N-hetereocyclic carbenes-catalyzed desymmetrization and rapid access to spirocyclic molecules

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**N-HETEREOCYCLIC CARBENES-CATALYZED
DESYMMETRIZATION AND RAPID ACCESS TO
SPIROCYCLIC MOLECULES**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCE

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SPIROCYCLIC MOLECULES**

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ABSTRACT

This thesis focuses on enantioselective desymmetrization reactions enabled by *N*-heterocyclic carbenes (NHCs) organocatalysts. It contains four parts:

Chapter 1 gives brief introductions to the history and development of NHCs organocatalysts classified by active intermediates within this field. Representative examples are summarized and reviewed as well in this part.

Chapter 2 describes an NHC-thiourea co-catalysis of optical pure spirocyclic skeletons via Stetter-aldol tandem reaction. Desymmetrization of a remote chiral center of the product was constructed successfully with three chiral centers, which included two remote chiral centers from the NHC catalyst reaction site. The desymmetrized products hold potential to serve as the building blocks in bioactive molecules and the chiral auxiliary, which further increases the utility of this reaction.

Chapter 3 is about NHC organocatalytic strategy for the enantioselective formal [4+2] construction of multisubstituted phenols, which represents the first intermolecular cycloaddition arene construction method. This method employs easily accessible enals and diketones to construct phenol framework with excellent regioselectivity, and simultaneously install a remote all-carbon quaternary chiral center with good enantioselectivity via desymmetrization.

Chapter 4 introduces an enantioselective approach to conformationally constrained carbocyclic β -amino acids via amine-catalyzed addition of unsaturated imine gamma-carbon to enal. Various imines and enal are well tolerated with excellent diastereoselectivity and enantioselectivity, which possess huge potential in the conformationally constrained β -peptides synthesis.

PUBLICATIONS

1. Access to All-Carbon Spirocycles through a Carbene and Thiourea Cocatalytic Desymmetrization Cascade Reaction
Shitian Zhuo, Tingshun Zhu, Leijin Zhou, Chengli Mou, Huifang Chai, Yunpeng Lu, Lutai Pan, Zhichao Jin, and Yonggui Robin Chi. *Angew. Chem. Int. Ed.* 10.1002/anie.201810638; *Angew. Chem.* 10.1002/ange.201810638.
2. Carbene catalyzed desymmetrization [4+2] arene construction.
Tingshun Zhu, Yingguo Liu, **Shitian Zhuo**, Marie Smetankova¹, Xuan Huang, Yonggui Robin Chi. (submitted)
3. Enantioselective Synthesis of Cyclic β -Amino Acid via Amine-Catalyzed Addition of Unsaturated Imine γ -Carbon to Enal.
Shitian Zhuo, Zhijian Huang, Zhichao Jin, Chengli Mou, Yonggui Robin Chi (to be submitted)

ABBREVIATIONS

^1H NMR	proton nuclear magnetic resonance
^{13}C NMR	carbon-13 nuclear magnetic resonance
Ac	acetyl
Boc	<i>tert</i> -butoxycarbonyl
BQ	benzoquinone
Bu	butyl
Bn	benzyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMAP	4-dimethylaminopyridine
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Equiv	equivalent
ESI	electrospray ionization
GC	gas chromatography
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
IPA	isopropyl alcohol
<i>i</i> Pr	isopropyl
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide

<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Mes	mesityl
Ms	mesyl (methanesulfonyl)
NBS	<i>N</i> -bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
OAc	acetoy
OTf	trifluoromethanesulfonate
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
SET	single electron transfer
TLC	thin layer chromatography
TMS	trimethylsilyl
α	alpha
β	beta
γ	gamma
μ	micro
°C	degree centigrade
mmol	millimole
mol%	mole percent

Chapter 1

Introduction

1.1 Introduction on Asymmetric Organocatalysis

The asymmetric synthesis is the hotspot of the current chemistry communities. Nowadays, enzymatic catalysis, organometallic catalysis, together with organocatalysis are widely accepted as the main branches of enantioselective synthesis. Among them, the development of organocatalysis is relatively new, although the application of organic compounds to facilitate enantioselective transformation can be traced back to a century ago, when Bredig and Fiske¹ reported an asymmetric reaction between hydrocyanic acid and benzaldehyde catalyzed by cinchonidine in 1912. Till the late 1990s, there were only a few researches demonstrating that small organocatalysts could be used to address practical problems in chemical synthesis. It was not until 2000, that the field of organocatalysis started to rekindle and flourish boom, inspired by two seminal publications which conceptualized the field of organocatalysis. Among the two highly influential publications, one focused on enamine catalysis, proposed by from Carlos Barbas, Richard Lerner and Benjamin List;^{2(a)} and the other focused on iminium catalysis, suggested by from David W. C. MacMillan.^{2(b)}

Numerous advantages offered by organocatalysis has led to wide application of organocatalysis in chemical synthesis. The advantages include:

(a) mild reaction conditions. Insensitivity to air and moisture makes organocatalysis reactions easy to be conducted.

(b) low cost. Optically pure starting materials are highly abundant in natural sources.

(c) low toxicity. In general, organocatalysts are less toxic than metal-based catalysts. Besides, they are more environmentally friendly.

1.2 Introduction on *N*-heterocyclic Carbenes

Since Arduengo isolated the first stable 1,3-di(adamantyl)imidazol-2-ylidene in 1991 (**Scheme 1.1**),³ *N*-heterocyclic carbenes (NHCs) have received great attention in the scientific community. Intense research has been conducted to widen the application of the NHCs in the synthesis of various structural scaffolds. Nowadays, *N*-heterocyclic carbenes is ranked as one of the most powerful tools in organic chemistry, with numerous applications in organic synthesis processes.

Scheme 1.1 First example of stable *N*-heterocyclic carbene

Its unique structural characteristics feature NHC's distinct properties. NHCs are defined as heterocyclic species containing a carbene carbon and at least one nitrogen atom within the ring structure.^{4,5} These neutral compounds contain a divalent carbon atom with a six-electron valence shell.

For a long time in history, carbenes were considered as species which are highly reactive and transient due to their coordinatively unsaturated and incomplete electron octet. In 1991, Arduengo *et al.* isolated the first stable carbene by tactfully introducing bulky substituents adjacent to the carbene carbon, which helped to sterically prevent dimerization to the corresponding olefin. The nitrogen atoms also helped to stabilize the species electronically by the σ -electron-withdrawing and π -electron-donating effects.

1.2.1 Properties of *N*-Heterocyclic Carbenes

In all NHCs, the carbene carbon is in a singlet state configuration, leaving the p_π orbital of the carbene centre empty. This allows the adjacent nitrogen atoms to stabilize the carbene by donating π -electron into the vacant p_π orbital, while lowering the energy of the occupied σ orbital simultaneously by exerting σ -electron withdrawing effects on the carbene centre.⁶ Bulky substituents adjacent to the carbene centre offer further stabilization, although this effect is secondary to the electronic stabilization provided by the nitrogen atoms.⁷ Meanwhile, the lone pair of electrons that lie on the plane of carbene grant NHCs to possess nucleophilic and σ -donor properties.⁸

Scheme 1.2 Structural features of NHCs

1.2.2 Applications of *N*-heterocyclic carbenes

The major applications of *N*-heterocyclic carbenes (NHCs) in modern chemistry can be divided into three categories. The σ -donor ability of NHCs makes them suitable ligands for coordination to transition metals, as well as enables them to form adducts by coordinating to p-block elements. The electronic properties of NHCs are also the factors that enables them attractive organocatalysts.

Scheme 1.3 Major applications of NHCs.

Deprotonation upon base treatment of the azolium precursor allows the generation of NHC. Based on the structural differences, NHCs could be classified into several classes (**Scheme 1.4**). Among them, imidazolylienes I, imidazolinylidenes II and triazolylienes III are particularly well-studied.

Scheme 1.4 Structures of commonly-used *N*-heterocyclic carbenes.

Through umpolung reactivity, NHCs are widely applied in areas such as benzoin condensation, ring-opening reaction, a^3 to d^3 umpolung, Stetter reaction, transesterification, and ring expansion polymerization. It is a good way to realize an effective synthesis through the creation of new basic activation modes, and through the development of better reaction controls.

In recent years, advanced progress has been made on organocatalysis using NHCs. The utilization of NHCs in organocatalysis offers a simple and straightforward way to construct complex molecules with highly enantioselectivity, which required multiple steps in traditional methods.

The four key intermediates in NHC-catalyzed transformations are: nucleophilic acyl anion, enolate, homoenolate species, and electrophilic acyl azolium (Scheme 1.5).⁸ Recent progress has seen the use of carboxylic acid,⁹ ketene¹⁰ and ester substrates,¹¹ however, simple aldehydes and α , β -unsaturated enals remain the most commonly-used substrates for NHC-catalyzed transformations.¹²

Scheme 1.5 Four key intermediates of NHC-catalyzed reaction pathways

1.3 Reactions that involve acyl anions intermediate

The two most well-known NHC-catalyzed reactions, which proceed through the formation of the acyl anion intermediate, are the benzoin condensation and the Stetter reaction. In both cases, simple aldehyde substrates are employed. The first example of an NHC-catalyzed benzoin condensation was reported by Ukai in 1943.¹³ However, the exact mode of reaction of the NHC was not known until 15 years later, when a mechanism was proposed by Breslow (Scheme 1.6).¹⁴ The NHC-catalyzed benzoin condensation starts with a nucleophilic attack of the carbene that is formed *in-situ* on the aldehyde, obtaining intermediate I. After the proton transfer, the enamine-like Breslow intermediate II is formed. Due to π -donation from the nitrogen atoms in the ring, the (normally electrophilic) carbonyl

carbon acts as a transient nucleophile. It can then attack the second equivalent of aldehyde, forming intermediate III. Subsequent elimination of the NHC leads to the formation of the final product.

Scheme 1.6 Catalytic cycle of NHC catalyzed benzoin condensation.

The electrophile scope of the benzoin condensation was extended to Michael acceptors by Stetter.¹⁵ For this type of reaction, the initial deprotonation of the aldehyde substrate and formation of the acyl anion equivalent II occurs the same way as the benzoin condensation. The Breslow intermediate then attacks an α, β -unsaturated compound. As a result, the reaction proceeds through intermediate IV, leading to the formation of the 1,4-addition product. A variety of Michael acceptors could be employed for the Stetter reaction, affording 1,4-diketones, 4-ketoesters and 4-ketonitriles as the products.¹⁶ In order to prevent self-condensation of the aldehyde (which acts as a donor), which may occur alongside the desired 1,4-addition that leads to an unwanted benzoin product, Scheidt *et al.* introduced the use of acylsilanes or pyruvates as precursors to the Breslow intermediate (**Scheme**

1.8).^{17,18} As with the benzoin condensation, intramolecular and enantioselective versions of the Stetter reaction have also been developed.^{19,20}

Scheme 1.7 The mechanism of the benzoin condensation and Stetter reaction.

Scheme 1.8 Acylsilanes or pyruvates as precursors to the Breslow intermediate developed by Scheidt

1.4 Reactions that involve enolate intermediate

β -protonation of the homoenolate intermediate leads to the formation of a zwitterionic intermediate, known as the azolium enolate (**Scheme 1.9**). This enolate intermediate can also be formed directly by the reaction of NHCs with ketenes²¹ or esters.²² The enolate and homoenolate intermediates react by two different pathways, which often compete with each other, resulting in the formation of different products. In the reactions of α , β -enals, it has been shown that the selection of the reaction pathway could be controlled to a certain degree by careful variation of catalyst and reaction conditions. Particularly, the choice of base is important.²³ Strong bases

promote the C-C bond formation, causing the reaction to proceed through the homoenolate pathway. In the presence of weaker bases, protonation of the homoenolate could occur, leading to subsequent enolate formation.²⁴ An example of how small variations in reaction conditions influence the reaction pathway is shown in the previously-discussed γ -butyrolactone formation. Glorius *et al.* initially reported the reaction of α , β -enals with activated ketones, which proceeded through the homoenolate pathway to afford γ -lactones (**Scheme 1.10**).²⁵ However, formation of β -lactone as the side product occurred in some cases. Further studies revealed that the formation of this side product occurred through the competing enolate pathway. This pathway could be greatly favored by using less polar solvents, higher temperatures and triethylamine as the base.²⁶ Various other NHC-catalyzed reactions could occur via the enolate pathway, resulting in β -lactams formation,³⁰ as well as unsaturated δ -lactams and δ -lactones formation.²⁷

Scheme 1.9 The generation of nucleophilic intermediates from α , β -unsaturated enals.

Scheme 1.10 Homo enolate mediate γ -lactones formation

1.5 Reactions that involve homoenolate intermediate

The usage of α , β -unsaturated enals instead of simple aldehydes as the nucleophile precursors leads to a number of different reaction pathways. Reactions employing enal substrates still proceed through a Breslow-like intermediate at the initial stage.

Nonetheless, a different intermediate is formed subsequently. In this reaction, the identity of the intermediate is used to determine the pathways that the reaction undergoes. Bode²⁸ and Glorius²⁵ reported separately the reaction of enals with aromatic aldehydes, which proceeded through a homoenolate intermediate to afford γ -butyrolactones. As an α , β -unsaturated aldehyde substrate is used, nucleophilic attack of the carbene results in the formation of a conjugated system, in which both the carbonyl carbon and the β -carbon could act as nucleophiles (**Scheme 1.9**). In homoenolate reaction, it is preferential to employ NHCs with bulky side-chains to block the carbonyl carbon sterically. This ensures that the carbonyl carbon will not react preferentially to the β -carbon, thus preventing the formation of a benzoin product. Homoenolate intermediates will then undergo self-condensation with another equivalent of enal,²⁴ as well as cross-condensation with a wide range of imines, aldehydes, enals or α -activated ketones to form γ -lactones, γ -lactams, spiro- and bicyclic lactones, and bicyclic β -lactams.²⁹ Apart from lactone and lactam formation, the utility of homoenolate intermediates has been expanded to reactions with α , β -unsaturated ketones, resulting in the formation of the substituted cyclopentenones.³⁰

1.6 Reactions that involve acyl azoliums intermediate

Another class of NHC-catalyzed reactions includes the reactions that proceed through the acyl azolium (or α , β -unsaturated acyl azolium) intermediate. In comparison to the nucleophilic intermediates commonly seen in NHC-catalyzed reactions, the acyl azolium behaves like an electrophile. After the formation of the Breslow intermediate, the acyl azolium will either be formed directly (if the Breslow intermediate possesses a leaving group at the α -position) or be oxidized by an external oxidant.³¹ This intermediate can then be trapped by a nucleophile to form final products. Formation of an acyl azolium intermediate could also occur by α -

protonation of an enolate. The relationship between the homoenolate, enolate and acyl azolium intermediates, as well as the various reactions they undergo, are summarized in **Scheme 1.11**.

Scheme 1.11 Summary of major NHC-catalyzed reaction pathways of enals.

1.7 Cooperative catalysis

N-heterocyclic carbenes (NHCs) are known for their ability to catalyze a wide variety of enantioselective transformations. Such transformations possess great potentials and they could be largely exploited with the use of cooperative catalysis. Cooperative catalysis using NHCs helps improving the yield and selectivity, besides expanding the substrate scope.

Cooperative Lewis acid/*N*-heterocyclic carbene catalysis is one of most widely use strategies.³²⁻³⁶

In 2010, Scheidt's group disclosed an enlightening cooperative NHC/Lewis acid system (**Scheme 1.12**). Magnesium (II) di-*tert*-butoxide was employed as the Lewis acid to lower the LUMO for the overall reaction, which favored the addition of homoenolate

intermediate to hydrazones, affording highly substituted γ -lactams in high yields and exceptionally high enantioselectivity.³²

Scheme 1.12 Cooperative NHC/Lewis acid system disclosed by Scheidt *et al*

Later, the same group demonstrated that lithium chloride could be used as the useful Lewis acid in the construction of spirooxindole lactones. In the presence of lithium chloride, this NHC-mediated annulation between β -aryl substituted enals and isatin afforded final product with up to 96% ee. The usage of Lewis acid has improved the ee significantly, as compared to the ee when Lewis acid was not used (34%).³³ (**Scheme 1.13**)

Scheme 1.13 Cooperative NHC/Lewis acid system disclosed by Scheidt *et al*

In Chi's published work on NHC-mediated oxidative activation of γ -position of enals, the challenging remote chiral control was realized through the introduction of a Lewis acid cocatalyst $[\text{Sc}(\text{OTf})_3/\text{Mg}(\text{OTf})_2]$.³⁵ (**Scheme 1.13**)

Scheme 1.13 Cooperative NHC/Lewis acid system disclosed by Chi *et al*

H-bond donors such as thiourea have also been demonstrated as useful co-catalysts in the field of NHC-catalyzed reaction.³⁷⁻³⁹

In 2006, Scheidt *et al.* demonstrated the utility of thiourea mediated activation of nitroalkenes to improve the reactivity of NHC-catalyzed direct nucleophilic acylation. The incorporation of chiral thiourea could further lead to 74% ee.³⁷ (**Scheme 1.14**)

Scheme 1.14 Cooperative NHC/Lewis acid system disclosed by Scheidt *et al*

In Chi's published study on NHC-catalyzed sulfonation of α , β -unsaturated ketones in the presence of sulfonyl imines, the incorporation of non-covalent thiourea/tertiary-amine has demonstrated great ability to control the stereoselectivity of the final product. After proper optimization, high enantioselectivity (up to 99% ee) could be achieved.³⁸ (**Scheme 1.15**)

Scheme 1.15 Cooperative NHC/Lewis acid system disclosed by Chi *et al*

Recently, Scheidt *et al.*³⁹ documented an enantioselective *N*-heterocyclic carbene (NHC)-catalyzed β -protonation by introducing carbonyl group elegantly next to the β -position of the substrates, which allowed for the stereoselective shielding of proton source enabled by incorporation of H-bond donor. (**Scheme 1.16**)

Scheme 1.16 Cooperative NHC/Lewis acid system disclosed by Scheidt *et al*

The above applications demonstrated that NHCs could tolerate well with various Lewis acids/Brønsted acids in proper conditions. The cooperative catalysis employed in NHCs-catalyzed reaction could lead to unexpected improvement in reactivity and selectivity, leading to the introduction of new mode of reactions.

1.8 NHCs as Lewis base catalysis and Brønsted base catalysis.

In addition to these classical activation model through a reversible carbon-carbon bond formation between the NHC catalyst and substrate, NHCs can also serve as a non-covalent Brønsted base catalyst.

In 2014, Huang Yong *et al* reported NHCs catalyzed Michael addition reaction between 1,3-dicarbonyl compounds and nitroalkene in the present of hexafluoroisopropanol (**Scheme 1.17, a**).⁴⁰ Asymmetric issue when NHCs used as chiral Brønsted base catalysts was addressed by proton-shuttling strategy.

Soon afterwards, the same group developed an asymmetric carbon–heteroatom bond formation version between mercaptans with electron deficient alkenes (**Scheme 1.17, b**).⁴¹ Mechanistic studies revealed that the NHC might serve as a dual functional catalyst through noncovalent interactions: hydrogen bonding and π – π stacking in these enantioselective sulfa-Michael addition reactions.

Scheme 1.17 NHCs as non-covalent chiral Brønsted base catalysts for asymmetric reactions.

In addition to serve as Brønsted base catalysts, NHCs can also employed as Lewis base catalysts. Song *et al* reported *N*-adamantyl carbene catalyzed trimethylsilyl ketene acetal addition to aldehydes producing Mukaiyama aldol products in good yield (**Scheme 1.18**).⁴² The NHC presumably acts as a Lewis base to activate the silicon-oxygen bond in order to promote reactivity of the enol silane.

Scheme 1.18 Reaction enable by NHCs as Lewis base catalysts.

1.9 Summary and research designs

The exploration and development of NHCs is an undeniably popular research area in current organocatalysis. Such potential could be greatly utilized with the use of cooperative catalysis. Cooperative catalysis offers various advantages, including yield and selectivity improvement, besides substrate scope expansion.

In this thesis, we first demonstrated that the scope of NHCs-catalyzed reaction could be largely expanded with the use of cooperative catalysts such H-bonding donors. Optical pure spirocyclic skeletons spiro[4.4]nonane could be constructed via the NHCs-thiourea cooperative desymmetrization process. Three stereocenters, with two all-carbon quaternary stereocenters, were constructed successfully by desymmetrization of a remote chiral centre of the 1, 3-dione substrates. Variations of both the aldehydes and 1, 3-dione compounds are generally well-tolerated with moderate yields and up to 96% ee.

In chapter 3, we will present the enantioselective formal [4+2] construction of multisubstituted phenols, which represents the first intermolecular cycloaddition arene construction method. This method employs easily accessible enals and diketones to construct phenol framework with excellent regioselectivity, and simultaneously installs a remote all-carbon quaternary chiral center with good enantioselectivity via desymmetrization.

In chapter 4, we will discuss an enantioselective approach to conformationally constrained carbocyclic β -amino acids via amine-catalyzed addition of unsaturated Imine gamma-carbon to enal. Various imines and enal were well tolerated with excellent diastereoselectivity and enantioselectivity, which possess huge potential in the conformationally constrained β -peptides synthesis.

1.10 References

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Chapter 2

Access to All-Carbon Spirocycles via Carbene and Thiourea Co-Catalytic Desymmetrization and Cascade Reaction

2.1 Introduction

2.1.1 Spiro[4.4]nonane construction and its applications

Spirocyclic skeletons bring about special spatial arrangement of the functional groups. As a result, the presence of spirocyclic skeletons gives rise to specific properties of organic molecules. Spiro[4.4]nonane, as a type of privileged structure, found its wide applications in the chiral ligand design,¹ and exists as key moieties in many natural products (**Scheme 2.1**).²

For example, pharbinilic acid (**Scheme 2.1, a**), which was found in the seeds of morning glory (*Pharbitis nil*) recently in 2013,^{2e} represents the first naturally occurring allogibberic acid. Pharbinilic acid and its derivatives are shown to display anticancer activity against various cancer cell lines by disturbing the NF- κ B pathway.^{2f}

Scheme 2.1 Examples of natural products containing the key spiro[4.4]nonane skeleton.

Enantiopure spirocycles, such as spiro[4.4]nonane 1,6-diol, could function as chiral ligands due to their rigid structures. One of the early examples of employing spiro[4.4]nonane as chiral auxiliary (**2**, **Scheme 2.2**) was reported by Kumar³ in the application of the reduction of ketones with exceptional enantioselectivities.

Scheme 2.2 Representative examples of spiro chiral ligands.

In 1997, Albert S. C. Chan reported a pioneering work of highly effective asymmetric hydrogenation of enamides catalyzed by rhodium complex bearing novel chiral phosphinite ligand, with remarkable yields and enantioselectivity was achieved.^{1e} In this case, the highly rigid spiro[4.4]nonane was employed to mimic the backbone of the binaphthyl rings of BINAP to create asymmetric induction environments in realizing highly enantioselective. (**Scheme 2.3**)

Scheme 2.3 The Rh (**1**)⁺-Catalyzed Asymmetric Hydrogenation

Based on this idea, a variety of chiral ligands derived from spiro[4.4]nonane were developed (**Scheme 2.4**). The introduction of substituents on achiral spiro[4.4]nonane results in more than one chiral center in the compound. On the other hand, benzo spiro[4.4]nonane, pirobiindane (**Scheme 3 c**, $n=0$) and spirobifluorene ($n=1$) which taking advantages of axial chirality and their rigid spiro structures make them highly potential backbones for chiral ligands.^{1f}

Scheme 2.4 The concept of spiro ligand design.

However, the introduction of chiral center or axial chirality increases the difficulty in the synthesis of its optically pure form. Most procedures for the preparation of spiro[4.4]nonane require multiple steps and optical resolution, especially for the enantiopure forms (**Scheme 2.5**). Thus, exploration on more direct and asymmetric strategies to construct this key motif is still necessary.

Scheme 2.5 Traditional methods for constructing spiro[4.4]nonane

In 2013, Zhang *et al.*⁶ reported a gold/chiral Brønsted acid catalyzed asymmetric synthesis of spirocyclic diketones based on the modification of redox-pinacol-Mannich cascade reaction developed by Shin *et al.* By taking advantages of Mannich addition catalyzed by chiral phosphoric acids prior to the gold mediated reaction, excellent enantioselectivity (>99%) could be achieved. (**Scheme 2.6**)

Scheme 2.6 Gold/chiral Brønsted acid catalyzed consecutive transformations.

Recently, Zhang *et al*⁷ reported the construction the chiral spiro[4.4]nonane skeleton with the use of *N*-triflylphosphoramidate organocatalysis. Cyclobutanol motif was introduced to the substrates to induce semipinacol rearrangement reaction followed by Nazarov cyclization. Excellent yields and enantioselective were achieved, with up to four consecutive stereocenters constructed in this tandem process. (**Scheme 2.7**)

Scheme 2.7 Tandem Nazarov Cyclization Semipinacol Rearrangement Approach to Spiro[4.4]nonane-1,6-diones

2.1.2 Desymmetrization reaction catalyzed by NHCs

Besides rapid construction of the functional molecules, *N*-heterocyclic carbenes (NHCs) organocatalysts also show great potential in desymmetrization reaction. One of the most employed areas is the kinetic resolution of diols.

In 2013, Takasu *et al*⁸ reported NHC-catalyzed resolution and desymmetrization of diols in high chemoselectivity and enantioselectivity (**Scheme 2.8**). Chiral acyl azolium species serve as key intermediates in these reactions.

Scheme 2.8 Resolution and desymmetrization of diols by Takasu and Yamada

In 2016, Chi's group reported a more challenging desymmetrization of P-stereogenic bisphenols, affording rarely explored P-stereogenic phosphinates with high yields and excellent enantioselectivity.⁹

Scheme 2.9 Access to P-Stereogenic Phosphinates via NHC-Catalyzed Desymmetrization of Bisphenols

Enantioselective C-C bond formation had also been utilized in NHC-catalyzed desymmetrization. Cyclohexadienones and 1,3-diketones were the most investigated substrates. The NHC-bonded chiral enolate or Breslow intermediate serve as key intermediates in these intramolecular desymmetrization reaction. Despite all these progresses, however, the intermolecular version is much less developed.

In 2006, Tomislav Rovis' group reported a pioneering work on NHC-catalyzed desymmetrization of cyclohexadienones via intramolecular Stetter reaction to synthesis hydrobenzofuranones.¹⁰ Electronic properties of aryl substitution in the aminoindanol-derived triazolium salt were systematically evaluated. The identified best catalyst

precursor bore an anisyl substituent for this reaction, affording the phenol-derived substrates with good yields besides high enantioselectivity and diastereoselectivity.

Scheme 2.10 NHC-catalyzed Desymmetrization of Cyclohexadienones via Intramolecular Stetter Reaction

In 2007, Karl A. Scheidt *et al.* disclosed an NHC-catalyzed desymmetrization of 1,3-diketones, affording α, α -disubstituted cyclopentenones. This process was initiated by chiral triazolium NHC addition to aldehyde, which led to the generation of chiral nucleophilic enols. The generated enols then underwent enantioselective aldol reaction, followed by a decarboxylation of a β -lactone intermediate. Functionalized carbocycles containing a quaternary carbon stereocenter was generated in this desymmetrization event.

Scheme 2.11 NHC-catalyzed Desymmetrization of 1,3-Diketones

2.1.3 Our Proposal.

The desymmetrization of achiral compounds is a powerful strategy for the quick access to optically pure molecules. It serves as a distinct method to construct stereogenic quaternary carbon centers. As described, NHCs have demonstrated great potential in promoting a desymmetrization event. Despite all these progresses, however, the intermolecular version is much less developed.

In this chapter, we introduced a method for highly enantioselective synthesis of spiro[4.4]nonane via NHCs-thiourea cooperative desymmetrization process (**Scheme 2.12**).

We assumed that desymmetric Stetter reaction of 2, 2-disubstituted cyclopent-1,3-dione could take place under NHC catalysis.

Intermolecular Stetter addition of Breslow intermediate to α , β -unsaturated 1, 3-dione compounds under activation of thiourea catalyst could give intermediate, which go through a proton shift to afford another zwitterionic. Such tautomerization occurs because it is stabilized by the additional electron-withdrawing group (carbonyl group) in the β -position of the Michael acceptor.³¹ Afterwards, zwitterion reacts via an intramolecular aldol reaction to give the final cascade product and regenerates the *N*-heterocyclic carbene to close the catalytic cycle.

The enantioselectivity could be induced by the NHC-bonded chiral Breslow intermediate, which was used to differentiate enantiotopic double bond (**Scheme 4.4**). The chiral spiro[4.4]nonane product obtained from our method could have wide applications such as organic catalysts or key intermediate of bioactive products.

Scheme 2.12 NHCs-thiourea cooperative desymmetrization process

2.2 Results and Discussions

Phthalaldehyde **1a** and 1, 3-dione compound **2a** were chosen as the model substrate to test the feasibility of this proposed cooperative catalysis strategy.

We started this investigation commenced by examining different substituted triazolium NHC using toluene as solvent and DMAP as base (**Table 2.1**). Initial screening came with no desired product. However, when thiourea organocatalyst, serve as H-bond donor, was added, **3a** was successfully afforded in some NHC entries. Albeit yield was low, it did provide a message that thiourea can well cooperate with NHC in this reaction under proper conditions.

Table 2.1 NHCs catalyst optimization studies.

Reactions conduct with 0.1 mmol **1a** and 0.1 mmol **2a**. Yields shown are of product isolated after chromatography. Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase.

The electronically differences resulted from *N*-aryl substituent of the triazolium salt had dramatic effect on the reaction potential. For example, NHC with an electron donating group such as mesitylene, 2,6-diethylphenyl, *p*-anisyl, 2,6-dimethoxy could give rise to different enantiomeric excess **3a** in different yield while electron withdrawing group like pentafluorophenyl, 2,6-ditrifluoromethylphenyl obtained no desired product at all.

Among those catalysts which afford desired product, mesitylene- (**A**) and 2,6-diethylphenyl-substituted NHC (**B**) show good enantioselective in this reaction (92% ee), changed to *p*-anisyl- or 2,6-dimethoxy-substituted (**C**) lead to a drop in enantiomeric excess (81% ee). *N*-alkyl NHC, such as tert-butyl-substituted (**I**), was also chosen to test its feasibility. However, both starting materials were remained without any new product being detected. Steric hindrance is believed to prevent NHC interact with phthalaldehyde to form the Breslow intermediate.

Table 2.2 H-bonding catalysts optimization studies.

Having successfully allocated the potential NHC catalyst, we next focused our attention on improving the reaction yields. Preliminary screening results revealed that the desired product can only be obtained within a narrow scope of solvents and bases (entry 7-8). Different H-bonding catalysts, including chiral and achiral architecture, were investigated, leading Thiourea-A as the optimal cocatalyst.

The key results of the reaction condition optimization are summarized in **Table 2.3**. The optimum reaction required NHC-A as the carbene precatalyst, DIPEA as the base, Thiourea-A as the thiourea cocatalyst and 2:1(v/v) chloroform/*t*BuOH as the solvent. With a slow addition of **1a**, the reaction proceeded smoothly at room temperature, obtaining **3a** as the product with the yield of 63%, 9:1 dr and 92% ee (entry 1). The results of the catalyst screening showed that the reaction did not work without NHC catalyst or thiourea cocatalyst (entry 2, 5). Other inferior NHC or thiourea gave lower yields or lower ee (entry 3, 4, 6). In addition, the base selected for this reaction is also important. When other inferior bases were used, the reaction gave lower yield (DMAP, DABCO, KOAc, *t*BuOK) or even gave no product (DBU, Cs₂CO₃, K₃PO₄, NaOMe, CsF, K₂CO₃) (entry 7). Solvents also played a crucial role in this reaction. A careful solvent screening exemplified that the chloroform and *t*BuOH are the best solvents (entries 9-10), and a mixture of 2:1 (v/v) can further increase the yield to 63% (entry 1). Slow addition of **1a** can prevent the homocoupling side reaction to a certain extent,⁴ whereas the normal one pot reaction gave lower yield (entry 11).

Having established the optimum reaction condition, the substrate scope was then investigated. The 1, 3-dione compounds **2a** allowed the incorporation of a wide variety of substituents into the desired products (**Table 2.4**). Various electron-withdrawing (-F, -Cl, -Br, -NO₂) and electron-donating groups (-OMe, -Me) were generally well tolerated, albeit with little decrease in yield. Optimal reactivity and enantioselectivity were obtained

when methyl substituent was added at the meta position (**3h**). On the other hand, as the methyl substituent was introduced at the para (**3f**) and ortho (**3g**) positions, the yield decreased slightly. More bulky groups (naphthyl, 4-OMe-C₆H₄, 4-NO₂-C₆H₄) were highly enantioselective, as expected, while heteroaromatic group resulted in decrease of both yield and enantioselectivity (**3j**). *N*-(2-*t*-butylphenyl)maleimide was also employed as one of the substrates to test its feasibility. To our delight, asymmetric desymmetrization of the substrate led to the successful construction of both atom chirality and axial chirality (**3k**).

Table 2.3 Condition optimization ^a

c1ccccc1C=O (**1a**) + c1ccc(cc1)C2C(=O)C(=O)C2 (**2a**) $\xrightarrow[\text{CHCl}_3:t\text{-BuOH} = 2:1, \text{rt, slow addition}]{\text{NHC-A (20 mol\%), DIPEA (20 mol\%), THU-A (20 mol\%)}}$ c1ccccc1C2C(=O)C(=O)C2 (**3a**)

NHC-A: R = H, NHC-J: R = NO₂
 THU-A

entry	Variation of standard condition	yield (%)	d.r.	ee (%)
1	standard condition, as shown in the scheme	63	9:1	92
2	no NHC	0	-	-
3	NHC J	60	3:1	88
4	inferior NHC (C-I)	<5	-	-
5	no thiourea	0	-	-
6	inferior thiourea (see SI for details)	44~53	9:1	92
7	inferior base (Cs ₂ CO ₃ , K ₃ PO ₄ , ^t BuOK, DBU, etc.)	0~20	9:1	90~92
8	inferior solvent (THF, acetone, Et ₂ O, DMF, etc.)	0~9	9:1	89~92
9	^t BuOH as solvent	32	9:1	92
10	CHCl ₃ as solvent	45	9:1	92
11	without slow addition	29	9:1	92

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.1 mmol), NHC (0.02 mmol), base (0.02 mmol), thiourea (0.02 mmol), solvent (1 mL), rt, 12 h. ^b Yields are isolated yields based on **2a**. ^c ee was determined via chiral phase HPLC analysis. ^d Absolute configuration of the major enantiomer was assigned by determination of X-ray crystallographic data.

Further investigation revealed that size difference of the two substituents in diones dominated the enantioselectivity of the final product. When the size difference became

smaller, the corresponding substrates tend to engender reduced enantioselectivity. The striking evidence can be found by comparing the ee of compound **3a** and **3r**, by replacing methyl group (**3a**) to more bulky ethyl group (**3r**), the enantioselectivity drop remarkably from 92% ee to 56% ee. Likewise, the replacement of the benzyl group (**3a**) with a more sterically hindered benzhydryl group (**3u**) increased the enantioselectivity to 96% ee. Nitro-substituted **NHC-J** could improve the enantioselectivity of some products (**3n**, **3o**, **3p**, **3q** and **3t**) to a certain degree. Intermolecular H-bonding served as another delicate factor that governed the enantioselectivity. By interacting with the free hydroxyl group of NHC Breslow intermediate, 2-nitro group (**3j**) and carbonyl group (**3s**) impaired the enantioselectivity of the final products, leading to a moderate 74% ee and 78% ee respectively.

Substrate scope of aldehydes was investigated next. The preliminary study revealed that the introduction of 4, 5-dimethyl groups in aldehydes led to favorable yield and enantioselectivity (**4a**). The replacement of methyl group with a more electron-donating methoxyl group resulted in a drop in reactivity albeit remained high enantioselectivity (**4b**). By replacing the phenyl substituent (**3a**) with a naphthyl (**4c**), no effect was observed on the enantioselectivity and diastereoselectivity. 4-Nitryl phthalaldehyde was found to be unaccommodating with the present reaction system. This is due to the decomposition of all the starting materials into complex mixtures with the unavailability to detect of the desired product.

Table 2.4 Substrate scope ^a

^a Reaction conditions as in Table 1, entry 1, unless otherwise noted. The absolute configuration of the major enantiomer was assigned on the basis of the X-ray structure of **3c**. ^b Used NHC-J instead of NHC-A.

The proposed pathway for the formation of cascade product **3/4** is depicted in **Scheme 2.13**. The triazolium salt is first deprotonated by base to form the active catalytic carbene, which subsequently reacts with the aldehyde substrate forming the Breslow intermediate **I**. Intermolecular Stetter addition of Breslow intermediate **I** to α, β -unsaturated 1, 3-dione compounds under activation of thiourea catalyst **II** could give intermediate **III**, which goes through a proton shift to afford another zwitterionic **V**. Such tautomerization occurs because it is stabilized by the additional electron-withdrawing group (carbonyl group) in the β -position of the Michael acceptor.³¹ Afterwards, zwitterion **V** reacts via an intramolecular aldol reaction to give the final cascade product and regenerates the *N*-heterocyclic carbene to close the catalytic cycle.

Scheme 2.13 Proposed mechanism

Absolute configurations of the spiro[4.4]nonane products **3/4** were assigned based on the crystal X-ray structures of **3c**. A colorless flaky crystal of **3c** was obtained by vaporization of a hexane/ethyl acetate/DCM (5:1:2) solution of compound **3c**. The absolute configuration of **3c** was determined by X-ray to be (1*R*,1'*S*,3*R*). (Scheme 2.14)

Scheme 2.14 Stereochemistry determination of spiro[4.4]nonane **3c** via X-ray crystallographic analysis

The potential synthetic utility of this protocol was demonstrated with a series of transformations. For examples, the hydroxyl group of **3a** could transform easily into azido groups to give **5** with 62% yield while maintaining the enantiomeric excess.

Scheme 2.15 Synthetic Transformations

Spiro heterocyclic is incorporated as an important structural component in many bioactive compounds. By refluxing **3j** with Zn powder in acetic acid, tetrahydrospiro cyclopenta[b]quinoline **6** could be obtained easily with satisfactory yield with little erosion of the enantiomeric excess. Similarly, satisfactory yield and enantiomeric excess could be obtained as acetyl group protected **3s** was refluxed with NH_4OAc in acetic acid, with spiro cyclopenta[b]pyrrole **7** obtained as the product.

The highly rigid and skewed spiro structures hold potential to mimic the naphthyl rings in BINAP applied in asymmetric reactivity. We demonstrated that our optical pure spiro cyclic can further transform into chiral phosphinite which might found wide applications in asymmetric reaction. By using the DIBAL-H/ $t\text{-BuLi}$ reduction system, the carbonyl groups of **3a** were reduced in a diastereoselectivity and chemoselectivity way, affording optical pure **8** in moderate yields. Subsequent incorporation with chlorodiphenylphosphine gave chiral phosphinite ligands **9**.

Moreover, the product **3** could also transform to chiral ligands with interesting applications in transition metal catalysis. For example, phosphite ligand **10** and **11** derived from **3a** and BINOL showed good activity and moderate enantioselectivity in rhodium-catalyzed 1,2-addition of arylboronic acid to aldehyde in our preliminary studies (Scheme 2.16). It is worth to note that the configuration of the product was mostly determined by the chiral moiety from **3a** in ligand **10** and **11**.

Scheme 2.16 Conversion of our products to chiral ligands

2.3 Summary.

In conclusion, an NHC-thiourea co-catalysed spiro[4.4]nonane construction was successfully carried out via Stetter-aldol tandem reaction. Desymmetrization of a remote chiral center of the product was achieved with three chiral centers, including two remote from the NHC catalyst reaction site, are successfully constructed. Variations of both the aldehydes and 1, 3-dione substrates were generally well-tolerated, with moderate yields and up to 96% ee.

The reaction cascade involves an intermolecular Stetter reaction, followed by an intramolecular aldol reaction. The step which involves Stetter reaction is also a desymmetrization process, with which a remote chiral carbon center is controlled by the

chiral catalyst. The subsequent aldol reaction step sets up a newly formed spirocyclic carbon center with high enantioselectivity. It is worth to note that both a *N*-heterocyclic carbene (NHC) catalyst and a thiourea co-catalyst are required in this catalytic reaction: no product is formed if the thiourea co-catalyst is absent. The spirocycles prepared using this approach bear multiple functional groups that are amenable for further transformations, which also provide a more direct and simplified route for the enantioselective preparation of sophisticated functional molecules with spirocyclic cores.

Scheme 2.16 NHCs catalyzed enantioselective synthesis of spiro[4.4]nonane.

2.4 Experimental Section

2.4.1 General Information.

Commercially available materials purchased from Sigma-Aldrich or Alfa Aesar were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), tt (triplet of triplets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400

MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.e.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

2.4.2 General procedure for the catalytic reactions

To a dry 4 mL vial equipped with a magnetic stir bar was successively charged with 1,3-dione **2a** (20 mg, 0.10 mmol, 1 equivalent), NHC pre-catalyst A (7.4 mg, 0.02 mmol, 0.2 equivalent) and thiourea (10.0 mg, 0.02 mmol, 0.2 equivalent), then closed with a septum. To this mixture was added 1:2 mix solvent of *t*BuOH-CHCl₃ (0.5 mL), followed by the addition of DIPEA (3.6 μ L, 0.02 mmol) via a micro syringe. Ortho-phthalaldehyde **1a** (53.6 mg, 0.40 mmol, 4 equivalent) was dissolved with 1:2 mix solvent of *t*BuOH-CHCl₃ (0.8 mL) then load into 1.0 mL syringe equip with long needle (dead volume of 0.2 mL). To this vial at room temperature under magnetic stirring is slow add the solution of ortho-phthalaldehyde **1a** over a period of 12 hours (0.05 mL per hour) via syringe pump. After the adding have completed, the solvent is evaporated under reduced pressure. The reaction mixture was subjected to column chromatography to yield the desired product **3a** as a white solid.

Note: The racemic catalyst that used for the preparation of the corresponding racemic products for HPLC analysis was synthesized by mixing chiral pre-catalyst **A** and *ent*-**A** in a 1:1 ratio.

2.4.3 Synthetic transformations of product

Transformation of **3a** to **5**:

To a 50 mL round bottom flask equipped with a magnetic stir bar, was added **3a** (33.4 mg, 0.1 mmol, 1.0 eq.), DMAP (1.2 mg, 0.01 mmol, 0.1 eq.), and anhydrous DCM (10 mL). To this stirring solution at room temperature was slowly added methanesulfonyl chloride (11.6 μL , 0.15 mmol, 1.5 eq.) and Et_3N (20.9 μL , 0.15 mmol, 1.5 eq.) successively.

After full consumption of **3a** monitored by TLC, water was added, and the mixture was extracted with DCM; the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4 . Evaporating the solvent afforded the crude intermediate, which was used without characterization.

The intermediate together with LiF (26 mg, 1.0 mmol) was dissolved in anhydrous THF (10 mL), to this stirring solution at room temperature was slowly added TMSN_3 (40 μL , 0.3 mmol). After full consumption of intermediate monitored by TLC, the solvent was removed under vacuum, and the reaction residue was directly subjected to column chromatography to afford the pure product **5** (23 mg, 62% yield).

The intermediate was transferred into a 4 mL vial, heated together with dry ammonium acetate (77 mg, 1.0 mmol) in acetic acid at 95 °C overnight. After the reaction has complexed, the solution was cooled to room temperature and diluted with water, the reaction was extracted three times with DCM. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and evaporated under reduced pressure. The reaction residue was directly subjected to column chromatography to afford the pure product **7** (31 mg, 75% yield).

Transformation of **3a** to **8** and **9**:

Step 1: Acetylation of **3a**

To a 50 mL round bottom flask equipped with a magnetic stir bar, was added **3a** (167 mg, 0.5 mmol, 1.0 eq.), DMAP (6.0 mg, 0.05 mmol, 0.1 eq.), and anhydrous DCM (30 mL). To this stirring solution at room temperature was slowly added acetic anhydride (70 μ L, 0.75 mmol, 1.5 eq.) and Et₃N (105 μ L, 0.75 mmol, 1.5 eq.) successively.

After full consumption of **3a** monitored by TLC, the solvent was removed under vacuum, and the reaction residue was directly subjected to column chromatography to afford the intermediate.

Step 2: Reduction of acetylated **3a**

Reduction of acetylated **3a** was performed according to the literature procedures.¹⁻⁴ Under an N₂ atmosphere, *tert*-butyllithium (1.6 M in pentane, 1.9 mL, 3.0 mmol, 6.0

equiv) was slowly added to a solution of DIBAL-H (1.0 M in hexane, 3.3 mL, 3.3 mmol, 6.6 equiv) at -78 °C. The colorless solution was stirred for 5 min and then warmed to room temperature. The solution was cooled again to -78 °C. To this solution, a suspension of the acetylated **3a** (188 mg, 0.50 mmol, 1.0 equiv) in THF (3.0 mL) was added dropwise over 10 min (additional 1.0 mL of THF was used to rinse the syringe), and the reaction mixture was stirred overnight at -78 °C. Afterward, saturated aqueous ammonium chloride was added to quench the reaction at -78 °C, and then the mixture was warmed to room temperature. The mixture was transferred to a beaker containing chloroform (10 mL) and saturated aqueous ammonium chloride (5.0 mL) and stirred for 30 min. The precipitated aluminum salts were removed, and the biphasic mixtures were extracted by addition of chloroform (10 mL $\times$ 3 times). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered to remove Na₂SO₄ added. The solution phase was then purified by silica gel chromatography to give the desired spirocyclic compound **8** as a white solid.

Step 3: Phosphinite derivative **9**

To a solution of **8** (76 mg, 0.2 mmol) in dry CH₂Cl₂ (12 mL), triethylamine (84 μ L, 0.6 mmol), DMAP (2.5 mg, 0.02 mmol) and chlorodiphenylphosphine (108 μ L, 0.6 mmol) were added dropwise under nitrogen atmosphere. After the mixture was heated to reflux overnight, the reaction was quenched with water at rt. The resulting solution was extracted with CH₂Cl₂ and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give the corresponding phosphinite derivative **9**.

Transformation of **3a** to **10** and **11**:

To a cooled solution of PCl_3 (1 mL, 11.5 mmol) in anhydrous DCM (10 mL) at $0\text{ }^\circ\text{C}$ was slowly added a solution of **3a** (67 mg, 0.2 mmol) in DCM (9.0 mL) dropwise over 3 h under argon atmosphere. After finishing slow addition, the reaction was stirred at room temperature overnight. Concentration *in vacuo* to remove excess DCM and PCl_3 afford **3a-PCl₂** as a light-yellow oil which used in next step without further purification.

R-(+)-1,1'-Bi-2-naphthol or *S*-(-)-1,1'-Bi-2-naphthol (56 mg, 0.2 mmol) was suspended in anhydrous dichloromethane (5 mL) under an atmosphere of argon. To this stirring solution at $0\text{ }^\circ\text{C}$ triethylamine (69 mL, 0.5 mmol) was slowly added followed by slow addition of **3a-PCl₂** (80 mg, 0.18 mmol) in anhydrous DCM (6 mL). The reaction mixture was then allowed to warm to room temperature and stirred for *ca.* 30 minutes. The reaction mixture was concentrated *in vacuo*. The resulting residue was purified by column chromatography to give the corresponding phosphite derivative **11**.

Phosphite derivative **10** can be acquired with this procedure by using 2, 2'-biphenol instead of 1,1'-Bi-2-naphthol.

Asymmetric Rh-catalyzed addition of arylboronic acids to aldehydes.

Under argon atmosphere, $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ (0.75 mol %) and the phosphite **11** (3 mol %) was pre-stirred in toluene (1 mL) for 30 min, then phenylboronic acid (24 mg, 0.1 mmol, 2 equiv), the aldehyde (15.6 mg, 0.1 mmol), KF (5.8 mg, 0.1 mol), and 1 M KOH (0.1 mL) were added sequentially. The mixture was stirred at $0\text{ }^\circ\text{C}$ and the reaction was monitored by TLC. After complete conversion, the mixture was filtered through a short silica gel pad and evaporated to yield the crude product. Chromatography on silica gel gave the pure diarylcarbinol.

The *ee* was determined by HPLC analyses on chiral stationary phases. Chiralcel OD, 0.75 mL/min, n-hexane/2-propanol 80:20.

Synthesis of NHC precursor

To a 250 mL round bottom flask equipped with a magnetic stir bar was added **S1** (18 mmol), **S2** (18 mmol), and MeOH (70 mL). The mixture was stirred at rt to form a clear solution and then HCl (4M in dioxane, 0.5 mL) was added. The solution was stirred at $60\text{ }^\circ\text{C}$ for 48 h and then concentrated and dried under vacuum. To the dried residue was added HC(OEt)_3 (33 mL), HCl (4M in dioxane, 6 mL), PhCl (26 mL) and the system was

sealed and stirred vigorously at 120 °C for 6 h. Then the solution was concentrated. After dried under high vacuum, the residue was treated with EtOAc (50 mL) and filtered to afford the pure NHC catalyst C as a white powder (29% yield based on S1)

2.4.4 Characterization of products.

(1R,1'S,3R)-3-benzyl-1'-hydroxy-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3a)

Colorless solid, yield: 21 mg (63%)

¹H NMR (400 MHz, CDCl₃) δ 7.68 (ddd, *J* = 8.2, 4.0, 1.1 Hz, 2H), 7.61 (s, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.18 – 7.10 (m, 2H), 4.98 (d, *J* = 2.4 Hz, 1H), 3.09 – 2.99 (m, 2H), 2.73 (d, *J* = 19.6 Hz, 1H), 2.45 (d, *J* = 19.6 Hz, 1H), 1.39 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 215.44, 215.07, 201.10, 154.41, 136.56, 136.13, 134.03, 130.33, 130.06, 128.78, 127.59, 126.14, 124.32, 72.59, 70.86, 59.75, 43.28, 41.95, 20.18.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r*(minor) = 29.0 min, *t_r*(major) = 33.1 min.

Opt. Rot.: [α]_D²¹ (c 1.0, CHCl₃) = -14.1°;

HRMS: (ESI) calcd for C₂₁H₁₉O₄ (M+H)⁺: 335.1278, Found: 335.1280.

(1R,1'S,3R)-3-(4-fluorobenzyl)-1'-hydroxy-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3b)

Colorless solid, yield: 20 mg (55%)

¹H NMR (400 MHz, CDCl₃) δ 7.75 – 7.68 (m, 2H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.07 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 4.99 (d, *J* = 7.1 Hz, 1H), 3.06 – 2.97 (m, 2H), 2.84 (d, *J* = 19.4 Hz, 1H), 2.48 (d, *J* = 19.4 Hz, 1H), 1.38 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 214.56, 214.20, 200.59, 163.26, 160.81, 154.42, 136.30, 134.00, 132.17, 132.14, 131.76, 131.68, 130.25, 126.17, 124.56, 115.69, 115.48, 72.40, 71.13, 59.84, 41.88, 41.74, 20.64.

¹⁹F NMR (376 MHz, CDCl₃) δ -113.95.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 96.5:3.5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r* (minor) = 33.0 min, *t_r* (major) = 35.3 min.

Opt. Rot.: [α]_D²¹ (c 1.0, CHCl₃) = -27.0°;

HRMS: (ESI) calcd for C₂₁H₁₈FO₄ (M+H)⁺: 353.1184, Found: 353.1183.

(1R,1'S,3R)-3-(4-chlorobenzyl)-1'-hydroxy-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3c)

Colorless solid, yield: 17 mg (46%)

¹H NMR (400 MHz, CDCl₃) δ 7.73 (t, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.00 (d, *J* = 6.8 Hz, 1H), 3.05 – 2.97 (m, 2H), 2.85 (d, *J* = 19.4 Hz, 1H), 2.50 (d, *J* = 19.5 Hz, 1H), 1.38 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 214.34, 213.99, 200.53, 154.43, 136.32, 134.84, 133.97, 133.54, 131.48, 130.26, 128.81, 126.19, 124.57, 72.40, 71.12, 59.78, 41.88, 41.77, 20.71.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r*(minor) = 24.3 min, *t_r*(major) = 25.5 min.

Opt. Rot.: [α]_D²¹ (c 1.0, CHCl₃) = -58.0°;

HRMS: (ESI) calcd for C₂₁H₁₈ClO₄ (M+H)⁺: 369.0888, Found: 369.0898.

(1R,1'S,3R)-3-(4-bromobenzyl)-1'-hydroxy-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3d)

Colorless solid, yield: 20 mg (47%)

¹H NMR (400 MHz, CDCl₃) δ 7.73 (t, *J* = 7.0 Hz, 2H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 5.01 (d, *J* = 5.7 Hz, 1H), 3.03 – 2.94 (m, 2H), 2.85 (d, *J* = 19.5 Hz, 1H), 2.50 (d, *J* = 19.5 Hz, 1H), 1.38 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 214.29, 213.95, 200.52, 154.45, 136.30, 135.35, 133.98, 131.84, 131.79, 130.25, 126.20, 124.57, 121.56, 72.40, 71.12, 59.71, 41.87, 41.79, 20.72.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 96.5:3.5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r*(minor) = 38.8 min, *t_r*(major) = 44.2 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{21}$ (c 1.0, CHCl_3) = -65.9° ;

HRMS: (ESI) calcd for $\text{C}_{21}\text{H}_{18}\text{BrO}_4$ ($\text{M}+\text{H}$) $^+$: 413.0383, Found: 413.0412.

(1R,1'S,3R)-1'-hydroxy-3-(4-methoxybenzyl)-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3e)

Colorless solid, yield: 20 mg (54%)

^1H NMR (400 MHz, CDCl_3) δ 7.70 (tt, J = 5.2, 2.5 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.90 – 6.82 (m, 2H), 5.07 (d, J = 5.8 Hz, 1H), 3.81 (s, 3H), 2.99 (s, 2H), 2.75 (d, J = 19.5 Hz, 1H), 2.47 (d, J = 19.5 Hz, 1H), 1.37 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 215.56, 215.18, 201.03, 159.00, 154.37, 136.12, 134.05, 131.33, 130.07, 128.38, 126.13, 124.36, 113.99, 72.53, 71.03, 59.83, 55.44, 42.45, 42.01, 20.11.

HPLC: 93% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 51.3 min, t_r (major) = 74.6 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 0.2, CHCl_3) = -22.7° ;

HRMS: (ESI) calcd for $\text{C}_{22}\text{H}_{21}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 365.1384, Found: 365.1396.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(4-methylbenzyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3f)

Colorless solid, yield: 19 mg (55%)

¹H NMR (400 MHz, CDCl₃) δ 7.69 (dt, J = 7.2, 3.5 Hz, 2H), 7.62 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 5.04 (d, J = 5.9 Hz, 1H), 3.04 – 2.95 (m, 2H), 2.71 (d, J = 19.5 Hz, 1H), 2.46 (d, J = 19.5 Hz, 1H), 2.36 (s, 3H), 1.37 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 215.72, 215.09, 201.14, 154.35, 137.49, 136.05, 134.04, 133.44, 130.24, 130.00, 129.33, 126.08, 124.29, 72.64, 70.93, 59.75, 43.02, 42.00, 21.02, 20.00.

HPLC: 91% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 93:7 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 16.5 min, t_r (major) = 19.1 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 1.0, CHCl₃) = -28.3°;

HRMS: (ESI) calcd for C₂₂H₂₁O₄ (M+H)⁺: 349.1434, Found: 349.1443.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(2-methylbenzyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3g)

Colorless solid, yield: 19 mg (53%)

¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.65 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.25 – 7.15 (m, 3H), 7.09 (d, J = 7.4 Hz, 1H), 4.99 (d, J = 6.4 Hz, 1H), 3.13 (q, J = 13.3 Hz, 2H), 2.72 (d, J = 19.4 Hz, 1H), 2.55 (d, J = 19.4 Hz, 1H), 2.31 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 215.86, 215.12, 201.28, 154.41, 137.82, 136.09, 135.16, 134.05, 131.47, 130.56, 130.03, 127.77, 126.17, 125.75, 124.28, 72.52, 70.82, 59.13, 42.08, 40.07, 20.27, 19.68.

HPLC: 90% ee, (1R,1'S,3R)-isomer as determined by HPLC (IB, 96.5:3.5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 21.8 min, t_r (major) = 23.5 min.

Opt. Rot.: $[\alpha]_{\text{D}^{22}}(\text{c } 1.0, \text{CHCl}_3) = -5.3^\circ$;

HRMS: (ESI) calcd for $\text{C}_{22}\text{H}_{21}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 349.1434, Found: 349.1421.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(3-methylbenzyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3h)

Colorless solid, yield: 21 mg (53%)

^1H NMR (400 MHz, CDCl_3) δ 7.74 – 7.66 (m, 2H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.29 – 7.21 (m, 1H), 7.14 (d, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 11.0$ Hz, 2H), 5.00 (d, $J = 5.8$ Hz, 1H), 3.05 – 2.96 (m, 2H), 2.71 (d, $J = 19.6$ Hz, 1H), 2.45 (d, $J = 19.6$ Hz, 1H), 2.35 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 215.74, 215.05, 201.18, 154.36, 138.80, 136.49, 136.08, 134.07, 131.08, 130.03, 128.61, 128.19, 127.26, 126.09, 124.29, 72.72, 70.81, 59.68, 43.46, 41.99, 21.29, 20.05.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (IB, 96.5:3.5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 17.8 min, t_r (major) = 21.0 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 1.0, CHCl_3) = -14.0°;

HRMS: (ESI) calcd for $\text{C}_{22}\text{H}_{21}\text{O}_4$ ($\text{M}+\text{H}$)⁺: 349.1434, Found: 349.1431.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(4-nitrobenzyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3i)

Colorless solid, yield: 20 mg (52%)

¹H NMR (400 MHz, CDCl_3) δ 8.19 – 8.10 (m, 2H), 7.80 – 7.71 (m, 2H), 7.67 (d, J = 7.9 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.29 – 7.26 (m, 2H), 4.97 (d, J = 7.5 Hz, 1H), 3.19 – 3.07 (m, 2H), 2.97 (d, J = 19.5 Hz, 1H), 2.56 (d, J = 19.5 Hz, 1H), 1.44 (s, 3H).

¹³C NMR (101 MHz, CDCl_3) δ 213.32, 212.57, 199.97, 154.42, 147.21, 143.84, 136.51, 133.91, 131.02, 130.45, 126.12, 124.80, 123.73, 72.32, 71.08, 59.83, 41.59, 41.18, 21.19.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (IB, 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (major) = 42. 2 min, t_r (minor) = 46. 9 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 0.2, CHCl_3) = -62.7°;

HRMS: (ESI) calcd for $\text{C}_{21}\text{H}_{18}\text{NO}_6$ ($\text{M}+\text{H}$)⁺: 380.1129, Found: 380.1114.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(2-nitrobenzyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3j)

Colorless solid, yield: 21 mg (54%)

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.81 – 7.66 (m, 3H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.48 (dd, *J* = 12.8, 6.8 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 5.52 (s, 1H), 3.57 (d, *J* = 13.5 Hz, 1H), 3.41 (d, *J* = 19.0 Hz, 1H), 3.35 (s, 1H), 3.16 (d, *J* = 13.5 Hz, 1H), 2.86 (d, *J* = 19.0 Hz, 1H), 1.37 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 212.85, 212.26, 201.20, 154.91, 148.68, 136.30, 133.95, 133.73, 133.66, 131.59, 130.03, 128.77, 126.34, 125.65, 124.36, 72.58, 71.28, 55.90, 40.57, 39.41, 19.34.

HPLC: 74% ee, (1R,1'S,3R)-isomer as determined by HPLC (OD, 90:10 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r*(minor) = 25.6 min, *t_r*(major) = 28.5 min.

Opt. Rot.: [α]_D²² (c 1.0, CHCl₃) = 48.7°;

HRMS: (ESI) calcd for C₂₁H₁₈NO₆ (M+H)⁺: 380.1129, Found: 380.1141.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(naphthalen-2-ylmethyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3k)

Colorless solid, yield: 17 mg (43%)

¹H NMR (400 MHz, CDCl₃) δ 7.87 – 7.77 (m, 3H), 7.65 (dd, *J* = 16.5, 7.6 Hz, 2H), 7.57 (s, 1H), 7.55 – 7.49 (m, 2H), 7.46 (dd, *J* = 13.0, 7.5 Hz, 2H), 7.23 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.93 (d, *J* = 6.5 Hz, 1H), 3.25 – 3.16 (m, 2H), 2.71 (d, *J* = 19.4 Hz, 1H), 2.31 (d, *J* = 19.4 Hz, 1H), 1.44 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 215.08, 214.80, 200.91, 154.37, 136.08, 133.94, 133.80, 133.11, 132.19, 130.05, 128.78, 128.24, 128.08, 127.79, 127.55, 127.00, 126.57, 126.12, 124.35, 72.25, 71.04, 59.81, 43.34, 42.01, 20.43.

HPLC: 93% ee, (1R,1'S,3R)-isomer as determined by HPLC (OD, 98.5:1.5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 71.0 min, t_r (major) = 97.9 min.

Opt. Rot.: $[\alpha]_{\text{D}^{22}}$ (c 0.5, CHCl_3) = -54.2°;

HRMS: (ESI) calcd for $\text{C}_{25}\text{H}_{21}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 385.1434, Found: 385.1455.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(thiophen-3-ylmethyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3l)

Colorless solid, yield: 11 mg (32%)

^1H NMR (400 MHz, CDCl_3) δ 7.72 (t, J = 6.9 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 7.02 – 6.96 (m, 1H), 6.81 (d, J = 3.1 Hz, 1H), 5.18 (d, J = 6.2 Hz, 1H), 3.33 – 3.21 (m, 2H), 2.88 (d, J = 19.5 Hz, 1H), 2.69 (d, J = 14.4 Hz, 1H), 1.38 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 214.61, 214.59, 200.85, 154.41, 138.15, 136.21, 134.08, 130.14, 127.94, 127.44, 126.21, 125.12, 124.42, 72.86, 71.10, 59.76, 41.89, 36.55, 20.12.

HPLC: 88% ee, (1R,1'S,3R)-isomer as determined by HPLC (IB, 97:3 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 36.0 min, t_r (major) = 39.8 min.

Opt. Rot.: $[\alpha]_{\text{D}^{22}}$ (c 0.5, CHCl_3) = 1.5°;

HRMS: (ESI) calcd for $\text{C}_{19}\text{H}_{17}\text{O}_4\text{S}$ ($\text{M}+\text{H}$) $^+$: 341.0842, Found: 341.0821.

(1S,2R)-1'-(2-(tert-butyl)phenyl)-1-hydroxyspiro[indene-2,3'-pyrrolidine]-2',3,5'(1H)-trione (3m)

Colorless solid, yield: 20 mg (56%)

¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.75 (t, *J* = 7.4 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.64 – 7.49 (m, 2H), 7.44 – 7.34 (m, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.61 (d, *J* = 6.9 Hz, 1H), 3.40 (d, *J* = 18.6 Hz, 1H), 3.03 (d, *J* = 18.6 Hz, 1H), 1.36 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 199.10, 176.46, 175.85, 154.32, 148.93, 136.60, 134.22, 130.79, 130.62, 130.38, 130.07, 128.63, 127.44, 126.27, 124.70, 72.53, 63.68, 35.44, 34.08, 31.26.

HPLC: 89% ee, (1S,2R)-isomer as determined by HPLC (ID, 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r* (major) = 52.8 min, *t_r* (minor) = 67.7 min.

Opt. Rot.: [α]_D²² (c 1.0, CHCl₃) = -28.2°;

HRMS: (ESI) calcd for C₂₂H₂₂NO₄ (M+H)⁺: 364.1543, Found: 364.1548.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-phenylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3n)

Colorless solid, yield: 16 mg (50%)

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.69 (m, 3H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.42 – 7.27 (m, 5H), 5.47 (d, *J* = 7.1 Hz, 1H), 3.42 (d, *J* = 18.6 Hz, 1H), 2.99 (d, *J* = 18.6 Hz, 1H), 2.11 (s, 1H), 1.61 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 211.23, 210.66, 200.87, 154.52, 136.65, 136.50, 134.48, 130.56, 129.53, 128.34, 126.68, 126.31, 124.83, 73.25, 71.20, 61.82, 41.22, 20.96.

HPLC: 70% ee, (1R,1'S,3R)-isomer as determined by HPLC (AZH 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r*(major) = 29.1 min, *t_r*(minor) = 34.2 min.

Opt. Rot.: [α]_D²² (c 0.1, CHCl₃) = -10.2°;

HRMS: (ESI) calcd for C₂₀H₁₇O₄ (M+H)⁺: 321.1121, Found: 321.1125.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(naphthalen-2-yl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3o)

Colorless solid, yield: 16 mg (44%)

¹H NMR (400 MHz, CDCl₃) δ 7.83 (dt, *J* = 10.0, 6.8 Hz, 4H), 7.76 (dd, *J* = 10.8, 4.0 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.44 (dd, *J* = 8.7, 2.0 Hz, 1H), 5.47 (s, 1H), 3.47 (d, *J* = 18.6 Hz, 1H), 3.03 (d, *J* = 18.6 Hz, 1H), 2.05 (s, 1H), 1.69 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 211.12, 210.70, 200.92, 154.51, 136.51, 134.51, 133.81, 133.44, 132.82, 130.57, 129.60, 128.37, 127.74, 126.98, 126.89, 126.33, 125.99, 124.84, 123.97, 73.20, 71.24, 61.94, 41.30, 21.04.

HPLC: 60% ee, (1R,1'S,3R)-isomer as determined by HPLC (IC 90:10 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (major) = 16.1 min, t_r (minor) = 18.2 min.

Opt. Rot.: $[\alpha]_{\text{D}^{22}}(\text{c } 0.5, \text{CHCl}_3) = -3.7^\circ$;

HRMS: (ESI) calcd for $\text{C}_{24}\text{H}_{19}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 371.1278, Found: 371.1275.

(1R,1'R,1''S)-1''-hydroxy-2,3-dihydrodispiro[indene-1,3'-cyclopentane-1',2''-indene]-2',3'',4'(1''H)-trione (3p)

Colorless solid, yield: 13 mg (37%)

^1H NMR (400 MHz, CDCl_3) δ 7.79 (dd, $J = 8.8, 6.0$ Hz, 3H), 7.57 (dt, $J = 8.0, 4.1$ Hz, 1H), 7.31 (d, $J = 7.4$ Hz, 1H), 7.24 (d, $J = 7.6$ Hz, 1H), 7.17 (t, $J = 7.4$ Hz, 1H), 6.93 (d, $J = 7.6$ Hz, 1H), 5.68 (d, $J = 7.9$ Hz, 1H), 3.55 (d, $J = 18.8$ Hz, 1H), 3.31 – 3.00 (m, 3H), 2.72 (ddd, $J = 14.3, 8.4, 6.1$ Hz, 1H), 2.55 – 2.30 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 211.38, 210.74, 200.63, 154.79, 145.78, 141.49, 136.62, 134.16, 130.62, 128.75, 127.23, 126.31, 125.55, 124.93, 123.16, 72.72, 71.48, 69.81, 42.13, 35.88, 31.99.

HPLC: 63% ee, (1R,1'R,1''S)-isomer as determined by HPLC (IC 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (major) = 35.9 min, t_r (minor) = 39.6 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 0.5, CHCl_3) = -37° ;

HRMS: (ESI) calcd for $\text{C}_{21}\text{H}_{17}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 333.1121, Found: 333.1131.

(1S,2R,3'R)-1-hydroxy-3'',4''-dihydro-2''H-dispiro[indene-2,1'-cyclopentane-3',1''-naphthalene]-2',3,4'(1H)-trione (3q)

Colorless solid, yield: 15 mg (42%)

^1H NMR (400 MHz, CDCl_3) δ 7.79 (dt, J = 8.9, 6.1 Hz, 3H), 7.62 – 7.50 (m, 1H), 7.22 – 7.04 (m, 3H), 6.58 (d, J = 7.7 Hz, 1H), 5.58 (d, J = 7.6 Hz, 1H), 3.49 (d, J = 19.5 Hz, 1H), 3.37 (d, J = 19.5 Hz, 1H), 2.94 – 2.73 (m, 2H), 2.34 (d, J = 8.1 Hz, 1H), 2.29 – 2.14 (m, 2H), 2.03 – 1.86 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 212.87, 211.63, 200.37, 154.70, 138.88, 136.56, 134.61, 132.51, 130.58, 130.23, 128.43, 128.01, 126.62, 126.31, 125.02, 73.95, 71.42, 63.09, 41.37, 30.12, 28.85, 18.01.

HPLC: 47% ee, (1S,2R,3'R)-isomer as determined by HPLC (IC 95:5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (major) = 34.3 min, t_r (minor) = 40.9 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 0.5, CHCl_3) = -57° ;

HRMS: (ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 347.1278, Found: 347.1281.

(1R,1'S,3R)-3-benzyl-3-ethyl-1'-hydroxyspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3r)

Colorless solid, yield: 20 mg (58%)

¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.64 (m, 2H), 7.55 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.16 (dd, *J* = 6.5, 2.9 Hz, 2H), 4.66 (d, *J* = 6.5 Hz, 1H), 3.11 (d, *J* = 12.7 Hz, 1H), 2.98 (d, *J* = 12.7 Hz, 1H), 2.85 (d, *J* = 19.8 Hz, 1H), 2.68 (d, *J* = 19.8 Hz, 1H), 1.93 (q, *J* = 7.5 Hz, 2H), 1.03 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 215.95, 215.36, 200.96, 154.09, 136.73, 135.96, 134.64, 130.68, 129.97, 128.76, 127.52, 126.17, 124.17, 73.44, 70.40, 64.49, 42.35, 41.32, 29.37, 8.86.

HPLC: 56% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 90:10 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r*(minor) = 13.5 min, *t_r*(major) = 17.6 min.

Opt. Rot.: [α]_D²² (c 0.5, CHCl₃) = -77°;

HRMS: (ESI) calcd for C₂₂H₂₁O₄ (M+H)⁺: 349.1434, Found: 349.1448

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(2-oxo-2-phenylethyl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3s)

Colorless solid, yield: 23 mg (63%)

¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, *J* = 7.8 Hz, 2H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.81 – 7.72 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H),

5.71 (s, 1H), 3.95 (s, 1H), 3.83 (dd, $J = 39.6, 18.5$ Hz, 2H), 3.60 (d, $J = 19.6$ Hz, 1H), 3.13 (d, $J = 19.6$ Hz, 1H), 1.42 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 214.25, 214.14, 202.12, 199.25, 154.84, 136.07, 134.78, 134.60, 134.34, 129.80, 128.83, 128.73, 126.31, 124.14, 75.17, 71.02, 53.55, 49.11, 40.70, 17.48.

HPLC: 78% ee, (1R,1'S,3R)-isomer as determined by HPLC (OD, 90:10 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (major) = 16.7 min, t_r (minor) = 19.7 min.

Opt. Rot.: $[\alpha]_{\text{D}^{22}}(\text{c } 1.0, \text{CHCl}_3) = -50.0^\circ$;

HRMS: (ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{O}_5(\text{M}+\text{H})^+$: 363.1227, Found: 363.1233.

(1R,1'S,3R)-1'-hydroxy-3-methyl-3-(prop-2-yn-1-yl)spiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3t)

Colorless solid, yield: 13 mg (44%)

^1H NMR (400 MHz, CDCl_3) δ 7.82 – 7.74 (m, 3H), 7.56 (td, $J = 8.4, 4.2$ Hz, 1H), 5.60 (d, $J = 6.4$ Hz, 1H), 3.37 (d, $J = 19.3$ Hz, 1H), 3.15 (d, $J = 19.3$ Hz, 1H), 2.53 (d, $J = 2.4$ Hz, 2H), 2.07 (t, $J = 2.6$ Hz, 1H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 212.55, 211.94, 200.46, 154.73, 136.43, 134.15, 130.36, 126.36, 124.74, 79.67, 72.79, 71.56, 70.88, 56.77, 41.97, 24.79, 19.56.

HPLC: 24% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 90:10 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 18.2 min, t_r (major) = 38.2 min.

Opt. Rot.: $[\alpha]_{\text{D}^{22}}(\text{c } 1.0, \text{CHCl}_3) = -2.5^\circ$;

HRMS: (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 283.0965, Found: 283.0969.

(1R,1'S,3R)-3-benzhydryl-1'-hydroxy-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3u)

Colorless solid, yield: 24 mg (58%)

^1H NMR (400 MHz, CDCl_3) δ 7.71 (dd, $J = 7.4, 6.1$ Hz, 2H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.59 – 7.54 (m, 2H), 7.54 – 7.46 (m, 3H), 7.40 – 7.33 (m, 4H), 7.32 – 7.27 (m, 2H), 5.02 (d, $J = 6.6$ Hz, 1H), 4.43 (s, 1H), 2.79 (d, $J = 19.4$ Hz, 1H), 2.56 (d, $J = 19.4$ Hz, 1H), 1.30 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 215.67, 215.02, 200.97, 154.33, 139.92, 139.69, 136.15, 134.07, 130.10, 130.08, 129.99, 128.79, 128.71, 127.49, 127.31, 126.17, 124.38, 73.00, 70.62, 61.90, 58.57, 41.96, 19.71.

HPLC: 96% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 90:10 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (major) = 11.7 min, t_r (minor) = 13.8 min.

Opt. Rot.: $[\alpha]_{\text{D}^{22}}(\text{c } 1.0, \text{CHCl}_3) = 5.2^\circ$;

HRMS: (ESI) calcd for $\text{C}_{27}\text{H}_{23}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 411.1591, Found: 411.1609.

(1R,1'S,3R)-3-benzyl-1'-hydroxy-3,5',6'-trimethylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3v)

Colorless solid, yield: 23 mg (63%)

¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1H), 7.34 (dd, *J* = 9.5, 4.2 Hz, 4H), 7.17 – 7.10 (m, 2H), 4.89 (d, *J* = 6.4 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.73 (d, *J* = 19.6 Hz, 1H), 2.42 (d, *J* = 19.6 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 1.38 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 215.65, 215.30, 200.63, 152.58, 146.84, 139.48, 136.63, 132.23, 130.34, 128.74, 127.53, 126.75, 124.56, 72.40, 71.10, 59.74, 43.24, 42.01, 20.90, 20.18, 19.93.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (IB, 98.5:1.5 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r* (minor) = 56.1 min, *t_r* (major) = 66.2 min.

Opt. Rot.: [α]_D²² (c 0.2, CHCl₃) = -28.7°;

HRMS: (ESI) calcd for C₂₃H₂₃O₄ (M+H)⁺: 363.1591, Found: 363.1596.

(1R,1'S,3R)-3-benzyl-1'-hydroxy-5',6'-dimethoxy-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (3w)

Colorless solid, yield: 17 mg (44%)

^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.30 (m, 3H), 7.19 – 7.10 (m, 2H), 7.06 (s, 1H), 7.00 (s, 1H), 4.88 (d, $J = 6.6$ Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.16 – 2.93 (m, 2H), 2.74 (d, $J = 19.6$ Hz, 1H), 2.42 (d, $J = 19.6$ Hz, 1H), 1.39 (s, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 216.01, 215.28, 199.30, 156.62, 151.44, 149.84, 136.68, 130.39, 128.74, 127.51, 127.02, 106.71, 104.13, 72.41, 70.77, 59.71, 56.46, 56.26, 43.43, 42.10, 20.07.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (ID, 90:10 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 60.5 min, t_r (major) = 74.2 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 0.5, CHCl_3) = -33.7°;

HRMS: (ESI) calcd for $\text{C}_{23}\text{H}_{23}\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 395.1489, Found: 395.1497.

(1R,1'S,3R)-3-benzyl-1'-hydroxy-3-methylspiro[cyclopentane-1,2'-cyclopenta[b]naphthalene]-2,3',4(1'H)-trione (3x)

Light yellow solid, yield: 17 mg (45%)

^1H NMR (400 MHz, CDCl_3) δ 8.26 (s, 1H), 8.02 (s, 1H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.90 (d, $J = 8.2$ Hz, 1H), 7.63 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 7.55 (ddd, $J = 8.0, 6.9, 1.1$ Hz, 1H), 7.44 – 7.31 (m, 3H), 7.20 – 7.10 (m, 2H), 5.16 (d, $J = 5.2$ Hz, 1H), 3.15 – 2.98 (m, 2H), 2.79 (d, $J = 19.6$ Hz, 1H), 2.52 (d, $J = 19.6$ Hz, 1H), 1.41 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 215.27, 214.99, 201.31, 147.02, 137.54, 136.61, 133.55, 131.22, 130.49, 130.35, 129.53, 128.80, 128.46, 127.60, 127.33, 125.82, 125.24, 72.58, 71.88, 59.86, 43.19, 41.92, 20.34.

HPLC: 92% ee, (1R,1'S,3R)-isomer as determined by HPLC (IC, 90:10 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (major) = 17.9 min, t_r (minor) = 31.8 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 1.0, CHCl_3) = -7.7°;

HRMS: (ESI) calcd for $\text{C}_{25}\text{H}_{21}\text{O}_4$ ($\text{M}+\text{H}$)⁺: 385.1434, Found: 385.1450.

(1R,1'R,3R)-1'-azido-3-benzyl-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (5)

Colorless solid, yield: 22 mg (62%)

^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd, J = 11.1, 4.3 Hz, 2H), 7.70 – 7.62 (m, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.06 (dd, J = 7.6, 1.8 Hz, 2H), 4.62 (s, 1H), 3.03 (s, 2H), 2.91 (d, J = 18.9 Hz, 1H), 2.18 (d, J = 18.9 Hz, 1H), 1.37 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 213.42, 212.02, 199.09, 151.35, 136.46, 135.82, 133.85, 130.63, 129.69, 128.92, 127.76, 126.04, 125.27, 70.17, 62.91, 59.58, 43.50, 42.96, 21.15.

HPLC: 92% ee, (1R,1'R,3R)-isomer as determined by HPLC (IA, 95:5 hexanes/i-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 8.9 min, t_r (major) = 10.8 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 0.05, CHCl_3) = 86.0°;

HRMS: (ESI) calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}_3$ ($\text{M}+\text{H}$)⁺: 360.1343, Found: 360.1339.

(1'S,2R,9aR)-1'-hydroxy-9a-methyl-3a,4,9,9a-tetrahydrospiro[cyclopenta[b]quinoline-2,2'-indene]-1,3'(1'H,3H)-dione (6)

Colorless solid, yield: 26 mg (78%)

¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 7.7 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.55 – 7.45 (m, 1H), 7.09 – 6.95 (m, 2H), 6.72 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 7.9 Hz, 1H), 5.11 (s, 1H), 3.88 (dd, J = 4.1, 3.0 Hz, 1H), 3.11 (d, J = 16.8 Hz, 1H), 2.72 (dd, J = 14.0, 4.4 Hz, 1H), 2.64 (t, J = 10.9 Hz, 1H), 2.44 (dd, J = 14.0, 2.7 Hz, 1H), 1.35 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 214.60, 202.03, 154.47, 142.42, 135.79, 135.20, 129.79, 129.36, 127.22, 126.23, 124.12, 119.62, 118.97, 114.30, 74.37, 68.67, 57.06, 50.14, 33.83, 32.04, 20.27.

HPLC: 48% ee, (1'S,2R,9aR)-isomer as determined by HPLC (ODH, 90:10 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 39.4 min, t_r (major) = 58.6 min.

Opt. Rot.: $[\alpha]_{D^{22}}$ (c 0.2, CHCl₃) = -18.1°;

HRMS: (ESI) calcd for C₂₁H₂₀NO₃ (M+H)⁺: 334.1438, Found: 334.1445.

(3aR,3'S,5R)-6a-hydroxy-3a-methyl-1',4-dioxo-2-phenyl-1',3a,3',4,6,6a-hexahydro-3H-spiro[cyclopenta[b]pyrrole-5,2'-inden]-3'-yl acetate (7)

Colorless solid, yield: 30 mg (75%)

¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.7 Hz, 2H), 7.53 (td, *J* = 7.6, 1.1 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.18 (m, 5H), 7.18 – 7.10 (m, 1H), 6.57 (s, 1H), 3.25 (d, *J* = 16.1 Hz, 1H), 3.11 (d, *J* = 12.1 Hz, 1H), 2.70 (dd, *J* = 16.1, 5.8 Hz, 1H), 2.59 (dd, *J* = 12.1, 6.8 Hz, 1H), 2.21 (s, 3H), 1.33 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 202.96, 201.31, 175.36, 171.01, 149.22, 136.64, 136.25, 135.20, 130.30, 128.68, 128.57, 126.53, 125.98, 123.92, 72.89, 64.76, 63.81, 58.01, 47.04, 40.53, 20.61, 12.91.

HPLC: 76% ee, (3aR,3'S,5R)-isomer as determined by HPLC (OD, 80:20 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r* (minor) = 12.8 min, *t_r* (major) = 20.0 min.

Opt. Rot.: [α]_D²² (c 1.0, CHCl₃) = -104.0°;

HRMS: (ESI) calcd for C₂₄H₂₂NO₅ (M+H)⁺: 404.1492, Found: 404.1503.

(1S,1'R,3R,3'S,4S)-3-benzyl-1',4-dihydroxy-3-methyl-2-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-inden]-3'-yl acetate (8)

Colorless solid, yield: 29 mg (65%)

¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, *J* = 4.4, 1.2 Hz, 2H), 7.39 – 7.23 (m, 5H), 7.14 – 7.08 (m, 2H), 5.84 (s, 1H), 5.29 (s, 1H), 4.32 (t, *J* = 5.2 Hz, 1H), 3.36 (s, 1H), 2.85 (d, *J* = 13.5 Hz, 1H), 2.68 (d, *J* = 13.5 Hz, 1H), 2.37 (s, 1H), 2.32 (dd, *J* = 14.1, 5.5 Hz, 1H), 2.18 (dd, *J* = 14.1, 5.1 Hz, 1H), 1.99 (s, 3H), 1.65 (s, 1H), 1.10 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 219.50, 170.37, 144.06, 138.72, 136.67, 130.22, 130.03, 129.02, 128.62, 127.04, 126.20, 123.84, 82.28, 72.68, 64.54, 56.38, 42.60, 35.78, 20.95, 15.93.

HPLC: 92% ee, determined by HPLC (OD, 80:20 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, *t_r*(minor) = 18.8 min, *t_r*(major) = 21.0 min.

Opt. Rot.: [α]_D²² (c 0.5, CHCl₃) = 75.4°;

HRMS: (ESI) calcd for C₂₃H₂₅O₅ (M+H)⁺: 381.1696, Found: 381.1721.

(1R,1'R,3R,3'S,4S)-3-benzyl-1',4-bis((diphenylphosphanyl)oxy)-3-methyl-2-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-inden]-3'-yl acetate (9)

Colorless solid, yield: 23 mg (75%)

¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.75 (m, 8H), 7.63 – 7.39 (m, 12H), 7.25 – 7.14 (m, 5H), 7.14 – 7.05 (m, 2H), 7.02 (dt, *J* = 5.1, 2.8 Hz, 1H), 6.99 – 6.89 (m, 1H), 5.87 (d, *J* = 9.7 Hz, 1H), 4.91 – 4.74 (m, 2H), 2.95 (d, *J* = 13.4 Hz, 1H), 2.80 (d, *J* = 13.5 Hz, 1H),

2.43 (dd, $J = 13.4, 10.1$ Hz, 1H), 2.24 (dd, $J = 13.5, 6.8$ Hz, 1H), 1.61 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 210.89, 168.99, 141.06, 141.03, 138.36, 136.65, 132.51, 132.48, 132.42, 132.39, 132.36, 132.33, 132.31, 132.23, 132.21, 132.14, 132.05, 132.03, 131.94, 131.93, 131.78, 131.71, 131.68, 131.61, 131.18, 131.03, 130.93, 130.81, 130.69, 129.70, 129.03, 128.69, 128.66, 128.62, 128.59, 128.56, 128.53, 128.49, 128.46, 128.27, 126.84, 126.06, 124.44, 79.88, 79.82, 73.60, 73.37, 73.31, 64.63, 64.59, 56.25, 56.21, 40.27, 31.83, 31.80, 20.44, 19.11.

^{31}P NMR (162 MHz, CDCl_3) δ 33.14, 30.91.

HPLC: 91% ee, (3aR,3'S,5R)-isomer as determined by HPLC (ADH, 80:20 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 254 nm, t_r (minor) = 32.8 min, t_r (major) = 39.0 min.

Opt. Rot.: $[\alpha]_{\text{D}}^{22}$ (c 1.0, CHCl_3) = 29.1°;

HRMS: (ESI) calcd for $\text{C}_{47}\text{H}_{43}\text{O}_5\text{P}_2$ ($\text{M}+\text{H}$) $^+$: 749.2580, Found: 749.2582.

(1R,1'S,3S)-3-benzyl-1'-(dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yloxy)-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (R-11)

^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.8$ Hz, 1H), 7.92 (d, $J = 8.2$ Hz, 1H), 7.85 (t, $J = 8.4$ Hz, 2H), 7.66 (d, $J = 7.7$ Hz, 2H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.44 (d, $J = 7.3$ Hz, 2H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.35 – 7.16 (m, 7H), 7.08 (d, $J =$

7.7 Hz, 2H), 7.00 (dd, $J = 8.8, 1.9$ Hz, 1H), 5.64 (dd, $J = 8.9, 1.9$ Hz, 1H), 2.98 (dt, $J = 31.2, 12.8$ Hz, 3H), 2.45 (dd, $J = 19.0, 2.5$ Hz, 1H), 1.35 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 213.73, 212.04, 199.58, 152.44, 147.80, 147.74, 147.06, 147.04, 136.36, 136.18, 134.40, 133.01, 132.75, 131.89, 131.38, 130.79, 130.63, 130.37, 130.13, 129.10, 128.64, 128.60, 128.14, 127.22, 127.03, 126.84, 126.72, 126.60, 125.57, 125.33, 124.92, 124.45, 124.40, 122.66, 121.75, 121.43, 74.75, 74.57, 70.80, 70.76, 59.73, 43.07, 42.44, 21.18.

^{31}P NMR (162 MHz, CDCl_3) δ 149.14.

Opt. Rot.: $[\alpha]_{\text{D}}^{21}$ (c 2.0, CHCl_3) = -105.85°;

HRMS: (ESI) calcd for $\text{C}_{41}\text{H}_{30}\text{O}_6\text{P}$ ($\text{M}+\text{H}$) $^+$: 649.1775, Found: 649.1772.

(1R,1'S,3S)-3-benzyl-1'-(((11bS)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)oxy)-3-methylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (S-11)

^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 8.8$ Hz, 1H), 7.98 – 7.83 (m, 3H), 7.80 (d, $J = 7.8$ Hz, 2H), 7.64 (dd, $J = 12.4, 6.1$ Hz, 2H), 7.50 – 7.41 (m, 2H), 7.38 (dd, $J = 13.0, 6.2$ Hz, 1H), 7.35 – 7.15 (m, 8H), 7.04 (d, $J = 6.4$ Hz, 2H), 6.66 (d, $J = 8.8$ Hz, 1H), 5.57 (d, $J = 8.9$ Hz, 1H), 3.07 – 2.90 (m, 2H), 2.83 (d, $J = 19.3$ Hz, 1H), 2.19 (d, $J = 19.3$ Hz, 1H), 1.32 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 213.56, 211.95, 199.43, 152.44, 152.42, 147.44, 147.39, 147.01, 146.98, 136.27, 136.15, 134.76, 133.05, 132.65, 131.87, 131.29, 130.97, 130.69,

130.05, 129.93, 129.13, 128.63, 128.50, 127.84, 127.36, 127.26, 127.07, 126.66, 126.51, 125.54, 125.31, 124.48, 124.43, 124.32, 122.91, 122.88, 121.70, 121.34, 74.67, 74.44, 71.55, 71.51, 59.98, 42.93, 30.58, 29.94, 21.33.

^{31}P NMR (162 MHz, CDCl_3) δ 153.54.

Opt. Rot.: $[\alpha]_{\text{D}}^{20}$ (c 0.5, CHCl_3) = 181.04°;

HRMS: (ESI) calcd for $\text{C}_{41}\text{H}_{30}\text{O}_6\text{P}$ ($\text{M}+\text{H}$)⁺: 649.1775, Found: 649.1839.

(1R,1'S,3R)-3-benzyl-1'-(dibenzo[d,f][1,3,2]dioxaphosphepin-6-yloxy)-3-ethylspiro[cyclopentane-1,2'-indene]-2,3',4(1'H)-trione (10)

^1H NMR (400 MHz, CDCl_3) δ 7.76 (ddd, J = 10.9, 9.0, 5.3 Hz, 3H), 7.59 – 7.49 (m, 1H), 7.42 (d, J = 6.6 Hz, 2H), 7.39 – 7.19 (m, 7H), 7.07 (d, J = 7.1 Hz, 2H), 6.96 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 5.68 (d, J = 9.2 Hz, 1H), 3.09 – 2.85 (m, 3H), 2.37 (d, J = 19.1 Hz, 1H), 1.35 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 213.66, 211.96, 199.59, 152.57, 152.56, 149.35, 149.28, 148.85, 148.80, 136.37, 136.13, 134.55, 131.40, 131.28, 131.25, 130.85, 130.78, 130.29, 130.22, 130.05, 129.57, 129.43, 129.10, 127.97, 127.05, 125.75, 125.66, 125.09, 122.08, 122.01, 74.48, 74.27, 71.23, 71.19, 59.85, 43.03, 42.70, 21.31.

^{31}P NMR (162 MHz, CDCl_3) δ 149.59.

HPLC: 96:4 *e.r.*, ODH, 90:10 hexanes/*i*-PrOH, 0.75mL/min, detection wavelength: 220 nm, t_r (major) = 10.9 min, t_r (minor) = 15.7 min.

HRMS: (ESI) calcd for $C_{21}H_{18}ClO_4$ ($M+H$) $^+$: 549.1462, Found: 549.1501.

(5a*S*,10b*R*)-2-mesityl-5a,10b-dihydro-4*H*,6*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium chloride

White solid. 1H NMR (400 MHz, DMSO- d_6) δ 11.89 (s, 1H), 7.70-7.63 (m, 2H), 7.45-7.33 (m, 5H), 6.24 (d, $J = 3.7$ Hz, 1H), 5.28 (d, $J = 16.0$ Hz, 1H), 5.12 (d, $J = 16.0$ Hz, 1H), 5.04 (t, $J = 4.3$ Hz, 1H), 3.51 (dd, $J = 17.1, 4.7$ Hz, 1H), 3.17 (d, $J = 17.1$ Hz, 1H), 2.40 (d, $J = 85.0$ Hz, 4H), 1.11 (d, $J = 35.1$ Hz, 6H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 150.7, 145.5, 141.5, 141.2, 136.7, 132.9, 132.6, 129.7, 127.7, 126.0, 124.4, 77.4, 61.8, 60.2, 37.5, 23.9, 15.6, 15.2; HRMS (ESI, m/z): calcd. for $C_{22}H_{24}N_3O^+$ 346.1914, found 346.1915.

(5a*S*,10b*R*)-2-(2,4,6-trichlorophenyl)-5a,10b-dihydro-4*H*,6*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium chloride

Pink solid. 1H NMR (400 MHz, DMSO- d_6) δ 11.64 (br s, 1H), 8.24 (s, 2H), 7.53 (d, $J = 7.4$ Hz, 1H), 7.45-7.34 (m, 3H), 6.22 (d, $J = 4.0$ Hz, 1H), 5.34 (d, $J = 16.2$ Hz, 1H), 5.13 (d, $J = 16.2$ Hz, 1H), 5.05 (t, $J = 4.5$ Hz, 1H), 3.50 (dd, $J = 17.1, 5.0$ Hz, 1H), 3.16 (d, $J =$

17.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 151.3, 147.3, 141.1, 138.9, 136.3, 130.1, 130.0, 129.9, 127.8, 126.0, 124.2, 77.4, 62.4, 60.1, 37.5, 23.9, 15.6, 15.2; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{13}\text{Cl}_3\text{N}_3\text{O}^+$ 392.0119, found 392.0122.

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Chapter 3

Carbene catalyzed desymmetrization

[4+2] arene construction

3.1 Introduction

3.1.1 Synthesis of chiral benzene unit

The benzene unit is a commonly-occurring scaffold, both in natural products and synthetic bioactive molecules. To date, several benzene construction strategies have been used for the organic synthesis, including [2+2+2] annulation, Stauter-Weinreb annulation, Hauser-Kraus annulation, electrocyclization *etc.*¹⁻⁷ One potential drawback of recent arene construction methods is the lack of enantioselectivity control: careful introduction of all chiral structures in different fragments are needed before arene formation. This process may cost tedious synthetic steps. The development of enantioselective arene construction methods could give rise the control of chiral centers attached to the arene ring, thus largely simplify the synthesis of these complicated molecules. To date, there are only two methods that could achieve the enantioselective arene construction.⁶ However, both transition-metal catalyzed enantioselective [2+2+2] cyclization and proline catalyzed intramolecular cyclization have limitations in (partial) intramolecular requirement, which somehow limits their applications in the synthesis of chiral multisubstituted arenes. On the other hand, organocatalyzed enantioselective intermolecular arene formation method is unprecedented.

An all-carbon quaternary chiral center is a fully substituted carbon atom with four different carbon neighbors. This highly diversified structure exists widely in natural products, pharmaceutical products and functional materials.⁹⁻¹¹ Notably, the absolute configuration of this fully substituted carbon stereocenter often influences the properties of the functional molecules greatly. Despite the vast demand to propose catalytically enantioselective methods for the efficient construction of all-carbon quaternary chiral center, the synthesis of several types of interesting compounds are still of great challenge. For example, as shown in **Scheme 3.1**, natural product coprinastatin epimer¹² and

preclinical drug MK-3207¹³ are still restricted to racemic synthesis and requires chiral chromatography to obtain the enantiomers. Bowl-shaped molecules tribenzotriquinacenes,^{14,15} an interesting type of molecular host or building blocks in supramolecular chemistry, are also not available in the catalytic asymmetric synthesis. Hence, isolation of the enantiomerically pure products requires kinetic resolution or other resolution methods. Fredericamycin A, which is a natural product, is an aromatic compound with a special all-carbon quaternary chiral center. To date, the shortest synthetic routes to synthesise fredericamycin A involves 25 steps, which was proposed by Kita.¹⁶ Among these synthetic steps, ~15 steps were required merely for the introduction of the chiral center. The construction of such fully substituted chiral carbon via conventional C-C bond forming reaction is of great challenge. One of the main challenges is attributable to the steric repulsion of the highly substituted substrate, which leads to the decrease in reactivity. Moreover, the less steric dissimilarity of the two carbon substituents on the prochiral center also makes it hard to achieve excellent enantiofacial discrimination. Desymmetrization reactions of prochiral molecules with a prochiral quaternary carbon provide alternative pathways for the all-carbon quaternary stereocenter. However, recent development of the desymmetrization reactions are still limited to the relatively simple reactions, such as intramolecular cyclization, hydrogenation, esterification *etc.* Thus, the current development is unable to satisfy the synthetic demand of these valuable compounds.

Scheme 3.1 Interesting chiral functional aromatics with a remote all-carbon quaternary center

3.1.2 NHC-catalyzed γ -sp³ carbon activation

Since the first NHC-catalyzed reaction in 1943, *N*-heterocyclic carbenes have become key players in the field of organocatalysis, and the development of enantioselective variants of NHC-catalyzed reactions has further popularized this class of catalysts.

In 2012, Chi's group reported the first NHC-catalyzed activation of enal γ -carbons.¹⁷ In this type of reaction, the Breslow intermediate is oxidized by an external oxidant to form an acyl azolium intermediate. Subsequent deprotonation by base at the γ -carbon results in formation of a vinyl enolate, which is the main intermediate through which the reaction proceeds (**Scheme 3.2**).

Scheme 3.2 The generation of vinyl enolate intermediates through γ -carbon activation

In this pioneering work, the activated enals underwent oxidative γ -addition with trifluoromethyl ketones to form unsaturated δ -lactones in very good yields and enantioselectivities (**Scheme 3.3**). Despite that the chiral information of the catalyst was quite remote from the γ -carbon, good stereo control was achieved by using a Lewis acid co-catalyst.

Scheme 3.3 The oxidative NHC-catalysed addition of γ -activated 3-phenylbut-2-enal to trifluoroacetophenone.

This study opened the possibility of many reactions that could proceed through the γ -carbon activation pathway. Heteroaryl aldehydes were reacted with trifluoromethyl ketones and isatins to give multicyclic and spirocyclic lactones, respectively. The reactions proceeded smoothly and with excellent enantioselectivity, without necessitating the use of a Lewis acid co-catalyst (**Scheme 3.4**).¹⁸ Numerous compounds containing isatin, oxindole or trifluoromethyl moieties have been found to display biological activity, and have been applied as anti-malarials, anti-cancer or anti-HIV agents.

Scheme 3.4 The [4+2] cycloaddition of aryl aldehydes with isatins/trifluoromethyl ketones

The γ -carbon activation methodology was also extended to α , β -unsaturated esters; the activated esters reacted with hydrazones resulting in optically enriched δ -lactam products. The chiral products could then readily undergo a 4-step transformation to form derivatives of bioactive pipecolic acid.¹⁹

Scheme 3.5 i) Examples of bioactive molecules with a 7-membered dinitrogen-fused heterocycle moiety.

ii) Chi group's [3+4] cycloaddition and kinetic resolution of azomethine imines

Chi' group also carried out the first NHC-catalyzed cycloaddition of γ -activated enals to azomethine imines, forming dinitrogen-fused 7-membered heterocyclic products. The 7-membered dinitrogen fused heterocycle motif can be found in a wide variety of biologically active compounds, such as insecticides, herbicides, or acetyl-CoA carboxylase inhibitors. Apart from forming the heterocyclic products in high optical purities, the reaction also provided the kinetic resolution of a remote chiral center on the azomethine imine substrate (**Scheme 3.5**).²⁰

3.1.3 Our proposal

Recently, our group has had significant success in NHC-mediated construction of multi-substituted benzene units. Usually, construction of such compounds involves a pre-existing benzene core, and requires many steps and functional group manipulations to get to the multi-substituted product. However, this novel NHC-catalyzed approach involved direct construction of the benzene core, significantly reducing the steps required to achieve the desired product. Enals underwent formal [3+3] cycloaddition to enones to form benzenes in a simple one-step process. The reaction proceeded with generally high yields and the products could be easily transformed into bicyclic and multicyclic aromatic molecules (**Scheme 3.6**).²¹

Scheme 3.6 Formal [3+3] construction of a multisubstituted benzene unit.

However, up until this point, the NHC-catalyzed benzene formations lacked an enantioselective component, such as the creation of a new chiral center, or desymmetrization of an existing one. Carrying out a construction of multisubstituted

benzene that would result in enantioenriched products would further increase the synthetic utility of this type of reaction.

As described in the previous chapter, the chiral NHC-bonded Breslow intermediate could be used to discriminate enantiotopic double bond of the prochiral 2, 2-disubstituted cyclopent-1,3-dione. We envisioned that the NHC-bonded vinyl enolate could also serve as nucleophile for the [4+2] cycloaddition to 1,3-dione substrates.

Based on the idea of NHC-catalyzed γ -activation of enals together with the recent developments in benzene construction, we design this [4+2] desymmetric benzene construction. Based on previous work, it was hypothesized that the enals would undergo oxidative addition to the 1,3-diones, to furnish partially oxidized product. Presence of excess oxidant would enable oxidative aromatization, leading to the desired benzene-containing product. The reaction would be made enantioselective by using chiral NHCs to desymmetrize the quaternary center originating from the 1,3-dione substrate. Although this carbon center is relatively remote from the NHC catalyst, past studies have shown remote chiral control by NHC catalysts is feasible.

Scheme 3.7 The proposed [4+2] desymmetric benzene construction reaction

3.2 Results and Discussions

3.2.1 Reaction optimization

We started by using enal **3a** and diketone **4a** in the presence of 2 equivalent of oxidant **6** and 10 mol% Cs₂CO₃ as a base. No proposed phenol **5a** was observed in the absence of an NHC precatalyst (Table 3.1, entry 1). Imidazolium precatalyst **A**, which gave best results in our previous works of benzene construction,²¹ could not initiate the reaction here. Fortunately, when

triazolium **C** and **D** were employed, the desired product **5a** was formed in moderate yield (Table 3.1, entries 4 & 5). Further screening of chiral triazolium precatalyst **E-H** (Table 3.1, entries 6-9) all showed better yields, and **H** afforded the best results of 85% yield and 94:6 er (Table 3.1, entry 9). The decrease in the catalyst loading of **H** dramatically slowed down the reaction, giving 34% yield after 8 hours and finally 61% yield after 2 days (Table 3.1, entry 10). We then evaluated the effects of base and solvents. Although the combination of Cs₂CO₃ and THF was optimal, other organic/inorganic base (such as DBU, K₂CO₃ and DIEA) and other organic solvents could also be used.

Table 3.1 condition optimization for NHC catalyzed desymmetric [4+2] benzene construction.

Entry	NHC (mol%)	base	yield (%)	er
1	-	Cs ₂ CO ₃	0	-
2	A (10)	Cs ₂ CO ₃	trace	-
3	B (10)	Cs ₂ CO ₃	trace	-
4	C (10)	Cs ₂ CO ₃	45	-
5	D (10)	Cs ₂ CO ₃	65	-
6	E (10)	Cs ₂ CO ₃	77	88:12
7	F (10)	Cs ₂ CO ₃	81	92:8
8	G (10)	Cs ₂ CO ₃	80	94:6
9	H (10)	Cs ₂ CO ₃	85	94:6
10	H (1)	Cs ₂ CO ₃	34 (61)*	94:6

all yields are isolated yields and the er was determined by chiral phase HPLC analysis. *in the parentheses is the yield after reacted for 48h.

3.2.2 Substrates scope

With an acceptable reaction condition in hand (**Table 3.1**, entry 9), the scope of the reaction was evaluated. We firstly chose diketone **4a** ($R^1 = \text{Me}$, $R^2 = \text{Bn}$) as a model diketone substrate to study the generality of the enal substrate (**Figure 3.1 A**, products **5a-m**). Both electro-donating (**5b-c**) and electron-withdrawing groups (**5d-f**) at the *para*-position (**5b-h**) and *meta*- position of the β -phenyl group (**5g**) were well tolerated. *Ortho*-substitution in β -phenyl group led to a slight decrease in enantioselectivity (**5h**). Replacement of the β -phenyl substituent with a naphthyl (**5i-j**), heteroaryl unit (**5l**) or alkenyl group (**5m**) had little effect on the reaction outcome. It is worth to note that the enals were synthesized via Vilsmeier formylation of commercially available styrene in nearly quantitative yields, and the *E*-/*Z*- mixture of enals can be directly used (the two isomers gave essentially the same yields and enantioselectivities).

With aldehyde **3a** as the model nucleophile, the scope of diketones was also examined. The widening of the scope of diketone substrates is as shown in **Figure 3.1 B**, products **5n-y**. Substituents with different electro-properties at the *para*- position (**5n-r**) and *meta*-position (**5s**) of the phenyl group were well tolerated. *Ortho*- substitution of the phenyl group led to some drop in enantioselectivity, which may be caused by undesired steric effect. Replacement of the phenyl substituent with a naphthyl (**5v**) or heteroaryl unit (**5w**) had little effect on the reaction outcome.

Although the reactivity of different diketones was shown to be general, the enantioselectivity of the reactions were highly dependent on the steric differences of two substituents in the quaternary carbon. The replacement of the benzyl group with a more sterically hindered benzhydryl group increased the enantioselectivity to 97:4 er (**5x**). Nevertheless, the replacement with a less steric phenyl group led to a sharp decline in enantioselectivity (**5y**).

Figure 3.1 Substrate Scope

A. Examples of different enals:

B. Examples of different 1,3-dione:

3.2.3 Product transformation.

We next demonstrated an effective transformation of our optically active products to different interesting multicyclic, endocyclic or spirocyclic compounds (**Scheme 3.8**), which were previously difficult to synthesize enantioselectively. For example, Nitrophenol **5u** could transform to tetracyclic benzoindenoquinolinone **7** with excellent regioselectivity and enantioselectivity under reductive cyclization condition. It is worth to note that the regioselectivity and chemoselectivity could be reversed completely by simply protecting the phenol group. Without intramolecular H-bonding, ketone in the other site with less steric hindrance is favored and the another tetracyclic molecule **8** was generated. These molecules were previously synthesized by methylation of the pre-existing multicyclic compounds, in which the manipulation of the enantioselectivity was hard to achieve. Phenol **5x** could transform to chiral tribenzotriquinacenes **6** with excellent regioselectivity and high enantiopurity via phenol protection, reduction and intramolecular Friedel-Crafts alkylation. Tribenzotriquinacene with unique bowl-shaped framework is an interesting building block for macromolecule construction.^{14,15} The chirality of these building blocks may have a crucial effect to decide the shape of the macromolecule. However, the asymmetric synthesis of chiral tribenzotriquinacene is very challenging. Thus far, there is only one report using enzyme catalyzed kinetic resolution to achieve this goal. Nonetheless, the product was gained with low yield (~10% from achiral tribenzotriquinacene).²² Comparatively, our method using enantioselective arene construction is much more efficient.

Scheme 3.8 Product transformation

3.2.4 Proposed mechanism

A plausible pathway of our NHC-catalyzed [4+2] cycloaddition involving formal γ - and carbonyl carbon activation of enal is illustrated in **Scheme 3.9**. Briefly, the reaction starts with the addition of the NHC catalyst to the aldehyde, followed by deprotonation to obtain the Breslow intermediate. This process is followed by oxidative transformation and enal γ -deprotonation, leading to vinyl enolate intermediate **II**. Since diketone **4** was proved to be good electrophile and poor dienophile in previous studies, we proposed a stepwise Michael addition & intramolecular Aldol reaction pathway instead of a [4+2] Diels-Alder reaction process (intermediate **II** to **III**). During the cycloaddition process, the more steric mesityl moiety (2,4,6-trimethylphenyl group, Mes) would be placed apart and the chiral indane moiety controls the direction of diketone **4** to set the more steric Bn group apart (intermediate **IIIb**). Finally, the carbene catalyst is released and oxidative aromatization takes place effectively, affording phenol product **5a** with four substituents in predictable substitution patterns and a remote all-carbon quaternary chiral center.

Scheme 3.9 Catalytic cycle

3.3 Summary.

In summary, we have developed a NHC organocatalytic strategy for the enantioselective formal [4+2] construction of multisubstituted phenols, which also represents the first intermolecular cycloaddition arene construction method. Our method employs easily accessible enals and diketones to construct phenol framework with excellent regioselectivity, and simultaneously install a remote all-carbon quaternary chiral center with good enantioselectivity via desymmetrization. As a result, this method offers practical insights into the design of concise synthetic strategies for complex molecules. Initial examples of practical application in the asymmetric synthesis of tribenzotriquinacene, the analogue of fredericamycin A and other structurally interesting molecules have showed great potential of the method. Further studies regarding mechanistic details of remote chirality control and other practical asymmetric synthesis of interesting compounds are in progress in our laboratory.

3.4 Experimental Section

3.4.1 General Information.

As refer to 2.4.1

3.4.2 General Procedure for the asymmetric synthesis of multisubstituted phenols

To a 10 mL Schlenk tube equipped with a magnetic stirring bar was added 1,3-dione **4a** (0.1 mmol), NHC precursor (0.01 mmol), Cs_2CO_3 (0.01 mmol) and oxidant **6** (0.2 mmol). The tube was closed with a septum, evacuated and refilled with nitrogen (3 cycles). Fresh distilled THF (4 mL) was added to the reaction mixture at room temperature followed by adding aldehyde **3a** (0.1 mmol) via microsyringe. Upon the reaction completed (monitored by TLC), the solvent was evaporated and subjected to SiO_2 column chromatography using hexane/EtOAc as eluent to yield the corresponding product as white solid.

3.4.3 Characterization of products.

(*S*)-2-benzyl-4-hydroxy-2-methyl-6-phenyl-1H-indene-1,3(2H)-dione

colorless oil, ν_{max} (film, cm^{-1}): 1735, 1681, 1618, 1337, 762, 700; ^1H NMR (400 MHz, CDCl_3) δ 8.70 (s, 1H), 7.59 (dd, $J = 7.9, 1.5$ Hz, 2H), 7.55 (d, $J = 1.1$ Hz, 1H), 7.52-7.43 (m, 3H), 7.35 (d, $J = 1.1$ Hz, 1H), 7.15-6.99 (m, 5H), 3.31-3.09 (m, 2H), 1.45 (s, 3H);

^{13}C NMR (101 MHz, CDCl_3) δ 206.9, 203.2, 156.6, 151.8, 141.8, 138.8, 135.7, 129.7,

129.2, 129.1, 128.2, 127.4, 126.9, 124.4, 120.9, 113.5, 56.7, 41.3, 20.1 ppm; HRMS (ESI) for $C_{23}H_{19}O_3^+$ $[M+H]^+$: calcd 343.1329, found 343.1331; 92:8 er was determined by HPLC (AD, 90:10 hexane/*i*PrOH, 0.7 mL/min, t_{maj} = 10.6 min, t_{min} = 18.6 min)

(*S*)-2-benzyl-4-hydroxy-2-methyl-6-(*p*-tolyl)-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1732, 1682, 1614, 1333, 818, 702; 1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.53 (d, J = 1.1 Hz, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 1.1 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.14-7.02 (m, 5H), 3.18 (d, J = 2.7 Hz, 2H), 2.42 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 203.3, 156.6, 151.8, 141.7, 139.5, 135.8, 135.7, 129.8, 129.7, 128.2, 127.3, 126.9, 124.2, 120.5, 113.2, 56.6, 41.2, 21.2, 20.2 ppm; HRMS (ESI) for $C_{24}H_{21}O_3^+$ $[M+H]^+$: calcd 357.1485, found 357.1488; 92:8 er was determined by HPLC (AD, 90:10 hexane/*i*PrOH, 1.0 mL/min, t_{maj} = 6.3 min, t_{min} = 11.4 min).

(*S*)-2-benzyl-4-hydroxy-6-(4-methoxyphenyl)-2-methyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1732, 1682, 1605, 1256, 1178, 831; 1H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 1.2 Hz, 1H), 7.27 (d, J = 1.2 Hz, 1H), 7.10-7.00 (m, 5H), 6.97 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.15 (d, J = 2.3 Hz, 2H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 203.4, 160.7, 156.6, 151.4, 141.7, 135.7, 131.0, 129.7, 128.7, 128.2, 126.9, 124.0, 120.0, 114.6, 112.8, 56.6, 55.4, 41.2, 20.2 ppm; HRMS (ESI) for $C_{24}H_{21}O_4^+$ $[M+H]^+$: calcd 373.1434,

found 373.1436; 89:11 er was determined by HPLC (AD, 70:30 hexane/iPrOH, 0.7 mL/min, $t_{\text{maj}} = 9.9$ min, $t_{\text{min}} = 15.8$ min).

(S)-2-benzyl-6-(4-fluorophenyl)-4-hydroxy-2-methyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1742, 1709, 1601, 1238, 833; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 1H), 7.55 (dd, $J = 8.7, 5.2$ Hz, 2H), 7.49 (d, $J = 1.0$ Hz, 1H), 7.29 (d, $J = 1.3$ Hz, 1H), 7.17 (t, $J = 8.6$ Hz, 2H), 7.13-7.01 (m, 5H), 3.18 (d, $J = 2.3$ Hz, 2H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.8, 203.1, 163.5 (d, $J_{\text{CF}} = 248$ Hz), 156.6, 150.7, 141.8, 135.7, 129.7, 129.3, 129.2, 128.2, 126.9, 124.4, 120.6, 116.18 (d, $J_{\text{CF}} = 21$), 113.2, 56.7, 41.3, 20.1; ^{19}F NMR (376 MHz, CDCl_3) δ -112.10; HRMS (ESI) for $\text{C}_{23}\text{H}_{18}\text{FO}_3^+ [\text{M}+\text{H}]^+$: calcd 361.1234, found 361.1240; 91:9 er was determined by HPLC (AD, 80:20 hexane/iPrOH, 0.7 mL/min, $t_{\text{maj}} = 15.1$ min, $t_{\text{min}} = 24.7$ min).

(S)-2-benzyl-6-(4-chlorophenyl)-4-hydroxy-2-methyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1732, 1682, 1616, 1337, 829, 702; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 1H), 7.54-7.48 (dd, $J = 8.4$ Hz, 1.2 Hz, 3H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 1.2$ Hz, 1H), 7.15-7.01 (m, 5H), 3.18 (d, $J = 2.3$ Hz, 2H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.8, 203.0, 156.6, 150.4, 141.8, 137.2, 135.6, 135.6, 129.7, 129.4, 128.7, 128.2, 126.9, 124.6, 120.7, 113.2, 56.7, 41.3, 20.2 ppm; HRMS (ESI) for $\text{C}_{23}\text{H}_{18}\text{ClO}_3^+ [\text{M}+\text{H}]^+$: calcd 377.0939, found 377.0944; 92:8 er was determined by HPLC (AD, 90:10 hexane/iPrOH, 0.7 mL/min, $t_{\text{maj}} = 14.9$ min, $t_{\text{min}} = 34.8$ min)

(S)-2-benzyl-6-(4-bromophenyl)-4-hydroxy-2-methyl-1H-indene-1,3(2H)-dione

light yellow oil; $\nu_{\max}$ (film, cm^{-1}): 1736, 1688, 1618, 1331, 825, 702; ^1H NMR (400 MHz, CDCl_3) δ 8.66 (s, 1H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 0.8$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 0.8$ Hz, 1H), 7.10-6.97 (m, 5H), 3.15 (d, $J = 2.4$ Hz, 2H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.9, 203.0, 156.6, 150.5, 141.8, 137.7, 135.6, 132.3, 129.7, 128.9, 128.2, 126.9, 124.6, 123.8, 120.6, 113.2, 56.7, 41.2, 20.2 ppm; HRMS (ESI) for $\text{C}_{23}\text{H}_{18}\text{BrO}_3^+$ $[\text{M}+\text{H}]^+$: calcd 421.0434, found 421.0428; 91:9 er was determined by HPLC (AD, 80:20 hexane/*i*PrOH, 0.7 mL/min, $t_{\text{maj}} = 25.0$ min, $t_{\text{min}} = 39.9$ min)

(S)-2-benzyl-4-hydroxy-6-(3-methoxyphenyl)-2-methyl-1H-indene-1,3(2H)-dione

light yellow oil; $\nu_{\max}$ (film, cm^{-1}): 1736, 1682, 1259, 1047, 702; ^1H NMR (400 MHz, CDCl_3) δ 8.66 (s, 1H), 7.50 (s, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.31 (s, 1H), 7.12 (d, $J = 7.8$ Hz, 1H), 7.09-6.99 (m, 6H), 6.96 (dd, $J = 8.2, 2.3$ Hz, 1H), 3.85 (s, 3H), 3.16 (d, $J = 2.6$ Hz, 2H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.9, 203.2, 160.1, 156.5, 151.7, 141.7, 140.2, 135.7, 130.2, 129.7, 128.2, 126.9, 124.5, 120.9, 119.8, 114.8, 113.5, 112.9, 56.7, 55.4, 41.3, 20.2 ppm; HRMS (ESI) for $\text{C}_{24}\text{H}_{21}\text{O}_4^+$ $[\text{M}+\text{H}]^+$: calcd 373.1434, found 373.1439; 92:8 er was determined by HPLC (AD, 90:10 hexane/*i*PrOH, 0.7 mL/min, $t_{\text{maj}} = 14.0$ min, $t_{\text{min}} = 18.8$ min)

(S)-2-benzyl-4-hydroxy-6-(2-methoxyphenyl)-2-methyl-1H-indene-1,3(2H)-dione

light yellow oil; $\nu_{\max}$ (film, cm^{-1}): 1732, 1686, 1248, 752;

^1H NMR (400 MHz, CDCl_3) δ 8.66 (s, 1H), 7.50 (d, $J = 1.1$ Hz, 1H), 7.40 (td, $J = 8.3, 1.7$ Hz, 1H), 7.34 (d, $J = 1.0$

Hz, 1H), 7.28 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.16-7.03 (m, 6H), 7.00 (d, $J = 8.3$ Hz, 1H), 3.83 (s, 3H), 3.18 (d, $J = 3.4$ Hz, 2H), 1.43 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.9, 203.2, 156.3, 155.9, 149.6, 140.8, 135.8, 130.7, 130.4, 129.8, 128.2, 128.2, 126.8, 124.1, 123.6, 121.0, 116.3, 111.4, 56.5, 55.6, 41.1, 20.2 ppm; HRMS (ESI) for $\text{C}_{24}\text{H}_{21}\text{O}_4^+$ $[\text{M}+\text{H}]^+$: calcd 373.1434, found 373.1437; 86:14 er was determined by HPLC (AD, 95:5 hexane/*i*PrOH, 0.7 mL/min, $t_{\text{maj}} = 11.4$ min, $t_{\text{min}} = 21.4$ min).

(S)-2-benzyl-4-hydroxy-2-methyl-6-(naphthalen-2-yl)-1H-indene-1,3(2H)-dione

light yellow oil; $\nu_{\max}$ (film, cm^{-1}): 1732, 1682, 1614,

1259, 744, 702; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 1H), 8.04 (d, $J = 1.2$ Hz, 1H), 7.92 (d, $J = 8.7$ Hz,

1H), 7.90-7.84 (m, 2H), 7.70-7.64 (m, 2H), 7.54 (dd, $J = 6.2, 3.2$ Hz, 2H), 7.45 (d, $J = 1.2$ Hz, 1H), 7.12-7.02 (m, 5H), 3.18 (d, $J = 2.9$ Hz, 2H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.9, 203.3, 156.6, 151.8, 141.8, 136.0, 135.7, 133.4, 129.7, 129.0, 128.5, 128.2, 127.7, 127.1, 126.94, 126.8, 124.8, 124.4, 121.0, 113.7, 56.7, 41.3, 20.2 ppm; HRMS (ESI) for $\text{C}_{27}\text{H}_{21}\text{O}_3^+$ $[\text{M}+\text{H}]^+$: calcd 393.1485, found 393.1488; 92:8 er was determined by HPLC (AD, 80:20 hexane/*i*PrOH, 0.7 mL/min, $t_{\text{maj}} = 9.8$ min, $t_{\text{min}} = 14.6$ min).

(S)-2-benzyl-4-hydroxy-2-methyl-6-(naphthalen-1-yl)-1H-indene-1,3(2H)-dione

light yellow oil; $\nu_{\max}$ (film, cm^{-1}): 1736, 1686, 1331, 777, 702; ^1H NMR (400 MHz, CDCl_3) δ 8.73 (s, 1H), 7.90 (dd, $J = 8.1, 4.2$ Hz, 2H), 7.61 (d, $J = 8.2$ Hz, 1H), 7.55-7.43 (m, 3H), 7.41 (s, 1H), 7.33 (d, $J = 7.0$ Hz, 1H), 7.23 (s, 1H), 7.16-7.03 (m, 5H), 3.18 (s, 2H), 1.46 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 207.1, 203.1, 156.2, 151.8, 148.7, 141.2, 137.8, 135.7, 133.7, 130.7, 129.7, 129.1, 128.5, 128.2, 126.9, 126.7, 126.2, 125.2, 125.1, 124.0, 116.6, 56.7, 41.7, 19.8 ppm; HRMS (ESI) for $\text{C}_{27}\text{H}_{21}\text{O}_3^+$ $[\text{M}+\text{H}]^+$: calcd 393.1485, found 393.1492; 90:10 er was determined by HPLC (AD, 90:10 hexane/*i*PrOH, 0.7 mL/min, $t_{\text{maj}} = 9.3$ min, $t_{\text{min}} = 19.3$ min)

(*S*)-6-(benzo[*d*][1,3]dioxol-5-yl)-2-benzyl-4-hydroxy-2-methyl-1H-indene-1,3(2*H*)-dione

light yellow solid; $\nu_{\max}$ (film, cm^{-1}): 1732, 1682, 1616, 1453, 764, 702; ^1H NMR (400 MHz, CDCl_3) δ 8.64 (s, 1H), 7.43 (d, $J = 1.3$ Hz, 1H), 7.22 (d, $J = 1.3$ Hz, 1H), 7.12-6.98 (m, 7H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.01 (s, 2H), 3.15 (d, $J = 2.4$ Hz, 2H), 1.40 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.7, 203.2, 156.7, 151.4, 148.8, 148.5, 141.7, 135.7, 132.9, 129.7, 128.2, 126.9, 124.1, 121.6, 120.3, 113.0, 108.8, 107.6, 101.6, 56.7, 41.2, 20.2 ppm; HRMS (ESI) for $\text{C}_{24}\text{H}_{19}\text{O}_5^+$ $[\text{M}+\text{H}]^+$: calcd 387.1227, found 387.1232; 88:12 er was determined by HPLC (AD, 70:30 hexane/*i*PrOH, 0.7 mL/min, $t_{\text{maj}} = 17.9$ min, $t_{\text{min}} = 21.6$ min).

(*S*)-2-benzyl-4-hydroxy-2-methyl-6-(thiophen-2-yl)-1H-indene-1,3(2*H*)-dione

light yellow oil; $\nu_{\max}$ (film, cm^{-1}): 1735, 1682, 1661, 1614, 1422, 1248, 702; ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 1.0$ Hz, 1H), 7.93 (dd, $J = 8.1, 1.6$ Hz, 1H), 7.82 (d, $J =$

8.1 Hz, 1H), 7.49 (d, $J = 3.7$ Hz, 1H), 7.44 (d, $J = 5.0$ Hz, 1H), 7.15 (dd, $J = 5.0, 3.8$ Hz, 1H), 7.08-6.99 (m, 5H), 3.18 (s, 2H), 1.42 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 204.1, 203.1, 142.4, 141.8, 141.6, 139.8, 135.9, 132.7, 129.7, 128.7, 128.1, 127.8, 126.8, 125.8, 123.8, 119.0, 56.3, 41.52, 20.4; HRMS (ESI) for $\text{C}_{21}\text{H}_{17}\text{O}_3\text{S}^+$ $[\text{M}+\text{H}]^+$: calcd 349.0893, found 349.0892; 83:17 er was determined by HPLC (AD, 70:30 hexane/iPrOH, 0.7 mL/min, $t_{\text{min}} = 21.5$ min, $t_{\text{maj}} = 25.6$ min).

(S)-2-benzyl-6-(furan-2-yl)-4-hydroxy-2-methyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1733, 1681, 1614, 705; ^1H NMR (400 MHz, CDCl_3) δ 8.71 (s, 1H), 7.56 (dd, $J = 6.5, 1.3$ Hz, 2H), 7.39 (d, $J = 1.0$ Hz, 1H), 7.11-7.01 (m, 5H), 6.86 (d, $J = 3.5$ Hz, 1H), 6.54 (dd, $J = 3.5, 1.8$ Hz, 1H), 3.17 (d, $J = 2.3$ Hz, 2H), 1.43 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.4, 203.2, 156.8, 151.7, 144.3, 140.1, 135.6, 129.6, 128.2, 126.9, 124.1, 116.5, 112.5, 110.0, 109.8, 109.7, 56.5, 41.4, 20.0; HRMS (ESI) for $\text{C}_{21}\text{H}_{17}\text{O}_4^+$ $[\text{M}+\text{H}]^+$: calcd 333.1121, found 333.1119; 82:18 er was determined by HPLC (AD, 70:30 hexane/iPrOH, 0.7 mL/min, $t_{\text{min}} = 13.4$ min, $t_{\text{maj}} = 14.5$ min).

(S)-4-hydroxy-2-methyl-2-(4-methylbenzyl)-6-phenyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1736, 1688, 1618, 1337, 1265, 739; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.60 (dd, $J = 7.9, 1.5$ Hz, 2H), 7.56 (d, $J = 1.1$ Hz, 1H), 7.53-7.40 (m, 3H), 7.36 (d, $J = 1.1$ Hz, 1H), 6.96-6.89 (m, 4H), 3.16 (d, $J = 2.9$ Hz,

2H), 2.19 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 207.0, 203.3, 156.6, 151.8, 141.8, 138.8, 136.4, 132.6, 129.6, 129.2, 129.1, 128.9, 127.4, 124.5, 120.8, 113.5, 56.7, 40.8, 21.0, 20.2 ppm; HRMS (ESI) for $\text{C}_{24}\text{H}_{21}\text{O}_3^+$ $[\text{M}+\text{H}]^+$: calcd 357.1485, found 357.1491; 93:7 er was determined by HPLC (AD, 90:10 hexane/ i PrOH, 0.7 mL/min, t_{maj} = 10.4 min, t_{min} = 23.8 min)

(S)-4-hydroxy-2-(4-methoxybenzyl)-2-methyl-6-phenyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1732, 1682, 1614, 1514, 1337, 1254; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.62-7.57 (m, 2H), 7.56 (d, J = 1.1 Hz, 1H), 7.53--7.41 (m, 3H), 7.36 (d, J = 1.1 Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 3.68 (s, 3H), 3.22-3.08 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 207.1, 203.4, 158.4, 156.6, 151.8, 141.8, 138.8, 130.7, 129.2, 129.1, 127.8, 127.4, 124.5, 120.9, 113.6, 113.5, 56.8, 55.1, 40.4, 20.1 ppm; HRMS (ESI) for $\text{C}_{24}\text{H}_{21}\text{O}_4^+$ $[\text{M}+\text{H}]^+$: calcd 373.1434, found 373.1440; 93:7 er was determined by HPLC (AD, 90:10 hexane/ i PrOH, 0.7 mL/min, t_{maj} = 15.0 min, t_{min} = 29.3 min)

(S)-2-(4-fluorobenzyl)-4-hydroxy-2-methyl-6-phenyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1732, 1682, 1620, 1510, 1337, 1223, 752; ^1H NMR (400 MHz, CDCl_3) δ 8.65 (s, 1H), 7.57 (dd, J = 8.0, 1.5 Hz, 2H), 7.53 (d, J = 1.1 Hz, 1H), 7.50-7.41 (m, 3H), 7.35 (d, J = 1.1 Hz, 1H), 6.99 (dd, J = 8.6, 5.5 Hz, 2H), 6.77 (t, J = 8.7 Hz, 2H), 3.22-3.06 (m, 2H), 2.17 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 206.7, 203.0, 161.7 (d, J_{CF} = 244 Hz), 156.5, 152.0, 141.6, 138.6, 131.2,

131.1, 129.2, 129.1, 127.4, 124.3, 121.0, 115.0 (d, $J_{CF} = 21$ Hz), 113.5, 56.6, 40.1, 20.1 ppm; HRMS (ESI) for $C_{23}H_{18}FO_3^+$ $[M+H]^+$: calcd 361.1234, found 361.1240;

91:9 er was determined by HPLC (AD, 90:10 hexane/ i PrOH, 0.7 mL/min, $t_{maj} = 9.6$ min, $t_{min} = 15.5$ min)

(S)-2-(4-chlorobenzyl)-4-hydroxy-2-methyl-6-phenyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1736, 1682, 1618,

1337, 760; 1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H),

7.57 (dd, $J = 7.9, 1.5$ Hz, 2H), 7.54 (d, $J = 1.1$ Hz, 1H),

7.49-7.42 (m, 3H), 7.36 (d, $J = 1.0$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz,

2H), 3.32-3.01 (m, 2H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 203.1, 156.9,

152.4, 141.8, 138.9, 134.5, 133.1, 131.3, 129.5, 129.4, 128.6, 127.7, 124.5, 121.4, 113.8,

56.7, 40.3, 20.6 ppm; HRMS (ESI) for $C_{23}H_{18}ClO_3^+$ $[M+H]^+$: calcd 377.0939, found

377.0934; 93:7 er was determined by HPLC (AD, 90:10 hexane/ i PrOH, 0.7 mL/min, t_{maj}

= 12.1 min, $t_{min} = 18.3$ min)

(S)-2-(4-bromobenzyl)-4-hydroxy-2-methyl-6-phenyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1732, 1684, 1616,

1337, 760; 1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H),

7.51-7.44 (m, 2H), 7.44 (s, 1H), 7.39-7.31 (m, 3H),

7.26 (s, 1H), 7.12 (d, $J = 8.3$ Hz, 2H), 6.81 (d, $J = 8.3$ Hz, 2H), 3.10-2.89 (m, 2H), 1.30 (s,

3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 203.1, 156.9, 152.4, 141.7, 138.9, 135.0,

131.7, 131.6, 129.5, 129.4, 127.68, 124.4, 121.4, 121.2, 113.9, 56.7, 40.3, 20.7 ppm;

HRMS (ESI) for $C_{23}H_{18}BrO_3^+$ $[M+H]^+$: calcd 421.0434, found 421.0431; 93:7 er was

determined by HPLC (AD, 90:10 hexane/*i*PrOH, 0.7 mL/min, t_{maj} = 12.7 min, t_{min} = 18.8 min)

(S)-4-hydroxy-2-methyl-2-(3-methylbenzyl)-6-phenyl-1H-indene-1,3(2H)-dione

light yellow oil; ν_{max} (film, cm^{-1}): 1736, 1682, 1620, 1377, 1337, 760, 700; ^1H NMR (400 MHz, CDCl_3) δ 8.71 (s, 1H), 7.59 (dd, J = 8.0, 1.5 Hz, 2H), 7.56 (d, J = 1.2 Hz, 1H), 7.51-7.45 (m, 3H), 7.35 (d, J = 1.2 Hz, 1H), 7.03-6.97 (m, 1H), 6.89-6.84 (m, 3H), 3.21-3.07 (m, 2H), 2.21 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 207.0, 203.2, 156.6, 151.8, 141.8, 138.8, 137.8, 135.9, 130.5, 129.2, 129.1, 128.1, 127.6, 127.4, 126.7, 124.5, 120.8, 113.4, 56.7, 41.3, 21.2, 20.1 ppm; HRMS (ESI) for $\text{C}_{24}\text{H}_{21}\text{O}_3^+$ $[\text{M}+\text{H}]^+$: calcd 357.1485, found 357.1486; 91:9 er was determined by HPLC (AD, 90:10 hexane/*i*PrOH, 0.7 mL/min, t_{maj} = 9.4 min, t_{min} = 15.5 min)

(S)-4-hydroxy-2-methyl-2-(2-methylbenzyl)-6-phenyl-1H-indene-1,3(2H)-dione

light yellow solid; ν_{max} (film, cm^{-1}): 1736, 1682, 1618, 1337, 766; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.60 (dd, J = 8.0, 1.5 Hz, 2H), 7.58 (d, J = 1.1 Hz, 1H), 7.53-7.42 (m, 3H), 7.38 (d, J = 1.1 Hz, 1H), 7.04-6.92 (m, 4H), 3.38-3.16 (m, 2H), 2.34 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 207.1, 203.4, 156.6, 151.9, 141.8, 138.8, 136.6, 134.2, 130.7, 130.0, 129.2, 129.1, 127.4, 127.0, 125.64, 124.5, 120.9, 113.5, 56.5, 37.6, 20.2, 19.8 ppm; HRMS (ESI) for $\text{C}_{24}\text{H}_{21}\text{O}_3^+$ $[\text{M}+\text{H}]^+$: calcd 357.1485, found 357.1480; 91:9 er was determined by HPLC (AD, 90:10 hexane/*i*PrOH, 0.7 mL/min, t_{maj} = 9.6 min, t_{min} = 15.5 min)

(S)-4-hydroxy-2-methyl-2-(2-nitrobenzyl)-6-phenyl-1H-indene-1,3(2H)-dione

light yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.60 (s, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 7.67-7.61 (m, 3H), 7.55-7.47 (m, 4H), 7.46 (d, $J = 1.0$ Hz, 1H), 7.40 (t, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 3.59 (s, 2H), 1.40 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ

205.6, 202.0, 157.0, 152.3, 141.0, 138.8, 133.4, 132.7, 130.8, 129.3, 129.2, 128.4, 127.5, 125.4, 123.6, 121.3, 114.0, 54.6, 36.8, 19.2 ppm; HRMS (ESI) for $\text{C}_{23}\text{H}_{18}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$: calcd 388.1179, found 388.1185; 80:20 er was determined by HPLC (AD, 80:20 hexane/ i PrOH, 0.5 mL/min, $t_{\text{maj}} = 37.3$ min, $t_{\text{min}} = 41.4$ min)

(S)-4-hydroxy-2-methyl-2-(naphthalen-2-ylmethyl)-6-phenyl-1H-indene-1,3(2H)-dione

light yellow solid; ν_{max} (film, cm^{-1}): 1732, 1682, 1618, 744; ^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 7.68 (dd, $J = 13.9, 7.5$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.52 (s, 1H), 7.48 (dd, $J = 6.0, 1.2$ Hz, 3H), 7.44-7.32 (m, 6H), 7.17 (dd, $J = 8.4, 1.6$ Hz, 1H), 3.43-3.24 (m, 2H), 1.47 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ

207.0, 203.4, 156.8, 152.1, 141.8, 138.9, 133.6, 133.4, 132.4, 129.4, 129.3, 128.9, 128.1, 128.0, 127.6, 127.6, 126.1, 125.8, 124.6, 121.2, 113.8, 57.0, 41.3, 20.8 ppm; HRMS (ESI) for $\text{C}_{27}\text{H}_{21}\text{O}_3^+$ $[\text{M}+\text{H}]^+$: calcd 393.1485, found 393.1492; 93:7 er was determined by HPLC (AD, 90:10 hexane/ i PrOH, 0.7 mL/min, $t_{\text{maj}} = 13.6$ min, $t_{\text{min}} = 22.7$ min)

(S)-4-hydroxy-2-methyl-6-phenyl-2-(thiophen-2-ylmethyl)-1H-indene-1,3(2H)-dione

light yellow solid; $\nu_{\max}$ (film, cm^{-1}): 1732, 1693, 1620, 1337, 698; ^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 7.66-7.53 (m, 3H), 7.50-7.41 (m, 3H), 7.37 (d, $J = 1.1$ Hz, 1H), 6.93 (dd, $J = 5.0, 1.1$ Hz, 1H), 6.75-6.65 (m, 2H), 3.39 (d, $J = 3.5$ Hz, 2H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 206.5, 202.8, 156.6, 152.0, 141.8, 138.8, 137.1, 129.3, 129.1, 127.5, 127.4, 126.7, 124.6, 121.0, 113.6, 56.5, 34.9, 20.2. ppm; HRMS (ESI) for $\text{C}_{21}\text{H}_{17}\text{O}_3\text{S}^+ [\text{M}+\text{H}]^+$: calcd 349.0893, found 349.0885; 93:7 er was determined by HPLC (AD, 90:10 hexane/ i PrOH, 0.7 mL/min, $t_{\text{maj}} = 15.0$ min, $t_{\text{min}} = 29.3$ min)

(S)-2-benzhydryl-4-hydroxy-2-methyl-6-phenyl-1H-indene-1,3(2H)-dione

light yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 1H), 7.61-7.51 (m, 5H), 7.50-7.39 (m, 6H), 7.33 (d, $J = 1.1$ Hz, 1H), 7.24-7.12 (m, 5H), 4.60 (s, 1H), 1.35 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 207.2, 203.4, 156.7, 151.8, 141.6, 139.6, 139.6, 138.8, 129.8, 129.6, 129.5, 129.3, 129.1, 128.5, 128.4, 127.4, 127.0, 124.4, 120.9, 113.5, 59.1, 57.7, 20.1 ppm; HRMS (ESI) for $\text{C}_{29}\text{H}_{23}\text{O}_3^+ [\text{M}+\text{H}]^+$: calcd 419.1642, found 419.1645; 93:7 er was determined by HPLC (AD, 90:10 hexane/ i PrOH, 0.7 mL/min, $t_{\text{maj}} = 15.0$ min, $t_{\text{min}} = 29.3$ min)

(R)-4-hydroxy-10a-methyl-2-phenyl-10H-indeno[1,2-b]quinolin-11(10aH)-one

light yellow crystal; $\nu_{\max}$ (film, cm^{-1}): 1732, 1715, 1472, 1337, 764; ^1H NMR (400 MHz, CDCl_3) δ 7.73 – 7.61 (m, 2H), 7.54 – 7.40 (m, 5H), 7.35 (td, $J = 7.4, 0.8$ Hz, 1H), 7.28

– 7.20 (m, 3H), 3.01 (d, $J = 15.8$ Hz, 1H), 2.92 (d, $J = 15.6$ Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 203.27, 172.17, 157.21, 148.67, 143.68, 139.72, 139.49, 129.99, 129.24, 128.85, 128.28, 127.56, 127.45, 126.74, 126.61, 126.41, 120.67, 114.42, 44.81, 31.81, 29.85, 19.42.; HRMS (ESI) for $\text{C}_{23}\text{H}_{18}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: calcd 340.1332, found 340.1329; 77:23 er was determined by HPLC (AZH, 95:5 hexane/ i PrOH, 0.75 mL/min, $t_{\text{maj}} = 20.3$ min, $t_{\text{min}} = 28.8$ min)

(10aS)-1-methoxy-10a-methyl-3-phenyl-4b,5,10,10a-

tetrahydro-11H-indeno[1,2-b]quinolin-11-one. light yellow oil; ν_{max} (film, cm^{-1}): 1717, 1265, 739; ^1H NMR (400 MHz, CDCl_3) δ 7.72 – 7.63 (m, 2H), 7.58 (t, $J = 8.5$ Hz, 1H), 7.53 – 7.45 (m, 3H), 7.41 (dd, $J = 8.5, 6.1$ Hz, 1H), 7.35 – 7.28 (m, 1H), 7.22 – 7.12 (m, 3H), 4.92 (s, 1H), 4.11 (s, 3H), 3.02 (t, $J = 15.0$ Hz, 1H), 2.88 (d, $J = 15.5$ Hz, 1H), 0.87 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.27, 173.42, 157.81, 152.75, 147.42, 146.28, 144.39, 143.71, 140.66, 129.08, 128.64, 128.42, 127.68, 127.60, 127.53, 126.59, 125.58, 122.03, 115.38, 110.16, 80.82, 56.34, 44.35, 37.09, 15.51. HRMS (ESI) for $\text{C}_{24}\text{H}_{22}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: calcd 356.1645, found 356.1655; 23:77 er was determined by HPLC (ID, 90:10 hexane/ i PrOH, 0.75 mL/min, $t_{\text{maj}} = 22.4$ min, $t_{\text{min}} = 39.6$ min)

(4b1S)-1-methoxy-4b1-methyl-3-phenyl-4b,4b1,8b,12b-

tetrahydrodibenzo[2,3:4,5]pentaleno[1,6-ab]indene

light yellow oil; ν_{max} (film, cm^{-1}): 1591, 1472, 1265, 1074, 742;

^1H NMR (400 MHz, CDCl_3) δ 7.86 – 7.75 (m, 1H), 7.53 (dd, $J = 7.6, 5.6$ Hz, 2H), 7.50 – 7.39 (m, 4H), 7.37 – 7.29 (m, 1H), 7.25 (s, 1H), 7.22 – 7.11 (m, 4H), 7.06 – 6.96 (m, 1H), 6.89 (s, 1H), 4.68 (s, 1H), 4.46 (s, 2H), 3.98 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.55, 148.03, 146.05, 146.02, 145.79, 145.77, 145.52, 145.50, 145.16, 145.14, 143.18, 143.15, 142.12, 142.04, 132.15, 128.81, 127.68, 127.66, 127.56, 127.50, 127.32, 126.91, 124.56, 124.26, 115.90, 108.49, 64.02, 63.48, 61.82, 61.40, 55.31, 29.85, 27.80. HRMS (ESI) for $\text{C}_{30}\text{H}_{25}\text{O}^+$ $[\text{M}+\text{H}]^+$: calcd 401.1900, found 401.1925; 95:5 er was determined by HPLC (ID, 99.5:0.5 hexane/ i PrOH, 0.75 mL/min, $t_{\text{maj}} = 8.2$ min, $t_{\text{min}} = 11.8$ min)

3.5 References

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Chapter 4

Enantioselective Synthesis of Cyclic β -Amino Acid via Amine-Catalyzed Addition of Unsaturated Imine γ -Carbon to Enal

4.1 Introduction

4.1.1 Conventional method for the synthesis of cyclic β -amino acid

Conformationally constrained carbocyclic β -amino acids and their derivatives are medicinally important compounds.¹ They are also used as the unique building blocks for peptidic foldamers (**Scheme 4.1**).² For an instance, cispentacin, icofungipen, are found to exhibit antifungal activities.³⁻¹¹ Gellman and co-workers have pioneered in constructing peptidic foldamers with interesting structures and activities using oligomers of (R,R)-trans-2-aminocyclopentanecarboxylic acid (ACPC) as the building blocks.¹² Despite the wide utilities and the relatively simple structural features of these cyclic beta-amino acids, efficient preparation of these molecules remains difficult. In addition, typically, multi-step synthetic routes are required. For example, to the best of our knowledge, the preparation of ACHCs that is frequently practiced in the Gellman lab relies on a 4-step protocol involving chiral auxiliaries and separation of diastereomer intermediates (**Scheme 4.2**).¹²⁻¹⁸ Asymmetric catalytic synthesis of cyclic beta-amino acids remains difficult. The organocatalytic Mannich reactions between aldehydes and imines works well for acyclic beta-amino acids, but not the related cyclic variants.¹ Zhang and co-workers reported the synthesis of chiral cyclic β -amino acid derivatives via Ru-catalyzed hydrogenation of enamine using 50 atm H₂.¹⁰ Chiral biaryl ligands such as C3-TunaPhos were employed with up to 99% ee have been achieved.

Scheme 4.1 Bioactive molecules containing cyclic β -amino acid

Scheme 4.2 Typical approaches for synthesis of cyclic β -amino acid

Organocatalytic cascade reactions, which comprise at least two consecutive reactions in a chemical process, play an important role in the efficient and rapid construction of complex architectures, especially in the efficient total synthesis of complex natural products. This strategy was first demonstrated as the key process in the concise synthesis of (-)-huperzine A (**1**) by Terashima *et al* in 1998.²³

The main benefits of organocatalytic cascade sequences include time-saving, avoids the isolation of reaction intermediates and be able to achieve high levels of stereoselectivity at the same time. Furthermore, numerous functional groups tolerance and mild reaction conditions enables organocatalysts to be used in a wide variety of cascade reactions.²⁴

So far, organocatalytic activation modes include enamine activation of aldehydes and ketones (HOMO raising), iminium activation of α , β -unsaturated aldehydes (LUMO lowering), hydrogen bonding activation (LUMO lowering), protonation activation (LUMO lowering) (counterion catalysis) and umpolung activation enable by NHCs (Breslow intermediate).

4.1.2 Our Proposal.

We assumed that asymmetric synthesis of cyclic β -amino aldehyde could take place under chiral amine catalysis between the readily available unsaturated imine (**1a**) and enal (**2a**) substrates.

Key steps of the reaction involved *in situ* deprotonation and generation of vinylogous enamide (I) with nucleophilic γ -carbon, and addition of the unsaturated imine γ -carbon to the catalytically formed α , β -unsaturated iminium intermediate (II) from enal. The

stereoselectivity of the reaction is controlled well by an inexpensive and commercially available amine catalyst (**A**) derived from proline.¹⁹⁻²⁰ Notably, amino catalysis via enamine and/or iminium intermediates is a well-developed activation method with many inexpensive catalysts available.²¹

Scheme 4.3 Construction of cyclic β -amino acid

4.2 Results and Discussions

We tested our reaction using readily available unsaturated imine (**1a**) and enal (**2a**) as substrates. The key results of the reaction condition optimization are summarized in **Table 4.1**. We initially attempted to use the secondary amine catalyst **A** as the iminium catalyst to activate enal **2a**. The secondary amine catalyst **A** was also used as a base for the γ -carbon deprotonation of **1a** (entry 1). We found that amine **A** (pK_a around 7)²² was unable to play a role as a base to realize the γ -carbon deprotonation of **1a**, since the proposed cyclic β -amino aldehyde product **3a** was not observed. We then decided to use an additional inorganic base to realize the deprotonation of **1a**. Bases such as Na₂CO₃ and K₂CO₃ and were not effective (entry 2). When K₃PO₄ was used, **3a** was observed in 15% yield and 0% ee (entry 3). Further studies revealed that this reaction proceeded without the presence of amine catalyst **A** when K₃PO₄ was used as the base (entry 3). We next moved to evaluate bases that are less basic than K₃PO₄ to minimize the base-

catalyzed background reaction without ee control. When K_2HPO_3 was used, **3a** was obtained with 29% yield and 87% ee (entry 4). The use of KH_2PO_3 led to no formation of **3a** (entry 5). When a combined K_2HPO_3 and KH_2PO_3 was used, **3a** was formed with an increased ee (96% ee; entry 6). KH_2PO_3 likely played dual roles: one is to act as a proton source that is beneficial for the iminium catalytic cycle; another is to minimize the background reaction mediated by K_2HPO_3 alone. The reaction yield was consistently improved to an acceptable level via the addition of NaCl as an additive (entry 7). The exact roles of NaCl remained unclear at this point. Several other common amine catalysts examined here did not provide acceptable results (entries 8-9). It should be noted that in both cases, diastereoselectivity was well control by the chiral amine catalyst with up to >20:1 d.r. was achieved.

Table 4.1 Condition optimization

Entry ^a	Catalyst	Base	Additive	Yield (%) ^b	d.r.	ee ^c
1	A	-	-	< 5%	-	N.D. ^d
2	A	Na_2CO_3 or K_2CO_3	-	Complex mixture	-	-
3	A	K_3PO_4	-	Complex mixture	-	-
4	A	K_2HPO_4	-	29	> 20:1	87
5	A	KH_2PO_4	-	< 5%	-	N.D. ^d
6	A	K_2HPO_4 , KH_2PO_4	-	30	> 20:1	95
7	A	K_2HPO_4 , KH_2PO_4	NaCl	72(69) ^e	> 20:1	99
8	B	K_2HPO_4 , KH_2PO_4	NaCl	20	> 20:1	16
9	C	K_2HPO_4 , KH_2PO_4	NaCl	-	-	-

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), amine (0.03 mmol), base (0.1 mmol), additive (0.1 mmol) in 1 mL methanol at 60 °C for 12 h. ^b NMR yield based on **1a** using trimethoxybenzene as internal standard. ^c Enantiomeric excess of **3a** determined *via* chiral phase HPLC analysis. ^d N.D. = not determined ^e Isolated yield.

With an optimal condition (Table 4.1, entry 7) in hand, we started to examine the generality of the reaction (Table 4.2). Cinnamaldehyde derivatives **1** with different substituents were tested in this reaction with imine **2a**. The reaction proceeded steadily with both electron-donating (**3b** and **3d**) and electron-withdrawing (**3e** and **3f**) group substituents on para-position of phenyl ring with high yield and excellent enantioselectivity. However, an obvious decrease in yield (**3c**) was observed when a methyl group was added in the *ortho*-position of the phenyl ring. This was probably due to the steric hindrance. Hence, extra reaction time was required compared to the standard reaction condition. Changing the phenyl group into other heteroaryl (**3g**) and naphthyl (**3h**) substituents did not influence the reaction outcomes. By extending the conjugated system of aldehyde (**3i**), the reaction also proceeded successfully with a slight decrease in yield and good enantioselectivity.

Next, we continued the experiment by examining the imine substrates **2** using cinnamaldehyde **1a** as the model electrophile. When R¹, R² were electron-donating group such as 4-toluene substituent (**3s**), the yield of the desired product decreased drastically due to catalyst deactivation. More electron-rich substituents such as 4-anisole or thienyl did not give any corresponding products. The deactivation pathway of catalyst was shown in Scheme 4.4.

Table 4.2 Substrate scope

Electron-withdrawing groups (**3j**, **3k** and **3l**) produced desired products with moderate yield and good enantioselectivity. It is worth to note that only two hours of reaction time was needed when 4-nitrophenyl imine was used, which was the most reactive substrate. Both isobutyl and ester groups (**3n** and **3o**) on R² positions were also well tolerated in the reaction. We also investigated imines with other *N*-protecting groups. Both 2- and 4-nitrobenzenesulfonyl protecting imines (**3p** and **3q**) were tolerated well with 79% and 59% yield respectively, with 99% ee for both **3p** and **3q**. Interestingly, the diphenylphosphinyl imine (**3r**) proceeded smoothly under reaction condition with prolonged time. The aldehyde product was reduced to alcohol with NaBH₄ once the reaction completed, owing to the instability of the aldehyde. Notably, when an electron-donating unit was placed on the beta-aryl substituent of the unsaturated imine substrate, the reaction yield reduced dramatically (**3s**, **3t**). The decrease in yield was due to the presence of several side reactions (**Scheme 4.4**).

Scheme 4.4 Catalyst deactivated pathway

Absolute configurations of the cyclic β -amino acid derivatives were assigned based on the crystal X-ray structures of **3a**. A colorless crystal of **3a** was obtained by vaporization of a hexane/ethyl acetate/DCM (5:1:1) solution of compound **3a**. The absolute configuration of **3a** was determined by X-ray to be (1'R,2'S,3'R). (**Scheme 4.5**)

Scheme 4.5 Stereochemistry determination of the cyclic β -amino acid derivatives **3a** via X-ray crystallographic analysis

Scheme 4.6 Model of transition state

Based on the observed absolute configurations of **3a** through crystal X-ray structures, a model of transition state was proposed in **Scheme 4.6** to explain the stereo outcome. The bulky auxiliary in the amine catalyst serve as the stereo hindrance induce vinylogous enamide to attack the α , β -unsaturated iminium intermediate from bottom, a six-membered boat conformation formed, leading to the high levels of stereoselectivity of final product.

Our catalytic reaction was found to be equally efficient on gram scale, with the formation of product **3a** in 67% yield (1.5 gram) and 99% enantiomeric excess. Oxidation of the aldehyde product **3r** in very mild condition delivered the acid **5** in nearly quantitative yield. Deprotected the nitrobenzenesulfonyl group with thiophenol gave the free cyclic β -amino acid **6** (**Scheme 4.7**).

Scheme 4.7 Transformations of **3**

4.3 Summary.

In summary, we have developed a feasible approach to synthesize cyclic β -amino acids with excellent diastereoselectivity and enantioselectivity. These optically rich cyclic β -amino aldehydes can be prepared in gram-scale with no erosion of enantioexcess. The synthesis of conformationally constrained β -peptides based on these amino acids are in progress in our laboratory.

4.4 Experimental Section

4.4.1 General Information.

As refer to **2.4.1**

4.4.2 General procedures for the catalytic reactions

To a dry Schlenk tube equipped with a magnetic stir bar, was added aldehyde **1** (0.4 mmol), imine **2** (0.2 mmol), diphenylprolinol silyl ether **A** (0.06 mmol), K_2HPO_4 (0.2 mmol), KH_2PO_4 (0.2 mmol), and NaCl (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. MeOH (2 mL) was added and the reaction mixture was then stirred at $60\text{ }^\circ\text{C}$ till imine was completely consumed (monitored by TLC). The

mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel to afford the desired product **3**.

Note: Racemic samples for chiral phase HPLC analysis were prepared using (*R*) and (*S*) mixture (1:1) of diphenylprolinol silyl ether **A**. Absolute configuration of the product was assigned based on x-ray structure of **3a**.

4.4.3 Characterization of Product

Characterization of products (**3**):

N-((1'*S*,2'*R*,3'*S*)-2'-formyl-5'-phenyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3a**). Colorless solid, yield: 70 mg (69%); $[\alpha]_{\text{D}}^{20} = -48.0^{\circ}$ (*c* 1.9, CHCl₃); ¹H NMR

(400 MHz, CDCl₃) δ 9.19 (d, *J* = 1.4 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.42-7.12 (m, 13H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.84 (s, 1H), 6.35 (s, 1H), 3.43 (dd, *J* = 12.0, 1.4 Hz, 1H), 3.27 (td, *J* = 11.3, 5.8 Hz, 1H), 2.61 (ddd, *J* = 18.1, 10.8, 2.0 Hz, 1H), 2.39 (ddd, *J* = 18.2, 5.7, 1.2 Hz, 1H), 2.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 206.7, 144.3, 142.5, 140.6, 140.0, 138.9, 138.9, 129.1, 129.1, 128.5, 128.3, 128.2, 127.5, 127.5, 127.4, 127.2, 126.0, 125.5, 125.2, 62.3, 61.0, 40.2, 36.8, 21.3. HRMS (ESI) calcd for C₃₂H₃₀NO₃S (M+H)⁺: 508.1941 Found: 508.1967; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.75ml/min), *t_r*_{maj} = 36.7 min, *t_r*_{min} = 44.3 min.

N-((1'*S*,2'*R*,3'*S*)-2'-formyl-4''-methyl-5'-phenyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3b**).

Colorless solid, yield: 90 mg (86%); $[\alpha]_{\text{D}}^{20} = -35.1^{\circ}$ (*c* 6.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.20 (d, *J* = 1.5 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.38-7.19 (m, 8H), 7.12-7.03 (m,

6H), 6.87 (s, 1H), 6.34 (s, 1H), 3.40 (dd, $J = 12.0, 1.1$ Hz, 1H), 3.23 (td, $J = 11.3, 5.8$ Hz, 1H), 2.59 (ddd, $J = 18.1, 10.8, 1.9$ Hz, 1H), 2.39-2.32 (m, 1H), 2.29 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.9, 144.4, 142.5, 140.0, 139.0, 138.9, 137.5, 137.2, 129.8, 129.0, 128.5, 128.3, 128.1, 127.4, 127.2, 126.0, 125.5, 125.2, 62.3, 61.1, 39.9, 36.9, 21.3, 21.0. HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{32}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 522.2097 Found: 522.2087; 98% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 20.7$ min, $t_{r\text{ min}} = 29.3$ min.

N-((1'*S*,2'*R*,3'*S*)-2'-formyl-2''-methyl-5'-phenyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3c**).

Colorless solid, yield: 45 mg (43%); $[\alpha]_{\text{D}}^{20} = -43.6^\circ$ (c 4.9, CHCl_3);

^1H NMR (400 MHz, CDCl_3) δ 9.20 (d, $J = 1.4$ Hz, 1H), 7.66 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 7.7$ Hz, 2H), 7.42-7.19 (m, 11H), 7.19-7.04 (m, 3H), 7.01 (d, $J = 8.1$ Hz, 2H), 6.87 (s, 1H), 6.38 (s, 1H), 3.69 (td, $J = 11.2, 5.9$ Hz, 1H), 3.47 (d, $J = 11.8$ Hz, 1H), 2.54 (dd, $J = 17.7, 10.9$ Hz, 1H), 2.46-2.33 (m, 1H), 2.29 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 207.1, 144.4, 142.4, 140.1, 139.3, 138.9, 138.8, 135.8, 130.9, 129.1, 128.6, 128.3, 128.2, 127.5, 127.2, 127.1, 126.8, 126.0, 125.9, 125.5, 125.1, 62.3, 61.1, 35.9, 34.6, 21.3, 19.9. HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{32}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 522.2097 Found: 522.2081; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 29.7$ min, $t_{r\text{ min}} = 43.3$ min.

N-((1'*S*,2'*R*,3'*S*)-2'-formyl-4''-methoxy-5'-phenyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3d**).

Colorless solid, yield: 78 mg (73%); $[\alpha]_{\text{D}}^{20} = -26.7^\circ$ (c 6.7, CHCl_3);

^1H NMR (400 MHz, CDCl_3) δ 9.20 (d, $J = 1.3$ Hz, 1H), 7.66 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 7.6$ Hz, 2H), 7.40-7.19 (m, 9H), 7.10 (d, $J =$

8.6 Hz, 2H), 7.04 (d, $J = 8.1$ Hz, 2H), 6.89 (s, 1H), 6.83 (d, $J = 8.6$ Hz, 2H), 6.34 (s, 1H), 3.75 (d, $J = 6.2$ Hz, 3H), 3.41 – 3.31 (m, 1H), 3.23 (td, $J = 11.2, 5.7$ Hz, 1H), 2.58 (ddd, $J = 18.1, 10.8, 1.8$ Hz, 1H), 2.37 (dd, $J = 18.8, 5.4$ Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 207.0, 158.8, 144.4, 142.5, 140.0, 139.0, 138.9, 132.4, 129.0, 128.5, 128.5, 128.3, 128.1, 127.4, 127.2, 125.96, 125.5, 125.2, 114.5, 62.3, 61.3, 55.2, 39.4, 36.9, 21.33. HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{32}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$: 538.2047 Found: 538.2020; 98% ee as determined by HPLC (IC, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 25.7$ min, $t_{r\text{ min}} = 27.3$ min.

N-((1'*S*,2'*R*,3'*S*)-4''-chloro-2'-formyl-5'-phenyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3e**). Colorless solid, yield: 76 mg (70%); $[\alpha]_{\text{D}}^{20} = -17.8^\circ$ (c 7.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.22 (d, $J = 1.6$ Hz, 1H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.52 (d, $J = 7.4$ Hz, 2H), 7.38-7.20 (m, 12H), 7.12 (d, $J = 8.4$ Hz, 2H),

7.04 (d, $J = 8.0$ Hz, 2H), 6.70 (s, 1H), 6.34 (s, 1H), 3.39 (dd, $J = 12.0, 1.5$ Hz, 1H), 3.35-3.24 (m, 1H), 2.55 (ddd, $J = 18.1, 10.6, 2.0$ Hz, 1H), 2.39 (ddd, $J = 18.1, 5.8, 1.3$ Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 206.3, 144.1, 142.6, 139.9, 139.3, 138.8, 138.7, 133.2, 129.2, 129.1, 128.9, 128.6, 128.3, 128.3, 127.6, 127.2, 125.9, 125.5, 125.2, 62.2, 61.0, 39.5, 36.6, 21.4. HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{ClNO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 542.1551 Found: 542.1531; 99% ee as determined by HPLC (ODH, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 22.7$ min, $t_{r\text{ min}} = 24.3$ min.

N-((1'*S*,2'*R*,3'*S*)-4''-bromo-2'-formyl-5'-phenyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3f**). Colorless solid, yield: 100 mg (85%); $[\alpha]_{\text{D}}^{20} = +17.8^\circ$ (c 5.3, CHCl_3); ^1H NMR

(400 MHz, CDCl₃) δ 9.22 (d, J = 1.6 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.57-7.47 (m, 2H), 7.44-7.19 (m, 11H), 7.07-7.04 (m, 4H), 6.67 (s, 1H), 6.34 (s, 1H), 3.39 (dd, J = 12.0, 1.6 Hz, 1H), 3.34-3.22 (m, 1H), 2.54 (ddd, J = 18.1, 10.6, 2.1 Hz, 1H), 2.39 (ddd, J = 18.1, 5.8, 1.3 Hz, 1H), 2.30 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 231.7, 206.2, 144.1, 142.63, 139.9, 139.9, 138.8, 138.7, 132.2, 129.3, 129.1, 128.6, 128.3, 128.3, 127.6, 127.2, 125.9, 125.5, 125.3, 121.3, 62.2, 61.0, 39.6, 36.6, 21.4. HRMS (ESI) calcd for C₃₂H₂₉BrNO₃S (M+H)⁺: 586.1046 Found: 586.1060; 99% ee as determined by HPLC (ID, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}}$ = 33.3 min, $t_{r\text{ min}}$ = 39.3 min.

N-((1'S,5'S,6'R)-6'-formyl-5'-(furan-2-yl)-5',6'-dihydro-[1,1':3',1''-terphenyl]-1'(4'H)-yl)-4-methylbenzenesulfonamide (**3g**). Colorless solid, yield: 69 mg (69%); $[\alpha]_D^{20}$ = -56.1° (*c* 5.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.20 (d, J = 1.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.55-7.48 (m, 2H), 7.39-7.18 (m, 10H), 7.03 (d, J = 8.1 Hz, 2H), 6.85 (s, 1H), 6.28 (dd, J = 3.3, 1.9 Hz, 2H), 6.08 (d, J = 3.2 Hz, 1H), 3.51 – 3.35 (m, 2H), 2.76 (ddd, J = 18.2, 10.3, 2.1 Hz, 1H), 2.43-2.35 (m, 1H), 2.30 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 205.5, 153.5, 144.0, 142.5, 142.0, 139.94, 138.9, 138.6, 129.1, 128.5, 128.3, 128.21, 127.5, 127.2, 126.0, 125.5, 125.2, 110.4, 107.0, 62.0, 60.0, 33.5, 33.2, 21.4. HRMS (ESI) calcd for C₃₀H₂₈NO₄S (M+H)⁺: 498.1734 Found: 498.1755; 99% ee as determined by HPLC (ID, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}}$ = 19.7 min, $t_{r\text{ min}}$ = 22.3 min.

N-((1'S,5'S,6'R)-6'-formyl-5'-(naphthalen-2-yl)-5',6'-dihydro-[1,1':3',1''-terphenyl]-1'(4'H)-yl)-4-methylbenzenesulfonamide (**3h**). Colorless solid, yield: 74 mg (66%); $[\alpha]_D^{20}$ = -4.6° (*c* 4.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.21 (d, J = 1.1 Hz, 1H), 7.79 (dd, J = 12.8,

8.2 Hz, 3H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.62-7.54 (m, 3H), 7.47 (td, $J = 6.8, 1.3$ Hz, 2H), 7.40-7.24 (m, 10H), 7.08 (d, $J = 8.2$ Hz, 2H), 6.89 (s, 1H), 6.39 (s, 1H), 3.54 (d, $J = 12.0$ Hz, 1H), 3.51-3.41 (m, 1H), 2.73 (ddd, $J = 18.0, 10.4, 1.6$ Hz, 1H), 2.47 (dd, $J = 18.3, 5.2$ Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 144.4, 142.6, 140.1, 139.0, 138.9, 138.0, 133.5, 132.7, 129.2, 129.1, 128.6, 128.3, 128.2, 127.7, 127.54, 127.51, 127.3, 126.67, 126.59, 126.1, 126.0, 125.5, 125.4, 125.0, 62.3, 61.0, 40.4, 36.8, 21.4. HRMS (ESI) calcd for $\text{C}_{36}\text{H}_{32}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 558.2097 Found: 558.2090; 99% ee as determined by HPLC (ODH, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{maj}} = 34.7$ min, $t_{r\text{min}} = 33.1$ min.

N-((1'*S*,5'*R*,6'*R*)-6'-formyl-5'-((*E*)-styryl)-5',6'-dihydro-[1,1':3',1''-terphenyl]-1'(4'*H*)-yl)-4-methylbenzenesulfonamide (**3i**). Colorless solid, yield: 40 mg (38%); $[\alpha]_{\text{D}}^{20} = -20.3^\circ$ (c 2.8, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.62 (d, $J = 1.5$ Hz, 1H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.50 (d, $J = 7.5$ Hz, 2H), 7.39-7.20 (m, 15H), 7.04 (d, $J = 8.1$ Hz, 2H), 6.84 (s, 1H), 6.41 (d, $J = 15.7$ Hz, 1H), 6.28 (s, 1H), 6.10 (dd, $J = 15.7, 9.0$ Hz, 1H), 3.11 (dd, $J = 11.7, 1.6$ Hz, 1H), 2.99 (dd, $J = 10.3, 6.8$ Hz, 1H), 2.42 (ddd, $J = 18.0, 10.1, 2.0$ Hz, 1H), 2.35-2.25 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 144.4, 142.5, 140.1, 139.1, 138.6, 136.2, 132.9, 129.1, 128.8, 128.7, 128.5, 128.3, 128.2, 127.9, 127.5, 127.2, 126.2, 126.0, 125.5, 125.4, 61.8, 61.0, 38.1, 34.5, 21.4. HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{32}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 534. 2097 Found: 534. 2067; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{maj}} = 25.7$ min, $t_{r\text{min}} = 29.2$ min.

N-((1'*S*,2'*R*,3'*S*)-4-fluoro-5'-(4-fluorophenyl)-2'-formyl-3',4'-

dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3j**). Colorless solid, yield: 48 mg (44%); $[\alpha]_{\text{D}}^{20} = +18.7^{\circ}$ (*c* 3.2, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.20 (d, *J* = 1.3 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.57-7.46 (m, 2H), 7.36-7.13 (m, 8H), 7.14-6.94 (m, 6H), 6.88 (s, 1H), 6.27 (s, 1H), 3.37 (dd, *J* = 12.0, 1.4 Hz, 1H), 3.33-3.19 (m, 1H), 2.60 (ddd, *J* = 18.1, 10.7, 2.0 Hz, 1H), 2.42-2.26 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.9, 144.5, 142.3, 140.1, 139.1, 139.0, 138.6, 138.3, 136.2, 132.9, 129.1, 128.8, 128.7, 128.5, 128.3, 128.2, 127.9, 127.5, 127.2, 126.2, 126.0, 125.5, 125.4, 61.8, 61.0, 38.1, 34.5, 21.4. ^{19}F NMR (376 MHz, CDCl_3) δ 113.4, 115.1. HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{28}\text{F}_2\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^{+}$: 544.1752 Found: 544.1727; 99% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{\text{r maj}} = 13.7$ min, $t_{\text{r min}} = 23.3$ min.

N-((1'*S*,2'*R*,3'*S*)-4-bromo-5'-(4-bromophenyl)-2'-formyl-3',4'-

dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3k**). Colorless solid, yield: 87 mg (65%); $[\alpha]_{\text{D}}^{20} = -80.8^{\circ}$ (*c* 4.4, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.18 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.43 (dt, *J* = 16.7, 8.7 Hz, 6H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.28-7.21 (m, 2H), 7.19 (d, *J* = 7.1 Hz, 2H), 7.09 (dd, *J* = 13.1, 8.4 Hz, 4H), 6.88 (s, 1H), 6.30 (s, 1H), 3.35 (d, *J* = 12.0 Hz, 1H), 3.31 – 3.19 (m, 1H), 2.60 (ddd, *J* = 18.1, 10.6, 1.8 Hz, 1H), 2.41-2.25 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.3, 143.3, 142.8, 140.1, 139.8, 138.3, 137.6, 131.7, 131.5, 129.3, 129.2, 127.9, 127.8, 127.5, 127.2, 127.1,

125.3, 122.5, 121.7, 61.9, 60.7, 40.2, 36.7, 21.4. HRMS (ESI) calcd for $C_{32}H_{28}Br_2NO_3S$ ($M+H$)⁺: 664.0151 Found: 664.0160; 98% ee as determined by HPLC (IC, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 13.3$ min, $t_{r\text{ min}} = 19.3$ min.

N-((1*S*,2*R*,3*S*)-2'-formyl-4-nitro-5'-(4-nitrophenyl)-3',4'-

dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3l**). Colorless solid, yield: 72 mg (60%); $[\alpha]_D^{20} = -64.4^\circ$ (*c* 5.0, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.25-8.17 (m, 4H), 7.72 (d, $J = 8.9$ Hz, 2H), 7.67 (d, $J = 8.3$ Hz, 2H), 7.45-7.22 (m, 10H), 7.12 (d, $J = 8.2$ Hz, 2H), 7.07 (s, 1H), 6.48 (s, 1H), 3.43-3.32 (m, 2H), 2.76 (dd, $J = 18.2, 8.2$ Hz, 1H), 2.48 (dd, $J = 18.3, 4.3$ Hz, 1H), 2.33 (d, $J = 8.5$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 150.9, 147.7, 147.4, 144.9, 143.4, 139.6, 139.2, 138.4, 129.6, 129.4, 128.2, 127.5, 127.4, 127.1, 126.4, 123.9, 123.8, 62.2, 60.5, 40.2, 36.8, 21.5. HRMS (ESI) calcd for $C_{32}H_{28}N_3O_7S$ ($M+H$)⁺: 598.1642 Found: 598.1639; 99% ee as determined by HPLC (ODH, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 27.2$ min, $t_{r\text{ min}} = 29.3$ min.

N-((1*S*,2*R*,3*S*)-2-formyl-3,5-di(naphthalen-2-yl)-1,2,3,6-

tetrahydro-[1,1'-biphenyl]-3-yl)-4-methylbenzenesulfonamide (**3m**). Colorless solid, yield: 55 mg (45%); $[\alpha]_D^{20} = -107.7^\circ$ (*c* 1.7, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, $J = 1.4$ Hz, 1H), 8.09 (d, $J = 1.5$ Hz, 1H), 7.83 (tdd, $J = 19.6, 7.5, 2.8$ Hz, 8H), 7.70 (d, $J =$

8.2 Hz, 2H), 7.66-7.57 (m, 2H), 7.57-7.38 (m, 7H), 7.38-7.30 (m, 3H), 7.26 (dd, $J = 7.4$, 3.2 Hz, 4H), 6.99 (d, $J = 8.9$ Hz, 3H), 6.60 (s, 1H), 3.62 (dd, $J = 12.0$, 1.5 Hz, 1H), 3.39 (td, $J = 11.2$, 5.8 Hz, 1H), 2.79 (ddd, $J = 18.0$, 10.8, 1.9 Hz, 1H), 2.57 (dd, $J = 18.1$, 4.9 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 206.7, 142.7, 141.6, 140.8, 140.1, 138.9, 136.1, 133.2, 133.2, 132.7, 129.3, 129.2, 128.6, 128.5, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 126.5, 126.4, 125.7, 125.3, 124.6, 124.0, 123.6, 62.6, 60.9, 40.4, 36.9, 21.4. HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{34}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 608.2254 Found: 608.2250; 99% ee as determined by HPLC (OD, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\text{ maj}} = 25.7$ min, $t_{r\text{ min}} = 28.1$ min.

N-((1'*S*,2'*R*,3'*S*)-2'-formyl-5'-isobutyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3n**).

Colorless solid, yield: 49 mg (50%); $[\alpha]_{\text{D}}^{20} = +32.1^\circ$ (c 1.7, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.16 (d, $J = 1.5$ Hz, 1H), 7.81-7.71 (m, 2H), 7.52-7.44 (m, 2H), 7.38-7.11 (m, 11H), 6.75 (s, 1H), 5.69 (s, 1H), 3.28 (dd, $J = 11.9$, 1.7 Hz, 1H), 3.24-3.14 (m, 1H), 2.41 (s, 3H), 2.22 (ddd, $J = 18.2$, 10.7, 1.9 Hz, 1H), 1.84-1.59 (m, 4H), 0.89 (dd, $J = 6.2$, 2.0 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.9, 144.6, 142.5, 140.9, 140.8, 140.4, 129.06, 129.0, 128.5, 127.5, 127.4, 127.4, 127.3, 126.0, 124.1, 62.2, 61.7, 46.8, 40.2, 38.5, 25.8, 23.2, 21.89, 21.5. HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{34}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 488.2254 Found: 488.2244; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 22.7$ min, $t_{r\text{ min}} = 25.3$ min.

methyl (1'S,2'R,3'S)-2'-formyl-1'-((4-methylphenyl)sulfonamido)-

1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-5'-carboxylate (**3o**). Colorless solid, yield: 32 mg (32%); $[\alpha]_D^{20} = -8.7^\circ$ (c 3.2, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.17 (d, $J = 1.4$ Hz, 1H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.50-7.15 (m, 14H), 7.11 (s, 1H), 6.91 (s, 1H), 3.77 (s, 3H), 3.32 (dd, $J = 12.0, 1.5$ Hz, 1H), 3.29-3.19 (m, 1H), 2.48 (ddd, $J = 19.0, 10.5, 2.3$ Hz, 1H), 2.41 (s, 3H), 2.35 (ddd, $J = 19.0, 5.8, 1.6$ Hz, 1H). HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{28}\text{NO}_5\text{S}$ ($\text{M}+\text{H}$) $^+$: 490. 1683 Found: 490. 1686; 99% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 23.7$ min, $t_{r\text{ min}} = 27.3$ min.

N-((1'S,2'R,3'S)-2'-formyl-5'-phenyl-3',4'-dihydro-[1,1':3',1''-

terphenyl]-1'(2'*H*)-yl)-2-nitrobenzenesulfonamide (**3p**). Colorless solid, yield: 85 mg (79%); $[\alpha]_D^{20} = +89.3^\circ$ (c 2.7, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.23 (d, $J = 1.0$ Hz, 1H), 7.79 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.68 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.63 (s, 1H), 7.54 (ddd, $J = 9.1, 5.6, 1.4$ Hz, 3H), 7.43-7.08 (m, 15H), 6.57 (s, 1H), 3.55-3.39 (m, 2H), 2.74-2.62 (m, 1H), 2.47-2.34 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 206.1, 147.6, 144.0, 140.2, 139.0, 138.5, 135.7, 132.8, 132.0, 131.4, 129.2, 128.7, 128.6, 128.5, 127.7, 127.7, 127.6, 126.0, 125.7, 125.5, 124.5, 63.1, 61.0, 40.2, 36.2. HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{27}\text{N}_2\text{O}_5\text{S}$ ($\text{M}+\text{H}$) $^+$: 539. 1635 Found: 539. 1644; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}} = 30.7$ min, $t_{r\text{ min}} = 34.4$ min.

3q

N-((1'*S*,2'*R*,3'*S*)-2'-formyl-5'-phenyl-3',4'-dihydro-[1,1':3',1''-

terphenyl]-1'(2'*H*)-yl)-4-nitrobenzenesulfonamide (**3q**). Colorless solid, yield: 64 mg (59%); $[\alpha]_D^{20} = +10.1^\circ$ (*c* 5.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.20 (d, *J* = 1.4 Hz, 1H), 8.08-7.99 (m, 2H), 7.97-7.89 (m, 2H), 7.55 -7.48 (m, 2H), 7.43 – 7.14 (m, 15H), 6.37 (s, 1H), 3.45 (dd, *J* = 12.0, 1.5 Hz, 1H), 3.26 (td, *J* = 11.2, 5.9 Hz, 1H), 2.63 (ddd, *J* = 18.4, 10.8, 2.1 Hz, 1H), 2.46 (ddd, *J* = 18.4, 5.9, 1.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 206.1, 147.6, 144.0, 140.2, 139.0, 138.5, 135.7, 132.8, 132.0, 131.4, 129.2, 128.7, 128.6, 128.5, 127.7, 127.7, 127.6, 126.0, 125.7, 125.5, 124.5, 63.1, 61.0, 40.2, 36.2. HRMS (ESI) calcd for C₃₁H₂₇N₂O₅S (M+H)⁺: 539.1635 Found: 539.1649; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.75ml/min), *t_r* *major* = 25.9 min, *t_r* *minor* = 29.3 min.

3r

N-((1'*S*,2'*R*,3'*S*)-2'-(hydroxymethyl)-5'-phenyl-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-P,P-diphenylphosphinic amide (**3r**)

Colorless solid, yield: 52 mg (47%); $[\alpha]_D^{20} = +17.1^\circ$ (*c* 5.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.79-7.73 (m, 4H), 7.65-7.55 (m, 6H), 7.45-7.05 (m, 13H), 6.95-6.83 (m, 2H), 5.97 (t, *J* = 2.0 Hz, 1H), 3.47 (dd, *J* = 24.7, 3.8 Hz, 1H), 3.32 (dd, *J* = 24.8, 3.7 Hz, 1H), 3.19 (dt, *J* = 24.3, 16.9 Hz, 1H), 2.91 – 2.51 (m, 2H), 2.22 (ddd, *J* = 24.8, 17.0, 2.0 Hz, 1H), 1.92 (s, 1H), 0.81 (s, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 150.36, 147.17, 143.22, 141.62, 137.95, 129.52, 129.32, 129.24, 129.11, 129.04, 129.01, 128.42, 128.37, 128.33, 128.21, 127.55, 126.90, 125.72, 66.19, 53.59, 44.21, 32.51. ^{31}P NMR (162 MHz, CDCl_3) δ 37.19. HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{35}\text{NO}_2\text{P}$ ($\text{M}+\text{H}$) $^+$: 556.2400 Found: 556.2386; 99% ee as determined by HPLC (IC, 80:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}}$ = 37.7 min, $t_{r\text{ min}}$ = 39.9 min.

N-((1'*S*,2'*R*,3'*S*)-2'-formyl-4-methyl-5'-(*p*-tolyl)-3',4'-dihydro-[1,1':3',1''-terphenyl]-1'(2'*H*)-yl)-4-methylbenzenesulfonamide (**3s**)

Colorless solid, yield: 70 mg (69%); $[\alpha]_{\text{D}}^{20}$ = -58.0° (*c* 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.19 (d, J = 1.4 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 7.5 Hz, 2H), 7.52-7.12 (m, 11H), 7.04 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 6.35 (s, 1H), 3.43 (dd, J = 12.0, 1.4 Hz, 1H), 3.27 (td, J = 11.3, 5.8 Hz, 1H), 2.61 (ddd, J = 18.1, 10.8, 2.0 Hz, 1H), 2.39 (ddd, J = 18.2, 5.7, 1.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.7, 144.3, 142.5, 140.6, 140.0, 138.9, 138.9, 129.1, 129.1, 128.5, 128.3, 128.2, 127.5, 127.5, 127.4, 127.2, 126.0, 125.5, 125.2, 62.3, 61.0, 40.2, 36.8, 21.9, 21.8, 21.3. HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{30}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 508.1941 Found: 508.1967; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.75ml/min), $t_{r\text{ maj}}$ = 12.7 min, $t_{r\text{ min}}$ = 13.7 min.

(1'S,2'R,3'S)-1'-((4-nitrophenyl)sulfonamido)-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic acid (**5**)

Colorless solid, yield: 70 mg (96%); $[\alpha]_{\text{D}}^{20} = -98.0^{\circ}$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.73 – 8.50 (m, 2H), 8.30 – 7.96 (m, 2H), 7.50 – 7.23 (m, 13H), 6.96 – 6.72 (m, 2H), 6.11 (s, 1H), 5.71 (t, $J = 2.0$ Hz, 1H), 3.72 – 3.58 (m, 2H), 2.51 (ddd, $J = 14.5$, 13.3, 11.9 Hz, 1H), 2.33 – 2.22 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 179.61, 155.88, 147.72, 145.51, 143.77, 140.86, 140.28, 130.00, 129.52, 129.11, 129.11, 128.33, 128.32, 128.31, 128.12, 126.90, 126.30, 125.21, 122.33, 44.80, 40.72, 39.21. HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{27}\text{N}_2\text{O}_6\text{S}$ ($\text{M}+\text{H}$) $^{+}$: 555.1584 Found: 555.1562.

(1'S,2'R,3'S)-1'-amino-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic acid (**6**). Colorless solid, yield: 50 mg (95%); $[\alpha]_{\text{D}}^{20} = -38.0^{\circ}$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.18 (m, 13H), 6.82 – 6.72 (m, 2H), 6.65 (t, $J = 2.0$ Hz, 1H), 3.65 – 3.32 (m, 2H), 2.62 – 2.58 (m, 1H), 2.33 – 2.13 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.26, 150.21, 143.86, 141.63, 140.68, 129.94, 128.81, 128.62, 128.55, 128.33, 128.31, 128.10, 126.90, 126.29, 123.62, 51.78, 44.44, 35.15. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_2$ ($\text{M}+\text{H}$) $^{+}$: 370.1802 Found: 370.1852.

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