



Entry	R^1, R^2	R^3, R^4	**21**	Yield (%)[b]	ee (%)[c]
1	Me, H	H, H	**21a**	95	94
2	Me, H	Me, H	**21b**	97	92
3	Me, H	H, Me	**21c**	93	90
4	Me, H	MeO, H	**21d**	89	94
5	Me, H	Br, H	**21e**	97	90
6	Me, H	H, Br	**21f**	94	93
7	Me, H	H, NO_2	**21g**	92	91
8	H, H	MeO, H	**21h**	85	92
9	Ph, H	H, H	**21i**	91	94
10	Ph, H	Br, H	**21j**	89	92
11	3-MeC_6H_4, H	Br, H	**21k**	93	92
12	4-MeC_6H_4, H	Br, H	**21l**	91	90
13	4-FC_6H_4, H	Me, H	**21m**	87	92
14	3-BrC_6H_4, H	Br, H	**21n**	83	92
15	3,4-$Cl_2C_6H_3$, H	Br, H	**21o**	88	94
16[d]	H, Me	Br, H	**21p**	81	90
17[e]	H, Me	H, NO_2	**21q**	91	92
18[f]	H, Et	H, NO_2	**21r**	89	90
19[g]	H, Pr	H, NO_2	**21s**	90	94

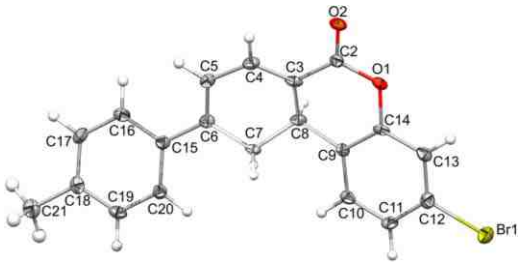
[a] Conditions: unless specified, see Experimental Section. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 15 h, 15:1 dr (determined by ^{1}H NMR of crude product). [e] 15 h, 14:1 dr. [f] 15 h, 21:1 dr. [g] 15 h, 13:1 dr.

With the optimized reaction conditions in hand for this **1i**-catalyzed Diels–Alder reaction, we probed its scope (Table 2.2). The results reveal that the process can be applied for both substrates with a broad generality. Uniformly high yields (81-95%) and high ee (90-94%) are obtained for all cases studied.

Investigation of the structural effect of courmarin-3-carboxylic acids **20** indicates that the electronic effect is very limited. The aromatic ring bearing electron-neutral (entries 1 and 9), -donating (entries 2-4, 8, and 13), -withdrawing (entries 5-7, 10-12 and 14-19) groups with different substitution patterns are well tolerated in the reaction and lead to structurally diverse compounds **21**. With respect to enals **2**, significant structural variations are explored. It appears that in addition to 3-methyl-2-butenal **2a** (entries 1-7), linear aldehydes (entries 8 and 16-19) and branched β,β'-disubstituted aldehydes (entries 9-15) can serve as effective dienes in the Diels–Alder reactions. In case of linear enals (entries 16-19), two new stereogenetic centers are formed with high enantio- and diastereoselectivities.

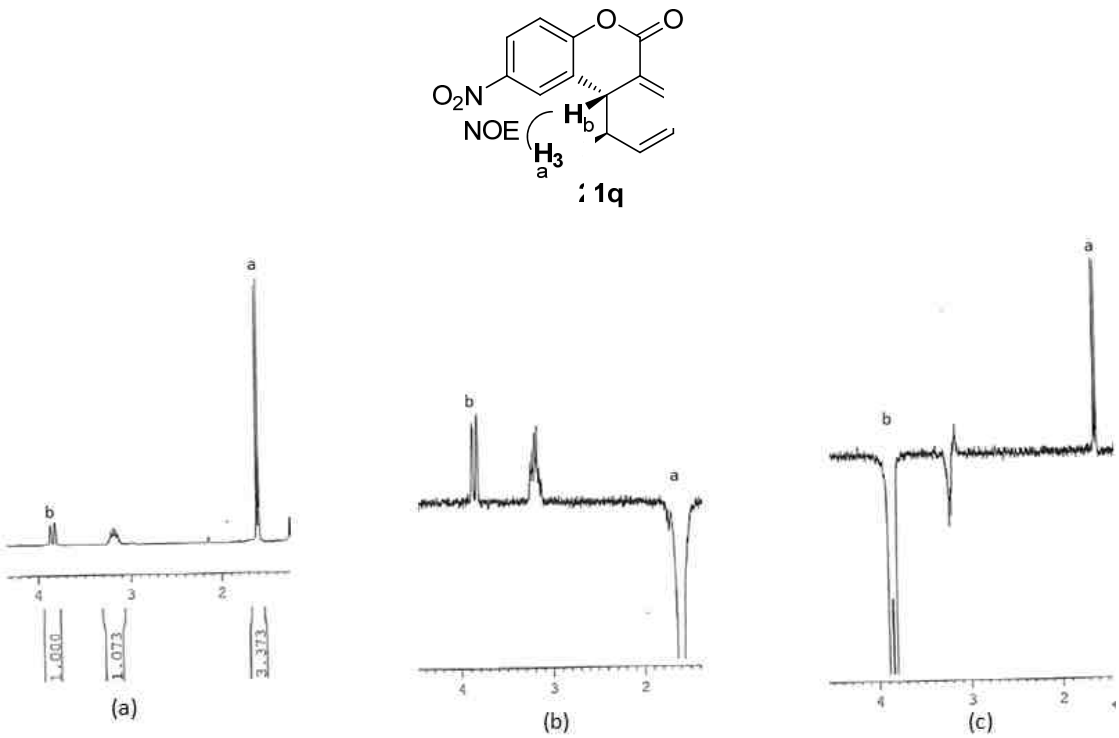
The absolute configuration of **21l** was determined by X-ray crystallographic analysis (Figure 2.2).

Figure 2.2 X-Ray Structure of **21l**



The relative stereochemistry of compound **21q** with *trans* geometry is determined by 1D shaped pulses NOE experiments (Figure 2.3). Irradiation of the methyl group protons leads to the appearance and inversion of the peaks of H proton at 3.85 ppm. Similarly, the peaks of protons on the methyl group appear and are inverted when the H at 3.85 ppm was irradiated. The relative configurations of **21q**, **21r** and **21s** are determined analogously.

Figure 2.3 Determination of relative stereochemistry of **21q**

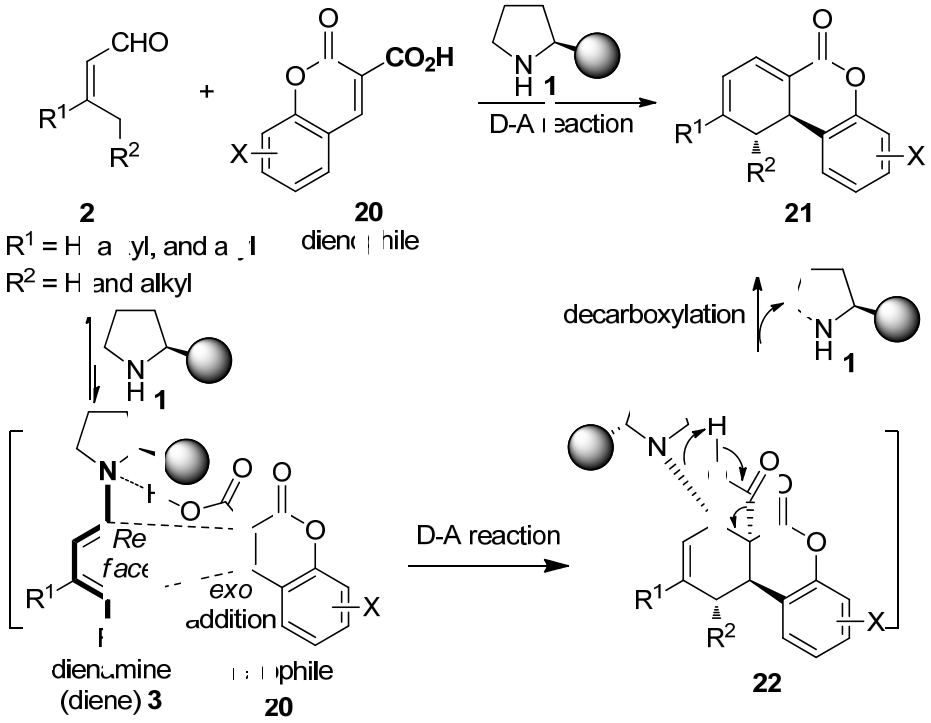


2.5 Discussion

The proposed configuration in 22 originates from *Re* face attack of the dienamine 3 by coumarin 3-carboxylic acids 20 in an *exo*-manner (Scheme 2.6). This is because the *Si* face blocked by the bulky side chain of the catalyst and the interaction between "*N*" atom of the catalyst and the carboxylic acid moiety in 20 dictates an *exo*-addition of the

dienophile.[6e] Furthermore, the steric hindrance between the bulky side chain of the catalyst and the lactone moiety in 22 leads to the *cis* configuration of the catalyst and the carboxylic acid. This geometry enables the facile decarboxylation to release the catalyst and products 21 with the observed configuration. In addition, the carboxylic acid enhances the reactivity of the coumarins as dienophiles. Indeed, without it, no desired Diels–Alder adduct was observed between coumarin and **2a** under the identical reaction conditions. In a controlled study, the carboxylic acid is masked as an ethyl ester, the Diels–Alder reaction with **2a** in the presence of 100 mol% catalyst **1i** occurred, but afforded a catalyst 'entrapped' product in 53% yield based on ^{1}H NMR analysis. However, the product was decomposed on silica gel column during purification to give back to coumarin-3-carboxylate ethyl ester starting material via a *retro*-Diels–Alder process.

Scheme 2.6 Process for Diels–Alder reactions



Conclusion

A novel amine catalyzed decarboxylative enantioselective Diels–Alder reaction between aldehydes and readily available coumarin-3-carboxylic acids as dienophiles has been implemented to construct the chiral precursors. The decarboxylation facilitates the release of the catalyst and achieves high reaction efficiency in terms of reaction time, yield and enantio- and diastereo-selectivity.

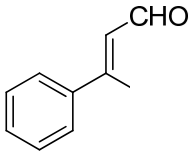
Experimental Section

General Information (This part is applied to all the sections)

Commercially available reagents were used as received without further purification unless otherwise specified. Merck 60 silica gel was used for column chromatography, and Whatman silica gel plates with fluorescence F254 were used for thin-layer chromatography (TLC) analysis. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 500 or 300. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double double doublet, td = triple doublet, dt = double triplet, m = multiplet, bs = broad signal). Data for ^{13}C NMR are reported as ppm. Catalysts **1a**, **1e** and **1g** were purchased from Sigma Aldrich. Catalysts **1b**,[7] **1c**,[7] **1d**,[8] **1f**,[8] **1h**[8] and **1i**[8] were prepared according to the literature procedures. Substrates **2a**, **2b**, **2i**, **2j**, **2k** and **20a** were purchased from Sigma Aldrich.

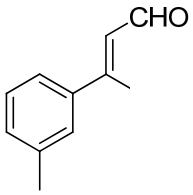
Preparation and Spectroscopic Data for Substrates 2c-2h

Substrates **2c**-**2h** were prepared according to literature procedure.[9]



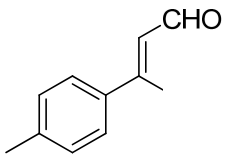
(*E*)-3-Phenylbut-2-enal (2c)

The title compound was obtained in 73% yield for three steps as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.18 (d, *J* = 7.8 Hz, 1H), 7.56-7.51 (m, 2H), 7.44-7.40 (m, 3H), 6.39 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 2.57 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 191.2, 157.6, 140.5, 130.0, 128.7, 127.2, 126.2, 16.3.



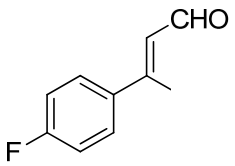
(*E*)-3-(*m*-Tolyl)but-2-enal (2d)

The title compound was obtained in 65% yield for three steps as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.17 (d, *J* = 7.8 Hz, 1H), 7.35-7.24 (m, 4H), 6.38 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 2.56 (d, *J* = 1.2 Hz, 3H), 2.39 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 191.3, 157.9, 140.5, 138.4, 130.8, 128.6, 127.1, 126.9, 123.4, 21.4, 16.4.



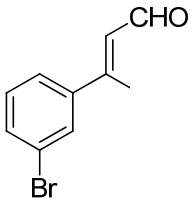
(*E*)-3-(*p*-Tolyl)but-2-enal (2e)

The title compound was obtained in 61% yield for three steps as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 10.16 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.39 (d, *J* = 8.0 Hz, 1H), 2.54 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 191.2, 157.5, 140.5, 137.4, 129.4, 126.4, 126.1, 21.2, 16.1.



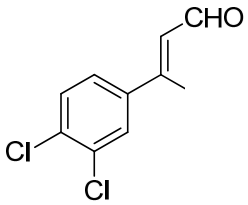
(*E*)-3-(4-Fluorophenyl)but-2-enal (2f)

The title compound was obtained in 52% yield for three steps as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.16 (d, *J* = 7.8 Hz, 1H), 7.57-7.52 (m, 2H), 7.13-7.08 (m, 2H), 6.35 (dd, *J* = 7.8 Hz, 0.9 Hz, 1H), 2.56 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 191.1, 156.3, 128.2, 128.1, 127.0, 115.9, 115.6, 16.3.



(*E*)-3-(3-Bromophenyl)but-2-enal (2g)

The title compound was obtained in 47% yield for three steps as yellow solid. M. P. 70-71 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.17 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 1.5 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 6.35 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 190.9, 155.7, 142.7, 132.8, 130.2, 129.3, 127.9, 124.8, 122.9, 16.4.



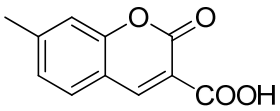
(*E*)-3-(3,4-Dichlorophenyl)but-2-enal (2h)

The title compound was obtained in 58% yield for three steps as yellow solid. M. P. 65-66 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.17 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 2.1

Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 6.35 (d, J = 7.5 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 191.7, 154.4, 140.4, 134.1, 133.1, 130.7, 128.2, 127.9, 125.4, 16.2.

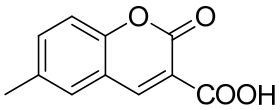
Preparation and Spectroscopic Data for Substrates 20b-20g

Substrates **20b-20g** were prepared according to literature procedure.[10]



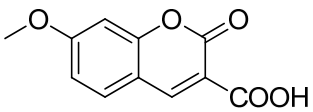
7-Methyl-2-oxo-2H-chromene-3-carboxylic acid (20b)

The title compound was obtained in 81% yield as white solid. M. P. 200-201 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.71 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.26 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 164.1, 156.9, 154.7, 148.6, 145.8, 129.9, 126.0, 116.9, 116.2, 115.6, 21.5.



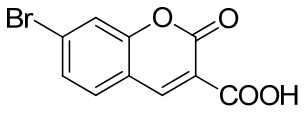
6-Methyl-2-oxo-2H-chromene-3-carboxylic acid (20c)

The title compound was obtained in 85% yield as white solid. M. P. 165-166 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.63 (s, 1H), 7.64 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 164.1, 157.0, 152.7, 148.3, 135.3, 134.2, 129.7, 118.3, 117.4, 116.0, 20.3.



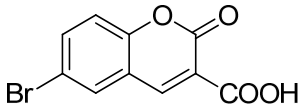
7-Methoxy-2-oxo-2H-chromene-3-carboxylic acid (20d)

The title compound was obtained in 80% yield as white solid. M. P. 193-194 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.71 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.02 (s, 1H), 6.99 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 164.7, 164.2, 157.2, 156.9, 149.1, 131.6, 113.8, 113.3, 111.6, 100.3, 56.3.



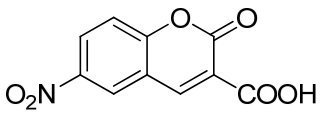
7-Bromo-2-oxo-2H-chromene-3-carboxylic acid (20e)

The title compound was obtained in 87% yield as white solid. M. P. 205-206 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.68 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 163.8, 156.0, 154.8, 147.8, 131.5, 128.0, 127.4, 119.2, 118.5, 117.3.



6-Bromo-2-oxo-2H-chromene-3-carboxylic acid (20f)

The title compound was obtained in 83% yield as white solid. M. P. 192-193 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.68 (s, 1H), 8.15 (d, J = 1.5 Hz, 1H), 7.85 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 163.8, 156.1, 153.6, 147.0, 136.4, 132.0, 119.9, 119.5, 118.5, 116.3.



6-Nitro-2-oxo-2H-chromene-3-carboxylic acid (20g)

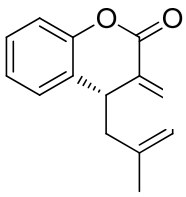
The title compound was obtained in 87% yield as light brown solid. M. P. 234-235 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.91 (d, J = 1.5 Hz, 1H), 8.89 (s, 1H), 8.49

(dd, J = 9.5 Hz, 2.0 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 163.5, 158.1, 155.4, 147.2, 143.6, 128.4, 126.0, 120.3, 118.4, 117.7.

General Procedure for Diels–Alder Reactions

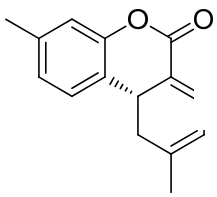
To a mixture of coumarin-3-carboxylic acid **20a** (0.023 g, 0.12 mmol) and catalyst **1i** (0.0094 g, 0.02 mmol) in 0.2 mL $CHCl_3$ was added **2a** (10 μL, 0.1 mmol). The reaction was stirred at room temperature until **2a** was consumed completely (7 h). The mixture was applied to column chromatography directly and eluted with hexane and ethyl acetate to give 0.0202 g pure product **21a** in 95% yield. The purified compound was used for characterization and chiral HPLC analysis.

Physical and Spectroscopic Data for Diels–Alder Products 21a-21s



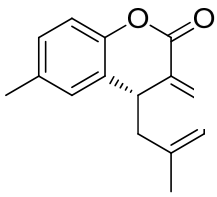
(*R*)-9-Methyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21a)

The title compound was obtained in 95% yield as white solid. M. P. 84-85 ºC; $[\alpha]_D^{25}$ = -47.0° (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39 (dd, J = 5.4 Hz, 3.6 Hz, 1H), 7.28-7.23 (m, 2H), 7.14 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.06 (dd, J = 9.6 Hz, 1.8 Hz, 1H), 6.06 (dd, J = 3.3 Hz, 1.5 Hz, 1H), 4.04 (dd, J = 17.7 Hz, 6.6 Hz, 1H), 2.80 (dd, J = 17.1 Hz, 8.7 Hz, 1H), 2.39 (dd, J = 19.2 Hz, 17.4 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.1, 150.5, 146.2, 138.8, 128.3, 126.1, 124.4, 123.3, 120.7, 118.0, 117.2, 34.4, 32.1, 23.7. The ee was determined to be 94% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.5 mL/min^{-1}, λ = 254 nm, t_r (major) = 14.61 min, t_r (minor) = 18.57 min.



(*R*)-3,9-Dimethyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21b)

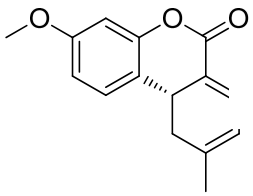
The title compound was obtained in 97% yield as white solid. M. P. 96-97 ºC; $[\alpha]_D^{25}$ = -67.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38 (dd, *J* = 5.4 Hz, 3.3 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 6.05 (dd, *J* = 3.6 Hz, 2.1 Hz, 1H), 3.99 (dd, *J* = 19.5 Hz, 7.8 Hz, 1H), 2.77 (dd, *J* = 17.1 Hz, 8.7 Hz, 1H), 2.42-2.30 (m, 4H), 2.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.4, 150.3, 146.1, 138.7, 138.6, 125.8, 125.2, 120.7, 120.2, 118.3, 117.6, 34.6, 31.9, 23.8, 21.0. The ee was determined to be 92% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 17.76 min, t_r (minor) = 61.27 min.



(*R*)-2,9-Dimethyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21c)

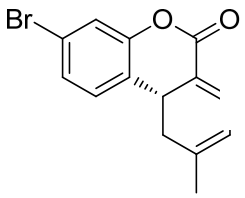
The title compound was obtained in 93% yield as white solid. M. P. 145-146 ºC; $[\alpha]_D^{25}$ = -33.1° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38 (t, *J* = 5.1 Hz, 1H), 7.05 (d, *J* = 6.6 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.06 (s, 1H), 4.00 (dd, *J* = 19.5 Hz, 7.2 Hz, 1H), 2.79 (dd, *J* = 17.1 Hz, 8.4 Hz, 1H), 2.41 (d, *J* = 19.2 Hz, 1H), 2.33 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.4, 148.4, 146.1, 138.7, 133.9, 128.9, 126.5, 122.9, 120.7, 118.3, 117.0, 34.5, 32.2, 23.8, 20.8. The ee was

determined to be 90% by HPLC on Daicel Chiralpak IC (25 cm), Hexanes / IPA = 85 / 15, 0.5 mL/min^{-1}, λ = 254 nm, t_r (major) = 52.80 min, t_r (minor) = 61.38 min.



(*R*)-3-Methoxy-9-methyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21d)

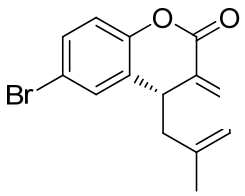
The title compound was obtained in 89% yield as colorless oil. $[\alpha]_D^{25}$ = -67.9° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38 (dd, *J* = 5.4 Hz, 3.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 8.7 Hz, 2.7 Hz, 1H), 6.61 (d, *J* = 2.7 Hz, 1H), 6.05 (dd, *J* = 3.3 Hz, 1.8 Hz, 1H), 3.97 (dd, *J* = 17.1 Hz, 6.0 Hz, 1H), 3.80 (s, 3H), 2.74 (dd, *J* = 17.1 Hz, 8.7 Hz, 1H), 2.35 (dd, *J* = 19.2 Hz, 17.4 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.3, 160.0, 151.2, 146.3, 138.9, 126.7, 120.7, 118.2, 115.3, 110.9, 102.2, 55.5, 34.8, 31.7, 23.8. The ee was determined to be 94% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.2 mL/min^{-1}, λ = 254 nm, t_r (major) = 44.44 min, t_r (minor) = 126.73 min.



(*R*)-3-Bromo-9-methyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21e)

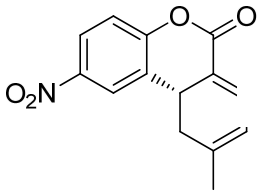
The title compound was obtained in 97% yield as white solid. M. P. 115-116 ºC; $[\alpha]_D^{25}$ = -91.9° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40 (dd, *J* = 5.7 Hz, 3.6 Hz, 1H), 7.28-7.22 (m, 2H), 7.11 (dd, *J* = 8.1 Hz, 0.9 Hz, 1H), 6.07 (dd, *J* = 3.3 Hz, 1.8 Hz, 1H), 3.98 (dd, *J* = 19.8 Hz, 6.3 Hz, 1H), 2.76 (dd, *J* = 17.1 Hz, 8.4 Hz, 1H), 2.38

(dd, J = 19.5 Hz, 17.7 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.5, 151.1, 146.4, 139.5, 127.5, 122.5, 121.1, 120.9, 120.4, 117.2, 34.4, 32.0, 23.8. The ee was determined to be 90% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 19.93 min, t_r (minor) = 34.02 min.



(*R*)-2-Bromo-9-methyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21f)

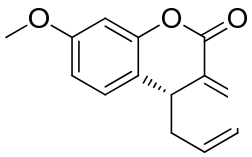
The title compound was obtained in 94% yield as white solid. M. P. 123-124 ºC; $[\alpha]_D^{25}$ = -103.2° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42-7.34 (m, 3H), 6.95 (d, J = 7.5 Hz, 1H), 6.07 (d, J = 5.1 Hz, 1H), 4.04 (dd, J = 19.8 Hz, 7.2 Hz, 1H), 2.76 (dd, J = 17.1 Hz, 8.7 Hz, 1H), 2.41 (dd, J = 19.5 Hz, 17.7 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 161.5, 149.7, 146.3, 139.4, 131.7, 129.1, 125.5, 120.8, 119.0, 117.0, 117.0, 34.4, 32.2, 23.8. The ee was determined to be 93% by HPLC on Daicel Chiralpak IC (25 cm), Hexanes / IPA = 90 / 10, 0.5 mL/min^{-1}, λ = 254 nm, t_r (major) = 119.84 min, t_r (minor) = 141.56 min.



(*R*)-9-Methyl-2-nitro-10,10a-dihydro-6H-benzo[c]chromen-6-one (21g)

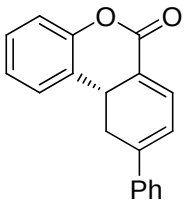
The title compound was obtained in 92% yield as white solid. M. P. 250 ºC decomposed; $[\alpha]_D^{25}$ = -46.9° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.19-8.16 (m, 2H), 7.47 (dd, J = 5.7 Hz, 3.6 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 6.13 (dd, J =

3.6 Hz, 1.8 Hz, 1H), 4.12 (dd, *J* = 18.3 Hz, 7.2 Hz, 1H), 2.91 (dd, *J* = 17.1 Hz, 8.7 Hz, 1H), 2.48 (dd, *J* = 19.5 Hz, 17.4 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 155.2, 146.9, 144.2, 140.5, 124.7, 124.4, 122.5, 121.0, 118.3, 115.8, 34.3, 32.3, 23.9. The ee was determined to be 91% by HPLC on Daicel Chiralpak IB (25 cm), Hexanes / IPA = 90 / 10, 0.3 mL/min^{-1}, λ = 254 nm, t_r (major) = 64.43 min, t_r (minor) = 72.11 min.



(*R*)-3-methoxy-10,10a-dihydro-6H-benzo[c]chromen-6-one (21h)

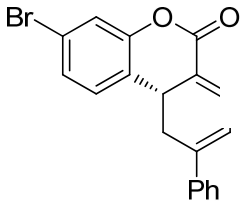
The title compound was obtained in 85% yield as yellow oil. $[\alpha]_D^{25}$ = -15.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40 (s, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.40-6.28 (m, 2H), 3.96 (dd, *J* = 20.4 Hz, 8.4 Hz, 1H), 3.80 (s, 3H), 2.99-2.88 (m, 1H), 2.31 (t, *J* = 19.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 159.6, 137.5, 134.4, 126.9, 125.1, 115.0, 111.1, 102.3, 55.5, 31.1, 28.8. The ee was determined to be 92% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 23.33 min, t_r (minor) = 39.18 min.



(*R*)-9-Phenyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21i)

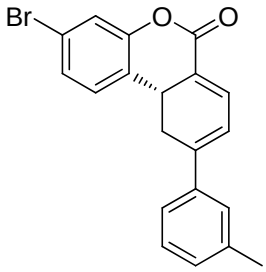
The title compound was obtained in 91% yield as yellow solid. M. P. 133-134 ºC; $[\alpha]_D^{25}$ = -309.4° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60-7.56 (m, 3H),

7.46-7.25 (m, 5H), 7.18 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.10 (dd, *J* = 8.1 Hz, 0.9 Hz, 1H), 6.67 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.18 (ddd, *J* = 20.0 Hz, 8.1 Hz, 3.0 Hz, 1H), 3.40 (dd, *J* = 16.5 Hz, 8.1 Hz, 1H), 2.87-2.74 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 161.9, 150.6, 144.9, 139.0, 138.6, 129.1, 128.8, 128.6, 126.2, 125.6, 124.6, 122.9, 121.0, 119.9, 117.4, 32.5, 31.9. The ee was determined to be 94% by HPLC on Daicel Chiralpak IB (25 cm), Hexanes / IPA = 90 / 10, 0.3 mL/min^{-1}, λ = 210 nm, t_r (major) = 40.94 min, t_r (minor) = 45.88 min.



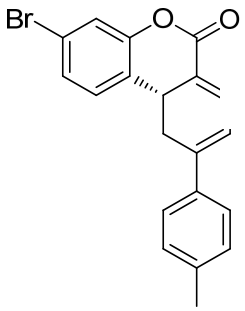
(*R*)-3-Bromo-9-phenyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21j)

The title compound was obtained in 89% yield as yellow solid. M. P. 182-183 ºC; $[\alpha]_D^{25}$ = -287.5° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.59-7.57 (m, 3H), 7.46-7.38 (m, 3H), 7.32-7.21 (m, 3H), 6.67 (dd, *J* = 6.0 Hz, 2.7 Hz, 1H), 4.11 (ddd, *J* = 20.0 Hz, 8.1 Hz, 3.3 Hz, 1H), 3.36 (dd, *J* = 16.5 Hz, 8.1 Hz, 1H), 2.85-2.72 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 161.2, 151.1, 145.1, 139.2, 138.8, 129.3, 128.8, 127.6, 125.6, 122.1, 121.3, 121.0, 120.5, 119.0, 32.3, 31.8. The ee was determined to be 92% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 25.62 min, t_r (minor) = 36.88 min.



(*R*)-3-Bromo-9-(m-tolyl)-10,10a-dihydro-6H-benzo[c]chromen-6-one (21k)

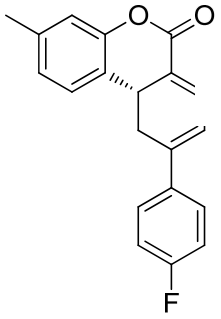
The title compound was obtained in 93% yield as yellow oil. $[\alpha]_D^{25}$ = -420.8° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.58 (dd, *J* = 6.0 Hz, 3.3 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.34-7.19 (m, 5H), 6.66 (dd, *J* = 6.0 Hz, 2.7 Hz, 1H), 4.10 (ddd, *J* = 20.0 Hz, 8.1 Hz, 3.0 Hz, 1H), 3.35 (dd, *J* = 16.8 Hz, 8.1 Hz, 1H), 2.83-2.70 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 161.2, 151.1, 145.3, 139.3, 138.8, 138.5, 130.1, 128.7, 127.6, 126.3, 122.8, 122.1, 121.3, 120.9, 120.5, 118.9, 32.4, 31.9, 21.5. The ee was determined to be 92% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 21.10 min, t_r (minor) = 28.83 min.



(*R*)-3-Bromo-9-(p-tolyl)-10,10a-dihydro-6H-benzo[c]chromen-6-one (21l)

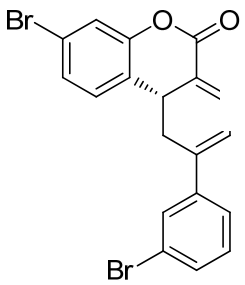
The title compound was obtained in 91% yield as yellow solid. M. P. 171-172 ºC; $[\alpha]_D^{25}$ = -370.2° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.58 (dd, *J* = 6.0 Hz, 3.3 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.32-7.21 (m, 5H), 6.65 (dd, *J* = 6.0 Hz, 2.7 Hz, 1H), 4.10 (ddd, *J* = 19.8 Hz, 8.1 Hz, 3.3 Hz, 1H), 3.36 (dd, *J* = 16.8 Hz, 8.1 Hz, 1H), 2.81-2.68 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 161.3, 151.2, 145.1, 139.6, 139.4, 135.8, 129.5, 127.6, 125.6, 122.2, 121.3, 120.5, 120.2, 118.5, 32.3, 31.7, 21.3. The ee was determined to be 90% by HPLC on Daicel Chiralpak AS-H (25

cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 23.47 min, t_r (minor) = 31.53 min.



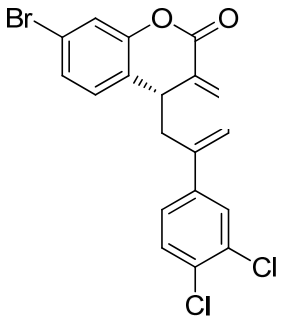
(*R*)-9-(4-Fluorophenyl)-3-methyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21m)

The title compound was obtained in 87% yield as yellow solid. M. P. 162-163 ºC; $[\alpha]_D^{25}$ = -304.7° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.59-7.54 (m, 1H), 7.26-7.21 (m, 1H), 7.12 (t, *J* = 6.6 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.92 (s, 1H), 6.61 (dd, *J* = 6.0 Hz, 2.7 Hz, 1H), 4.14 (ddd, *J* = 19.8 Hz, 7.8 Hz, 3.0 Hz, 1H), 3.33 (dd, *J* = 16.5 Hz, 8.1 Hz, 1H), 2.82-2.69 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.1, 150.4, 143.7, 138.9, 138.3, 135.2, 127.5, 127.4, 125.9, 125.4, 120.9, 120.2, 119.7, 117.8, 115.9, 115.7, 32.3, 32.1, 21.0. The ee was determined to be 92% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 28.48 min, t_r (minor) = 75.83 min.



(*R*)-3-Bromo-9-(3-bromophenyl)-10,10a-dihydro-6H-benzo[c]chromen-6-one (21n)

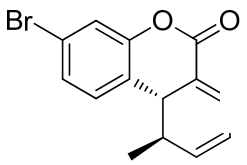
The title compound was obtained in 83% yield as yellow oil. $[\alpha]_D^{25}$ = -206.7° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69 (t, *J* = 1.8 Hz, 1H), 7.57 (dd, *J* = 6.0 Hz, 3.6 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.33-7.22 (m, 4H), 6.66 (dd, *J* = 5.7 Hz, 2.7 Hz, 1H), 4.12 (ddd, *J* = 20.0 Hz, 8.4 Hz, 3.3 Hz, 1H), 3.30 (dd, *J* = 16.8 Hz, 8.4 Hz, 1H), 2.83-2.70 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 161.0, 151.0, 143.3, 141.0, 138.6, 132.0, 130.3, 128.7, 127.7, 127.6, 124.2, 123.1, 122.0, 121.8, 121.5, 120.6, 119.9, 32.3, 31.6. The ee was determined to be 92% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 29.37 min, t_r (minor) = 39.79 min.



(*R*)-3-Bromo-9-(3,4-dichlorophenyl)-10,10a-dihydro-6H-benzo[c]chromen-6-one (21o)

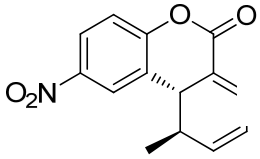
The title compound was obtained in 88% yield as yellow solid. M. P. 202-203 ºC; $[\alpha]_D^{25}$ = -284.7° (*c* = 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.64 (d, *J* = 2.0 Hz, 1H), 7.56 (dd, *J* = 5.5 Hz, 3.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.41 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.32 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.13 (ddd, *J* = 20.0 Hz, 8.0 Hz, 3.0 Hz, 1H), 2.81-2.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.9, 151.0, 142.2, 138.8, 138.4, 133.2, 133.1, 130.8, 127.8, 127.5, 124.8, 122.2, 121.6, 121.6, 120.6, 120.2, 32.3, 31.5.

The ee was determined to be 94% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (major) = 30.05 min, t_r (minor) = 40.02 min.



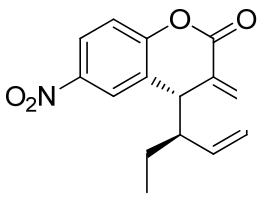
(10*R*,10a*R*)-3-Bromo-10-methyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21p)

The title compound was obtained in 81% yield as colorless oil. $[\alpha]_D^{25}$ = -199.1° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.31-7.14 (m, 4H), 6.12-5.99 (m, 2H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.12-3.00 (m, 1H), 1.51 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.9, 151.5, 139.9, 135.7, 127.5, 125.8, 124.3, 121.1, 120.6, 38.5, 33.3, 23.7. The ee was determined to be 90% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 90 / 10, 0.2 mL/min^{-1}, λ = 254 nm, t_r (minor) = 53.02 min, t_r (major) = 72.42 min.



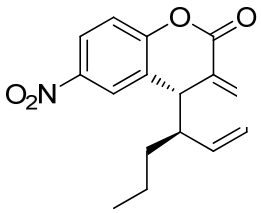
(10*R*,10a*R*)-10-Methyl-2-nitro-10,10a-dihydro-6H-benzo[c]chromen-6-one (21q)

The title compound was obtained in 91% yield as white solid. M. P. 114-115 ºC; $[\alpha]_D^{25}$ = -288.2° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.26-8.18 (m, 2H), 7.28-7.21 (m, 2H), 6.17-6.07 (m, 2H), 3.85 (d, *J* = 14.7 Hz, 1H), 3.22-3.14 (m, 1H), 1.60 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 155.6, 144.4, 140.2, 136.8, 126.6, 124.3, 121.1, 120.8, 119.2, 118.4, 38.7, 33.3, 23.7. The ee was determined to be 90% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes/IPA = 70/30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (minor) = 29.15 min, t_r (major) = 44.51 min.



(10*R*,10a*R*)-10-Ethyl-2-nitro-10,10a-dihydro-6H-benzo[c]chromen-6-one (21r)

The title compound was obtained in 89% yield as light yellow oil. $[\alpha]_D^{25}$ = -409.7° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.21-8.15 (m, 2H), 7.27-7.19 (m, 2H), 6.22-6.13 (m, 2H), 3.92 (dd, *J* = 13.2 Hz, 1.8 Hz, 1H), 3.14-3.06 (m, 1H), 2.04-1.76 (m, 2H), 1.19 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.2, 155.6, 144.4, 137.7, 136.2, 127.4, 124.2, 121.4, 120.5, 119.3, 118.3, 38.9, 36.0, 29.9, 10.7. The ee was determined to be 90% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes/IPA = 70/30, 0.4 mL/min^{-1}, λ = 254 nm, t_r (minor) = 26.37 min, t_r (major) = 38.99 min.



(10*R*,10a*R*)-2-Nitro-10-propyl-10,10a-dihydro-6H-benzo[c]chromen-6-one (21s)

The title compound was obtained in 90% yield as light yellow solid. M. P. 86-87 ºC; $[\alpha]_D^{25}$ = -464.7° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.21-8.18 (m, 2H), 7.27-7.19 (m, 2H), 6.22-6.11 (m, 2H), 3.91 (dd, *J* = 13.8 Hz, 1.8 Hz, 1H), 3.17-3.11 (m, 1H), 1.90-1.74 (m, 2H), 1.71-1.55 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.2, 155.6, 144.4, 138.0, 136.2, 127.4, 124.2, 121.1, 120.5, 119.4, 118.3, 39.4, 37.4, 36.4, 19.6, 14.2. The ee was determined to be 94% by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 90 / 10, 0.2 mL/min^{-1}, λ = 254 nm, t_r (minor) = 83.68 min, t_r (major) = 107.78 min.

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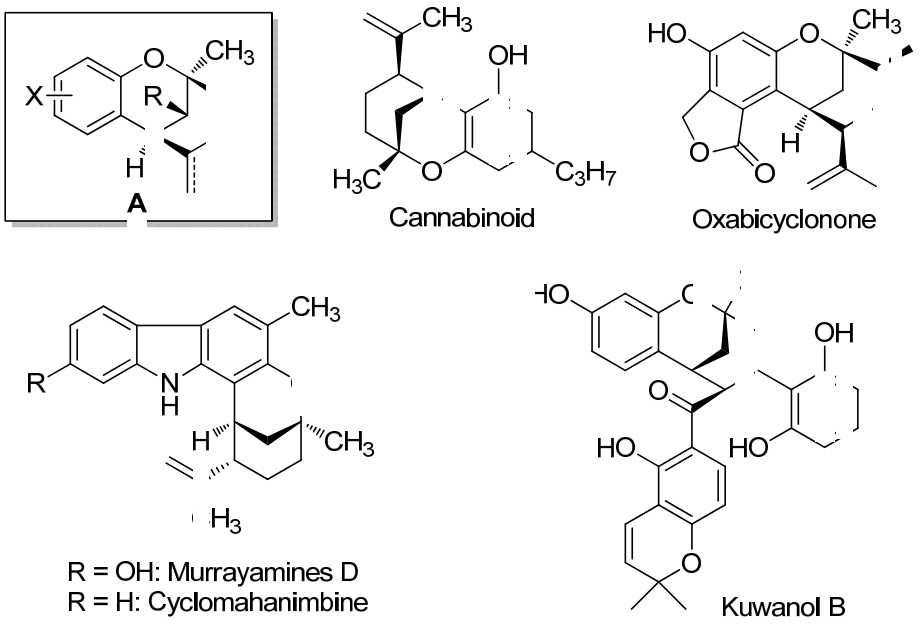
Chapter 3

Construction of Chiral Bridged Tricyclic Benzopyrans

3.1 Background

The discovery of powerful simplifying transformations for rapid access to the core structures featured in natural products is a central goal of organic synthesis. The bridged tricyclic benzopyran framework **A** is present in a fascinating array of structurally diverse, biologically intriguing complex natural products, such as cannabinoid,[1] oxabicyclononane, murrayamines D and cyclomahanimbine,[2] and kuwanol B (Figure 1),[3] sanggenone R,[4a] mulberrofurans I and S and sorocenol B,[4b] and saustralisin B,[4c] mongolicin C,[4d] and isorubraine, etc.[4e]

Figure 3.1 Bridged tricyclic benzopyran core unit **A** in natural products

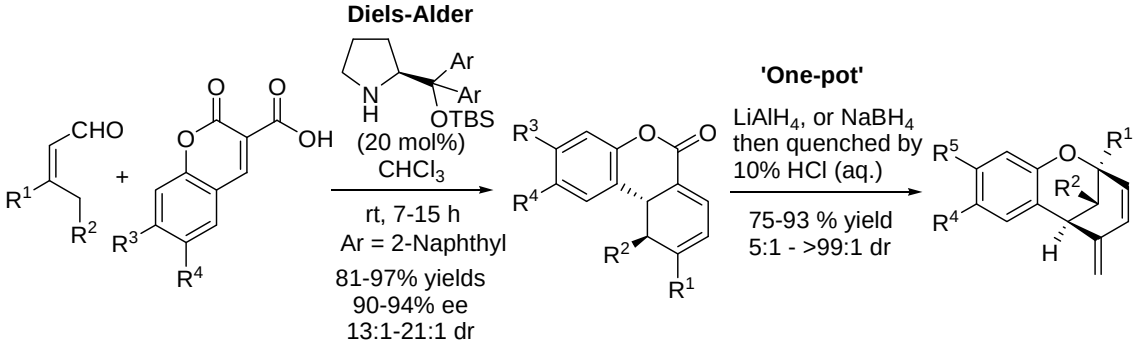


The construction of the bridged scaffold requires installing two contiguous chiral centers including one quaternary center. Typically, this substructure is built through acid catalyzed cyclizations of phenolic alkene precursors.[5] However, asymmetric synthesis of the scaffolds remains elusive. To the best of our knowledge, only a single study was reported by Yao and coworkers using a binary $Pd(OAc)_2$ and (*S*)-Trip system catalyzed an enantioselective cascade annulation process between 2-hydroxystyrenes and 2-alkynylbenaldehyes or 1-(2-alkynylphenyl)ketones.[6] To streamline substantial advances in this arena, new catalytic asymmetric methodologies using simple substances are more appealing.

3.2 Research Design

An efficient 2-step access to the chiral complex molecular architecture **A** was investigated (Scheme 3.1). Enantioselective decarboxylative Diels–Alder reaction and a 'one-pot' reduction-acid catalyzed stereoselective cyclization proceeded smoothly to furnish the desired structure.

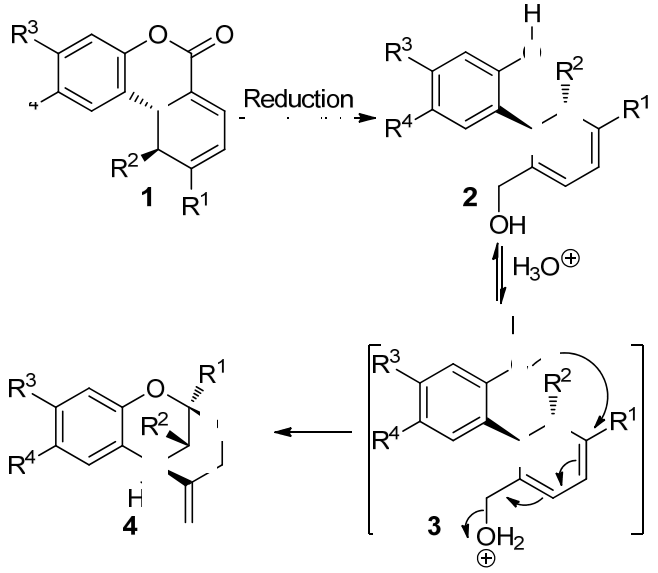
Scheme 3.1 Two-step synthesis of bridged tricyclic benzopyran



As a useful application of the asymmetric decarboxylative Diels–Alder reaction adducts, a reduction-acid catalyzed stereoselective cyclization sequence for the access to bridged tricyclic benzopyran is discovered unexpectedly. A new 'one-pot' protocol of

$LiAlH_4$ or $NaBH_4$ mediated reduction of Diels–Alder product and subsequent acid (workup) catalyzed intramolecular highly stereoselective cyclization of the Diels–Alder adducts was identified for the efficient formation of the chiral bridged tricyclic benzopyran framework **4**. The cyclization involves an interesting phenolic attack of the diene moiety driven by dehydration of the allylic alcohol in **3** (Scheme 3.2).

Scheme 3.2 Sequence of transforming **1** to bridged tricyclic benzopyran **4**

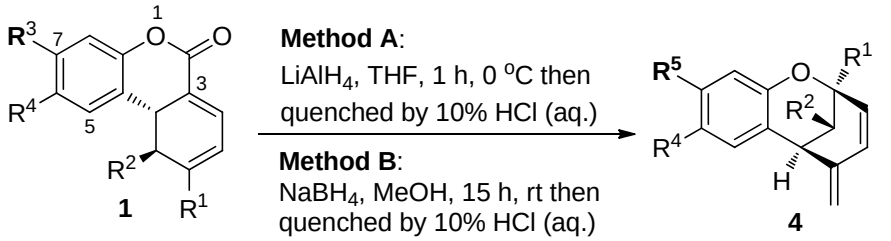


3.3 Scope Expansion

With Diels–Alder products **1** in hand, we performed the investigation for their transformation to the bridged tricyclic benzopyrans **4** (Scheme 3.1). As mentioned above, acid triggered cyclization of phenols with alkenes has been studied in the synthesis of the scaffold.[5] Inspired by the studies, we conceived a possibility of new cyclization between a phenol and a diene in the presence of an acid (Scheme 3.2). The required precursor diol **2** could be obtained via the reduction of the corresponding lactone **1** (Table 3.1, entry 1). Surprisingly, after the reduction by $LiAlH_4$, the chiral bridged tricyclic benzopyran **4a** was obtained directly after workup with 10% HCl aqueous solution without requiring an

additional acid treatment. Moreover, the unexpected 'one-pot' procedure proceeded smoothly in 86% yield and with excellent diastereoselectivity (> 20:1 dr).

Table 3.1 Formation of **4** by 'one-pot' reduction-acid catalyzed cyclization of **1**.[a]



Entry	R^1, R^2, R^3, R^4, R^5	**1**	**4**	Method	Yield (%)[b]	dr (%)[c]
1	Me, H, H, H, H, H	**1a**	**4a**	**A**	86	>20:1
2	Me, H, Me, H, Me	**1b**	**4b**	**A**	91	>20:1
3	Me, H, H, Me, H	**1c**	**4c**	**A**	93	>20:1
4	Me, H, MeO, H, MeO	**1d**	**4d**	**A**	87	>20:1[d]
5	Me, H, H, Br, H	**1f**	**4e**	**A**	85	5.5:1
6	H, H, MeO, H, MeO	**1h**	**4f**	**A**	84	>20:1
7	Ph, H, **Br**, H, **H**	**1j**	**4g**	**A**	89	>20:1
8	3-MePh, H, **Br**, H, **H**	**1k**	**4h**	**A**	87	>20:1
9	H, Me, **Br**, H, **H**	**1p**	**4i**	**A**	83	12:1
10	H, Me, **Br**, H, **Br**	**1p**	**4j**	**B**	75	>20:1

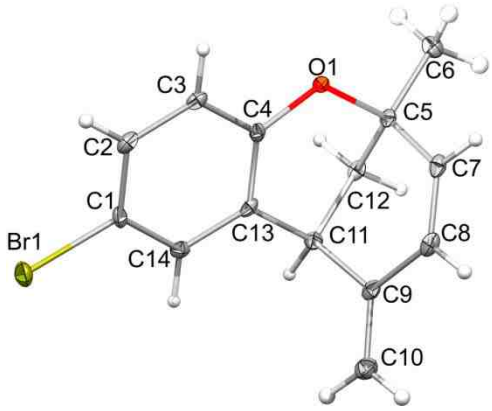
[a] Conditions: unless specified, see Experimental Section. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC using a chiral stationary phase with 91% ee.

We also extended the protocol to other substrates (entries 2-9). In general, high yields (83-93%) and good to excellent dr (5.5:1 - >20:1) were achieved with these representative structurally diverse molecules **1**. Furthermore, the enantioselectivity was largely maintained in the two step transformations, as demonstrated in the case of **4d** with 91% ee (Table 3.1, entry 4). It is noteworthy that unexpectedly, the debromination concurred with substrates bearing the bromo atom at position 7 (e.g., R^3, entries 7-9),

while Br at 6-position is not affected (entry 5). The use of milder $NaBH_4$ could overcome this problem (entry 10).

The absolute configuration was confirmed by X-ray crystallographic analysis of single crystal **4e** (Figure 3.2).

Figure 3.2 X-Ray Structure of **4e**



Conclusion

The Diels–Alder adducts are smoothly transformed into the targets by a novel but unexpected 'one-pot' protocol of $LiAlH_4$ or $NaBH_4$ mediated reduction and subsequent acid (workup) catalyzed highly stereoselective cyclization. We anticipate that the two new synthetic strategies hold great potential in the exploration of novel organic transformations. The application of the chiral bridged tricyclic benzopyran core in the synthesis of natural products and biologically relevant molecules is also under investigation.

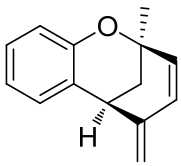
Experimental Section

General Procedure for the Preparation of 4a-j

Method A: A solution of Diels–Alder product **1a** (0.064 g, 0.30 mmol) in 0.5 mL of THF was injected to the mixture of $LiAlH_4$ (0.023 g, 0.60 mmol) in 5 mL of THF at 0 ºC. The mixture was stirred for 1 h at 0 ºC and quenched with 20 mL of 10% HCl solution. The reduced product was consumed completely monitored by TLC after stirring for 1 h. The product was extracted with 10 mL of ethyl acetate three times. The combined organic layer was dried with sodium sulfate and evaporated. The crude product was purified by column chromatography with hexane and ethyl acetate to give 0.0516 g of product.

Method B: To a solution of Diels–Alder product **1p** (0.082 g, 0.28 mmol) in 2 mL MeOH was added $NaBH_4$ (0.053 g, 1.40 mmol) at room temperature. The mixture was stirred for 15 h and quenched with 20 mL 10% HCl solution. The reduced product was consumed completely monitored by TLC after stirring for 1 h. The product was extracted with 10 mL ethyl acetate three times. The combined organic layer was dried with sodium sulfate and evaporated. The crude product was purified by column chromatography with hexane and ethyl acetate to give 0.058 g of product.

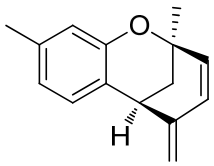
Physical and Spectroscopic Data for 4a-j



(2*R*,6*S*)-2-Methyl-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4a)

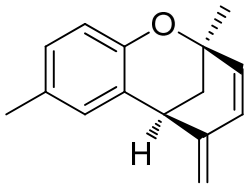
The title compound was obtained in 86% yield for two steps by method **A** as colorless oil. $[\alpha]_D^{25}$ = +398.0° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.13-7.08 (m, 2H), 6.86-6.77 (m, 2H), 6.21 (d, *J* = 9.6 Hz, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 5.14

(s, 1H), 4.86 (s, 1H), 3.61 (t, *J* = 2.7 Hz, 1H), 1.96 (d, *J* = 2.1 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 153.1, 147.3, 131.6, 130.7, 128.9, 128.1, 125.0, 120.1, 117.1, 111.4, 70.7, 39.4, 34.2, 27.3; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 131.6, 130.7, 128.9, 128.1, 120.1, 117.1, 111.4, 39.4, 34.2, 27.3.



(2*R*,6*S*)-2,9-Dimethyl-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4b)

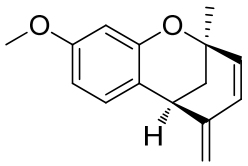
The title compound was obtained in 91% yield for two steps by method **A** as white solid. M. P. 77-78 ºC; $[\alpha]_D^{25}$ = +416.7° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.96 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.62 (s, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 5.63 (d, *J* = 9.6 Hz, 1H), 5.11 (s, 1H), 4.84 (s, 1H), 3.56 (s, 1H), 2.24 (s, 3H), 1.93 (d, *J* = 2.4 Hz, 2H), 1.54 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 152.8, 147.4, 138.0, 131.6, 130.7, 128.6, 122.1, 121.2, 117.4, 111.2, 70.6, 39.0, 34.4, 27.3, 21.1; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 131.6, 130.7, 128.6, 121.2, 117.4, 111.2, 39.0, 34.4, 27.3, 21.1.



(2*R*,6*S*)-2,8-Dimethyl-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4c)

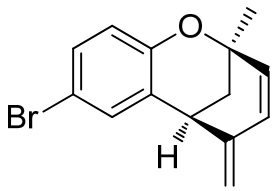
The title compound was obtained in 93% yield for two steps by method **A** as colorless oil. $[\alpha]_D^{25}$ = +375.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.93-6.89 (m, 2H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.20 (d, *J* = 9.6 Hz, 1H), 5.63 (d, *J* = 9.6 Hz, 1H), 5.14 (s,

1H), 4.86 (s, 1H), 3.55 (t, *J* = 2.7 Hz, 1H), 2.24 (s, 3H), 1.93 (d, *J* = 2.4 Hz, 2H), 1.55 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 150.9, 147.4, 131.6, 130.6, 129.2, 128.9, 124.6, 116.8, 111.3, 70.5, 39.4, 34.4, 27.4, 20.5; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 131.6, 130.6, 129.2, 128.9, 116.8, 111.3, 39.4, 34.4, 27.4, 20.5.



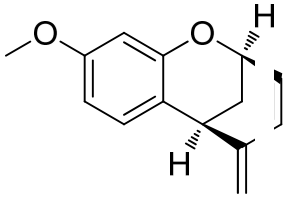
(2*R*,6*S*)-9-Methoxy-2-methyl-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4d)

The title compound was obtained in 87% yield for two steps by method **A** as colorless oil. $[\alpha]_D^{25}$ = +432.9° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.97 (d, *J* = 8.4 Hz, 1H), 6.44 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 9.6 Hz, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 5.11 (s, 1H), 4.84 (s, 1H), 3.72 (s, 3H), 3.54 (t, *J* = 2.7 Hz, 1H), 1.93 (d, *J* = 2.7 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 159.7, 153.8, 147.4, 131.4, 130.8, 129.3, 117.4, 111.1, 107.5, 101.4, 70.8, 55.2, 38.7, 34.5, 27.3; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 131.4, 130.8, 129.3, 111.1, 107.5, 101.4, 55.2, 38.7, 34.5, 27.3. The ee was determined to be 91% by HPLC on Daicel Chiralpak IC (25 cm), Hexanes/IPA= 90/10, 0.5 mL/min^{-1}, λ = 254 nm, t_r (major) = 9.86 min, t_r (minor) = 11.43 min.



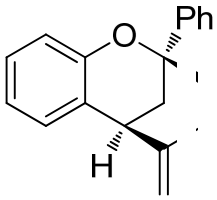
(2*R*,6*S*)-8-Bromo-2-methyl-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4e)

The title compound was obtained in 85% yield for two steps by method **A** as white solid. $[\alpha]_D^{25}$ = +297.4° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.20-7.16 (m, 2H), 6.66 (d, *J* = 8.7 Hz, 1H), 6.21 (d, *J* = 9.6 Hz, 1H), 5.63 (d, *J* = 9.6 Hz, 1H), 5.15 (s, 1H), 4.90 (s, 1H), 3.56 (t, *J* = 2.7 Hz, 1H), 1.93 (d, *J* = 2.7 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 152.4, 146.6, 131.5, 131.4, 130.9, 130.7, 127.2, 119.0, 112.1, 112.0, 71.0, 39.3, 33.9, 27.2; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 131.5, 131.4, 130.9, 130.7, 119.0, 112.1, 39.3, 33.9, 27.2.



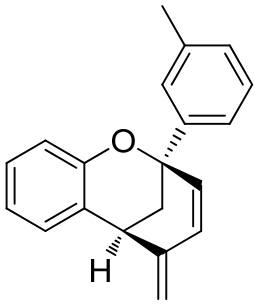
(2*R*,6*S*)-9-Methoxy-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4f)

The title compound was obtained in 84% yield for two steps by method **A** as colorless oil. $[\alpha]_D^{25}$ = +229.4° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.96 (d, *J* = 8.4 Hz, 1H), 6.44 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 6.30 (d, *J* = 9.6 Hz, 1H), 5.93 (dd, *J* = 9.6 Hz, 6.0 Hz, 1H), 5.14 (s, 1H), 4.86 (s, 1H), 4.85-4.82 (m, 1H), 3.73 (s, 3H), 3.53 (s, 1H), 2.13 (dt, *J* = 12.9 Hz, 2.7 Hz, 1H), 1.98 (dt, *J* = 12.6 Hz, 2.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 159.8, 152.8, 147.6, 132.4, 129.6, 126.1, 117.9, 111.8, 107.4, 101.8, 66.4, 55.2, 37.2, 27.9; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 132.4, 129.6, 126.1, 111.8, 107.4, 101.8, 66.4, 55.2, 37.2, 27.9.



(2*R*,6*S*)-5-Methylene-2-phenyl-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4g)

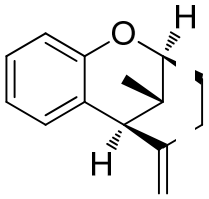
The title compound was obtained in 89% yield for two steps by method **A** as colorless oil. $[\alpha]_D^{25}$ = +141.3° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.61-7.57 (m, 2H), 7.44-7.38 (m, 2H), 7.32 (tt, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.20-7.12 (m, 2H), 6.96 (dd, *J* = 8.1 Hz, 0.9 Hz, 1H), 6.91-6.86 (m, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 5.86 (d, *J* = 9.6 Hz, 1H), 5.22 (s, 1H), 4.95 (s, 1H), 3.68 (t, *J* = 2.7 Hz, 1H), 2.22 (dd, *J* = 12.9 Hz, 2.4 Hz, 1H), 2.12 (ddd, *J* = 12.9 Hz, 3.6 Hz, 1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 152.9, 146.9, 144.9, 131.7, 130.7, 129.0, 128.4, 128.3, 127.5, 125.0, 120.5, 117.5, 111.9, 74.3, 39.6, 36.5; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 131.7, 130.7, 129.0, 128.4, 128.3, 127.5, 125.0, 120.5, 117.5, 111.9, 39.6, 36.5.



(2*R*,6*S*)-5-Methylene-2-(*m*-tolyl)-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4h)

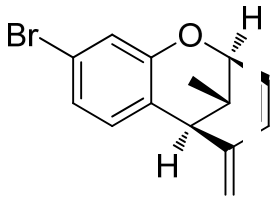
The title compound was obtained in 87% yield for two steps by method **A** as colorless oil. $[\alpha]_D^{25}$ = +123.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.41-7.38 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.20-7.13 (m, 3H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.92-6.87 (m, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 5.86 (d, *J* = 9.6 Hz, 1H), 5.23 (s, 1H), 4.95 (s, 1H), 3.68 (t,

J = 2.7 Hz, 1H), 2.40 (s, 3H), 2.22 (dd, *J* = 12.9 Hz, 2.4 Hz, 1H), 2.12 (ddd, *J* = 12.9 Hz, 3.3 Hz, 1.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 153.0, 147.0, 144.9, 138.0, 131.6, 130.9, 128.9, 128.2, 125.7, 125.1, 122.1, 120.4, 117.5, 111.8, 74.3, 39.7, 36.5, 21.6; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 131.6, 130.9, 128.9, 128.2, 125.7, 122.1, 120.4, 117.5, 111.8, 39.7, 36.5, 21.6.



(2*S*,6*S*,11*S*)-11-Methyl-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*]oxocine (4i)

The title compound was obtained in 83% yield for two steps by method **A** as colorless oil. $[\alpha]_D^{25}$ = +287.1° (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.96 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.04 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 6.86-6.79 (m, 2H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.75 (dd, *J* = 9.6 Hz, 5.7 Hz, 1H), 5.18 (s, 1H), 4.96 (s, 1H), 4.49 (td, *J* = 4.1 Hz, 2.1 Hz, 1H), 3.32 (s, 1H), 2.34-2.27 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 151.8, 144.9, 132.2, 129.1, 128.2, 126.6, 123.1, 120.2, 117.2, 114.2, 71.4, 44.5, 30.6, 14.8; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 132.2, 129.1, 128.3, 123.1, 120.2, 117.2, 114.2, 71.4, 44.5, 30.6, 14.8.



(2*S*,6*S*,11*S*)-9-Bromo-11-methyl-5-methylene-5,6-dihydro-2*H*-2,6-methanobenzo[*b*] oxocine (4j)

The title compound was obtained in 75% yield for two steps by method **B** as white solid. M. P. 80-81 ºC; $[\alpha]_D^{25}$ = +292.7° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 6.97-6.88 (m, 3H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.74 (dd, *J* = 9.6 Hz, 5.7 Hz, 1H), 5.17 (s, 1H), 4.97 (d, *J* = 0.3 Hz, 1H), 4.51-4.47 (m, 1H), 3.28 (s, 1H), 2.28-2.22 (m, 1H), 0.97 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 152.8, 144.4, 132.3, 130.2, 125.7, 123.2, 123.0, 120.8, 120.2, 114.7, 71.5, 44.1, 30.4, 14.6; DEPT-135 (75.5 MHz, $CDCl_3$) δ (ppm) 132.3, 130.2, 123.2, 123.0, 120.2, 114.7, 71.5, 44.1, 30.4, 14.6.

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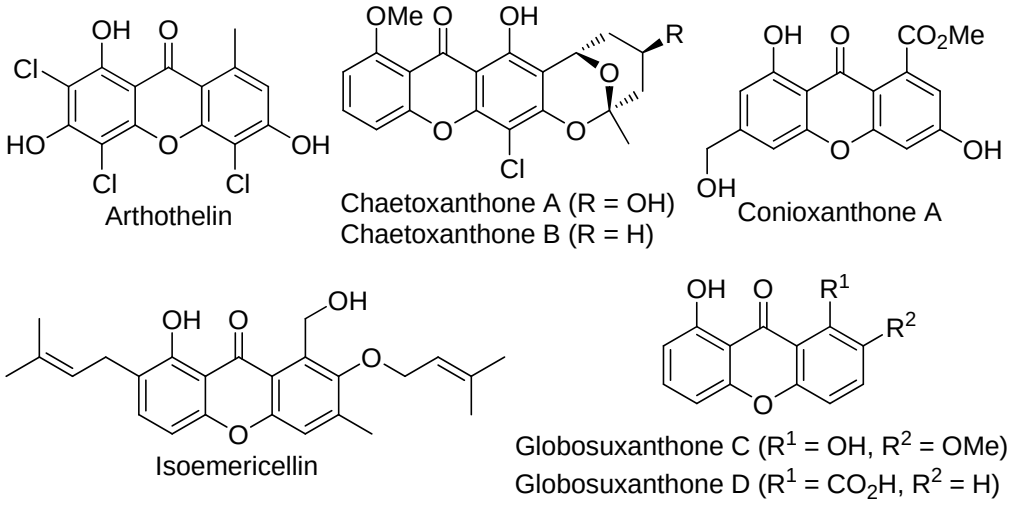
Chapter 4

Organocatalytic Casacde Synthesis of Xanthones

4.1 Background

Xanthones, as secondary metabolites of fungi, lichens, and bacteria, have been regarded as privileged structures because of their broad spectrum of biological activities.[1] The xanthone skeletons are widespread in a diverse range of biologically interesting and medicinal compounds such as arthothelin,[2] chaetoxanthone A and B,[3] conioxanthone A,[4] isoemericellin,[5] and globosuxanthone C and D (Figure 4.1).[6]

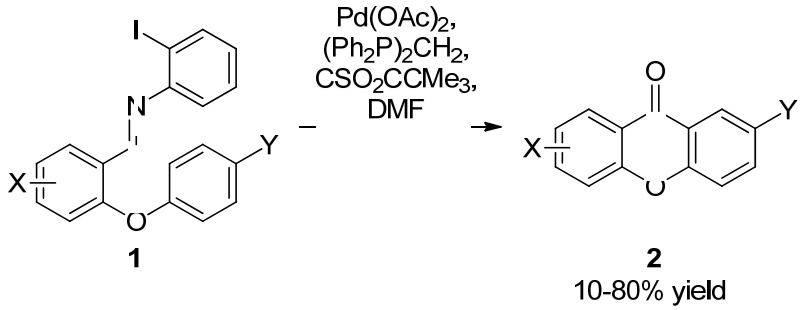
Figure 4.1 Natural products with xanthone core



Due to the prevalence and significance of the xanthone scaffolds, considerable efforts have been devoted to the organic synthesis of the structures since 100 years ago.[1] Different from the previously reported methods utilizing Friedel–Crafts reactions, rearrangements or photo-reactions for ring formation, more efficient processes including Michael-aldol sequences,[7] coupling with arynes,[8] xoidation reactions,[9] coupling reactions[10] for the synthesis of xanthone scaffolds have also been developed recently.

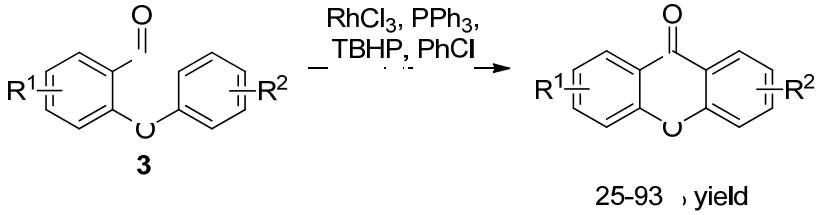
It is noteworthy that C-H activation-intramolecular coupling processes were explored with imine **1** to furnish xanthones **2** with up to 80% yield (Scheme 4.1).[11] The 2-iodophenyl group on imine was proposed to be crucial for efficient transformation. Oxidative addition of C-I site to Pd followed by palladium migration would produce the key intermediate for the formation of xanthones **2**.

Scheme 4.1 Synthesis of xanthones **2** via C-H activation from imine



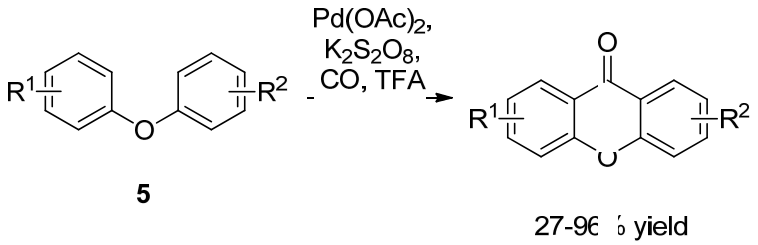
Li and co-workers reported that synthesis of xanthones could also be relealized through C-H activation-intramolecular coupling of aldehyde **3** with low to good yields (Scheme 4.2).[12] It was disclosed that the process could be accomplished with inexpensive iron catalyst.[13]

Scheme 4.2 Synthesis of xanthones **4** via C-H activation from aldehyde



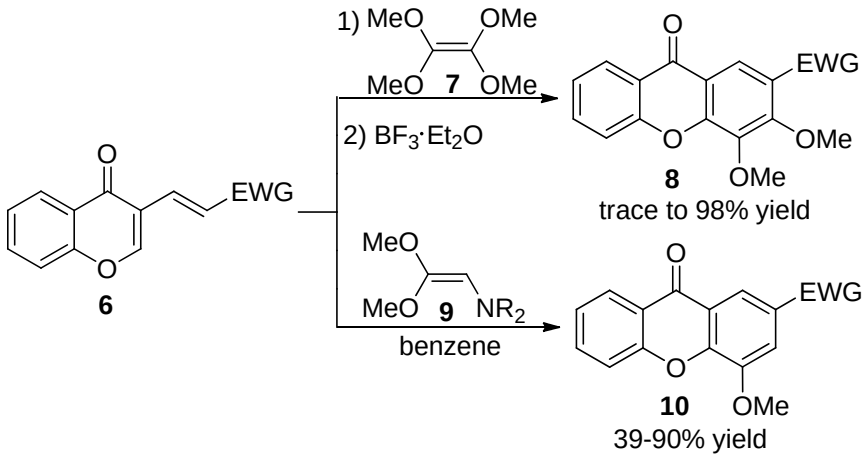
An ingenious process designed by Lei and co-workers was achieved for the synthesis of xanthones from simple diaryl ethers in 2012 (Scheme 4.3).[14] Double C-H activation/carbonylation sequence was proposed for the efficient transformation from ether **5** to xanthones **4** in the presence of CO.

Scheme 4.3 Oxidative double C-H carbonylation of diaryl ethers



Inverse-electron-demanding Diels–Alder reactions between diene **6** and dienophiles **7** or **9** were conducted to provide xanthones **8** or **10** with low to 98% yield (Scheme 4.4).[15]

Scheme 4.4 Synthesis of xanthones via Diels–Alder reactions



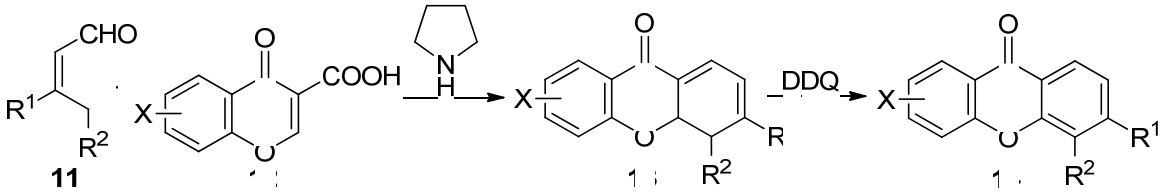
It is obvious that low to moderate yields are generally obtained for most of the cases in the synthesis of xanthones through previously reported methods. Besides, the scope of these methods, especially the Diels–Alder reaction,[15] is rather limited. The difficulty in preparing the substrates can also prevent the application of the process.

4.2 Research Design

Toward this end, we have designed a 'one-pot' strategy for the efficient synthesis of xanthones from readily available chromone-3-carboxylic acids and α,β-unsaturated

aldehydes (Scheme 4.5). Secondary amine catalyzed Diels–Alder reactions between enal **11** and **12** followed by oxidation with DDQ would furnish the desired xanthone **14**. The process can be performed in a 'one-pot' fashion since the same solvent can be utilized in the successive steps

Scheme 4.5 Design of 'one-pot' synthesis of xanthones



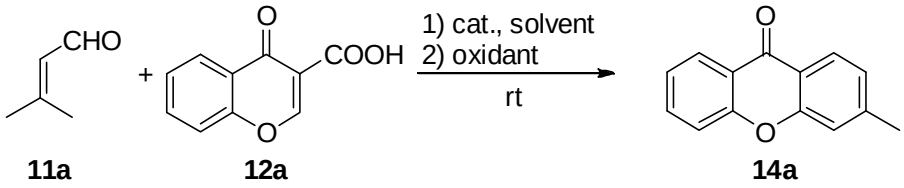
4.3 Optimization of Reaction Conditions

The readily available 3-methyl-2-butenal **11a** and chromone-3-carboxylic acid **12a** are utilized as the model substrates for the two-step synthesis of xanthone **14a** through a Diels–Alder-oxidation sequence (Table 4.1).

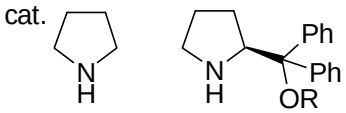
It is found that decarboxylative Diels–Alder reaction between 3-methyl-2-butenal **11a** and chromone-3-carboxylic acid **12a** in DCM proceeds smoothly to give the Diels–Alder product **13a** in 2h. However, transformation of **13a** to xanthone **14a** by directly adding PCC to the above mixture is sluggish to give 11% yield in 1h (Table 4.1, entry 1). The same process employing MnO_2 as oxidant yields similar result (Table 4.1, entry 2). To our delight, the yield of **14a** is improved significantly to 89% by the replacement of the oxidants with DDQ (Table 4.1, entry 3). More bulky secondary amine catalysts are proposed to be effective in improving reaction yields by the inhibition of side reactions. However, no benefit is gained regarding the yield of **14a** by switching pyrrolidine to catalysts **15a** or **15b** (Table 4.1, entry 4-5). Screening solvents reveals that chloroform is

more beneficial to the process to furnish the desired product in 93% yield (Table 4.1, entry 6-7).

Table 4.1 Optimization of reaction conditions[a]



11a **12a** **14a**



15a R = H
15b R = TMS

entry	cat.	oxidant	solvent	yield (%)[b]
1	Pyrrolidine	PCC	DCM	11
2	Pyrrolidine	MnO_2	DCM	9
3	Pyrrolidine	DDQ	DCM	89
4	**15a**	DDQ	DCM	62
5	**15b**	DDQ	DCM	85
6	Pyrrolidine	DDQ	$CHCl_3$	93
7	Pyrrolidine	DDQ	toluene	87

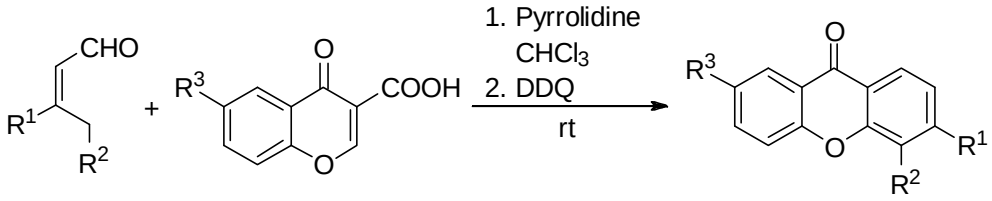
[a] Conditions: a mixture of 0.12 mmol **12a**, 0.10 mmol **11a** and 0.02 mmol catalyst in 0.50 mL solvent is stirred for 2h. Then the reaction is stirred for additional 1h after the addition of 0.20 mmol oxidant. [b] Isolated yields.

4.4 Expansion of Substrate Scope

With the optimized reaction conditions in hand, the scope for the 'one-pot' synthesis of xanthones **14** is explored (Table 4.2). Various chromone-3-carboxylic acids are applied in the process with 3-methyl-2-butenal to give several kinds of substituted xanthones in 85-93% yields (Table 4.2, entry 1-4). The yields of the desired xathones decrease slightly when chromone-3-carboxylic acids **12** bearing electron-withdrawing

group at R^3 position are utilized (Table 4.2, entry 3-4). Variation of the enal part is then investigated for the transformation. The yields of xathones **14e-14g** further drop to 75-81% when γ-substituted enals are employed (Table 4.2, entry 5-7). In accordance with the previous result (Table 4.2, entry 2), the methyl group on chromone-3-carboxylic acid is beneficial to the yields of the corresponding xanthones (Table 4.2, entry 8-10).

Table 4.2 Scope of 'one-pot' synthesis of xanthones[a]



11 **12** **14**

Entry	R^1	R^2	R^3	**14**	Yield (%)[b]
1	Me	H	H	**14a**	93
2	Me	H	Me	**14b**	90
3	Me	H	F	**14c**	85
4	Me	H	Br	**14d**	89
5	H	Me	H	**14e**	81
6	H	Et	H	**14f**	75
7	H	*n*-Pr	H	**14g**	77
8	H	Me	Me	**14h**	89
9	H	Et	Me	**14i**	85
10	H	*n*-Pr	Me	**14j**	83

[a] Conditions: a mixture of 0.12 mmol **12**, 0.10 mmol **11** and 0.02 mmol pyrrolidine in 0.50 mL $CHCl_3$ is stirred for 2h. Then the reaction is stirred for additional 1h after the addition of 0.20 mmol DDQ. [b] Isolated yields.

Conclusion

Efficient 'one-pot' synthesis of aromatized xanthones has been accomplished by pyrrolidine catalyzed Diels–Alder reactions of readily available enals **11** and subsequent

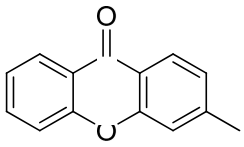
oxidation reactions using DDQ. Application of the process in the synthesis of biologically significant molecules is under investigation.

Experimental Section

General Procedure for 'one-pot' synthesis of xanthones

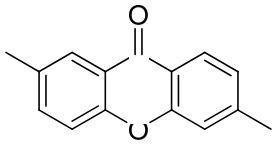
To a mixture of 0.12 mmol **12** and 0.02 mmol pyrrolidine in 0.50 mL $CHCl_3$ is added 0.10 mmol **11**. The reaction is allowed to be stirred for 2h under room temperature. Then the solution is stirred for another 1h after the addition of 0.20 mmol DDQ. The mixture was applied to column chromatography directly and eluted with hexane and ethyl acetate to give pure product **14**. The purified compound is used for characterization.

Physical and Spectroscopic Data for Oxathones 14a-14j



3-Methyl-9*H*-xanthen-9-one (14a)

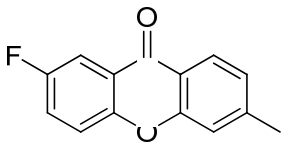
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.33 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.73-7.67 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.27 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.0, 156.3, 156.1, 146.3, 134.5, 126.7, 126.5, 125.4, 123.7, 121.9, 119.6, 117.9, 117.7, 22.0.



2,6-Dimethyl-9*H*-xanthen-9-one (14b)

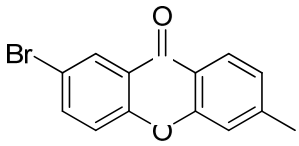
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.21 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 1.2 Hz, 1H), 7.50 (dd, *J* = 8.7 Hz, 2.1 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.25 (s, 1H), 7.17 (dd, *J*

= 8.1 Hz, 0.9 Hz, 1H), 2.49 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.1, 156.3, 154.3, 146.1, 135.8, 133.5, 126.5, 126.0, 125.2, 121.5, 119.6, 117.6, 21.9, 20.8.



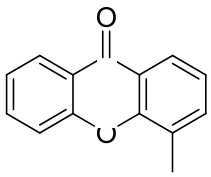
2-Fluoro-6-methyl-9*H*-xanthen-9-one (14c)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.19 (d, *J* = 8.1 Hz, 1H), 7.95 (dd, *J* = 8.1 Hz, 2.7 Hz, 1H), 7.46-7.41 (m, 2H), 7.26 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 176.2, 160.3, 156.2, 152.3, 146.7, 126.4, 125.7, 122.8, 122.4, 119.9, 119.8, 118.8, 117.7, 111.5, 111.2, 22.0.



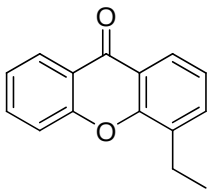
2-Bromo-6-methyl-9*H*-xanthen-9-one (14d)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.41 (d, *J* = 2.4 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.25 (s, 1H), 7.19 (dd, *J* = 8.1 Hz, 0.6 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 175.7, 156.1, 154.8, 146.8, 137.3, 129.1, 126.5, 125.8, 123.1, 119.9, 119.2, 117.7, 116.9, 22.0.



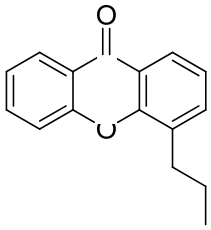
4-Methyl-9*H*-xanthen-9-one (14e)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.34 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 8.19 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.75-7.69 (m, 1H), 7.54 (t, *J* = 8.4 Hz, 2H), 7.40-7.35 (m, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.5, 156.1, 154.5, 135.7, 134.6, 127.2, 126.7, 124.3, 123.8, 121.6, 118.0, 15.8.



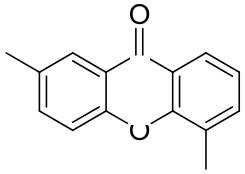
4-Ethyl-9*H*-xanthen-9-one (14f)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.34 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 8.20 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.76-7.70 (m, 1H), 7.59 (dt, *J* = 7.2 Hz, 0.9 Hz, 1H), 7.53 (dd, *J* = 8.4 Hz, 0.3 Hz, 1H), 7.41-7.26 (m, 2H), 3.00 (q, *J* = 7.8 Hz, 2H), 1.37 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.6, 156.0, 154.2, 134.6, 134.1, 133.1, 126.7, 124.3, 123.8, 123.6, 121.8, 121.6, 118.0, 22.9, 14.1.



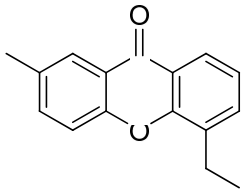
4-Propyl-9*H*-xanthen-9-one (14g)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.34 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 7.76-7.70 (m, 1H), 7.58-7.51 (m, 2H), 7.40-7.26 (m, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 1.85-1.72 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.6, 156.0, 154.3, 135.0, 134.6, 131.6, 126.7, 124.4, 123.8, 123.4, 121.8, 121.6, 118.0, 31.8, 23.0, 14.0.



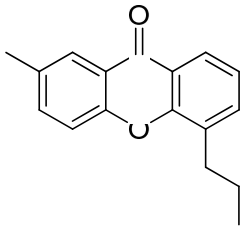
2,5-Dimethyl-9*H*-xanthen-9-one (14h)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.18 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 8.11 (d, *J* = 1.2 Hz, 1H), 7.55-7.41 (m, 3H), 7.27-7.22 (m, 1H), 2.55 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.6, 154.5, 154.3, 135.9, 135.5, 133.6, 127.2, 125.9, 124.3, 123.2, 121.6, 121.2, 117.8, 20.8, 15.8.



5-Ethyl-2-methyl-9*H*-xanthen-9-one (14i)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.19 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 8.11 (d, *J* = 1.2 Hz, 1H), 7.58-7.51 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 2.99 (q, *J* = 7.5 Hz, 2H), 2.47 (s, 3H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.6, 154.3, 154.2, 135.9, 133.9, 133.6, 133.0, 125.9, 124.3, 123.3, 121.7, 121.2, 117.8, 22.9, 20.8, 14.1.



2-Methyl-5-propyl-9*H*-xanthen-9-one (14j)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.20 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 7.56-7.51 (m, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.30-7.25 (m, 1H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.47 (s, 3H), 1.84-1.69 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 177.6, 154.2, 135.9, 134.8, 133.6, 131.5, 125.9, 124.4, 123.2, 121.7, 121.2, 117.7, 31.8, 23.0, 20.8, 14.0.

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Chapter 5

[4+1] Annulations of Alkynals via an Organocatalytic Double Michael Cascade

5.1 Background

Organocatalysis has emerged as a powerful approach to the construction of structurally diverse molecular architectures in the last decade.[1] Aminocatalysis pioneered by Barbas, List, and MacMillan, has become the landmark of the field.[2,3] A number of unprecedented organic transformations have been realized with the strategy. Furthermore, capitalizing on reversible iminium-enamine catalysis, many synthetically efficient catalytic cascade processes have been developed for the facile construction of complex molecular architectures.[4] Notably, various cyclic ring structures ranging from 3 to 7 membered sizes have been constructed.[5] Despite these impressive achievements, to the best of our knowledge, there currently exists no amine catalyzed [4+1] annulation reaction to produce five-membered rings.[6-8] Thus, the identification of an amine catalyzed [4+1] annulation that is general and operational simple remaines a prominent and challenging goal. Towards this end, herein we wish to report a catalytic platform for [4+1] annulation. Notably, the process involving an unprecedented conjugate addition-protonation-conjuagte addition cascade sequence, is catalyzed by simple pyrrolidine using readily available *N*-tosyl-2-aminophenols and ynals as reactants under mild reaction conditions to give synthetically and biologically valuable benzoxazoles in high yield.[9]

Amine catalyzed 1,3-dipolar cycloaddition reactions for the formation of five-membered rings have been subjected to intensively studies.[10] In these approaches, α,β-unsaturated aldehydes are genreally used as essential substrates through iminium activation with an amine promoter to react with 1,3-dipolar components such as nitrones[11] and azomethine ylides[12] in concerted or iminium-enamine stepwise process. In contrast, the otherwise inaccessible modality, [4+1] annulation offers an alternative versatile route to five-membered scaffolds because of their readily availability of starting materials. Nevertheless, survey of literature reveals that the only a handful organocatalyzed [4+1] annulation reactions are reported.[6-8] Elegant examples include Kwon's phosphine promoted[6] and Xiao's sulfur ylide[7] [4+1] annulations.

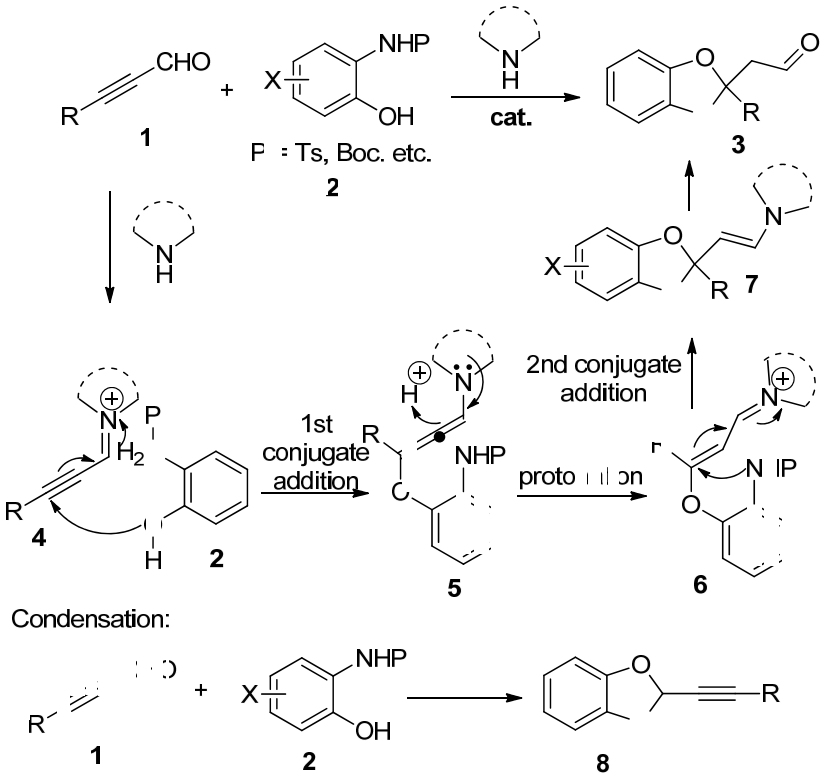
Although iminium catalysis with enals has enjoyed great success,[3] reactions with ynals have emerged slowly. Limited examples of ynals in iminium catalysis have been reported.[13,14] This may attribute to similar reaction behavior to enals people think while a non-stereogenic center generated in conjugate addition adducts diminishes synthetic interest. However, recent studies from our group and others reveal a number of interesting chemistries beyond original expection.[13,14] We have developed unprecedented chiral allenamine cascade reactions for the facile assembly of important molecular architectues, which are difficult to achieve with enal-based reactions.

5.2 Research Design

In our continuing effort on this avenue, we proposed a new amine catalyzed [4+1] cyclization reaction (Scheme 5.1). Given the importance of benzoxazoles in synthesis and pharmaceuticals,[9] we devised the biuncleophilic *N*-tosyl-2-aminophenol substrates (**2**) for the proposed [4+1] annulation reaction with ynals **1**. It is hypothesized that

activation of ynal **1** via iminium ion **4** renders the nucleophilic phenol –OH **2** conjugate attack the β-position. Protonation of the resulting allenamine **5** gives a new iminium ion **6**. Then an intramolecular conjugate addition proceeds to form a benzoxazole ring **3**.

Scheme 5.1 Proposed amine catalyzed [4+1] annulations



Although the proposed reaction looks simple on paper, there are significant barriers to overcome. The first concern is the second conjugate reaction in the cascade. The significant steric hindrance induced by β,β'-disubstituted enals renders the conjugate addition difficult. It is even more difficult with bulky protected "N" nucleophile. It should be noted that the examples of β,β'-disubstituted enals in aminocatalyzed conjugate additions are scarce.[15] Moreover, the "O" added adduct **5** significantly reduce the reactivity for the second conjugate addition reaction due to the formation of a

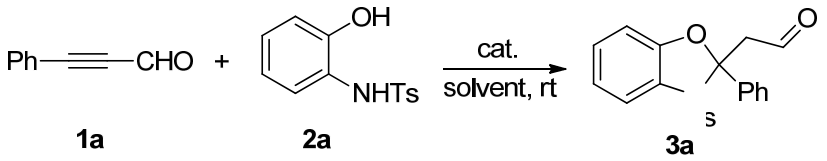
deactivated electron-rich enol ether. Third, a condensation reaction between the highly active aldehyde **1** and **2** could compete with the proposed [4+1] process.

5.3 Optimization of Reaction Conditions

To test the validity of our proposed organocatalytic [4+1] annulation process, we probed a model reaction of ynal **1a** with *N*-tosyl-2-aminophenol (**2a**) in the presence of simple pyrrolidine (20 mol %) as a promoter, which can readily engage in iminium formation with aldehyde functionality in ynal **1a** (Table 5.1). To our delight, pyrrolidine readily effects the [4+1] annulation reaction. The reaction proceeded smoothly to afford the desired benzoxazole **3a** in 5 min with good yield (75%, entry 1). Furthermore, under the reaction condition, we did not observe condensation product between aldehyde **1a** and *N*-tosyl-2-aminophenol (**2a**). It is believed that under the mild non-acidic condition, it is difficult to form the product, whose formation is required an acid promoter. In addition, it appears that the second conjugate addition reaction went smoothly. The reason for this may be because the intramolecular process. With pyrrolidine as catalyst, we examined the solvent effect on the process (entries 2-5). Dichloroethane (DCE) was identified as optimal reaction medium for the reaction (entry 5). In this instance, the reaction was accomplished in 5 min to produce product **3a** in 84% yield. Furthermore, notably, lowering catalyst loading to 5 mol % gave even higher yield (93%) of the product formed despite prolonging reaction time (15 h) (entry 6). The increase of the yield could be explained by minimization of undesired aldol reaction between product **3a** and reactant **1a**, which was observed with 20 mol % catalyst loading. Importantly, no product was observed when a background reaction was carried out without any catalyst

(entry 7). Besides, TEA failed to promote the reaction indicating that the [4+1] annulation reaction did not proceed via base-catalyzed process (entry 8).

Table 5.1 Optimization of Reaction Conditions[a]



1a **2a** **3a**

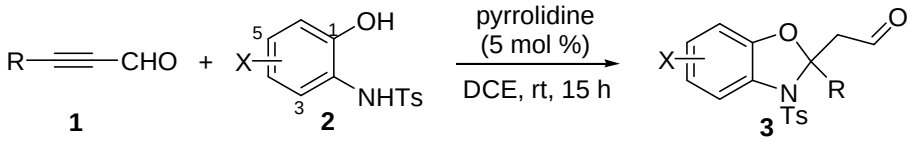
entry	cat. (mol %)	solvent	*t*	% yield[b]
1	pyrrolidine (20)	CH_2Cl_2	5 min	75
2	pyrrolidine (20)	$CHCl_3$	5 min	73
3	pyrrolidine (20)	CH_3CN	5 min	69
4	pyrrolidine (20)	toluene	5 min	61
5	pyrrolidine (20)	$Cl(CH_2)_2Cl$	5 min	84
6	pyrrolidine (5)	$Cl(CH_2)_2Cl$	15 h	93
7	none	CH_2Cl_2	1 h	0
8	TEA	CH_2Cl_2	1 h	0

[a] Reactions were carried out with **1a** (0.1 mmol) and **2a** (0.11 mmol) at rt in 0.2 mL of solvent. [b] Isolated yields.

5.4 Expansion of Substrate Scope

The simple pyrrolidine catalyzed [4+1] annulation reaction serves as a general approach to structurally diverse benzoxazoles under mild reaction conditions (Table 5.2). The examination of the substrate scope of reactants ynals **1** has revealed a significant tolerance (entries 1-16). In addition unsubstituted ynal (entry 1), the aromatic ring bearing electron-withdrawing (entries 2-6) and –donating (entries 7-9) can be applied for the protocol. In all cases, uniformly high yields (85-93%) are achieved.

Table 5.2 Scope of Pyrrolidine Catalyzed [4+1] Annulation Reactions[a]



1 **2** **3**

entry	R, X	**3**	% yield[b]
1	Ph, H	**3a**	93
2	4-FC_6H_4, H	**3b**	88
3	4-ClC_6H_4, H	**3c**	95
4	4-BrC_6H_4, H	**3d**	92
5	4-$NO_2C_6H_4$, H	**3e**	89
6	4-CNC_6H_4, H	**3f**	85
7	4-MeC_6H_4, H	**3g**	93
8	4-$MeOC_6H_4$, H	**3h**	86
9	3-MeC_6H_4, H	**3i**	91
10	$BnOCH_2$, H	**3j**	88
11	2-thienyl, H	**3k**	91
12[c]	Ph, 4-Me	**3l**	91
13[c]	Ph, 5-Me	**3m**	89
14[c]	Ph, 4-*t*-Bu	**3n**	83
15[c]	Ph, 4-Cl	**3o**	87
16[c]	Ph, 4-NO_2	**3p**	84
17[c]	4-ClC_6H_4, 4-Me	**3q**	92
18[c]	4-$NO_2C_6H_4$, 4-Cl	**3r**	90

[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] With pyrrolidine (0.020 mmol) at 40 °C for 24 h.

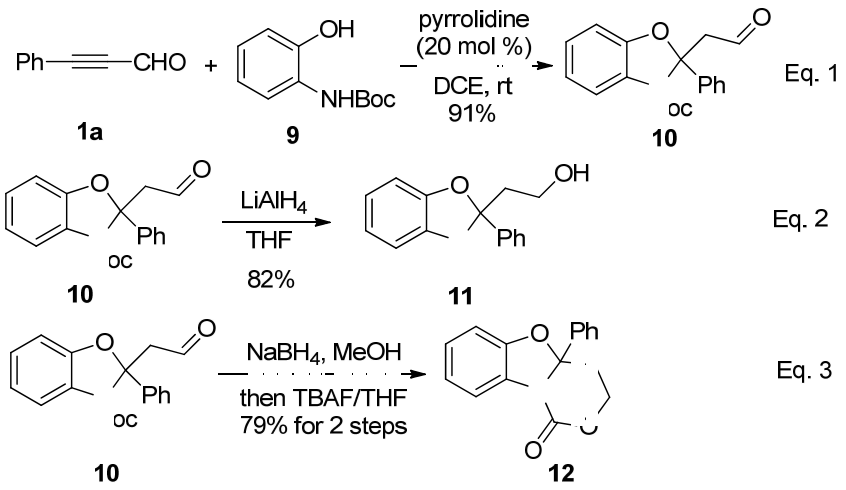
Furthermore, the pyrrolidine promoted process can be extended to aliphatic (entry 10) and heterocyclic (entry 11) ynals with high efficiency. Structural variation of *N*-tosyl-2-aminophenols is then probed (entries 12-18). The catalytic system is generally applicable to a variety of *N*-tosyl-2-aminophenols under the optimized conditions.

Again, high yields (83-92%) are achieved in these examples. However, interestingly it appears that the substituents on the aromatic system have impact on the reaction. The rate of conversion with these substrates is noticeably slower than without substituents no matter what the electron-donating (entries 12-14, and 17), and withdrawing groups are attached (entries 15-17 and 18). Therefore, the corresponding reactions are carried out with 20 mol % catalyst and at 40 °C for 24 h to facilitate these transformations.

5.5 Application

In addition, the pyrrolidine catalyzed [4+1] annulation reaction can be applied with Boc-protected 2-aminophenols **10** (Scheme 5.2, Eq. 1). Under similar reaction conditions with 20 mol % catalyst, the process proceeded smoothly to afford the desired product **10** in 91% yield. The [4+1] annulation product **11** can be deprotected to give **12** by reduction with $LiAlH_4$ in 82% yield (Eq. 2).

Scheme 5.2 Synthetic Elaboration of [4+1] Annulation Products

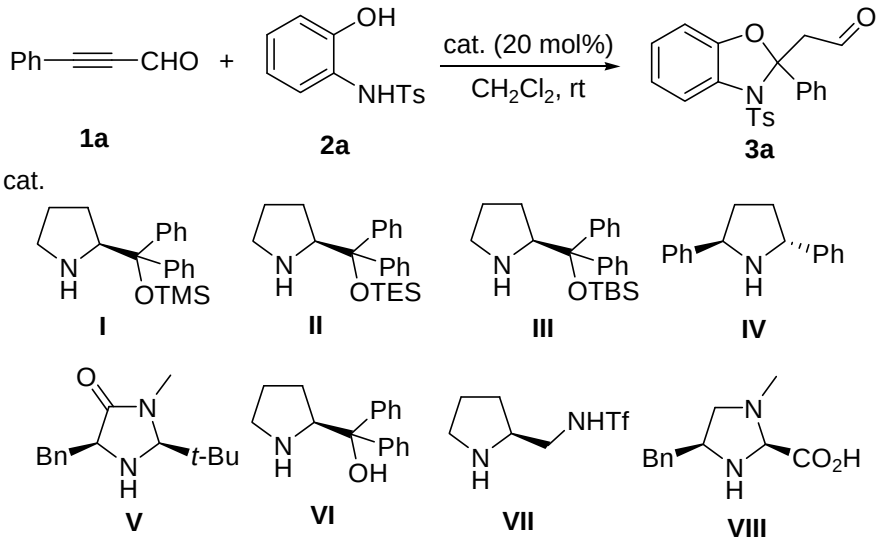


Furthermore, reduction of **11** to alcohol by $NaBH_4$ followed by the treatment with TBAF afforded the cyclization product **13** in 79% yield in 2-step transformation (Eq. 3).

5.6 Discussion

Having demonstrated a simple pyrrolidine catalyzed [4+1] annulation reaction of ynals with *N*-tosyl/Boc-2-aminophenols, weattempted to probe a catalytic enantioselective version with a chiral organocatalyst (Table 5.3). Disappointedly, very poor ees were observed in these cases.

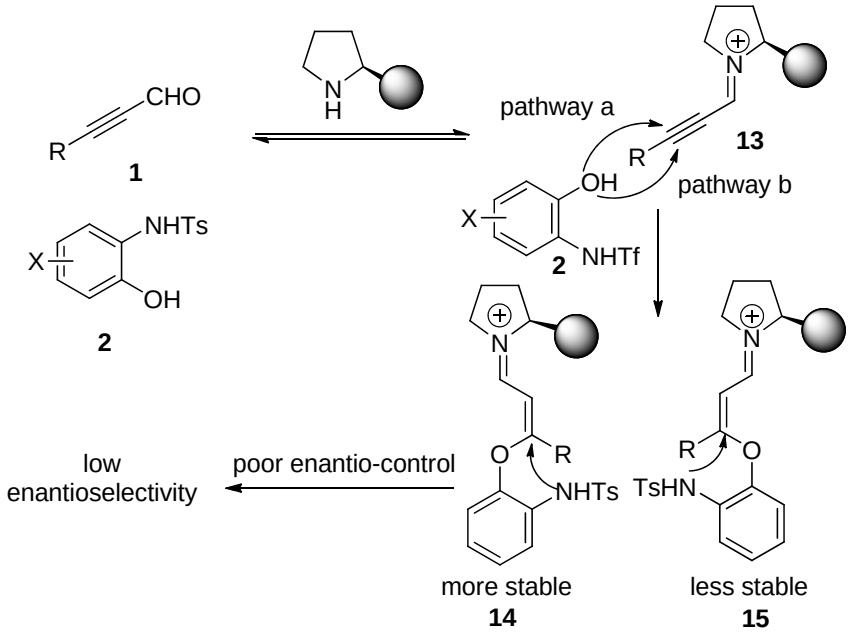
Table 5.3 Exploration of enantioselective [4+1] annulations[a]



Entry	Cat.	t	Yield (%)[b]	ee (%)[c]
1	**I**	10 min	93	2
2	**II**	10 min	90	3
3	**III**	10 min	92	3
4	**IV**	15 h	85	2
5	**V**	15 h	87	3
6	**VI**	15 h	82	0
7	**VII**	15 h	80	0
8	**VIII**	15 h	0	nd[d]

[a] Reaction conditions: unless specified, reactions were carried out with **1a** (0.1 mmol) and **2a** (0.11 mmol) at rt in 0.2 mL of solvent in the presence of a catalyst (0.02 mmol). [b] Isolated yields. [c] Determined by chiral HPLC analysis.

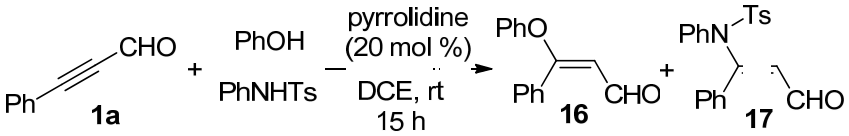
Scheme 5.3 Rationalization of Low Enantioselectivity of Chiral Amine Catalyzed [4+1] Annulation



The observed results could be rationalized in the proposed model (Scheme 3). The "O"-centered nucleophilic species in **2** is involved in the first conjugate addition (see below preliminary mechanic study). The nucleophilic addition could proceed in two possible ways a and b due to the linear geometry of the C≡C triple bond and lead to respective adducts **14** and **15**. Compound **14** is believed to be formed more favorably since the "O" attacks the less steric side of a chiral amine derived iminium ion **13**. Furthermore, the bulky NHTs moiety in **14** and **15** are oriented in position to minimize the interaction with big side chain of the catalyst. The new stereogenic center is created

in the second conjugate addition. However, the chiral center of the catalyst (e.g., **14** and **15**) is far away from the conjugate addition reaction center in both cases. Accordingly, it is expected that poor enantiocontrol is observed in both chiral iminiums **14** and **15**. This is also evidenced in chiral amine catalyzed nuelcophilic conjugate addition of β,β'-disubstituted α,β-unsaturated aldehydes. A very limited number of examples in achieving good enantioselectivity have been reported.[15]

Table 5.4 Addition Sequence Tests of [4+1] Annulation Reactions[a]



entry	PhOH	PhNHTs	% yield[b]	% yield[b]
1	1.1 equiv	0.0 equiv	92	0
2	0.0 equiv	1.1 equiv	0	0
3	1.1 equiv	1.1 equiv	90	0

[a] Reaction condition: a mixture of PhOH (0.11 mmol) and/or PhNHTs (0.11 mmol), **1a** (0.1 mmol) and pyrrolidine (0.005 mmol) in 0.5 mL of DCE was stirred at rt for 15 h. [b]Isolated yields.

Although the addition sequence of "O" and "N" nucleophiles does not affect the structures of reaction products, the studies may help to understand their nucleophilic nature. Furthermore, such insight may also assist us to develop asymmetric version of the process. Under the same reaction conditions we employed above (Table 5.4), we performed the conjugate addition reactions of alkynal **1a** with PhOH or PhNHTs, respectively. Oxo-conjugate addition adduct **16** was formed in 92% yield (entry 1), while no detectable aza-conjugate addition product **17** was observed (entry 2). The competition

reaction between PhOH and PhNHTs furthermore confirmed that the O nucleophile in **1** should be added to alkynals firstly (entry 3). The "O" addition occurred first may be due to its less hindrance. The results could help us to develop asymmetric synthesis of enantioenriched benzoxazoles where the 2nd conjugate addition is responsible for the formation of stereogenic center.

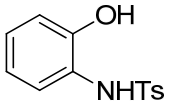
Conclusion

In conclusion, we have designed and implemented an unprecedented amine-catalyzed [4+1] annulation reaction. The notable features of the process include a new conjugate addition-protonation-conjugate addition cascade sequence by employing readily available ynals and *N*-protected-2-aminophenols as reactants. Moreover, an iminium-allenamine-iminium activation mode promoted by simple pyrrolidine is reported for the first time. The mild reaction protocol allows for a broad spectrum of ynals and 2-aminophenols to engage in the cascade sequence with high efficiency. Furthermore, synthetically and biologically important benzoxazoles are created in one-pot operation. The development of enantioselective [4+1] annulation reactions for the formation of enantioenriched benzoxazoles and expansion of the activation mode using underexplored ynals in aminocatalysis are being pursued in our laboratory.

Experimental Section

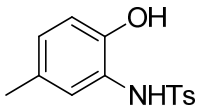
Preparation and physical and spectroscopic data for substrates 2a-2f and 9

Substrates **2a**-**2f**[16] and **9**[17] were prepared according to the literature reported procedure.



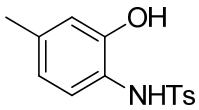
***N*-(2-Hydroxyphenyl)-4-methylbenzenesulfonamide (2a)**

The title compound was obtained in 92% yield as white solid. M. P. 139-140 ºC; ^{1}H NMR (300 MHz, DMSO-d^{6}) δ (ppm) 9.55 (s, 1H), 9.13 (s, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.16 (dd, J = 7.8 Hz, 1.2 Hz 1H), 6.95-6.89 (m, 1H), 6.75-6.66 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d^{6}) δ (ppm) 150.1, 142.8, 137.8, 129.3, 126.8, 126.1, 124.4, 124.2, 119.0, 115.6, 21.0.



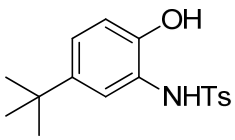
***N*-(2-Hydroxy-5-methylphenyl)-4-methylbenzenesulfonamide (2b)**

The title compound was obtained in 87% yield as grey solid. M. P. 146-147 ºC; ^{1}H NMR (300 MHz, DMSO-d^{6}) δ (ppm) 9.33 (bs, 1H), 9.03 (s, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 6.97 (d, J = 1.8 Hz, 1H), 6.72 (dd, J = 8.1 Hz, 1.5 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 2.32 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d^{6}) δ (ppm) 147.8, 142.9, 137.8, 129.4, 127.6, 126.9, 126.6, 124.9, 123.9, 115.4, 21.1, 20.3.



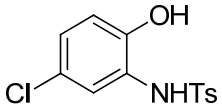
***N*-(2-Hydroxy-4-methylphenyl)-4-methylbenzenesulfonamide (2c)**

The title compound was obtained in 82% yield as white solid. M. P. 105-106 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.86 (bs, 1H), 6.72-6.68 (m, 3H), 6.49 (dd, J = 8.1 Hz, 1.2 Hz 1H), 2.34 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 150.4, 144.2, 138.5, 135.0, 130.0, 127.6, 125.5, 121.6, 120.2, 117.4, 21.6, 21.1.



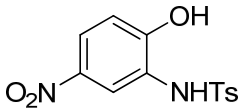
***N*-(5-(*tert*-Butyl)-2-hydroxyphenyl)-4-methylbenzenesulfonamide (2d)**

The title compound was obtained in 84% yield as pink solid. M. P. 107-108 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.59 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.08 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.35 (bs, 1H), 6.29 (s, 1H), 2.38 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 149.0, 144.4, 144.0, 134.7, 129.7, 127.9, 125.4, 123.6, 122.0, 116.6, 34.0, 31.3, 21.7.



***N*-(5-Chloro-2-hydroxyphenyl)-4-methylbenzenesulfonamide (2e)**

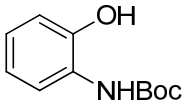
The title compound was obtained in 87% yield as pink solid. M. P. 189-190 ºC; ^{1}H NMR (300 MHz, DMSO-d^6) δ (ppm) 9.93 (s, 1H), 9.44 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 2.7 Hz, 1H), 6.96 (dd, *J* = 8.7 Hz, 2.7 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d^6) δ (ppm) 148.9, 143.1, 137.4, 129.5, 126.7, 125.7, 125.5, 123.4, 122.0, 116.7, 21.0.



***N*-(2-Hydroxy-5-nitrophenyl)-4-methylbenzenesulfonamide (2f)**

The title compound was obtained in 85% yield as yellow solid. M. P. 202-203 ºC; ^{1}H NMR (300 MHz, DMSO-d^6) δ (ppm) 11.48 (bs, 1H), 9.80 (bs, 1H), 8.07 (d, *J* = 2.1 Hz, 1H), 7.89 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz,

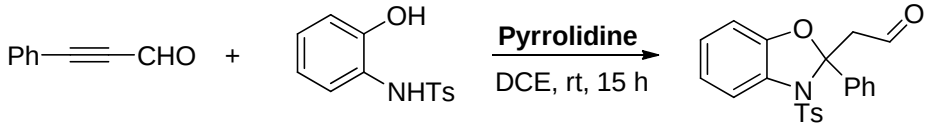
2H), 6.90 (d, J = 9.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d^6) δ (ppm) 156.6, 143.5, 139.3, 137.3, 129.7, 126.9, 125.1, 122.4, 119.1, 115.4, 21.1.



***tert*-Butyl (2-hydroxyphenyl)carbamate (9)**

The title compound was obtained in 95% yield as yellow solid. M. P. 141-143 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.21 (bs, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.74 (s, 1H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 155.1, 147.4, 125.7, 125.6, 121.4, 120.9, 118.8, 82.2, 28.4.

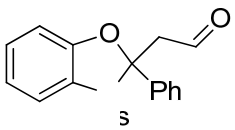
General Procedure for Organocatalytic [4+1] Annulations



1a **2a** **3a**

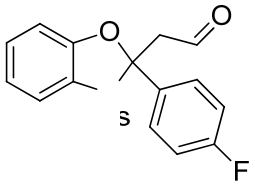
To a solution of **2a** (29 mg, 0.11 mmol) in 0.5 mL DCE were added pyrrolidine (0.4 uL, 0.005 mmol) and **1a** (13.5 μL, 0.1 mmol) at room temperature. The mixture was stirred at room temperature for 15 h. Then the mixture was applied to column chromatography directly and eluted with ethyl acetate and hexane to give product **3a** (36.4 mg, 93% yield) as a yellow solid.

Physical and Spectroscopic Data for Organocatalytic [4+1] Annulation Products



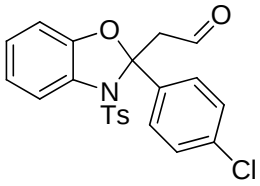
2-(2-Phenyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3a)

The title compound was prepared according to the general procedure in 93% yield as yellow solid. M. P. 127-128 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.72 (dd, *J* = 3.0 Hz, 2.1 Hz, 1H), 7.57-7.54 (m, 1H), 7.41-7.36 (m, 2H), 7.34-7.31 (m, 1H), 7.26-7.19 (m, 2H), 7.07-6.95 (m, 6H), 6.89-6.86 (m, 1H), 3.77 (dd, *J* = 16.5 Hz, 3.3 Hz, 1H), 3.69 (dd, *J* = 16.5 Hz, 1.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 198.3, 148.9, 144.1, 136.7, 136.5, 130.0, 129.5, 128.4, 127.4, 126.6, 124.6, 122.5, 113.8, 109.6, 102.0, 51.9, 21.6.



2-(2-(4-Fluorophenyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3b)

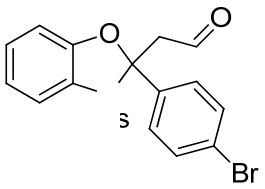
The title compound was prepared according to the general procedure in 88% yield as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.71 (dd, *J* = 3.0 Hz, 2.1 Hz, 1H), 7.60-7.57 (m, 1H), 7.39-7.34 (m, 2H), 7.12-6.99 (m, 6H), 6.90-6.85 (m, 3H), 3.77-3.64 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 197.9, 148.6, 144.3, 136.7, 132.7, 129.6, 129.5, 129.4, 126.4, 124.7, 122.7, 115.4, 115.1, 113.9, 109.7, 101.4, 52.0, 21.6.



2-(2-(4-Chlorophenyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3c)

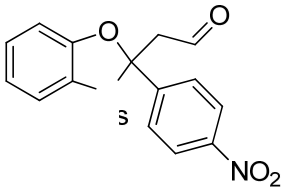
The title compound was prepared according to the general procedure in 95% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.71 (t, *J* = 2.4 Hz, 1H), 7.61-7.58

(m, 1H), 7.31-7.26 (m, 2H), 7.16-6.97 (m, 8H), 6.90-6.87 (m, 1H), 3.76-3.64 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 197.7, 148.6, 144.4, 136.7, 136.3, 135.2, 129.5, 129.4, 128.8, 128.5, 126.4, 124.7, 122.7, 113.9, 109.7, 101.3, 51.7, 21.6.



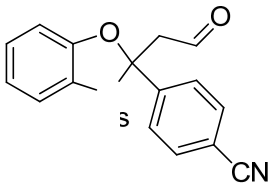
2-(2-(4-Bromophenyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3d)

The title compound was prepared according to the general procedure in 92% yield as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.71 (t, *J* = 2.0 Hz, 1H), 7.62-7.60 (m, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.04-6.98 (m, 4H), 6.89-6.87 (m, 1H), 3.70 (d, *J* = 2.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 197.7, 148.6, 144.4, 136.6, 135.6, 131.4, 129.5, 129.4, 129.0, 126.3, 124.7, 124.6, 122.8, 113.9, 109.7, 101.3, 51.7, 21.7.



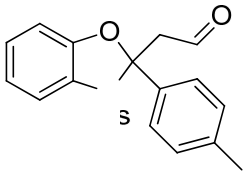
2-(2-(4-Nitrophenyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3e)

The title compound was prepared according to the general procedure in 89% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.68 (dd, *J* = 2.4 Hz, 1.8 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.63-7.59 (m, 3H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.10-7.00 (m, 4H), 6.94-6.91 (m, 1H), 3.79 (dd, *J* = 16.5 Hz, 2.7 Hz, 1H), 3.72 (dd, *J* = 16.5 Hz, 1.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.7, 148.6, 148.5, 145.0, 143.4, 136.6, 129.7, 129.2, 128.3, 126.3, 125.2, 123.4, 123.1, 114.4, 110.0, 100.7, 51.2, 21.6.



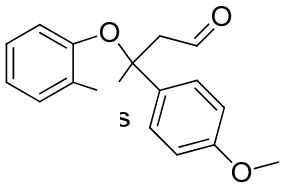
4-(2-(2-Oxoethyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)benzonitrile (3f)

The title compound was prepared according to the general procedure in 85% yield as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.67 (t, *J* = 2.1 Hz, 1H), 7.60-7.49 (m, 5H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.08-6.99 (m, 4H), 6.92-6.89 (m, 1H), 3.72 (t, *J* = 3.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.9, 148.6, 144.9, 141.7, 136.6, 132.1, 129.8, 129.2, 128.0, 126.4, 125.2, 123.1, 114.3, 113.8, 109.9, 100.9, 51.2, 29.8, 21.7.



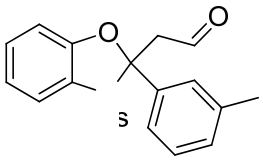
2-(2-(*p*-Tolyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3g)

The title compound was prepared according to the general procedure in 93% yield as yellow solid. M. P. 95-96 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.72 (dd, *J* = 3.0 Hz, 1.8 Hz, 1H), 7.58-7.55 (m, 1H), 7.24 (dd, *J* = 6.6 Hz, 1.8 Hz, 2H), 7.07 (dd, *J* = 6.6 Hz, 1.8 Hz, 1H), 7.03-6.93 (m, 6H), 6.88-6.85 (m, 1H), 3.77 (dd, *J* = 16.5 Hz, 3.0 Hz, 1H), 3.66 (dd, *J* = 16.5 Hz, 1.8 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 198.5, 148.9, 143.9, 140.1, 136.7, 133.8, 129.6, 129.3, 128.9, 127.3, 126.6, 124.5, 122.4, 113.7, 109.5, 102.0, 51.9, 21.6, 21.3.



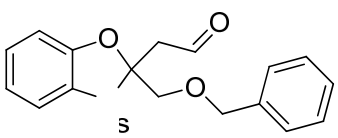
2-(2-(4-Methoxyphenyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3h)

The title compound was prepared according to the general procedure in 86% yield as yellow solid. M. P. 134-135 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.72 (dd, *J* = 3.3 Hz, 1.8 Hz, 1H), 7.59-7.56 (m, 1H), 7.28-7.24 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.01-6.85 (m, 5H), 6.68 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H), 3.74 (dd, *J* = 16.5 Hz, 3.3 Hz, 1H), 3.66 (dd, *J* = 16.5 Hz, 1.8 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 198.5, 160.8, 148.7, 143.9, 136.8, 133.8, 129.5, 129.3, 129.0, 128.6, 126.6, 124.4, 122.4, 113.7, 113.5, 109.6, 102.0, 55.5, 52.1, 21.6.



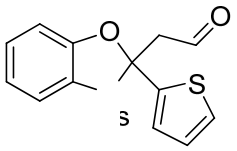
2-(2-(*m*-Tolyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3i)

The title compound was prepared according to the general procedure in 91% yield as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.73 (dd, *J* = 3.3 Hz, 2.1 Hz, 1H), 7.61-7.58 (m, 1H), 7.26-7.22 (m, 1H), 7.18-7.10 (m, 2H), 7.06-6.86 (m, 8H), 3.75 (dd, *J* = 16.5 Hz, 3.3 Hz, 1H), 3.67 (dd, *J* = 16.5 Hz, 1.8 Hz, 1H), 2.31 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 198.4, 148.9, 143.9, 138.3, 136.6, 136.2, 130.7, 129.6, 129.3, 128.2, 128.0, 126.5, 124.7, 124.5, 122.5, 113.8, 109.6, 102.0, 52.0, 21.5, 21.3.



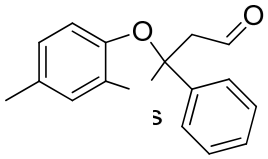
2-(2-((Benzyloxy)methyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3j)

The title compound was prepared according to the general procedure in 88% yield as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.69 (dd, *J* = 3.0 Hz, 1.8 Hz, 1H), 7.76 (dd, *J* = 6.6 Hz, 1.5 Hz, 2H), 7.41-7.13 (m, 8H), 6.95-6.79 (m, 3H), 4.48 (s, 2H), 3.93 (s, 2H), 3.28 (dd, *J* = 16.5 Hz, 3.0 Hz, 1H), 3.20 (dd, *J* = 16.5 Hz, 1.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 197.3, 148.5, 144.9, 137.3, 137.1, 130.0, 128.5, 127.9, 127.6, 127.1, 124.3, 122.0, 112.9, 109.7, 102.8, 73.8, 72.7, 48.4, 21.7.



2-(2-(Thiophen-2-yl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3k)

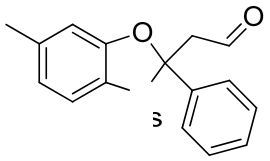
The title compound was prepared according to the general procedure in 91% yield as yellow solid. M. P. 115-116 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.75 (t, *J* = 2.4 Hz, 1H), 7.54-7.51 (m, 1H), 7.29-7.19 (m, 4H), 7.04-6.85 (m, 6H), 3.74 (d, *J* = 2.4 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 197.7, 147.8, 144.1, 140.6, 136.5, 129.5, 129.2, 129.0, 128.3, 126.9, 126.6, 124.4, 122.7, 113.5, 109.8, 100.0, 53.2, 21.6.



2-(5-Methyl-2-phenyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3l)

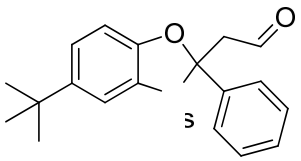
The title compound was prepared according to the general procedure in 91% yield as yellow solid. M. P. 167-168 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.71 (dd, *J* = 2.7 Hz, 2.1 Hz, 1H), 7.38-7.37 (m, 3H), 7.35-7.29 (m, 1H), 7.23-7.18 (m, 2H), 7.06 (d, *J* =

8.4 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.80 (dd, *J* = 8.1 Hz, 0.9 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 3.74 (dd, *J* = 16.5 Hz, 3.0 Hz, 1H), 3.67 (dd, *J* = 16.5 Hz, 2.1 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 198.4, 146.8, 144.0, 136.8, 136.7, 132.3, 130.0, 129.4, 128.4, 127.3, 126.5, 124.7, 114.5, 109.1, 102.0, 51.8, 21.6, 21.5.



2-(6-Methyl-2-phenyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3m)

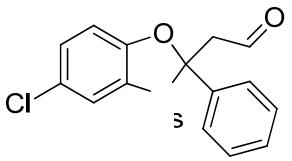
The title compound was prepared according to the general procedure in 89% yield as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.70 (dd, *J* = 2.7 Hz, 2.1 Hz, 1H), 7.44-7.37 (m, 3H), 7.35-7.29 (m, 1H), 7.23-7.18 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.77 (dd, *J* = 8.1 Hz, 0.9 Hz, 1H), 6.70 (s, 1H), 3.73 (dd, *J* = 16.2 Hz, 2.7 Hz, 1H), 3.63 (dd, *J* = 16.5 Hz, 2.1 Hz, 1H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 198.3, 149.0, 143.9, 136.8, 136.6, 134.9, 129.9, 129.4, 128.4, 127.3, 127.1, 126.6, 122.7, 113.6, 110.4, 102.0, 51.8, 21.6, 21.4.



2-(5-(*tert*-Butyl)-2-phenyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3n)

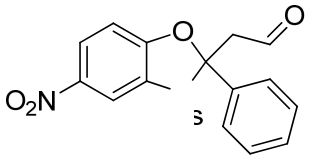
The title compound was prepared according to the general procedure in 83% yield as brown solid. M. P. 148-149 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.72 (s, 1H), 7.60 (s, 1H), 7.40 (d, *J* = 4.8 Hz, 1H), 7.34 (t, *J* = 4.2 Hz, 2H), 7.23 (t, *J* = 4.5 Hz, 2H), 7.04-6.99 (m, 3H), 6.96 (d, *J* = 4.8 Hz, 2H), 6.77 (d, *J* = 4.8 Hz, 1H), 3.73 (dd, *J* = 9.6

Hz, 1.8 Hz, 2H), 2.30 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 198.5, 146.8, 145.9, 144.0, 136.9, 136.5, 129.9, 129.4, 129.1, 128.4, 127.5, 126.7, 121.0, 111.5, 108.5, 102.3, 52.0, 35.0, 31.7, 21.6.



2-(5-Chloro-2-phenyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3o)

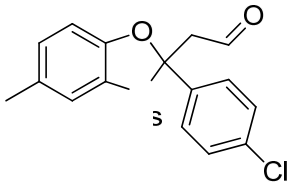
The title compound was prepared according to the general procedure in 87% yield as yellow solid. M. P. 163-164 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.71 (dd, *J* = 3.0 Hz, 1.8 Hz, 1H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.37-7.33 (m, 3H), 7.25-7.20 (m, 2H), 7.06-6.95 (m, 5H), 6.78 (d, *J* = 8.4 Hz, 1H), 3.78 (dd, *J* = 16.5 Hz, 3.0 Hz, 1H), 3.69 (dd, *J* = 16.5 Hz, 1.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 197.8, 147.5, 144.4, 136.2, 130.7, 130.2, 129.6, 128.5, 127.5, 127.4, 126.6, 124.1, 117.2, 113.9, 110.1, 103.1, 51.8, 21.7.



2-(5-Nitro-2-phenyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3p)

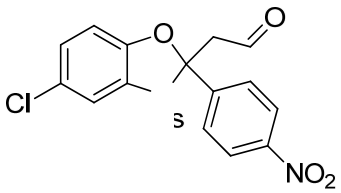
The title compound was prepared according to the general procedure in 84% yield as brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.71 (dd, *J* = 2.7 Hz, 1.8 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 8.01 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 7.43-7.24 (m, 5H), 7.06-6.98 (m, 4H), 6.93 (d, *J* = 9.0 Hz, 1H), 3.89 (dd, *J* = 16.8 Hz, 2.7 Hz, 1H), 3.81 (dd, *J* = 16.8 Hz, 1.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.8, 153.7, 144.9,

143.4, 135.6, 135.5, 130.8, 130.6, 129.7, 128.7, 127.2, 126.8, 121.7, 108.7, 108.6, 104.7, 51.7, 21.7.



2-(2-(4-Chlorophenyl)-5-methyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3q)

The title compound was prepared according to the general procedure in 92% yield as yellow solid. M. P. 92-93 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.69 (s, 1H), 7.43 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 9.3 Hz, 4H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 3.67 (d, *J* = 1.8 Hz, 2H), 2.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 197.9, 146.6, 144.3, 136.8, 136.2, 135.3, 132.6, 129.5, 129.4, 128.7, 128.4, 126.3, 124.9, 114.6, 109.2, 101.4, 51.7, 21.6, 21.5.

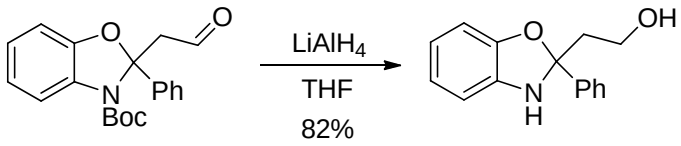


2-(5-Chloro-2-(4-nitrophenyl)-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)acetaldehyde (3r)

The title compound was prepared according to the general procedure in 90% yield as yellow solid. M. P. 152-153 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.67 (dd, *J* = 2.7 Hz, 1.8 Hz, 1H), 8.05 (t, *J* = 2.1 Hz, 1H), 8.02 (t, *J* = 2.1 Hz, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.58 (t, *J* = 2.1 Hz, 1H), 7.56 (t, *J* = 2.1 Hz, 1H), 7.17 (dd, *J* = 6.6 Hz, 1.5 Hz, 2H), 7.05-7.01 (m, 3H), 6.84 (d, *J* = 8.7 Hz, 1H), 3.83 (dd, *J* = 16.5 Hz, 2.4 Hz, 1H), 3.73 (dd,

J = 16.5 Hz, 1.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.2, 148.7, 147.2, 145.4, 142.8, 136.3, 130.5, 129.8, 128.3, 128.2, 126.3, 124.8, 123.5, 114.5, 110.5, 101.8, 51.1, 21.7.

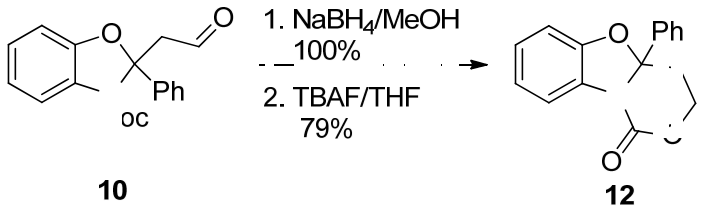
Preparation and Physical and Spectroscopic Data for 11-13



10 **11**

2-(2-Phenyl-2,3-dihydrobenzo[d]oxazol-2-yl)ethanol (11)

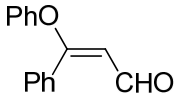
According to the general procedure for the [4+1] annulations, **10** was prepared in 91% yield and subjected to the following reactions. First, **10** (31 mg, 0.09 mmol) was dissolved in 5 mL THF and the mixture was cooled to 0 ºC. $LiAlH_4$ (9.5 mg, 0.25 mmol) was added slowly to the above mixture. After stirring for 1 h, the reaction was quenched by addition of 0.5 mL water. Then the mixture was passed through a short pad of celite and washed with DCM. The liquid was dried with Na_2SO_4 and was evaporated to give a crude mixture. The mixture was applied to column chromatography to give **11** as red solid. M. P. 97-98 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32-7.25 (m, 4H), 7.20 (t, J = 7.0 Hz, 1H), 6.67 (q, J = 7.5 Hz, 2H), 6.56 (t, J = 7.5 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.55 (t, J = 6.5 Hz, 1H), 4.55 (bs, 1H), 3.85-3.77 (m, 2H), 2.07-2.05 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 144.1, 143.5, 136.0, 128.8, 127.2, 126.4, 121.4, 118.3, 114.7, 114.0, 61.0, 57.2, 40.5.



10 **12**

4α-Phenyl-4,4α-dihydrobenzo[4,5]oxazolo[3,2-c][1,3]oxazin-1(3H)-one (12)

To a mixture of **10** (34 mg, 0.1 mmol) in MeOH (2 mL) was added $NaBH_4$ (7.6 mg, 0.2 mmol) at 0 ºC. The mixture was stirred for 1 h at 0 ºC, and quenched with 5 mL of water. The product was extracted with ethyl acetate and the organic layer was dried with Na_2SO_4. Pure reduced product was obtained in 100% yield after evaporation of the solvent. The reduced product was dissolved in 3 mL THF, and treated with 1M TBAF in THF (0.5 mL, 0.5 mmol). After stirring for 2 h, the reaction was quenched with water (10 mL). The product was extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated to give the crude mixture which was purified by column chromatography to give **12** as pink solid. M. P. 84-85 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.00-7.97 (m, 2H), 7.49-7.38 (m, 4H), 7.18-7.04 (m, 3H), 4.66 (t, J = 5.7 Hz, 2H), 3.15 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 168.4, 149.8, 141.0, 139.1, 130.6, 129.6, 128.7, 128.6, 127.2, 127.0, 124.1, 121.6, 75.9, 32.9.



(*E*)-3-Phenoxy-3-phenylacrylaldehyde (16)

To a solution of PhOH (10 mg, 0.11 mmol) in 0.5 mL DCE were added pyrrolidine (1.64 μL, 0.020 mmol) and **2a** (13.5 μL, 0.1 mmol) at room temperature. The mixture was stirred at room temperature for 15 h. Then the mixture was applied to column chromatography directly and eluted with ethyl acetate and hexane to give product **16** in

92% yield as yellow oil. *E*/*Z* = 33; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.09 (d, *J* = 7.5 Hz, 1H), 7.61-7.58 (m, 2H), 7.41-7.23 (m, 5H), 7.04-6.97 (m, 3H), 6.26 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 190.9, 167.3, 157.4, 133.0, 131.5, 130.1, 129.1, 127.6, 123.4, 117.0, 116.7.

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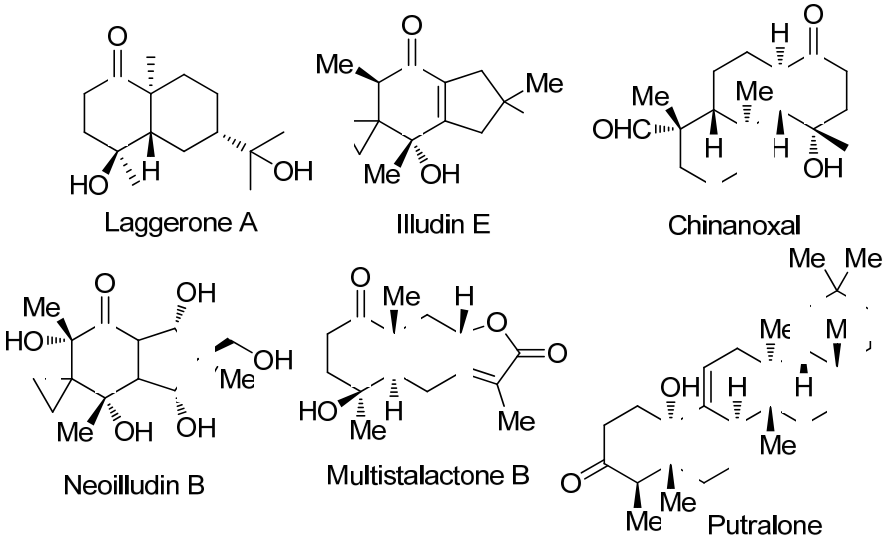
Chapter 6

Asymmetric Desymmetrization of *p*-Quinols

6.1 Background

Synthesis of valuable optically active building blocks from simple starting materials is highly valuable in organic synthesis. As an important representative scaffold, 4-hydroxycyclohexanone is present in numerous biologically significant molecules such as laggerone A,[1] illudin E,[2] chinanoxal,[3] neoilludin B,[4] multistalactone B,[5] putralone[6] (Figure 6.1). However, asymmetric synthesis of this target remains challenging due to the difficulty in controlling stereoselectivity at 4-OH attached chiral center.

Figure 6.1 Natural products with 4-hydroxycyclohexanone scaffold



Desymmetrization of readily available and simple prochiral molecules represents a viable approach in asymmetric synthesis.[7] Asymmetric opening of symmetric epoxides, aziridines and anhydrides is achieved with high yields and excellent stereoselectivities.[8]

Desymmetrization via selective alcohol acylations, Wittig reactions, and Tusji-Trost reactions have been accomplished.[9] Besides, titanium, copper and pig liver esterase mediated desymmetrization processes are also developed.[10]

Prochiral cyclohexadienones have been subjected to versatile asymmetric desymmetrization processes for the synthesis of optically active six-membered ring structures. Initially, diastereoselective desymmetrization of cyclohexadienone scaffolds via chiral auxiliary approach was developed.[11] In 1999, Feringa et al. discovered that copper-phosphoramidite catalyst showed remarkably high levels of stereoselectivity in the conjugate addition of dialkylzinc reagents (R_2Zn) to several 4,4-disubstituted cyclohexadienones.[12] Feringa and co-workers also carried out an efficient enantioselective intramolecular Heck reaction of cyclohexadienones with modular TADDOL-based mono-phosphoramidite as chiral ligand.[13] Chiral Lewis acids catalyzed enantioselective desymmetrization of cyclohexadienone derivatives through asymmetric reduction,[14] epoxidation[15] and Diels–Alder[16] reactions were also reported.

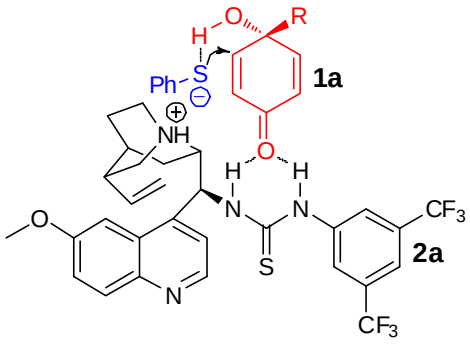
Recently, organocatalytic systems have been proved to be powerful in controlling stereoselectivities in the desymmetrization of cyclohexadienones via asymmetric Michael,[17] oxo-Michael[18] and Setter[19] reactions. These organocatalytic desymmetrization reactions are limited to intramolecular reactions. Intermolecular desymmetrization of *p*-quinols via oxo-Michael/Michael addition cascade reactions is also reported.[20]

6.2 Research Design

As a special cyclohexadienone, *p*-quinols are synthetically useful in the formation of chiral 4-hydroxyl cyclohexanones. However, synthesis of medicinally important cyclohexanones bearing free 4-OH group via asymmetric desymmetrization of *p*-quinols

is challenging due to the difficult in controlling stereoselectivity at 4-position of *p*-quinols.

Scheme 6.1 Design of thiourea catalyzed desymmetrization of *p*-quinols



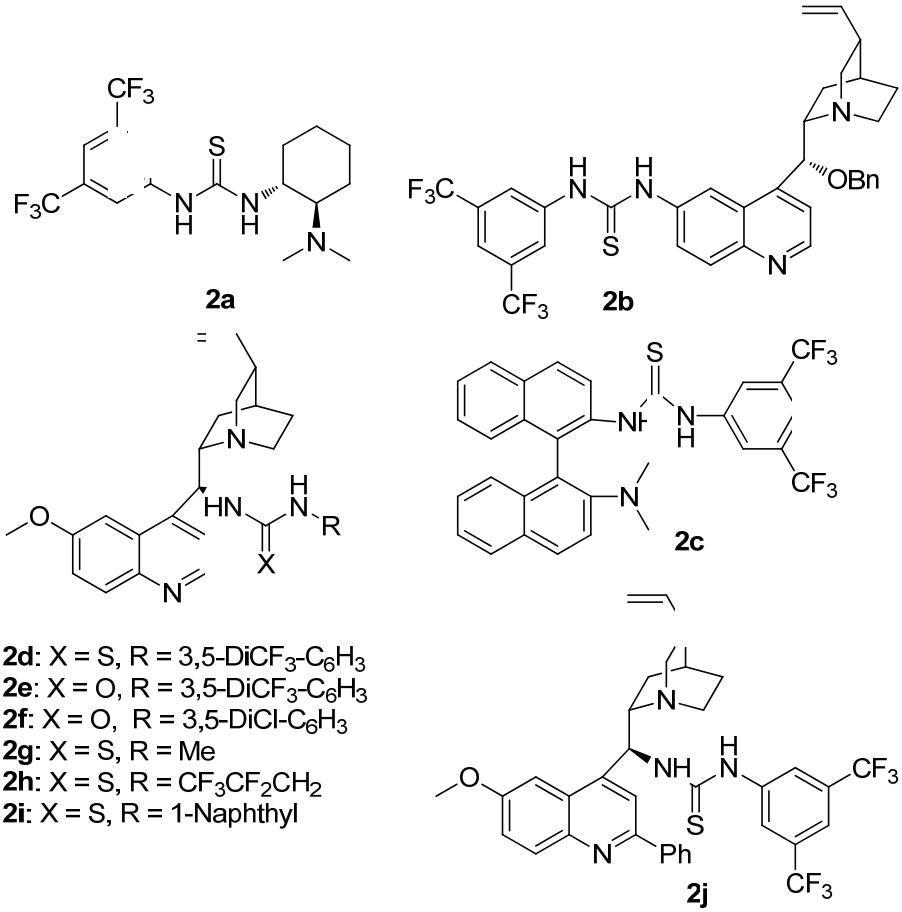
Chiral ureas/thioureas are found to be powerful organocatalysts for asymmetric transformations. We envision that stereoselectivity at 4-position of *p*-quinols can be controlled by the H-bonding interaction formed between the free hydroxyl group and thiourea catalyst. It is proposed that bifunctional catalyst **2a** can activate the electrophile **1a** with the thiourea unit through H-bonding and the nucleophile PhSH with Brønsted base unit simultaneously (Scheme 6.1). It is speculated that PhSH will be deprotonated by bifunctional catalyst **2a** to afford an ion pair initially. H-bonding can be formed between OH group of *p*-quinol **1a** and the deprotonated ion PhS^-. It is expected that the synergistic interaction can result in high efficiency in terms of reaction yield and stereoselectivity for the sulfa-Michael addition reaction.

Although the OH group at the 4-position of the *p*-quinol **1a** does not take part in the catalytic reaction, the functionality may direct the nucleophilic addition in a high stereo-controlled manner. Therefore, good diastereoselectivity and enantioselectivity can be achieved in the desymmetrization process via an intermolecular Michael addition reaction.

6.3 Optimization of Reaction Conditions

In an exploratory study, desymmetrization of *p*-quinol **1a** by bifunctional catalyst **2a** catalyzed sulfa-Michael addition of PhSH is conducted to give the desired product 3a in 64% yield and 0% ee as a single diastereomer (Table 6.1, entry 1).

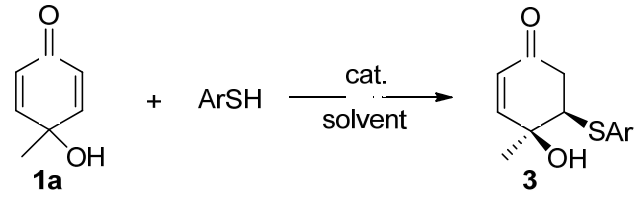
Figure 6.2 Chiral urea and thiourea catalysts



Cinchona alkaloid-derived thiourea catalysts are always considered to be superior. Indeed, improved but still low ee values are observed when cinchona alkaloid catalyst **2b** and binaphthyl catalyst **2c** are utilized (Table 6.1, entry 2-3). To our delight, the enantiomeric excess of **3a** is increased dramatically to 85% in the presence of catalyst **2d** (Table 6.1, entry 4). Investigation (Table 6.1, entry 5-10) of the cinchona alkaloid-

derived thiourea/urea catalysts reveals that catalyst **2f** is more suitable to produce the adduct **3a** in 79% yield and 90% ee (Table 6.1, entry 6).

Table 6.1 Optimization of Reaction Conditions[a]



entry	Ar	ArSH	cat.	solvent	**3**	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	1 eq	**2a**	toluene	**3a**	64	>99:1	0
2	Ph	1 eq	**2b**	toluene	**3a**	74	>99:1	19
3	Ph	1 eq	**2c**	toluene	**3a**	48	>99:1	40
4	Ph	1 eq	**2d**	toluene	**3a**	70	>99:1	85
5	Ph	1 eq	**2e**	toluene	**3a**	73	>99:1	87
6	Ph	1 eq	**2f**	toluene	**3a**	79	>99:1	90
7	Ph	1 eq	**2g**	toluene	**3a**	81	>99:1	79
8	Ph	1 eq	**2h**	toluene	**3a**	78	>99:1	81
9	Ph	1 eq	**2i**	toluene	**3a**	23	>99:1	66
10	Ph	1 eq	**2j**	toluene	**3a**	63	>99:1	82
11	Ph	1.2	**2f**	toluene	**3a**	93	>99:1	91
12	Ph	1.2	**2f**	DCM	**3a**	87	>99:1	78
13	Ph	1.2	**2f**	$CHCl_3$	**3a**	67	>99:1	81
14	Ph	1.2	**2f**	hexane	**3a**	26	>99:1	32
15[e]	Ph	1.2	**2f**	toluene	**3a**	96	>99:1	80
16[f]	Ph	1.2	**2f**	toluene	**3a**	90	>99:1	84
17[g]	Ph	1.2	**2f**	toluene	**3a**	68	>99:1	83
18	2-Me-C_6H_4	1.2	**2f**	toluene	**3ab**	99	>99:1	81
19	4-MeO-C_6H_4	1.2	**2f**	toluene	**3ac**	99	>99:1	88
20	4-Cl-C_6H_4	1.2	**2f**	toluene	**3ad**	75	>99:1	40

[a] See experimental section. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] -20 ºC. [f] 0 ºC. [g] 35 ºC.

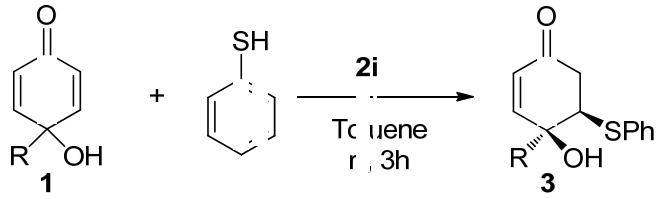
It is found that the yield of **3a** can be increased to 93% with 91% ee when 1.2 eq of PhSH is utilized in the desymmetrization process (Table 6.1, entry 11). Screening of solvents shows that toluene is optimal for the reaction in terms of yield and ee (Table 6.1, entry 11-14). Besides, decreased enantioselectivities are observed when the reaction is conducted under low or high temperature (Table 6.1, entry 15-17). Finally, lower enantioselectivities are obtained for the transformations employing substituted thiophenols with electron-donating or -withdrawing groups (Table 6.1, entry 18-20).

6.4 Expansion of Substrate Scope

The desymmetrization of *p*-quinols by catalyst **2f**-mediated sulfa-Michael addition reactions of PhSH in toluene under room temperature is carried out accordingly employing *p*-quinols bearing versatile substituents. High yield as 87% and 88% ee are obtained for the desymmetrization process with 4-ethyl *p*-quinol as expected (Table 6.2, entry 2). However, only moderate enantioselectivity for Michael product **3c** is observed when more bulky substrate is utilized (Table 6.2, entry 3). The decreased enantioselectivity may be attributed to the weaker H-bonding interaction with the 4-OH group (as described in scheme 6.1) resulting from steric effects.

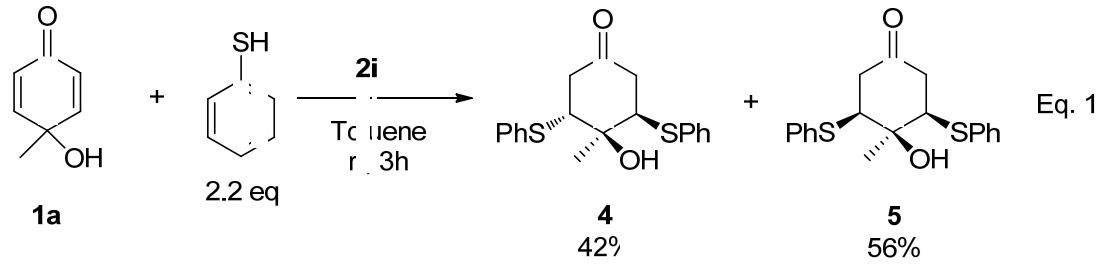
Similarly, transformations with bulky 4-aryl *p*-quinols only provide the corresponding desymmetrization products with 74-88% ee as single diastereomers (Table 6.2, entry 4-9). Other 4-alkyl substrates are also applied in the process to furnish products **3j** and **3k** in good yields and ee values (Table 6.2, entry 10-11).

Table 6.2 Substrate scope expansion of organocatalytic sulfa-Michael addition reaction[a]



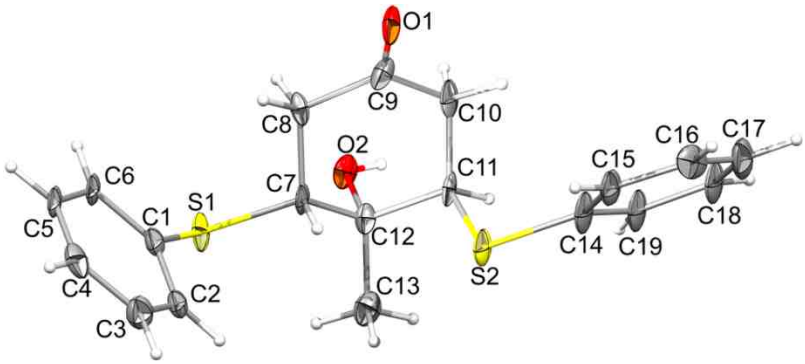
entry	R	3	Yield (%)[b]	d.r.[c]	ee (%)[d]
1	Me	**3a**	93	>99:1	91
2	Et	**3b**	87	>99:1	88
3	$(CH_3)_2CH$	**3c**	78	>99:1	71
4	Ph	**3d**	85	>99:1	83
5	4-Me-C_6H_4	**3e**	73	>99:1	77
6	4-F-C_6H_4	**3f**	91	>99:1	75
7	2-F-C_6H_4	**3g**	86	>99:1	88
8	4-Cl-C_6H_4	**3h**	79	>99:1	76
9	4-Br-C_6H_4	**3i**	83	>99:1	74
10	$AcOCH_2$	**3j**	89	>99:1	83
11	$MeOOC(CH_2)_2$	**3k**	85	>99:1	80

[a] Reaction conditions: PhSH (0.12 mmol) in 3 mL toluene was added to a mixture of *p*-quinols (0.1 mmol) and the catalyst (10 mol %) in toluene (1.0 mL) in 3 hrs. The reaction was stirred at ambient temperature until reaction was complete monitored by TLC. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by HPLC, absolute configuration was not determined.



Finally, double sulfa-Michael addition reaction is conducted by the treatment of **1a** with 2.2 eq of thiophenol (Eq. 1). Double sulfa-Michael product **4** and meso-**5** are obtained. The absolute configuration of **4** is determined by crystallographic analysis (Figure 6.3).

Figure 6.3 X-ray structure of product **4**



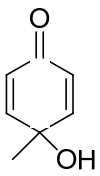
Conclusion

Intermolecular enantioselective desymmetrization of *p*-quinols by thiourea catalyst mediated sulfa-Michael addition reactions has been developed to furnish the corresponding product in good yields and moderate to good enantioselectivities as single diastereomers. Application of the process in natural product synthesis will be investigated.

Experimental Section

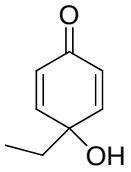
Preparation and Spectroscopic Data for Substrates 1a-1c

Substrates **1a-1c** are prepared according to reported procedure.[21]



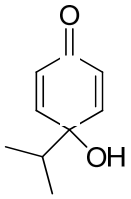
4-Hydroxy-4-methylcyclohexa-2,5-dienone (1a)

The title compound was obtained in 72% yield as white solid. M. P. 70-71 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.89 (d, *J* = 10.0 Hz, 2H), 6.09 (d, *J* = 10.0 Hz, 2H), 3.27 (bs, 1H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 185.7, 152.7, 126.9, 67.0, 26.6.



4-Ethyl-4-hydroxycyclohexa-2,5-dienone (1b)

The title compound was obtained in 69% yield as light yellow solid. M. P. 58-59 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.81 (d, *J* = 9.9 Hz, 2H), 6.18 (d, *J* = 10.2 Hz, 2H), 2.73 (s, 1H), 1.81 (q, *J* = 7.8 Hz, 2H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 186.2, 152.2, 127.8, 70.1, 32.5, 7.7.

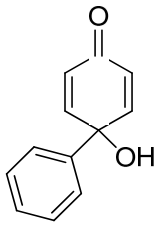


4-Hydroxy-4-isopropylcyclohexa-2,5-dienone (1c)

The title compound was obtained in 65% yield as light brown solid. M. P. 75-76 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 6.82 (d, *J* = 10.0 Hz, 2 H), 6.20 (d, *J* = 10.5 Hz, 2 H), 2.46 (s, 1 H), 2.00 (m, *J* = 7.0 Hz, 1 H), 0.96 (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 185.8, 150.3, 129.0, 72.3, 36.7, 16.8.

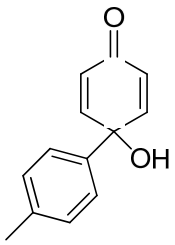
Preparation and Spectroscopic Data for Substrates 1d-1k

Substrates 1d-1k are prepared according to reported procedure.[22]



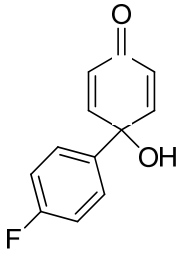
1-Hydroxy-[1,1'-biphenyl]-4(1H)-one (1d)

The title compound was obtained in 41% yield as white solid. M. P. 92-93 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48-7.44 (m, 2H), 7.40-7.29 (m, 3H), 6.88 (dt, *J* = 9.9 Hz, 3 Hz, 2H), 6.20 (dt, *J* = 9.9 Hz, 3 Hz, 2H), 2.76 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 186.3, 151.7, 138.6, 128.8, 128.2, 126.3, 125.2, 70.8.



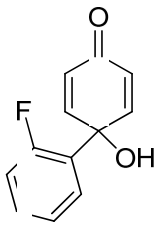
1-Hydroxy-4'-methyl-[1,1'-biphenyl]-4(1H)-one (1e)

The title compound was obtained in 39% yield as light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.36 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 10.2 Hz, 2H), 6.18 (d, *J* = 10.2 Hz, 2H), 3.16 (s, 1H) , 2.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 186.0, 151.3, 138.3, 135.7, 129.6, 126.5, 125.2, 70.85, 21.04.



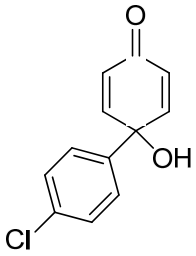
4'-Fluoro-1-hydroxy-[1,1'-biphenyl]-4(1H)-one (1f)

The title compound was obtained in 37% yield as light yellow solid. M. P. 169-170 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 9.9 Hz, 2H), 6.16 (d, *J* = 9.9 Hz, 2H), 2.81 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 186.3, 151.7, 137.7, 134.1, 128.9, 126.9, 126.4, 70.2.



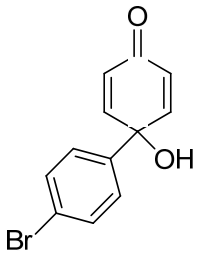
2'-Fluoro-1-hydroxy-[1,1'-biphenyl]-4(1H)-one (1g)

The title compound was obtained in 27% yield as light yellow solid. M. P. 103-104 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.72 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.37-7.29 (m, 1H), 7.20 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.04-6.97 (m, 1H), 4.05 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 186.1, 161.4, 158.1, 149.2, 130.4, 130.3, 127.3, 127.1, 126.4, 126.3, 124.7, 124.6, 116.3, 116.1, 68.3.3



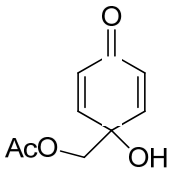
4'-Chloro-1-hydroxy-[1,1'-biphenyl]-4(1H)-one (1h)

The title compound was obtained in 29% yield as white solid. M. P. 124-125 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48-7.43 (m, 2H), 7.10-7.02 (m, 2H), 6.87 (d, *J* = 9.9 Hz, 2H), 6.21 (d, *J* = 9.9 Hz, 2H), 2.89 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 185.6, 164.3, 161.0, 150.7, 134.4, 127.3, 127.1, 126.9, 116.0, 115.7, 70.6.



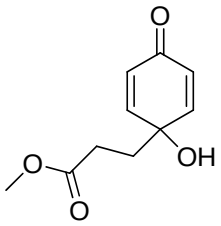
4'-Bromo-1-hydroxy-[1,1'-biphenyl]-4(1H)-one (1i)

The title compound was obtained in 45% yield as yellow solid. M. P. 175-176 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.51 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 9.9 Hz, 2H), 6.23 (d, *J* = 9.9 Hz, 2H), 2.67 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 185.4, 150.2, 137.7, 132.0, 127.1, 127.1, 122.6, 70.7.



(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)methyl acetate (1j)

The title compound was obtained in 61% yield as white brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.90 (d, *J* = 10.2 Hz, 2H), 6.22 (d, *J* = 10.2 Hz, 2H), 4.18 (s, 2H), 4.07 (s, 1H), 2.07 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 185.4, 170.6, 148.3, 129.1, 68.3, 67.8, 20.6.



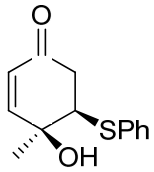
Methyl 3-(1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)propanoate (1k)

The title compound was obtained in 52% yield as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.85 (d, *J* = 10.2 Hz, 2H), 6.13 (d, *J* = 9.9 Hz, 2H), 4.34 (s, 1H), 3.64 (s, 3H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.08 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 185.5, 173.1, 151.1, 127.8, 68.7, 51.6, 34.2, 28.2.

General Procedure for Sulfa-Michael Addition Reactions

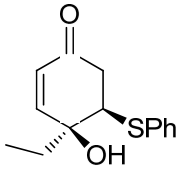
To a solution of **1a** (0.012 g, 0.1 mmol) and catalyst **2f** (0.006 g, 0.01 mmol), PhSH (12 μL, 0.12 mmol) diluted in 3 mL toluene is added over 3 h under room temperature. Solvent is evaporated under reduced pressure. The crude product is purified by flash chromatography with ethyl acetate and hexane.

Physical and Spectroscopic Data for Sulfa-Michael Addition Products



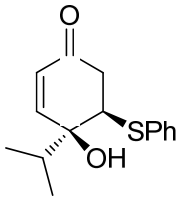
(4*S*,5*R*)-4-Hydroxy-4-methyl-5-(phenylthio)cyclohex-2-enone (3a)

The title compound was obtained in 93% yield as colorless oil. $[\alpha]_D^{25}$ = -99.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49-7.46 (m, 2H), 7.36-7.28 (m, 3H), 6.76 (dd, *J* = 10.2 Hz, 1.2 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H), 3.60 (ddd, *J* = 6.9 Hz, 4.5 Hz, 0.9 Hz, 1H), 3.16 (s, 1H), 2.95 (dd, *J* = 16.8 Hz, 6.9 Hz, 1H), 2.85 (dd, *J* = 17.1 Hz, 4.5 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 196.3, 153.3, 133.8, 132.8, 129.4, 128.4, 128.1, 69.9, 58.7, 42.3, 26.7. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.5 mL/min^{-1}, λ = 254 nm, t_r (minor) = 18.25 min, t_r (major) = 32.21 min.



(4*S*,5*R*)-4-Ethyl-4-hydroxy-5-(phenylthio)cyclohex-2-enone (3b)

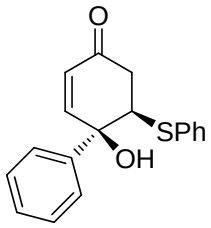
The title compound was obtained in 87% yield as colorless oil. $[\alpha]_D^{25}$ = -113.8 (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.48 (d, *J* = 6.0 Hz, 2H), 7.34-7.30 (m, 3H), 6.78 (d, *J* = 10.5 Hz, 1H), 6.00 (d, *J* = 10.5, 1H), 3.67 (t, *J* = 4.5, 1H), 3.08 (s, 1H), 2.95 (dd, *J* = 17.5 Hz, 7.5 Hz, 1H), 2.85 (dd, *J* = 17.0 Hz, 4.5 Hz, 1H), 2.08-2.01 (m, 1H), 1.85-1.78 (m, 1H), 0.98 (t, *J* = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 196.4, 153.0, 133.8, 132.9, 129.4, 129.2, 128.1, 72.2, 56.2, 42.1, 32.0, 8.2. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.5 mL/min^{-1}, λ = 254 nm, t_r (minor) = 17.53 min, t_r (major) = 44.13 min.



(4*S*,5*R*)-4-Hydroxy-4-isopropyl-5-(phenylthio)cyclohex-2-enone (3c)

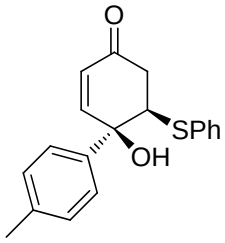
The title compound was obtained in 78% yield as colorless oil. $[\alpha]_D^{25}$ = -108.5 (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49-7.44 (m, 2H), 7.36-7.29 (m, 3H), 6.88 (dd, *J* = 10.2 Hz, 1.2 Hz, 1H), 6.01 (d, *J* = 10.5 Hz, 1H), 3.83-3.79 (m, 1H), 3.05 (d, *J* = 0.6 Hz, 1H), 2.95 (dd, *J* = 17.1 Hz, 6.0 Hz, 1H), 2.85 (dd, *J* = 17.4 Hz, 4.5 Hz, 1H), 2.33-2.24 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.2, 152.8, 134.0, 132.9, 129.4, 129.2, 128.1, 73.7, 56.6, 42.0, 34.8, 17.7, 16.5. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm),

Hexanes / IPA = 70 / 30, 0.6 mL/min^{-1}, λ = 254 nm, t_r (minor) = 16.63 min, t_r (major) = 49.22 min.



(1*R*,2*R*)-1-Hydroxy-2-(phenylthio)-2,3-dihydro-[1,1'-biphenyl]-4(1*H*)-one (3d)

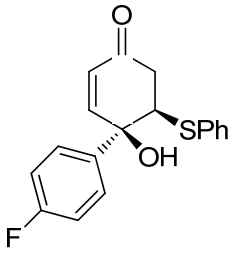
The title compound was obtained in 85% yield as colorless oil. $[\alpha]_D^{25}$ = -161.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.50-7.47 (m, 2H), 7.39-7.31 (m, 8H), 6.83 (dd, *J* = 9.9 Hz, 1.2 Hz, 1H), 6.23 (d, *J* = 10.2 Hz, 1H), 3.87 (s, 1H), 3.82 (ddd, *J* = 6.9 Hz, 4.2 Hz, 1.2 Hz, 1H), 2.89 (dd, *J* = 16.8 Hz, 7.2 Hz, 1H), 2.73 (dd, *J* = 16.8 Hz, 4.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.5, 151.0, 141.1, 133.4, 133.0, 129.8, 129.2, 128.6, 128.4, 128.1, 126.0, 74.1, 60.7, 42.0. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.6 mL/min^{-1}, λ = 254 nm, t_r (minor) = 18.87 min, t_r (major) = 31.35 min.



(1*R*,2*R*)-1-Hydroxy-4'-methyl-2-(phenylthio)-2,3-dihydro-[1,1'-biphenyl]-4(1*H*)-one (3e)

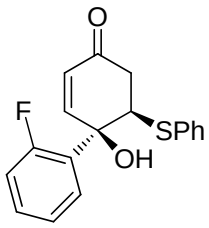
The title compound was obtained in 73% yield as light yellow oil. $[\alpha]_D^{25}$ = -142.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37-7.32 (m, 4H), 7.27-7.23 (m, 3H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.82 (dd, *J* = 10.2 Hz, 1.2 Hz, 1H), 6.22 (d, *J* = 10.2 Hz,

1H), 3.83-3.79 (m, 2H), 2.87 (dd, *J* = 17.1 Hz, 6.9 Hz, 1H), 2.72 (dd, *J* = 16.8 Hz, 4.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.6, 151.2, 138.2, 138.0, 133.5, 133.0, 129.7, 129.3, 129.2, 128.0, 125.9, 60.8, 42.0, 21.0. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.6 mL/min^{-1}, λ = 254 nm, t_r (minor) = 36.57 min, t_r (major) = 42.21 min.



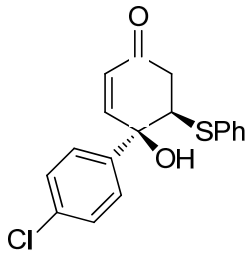
(1*R*,2*R*)-4'-Fluoro-1-hydroxy-2-(phenylthio)-2,3-dihydro-[1,1'-biphenyl]-4(1*H*)-one (3f)

The title compound was obtained in 91% yield as light yellow oil. $[\alpha]_D^{25}$ = -93.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41-7.37 (m, 2H), 7.32-7.23 (m, 7H), 6.78 (dd, *J* = 10.2 Hz, 0.9 Hz, 1H), 6.23 (d, *J* = 10.2 Hz, 1H), 3.81 (s, 1H), 3.77 (ddd, *J* = 7.8 Hz, 4.2 Hz, 1.2 Hz, 1H), 2.90 (dd, *J* = 17.1 Hz, 7.8 Hz, 1H), 2.73 (dd, *J* = 17.1 Hz, 4.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.1, 150.3, 139.9, 134.4, 133.1, 130.1, 129.3, 128.7, 128.2, 127.5, 73.7, 60.4, 41.8. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.5 mL/min^{-1}, λ = 254 nm, t_r (minor) = 19.28 min, t_r (major) = 37.32 min.



(1*R*,2*R*)-2'-Fluoro-1-hydroxy-2-(phenylthio)-2,3-dihydro-[1,1'-biphenyl]-4(1*H*)-one (3g)

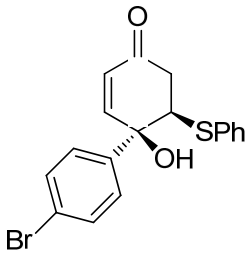
The title compound was obtained in 86% yield as light yellow oil. $[\alpha]_D^{25}$ = -109.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.61 (t, *J* = 4.8 Hz, 1H), 7.26-7.10 (m, 7H), 6.87-6.80 (m, 2H), 6.17 (d, *J* = 6.0 Hz, 1H), 3.81 (s, 1H), 4.27 (dd, *J* = 6.0 Hz, 2.4 Hz, 1H), 3.59 (s, 1H), 2.96 (dd, *J* = 7.8 Hz, 6.6 Hz, 1H), 2.73 (dd, *J* = 10.2 Hz, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 197.0, 150.4, 132.8, 130.3, 130.2, 129.8, 129.5, 128.9, 128.1, 127.7, 124.1, 116.2, 116.0, 71.7, 55.4, 41.6. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.5 mL/min^{-1}, λ = 254 nm, t_r (minor) = 20.32 min, t_r (major) = 33.62 min.



(1*R*,2*R*)-4'-Chloro-1-hydroxy-2-(phenylthio)-2,3-dihydro-[1,1'-biphenyl]-4(1*H*)-one (3h)

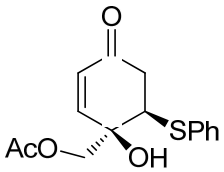
The title compound was obtained in 79% yield as light yellow oil. $[\alpha]_D^{25}$ = -118.9 (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49-7.43 (m, 2H), 7.36-7.25 (m, 5H), 7.08-7.00 (m, 2H), 6.82 (dd, *J* = 10.2 Hz, 1.2 Hz, 1H), 6.25 (d, 1H, *J* = 10.2), 3.85 (s, 1H), 3.80 (ddd, *J* = 7.2 Hz, 4.2 Hz, 1.2 Hz, 1H), 2.91 (dd, *J* = 16.8 Hz, 7.2 Hz, 1H), 2.75 (dd, *J* = 16.8 Hz, 4.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 196.2, 150.6, 133.3, 133.0, 130.0, 129.3, 128.2, 127.9, 127.8, 115.6, 115.3, 73.7, 60.8, 41.9. The ee was

determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.5 mL/min^{-1}, λ = 254 nm, t_r (minor) = 21.35 min, t_r (major) = 51.33 min.



(1*R*,2*R*)-4'-Bromo-1-hydroxy-2-(phenylthio)-2,3-dihydro-[1,1'-biphenyl]-4(1*H*)-one (3i)

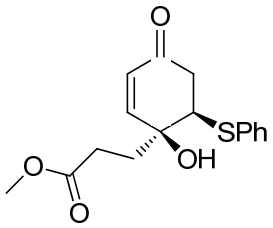
The title compound was obtained in 83% yield as light yellow solid. M. P. 112-113 ºC; $[\alpha]_D^{25}$ = -156.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47-7.42 (m, 2H), 7.34-7.23 (m, 5H), 7.05-6.99 (m, 2H), 6.80 (dd, *J* = 10.2 Hz, 1.2 Hz, 1H), 6.23 (d, *J* = 10.2 Hz, 1H), 3.85 (s, 1H), 3.78 (ddd, *J* = 7.2 Hz, 4.2 Hz, 1.2 Hz, 1H), 2.89 (dd, *J* = 16.8 Hz, 7.5 Hz, 1H), 2.73 (dd, *J* = 16.8 Hz, 4.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.2, 150.3, 140.5, 133.1, 131.6, 130.1, 129.3, 128.2, 127.8, 122.5, 73.7, 60.3, 41.8. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.5 mL/min^{-1}, λ = 254 nm, t_r (minor) = 19.75 min, t_r (major) = 36.69 min.



((1*R*,6*R*)-1-hydroxy-4-oxo-6-(phenylthio)cyclohex-2-en-1-yl)methyl acetate (3j)

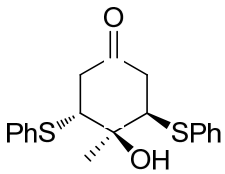
The title compound was obtained in 89% yield as light yellow oil. $[\alpha]_D^{25}$ = -95.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49-7.46 (m, 2H), 7.35-7.31 (m, 3H), 6.78 (d, *J* = 10.2 Hz, 1H), 4.42 (d, *J* = 11.4, 1H), 4.22 (d, *J* = 11.4, 1H), 3.77 (dd, *J*

= 8.7 Hz, 5.1 Hz, 1H), 3.24 (s, 1H), 2.96 (dd, *J* = 17.1 Hz, 8.7 Hz, 1H), 2.88 (dd, *J* = 17.1 Hz, 5.1 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 196.2, 170.3, 148.4, 133.2, 132.9, 131.0, 129.4, 128.3, 70.9, 67.0, 52.9, 41.4, 20.6. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.6 mL/min^{-1}, λ = 254 nm, t_r (minor) = 11.79 min, t_r (major) = 14.61 min.



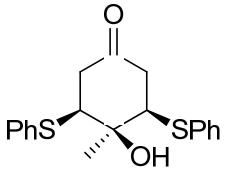
Methyl 3-((1*S*,6*R*)-1-hydroxy-4-oxo-6-(phenylthio)cyclohex-2-en-1-yl)propanoate (3k)

The title compound was obtained in 85% yield as light yellow oil. $[\alpha]_D^{25}$ = -34.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48-7.45 (m, 2H), 7.35-7.27 (m, 3H), 6.75 (dd, *J* = 10.5 Hz, 1.5 Hz, 1H), 5.99 (d, *J* = 10.2 Hz, 1H), 3.68 (s, 3H), 3.63-3.60 (m, 1H), 3.50 (s, 1H), 2.95-2.92 (m, 2H), 2.58-2.49 (m, 2H), 2.23 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 195.7, 173.6, 151.9, 133.6, 132.9, 129.4, 129.2, 128.2, 71.3, 57.7, 51.9, 42.2, 33.6, 28.5. The ee was determined by HPLC on Daicel Chiralpak AS-H (25 cm), Hexanes / IPA = 70 / 30, 0.6 mL/min^{-1}, λ = 254 nm, t_r (minor) = 18.49 min, t_r (major) = 22.58 min.



(3*R*,5*R*)-4-Hydroxy-4-methyl-3,5-bis(phenylthio)cyclohexanone (4)

The title compound was obtained in 42% yield as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47-7.40 (m, 4H), 7.33-7.25 (m, 6H), 3.76 (t, *J* = 7.5 Hz, 1H), 3.69 (t, *J* = 4.8 Hz, 1H), 3.09 (dd, *J* = 15.3 Hz, 4.8 Hz, 1H), 2.81 (s, 1H), 2.72 (d, *J* = 8.1 Hz, 2H), 2.40 (dd, *J* = 15.3 Hz, 4.8 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 206.1, 133.6, 133.1, 132.8, 132.5, 129.2, 128.0, 127.8, 77.4, 77.0, 76.6, 73.7, 55.9, 54.4, 44.8, 42.8, 26.4.



(3*R*,4*S*,5*S*)-4-Hydroxy-4-methyl-3,5-bis(phenylthio)cyclohexanone (5)

The title compound was obtained in 56% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.44-7.39 (m, 4H), 7.32-7.25 (m, 6H), 3.26 (dd, *J* = 13.5 Hz, 4.5 Hz, 2H), 2.91 (t, *J* = 14.1 Hz, 2H), 2.60 (dd, *J* = 13.8 Hz, 3.9 Hz, 2H), 2.47 (s, 1H), 1.71 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 206.0, 134.0, 132.6, 129.2, 127.8, 73.9, 56.5, 45.0, 26.9.

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