New reaction development using N-hetereocyclic carbenes and phosphines as nucleophilic organocatalysts

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**NANYANG
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**New Reaction Development Using *N*-Heterocyclic Carbenes
and Phosphines as Nucleophilic Organocatalysts**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCE

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**New Reaction Development Using *N*-Heterocyclic Carbenes
and Phosphines as Nucleophilic Organocatalysts**

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ABSTRACT

This thesis focuses on exploring new reaction modes that enabled by nucleophilic organocatalysts including *N*-heterocyclic carbenes (NHCs) and organophosphines. It contains five parts:

Chapter 1 gives brief introductions to the history and development of both NHC catalysis and organophosphine catalysis, and shows the future challenges in these fields.

Chapter 2 describes a highly enantioselective cascade reaction that consisted of an NHC catalyzed N-S bond cleavage and the stereoselective Michael addition that induced by a thiourea-tertiary amine based multifunctional cocatalyst. Substituted 3-tosylpropan-1-one could be obtained in up to 84% yield with up to >99:1 er value. This work represents the first example of NHC/thiourea/tertiary amine co-catalysis.

Chapter 3 is about the direct β -activation of aliphatic substituted carboxylic anhydride. We demonstrate the efficiency of this methodology through reactions of simple anhydrides with several nucleophiles. The product of (*E*)-((4*R*,5*R*)-4-methyl-2,5-diphenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate and its analogues could be obtained in up to 75% yield with up to 99:1 er value as single diastereomers. The product of ((1*R*,5*R*)-5-methylcyclopent-3-ene-1,3-diyl)dibenzene and its analogues could be obtained in up to 95% yield in up to 98:2 er value and up to >20:1 dr value. The product of (2*S*,3*S*)-3-methyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione and its analogues could be obtained in up to 96% yield with up to >99:1 er value and up to 12:1 dr value.

Chapter 4 introduces the one-pot cascade reactions of β -activation of the simplest propionic carboxylic acid. We again showed the efficiency of this approach through reactions with various nucleophilic substrates. (*S*)-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione and its analogues could be obtained in up to 99% yield with up to

96:4 er. Benzhydryl (*R*)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate and its analogues could be obtained in up to 99% yield with up to 96:4 er. We also showed the necessity of this methodology by comparing the acid activation approach with the anhydride approach using the same substrates under similar reaction conditions.

Chapter 5 describes a novel [4+2] cycloaddition reaction catalyzed by organophosphines. This transformation could go through a highly enantio- and diastereoselective manner by applying a multifunctional phosphine catalyst that derived from natural exsited amino acid. Corresponding product 2-phenyl-3-tosyl-4,4a-dihydro-3*H*-chromeno[3,4-*c*]pyridin-5(10*bH*)-one and its analogue could be obtained in up to 99% yield with up to >99:1 er value as single diastereomers.

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Jianfeng Xu, **Zhichao Jin**, and Yonggui Robin Chi.

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ABBREVIATIONS

Ac	acetate
AIBN	2,2'-azo <i>bisisobutyronitrile</i>
Am	amyl (<i>n</i> -pentyl)
Boc	<i>tert</i> -butoxycarbonyl
BQ	benzoquinone
Bu	butyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Equiv	equivalent
ESI	electrospray ionization

GC	gas chromatography
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
IBX	<i>o</i> -iodoxybenzoic acid
IPA	isopropyl alcohol
<i>i</i> Pr	isopropyl
KIE	kinetic isotope effect
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Mes	mesityl
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
NBS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine oxide
OAc	acetoy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
SET	single electron transfer
TBAB	tetra- <i>n</i> -butylammonium bromide

TLC	thin layer chromatography
TMS	trimethylsilyl
α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1

Introduction

1.1 *N*-Heterocyclic Carbenes as Nucleophilic Organocatalysts

N-heterocyclic carbenes (NHCs) have been intensively studied and applied by scientists as useful ligands in transition metal catalysis.¹ Due to their strong electron-donating features, they could also react as powerful nucleophilic organocatalysts in a variety of chemical transformations.² Although the application of NHC as organocatalyst could be found early in the 1940s,³ it was not until the last decade did NHC organocatalysis experience an explosive development with numerous novel activation modes and exceptional chemo- and stereo-selectivities.⁴

1.1.1 NHC-Catalyzed Benzoin Condensation

The first application of NHC as an efficient organocatalyst could be dated back to 1943,⁵ when Ugai and coworkers realized the benzoin reaction using a thiazolium salt as the catalyst. Fifteen years later, Breslow proposed a reaction mechanism based on previous works (Scheme 1.1), which has been widely acknowledged in the following explorations within this field and became one of the most basic activation modes in NHC organocatalysis.⁶ In Breslow's proposal, free carbene **1-1** first attacked benzaldehyde to form a zwitterion **1-2**, which would then go through a proton transfer to afford the so-called Breslow intermediate **1-3**. Then the critical Breslow intermediate **1-3** would then go through an enamine activation to react with another benzaldehyde to form intermediate **1-4**, which would then go through proton transfer to finally release the benzoin product and the free carbene catalyst for the next catalytic cycle.

Scheme 1.1 Mechanism of the Benzoin Condensation Catalyzed by NHC

With the success of this catalytic pathway, asymmetric benzoin condensations enabled by chiral NHC catalysts were then investigated.⁷ This resulted in the development of a series of chiral carbenes (Scheme 1.2) and the products could now be obtained with an ee value of up to 99%.

Scheme 1.2 Development of Various Chiral NHCs for the Asymmetric Benzoin Reactions

1.1.2 NHC-Catalyzed Stetter Reactions

Early in the 1970s, the nucleophilic acylation catalyzed by thiazolium catalysts was successfully extended to various α,β -unsaturated compounds as the Michael acceptor by Stetter and co-workers (Scheme 1.3).⁸ And this type of reactions was then called Stetter

reaction. Nearly all kinds of Michael acceptors could be included in this process and a variety of 1,4-bifunctional compounds such as 1,4-diketones, 4-ketonitriles and 4-ketoesters could be synthesized. Thiazolium salts were widely used for the racemic Stetter reactions.

Scheme 1.3 Basic Pathways for Stetter Reaction

As claimed by Enders and co-workers in their review,^{2c} their group have developed the asymmetric Stetter reaction early in 1989 with the chiral thiazolium salt **1-5** as the catalyst.⁹ But only a low ee of 39% could be reached with a very poor yield (Scheme 1.4). However, great efforts have been made in the chirality control by scientists since then involving both inter- and intra-molecular Stetter reaction and a huge number of chiral NHC catalysts were applied in these transformations.¹⁰ One of the most developed asymmetric Stetter reactions is the intramolecular variant initiated by Ciganek in 1995 (Scheme 1.5),¹¹ which has been intensively studied by Enders, Rovis and many others.¹²

Scheme 1.4 Asymmetric Intermolecular Stetter Reaction.

Scheme 1.5 Asymmetric Intramolecular Stetter Reactions Developed by Enders and Rovis.

1.1.3 NHC-Catalyzed Homoenolate Reactions

Besides the above mentioned α^1 - δ^1 Umpolung (polarity inversion of the 1st carbon from electron accepting position to electron donating position)¹² process that has been well developed in the NHC organocatalytic reactions, the usage of α,β -unsaturated aldehydes represents another important extension within this research field.¹³ The α^1 - δ^1 Umpolung could be effectively transferred along the conjugated system to furnish the α^3 - δ^3 Umpolung, which is now generally called “homoenolate activation” (Scheme 1.6).

Scheme 1.6 Pathway of Homoenolate Activation Enabled by NHC Catalyst.

The pioneering reports on NHC catalyzed homoenolate activation were simultaneously published by Glorius and Bode in 2004.¹³ Both of them reported the same lactone formation starting from α,β -unsaturated aldehydes and simple aldehydes (Scheme 1.7). The usage of the readily available imidazolium salt **1-6** was crucial in this transformation, as the use of triazolium salts precatalysts would only afford the benzoin products in poor yields.

Scheme 1.7 The Pioneering Report on NHC Catalyzed Homoenolate Activation.

Soon after the first success in the homoenolate process, this reaction pathway was rapidly extended to a large variety of electrophiles in both racemic¹⁴ and asymmetric

versions.¹⁵ Typical electrophiles included simple aldehydes, imines, isatins and their derivatives, as well as the 1,4-conjugated ketones and imines. The corresponding homoenolate adducts could be obtained in excellent yield and exceptional stereoselectivities by fine tuning of the catalyst and the reaction conditions (Scheme 1.8).

Besides the α,β -unsaturated aldehydes, α' -hydroxyenone could also behave as the homoenolate precursor under the catalysis of NHCs. The first report on this type of novel strategy was from Bode's group in 2009,¹⁶ where a retro-benzoin process was assumed at the beginning of this catalytic pathway to form the desired homoenolate intermediate (Scheme 1.9).

Scheme 1.8 Selected Examples of Homoenolate Process with Different Electrophiles.

Scheme 1.9 Alternative Precursor for Homoenolate Activation.

1.1.4 NHC-Catalyzed Enolate Activation

During the research of the initial homoenolate activation of α,β -unsaturated aldehyde with activated ketones, Glorius and co-workers observed another cyclization product of β -lactone **1-7** as a side-product under certain catalytic conditions.¹⁷ Further investigations towards this β -lactone formation revealed another type of novel catalytic process, which is called enolate activation in NHC organocatalysis. Glorius and co-workers proposed a proton transfer mechanism for this transformation as illustrated in Scheme 1.10.

Scheme 1.10 Enolate Activation Reported by Glorius and co-workers.

Almost at the same time, Bode's group reported the first formal aza-Diels-Alder reaction of α,β -unsaturated aldehydes with α,β -unsaturated aldehyde derived imines.¹⁸ This was an excellent application of the enolate activation that operated in an exclusive chemo- and stereo-selective manner. Numerous reports on this type of NHC catalyzed transformations, involving both racemic and asymmetric versions, have been reported since then (Scheme 1.11).¹⁹

Scheme 1.11 Enolate Activation Process Developed for α,β -Unsaturated Aldehydes.

The precursors for corresponding enolate activation in NHC catalysis have proved to be more abundant than the other types of activation modes within this field. Ye and Smith independently developed the enolate activation of ketenes under NHC catalysis, and could obtain various lactones and lactams in good yields and stereoselectivities.²⁰ Bode and co-workers initiated the enolate activation of α -chloroaldehyde derivatives with various electrophiles.²¹ By applying the oxidative NHC catalytic process, Rovis and Chi independently realized the α -activation of saturated aldehydes.²² And more recently, our group have reported the ester activation pathways in the α -activation with electrophiles (Scheme 1.12).²³

Scheme 1.12 Different Enolate Precursors that Developed in NHC Catalysis.

1.1.5 NHC-Catalyzed Reactions Involving Acyl Azoliums.

Most of the NHC-catalyzed reaction pathways would involve the formation of acyl azolium intermediates. The acyl azolium intermediate was then attacked by another

nucleophilic species to release the free carbene catalyst for the next catalytic cycle. Here we mainly focused on two kinds of acyl azolium type activations, that is, esterification reactions and Michael additions with α,β -unsaturated acyl azolium intermediates.

One of the most well developed esterification reactions that are catalyzed by NHCs involves a homoenolate activation of α,β -unsaturated aldehydes.²⁴ With simple alcohols as the nucleophiles, the homoenolate intermediate derived from α,β -unsaturated aldehyde could be protonated to form a saturated ester. A typical work with α,β -unsaturated aldehyde in this pathway was independently reported by Scheidt and Bode in 2005 (Scheme 1.13). However, looking into literatures we could find that similar transformations using other types of modified aldehyde in the esterifications were established even earlier (Scheme 1.13).²⁵

Scheme 1.13 Esterification of the Homoenolate Intermediates.

Another type of esterifications enabled by NHC catalysis is the transesterification of ester substrates.²⁶ The first example of this process was reported by Nolan and Hedrich respectively in 2002 (Scheme 1.14), and then was followed by many others.²⁷ One of the most interesting applications of this process is the kinetic resolution of racemic alcohols or phenols bearing one or more chiral elements.²⁸ Suzuki exhibited the first example in the resolution of secondary alcohols (Scheme 1.15).

Scheme 1.14 NHC Catalyzed Transesterification by Nolan and Hedrick.

Scheme 1.15 NHC Catalyzed Kinetic Resolution by Suzuki.

The first example of the Michael additions with the α,β -unsaturated acyl azolium intermediate was reported by Studer's group in 2010, with the application of oxidant **1-8** in the NHC catalytic process in the activation of α,β -unsaturated aldehyde to form the desired activated α,β -unsaturated acyl azolium (Scheme 1.16).²⁹ However, after further experimental exploration and detailed mechanistic studies by Bode and coworkers, they assumed that a Claisen-type rearrangement was in fact taking place during the annulation step (Scheme 1.17).³⁰ Since then several other electrophiles have been applied in this process, and some alternative precursors of the α,β -unsaturated acyl azolium have been explored.³¹

Scheme 1.16 NHC Catalyzed Acyl Azolium Activation by Studer.

Scheme 1.17 NHC Catalyzed Acyl Azolium Activation by Bode.

1.2 Organophosphines as Nucleophilic Organocatalysts

Phosphine catalysis has been investigated for quite a long time. The most fundamental reaction within this field would certainly be the so-called Baylis-Hillman reaction.³² This type of transformations could be dated back to as early as 1963, when Rauhut and Currier reported the pioneering work of phosphine-catalyzed dimerization of electron-deficient alkenes, acrylonitrile and ethyl acrylate.³³ Five years later, Morita described the reaction of an aldehyde with acrylic compounds catalyzed by tricyclohexylphosphine, although the yield of the reaction was extremely poor.³⁴ In 1972, Baylis and Hillman performed the same reaction using a tertiary amine catalyst, DABCO, instead of a phosphine catalyst, and obtained the product in 75% yield.³⁵ Currently, this kind of transformation is more commonly named as the Morita-Baylis-Hillman Reaction.³⁶

1963: Rauhut-Currier Reaction **1968: Morita Reaction** **1972: Baylis-Hillman Reaction** **Scheme 1.18** History of Baylis-Hillman Reaction

Annulations catalyzed by organophosphines have appeared ever since the pioneering work of Lu's [3+2] annulation using allenolate in 1995,³⁷ and various annulations of this allenolate involving both racemic and asymmetric versions have been intensively studied in the past few decades.³⁸

Lu's [3+2] annulation **Scheme 1.19** Lu's [3+2] Annulations Reactions.

Early in this century, Kwon and co-workers modified the allenolate molecule and introduced an alkyl group at the α -position.³⁹ They envisioned that substitution of the hydrogen at the α -position with an alkyl group might block the α -attack so that the reaction could be initiated by γ -addition. In their series of works, various [4+2] reactions were realized with the catalysis of simple phosphines, together with different [m+n] reactions by using different electrophilic substrates.⁴⁰ The asymmetric versions of Kwon's [4+2] annulations were also developed by many other research groups.⁴¹

Scheme 1.20 Kwon's [m+n] Annulations Reactions.

Besides the above classic works, Kumar reported a novel type of [4+2] reaction catalyzed by simple phosphines using electron-deficient alkyne as the activated substrate.⁴² By further modifying the substituted allenolate by introducing a leaving group next to the α -position, a [4+1] reaction was realized by Tong and co-workers using triphenyl phosphine.⁴³

Scheme 1.21 Other Annulation Reactions.

1.3 Summary and Research Designs

Both initiated in the mid of the 20th centry, NHC catalysis and organophosphine catalysis have experienced explosive and rapid development during the last decade. Although a huge number of novel catalytic processes have been well studied, there are

still challenges that exist within both fields.

Besides the intensively developed aldehyde activations enabled by NHC organocatalysts, the activation of various carboxylic acid derivatives has been much less studied, especially in the formal homoenolate activation pathway. Therefore, we aimed at developing novel catalytic pathways by applying novel carboxylic acid derivatives as well as substrates beyond the carbonyl compounds. Moreover, cooperative catalysis within NHC catalysis represents another challenge, especially when the chirality inducement could not be accomplished by solely applying NHC catalysts. We will also focus on novel cooperative catalysis with other organocatalysts in NHC catalyzed reactions.

Electron-deficient simple alkenes were well investigated within phosphine catalysis, but only restricted to simple RC and MBH reactions. For various cycloadditions, researchers have mainly focused on allenolates or their equivalents as three-carbon synthons for Lu's [3+2] reactions, as well as the α -substituted allenolates for Kwon's [4+2] reactions and electron-deficient alkynes. Simple alkenes have seldom been used as the two-carbon synthons for any cycloadditions, which is probably due to their easy self-dimerization, as well as the inert reactivity of both reactants in the ring-closing step. We would like to investigate the cycloaddition reactions using electron-deficient alkene as the 2-carbon synthon catalyzed by simple phosphines.

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Chapter 2

Asymmetric Sulfonation of Enones via NHC/ Thiourea/Tertiary-Amine Cooperative Multicatalysis

2.1 Introduction

2.1.1 Sulfonation reactions.

Sulfones have always been of great interest and importance in organic synthesis not only due to their well-developed applications as versatile synthetic intermediates,¹ but also their attractive biological activities exhibited in various biomolecules and drugs.² Sulfones are typically prepared through oxidation of sulfides or sulfoxides³, nucleophilic displacements by a sulfinic acid or its salt⁴ and reactions of sulfonyl halide with activated nucleophiles such as organolithium reagents, Grignard reagents and even activated aromatic compounds for Friedel-Crafts reactions.⁵ Besides these well-developed pathways, direct Michael addition of sulfonyl groups to α,β -unsaturated systems also represents an efficient methodology for preparing sulfones.⁶ While numerous non-chiral sulfonations have been intensively studied, corresponding stereoselective versions have been much less investigated,⁷ especially for the 1,4-addition reactions. Besides challenges that exist in the skeleton design of corresponding chiral catalysts, the method for the generation of the sulfonyl anion is also crucial for the asymmetric induction. Therefore, looking for novel readily available sulfonation reagents that exhibit good reactivity under mild reaction conditions would still be an interesting task and provide novel pathways for sulfone synthesis, especially for realizing direct asymmetric sulfonations. In this work, we present that tosyl imines would act as an excellent sulfonation reagent under the catalysis of NHCs under mild conditions.

2.1.2 NHC Catalyzed Imine Activation.

Ever since the first report of stable carbenes in the late 1980s,⁸ *N*-heterocyclic carbenes (NHCs) have been intensively studied either as excellent ligands for transmetal catalysis⁹ or as organocatalysts for various transformations.¹⁰ During the last two decades, the

organocatalytic NHC catalysis have attracted great interest.¹¹ Most of the well established NHC activation would require a carbonyl group in the starting material. Aldehyde derived imines have presented similar reactivities with corresponding aldehydes in many aspects.¹² Specifically, the N-S bond cleavage on tosyl imines by NHC catalysts was discovered by Hou and coworkers in 2008 (Scheme 2.1).¹³ Recently, Rovis have disclosed the first isolable Breslow-typed intermediate that is derived from an iminium salt (Scheme 2.2).¹⁴ However, asymmetric catalytic reactions with simple imines as the activated substrates in NHC catalysis have not been reported till now and is still of great interest.

Scheme 2.1 Hou's N-S Bond Cleavage of Tosyl Imine by NHCs.

Scheme 2.2 Aza-Breslow-Typed Intermediate Reported by Rovis.

2.1.3 Our Proposal.

We assumed that the Michael addition of sulfinate anion to α,β -unsaturated ketones could take place under the catalysis of NHCs when using tosyl imines as the sulfinate source (Scheme 2.3). The enantioselectivity could be induced by a multifunctional thiourea-amino co-catalyst after releasing the free sulfinate anion. Meanwhile, the amino

group on the multifunctional co-catalyst could also behave as the Brønsted base to deprotonate the NHC precatalyst (Scheme 2.4).

Scheme 2.3 Generation of Free Sulfinic Anion by NHC Catalyst.

Scheme 2.4 Cooperation of Multiple Organocatalysts.

2.2 Results and Discussions

First of all, we took *N*-benzylidene-toluenesulfonamide **2-1a** and chalcone **2-2a** as the model substrates and our investigation began with the frequently used NHCs **2-4a** and **2-4b** as the catalysts to check the feasibility of our proposed reaction process. Initial experiments indicated the formation of the target product in less than 20% NMR conversion, where catalyst **2-4a** showed superior reactivity over **2-4b** (Table 2.1, entries 1 and 2). Since the amount of base did not have any significant impact on the product yield (Entries 3 and 4), the reaction temperature was then examined. By heating the reaction system, the yield was significantly increased (Entries 5 and 6). Further optimizations involving base and solvent screening were carried out at 75°C using 20 mol% of **2-4a**

(Entries 7 to 17). At last, the yield of our desired product could be increased to almost quantitative when the reaction was carried out in 2-propanol with DABCO as the base (Entry 16). Decreasing the catalyst loading resulted in a lower yield (Entry 18).

Table 2.1 Condition Optimization for Racemic Sulfonation^[a]

Entry	NHC	Base	Base amount (eq)	Solvent	T (°C) ^[b]	Yield (%) ^[c]
1	2-4a	TEA	0.2	THF	24	16
2	2-4b	TEA	0.2	THF	24	<7
3	2-4a	TEA	1.0	THF	24	16
4	2-4a	TEA	5.0	THF	24	10
5	2-4a	TEA	0.2	THF	55	24
6	2-4a	TEA	0.2	THF	75	36
7	2-4a	DBU	0.2	THF	75	63
8	2-4a	TBD	0.2	THF	75	10
9	2-4a	Cs ₂ CO ₃	0.2	THF	75	46
10	2-4a	DABCO	0.2	THF	75	68
11	2-4a	DABCO	0.2	TCM	75	45
12	2-4a	DABCO	0.2	Dioxane	75	60
13	2-4a	DABCO	0.2	DMF	75	60
14	2-4a	DABCO	0.2	Toluene	75	72
15	2-4a	DABCO	0.2	EtOH	75	80
16	2-4a	DABCO	0.2	i-PrOH	75	99
17	2-4a	DABCO	0.2	ACN	75	65
18 ^[d]	2-4a	DABCO	0.2	i-PrOH	75	85

[a] Unless otherwise noted, all the reactions were carried out at room temperature using **2-1a** (0.10 mmol), **2-2a** (0.05 mmol), 20 mol % of **2-4a**, and 0.5 mL of solvent. [b] T represents the reaction temperature. [c] NMR conversion based on trimethoxybenzene as the inner standard. [d] 10 mol % of **2-4a** was used.

After the optimization of the reaction conditions (Table 2.1, entry 16), we were quite interested in the scope of the above sulfonation process. Thus, various substrates were then examined. Various substituted chalcones underwent the sulfonation reaction smoothly to afford corresponding γ -ketone sulfones in good to excellent isolated yields, regardless of the electronic nature or the substitution pattern (Table 2.2, entries 1 to 12).

Different substituents on the sulfonyl group including phenyl, 4-methoxyphenyl, and methyl groups, were also tolerated (Entries 13 to 15). By increasing the catalyst and base loadings, 4-nitrobenzenesulfonation could be realized in moderate yield (Entry 16). Furthermore, both aromatic rings of the chalcone substrate could be switched to non-aromatic groups such as alkyl and ester groups (Entries 17 to 20). All these products were formed in good to excellent yields.

Table 2.2 Scope of the Racemic Sulfonation Process^[a]

Entry	2-1	R^1	R^2	Product	Yield (%) ^[b]
1	2-1a	Ph	Ph	2-3a	90
2	2-1a	4-MeOC ₆ H ₄	Ph	2-3b	87
3	2-1a	3-NO ₂ C ₆ H ₄	Ph	2-3c	76
4	2-1a	4-ClC ₆ H ₄	Ph	2-3d	79
5	2-1a	4-MeC ₆ H ₄	Ph	2-3e	82
6	2-1a	4-NO ₂ C ₆ H ₄	Ph	2-3f	74
7	2-1a	Ph	4-MeOC ₆ H ₄	2-3g	>99
8	2-1a	Ph	4-ClC ₆ H ₄	2-3h	67
9	2-1a	Ph	4-BrC ₆ H ₄	2-3i	99
10	2-1a	Ph	2-naphthyl	2-3j	80
11	2-1a	4-ClC ₆ H ₄	4-ClC ₆ H ₄	2-3k	63
12	2-1a	Ph	2-furyl	2-3l	88
13	2-1b	Ph	Ph	2-3m	99
14	2-1c	Ph	Ph	2-3n	75
15	2-1d	Ph	Ph	2-3o	89
16	2-1e	Ph	Ph	2-3p	40 ^[c]
17	2-1a	COOEt	Ph	2-3q	86
18	2-1a	Ph	Me	2-3r	68
19	2-1a	n-Bu	Me	2-3s	99
20	2-1a	Me	Ph	2-5a	98

[a] Unless otherwise noted, all the reactions were carried out at room temperature using **2-1a** (0.20 mmol), **2-2** (0.10 mmol), 20 mol % of **2-4a**, 20 mol % of DABCO, 1.0 mL of 2-propanol and stirred at 75 °C for 12h. [b] Isolated yield. [c] The reaction was carried using 40 % of **2-4a** and 40 % of DABCO.

Having established the sulfonation process with a broad substrate scope, we next paid our attention to realizing the asymmetric version of this transformation. During our initial

trials using various chiral NHC catalysts (Scheme 2.5), all the products that we got were racemic regardless of the catalyst structure or any other conditions such as the solvent and the reaction temperature (Table 2.3, entries 1 to 4). This prompted us to re-consider the reaction passway, and we envisioned that the sulfonyl group would most likely to be released as relatively free counter anion in the process. However, we found that some common chiral NHCs could more efficiently promote this reaction under milder conditions, which is more suitable for chiral induction (Entry 4). Therefore, we then switched to examine some readily available chiral bases (Scheme 2.6, **2-6a** and **2-6b**) using **2-4a** or **2-4f** as the catalyst in toluene. To our great delight, the product could be formed in up to moderate *er* values by applying this protocol (Entries 5 to 8). From the experimental data we found that thiourea group would be crucial for chiral induction, while tertiary amine moiety would serve as the base for the generation of the NHC catalyst. Therefore, a series of bifunctional chiral bases bearing both tertiary amino and thiourea groups were synthesized in order to improve the enantioselectivity. During our investigation, we discovered that bis-tertiary amines that are connected by a thiourea group based on 9-amino-*epi*-quinine chiral skeleton could serve as unique efficient chirality inducing catalysts (Scheme 2.6, **2-6c** to **2-6f**). After a series of simple modification of the established catalyst structure, the enantiomeric ratio of the product could be increased to 89:11 using chiral base **2-6e** (Table 2.3, entry 11). As further catalyst structure modification would no longer improve the enantioselectivity, we then checked the solvent effect but failed to see any improvement (Entry 13 to 16). The *er* value could be improved to 90:10 by decreasing the base loading to 10 mol% (Entry 17). Diluting the reaction concentration could also enhance the enantioselectivity, and a greater promotion of the *er* value could be achieved when decreasing the reaction temperature to freezing point albeit in a much lower yield (Entries 18 and 19). Finally, by re-examination of the series of bifunctional chiral bases under the optimized loading,

temperature and reaction concentration, **2-6f** showed even better enantioselectivity (up to 96:4 er) with little erosion of the isolated yield (Entry 20, 67% yield compared to entry 12, 68% yield).

Scheme 2.5 Typical Chiral NHCs Examined.

Scheme 2.6 Typical Chiral Bases Examined.

Table 2.3 Conditional Optimization for Enantioselective Sulfonation^[a]

Entry	NHC	Base	Base amount (eq)	Solvent	Yield (%) ^[b]	Er ^[c]
1	2-4c	DABCO	0.2	Toluene	43	50:50
2	2-4d	DABCO	0.2	Toluene	<10	50:50
3	2-4e	DABCO	0.2	Toluene	68	50:50
4	2-4f	DABCO	0.2	Toluene	80	50:50
5	2-4a	2-6a	0.4	Toluene	18	55:45
6	2-4a	2-6b	0.4	Toluene	<10	54:46
7	2-4f	2-6a	0.4	Toluene	45	52:48
8	2-4f	2-6b	0.4	Toluene	38	70:30
9	2-4f	2-6c	0.4	Toluene	79	73:27
10	2-4f	2-6d	0.4	Toluene	52	76:24
11	2-4f	2-6e	0.4	Toluene	70	89:11
12	2-4f	2-6f	0.4	Toluene	68	88:12
13	2-4f	2-6e	0.4	DCM	52	64:36
14	2-4f	2-6e	0.4	THF	31	78:22
15	2-4f	2-6e	0.4	Dioxane	73	81:19
16	2-4f	2-6e	0.4	IPA	66	57:43
17	2-4f	2-6e	0.1	Toluene	55	90:10
18 ^[d]	2-4f	2-6e	0.1	Toluene	59	91:9
19 ^[d,e]	2-4f	2-6e	0.1	Toluene	30	95:5
20 ^[d,e]	2-4f	2-6f	0.1	Toluene	67	96:4

[a] Unless otherwise noted, all the reactions were carried out at rt using **2-1a** (0.10 mmol), **2-2a** (0.05

mmol), 20 mol % of NHC, 40 mol% of chiral base and 0.5 mL of solvent. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 2 ML solvent was used. [e] The reaction was carried out at 0 °C and stirred for 72h.

With the optimized reaction conditions in hand, we went on to check the scope of the enantioselective sulfonation process (Table 2.4). Most of substituted chalcones afforded the desired adducts in moderate to good yields with excellent *er* values. However, an electron-donating substituent on the aromatic ring of R¹ group deactivated the β-position of the α,β-unsaturated ketone substrate, and therefore severely decreased the product yield of the reactions at 0 °C. However, products of this type of substrates could be obtained in acceptable yields without much erosion of *ee* values when increasing the reaction temperature to rt (Table 2.4, entry 2, product **2-3b** was obtained in 4% yield and 90:10 *er* at 0 °C). Strong electron-withdrawing substituents on R¹ group such as *m*-nitrophenyl group (Entry 3) and ester group (Entry 17) accelerated racemization of the sulfone product. Variations of the tosyl group were also tolerated in this asymmetric process and different aromatic sulfonyl products could be afforded in good to excellent *ers* with different isolated yields depending on the electronic nature of the substituent (Entries 13 to 16). A mesylated product could also be afforded in moderate yield but with lower enantioselectivity (Entry 15). Replacement of either R¹ or R² group by an aliphatic group severely deteriorated the enantioselectivity (Entries 18 to 20). This might be due to the huge steric and electronic differences between chalcones and corresponding aliphatic enones.

Table 2.4 Scope of the Enantioselective Sulfonation Process^[a]

Entry	2-1	R ¹	R ²	Product	Yield (%) ^[b]	Er
1 ^[b]	2-1a	Ph	Ph	2-3a	69	96:4
2 ^[c]	2-1a	4-MeOC ₆ H ₄	Ph	2-3b	60	90:10
3	2-1a	3-NO ₂ C ₆ H ₄	Ph	2-3c	76	89:11
4	2-1a	4-ClC ₆ H ₄	Ph	2-3d	49	95:5
5	2-1a	4-MeC ₆ H ₄	Ph	2-3e	54	94:6
6	2-1a	4-NO ₂ C ₆ H ₄	Ph	2-3f	84	>99:1
7	2-1a	Ph	4-MeOC ₆ H ₄	2-3g	64	97:3
8	2-1a	Ph	4-ClC ₆ H ₄	2-3h	79	97:3
9 ^[b]	2-1a	Ph	4-BrC ₆ H ₄	2-3i	77	>99:1
10	2-1a	Ph	2-naphthyl	2-3j	57	91:9
11	2-1a	4-ClC ₆ H ₄	4-ClC ₆ H ₄	2-3k	52	99:1
12	2-1a	Ph	2-furyl	2-3l	63	95:5
13	2-1b	Ph	Ph	2-3m	52	96:4
14	2-1c	Ph	Ph	2-3n	67	92:8
15	2-1d	Ph	Ph	2-3o	44	73:27
16 ^[c]	2-1e	Ph	Ph	2-3p	13	93:7
17	2-1a	COOEt	Ph	2-3q	50	50:50
18 ^[c]	2-1a	Ph	Me	2-3r	30	77:23
19	2-1a	n-Bu	Me	2-3s	58	60:40
20	2-1a	Me	Ph	2-5a	86	50:50

[a] General condition (unless otherwise specified): As in Table 2.3 entry 20. [b] Reaction was carried out at 0.5 mmol (**2-2**) scale. [c] Reaction was carried out at rt (24 °C) for 24 h.

As stated above, although we could successfully get various substituted chalcone substrates to react in a highly enantioselective manner, enones other than the chalcone derivatives resulted in rather low er values (Table 2.4, entries 17 to 20). To further demonstrate the versatility of this cooperative multicatalytic methodology, we decided to continue optimization of the er values of the β -alkyl substituted α,β -unsaturated enones.

We chose 1-phenylhex-2-en-1-one **2-7c** and the tosyl imine **2-1a** as the model substrates for the optimization. We could only obtain a poor er value under our previously established reaction conditions for chalcone (Table 2.5, entry 1). Further examination of a large number of chiral bases revealed that the chiral base **2-6h** could give the best er value, but only around the moderate level of 26:74 (Entry 3). Screening of solvents slightly improved the er to 23:77 (Entry 5). Various additives were tested, and it was shown that 3Å MS promotes the er value to 17:83 (Entry 8). The use of a modified NHC precatalyst **2-4g** slightly improved the er value (Entry 10). Finally, we managed to achieve an er value of 14:86 by diluting the reaction concentration (Entry 12). Although the er value

were not quite satisfactory, it has already been largely improved, and it was worth noting that the use of this kind of alkyl enones were always challenging in many catalytic asymmetric reactions.¹⁵

Scheme 2.7 Typical Chiral NHCs and Bases Examined.

Table 2.5 Conditional Optimization for Alkyl enone.^[a]

Entry	NHC	Base	Solvent	3A MS (mg)	Yield (%) ^[b]	Er ^[c]
1	2-4f	2-6f	Toluene	0	69	58:42
2	2-4f	2-6g	Toluene	0	88	32:68
3	2-4f	2-6h	Toluene	0	63	26:74
4	2-4f	2-6h	DCM	0	61	26:74
5	2-4f	2-6h	CHCl ₃	0	62	23:77
6	2-4f	2-6h	Dioxane	0	65	28:72
7	2-4f	2-6h	CHCl ₃	20	nd	18:82
8	2-4f	2-6h	CHCl ₃	40	nd	17:83
9	2-4f	2-6h	CHCl ₃	60	nd	17:83
10	2-4g	2-6h	CHCl ₃	40	nd	16:84
11	2-4g	2-6h	CHCl ₃	10	nd	15:85
12 ^[d]	2-4g	2-6h	CHCl ₃	10	70	14:86

[a] Unless otherwise noted, all the reactions were carried out at rt using **2-1a** (0.10 mmol), **2-7c** (0.05 mmol), 20 mol % of NHC, 20 mol% of chiral base and 0.5 mL of solvent and stirred for 48h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 2 ML solvent was used.

Then the scope of alkyl substituted enones was examined as summarized in Table 2.6. All the products were obtained in good yields with similar er values. And it was worth noting that only racemic product (**2-5a**) or products with poor er values (**2-5c**, **2-5h**) could be obtained under the previously optimized conditions for chalcone substrates.

Table 2.6 Conditional Optimization for Alkyl enone.^[a]

[a] Unless otherwise noted, all the reactions were carried out under condition as in Table 2.5, entry 12. [b] Results were obtained under conditions as in Table 2.3, entry 20. [c] The reaction was carried out without molecular sieves.

The γ -ketosulfones we obtained are useful precursors for preparing interesting molecules.¹⁶ The ketone group of the chiral product could be reduced by LiAlH_4 to afford γ -hydroxyl sulfone **2-8** with little erosion of the optical purity as a single diastereomer. The γ -hydroxyl sulfone **2-8** could then be transformed to chiral cyclopropane **2-9** with retention of the chirality.¹⁷ The structure of the chiral cyclopropane is frequently found in various bioactive natural and non-natural products (Scheme 2.10).¹⁸

Scheme 2.8 Synthetic Transformations of the Chiral Product **2-3a**.

2.3 Mechanistic Study.

2.3.1 Reaction Pathway.

After all the efforts towards optimization and scope investigation have been made, we then sought to gain some insights into the reaction mechanism. We have proposed that free sulfinic anion should have been released during the catalytic cycle due to the fact that only racemic product could be formed when using chiral NHCs with achiral bases. This assumption could also be partially supported by the isolation of corresponding byproduct of phenyl nitrile and a crossover experiment using substrate **2-1c** and sodium p-toluenesulfinate as the mixed sulfonation reagent (Scheme 2.9). Both the product **2-3a** and **2-3n** were formed with a ratio of 1:1. When using sodium p-toluenesulfinate instead of tosylimine as the single sulfonation reagent, no corresponding product were formed under otherwise the same reaction conditions. Based on literature works, we could postulate two possible ways through which tosyl anion could be generated in situ (Scheme 2.10). In pathway A, NHC serve as a simple base that deprotonates tosylimine. Our attempts on using other bases for this deprotonation were unsuccessful. Pathway B was also reasonable as the sulfinic anions could be formed through the classic NHC catalytic process, which have been intensively studied in carbonyl compound activation. However, after a few experimental investigations we could prove that pathway B is more possible. Besides the fact that no product was formed when other bases were used in the absence of NHC catalysts, the proton acidity of the imine is proved to be much weaker than the NHC pre-catalyst, which is evidenced by ^1H NMR analysis on the H/D exchanges in D_2O (Figure 2.1 to Figure 2.4). Deprotonation of the weak acid (the imine) by the weak base (the free carbene) is unfavorable.

Scheme 2.9 Crossover and Control Experiment.

Passway A:

Passway B:

Scheme 2.10 Possible Sulfonyl Group Generation.

Figure 2.1 ^1H NMR Spectra of Tosyl Imine in DMSO-d_6 . **Figure 2.2** ^1H NMR Spectra of H-D Exchanging Experiment of Tosyl Imine in DMSO-d_6 . **Figure 2.3** ^1H NMR Spectra of NHC Salt in DMSO-d_6 .

Figure 2.3 ^1H NMR Spectra of H-D Exchanging Experiment of NHC Salt in DMSO-d_6 .

2.3.2 Chiral Induction.

To get some insight to the chirality induction, we did comparing experiment using catalyst **2-6c**, **2-6d**, **2-6e**, and **2-6f**. The reactions were carried out under the optimized reaction condition as stated in Table 2.3, Entry 20. The results are summarized in Scheme 2.11.

Scheme 2.11 Comparing Experiment using Different Catalysts.

The steric hindrance of the R group on the catalyst has significant effect on the *er* value. Therefore, we proposed a possible transition state for the Re face attack for the chiral induction, as illustrated in Scheme 2.12.

Scheme 2.12 Possible Transition State for the Chiral Induction.

2.4 Summary.

In summary, we have disclosed the first enantioselective organocatalytic synthesis of β -sulfonyl ketones. The sulfinic anion was released from sulfonyl imines under the catalysis of NHCs. The enantioselectivity was realized through the non-covalent co-catalysis of thiourea/tertiary amine organocatalysts. We hope this work would give contributions to the field of both NHC catalysis and sulfone synthesis.

2.5 Experimental Section

2.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich 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.

2.5.2 Preparation of Racemic Sulfonation Product.

To a 10 mL Schlenk tube equipped with a magnetic stir bar was added **2-1** (0.2 mmol), **2-2** (0.1 mmol), **2-4a** (0.02 mmol) and DABCO (0.02 mmol). The tube was sealed with a septum, evacuated, and then refilled with nitrogen ($\times 3$ cycles). 2-Propanol (1.0 mL) was added and the reaction mixture was allowed to stir for 12 h at 75 °C. The solvent was removed under vacuum and the residue was subjected to SiO_2 column chromatography using hexane/ $\text{CH}_2\text{Cl}_2 = 3/2$ to pure CH_2Cl_2 as eluents to yield the desired product **2-3**.

2.5.3 General Procedures for Enantioselective Catalytic Reactions.

To a 10 mL Schlenk tube equipped with a magnetic stir bar was added **2-1** (0.1 mmol), **2-2** (0.05 mmol), **2-4f** (0.01 mmol) and **2-6f** (0.005 mmol). The tube was sealed with a septum, evacuated, and then refilled with nitrogen ($\times$ 3 cycles). The reaction tube was then cooled to 0 °C and toluene (2 mL) was added. The reaction was allowed to stir at 0 °C for 72 h. The crude reaction mixture was directly subjected to SiO₂ column chromatography using hexane/CH₂Cl₂ = 3/2 to pure CH₂Cl₂ as eluents to yield the chiral product **2-3**.

2.5.4 General Procedure for Enantioselective Catalytic Reactions.

To a 10 mL tube equipped with a magnetic stir bar was added **2-1** (0.1 mmol), **2-2** (0.05 mmol), **2-4g** (0.01 mmol) and **2-6h** (0.01 mmol). Then 10 mg 3A molecular sieve was added in glovebox, followed by 2 mL of dry chloroform. The tube was then sealed and the reaction was stirred at rt for 48 h. The crude reaction mixture was directly subjected to SiO₂ column chromatography using hexane/CH₂Cl₂ = 3/2 to pure CH₂Cl₂ as eluents to yield the chiral product **2-5**.

3.5.5 Synthetic Transformation of Sulfonation Product 2-3a.

To a 10 mL Schlenk tube equipped with a magnetic stir bar was added chiral **2-3a** (0.1 mmol, 96:4 er) and LiAlH_4 (0.15 mmol). The tube was sealed with a septum, evacuated, and then refilled with nitrogen ($\times 3$ cycles). The reaction tube was cooled to $0\text{ }^\circ\text{C}$ and dry ether (3.5 mL) was added. The reaction mixture was allowed to stir at $0\text{ }^\circ\text{C}$ for 3 h. The reaction mixture was quenched with aqueous NH_4Cl and then filtered. The residue was washed with CH_2Cl_2 and the filtrate was separated and extracted with CH_2Cl_2 . The organic layers were combined, dried over MgSO_4 , and filtered. The solvent was removed, and the resulting residue was subjected to SiO_2 column chromatography using hexane/DCM = 3/2 to pure CH_2Cl_2 as eluents to yield **2-8** as a single diastereomer (with 93:7 er) in 67% yield.

To a 25 mL round bottom flask equipped with a magnetic stir bar was added chiral **2-8** (0.3 mmol, 92:8 er), toluene (10 mL) and triethylamine (1.2 mmol). The reaction system was then cooled to $0\text{ }^\circ\text{C}$ and methanesulfonyl chloride (0.4 mmol) was added. The reaction mixture was allowed to stir at $0\text{ }^\circ\text{C}$ for 12 h and then quenched with water. The product was extracted with ether and the combined organic phase was washed sequentially with 1N HCl, water and saturated aqueous NaHCO_3 . The organic layer were dried over MgSO_4 , and filtered. After removing the solvent under vacuum, and the resulting residue was used directly in the next step.

To a 25 mL round bottom flask containing Ms protected alcohol from the last step (~ 0.3 mmol) was added a magnetic stir bar, toluene (10 mL), 18-crown-6 (0.03 mmol) and $t\text{-BuOK}$ (0.35 mmol). The reaction mixture was stirred at rt for 8 h and then subjected to SiO_2 column chromatography directly using hexane/DCM = 9/1 to pure CH_2Cl_2 as eluents to yield **2-9** as a single diastereomer (with 89:11 er) in 80% yield. After

recrystallization from DCM/Hexanes, the product could be obtained with 98:2 er.²

2.5.6 X-Ray Structure of 2-3i and 2-9.

Stereochemistry determination *via* X-ray crystallographic analysis:

Absolute configurations of the products **2-3** were assigned based on the crystal X-ray structures of **2-3i**. CCDC 922430 (**2-3i**, obtained as colorless needles *via* vaporization of a hexane/EtOAc/trace CH₂Cl₂ solution) contains the supplementary X-ray crystallographic data.

Absolute configuration of the product **2-9** was assigned based on the crystal X-ray structures of **2-9**. CCDC 941620 (**2-9**, obtained as colorless needles *via* vaporization of a hexane/CH₂Cl₂ solution) contains the supplementary X-ray crystallographic data.

2.5.7 Characterization of Catalysts and Products.

1-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-3-((S)-1-phenyl-3-(piperidin-1-yl)propan-2-yl)thiourea (2-6c): White foam solid. ^1H NMR (400 MHz, CDCl_3) δ 8.71 (d, $J = 4.4$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 7.79 (br s, 1H), 7.40 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.30 (d, $J = 3.6$ Hz, 1H), 7.15 (br s, 3H), 7.00 (br s, 2H), 6.50 (br s, 1H), 5.75-5.66 (m, 1H), 5.00-4.94 (m, 2H), 4.24 (br s, 1H), 3.99 (s, 3H), 3.26-3.17 (m, 2H), 2.85 (dd, $J = 4.8, 13.6$ Hz, 1H), 2.71-2.68 (m, 3H), 2.35-2.22 (m, 7H), 1.67-1.26 (m, 12H), 0.89 (dd, $J = 7.2, 14.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 182.3, 158.0, 147.4, 144.9, 141.3, 137.3, 131.8, 129.4, 128.3, 126.4, 121.9, 114.6, 102.5, 55.9, 55.7, 54.5, 39.5, 34.7, 31.6, 29.1, 27.9, 27.5, 26.9, 26.1, 26.0, 25.3, 24.2, 22.6, 14.1. $[\alpha]^{20}_{\text{D}} = -71$ ($c = 1.0$ in CH_2Cl_2); LCMS (ESI, m/z): calcd. for $\text{C}_{35}\text{H}_{45}\text{N}_5\text{OSH}^+$ 584.34, found 584.25.

1-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-3-((1S,2S)-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)cyclohexyl)thiourea (2-6h): White solid. ^1H NMR (400 MHz, CDCl_3) δ 9.10 (br s, 0.5H), 8.77 (d, $J = 3.3$ Hz, 1H), 8.01 (d, $J = 9.2$ Hz, 1H), 7.92 (br s, 1H), 7.41 (d, $J = 4.3$ Hz, 1H), 7.37 (d, $J = 9.2$ Hz, 1H), 6.30 (br s, 1.5H), 5.71-5.63 (m, 1H), 5.11-5.07 (m, 2H), 4.88 (br s, 1H), 3.93 (s, 3H), 3.83-3.69 (m, 2H), 3.45 (t, $J = 12.0$ Hz, 1H), 2.94-2.91 (m, 2H), 2.61-2.55 (m, 2H), 2.06

(s, 2H), 1.84-1.72 (m, 6H), 1.53-1.22 (m, 5H), 0.91-0.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 181.5, 179.7, 163.8, 157.9, 147.9, 144.4, 143.4, 139.1, 137.3, 131.5, 128.6, 127.4, 122.8, 119.6, 117.0, 101.8, 59.8, 56.2, 55.9, 54.2, 53.6, 41.5, 36.9, 32.3, 27.9, 26.8, 25.3, 24.6, 23.9. $[\alpha]_D^{20} = 18$ (c = 1.0 in CH_2Cl_2); LCMS (ESI, m/z): calcd. for $\text{C}_{35}\text{H}_{35}\text{Cl}_4\text{N}_5\text{O}_3\text{SH}^+$ 748.13, found 748.36.

1-((S)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)-3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)thiourea hydrochloride (2-6f·HCl):

Brown solid. ^1H NMR (400 MHz, D_2O) δ 8.92 (d, $J = 5.6$ Hz, 1H), 8.28 (br s, 1H), 8.13 (d, $J = 9.4$ Hz, 1H), 8.04 (d, $J = 5.7$ Hz, 1H), 7.75 (dd, $J = 2.4, 9.4$ Hz, 1H), 6.80 (d, $J = 10.5$ Hz, 1H), 5.86-5.77 (m, 1H), 5.17 (d, $J = 12.0$ Hz, 1H), 5.14 (d, $J = 5.2$ Hz, 1H), 4.63 (d, $J = 10.8$ Hz, 1H), 4.38-4.35 (m, 1H), 4.22-4.08 (m, 1H), 4.05 (s, 3H), 3.72 (dd, $J = 10.7, 13.2$ Hz, 1H), 3.56-3.51 (m, 2H), 3.39-3.30 (m, 2H), 3.26 (d, $J = 12.3$ Hz, 1H), 3.07-3.00 (m, 2H), 2.89-2.63 (m, 3H), 2.08-1.82 (m, 6H), 1.54-1.39 (m, 3H), 3.39-3.30 (m, 2H), 1.24-1.02 (m, 3H), 0.89 (s, 9H); ^{13}C NMR (100 MHz, D_2O) δ 183.7, 160.1, 151.0, 141.9, 137.2, 135.4, 129.3, 127.3, 124.0, 120.7, 116.8, 104.4, 59.1, 58.0, 57.7, 56.6, 55.3, 54.6, 53.8, 52.9, 42.7, 35.8, 35.1, 33.0, 25.8, 25.4, 24.6, 23.3, 23.2, 22.5, 22.5, 20.9, 20.7. LCMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{46}\text{N}_5\text{OSH}^+$ 550.36, found 550.25.

1,3-diphenyl-3-tosylpropan-1-one (2-3a): 69% yield. White solid. mp 179 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.94-7.92 (m, 2H), 7.57 (tt, $J = 1.2, 7.6$ Hz, 1H), 7.47-7.41 (m, 4H),

7.26-7.16 (m, 7H), 4.92 (dd, $J = 3.6, 10.0$ Hz, 1H), 4.11 (dd, $J = 3.6, 17.6$ Hz, 1H), 3.93 (dd, $J = 9.6, 18.0$ Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.0, 144.7, 136.2, 134.0, 133.7, 132.7, 129.8, 129.4, 129.0, 128.8, 128.5, 128.1, 66.5, 37.1, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{21}\text{O}_3\text{SH}^+$ 365.1211, found 365.1214; $[\alpha]^{20}_{\text{D}} = -93$ ($c = 0.6$ in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 1.0 mL/min), R_t (minor) = 5.2 min, R_t (major) = 6.4 min.

3-(4-methoxyphenyl)-1-phenyl-3-tosylpropan-1-one (2-3b): 60% yield. White solid. mp 174 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.96-7.94 (m, 2H), 7.59 (tt, $J = 1.2, 7.2$ Hz, 1H), 7.50-7.46 (m, 4H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.15-7.13 (m, 2H), 6.77-6.75 (m, 2H), 4.89 (dd, $J = 3.2, 9.6$ Hz, 1H), 4.09 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.90 (dd, $J = 9.6, 17.6$ Hz, 1H), 3.77 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.1, 159.9, 144.6, 136.2, 134.1, 133.6, 130.9, 129.4, 129.1, 128.7, 128.1, 124.4, 113.9, 65.9, 55.2, 37.1, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{23}\text{O}_4\text{SH}^+$ 395.1317, found 395.1317; $[\alpha]^{20}_{\text{D}} = -94$ ($c = 1.2$ in CH_2Cl_2); HPLC analysis: 90:10 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 7.3 min, R_t (major) = 9.1 min.

3-(4-nitrophenyl)-1-phenyl-3-tosylpropan-1-one (2-3c): 76% yield. White solid. mp 195-197 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.17-8.14 (m, 1H), 8.05-8.04 (m, 1H), 7.96-7.94 (m, 2H), 7.63 (tt, $J = 1.2, 8.4$ Hz, 2H), 7.52-7.44 (m, 5H), 7.25 (d, $J = 8.0$ Hz, 2H), 5.01 (dd, $J = 3.6, 10.4$ Hz, 1H), 4.18 (dd, $J = 3.2, 18.0$ Hz, 1H), 3.98 (dd, $J = 10.0, 18.0$ Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.4, 148.1, 145.6, 135.8, 135.7,

135.1, 134.0, 133.4, 129.8, 129.5, 129.0, 128.9, 128.1, 124.7, 123.7, 65.9, 37.1, 21.7; HRMS (ESI, m/z): calcd. for $C_{22}H_{20}NO_5SH^+$ 410.1062, found 410.1056; $[\alpha]^{20}_D = -76$ ($c = 1.4$ in CH_2Cl_2); HPLC analysis: 89:11 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 7/3$, 1.0 mL/min), R_t (minor) = 16.7 min, R_t (major) = 23.0 min.

3-(4-chlorophenyl)-1-phenyl-3-tosylpropan-1-one (2-3d): 49% yield. White solid. mp 182-183 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.93 (m, 2H), 7.61 (tt, $J = 1.2, 7.2$ Hz, 1H), 7.50-7.47 (m, 4H), 7.25-7.16 (m, 6H), 4.90 (dd, $J = 3.2, 10.0$ Hz, 1H), 4.12 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.90 (dd, $J = 10.4, 18.0$ Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 145.0, 136.0, 134.9, 133.8, 131.3, 131.0, 129.6, 129.0, 128.8, 128.7, 128.1, 65.8, 37.1, 21.7; HRMS (ESI, m/z): calcd. for $C_{22}H_{20}O_3SClH^+$ 399.0822, found 399.0822; $[\alpha]^{20}_D = -106$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 1/1$, 0.8 mL/min), R_t (minor) = 6.8 min, R_t (major) = 8.4 min.

1-phenyl-3-(p-tolyl)-3-tosylpropan-1-one (2-3e): 54% yield. White solid. mp 169-170 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.59 (tt, $J = 1.2, 7.6$ Hz, 1H), 7.49-7.45 (m, 4H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 4.91 (dd, $J = 3.6, 9.6$ Hz, 1H), 4.09 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.92 (dd, $J = 9.6, 17.6$ Hz, 1H), 2.41 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 144.7, 138.7, 136.2, 134.1, 133.6, 129.6, 129.5, 129.4, 129.2, 129.1, 128.7, 128.1, 66.2, 37.1, 21.7, 21.2; HRMS (ESI, m/z): calcd. for $C_{23}H_{23}O_3SH^+$ 379.1368, found 379.1368; $[\alpha]^{20}_D = -78$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 94:6 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 1/1$, 0.8 mL/min),

Rt (minor) = 6.5 min, Rt (major) = 7.8 min.

3-(4-nitrophenyl)-1-phenyl-3-tosylpropan-1-one (2-3f): 84% yield. White solid. mp 187-188 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.10-8.06 (m, 2H), 7.93-7.91 (m, 2H), 7.60 (tt, $J = 1.2, 7.6$ Hz, 1H), 7.50-7.41 (m, 6H), 7.23 (d, $J = 8.0$ Hz, 2H), 4.99 (dd, $J = 3.6, 10.4$ Hz, 1H), 4.17 (dd, $J = 3.6, 18.4$ Hz, 1H), 3.96 (dd, $J = 10.4, 18.0$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.5, 147.9, 145.6, 140.2, 135.7, 134.1, 133.5, 130.7, 129.8, 128.9, 128.1, 123.5, 66.1, 37.2, 21.7; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{20}\text{NO}_5\text{SH}^+$ 410.1062, found 410.1066; $[\alpha]^{20}_{\text{D}} = -112$ ($c = 1.7$ in CH_2Cl_2); HPLC analysis: >99:1 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), Rt (minor) = 9.1 min, Rt (major) = 10.0 min.

1-(4-methoxyphenyl)-3-phenyl-3-tosylpropan-1-one (2-3g): 64% yield. White solid. mp 198 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.95-7.93 (m, 2H), 7.45-7.43 (m, 2H), 7.26-7.18 (m, 7H), 6.95-6.93 (m, 2H), 4.93 (dd, $J = 3.6, 10.0$ Hz, 1H), 4.07 (dd, $J = 3.6, 17.6$ Hz, 1H), 3.91 (dd, $J = 10.0, 17.6$ Hz, 1H), 3.88 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.4, 163.9, 144.7, 134.1, 132.8, 130.5, 129.8, 129.4, 129.3, 129.0, 128.7, 128.4, 113.9, 66.6, 55.5, 36.6, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{23}\text{O}_4\text{SH}^+$ 395.1317, found 395.1319; $[\alpha]^{20}_{\text{D}} = -28$ ($c = 1.3$ in CH_2Cl_2); HPLC analysis: 97:3 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), Rt (minor) = 7.4 min, Rt (major) = 8.9 min.

1-(4-chlorophenyl)-3-phenyl-3-tosylpropan-1-one (2-3h): 79% yield. White solid. mp 190-191 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.92-7.89 (m, 2H), 7.47-7.42 (m, 4H), 7.29-7.18 (m, 7H), 4.91 (dd, $J = 3.6, 9.6$ Hz, 1H), 4.12 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.89 (dd, $J = 9.6, 18.0$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.9, 144.8, 140.2, 134.5, 133.9, 132.6, 129.7, 129.6, 129.4, 129.1, 129.0, 128.8, 128.5, 66.4, 37.0, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_3\text{SClH}^+$ 399.0822, found 399.0815; $[\alpha]^{20}_{\text{D}} = -92$ ($c = 1.6$ in CH_2Cl_2); HPLC analysis: 97:3 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 6.7 min, R_t (major) = 7.5 min.

1-(4-bromophenyl)-3-phenyl-3-tosylpropan-1-one (2-3i): 77% yield. White solid. mp 197 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.28-7.18 (m, 7H), 4.91 (dd, $J = 3.6, 9.2$ Hz, 1H), 4.11 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.88 (dd, $J = 9.6, 18.0$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.1, 144.8, 134.9, 133.9, 132.6, 132.1, 129.7, 129.6, 129.4, 129.0, 128.9, 128.8, 128.5, 66.4, 37.0, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_3\text{SBrH}^+$ 443.0317, found 443.0321; $[\alpha]^{20}_{\text{D}} = -63$ ($c = 1.6$ in CH_2Cl_2); HPLC analysis: >99:1 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 6.9 min, R_t (major) = 7.6 min.

1-(naphthalen-2-yl)-3-phenyl-3-tosylpropan-1-one (2-3j): 57% yield. White solid. mp 186-187 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.97

(dd, $J = 2.0, 8.8$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 2H), 7.66-7.57 (m, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.30-7.19 (m, 7H), 5.01 (dd, $J = 3.6, 9.6$ Hz, 1H), 4.28 (dd, $J = 3.6, 17.6$ Hz, 1H), 4.12 (dd, $J = 9.6, 17.6$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.9, 144.8, 135.8, 134.0, 133.5, 132.7, 132.4, 130.1, 129.8, 129.7, 129.4, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 127.8, 127.0, 123.6, 66.6, 37.0, 21.7; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{O}_3\text{SH}^+$ 415.1368, found 415.1364; $[\alpha]^{20}_{\text{D}} = -125$ ($c = 1.2$ in CH_2Cl_2); HPLC analysis: 91:9 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 6.9 min, R_t (major) = 7.5 min.

1,3-bis(4-chlorophenyl)-3-tosylpropan-1-one (2-3k): 52% yield. White solid. mp 191-192 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.90-7.87 (m, 2H), 7.47-7.45 (m, 4H), 7.24-7.14 (m, 6H), 4.87 (dd, $J = 3.6, 10.0$ Hz, 1H), 4.10 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.84 (dd, $J = 10.0, 18.0$ Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.7, 145.1, 140.4, 134.9, 134.3, 133.7, 131.2, 131.0, 129.9, 129.7, 129.6, 129.5, 129.3, 129.2, 129.0, 128.8, 65.8, 37.0, 21.7; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{O}_3\text{SH}^+$ 433.0432, found 433.0439; $[\alpha]^{20}_{\text{D}} = -100$ ($c = 1.1$ g/L in CH_2Cl_2); HPLC analysis: 99:1 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 7.2 min, R_t (major) = 7.9 min.

1-(furan-2-yl)-3-phenyl-3-tosylpropan-1-one (2-3l): 63% yield. White solid. mp 178-179 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.80 (dd, $J = 1.2, 4.0$ Hz, 1H), 7.64 (dd, $J = 1.2, 5.2$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.26-7.13 (m, 8H), 4.88 (dd, $J = 4.0, 10.0$ Hz, 1H), 4.03 (dd, $J = 4.0, 17.2$ Hz, 1H), 3.85 (dd, $J = 9.6, 17.2$ Hz, 1H), 2.38 (s, 3H); ^{13}C NMR

(100 MHz, CDCl_3) δ 187.7, 144.8, 143.3, 134.4, 133.9, 132.5, 132.4, 129.8, 129.4, 129.0, 128.8, 128.5, 128.3, 66.4, 37.6, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{19}\text{O}_4\text{SH}^+$ 355.1004, found 355.0987; $[\alpha]_{\text{D}}^{20} = -76$ ($c = 1.1$ g/L in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 6.9 min, R_t (major) = 9.7 min.

1,3-diphenyl-3-(phenylsulfonyl)propan-1-one (2-3m): 52% yield. White solid. mp 152-153 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.95-7.92 (m, 2H), 7.59-7.51 (m, 4H), 7.48-7.44 (m, 2H), 7.40-7.36 (m, 2H), 7.24-7.19 (m, 5H), 4.94 (dd, $J = 3.6, 10.0$ Hz, 1H), 4.13 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.95 (dd, $J = 9.6, 17.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.9, 136.9, 136.1, 133.7, 132.7, 132.5, 129.8, 129.1, 129.0, 128.8, 128.7, 128.5, 128.2, 126.4, 66.5, 36.9; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{19}\text{O}_3\text{SH}^+$ 351.1055, found 351.1055; $[\alpha]_{\text{D}}^{20} = -86$ ($c = 0.9$ in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 6.5 min, R_t (major) = 8.1 min.

3-((4-methoxyphenyl)sulfonyl)-1,3-diphenylpropan-1-one (2-3n): 67% yield. White solid. mp 162-163 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.94 (dd, $J = 1.2, 8.4$ Hz, 2H), 7.57 (tt, $J = 1.2, 7.6$ Hz, 1H), 7.48-7.43 (m, 4H), 7.27-7.20 (m, 5H), 6.85-6.81 (m, 2H), 4.90 (dd, $J = 3.6, 10.0$ Hz, 1H), 4.12 (dd, $J = 3.6, 18.0$ Hz, 1H), 3.93 (dd, $J = 9.6, 18.0$ Hz,

1H), 3.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.0, 163.7, 136.2, 133.7, 132.8, 131.2, 129.8, 128.7, 128.5, 128.1, 113.9, 66.7, 55.6, 37.1; HRMS (ESI, m/z): calcd. for C₂₂H₂₁O₄SH⁺ 381.1161, found 381.1161; [α]_D²⁰ = -96 (c = 1.3 g/L in CH₂Cl₂); HPLC analysis: 92:8 er (Chiralcel IA, Hexane/CH₂Cl₂ = 1/1, 0.8 mL/min), Rt (minor) = 7.3 min, Rt (major) = 8.9 min.

3-(methylsulfonyl)-1,3-diphenylpropan-1-one (2-3o): 44% yield. White solid. mp 148-149 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.60-7.54 (m, 3H), 7.48-7.42 (m, 2H), 7.42-7.36 (m, 3H), 4.95 (dd, *J* = 3.6, 9.6 Hz, 1H), 4.08 (dd, *J* = 3.6, 18.0 Hz, 1H), 3.85 (dd, *J* = 9.6, 18.0 Hz, 1H), 2.70 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 194.8, 136.0, 133.8, 133.3, 129.5, 129.3, 129.2, 128.8, 128.2, 65.0, 38.8, 36.7; HRMS (ESI, m/z): calcd. for C₁₆H₁₇O₃SH⁺ 289.0898, found 289.0899; [α]_D²⁰ = -20 (c = 0.6 in CH₂Cl₂); HPLC analysis: 73:27 er (Chiralcel IA, Hexane/CH₂Cl₂ = 1/1, 0.8 mL/min), Rt (minor) = 9.2 min, Rt (major) = 11.7 min.

3-((4-nitrophenyl)sulfonyl)-1,3-diphenylpropan-1-one (2-3p): 13% yield. White solid. mp 170 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.30-7.20 (m, 5H), 5.01 (dd, *J* = 4.0, 9.6 Hz, 1H), 4.18 (dd, *J* = 3.6, 18.0 Hz, 1H), 3.95 (dd, *J* = 9.2, 17.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 194.3, 150.8, 142.9, 136.0, 133.9, 131.9,

130.5, 129.8, 129.4, 128.9, 128.2, 123.8, 66.7, 36.6; HRMS (ESI, m/z): calcd. for $C_{21}H_{18}NO_5SH^+$ 396.0906, found 396.0901; $[\alpha]^{20}_D = -47$ ($c = 0.3$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 1/1$, 0.8 mL/min), R_t (minor) = 7.4 min, R_t (major) = 9.0 min.

ethyl 4-oxo-4-phenyl-2-tosylbutanoate (2-3q): 50% yield. White solid. mp 90-92 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.2$ Hz, 2H), 7.81 (d, $J = 8.0$ Hz, 2H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 4.61 (dd, $J = 3.2, 10.4$ Hz, 1H), 4.16-4.01 (m, 2H), 3.94 (dd, $J = 10.8, 18.0$ Hz, 1H), 3.79 (dd, $J = 3.6, 18.0$ Hz, 1H), 2.48 (s, 3H), 1.10 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 165.2, 145.6, 135.6, 134.7, 133.9, 129.8, 129.0, 128.8, 128.2, 66.2, 62.4, 35.3, 21.7, 13.7; HRMS (ESI, m/z): calcd. for $C_{19}H_{21}O_5SH^+$ 361.1110, found 361.1112; $[\alpha]^{20}_D = 0$ ($c = 0.9$ in CH_2Cl_2); HPLC analysis: 50:50 er (Chiralcel OD-H, Hexane/2-PrOH = 4/1, 0.5 mL/min), R_t = 23.2 min, 27.5 min.

4-phenyl-4-tosylbutan-2-one (2-3r): 30% yield. White solid. mp 123-125 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.4$ Hz, 2H), 7.41-7.13 (m, 7H), 4.73 (dd, $J = 4.4, 9.2$ Hz, 1H), 3.61 (dd, $J = 4.4, 17.6$ Hz, 1H), 3.29 (dd, $J = 9.2, 18.0$ Hz, 1H), 2.41 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 144.7, 133.9, 132.6, 129.7, 129.4, 129.0, 128.8, 128.5, 66.2, 41.6, 30.5, 21.6; HRMS (ESI, m/z): calcd. for $C_{17}H_{19}O_3SH^+$ 303.1055, found 303.1054; $[\alpha]^{20}_D = -32$ ($c = 0.5$ in CH_2Cl_2); HPLC analysis: 77:23 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 7/3$, 1.0 mL/min), R_t (minor) = 13.0 min, R_t (major) =

15.8 min.

4-tosyloctan-2-one (2-3s): 58% yield. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 3.74-3.67 (m, 1H), 3.12 (dd, $J = 5.6, 18.4$ Hz, 1H), 2.58 (dd, $J = 6.8, 18.4$ Hz, 1H), 2.45 (s, 3H), 2.18 (s, 3H), 1.85-1.76 (m, 1H), 1.52-1.43 (m, 1H), 1.31-1.13 (m, 4H), 0.81 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 204.1, 144.8, 134.7, 129.9, 128.8, 59.5, 41.3, 30.2, 28.6, 28.5, 22.4, 21.7, 13.7; HRMS (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_{23}\text{O}_3\text{SH}^+$ 283.1368, found 283.1367; $[\alpha]^{20}_{\text{D}} = -3$ ($c = 0.8$ in CH_2Cl_2); HPLC analysis: 60:40 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (minor) = 6.3 min, R_t (major) = 7.1 min.

1-phenyl-3-tosylbutan-1-one (2-5a): 66% yield. White solid. mp 105 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.95 (dd, $J = 1.2, 8.4$ Hz, 2H), 7.83 (d, $J = 8.0$ Hz, 2H), 7.61 (t, $J = 7.2$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 3.89-3.81 (m, 1H), 3.73 (dd, $J = 2.8, 17.6$ Hz, 1H), 3.19 (dd, $J = 9.6, 17.2$ Hz, 1H), 2.47 (s, 3H), 1.33 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.8, 144.9, 136.2, 134.1, 133.7, 129.9, 128.9, 128.8, 128.1, 55.9, 37.9, 21.7, 14.2; HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{19}\text{O}_3\text{SH}^+$ 303.1055, found 303.1053; $[\alpha]^{20}_{\text{D}} = -15$ ($c = 0.9$ in CH_2Cl_2); HPLC analysis: 83:17 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 7/3$, 1.0 mL/min), R_t (major) = 10.6 min, R_t (minor) = 14.2 min.

1-phenyl-3-tosylpentan-1-one (2-5b): 63% yield. Colorless oil. ^1H NMR (400 MHz,

CDCl₃) δ 7.96-7.94 (m, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 3.94-3.88 (m, 1H), 3.68 (dd, J = 4.4, 18.0 Hz, 1H), 3.21 (dd, J = 7.6, 18.0 Hz, 1H), 2.46 (s, 3H), 2.06-1.95 (m, 1H), 1.76-1.64 (m, 1H), 0.96 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.8, 144.8, 136.2, 134.9, 133.6, 129.9, 128.8, 128.7, 128.1, 61.0, 36.3, 22.1, 21.6, 11.2; LCMS (ESI, m/z): calcd. for C₁₈H₂₀O₃SH⁺ 317.12, found 317.11; $[\alpha]^{20}_D$ = -8 (c = 0.9 in CH₂Cl₂); HPLC analysis: 85:15 er (Chiralcel IA, Hexane/CH₂Cl₂ = 7/3, 1.0 mL/min), Rt (major) = 10.0 min, Rt (minor) = 13.6 min.

1-phenyl-3-tosylhexan-1-one (2-5c): 70% yield. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.93-7.91 (m, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.60 (tt, J = 1.2, 7.2 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.00-3.94 (m, 1H), 3.67 (dd, J = 4.4, 18.0 Hz, 1H), 3.17 (dd, J = 7.2, 18.0 Hz, 1H), 2.45 (s, 3H), 1.97-1.88 (m, 1H), 1.65-1.56 (m, 1H), 1.46-1.23 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.7, 144.8, 136.1, 134.8, 133.6, 129.9, 128.8, 128.7, 128.1, 59.6, 37.0, 31.1, 21.6, 20.0, 13.9; HRMS (ESI, m/z): calcd. for C₁₉H₂₃O₃SH⁺ 331.1368, found 331.1368; $[\alpha]^{20}_D$ = -6 (c = 1.2 g/L in CH₂Cl₂); HPLC analysis: 86:14 er (Chiralcel IA, Hexane/CH₂Cl₂ = 7/3, 1.0 mL/min), Rt (major) = 9.1 min, Rt (minor) = 12.0 min.

1-phenyl-3-tosylheptan-1-one (2-5d): 70% yield. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.94-7.92 (m, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 3.99-3.93 (m, 1H), 3.68 (dd, J = 4.4, 18.0 Hz, 1H),

3.17 (dd, $J = 7.2, 18.0$ Hz, 1H), 2.45 (s, 3H), 2.00-1.92 (m, 1H), 1.67-1.58 (m, 1H), 1.39-1.24 (m, 4H), 0.83 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.8, 144.8, 136.2, 134.8, 133.6, 129.9, 128.8, 128.7, 128.1, 59.7, 37.0, 28.7, 28.6, 22.5, 21.6, 13.7; LCMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{SH}^+$ 345.15, found 345.06; $[\alpha]^{20}_{\text{D}} = -7$ ($c = 0.5$ g/L in CH_2Cl_2); HPLC analysis: 83:17 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (major) = 5.8 min, R_t (minor) = 6.7 min.

5-methyl-1-phenyl-3-tosylhexan-1-one (2-5e): 62% yield. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 7.6$ Hz, 2H), 7.80 (d, $J = 8.0$ Hz, 2H), 7.61 (t, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 4.10-4.04 (m, 1H), 3.72 (dd, $J = 5.2, 18.0$ Hz, 1H), 3.05 (dd, $J = 6.4, 18.0$ Hz, 1H), 2.45 (s, 3H), 1.82-1.76 (m, 1H), 1.63-1.50 (m, 2H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.82 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.7, 144.7, 136.2, 134.7, 133.6, 129.8, 128.9, 128.7, 128.1, 58.1, 38.1, 37.7, 29.7, 25.5, 23.0, 21.6; LCMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{SH}^+$ 345.15, found 345.12; $[\alpha]^{20}_{\text{D}} = -4$ ($c = 0.4$ g/L in CH_2Cl_2); HPLC analysis: 81:19 er (Chiralcel IA, Hexane/ $\text{CH}_2\text{Cl}_2 = 1/1$, 0.8 mL/min), R_t (major) = 5.8 min, R_t (minor) = 6.5 min.

1-phenyl-3-tosyloctan-1-one (2-5f): 69% yield. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.94-7.92 (m, 2H), 7.82 (d, $J = 8.0$ Hz, 2H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 3.99-3.93 (m, 1H), 3.68 (dd, $J = 4.4, 18.0$ Hz, 1H), 3.17 (dd, $J = 7.2, 17.6$ Hz, 1H), 2.46 (s, 3H), 2.00-1.88 (m, 1H), 1.67-1.58 (m, 1H), 1.45-1.19 (m, 6H), 0.83 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.8, 144.8, 136.2,

134.8, 133.6, 129.9, 128.8, 128.7, 128.1, 59.8, 37.0, 31.6, 31.5, 29.7, 28.9, 26.3, 22.2, 21.6, 13.9; LCMS (ESI, m/z): calcd. for $C_{21}H_{26}O_3SH^+$ 359.17, found 359.07; $[\alpha]^{20}_D = -7$ ($c = 0.6$ g/L in CH_2Cl_2); HPLC analysis: 85:15 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 7/3$, 1.0 mL/min), R_t (major) = 8.4 min, R_t (minor) = 11.1 min.

1,4-diphenyl-3-tosylbutan-1-one (2-5g): 86% yield. White solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.75 (m, 4H), 7.58-7.54 (m, 1H), 7.42 (t, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 7.2$ Hz, 3H), 7.21-7.12 (m, 5H), 4.43-4.36 (m, 1H), 3.69 (dd, $J = 6.0, 17.6$ Hz, 1H), 3.38 (dd, $J = 4.8, 14.4$ Hz, 1H), 3.07 (dd, $J = 5.6, 18.0$ Hz, 1H), 2.94 (dd, $J = 10.0, 14.4$ Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 144.8, 136.2, 134.7, 133.4, 129.9, 129.3, 128.9, 128.6, 128.5, 128.0, 126.9, 60.9, 36.0, 34.4, 29.7, 21.6; LCMS (ESI, m/z): calcd. for $C_{23}H_{22}O_3SH^+$ 379.14, found 379.05; $[\alpha]^{20}_D = -4$ ($c = 1.2$ g/L in CH_2Cl_2); HPLC analysis: 78:22 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 7/3$, 1.0 mL/min), R_t (major) = 10.8 min, R_t (minor) = 12.5 min.

1,5-diphenyl-3-tosylpentan-1-one (2-5h): 60% yield. White solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.26-7.23 (m, 2H), 7.19-7.17 (m, 1H), 7.09-7.08 (m, 2H), 4.04-3.98 (m, 1H), 3.73 (dd, $J = 4.0, 17.6$ Hz, 1H), 3.24 (dd, $J = 7.6, 18.0$ Hz, 1H), 2.78-2.71 (m, 1H), 2.68-2.60 (m, 1H), 2.47 (s, 3H), 2.33-2.24 (m, 1H), 2.00-1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 144.9, 140.5, 136.1, 134.7, 133.7, 130.0, 128.8, 128.8, 128.5, 128.3, 128.1, 126.2, 59.5, 37.1, 33.0, 30.8, 29.7, 21.7; LCMS (ESI, m/z):

calcd. for $C_{24}H_{24}O_3SH^+$ 393.15, found 393.01; $[\alpha]^{20}_D = 2$ ($c = 1.1$ g/L in CH_2Cl_2); HPLC analysis: 84:16 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 7/3$, 1.0 mL/min), R_t (minor) = 10.2 min, R_t (major) = 13.1 min.

3-((4-methoxyphenyl)sulfonyl)-1-phenylhexan-1-one (2-5i): 86% yield. Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.87-7.83 (m, 2H), 7.61 (t, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 2H), 7.03-6.99 (m, 2H), 3.97-3.92 (m, 1H), 3.89 (s, 3H), 3.68 (dd, $J = 4.4, 18.0$ Hz, 1H), 3.16 (dd, $J = 7.2, 18.0$ Hz, 1H), 1.98-1.88 (m, 1H), 1.66-1.56 (m, 1H), 1.45-1.27 (m, 2H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 183.8, 136.2, 133.6, 131.0, 129.2, 128.7, 128.7, 128.1, 114.5, 114.3, 59.8, 55.7, 37.1, 31.1, 20.0, 13.9; LCMS (ESI, m/z): calcd. for $C_{19}H_{22}O_4SH^+$ 347.13, found 347.11; $[\alpha]^{20}_D = -7$ ($c = 0.9$ g/L in CH_2Cl_2); HPLC analysis: 83:17 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 7/3$, 1.0 mL/min), R_t (major) = 11.8 min, R_t (minor) = 15.5 min.

1-phenyl-3-(phenylsulfonyl)hexan-1-one (2-5j): 87% yield. Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.92 (m, 4H), 7.68-7.55 (m, 4H), 7.49 (t, $J = 8.0$ Hz, 2H), 4.04-3.98 (m, 1H), 3.69 (dd, $J = 4.0, 18.0$ Hz, 1H), 3.19 (dd, $J = 8.0, 18.0$ Hz, 1H), 1.98-1.89 (m, 1H), 1.67-1.58 (m, 1H), 1.46-1.23 (m, 2H), 0.87 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 137.8, 136.1, 133.8, 133.7, 129.3, 128.8, 128.8, 128.1, 114.5, 114.3, 59.8,

36.9, 31.0, 20.0, 13.9; LCMS (ESI, m/z): calcd. for $C_{18}H_{20}O_3SH^+$ 317.12, found 317.06; $[\alpha]^{20}_D = -5$ ($c = 0.9$ g/L in CH_2Cl_2); HPLC analysis: 82:18 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 7/3$, 1.0 mL/min), R_t (major) = 8.3 min, R_t (minor) = 10.7 min.

3-(methylsulfonyl)-1-phenylhexan-1-one (2-5k): 79% yield. Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H), 7.64 (tt, $J = 1.2, 7.2$ Hz, 1H), 7.53 (t, $J = 8.0$ Hz, 1H), 3.93-3.87 (m, 1H), 3.76 (dd, $J = 5.2, 18.4$ Hz, 1H), 3.26 (dd, $J = 6.0, 18.4$ Hz, 1H), 2.93 (s, 3H), 2.12-2.03 (m, 1H), 1.78-1.67 (m, 1H), 1.56-1.39 (m, 2H), 0.99 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 136.0, 133.9, 128.9, 128.2, 58.5, 39.7, 37.2, 30.9, 20.1, 13.9; LCMS (ESI, m/z): calcd. for $C_{13}H_{18}O_3SH^+$ 255.11, found 255.03; $[\alpha]^{20}_D = 13$ ($c = 0.5$ g/L in CH_2Cl_2); HPLC analysis: 85:15 er (Chiralcel IA, Hexane/ $CH_2Cl_2 = 1/1$, 0.8 mL/min), R_t (major) = 7.9 min, R_t (minor) = 8.9 min.

(1R,3S)-1,3-diphenyl-3-tosylpropan-1-ol (2-8): 67% yield. White solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, $J = 8.0$ Hz, 2H), 7.34-7.26 (m, 8H), 7.20-7.15 (m, 4H), 4.53 (dd, $J = 3.6, 11.6$ Hz, 1H), 4.38 (td, $J = 3.2, 10.8$ Hz, 1H), 2.81-2.74 (m, 1H), 2.48-2.41 (m, 1H), 2.38 (s, 3H), 1.92 (d, $J = 4.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 143.8, 134.4, 132.2, 130.1, 129.3, 129.1, 128.8, 128.7, 128.6, 128.0, 125.6, 70.9, 68.6, 37.0, 21.6; $[\alpha]^{20}_D = -3.4^\circ$ ($c = 0.7$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel ID, CH_2Cl_2 , 0.7 mL/min), R_t (minor) = 7.3 min, R_t (major) = 11.2 min. LCMS (ESI, m/z): calcd. for $C_{22}H_{22}O_3SH^+$ 367.14, found 367.51.

((1R,2S)-1-tosylcyclopropane-1,2-diyl)dibenzene (2-9): 80% yield. White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.40 (d, $J = 8.0$ Hz, 2H), 7.21-7.15 (m, 3H), 7.11-7.10 (m, 3H), 7.04 (t, $J = 8.0$ Hz, 2H), 6.84-6.80 (m, 4H), 3.59 (dd, $J = 7.2, 9.6$ Hz, 1H), 2.42 (s, 3H), 2.40 (dd, $J = 6.0, 10.0$ Hz, 1H), 1.84 (dd, $J = 6.0, 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.3, 135.1, 134.4, 133.4, 130.0, 129.2, 129.1, 128.5, 128.0, 127.9, 127.7, 126.8, 54.2, 28.1, 21.6, 17.8; LCMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_2\text{SH}^+$ 349.13, found 349.05; $[\alpha]_{\text{D}}^{20} = 135^\circ$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 98:2 er (Chiralcel IC, Hex/2-PrOH = 9/1, 1.0 mL/min), R_t (minor) = 19.4 min, R_t (major) = 20.3 min.

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Chapter 3

Enantioselective Direct β -Functionalization of Simple Aliphatic Anhydride through N-Heterocyclic Carbene Catalysis

3.1 Introduction

3.1.1 β -Activation of Saturated Carbonyl Compounds.

Direct β -activation of saturated carbonyl compounds has emerged as one of the most challenging and attractive research topics at the forefront of organic chemistry.^{1-2,5-6} Besides limited studies involving palladium-based, directing group assisted sp^3 C-H activation,² organocatalysis represents one powerful strategy within this field.^{3,4} Traditional ways to achieve β -functionalization of saturated carbonyl compounds are to apply an oxidative catalytic process with an α,β -unsaturated carbonyl species as the intermediate.⁵ However, the direct activation of the β -carbon is much rarer and still remains challenging,⁶ especially with a high degree of stereoselectivity. One methodology to achieve this goal is the photoredox β -functionalization of saturated aldehydes and cyclic ketones through a radical coupling.^{6a,b} However, the steric control of this process is still pending to be developed. The other way is the NHC-catalyzed direct generation of nucleophilic β -carbon from saturated esters that has recently been developed in our group (Scheme 3.1, a-c).^{6d}

Scheme 3.1 Organocatalytic β -Activation of Carbonyl Compounds.

3.1.2 Our Proposal.

We have previously showed the generality of the ester β -activation strategy through reactions with different electrophiles involving enones, hydrazones and trifluoroketones with generally good to excellent yields and stereoselectivities. However, an aromatic substituent was generally required at the β -carbon to achieve acceptable yield and selectivity. In addition, a pre-activated ester derived from 4-nitrophenol was crucial in these processes.⁷ Simple aliphatic carboxylic acids and their derivatives remain unexplored in this area.⁸⁻⁹

Here we study the direct β -activation of simple aliphatic anhydride with various electrophiles (Scheme 3.1, d).

3.2 Results and Discussions

Butyric anhydride **3-1a** and benzylidene diketone **3-2a** were first chosen as the model substrates. To our delight, an unrepresented homoenolate product **3-4a** was observed, which could not be obtained in our previous study involving the benzylidene diketones **3-2** with corresponding α,β -unsaturated aldehyde (Scheme 3.2).¹⁰

Scheme 3.2 Our Works Involving Benzylidene Diketone with α,β -Unsaturated Aldehyde..

We started by first establishing an optimal reaction condition for the model reaction.

Several typical NHC precursors were initially examined (Table 3.1, entries 1-5). The desired product could only be effectively formed when using triazolium catalysts bearing an *N*-Mes substituent (Entry 5). Then different chiral NHC catalysts were checked (Entries 6-12). *N*-Mes (or other electron-donating groups) substituted chiral catalyst gave the desired product in good yields but only with moderate *er* values (Entries 7, 9, 10). When using *N*-Ph substituted chiral catalyst, the product *er* value could be better, but the yield was rather low (Entries 6, 8). Strong *N*-electron-withdrawing group on the NHC structure resulted in no product formation (Entry 12). However, when switching the *N*-substituent on the catalyst to 2,4,6-trichlorophenyl group, the target molecule was obtained in a low yield, but with a significantly improved *er* value (Entry 11). Then we decided to go on optimizing with the catalyst **3-5k** trying to improve the yield while maintaining the high enantioselectivity. In the screening of different bases we found that DMAP gave the best yield with little erosion of the enantioselectivity (Entries 13-18). As the yield was still unsatisfactory, we went on to check the solvent effect. At this stage non-polar solvents generally present better yields than polar ones (Entries 19-22). At last, our β -activation product could be isolated in 62% yield with 95:5 *er* in cyclohexane after stirring at 30°C for 36 hours (Entry 23). Notably, only one diastereomer was observed in all the reactions we carried out.

Table 3.1 Condition Optimization.^[a]

Entry	NHC	Base	Solvent	Yield ^[b]	Er ^[c]
1	3-5a	Cs_2CO_3	Ether	0	-
2	3-5b	Cs_2CO_3	Ether	0	-
3	3-5c	Cs_2CO_3	Ether	<5	-
4	3-5d	Cs_2CO_3	Ether	<10	-
5	3-5e	Cs_2CO_3	Ether	54	-
6	3-5f	Cs_2CO_3	Ether	<10	94:6
7	3-5g	Cs_2CO_3	Ether	73	88:12
8	3-5h	Cs_2CO_3	Ether	<10	87:13
9	3-5i	Cs_2CO_3	Ether	74	81:19
10	3-5j	Cs_2CO_3	Ether	60	81:19
11	3-5k	Cs_2CO_3	Ether	22	98:2
12	3-5l	Cs_2CO_3	Ether	0	-
13	3-5k	DBU	Ether	5	-
14	3-5k	TEA	Ether	18	-
15	3-5k	K_2CO_3	Ether	18	-
16	3-5k	DMAP	Ether	28	96:4
17	3-5k	NaHDMS	Ether	26	95:5
18	3-5k	DMAP	THF	13	-
19	3-5k	DMAP	ACN	7	-
20	3-5k	DMAP	DCM	13	-
21	3-5k	DMAP	Hexane	36	94:6
22	3-5k	DMAP	Cyclohexane	44	96:4
23 ^[d]	3-5k	DMAP	Cyclohexane	61(62)	95:5

[a] 4 eq of **3-1a**, 1 eq of **3-2a** (0.1 mmol), 20 mol% of NHC, 3 eq of base and 1 mL of solvent at rt (24 °C) for 24 h. [b] Yield was determined by ^1H NMR, and yield in parenthesis was isolated yield after column chromatography. [c] Er of **3-4a**, determined *via* chiral HPLC. [d] The reaction was carried out using 2 eq of **3-1a**, and 4 eq of DMAP in 0.2 mL cyclohexane at 30 °C for 36 h.

With the optimized reaction conditions in hand, we next checked the reaction scope with different substituted alkylidene diketones as well as different anhydrides (Table 3.2).

Enantioselectivities of all the substrates we checked were excellent. A bulky substituent on the 2-position of R^1 group decreased the product yield probably due to steric hindrance, together with the low reactivity of the inert β -carbon of the anhydride (Entries 3, 9). Heteroaromatic rings were also tolerated, and the corresponding products could be obtained with good yields and excellent er values (Entries 10-13). However, displacement of either R^1 or R^2 group with an alkyl substituent did not afford the corresponding product (Entries 24, 25). Different aliphatic anhydrides with longer chains also played well in this reaction to give the desired products with similar yields and er values (Entries 16-23). However, challenging substrates such as propionic anhydride with a terminal β -carbon or isovaleric anhydride with a disubstituted β -carbon were unsuccessful in this process. Anhydrides bearing an aryl group as the R group, with some modification of the reaction conditions, afforded the desired products in good yields, albeit with moderated enantioselectivity (Entries 26-28).

Table 3.2 Scope of Anhydrides and Alkylidene Diketones.^[a]

Entry	R	R ¹	R ²	3-4	Yield (%) ^[b]	Er ^[c]
1	Me	Ph	Ph	3-4a	62	95:5
2	Me	3-BrC ₆ H ₄	Ph	3-4b	75	97:3
3	Me	2-ClC ₆ H ₄	Ph	3-4c	52	98:2
4	Me	3-FC ₆ H ₄	Ph	3-4d	73	96:4
5	Me	4-FC ₆ H ₄	Ph	3-4e	60	94:6
6	Me	3-MeOC ₆ H ₄	Ph	3-4f	65	96:4
7	Me	4-MeC ₆ H ₄	Ph	3-4g	71	96:4
8	Me	4-NO ₂ C ₆ H ₄	Ph	3-4h	58	97:3
9	Me	2-naphthyl	Ph	3-4i	53	95:5
10	Me	2-furanyl	Ph	3-4j	47	97:3
11	Me	2-thiophenyl	Ph	3-4k	64	98:2
12	Me	4-pyridinyl	Ph	3-4l	62	98:2
13	Me	3-pyridinyl	Ph	3-4m	60	98:2
14	Me	Ph	4-FC ₆ H ₄	3-4n	62	94:6
15	Me	3-MeOC ₆ H ₄	4-BrC ₆ H ₄	3-4o	64	95:5
16	Et	Ph	Ph	3-4p	50	97:3
17	Et	3-BrC ₆ H ₄	Ph	3-4q	68	98:2
18	Et	4-MeC ₆ H ₄	Ph	3-4r	68	98:2

19	<i>n</i> -Pr	Ph	Ph	3-4s	63	98:2
20	<i>n</i> -Pr	3-BrC ₆ H ₄	Ph	3-4t	67	98:2
21	<i>n</i> -Pr	3-MeOC ₆ H ₄	Ph	3-4u	61	99:1
22	<i>n</i> -Pr	Ph	4-FC ₆ H ₄	3-4v	68	97:3
23	<i>n</i> -Pr	3-MeOC ₆ H ₄	4-BrC ₆ H ₄	3-4w	67	97:3
24	Me	Me	Ph	-	0	-
25	Me	Ph	Et	-	0	-
26 ^[d]	Ph	Ph	Ph	3-4x	60	84:16
27 ^[d]	Ph	4-ClC ₆ H ₄	Ph	3-4y	72	87:13
28 ^[d]	4-BrC ₆ H ₄	3-BrC ₆ H ₄	Ph	3-4z	60	81:19

[a] 2 Eq of **3-1**, 1 eq of **3-2** (0.1 mmol), 20 mol% of **3-5k**, 4 eq of DMAP and 0.2 mL of solvent at 30 °C for 36 h. [b] Isolated yield. [c] Er is determined *via* chiral HPLC. [d] 2 Eq of **3-1**, 1 eq of **3-2** (0.1 mmol), 20 mol% of **3-5i**, 1 eq of K₃PO₄ and 1 mL of MTBE at rt (24 °C) for 36 h.

Having examined the scope of the benzyldiene diketone substrates, we wished to further demonstrate the generality of the present methodology with other electrophiles. Thus we went on to check this process utilizing simple chalcones as the substrates. It is worth noting that corresponding cyclopentene products have not been obtained with excellent optical purity through traditional homoenolate activation of aliphatic α,β -unsaturated aldehydes.¹¹ After a series of screening experiments, we finally obtained the desired product in good to excellent yields with high stereoselectivities (Table 3.3). It is worth noting that the product consisted of two diastereomers. This most likely resulted from the reduced steric hindrance. When an anhydride with longer aliphatic chain was applied, the dr values could be significantly improved to more than 20:1 (Table 3.4).

Table 3.3 Condition optimization of the asymmetric reaction of butyric anhydride **3-1a** and chalcone **3-6a**.^[a]

Entry	NHC	Solvent	Yield ^[b]	Er ^[c]	Dr ^[d]
1	3-5h	Cyclohexane	<10	-	-
2	3-5i	Cyclohexane	58	94:6	9:1
3	3-5i'	Cyclohexane	52	93:7	10:1

4	3-5k'	Cyclohexane	<10	ND	ND
5	3-5k	Cyclohexane	<10	ND	ND
6	3-5i	THF	12	ND	ND
7	3-5i	MeCN	3	ND	ND
8	3-5i	MTBE	27	92:8	3:1
9	3-5i	EA	17	ND	ND
10	3-5i	Toluene	26	94:6	18:1
11	3-5i	Hexane	73	91:9	7:1
12 ^[d]	3-5i	Hexane	(63)	93:7	6:1
13 ^[d,e]	3-5i	Hexane	(59)	96:4	10:1
14 ^[d,f]	3-5i	Hexane	(15)	98:2	10:1

[a] Unless otherwise noted, the reaction was carried out with 4 eq of **3-1a** (0.4 mmol), 1 eq of **3-6a** (0.1 mmol), 20 mol% of NHC (0.2 mmol), 3 eq of Cs₂CO₃ (0.3 mmol) and 1 mL of solvent (0.1 M) at 50 °C for 24 h. [b] Yield was determined by ¹H NMR, and yield in parenthesis indicated isolated yield after column chromatography. [c] Ee was determined by HPLC. [d] The reaction was carried out using 3 eq of **3-1a**. [e] At 40 °C. [f] At rt.

Table 3.4 Reaction Scope of Anhydrides and Chalcones.^[a]

[a] Unless otherwise noted, the reaction was carried out with 3 eq of **3-1** (0.3 mmol), 1 eq of **3-6** (0.1 mmol), 20 mol% of **3-5i** (0.02 mmol), 3 eq of Cs₂CO₃ (0.3 mmol) and 1 mL of solvent (0.1M) at 50 °C for 36h. Yields are isolated yields. Ers were determined via chiral HPLC of the major diastereomer. Drs were determined by ¹H NMR of crude product mixture.

N-protected isatins also represented good reactants in this process. With a sterically bulky, easily removed trityl group as the protecting group, we could obtain corresponding spiro furanones in moderate to good yields and excellent enantioselectivities (Table 3.5). Interestingly, although the ers were similar with a variety of bases, the diastereoselectivity

was apparently better when DMAP was used as the base. Under the optimized conditions, we were able to obtain a series of spiro furanones in excellent enantio- and diastereoselectivities (Table 3.6, Condition A). While isatins with electron donating substituents worked well, electron withdrawing substituents seriously decreased the product yields (Condition A, **3-9d**, **3-9e**, **3-9f**). These lower yields could be compensated by applying other catalytic conditions with some sacrificing of dr values (Condition B).

Table 3.5 Condition Optimization.^[a]

Entry	NHC	Base	Solvent	Yield	Er	Dr
1	3-5i'	DBU	THF	97	98:2 / 90:10	2:1
2	3-5j	DBU	THF	93	99:1 / 91:9	3:1
3	3-5j	DBU	DCM	68	93:7 / 87:13	2:1
4	3-5j	DBU	EE	99	99:1 / 91:9	3:1
5	3-5j	DBU	Dioxane	97	98:2 / 86:14	4:1
6	3-5j	DBU	EA	69	98:2 / 90:10	2:1
7	3-5j	DBU	Acetone	33	94:6 / 91:9	1:1
8	3-5j	DBU	MTBE	99	99:1 / 94:6	3:1
9	3-5j	DBU	ACN	26	82:18 / 85:15	1:1
10	3-5j	DBU	Toluene	79	98:2 / 90:10	3:1
11	3-5j	DMAP	Dioxane	67	99:1 / 75:25	8:1
12	3-5j	DIEA	Dioxane	99	98:2 / 84:16	5:1
13	3-5j	TEA	Dioxane	99	98:2 / 84:16	4:1
14	3-5j	K ₂ CO ₃	Dioxane	99	98:2 / 84:16	5:1
15	3-5j	Cs ₂ CO ₃	Dioxane	99	98:2 / 80:20	4:1
16	3-5j	KOAc	Dioxane	99	98:2 / 84:16	4:1
17	3-5j	KOtBu	Dioxane	99	98:2 / 83:17	5:1
18	3-5j	K ₃ PO ₄	Dioxane	99	98:2 / 83:17	5:1
19	3-5j	DABCO	Dioxane	99	98:2 / 84:16	4:1
20	3-5j	TBD	Dioxane	99	98:2 / 84:16	5:1
21 ^[e]	3-5j	DMAP	Dioxane	78	99:1 / 75:25	7:1
22 ^[e,f]	3-5j	DMAP	Dioxane	93	99:1 / 75:25	8:1
23 ^[e,f]	3-5j	DMAP	THF	91	99:1 / 71:29	8:1
24 ^[e,f]	3-5j	DMAP	DCM	67	99:1 / 69:31	4:1
25 ^[e,f]	3-5j	DMAP	EE	>99	>99:1 / 80:20	10:1
26 ^[e,f]	3-5j	DMAP	MTBE	94	>99:1 / 82:18	9:1
27 ^[e,f,g]	3-5j	DMAP	EE	96	>99:1	10:1

[a] Unless otherwise noted, the reaction was carried out with 4 eq of **3-1a** (0.4 mmol), 1 eq of **3-8a** (0.1 mmol), 10 mol% of NHC (0.2 mmol), 2 eq of base (0.2 mmol) and 2 mL of solvent (0.1 M) for 12 h. [b]

Yield was isolated yield after column chromatography. [c] Ee was determined by HPLC. [d] Dr was determined by ^1H NMR. [e] 20 Mol% of NHC was used. [f] 4 Eq of DMAP was used. [g] 3Eq of **3-1a** was used.

Table 3.6 Reaction Scope.^[a]

[a] **Condition A:** 3 eq of **3-1** (0.3 mmol), 1 eq of **3-8** (0.1 mmol), 20 mol% of **3-5j** (0.02 mmol), 4 eq of DMAP (0.4 mmol) and 2 mL of ethyl ether at 24°C for 12h. **Condition B:** 2 eq of **3-1** (0.2 mmol), 1 eq of **3-8** (0.1 mmol), 10 mol% of **3-5j** (0.01 mmol), 2 eq of DIEA (0.2 mmol) and 2 mL of dioxane at 24°C for 12h.

The chiral cyclopentene product was amenable to further transformations (Scheme 3.3). The enol ester group in the product **3-4o** could be reduced by LiAlH_4 in good yield without erosion of the er value. The resulting cyclopentene **3-10** could be epoxidized by *m*-CPBA to afford an oxabicyclo[3.1.0]hexane **3-11**, which could be easily crystallized to afford optically pure crystals.¹² Moreover, the structure of the oxabicyclo **3-11** was already recognized as the core structure in some antibiotic chemicals such as the methylenomycin A. The C=C bond in the product **3-10** could also be broken up by ozone to afford the δ -keto carboxylic acid **3-12** in good yield and excellent er as an isolable single diastereomer.

Scheme 3.3 Derivatization of Product **3-4o**.

The structures of the product **3-3**, **3-4**, **3-9** and **3-10** could be determined by X-ray analysis of the corresponding racemic crystals. The absolute configurations could be confirmed with single crystals of the optically pure product **3-11**.

3.3 Mechanistic Study.

3.3.1 Comparison of the Anhydride β -Carbon Activation with Reactions Using Enals as Substrates.

Our previous studies regarding reactions of benzylidene diketone with α,β -unsaturated aldehydes are summarized in Scheme 3.4.

Scheme 3.4 Our Previous Works Using Cinnamylaldehydes and Benzylidene Diketone.

The reaction of the benzylidene diketone with cinnamaldehyde afforded an enolate product in excellent yield and ee value (eq 1). On the other hand, the reaction of an alkyl enal under similar conditions afforded the Stetter product as the main product (eq 3). The corresponding enolate product could only be obtained in its racemic form when using imidazolium NHC precursor (eq 2). Stetter products of cinnamaldehyde could be obtained in lower yield in toluene at 0 °C (eq 4).

Based on the experimental results of our current work, we chose the catalytic condition from which the best yield of the formal homoenolate product was obtained for further investigation (eq 5).

When crotonaldehyde was applied under the same catalytic conditions in eq 6, the Stetter product was still dominant, along with a small amount of the enolate product without any of the homoenolate product.

When butyric anhydride was applied under catalytic conditions in eq 3 (under which Stetter product was formed in high yield with crotonaldehyde), the homoenolate product was the dominant product among all possible products assumed (in about 10% yield while

most of the benzylidene diketone remained).

The above results illustrate that different reaction pathways can operate under similar reaction conditions (eq 3, 5, 6, 7). One of the main differences between reactions (3), (6) and (5), (7) was the enolization-acylation process. Therefore, we assume that the driving force of the enolization-acylation process would be one of the reasons towards the formation of the formal homoenolate product, as shown below:

We assume the enolization-acylation process happening right after the Michael addition (8) rather than happening during the decarboxylation process (9). Several experimental results would partially support this assumption:

1) Although numerous reaction conditions were tested, the desired final product could not be obtained from the starting material in eq 10.

2) The desired final product could not be obtained from the starting material in eq 11 either, even after great efforts made.

Therefore, we proposed the reaction pathway described Scheme 3.5:

Butyric anhydride **3-1a** first reacts with the NHC catalyst to form the NHC-bound ester

intermediate **I** that undergoes α -CH deprotonation to form the enolate intermediate **II**. A subsequent deprotonation/ proton transfer process of **II** involving the formal anhydride β -carbon forms the key intermediate **III** bearing a reactive nucleophilic β -carbon. Michael adduct of the intermediate **III** with the electrophile **3-2a** could isomerize to the corresponding enolate **IV**, which would be esterified by another anhydride **3-1a** or **I** under the current catalytic conditions to form the intermediate **V**. The intermediate **V** would then go through an intramolecular aldol reaction followed by a lactone formation to form intermediate **VII**, which would easily be decarboxylated to afford the final product **3-4a**.

3.3.2 Comparison of the β -Activation of Anhydride and Ester.

Different electrophiles (esters and anhydrides) were tested with chalcone as the model nucleophile under different reaction conditions.

To probe the strengths and limitations of our earlier ester approach and the present anhydride approach, we systematically compared the two reaction systems. A part of the results is summarized in Table 3.6. The condition (Condition #1) optimal for β -alkyl anhydride (Entry 1) did not work well for β -aryl anhydride or esters with β -alkyl and aryl substituents (Entries 2-4). Similarly, the condition (Condition #2) optimal for β -aryl ester (Entry 8) did not work well for β -alkyl ester or anhydrides with β -alkyl or aryl substituents (Entries 5-7). The mechanistic origins accounting for the distinctions are rather complicated and are under investigation. Our preliminary studies at this point suggested that the anions (4-nitrophenolate and alkylcarboxylate) released from addition of carbene catalyst to the substrates could affect multiple steps during the reaction.

The results showed that ester substrate with either aliphatic or aromatic substituent on the β -carbon would not afford the corresponding products under the “anhydride conditions (Condition #1)” (Entries 2, 5). On the other hand, anhydride substrate with

either aliphatic or aromatic substituent on the β -carbon would not afford the corresponding products under the “ester conditions (Condition #2)” (Entries 8, 11).

As butyric acid is afforded in the anhydride reactions, we use butyric acid as the additive in Condition #1 for ester substrates. But still there is no improvement in the product yield (Entries 3, 6).

Table 3.6 Differences between Anhydride and Ester Approach.^[a]

Entry	Reaction (Substrate)	Acidic additives	Condition	yield [%] ^[a]
1	3-1a (0.3 mmol)	-	#1	59 (10:1)
2	3-13a (0.3 mmol)	-	#1	4
3	3-13a (0.3 mmol)	Butyric acid (1.5 eq)	#1	3
4	3-1d (0.3 mmol)	-	#1	6
5	3-13b (0.3 mmol)	-	#1	0
6	3-13b (0.3 mmol)	Butyric acid (1.5 eq)	#1	0
7	3-13b + 3-1a (each 0.3 mmol)	-	#1	1 (for 3-13b) + 25 (for 3-1a , 8:1)
8	3-1a (0.2 mmol)	-	#2	7
9	3-1a (0.2 mmol)	4-Nitrophenol (1.5 eq)	#2	3
10	3-13a (0.2 mmol)	-	#2	18 (>20:1)
11	3-1d (0.2 mmol)	-	#2	5
12	3-1d (0.2 mmol)	4-Nitrophenol (1.5 eq)	#2	21 (4:1)
13	3-13b (0.2 mmol)	-	#2	66 (7:1)
14	3-13b + 3-1a (each 0.2 mmol)	-	#2	0 (for 3-13b) + 2 (for 3-1a)

[a] Yield of product **3-7a**, determined by ¹H NMR. Dr ratios are shown within parenthese

Similarly, 4-nitrophenol is used as the acidic additives in Condition #2 for anhydride substrates. While there is still no improvement in product yield for alkyl substrate **3-1a** (Entry 9), we observed a significant increase in product yield for aryl substrate **3-1d** (Entry 12 vs 11).

Mixing ester and anhydride substrates in both conditions for competing experiment, we observed significant drop in the product yields for both the substrates (Entries 7, 14).

From the above comparing experiments we could see obvious distinctions between the anhydride and ester β -activation systems. The anhydride reaction needs to be proceeded in non-polar system while the polarity of the ester activation system was higher. The reasons for this phenomenon would be too complex for us to explain at this stage. Multiple factors including concentration, solvent, base and even molecular sieves have serious effects on the product yields. At present we could only summarize some empirical rules for both catalytic pathways, as stated above.

3.3.3 Chiral Induction.

Based on literature works and the absolute structure of our product, we proposed the chiral induction pathway, which is illustrated in Scheme 3.6.

Scheme 3.6 Proposed Chiral Induction.

3.4 Summary.

In summary, we have developed the first β -activation of simple aliphatic anhydride, which would be an important constitution of the NHC catalyzed β -activation of saturated carbonyl compounds. Moreover, the resulting chiral molecules could not be effectively prepared through existing homoenolate process with α,β -unsaturated aldehydes. We hope this methodology could provide an alternative method for the inert C-H bond activation in organic synthesis.

3.5 Experimental Section

3.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (300 or 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); 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.r.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer. 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.

3.4.2 General Procedures.

Synthesis of NHC Precursor 3-5j.

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 (4 M in dioxane, 0.5 mL) was added. The solution was stirred at 60°C for 48h 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 6h. 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 **3-5j** as a white powder (29% yield based on **S1**).

Synthesis of NHC Precursor 3-5k.

To a 250 mL round bottom flask equipped with a magnetic stir bar was added **S1** (10 mmol), **S4** (10 mmol), and MeOH (40 mL). The mixture was stirred at rt for 10 min and

then HCl (4M in dioxane, 0.25 mL, 1 mmol) was added. The solution was stirred at 60°C for 48h and then concentrated and dried under vacuum. To the dried residue was added HC(OEt)₃ (80 mL), HCl (4M in dioxane, 6 mL), PhCl (50 mL) and the system was sealed and stirred vigorously at 120°C for 36h. Then the clear dark solution was concentrated. After dried under high vacuum, the residue was treated with EtOAc (50 mL) and filtered to afford the pure NHC catalyst **3-5k** as pink powder (35% yield based on **S1**).

General Procedure for the Synthesis of Substrate 3-2.

To a 25 mL Schlenk tube equipped with a magnetic stir bar was added **S6** (1 mmol), **S7** (1 mmol), toluene (5 mL), pyridine (0.2 mmol) and AcOH (0.2 mmol). The tube was closed with a septum and the reaction mixture was stirred for 12h at 110°C. Then the reaction mixture was directly subjected to column chromatography using hexane/EtOAc = 10/1 as eluent to yield the desired product **3-2d** as a white solid.

General Procedure for the Synthesis of Anhydride 3-1e.

To a 50 mL round bottom flask equipped with a magnetic stir bar was added **S8** (10 mmol), DCC (5 mmol) and DCM (20 mmol). The reaction mixture was stirred for 12h at rt. Then the reaction mixture was filtered and the filtrate was collected and washed with saturated aqueous Na₂CO₃ solution and brine. After dried with Na₂SO₄, the solution was concentrated to afford the crude product **3-1e**. Crude product **3-1e** was then re-crystallized by n-hexane to afford pure **3-1e** as a white solid.

General Procedure for the Asymmetric Reaction of Aliphatic Anhydride **3-1a** and Benzyldiene Diketone **3-2a**.

To a 10 mL Schlenk tube equipped with a magnetic stir bar was added **3-2a** (0.1 mmol), NHC precursor **3-5k** (0.02 mmol), and DMAP (0.4 mmol). The tube was closed with a septum, evacuated and refilled with nitrogen ($\times 3$ cycles). Cyclohexane (0.2 mL) and butyric anhydride **3-1a** (0.2 mmol) were added and the reaction mixture was stirred for 36 h at 30°C. Then the reaction mixture was directly subjected to column chromatography using hexane/EtOAc = 30/1 as eluent to yield the desired product **3-4a** in 62% yield as a colorless oil.

General Procedure for the Asymmetric Reaction of Phenyl Propionic Anhydride **3-1d** and Benzyldiene Diketone **3-2a**.

To a 10 mL Schlenk tube equipped with a magnetic stir bar was added **3-2a** (0.1 mmol), NHC precursor **3-5i** (0.02 mmol), and K_3PO_4 (0.1 mmol). The tube was closed with a septum, evacuated and refilled with nitrogen ($\times 3$ cycles). A solution of phenyl propionic anhydride **3-1d** (0.2 mmol) in MTBE (1 mL) was added and the reaction mixture was stirred for 36 h at room temperature. Then the reaction mixture was concentrated and the residue was directly subjected to column chromatography using hexane/EtOAc = 30/1 as eluent to yield the desired product **3-4x** in 60% yield as a reddish oil.

General Procedure for the Asymmetric Reaction of Aliphatic Anhydride **3-1a** and Chalcone **3-6a**.

To a 10 mL Schlenk tube equipped with a magnetic stir bar was added **3-6a** (0.1 mmol), NHC precursor **3-5i** (0.02 mmol), and Cs_2CO_3 (0.3 mmol). The tube was closed with a septum, evacuated and refilled with nitrogen ($\times 3$ cycles). Hexane (1 mL) and butyric anhydride **3-1a** (0.3 mmol) were added and the reaction mixture was stirred for 36 h at 50°C . Then the reaction mixture was directly subjected to column chromatography using hexane/EtOAc = 100/1 as eluent to yield the desired product **3-7a** in 59% yield as a colorless oil.

General Procedure for the Asymmetric Reaction of Aliphatic Anhydride **3-1a** and Protected Isatin **3-8a**.

Condition A: To a 4 mL vial equipped with a magnetic stir bar was added **3-8a** (0.1 mmol), NHC precursor **3-5j** (0.02 mmol), DMAP (0.4 mmol), ethyl ether (2 mL) and butyric anhydride **3-1a** (0.3 mmol). Then the reaction mixture was stirred at rt for 12h. The reaction mixture was then concentrated and subjected to column chromatography using hexane/EtOAc = 7/1 as eluent to yield the desired product **3-9a** in 96% yield as a white solid.

Condition B: To a 4 mL vial equipped with a magnetic stir bar was added **3-8d** (0.1 mmol), NHC precursor **3-5j** (0.01 mmol), DIEA (0.2 mmol), dioxane (2 mL) and butyric anhydride **3-1a** (0.2 mmol). Then the reaction mixture was stirred at rt for 12h. The reaction mixture was then concentrated and subjected to column chromatography using hexane/EtOAc = 7/1 as eluent to yield the desired product **3-9d** in 74% yield as a yellow oil.

Reduction of 3-4o.

To a stirred suspension of LiAlH_4 (0.3 mmol) in dry ethyl ether (3 mL) was added **3-4o** (0.1 mmol) in one portion. The mixture was stirred under N_2 for 12h at room temperature. Water was then added to quench the reaction and the mixture was filtered. The filtrate was separated and extracted with ethyl ether for 3 times. The collected organic phase was dried and concentrated and then purified by column chromatography using hexane/EtOAc = 10/1 as eluent to yield the product **3-10** in 71% yield.

Epoxidation of 3-10.

To a stirred solution of **3-10** (0.1 mmol) in DCM (2mL) was added m-CPBA (50%, 0.12mmol) in one portion and the mixture was stirred at rt for 12h. Then the mixture was concentrated and subject to column chromatography using hexane/EtOAc = 10/1 as eluent to yield the product **3-11** in 73% yield.

C=C Breaking of **3-10**.

To a solution of **3-10** (1 mmol) in DCM (10mL) was bubbled O₃ at -78°C until the solution became light blue. Then Et₃N (0.5 mL) was added in one portion to quench the reaction and the solution was stirred at room temperature for 1h. The solution was acidified by 1N aqueous HCl and then extracted by DCM for 5 times. The collected organic phase was then concentrated and purified by column chromatography using hexane/EtOAc = 2/1 as eluent to yield the product **3-12** in 85% yield.

4.4.3 Stereochemistry Determination via X-Ray Crystallographic Analysis.

Relative configurations of the product **3-4** were assigned based on the crystal X-ray structures of **3-4z**. CCDC 995782 (**3-4z**, obtained as colorless needles *via* evaporation of a EtOH/CH₂Cl₂ solution) contains the supplementary X-ray crystallographic data.

Relative configurations of the products **3-9** were assigned based on the crystal X-ray

structures of **3-9g**. CCDC 995785 (**3-9g**, obtained as colorless particles *via* evaporation of a EtOAc/CH₂Cl₂ solution) contains the supplementary X-ray crystallographic data.

Relative configuration of the product **3-10** was assigned based on the crystal X-ray structures of **3-10**. CCDC 995783 (**3-10**, obtained as colorless needles *via* evaporation of a EtOH/CH₂Cl₂ solution) contains the supplementary X-ray crystallographic data.

Absolute configuration of the product **3-11** was assigned based on the single crystal X-ray structures of **3-11**. CCDC 995784 (**3-11**, obtained as colorless needles *via* evaporation of a MeOH/CH₂Cl₂ solution) contains the supplementary X-ray crystallographic data.

3.4.4 Characterization of Catalysts, Substrates, and Products.

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

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); ¹³C 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 C₂₂H₂₄N₃O⁺ 346.1914, found 346.1915.

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

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.

2-(3-fluorobenzylidene)-1,3-diphenylpropane-1,3-dione (3-2d)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.97-7.94 (m, 2H), 7.89-7.87 (m, 2H), 7.61-7.39 (m, 7H), 7.24-7.18 (m, 1H), 7.13-7.11 (m, 1H), 7.05-7.02 (m, 1H), 7.00-6.95 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.3, 194.5, 163.8, 161.3, 141.9, 141.9, 140.8, 137.1, 136.2, 135.3, 135.2, 134.1, 132.8, 130.4, 130.3, 129.6, 129.4, 128.9, 128.6, 125.8, 125.7, 117.4, 117.1, 116.6, 116.4; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{16}\text{FO}_2^+$ 331.1129, found 331.1131.

1,3-diphenyl-2-(pyridin-4-ylmethylene)propane-1,3-dione (3-2l)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 8.51 (d, J = 5.9 Hz, 2H), 7.93 (dd, J = 12.5,

7.7 Hz, 4H), 7.63-7.38 (m, 7H), 7.18 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.4, 193.8, 150.4, 143.7, 140.6, 139.3, 136.5, 135.9, 134.4, 133.3, 129.7, 129.5, 129.0, 128.7, 123.3; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{NO}_2^+$ 314.1176, found 314.1172.

1,3-diphenyl-2-(pyridin-3-ylmethylene)propane-1,3-dione (3-2m)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.58 (d, $J = 2.0$ Hz, 1H), 8.49 (dd, $J = 4.8$, 1.3 Hz, 1H), 7.97-7.95 (m, 2H), 7.90-7.88 (m, 2H), 7.66-7.40 (m, 8H), 7.16 (dd, $J = 8.0$, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.0, 194.1, 151.1, 150.9, 141.9, 139.4, 136.9, 136.1, 136.0, 134.3, 133.0, 129.6, 129.5, 129.2, 129.0, 128.8, 128.7, 123.5; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{NO}_2^+$ 314.1176, found 314.1178.

3-(4-bromophenyl)propanoic anhydride (3-1e)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.42 (d, $J = 8.3$ Hz, 4H), 7.07 (d, $J = 8.3$ Hz, 4H), 2.91 (t, $J = 7.5$ Hz, 4H), 2.71 (t, $J = 7.6$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.2, 138.5, 131.7, 130.1, 120.4, 36.6, 29.6; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{17}\text{Br}_2\text{O}_3^+$ 438.9539, found 438.9542.

(*E*)-((4*R*,5*R*)-4-methyl-2,5-diphenylcyclopent-2-en-1-ylidene)(phenyl)methyl

butyrate (3-4a)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.28 (m, 4H), 7.24-7.19 (m, 1H), 6.98-6.88 (m, 8H), 6.85-6.81 (m, 2H), 6.13 (d, $J = 2.7$ Hz, 1H), 3.75 (d, $J = 3.2$ Hz, 1H), 2.89-2.82 (m, 1H), 2.00-1.87 (m, 2H), 1.48-1.33 (m, 2H), 1.27 (d, $J = 7.0$ Hz, 3H), 0.81 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 144.8, 143.9, 142.6, 141.4, 136.4, 136.3, 135.2, 129.0, 128.4, 127.8, 127.4, 127.2, 127.1, 126.8, 126.4, 126.2, 58.7, 49.4, 35.5, 20.2, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{29}\text{O}_2^+$ 409.2162, found 409.2167; $[\alpha]_D^{20} = -30$ ($c = 3.2$ in CHCl_3); HPLC analysis: 95:5 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.4 min, R_t (major) = 6.8 min.

(*E*)-((4*R*,5*R*)-5-(3-bromophenyl)-4-methyl-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4b)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (t, $J = 1.7$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 6.8$ Hz, 1H), 7.19 (d, $J = 7.7$ Hz, 1H), 6.96-6.88 (m, 8H), 6.85-6.81 (m, 2H), 6.12 (d, $J = 2.7$ Hz, 1H), 3.70 (d, $J = 3.0$ Hz, 1H), 2.87-2.81 (m, 1H), 2.05-1.96 (m, 2H), 1.50-1.41 (m, 2H), 1.27 (d, $J = 7.0$ Hz, 3H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 147.2, 143.7, 142.6, 141.8, 136.0, 134.9, 130.4, 130.2, 129.3, 129.0, 127.8, 127.5, 127.3, 126.9, 126.5, 125.6, 122.3, 58.1, 49.2, 35.6, 20.2, 18.0, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{28}\text{BrO}_2^+$ 487.1267, found 487.1272; $[\alpha]_D^{20} = -19.6$ ($c = 3.3$ in CHCl_3); HPLC analysis: 97:3 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.6 min, R_t (major) = 8.4 min.

(*E*)-((4*R*,5*S*)-5-(2-chlorophenyl)-4-methyl-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4c)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.38 (dd, $J = 1.2, 7.8$ Hz, 1H), 7.35 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.21 (td, $J = 1.2, 7.4$ Hz, 1H), 7.15 (td, $J = 1.8, 7.7$ Hz, 1H), 6.99-6.92 (m, 8H), 6.86-6.82 (m, 2H), 6.13 (d, $J = 2.8$ Hz, 1H), 4.31 (d, $J = 1.6$ Hz, 1H), 2.82-2.80 (m, 1H), 2.15-1.98 (m, 2H), 1.48-1.35 (m, 2H), 1.37 (d, $J = 7.0$ Hz, 3H), 0.80 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 144.0, 142.6, 142.4, 141.8, 136.0, 135.9, 135.0, 133.2, 130.4, 129.3, 129.0, 128.4, 127.8, 127.5, 127.3, 127.3, 127.2, 126.9, 126.5, 54.0, 48.5, 35.6, 20.8, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{28}\text{ClO}_2^+$ 443.1772, found 443.1780; $[\alpha]_D^{20} = 10$ ($c = 3.8$ in CHCl_3); HPLC analysis: 98:2 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.3 min, R_t (major) = 7.4 min.

(*E*)-((4*R*,5*R*)-5-(3-fluorophenyl)-4-methyl-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4d)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.24 (m, 1H), 7.10 (d, $J = 7.7$ Hz, 1H), 7.02 (td, $J = 1.9, 10.2$ Hz, 1H), 6.98-6.89 (m, 9H), 6.86-6.82 (m, 2H), 6.12 (d, $J = 2.7$ Hz, 1H), 3.74 (d, $J = 2.9$ Hz, 1H), 2.87-2.80 (m, 1H), 2.07-1.94 (m, 2H), 1.51-1.37 (m, 2H), 1.28 (d, $J = 7.0$ Hz, 3H), 0.83 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1,

164.2, 147.6, 147.5, 143.7, 142.6, 141.8, 136.0, 135.0, 129.9, 129.8, 129.0, 127.8, 127.5, 127.3, 126.9, 126.5, 122.7, 114.0, 113.8, 113.1, 112.9, 58.1, 49.2, 35.6, 20.3, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $C_{29}H_{28}FO_2^+$ 427.2068, found 427.2072; $[\alpha]^{20}_D = -30$ ($c = 3.0$ in $CHCl_3$); HPLC analysis: 96:4 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.5 min, R_t (major) = 7.4 min.

(*E*)-((4*R*,5*R*)-5-(4-fluorophenyl)-4-methyl-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4e)

Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.10-6.88 (m, 10H), 6.85-6.81 (m, 2H), 6.12 (d, $J = 2.7$ Hz, 1H), 3.74 (d, $J = 3.0$ Hz, 1H), 2.83-2.77 (m, 1H), 2.04-1.91 (m, 2H), 1.50-1.38 (m, 2H), 1.26 (d, $J = 7.0$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 143.7, 142.6, 141.6, 140.6, 136.3, 136.1, 135.1, 129.0, 128.5, 128.4, 127.8, 127.5, 127.3, 126.9, 126.4, 122.7, 115.3, 115.1, 57.8, 49.5, 35.6, 20.2, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $C_{29}H_{28}FO_2^+$ 427.2068, found 427.2078; $[\alpha]^{20}_D = -32$ ($c = 2.5$ in $CHCl_3$); HPLC analysis: 94:6 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.4 min, R_t (major) = 7.2 min.

(*E*)-((4*R*,5*R*)-5-(3-methoxyphenyl)-4-methyl-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4f)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.22 (t, $J = 14.4$ Hz, 1H), 6.97-6.75 (m, 13H), 6.13 (d, $J = 2.5$ Hz, 1H), 3.80 (s, 3H), 3.72 (d, $J = 4.3$ Hz, 1H), 2.88-2.83 (m, 1H), 2.05-1.93 (m, 2H), 1.48-1.38 (m, 2H), 1.27 (d, $J = 7.0$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 159.7, 146.5, 143.9, 142.6, 141.5, 136.3, 136.2, 135.2, 129.4, 129.0, 128.7, 127.8, 127.4, 127.2, 126.8, 126.4, 119.6, 112.9, 111.4, 58.6, 55.1, 49.3, 35.5, 20.3, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{31}\text{O}_3^+$ 439.2268, found 439.2266; $[\alpha]^{20}_{\text{D}} = -31$ ($c = 2.1$ in CHCl_3); HPLC analysis: 96:4 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 7.3 min, R_t (major) = 8.3 min.

(*E*)-((4*R*,5*R*)-4-methyl-2-phenyl-5-(*p*-tolyl)cyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4g)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.21 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 7.9$ Hz, 2H), 6.97-6.80 (m, 10H), 6.13 (d, $J = 2.7$ Hz, 1H), 3.71 (d, $J = 3.0$ Hz, 1H), 2.86-2.79 (m, 1H), 2.33 (s, 3H), 2.01-1.89 (m, 2H), 1.47-1.36 (m, 2H), 1.26 (d, $J = 7.0$ Hz, 3H), 0.81 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 144.0, 142.6, 141.8, 141.3, 136.6, 136.3, 135.6, 135.3, 129.1, 129.0, 128.7, 127.8, 127.3, 127.2, 127.0, 126.8, 126.3, 113.8, 58.3, 49.5, 35.5, 21.1, 20.2, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{31}\text{O}_2^+$ 423.2319, found 423.2325; $[\alpha]^{20}_{\text{D}} = -32$ ($c = 2.3$ in CHCl_3); HPLC analysis: 96:4 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.0 min, R_t (major) = 7.0 min.

(E)-((4R,5R)-4-methyl-5-(4-nitrophenyl)-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4h)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 8.11-8.09 (m, 1H), 7.67 (d, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 6.99-6.82 (m, 10H), 6.16 (d, $J = 2.7$ Hz, 1H), 3.86 (d, $J = 2.5$ Hz, 1H), 2.87-2.82 (m, 1H), 2.09-1.96 (m, 2H), 1.48-1.38 (m, 2H), 1.32 (d, $J = 7.0$ Hz, 3H), 0.81 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.0, 148.3, 147.1, 143.4, 142.6, 142.4, 135.7, 135.6, 134.6, 133.1, 129.5, 129.0, 127.8, 127.3, 127.0, 126.6, 122.2, 121.4, 57.6, 49.1, 35.7, 20.5, 18.0, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{28}\text{NO}_4^+$ 454.2013, found 454.2014; $[\alpha]_D^{20} = 59$ ($c = 1.8$ in CHCl_3); HPLC analysis: 97:3 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 10.4 min, R_t (major) = 16.6 min.

(E)-((4R,5R)-4-methyl-5-(naphthalen-2-yl)-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4i)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.81-7.79 (m, 3H), 7.71 (s, 1H), 7.51-7.41 (m, 3H), 6.99-6.90 (m, 8H), 6.86-6.81 (m, 2H), 6.18 (d, $J = 2.6$ Hz, 1H), 3.92 (d, $J = 3.3$ Hz, 1H), 2.98-2.92 (m, 1H), 1.85-1.71 (m, 2H), 1.30 (d, $J = 7.0$ Hz, 3H), 1.31-1.14 (m, 2H), 0.64 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 144.0, 142.8, 142.1,

141.6, 136.4, 136.3, 135.2, 133.5, 132.3, 129.0, 128.4, 127.9, 127.7, 127.5, 127.4, 127.3, 127.2, 126.9, 126.4, 126.0, 125.7, 125.5, 125.2, 59.0, 49.2, 35.4, 20.1, 17.7, 13.4; HRMS (ESI, m/z): calcd. for $C_{33}H_{31}O_2^+$ 459.2319, found 459.2323; $[\alpha]^{20}_D = -20$ ($c = 2.6$ in $CHCl_3$); HPLC analysis: 95:5 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 7.4 min, R_t (major) = 9.5 min.

(*E*)-((4*R*,5*S*)-5-(furan-2-yl)-4-methyl-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4j)

Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.96-6.82 (m, 10H), 6.31 (dd, $J = 3.0, 2.0$ Hz, 1H), 6.13 (d, $J = 3.1$ Hz, 1H), 6.11 (d, $J = 2.7$ Hz, 1H), 3.86 (d, $J = 3.3$ Hz, 1H), 3.07-3.02 (m, 1H), 2.17 (td, $J = 7.6, 3.3$ Hz, 2H), 1.60-1.50 (m, 2H), 1.26 (d, $J = 7.0$ Hz, 3H), 0.88 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 156.4, 143.3, 142.1, 141.6, 141.1, 136.0, 135.0, 133.7, 129.0, 127.8, 127.5, 127.2, 126.9, 126.4, 110.1, 104.9, 51.7, 45.6, 35.8, 20.0, 18.1, 13.7; HRMS (ESI, m/z): calcd. for $C_{27}H_{27}O_3^+$ 399.1955, found 399.1959; $[\alpha]^{20}_D = 9$ ($c = 3.2$ in $CHCl_3$); HPLC analysis: 97:3 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.5 min, R_t (major) = 7.0 min.

(*E*)-((4*R*,5*S*)-4-methyl-2-phenyl-5-(thiophen-2-yl)cyclopent-2-en-1-ylidene)(phenyl)methyl butyrate

ylidene)(phenyl)methyl butyrate (3-4k)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.13 (t, $J = 3.2$ Hz, 1H), 6.95-6.82 (m, 12H), 6.17 (d, $J = 2.8$ Hz, 1H), 4.02 (d, $J = 2.0$ Hz, 1H), 2.98-2.92 (m, 1H), 2.20 (t, $J = 7.3$ Hz, 2H), 1.60-1.51 (m, 2H), 1.29 (d, $J = 7.0$ Hz, 3H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 148.0, 143.1, 142.0, 141.9, 135.9, 135.9, 134.9, 129.0, 127.8, 127.6, 127.3, 126.9, 126.5, 126.3, 123.2, 122.9, 53.3, 49.5, 35.8, 20.2, 18.1, 13.7; HRMS (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{27}\text{O}_2\text{S}^+$ 415.1726, found 415.1733; $[\alpha]^{20}_{\text{D}} = 112$ ($c = 2.2$ in CHCl_3); HPLC analysis: 98:2 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.8 min, R_t (major) = 7.5 min.

(E)-((4R,5R)-4-methyl-2-phenyl-5-(pyridin-4-yl)cyclopent-2-en-1-**ylidene)(phenyl)methyl butyrate (3-4l)**

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.54 (d, $J = 5.7$ Hz, 2H), 7.25 (d, $J = 5.9$ Hz, 2H), 6.99-6.83 (m, 10H), 6.13 (d, $J = 2.6$ Hz, 1H), 3.73 (d, $J = 2.7$ Hz, 1H), 2.85-2.78 (m, 1H), 2.03-1.98 (m, 2H), 1.48-1.38 (m, 2H), 1.30 (d, $J = 7.0$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 153.6, 145.0, 143.4, 142.6, 142.1, 135.7, 135.0, 134.7, 128.9, 127.8, 127.7, 127.3, 127.0, 122.4, 57.5, 48.8, 35.6, 20.4, 18.0, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{28}\text{NO}_2^+$ 410.2115, found 410.2121; $[\alpha]^{20}_{\text{D}} = -3$ ($c = 2.1$ in CHCl_3); HPLC analysis: 98:2 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 6.2 min, R_t (major) = 7.7 min.

(*E*)-((4*R*,5*R*)-4-methyl-2-phenyl-5-(pyridin-3-yl)cyclopent-2-en-1-ylidene)(phenyl)methyl butyrate (3-4m)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.58 (d, $J = 1.6$ Hz, 2H), 8.49 (dd, $J = 4.6$, 1.0 Hz, 2H), 7.65 (d, $J = 7.9$ Hz, 1H), 7.24 (dd, $J = 7.8$, 3.0 Hz, 1H), 6.98-6.82 (m, 10H), 6.15 (d, $J = 2.6$ Hz, 1H), 3.77 (d, $J = 2.6$ Hz, 1H), 2.86-2.80 (m, 1H), 2.08-1.94 (m, 2H), 1.48-1.38 (m, 2H), 1.30 (d, $J = 7.0$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 148.9, 147.8, 143.5, 142.6, 142.0, 140.3, 135.8, 135.6, 134.8, 134.1, 128.9, 127.8, 127.6, 127.3, 126.9, 126.6, 123.7, 55.5, 49.1, 35.7, 20.3, 18.0, 13.6; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{28}\text{NO}_2^+$ 410.2115, found 410.2122; $[\alpha]_D^{20} = -27$ ($c = 1.9$ in CHCl_3); HPLC analysis: 98:2 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 5.7 min, R_t (major) = 7.3 min.

(*E*)-((4*R*,5*R*)-2-(4-fluorophenyl)-4-methyl-5-phenylcyclopent-2-en-1-ylidene)methyl butyrate (3-4n)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.28 (m, 4H), 7.24-7.20 (m, 1H), 6.92-6.86 (m, 4H), 6.65 (t, $J = 8.7$ Hz, 2H), 6.57 (t, $J = 8.7$ Hz, 2H), 6.11 (d, $J = 2.7$ Hz, 1H), 3.72 (d, $J = 3.2$ Hz, 1H), 2.88-2.81 (m, 1H), 1.98-1.85 (m, 2H), 1.44-1.34 (m, 2H), 1.26 (d, $J = 7.0$ Hz, 3H), 0.80 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 162.9, 160.8, 160.4, 144.5, 144.2, 141.3, 140.4, 136.9, 132.2, 132.2, 131.4, 130.9, 130.8, 129.5,

129.4, 128.5, 127.1, 126.3, 114.3, 114.1, 114.1, 113.8, 58.5, 49.4, 35.4, 26.9, 20.1, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $C_{29}H_{27}F_2O_2^+$ 445.1974, found 445.1944; $[\alpha]^{20}_D = -37$ ($c = 2.6$ in $CHCl_3$); HPLC analysis: 94:6 er (Chiralcel IA, Hexane/2-PrOH = 99.5/0.5, 0.7 mL/min), R_t (major) = 11.4 min, R_t (minor) = 11.8 min.

(*E*)-((4*R*,5*R*)-2-(4-bromophenyl)-5-(3-methoxyphenyl)-4-methylcyclopent-2-en-1-ylidene)methyl butyrate (3-4o)

Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, $J = 7.8$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 7.7$ Hz, 1H), 6.82 (t, $J = 1.4$ Hz, 1H), 6.78-6.73 (m, 5H), 6.29 (d, $J = 2.6$ Hz, 1H), 3.79 (s, 3H), 3.69 (d, $J = 3.1$ Hz, 1H), 2.88-2.82 (m, 1H), 2.02-1.87 (m, 2H), 1.45-1.34 (m, 2H), 1.25 (d, $J = 7.0$ Hz, 3H), 0.80 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.7, 145.9, 144.7, 141.2, 140.4, 137.1, 135.0, 134.1, 130.5, 130.2, 129.5, 122.0, 120.6, 119.6, 113.0, 111.3, 58.4, 55.1, 49.5, 35.4, 20.1, 17.9, 13.6; HRMS (ESI, m/z): calcd. for $C_{30}H_{29}Br_2O_3^+$ 595.0478, found 595.0477; $[\alpha]^{20}_D = -4$ ($c = 3.5$ in $CHCl_3$); HPLC analysis: 95:5 er (Chiralcel IA, Hexane/2-PrOH = 99.5/0.5, 0.7 mL/min), R_t (major) = 15.5 min, R_t (minor) = 16.3 min.

(*E*)-((4*R*,5*R*)-4-ethyl-2,5-diphenylcyclopent-2-en-1-ylidene)(phenyl)methyl pentanoate (3-4p)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.28 (m, 4H), 7.24-7.19 (m, 1H), 6.97-6.90 (m, 8H), 6.85-6.81 (m, 2H), 6.21 (d, $J = 2.8$ Hz, 1H), 3.84 (d, $J = 2.4$ Hz, 1H), 2.73-2.68 (m, 1H), 2.12-1.98 (m, 2H), 1.75-1.59 (m, 2H), 1.45-1.32 (m, 2H), 1.26-1.16 (m, 2H), 1.04 (t, $J = 7.3$ Hz, 3H), 0.83 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 145.4, 143.3, 142.2, 141.5, 136.6, 136.3, 135.2, 129.0, 128.5, 127.8, 127.4, 127.2, 127.0, 126.8, 126.4, 126.1, 56.2, 55.9, 33.5, 28.2, 26.6, 22.2, 13.7, 11.8; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{33}\text{O}_2^+$ 437.2475, found 437.2481; $[\alpha]^{20}_{\text{D}} = 96$ ($c = 2.2$ in CH_2Cl_2); HPLC analysis: 97:3 er (Chiralcel AD-H, Hexane/2-PrOH = 99.5/0.5, 0.7 mL/min), R_t (major) = 10.2 min, R_t (minor) = 11.0 min.

(*E*)-((4*R*,5*R*)-5-(3-bromophenyl)-4-ethyl-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl pentanoate (3-4q)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.43 (t, $J = 1.7$ Hz, 1H), 7.43 (m, 1H), 7.24 (dt, $J = 1.3, 7.6$ Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 6.98-6.88 (m, 8H), 6.85-6.81 (m, 2H), 6.20 (d, $J = 2.8$ Hz, 1H), 3.79 (d, $J = 2.4$ Hz, 1H), 2.71-2.67 (m, 1H), 2.17-2.04 (m, 2H), 1.75-1.57 (m, 2H), 1.47-1.38 (m, 2H), 1.29-1.20 (m, 2H), 1.04 (t, $J = 7.3$ Hz, 3H), 0.86 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 147.8, 143.3, 142.0, 141.9, 136.1, 136.0, 134.9, 130.3, 130.2, 129.2, 129.0, 128.1, 127.8, 127.6, 127.3, 126.9, 126.5, 125.5, 122.4, 56.0, 55.4, 33.6, 29.7, 28.2, 26.6, 22.2, 13.7, 11.8; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{32}\text{BrO}_2^+$ 517.1560, found 517.1557; $[\alpha]^{20}_{\text{D}} = 80$ ($c = 3.5$ in CH_2Cl_2); HPLC analysis: 98:2 er (Chiralcel IB, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 5.8 min, R_t (major) = 7.0 min.

(*E*)-((4*R*,5*R*)-4-ethyl-2-phenyl-5-(*p*-tolyl)cyclopent-2-en-1-ylidene)(phenyl)methyl pentanoate (3-4r)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.19 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 7.8$ Hz, 2H), 6.96-6.89 (m, 8H), 6.84-6.81 (m, 2H), 6.21 (d, $J = 2.8$ Hz, 1H), 3.80 (d, $J = 2.3$ Hz, 1H), 2.70-2.65 (m, 1H), 2.33 (s, 3H), 2.14-2.00 (m, 2H), 1.73-1.58 (m, 2H), 1.45-1.32 (m, 2H), 1.26-1.17 (m, 2H), 1.03 (t, $J = 7.4$ Hz, 3H), 0.84 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 143.2, 142.4, 142.3, 141.4, 136.7, 136.3, 135.5, 135.2, 129.1, 129.0, 127.8, 127.3, 127.2, 126.9, 126.8, 126.4, 56.3, 55.6, 33.5, 28.2, 26.5, 22.2, 21.1, 13.7, 11.8; HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{35}\text{O}_2^+$ 451.2632, found 451.2640; $[\alpha]_D^{20} = 98$ ($c = 3.1$ in CH_2Cl_2); HPLC analysis: 98:2 er (Chiralcel IC, Hexane/2-PrOH = 99.5/0.5, 0.7 mL/min), R_t (minor) = 6.4 min, R_t (major) = 7.0 min.

(*E*)-((4*R*,5*R*)-2,5-diphenyl-4-propylcyclopent-2-en-1-ylidene)(phenyl)methyl hexanoate (3-4s)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.29 (m, 4H), 7.23-7.18 (m, 1H), 6.98-6.89 (m, 8H), 6.84-6.81 (m, 2H), 6.20 (d, $J = 2.8$ Hz, 1H), 3.83 (d, $J = 2.4$ Hz, 1H), 2.78-2.73 (m, 1H), 2.11-1.98 (m, 2H), 1.70-1.12 (m, 10H), 0.94 (t, $J = 7.2$ Hz, 3H), 0.85 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 145.4, 143.0, 142.6, 141.6, 136.6,

136.3, 135.2, 129.0, 128.5, 127.8, 127.4, 127.2, 127.0, 126.8, 126.4, 126.1, 56.3, 54.6, 37.8, 33.8, 31.2, 24.2, 22.3, 20.8, 14.3, 13.9; HRMS (ESI, m/z): calcd. for $C_{33}H_{37}O_2^+$ 465.2788, found 465.2795; $[\alpha]^{20}_D = -65$ ($c = 2.4$ in $CHCl_3$); HPLC analysis: 98:2 er (Chiralcel IA, Hexane/2-PrOH = 99.5/0.5, 0.7 mL/min), R_t (major) = 7.3 min, R_t (minor) = 7.6 min.

(*E*)-((4*R*,5*R*)-5-(3-bromophenyl)-2-phenyl-4-propylcyclopent-2-en-1-ylidene)(phenyl)methyl hexanoate (3-4t)

Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, $J = 1.6$ Hz, 1H), 7.43 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.25-7.23 (m, 1H), 7.18 (t, $J = 7.7$ Hz, 1H), 6.98-6.88 (m, 8H), 6.86-6.81 (m, 2H), 6.20 (d, $J = 2.8$ Hz, 1H), 3.78 (d, $J = 2.3$ Hz, 1H), 2.77-2.72 (m, 1H), 2.15-2.03 (m, 2H), 1.69-1.15 (m, 10H), 0.95 (t, $J = 7.2$ Hz, 3H), 0.86 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 147.8, 143.0, 142.4, 141.9, 136.1, 136.0, 134.9, 130.3, 130.2, 129.2, 129.0, 127.8, 127.6, 127.3, 126.9, 126.5, 125.5, 122.4, 55.8, 54.4, 37.8, 33.9, 31.2, 24.2, 22.3, 20.8, 14.3, 13.9; HRMS (ESI, m/z): calcd. for $C_{33}H_{36}BrO_2^+$ 543.1893, found 543.1898; $[\alpha]^{20}_D = -40$ ($c = 3.6$ in $CHCl_3$); HPLC analysis: 98:2 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 9.1 min, R_t (major) = 10.6 min.

(*E*)-((4*R*,5*R*)-5-(3-methoxyphenyl)-2-phenyl-4-propylcyclopent-2-en-1-ylidene)(phenyl)methyl hexanoate (3-4u)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.22 (t, $J = 7.8$ Hz, 1H), 6.97-6.81 (m, 12H), 6.75 (dd, $J = 8.0, 2.2$ Hz, 1H), 6.20 (d, $J = 2.8$ Hz, 1H), 3.80 (d, $J = 2.4$ Hz, 1H), 3.79 (s, 3H), 2.78-2.73 (m, 1H), 2.15-2.01 (m, 2H), 1.70-1.13 (m, 10H), 0.95 (t, $J = 7.2$ Hz, 3H), 0.85 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 159.7, 147.1, 143.0, 142.6, 141.6, 136.4, 136.3, 135.1, 129.4, 129.0, 127.8, 127.4, 127.3, 126.8, 126.4, 119.5, 112.9, 111.2, 56.2, 55.1, 54.5, 37.9, 33.8, 31.2, 24.2, 22.3, 20.8, 14.3, 13.9; HRMS (ESI, m/z): calcd. for $\text{C}_{34}\text{H}_{39}\text{O}_3^+$ 495.2894, found 495.2899; $[\alpha]^{20}_{\text{D}} = -30$ ($c = 2.7$ in CHCl_3); HPLC analysis: 99:1 er (Chiralcel OD-H, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (minor) = 6.7 min, R_t (major) = 7.7 min.

(*E*)-(4-fluorophenyl)((4*R*,5*R*)-2-(4-fluorophenyl)-5-phenyl-4-propylcyclopent-2-en-1-ylidene)methyl hexanoate (3-4v)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.17 (m, 5H), 6.93-6.86 (m, 4H), 6.65 (t, $J = 8.7$ Hz, 2H), 6.57 (t, $J = 8.7$ Hz, 2H), 6.18 (d, $J = 2.8$ Hz, 1H), 3.80 (d, $J = 2.4$ Hz, 1H), 2.77-2.73 (m, 1H), 2.10-1.96 (m, 2H), 1.68-1.11 (m, 10H), 0.94 (t, $J = 7.2$ Hz, 3H), 0.84 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 163.3, 162.9, 160.9, 160.4, 145.1, 142.9, 141.7, 140.5, 137.0, 132.2, 131.3, 131.0, 130.9, 129.6, 129.5, 129.4, 129.4, 128.5, 127.0, 126.2, 114.3, 114.1, 114.0, 113.8, 56.1, 54.5, 37.8, 33.7, 31.2, 24.1, 22.3, 20.8, 14.3, 13.9; HRMS (ESI, m/z): calcd. for $\text{C}_{33}\text{H}_{35}\text{F}_2\text{O}_2^+$ 501.2600, found 501.2599; $[\alpha]^{20}_{\text{D}} = -49$ ($c = 3.2$ in CHCl_3); HPLC analysis: 97:3 er (Chiralcel IA, Hexane/2-PrOH =

99/1, 0.7 mL/min), Rt (minor) = 7.2 min, Rt (major) = 8.1 min.

(*E*)-(4-bromophenyl)((4*R*,5*R*)-2-(4-bromophenyl)-5-(3-methoxyphenyl)-4-propylcyclopent-2-en-1-ylidene)methyl hexanoate (3-4w)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.22 (t, $J = 7.8$ Hz, 1H), 7.09 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 7.6$ Hz, 2H), 6.81-6.73 (m, 6H), 6.21 (d, $J = 2.6$ Hz, 1H), 3.79 (s, 3H), 3.77 (s, 1H), 2.77-2.74 (m, 1H), 2.12-1.97 (m, 2H), 1.65-1.12 (m, 10H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.85 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 159.7, 146.5, 143.5, 141.6, 140.5, 137.3, 135.0, 134.0, 130.6, 130.5, 130.2, 129.5, 129.5, 122.0, 120.6, 119.4, 113.0, 111.1, 56.0, 55.1, 54.6, 37.7, 33.7, 31.2, 24.1, 22.3, 20.8, 14.3, 13.9; HRMS (ESI, m/z): calcd. for $\text{C}_{34}\text{H}_{37}\text{Br}_2\text{O}_3^+$ 651.1104, found 651.1093; $[\alpha]^{20}_{\text{D}} = 10$ ($c = 4.1$ in CHCl_3); HPLC analysis: 97:3 er (Chiralcel IA, Hexane/2-PrOH = 99/1, 0.7 mL/min), Rt (minor) = 9.4 min, Rt (major) = 10.7 min.

(*E*)-phenyl((4*R*,5*R*)-2,4,5-triphenylcyclopent-2-en-1-ylidene)methyl-3-phenylpropanoate (3-4x)

Red oil. ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.22 (m, 8H), 7.18-7.11 (m, 5H), 7.03-6.90 (m, 10H), 6.86-6.83 (m, 2H), 6.26 (d, $J = 2.9$ Hz, 1H), 4.05 (d, $J = 2.7$ Hz, 1H), 3.92 (t, J

= 2.8 Hz, 1H), 2.73-2.66 (m, 1H), 2.62-2.55 (m, 1H), 2.28 (t, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 144.6, 144.1, 143.8, 142.0, 141.4, 140.5, 136.5, 135.9, 134.9, 129.1, 128.8, 128.6, 128.4, 128.4, 127.9, 127.6, 127.5, 127.4, 127.1, 127.0, 126.8, 126.7, 126.4, 126.2, 60.3, 59.5, 35.4, 30.4; HRMS (ESI, m/z): calcd. for $\text{C}_{39}\text{H}_{33}\text{O}_2^+$ 533.2475, found 533.2482; $[\alpha]_D^{20} = -0.3$ ($c = 2.0$ in CH_2Cl_2); HPLC analysis: 84:16 er (Chiralcel IA, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (major) = 8.9 min, R_t (minor) = 11.4 min.

(*E*)-((4*R*,5*R*)-5-(4-chlorophenyl)-2,4-diphenylcyclopent-2-en-1-ylidene)(phenyl)methyl 3-phenylpropanoate (3-4y)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.40 (m, 2H), 7.35-7.27 (m, 5H), 7.17-7.15 (m, 3H), 7.09-6.88 (m, 14H), 6.29 (d, $J = 2.9$ Hz, 1H), 4.02 (d, $J = 2.7$ Hz, 1H), 3.89 (t, $J = 2.8$ Hz, 1H), 2.82-2.74 (m, 1H), 2.69-2.62 (m, 1H), 2.38-2.33 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 144.1, 143.4, 143.2, 142.2, 141.3, 140.4, 136.1, 135.6, 134.6, 132.1, 129.1, 128.9, 128.7, 128.5, 128.4, 127.9, 127.8, 127.4, 127.4, 127.0, 127.0, 126.8, 126.3, 60.2, 58.7, 35.5, 30.5; HRMS (ESI, m/z): calcd. for $\text{C}_{39}\text{H}_{32}\text{ClO}_2^+$ 567.2085, found 567.2101; $[\alpha]_D^{20} = 5$ ($c = 3.6$ in CH_2Cl_2); HPLC analysis: 87:13 er (Chiralcel IA, Hexane/2-PrOH = 99/1, 0.7 mL/min), R_t (major) = 8.4 min, R_t (minor) = 10.2 min.

(*E*)-((4*R*,5*R*)-5-(3-bromophenyl)-4-(4-bromophenyl)-2-phenylcyclopent-2-en-1-ylidene)(phenyl)methyl 3-(4-bromophenyl)propanoate (3-4z)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 8.6$ Hz, 1H), 7.29-7.26 (m, 3H), 7.22 (t, $J = 7.8$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 7.8$ Hz, 1H), 7.05-6.95 (m, 8H), 6.90 (d, $J = 4.4$ Hz, 4H), 6.24 (d, $J = 2.7$ Hz, 1H), 3.89-3.87 (m, 2H), 2.78-2.70 (m, 1H), 2.68-2.61 (m, 1H), 2.38 (t, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 146.6, 144.4, 142.5, 142.3, 140.5, 139.2, 135.6, 135.3, 134.3, 132.0, 131.6, 130.4, 130.3, 130.2, 129.7, 129.1, 129.0, 127.9, 127.8, 127.5, 127.1, 127.0, 125.3, 122.6, 120.9, 120.1, 59.3, 58.8, 35.2, 29.8; HRMS (ESI, m/z): calcd. for $\text{C}_{39}\text{H}_{30}\text{Br}_3\text{O}_2^+$ 766.9790, found 766.9796; $[\alpha]^{20}_{\text{D}} = -18$ ($c = 4.3$ in CH_2Cl_2); HPLC analysis: 81:19 er (Chiralcel OD-H, Hexane/2-PrOH = 95/5, 0.7 mL/min), R_t (minor) = 8.9 min, R_t (major) = 13.1 min.

((1*R*,5*R*)-5-methylcyclopent-3-ene-1,3-diyl)dibenzene (3-7a)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 7.7$ Hz, 2H), 7.34-7.31 (m, 6H), 7.25-7.20 (m, 2H), 6.11 (d, $J = 1.3$ Hz, 1H), 3.23-3.17 (m, 1H), 3.07-2.98 (m, 2H), 2.93-2.86 (m, 1H), 1.17 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.8, 140.0, 136.4, 130.7, 128.4, 128.4, 127.5, 127.1, 126.1, 125.6, 53.3, 49.4, 42.1, 19.9; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{19}^+$ 235.1481, found 235.1484; $[\alpha]^{20}_{\text{D}} = -7$ ($c = 1.4$ in CH_2Cl_2); HPLC

analysis: 96:4 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), Rt (minor) = 12.9 min, Rt (major) = 17.1 min.

1-bromo-4-((3*R*,4*R*)-3-methyl-4-phenylcyclopent-1-en-1-yl)benzene (3-7b)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 8.5$ Hz, 2H), 7.28-7.17 (m, 6H), 7.16-7.13 (m, 1H), 6.03 (d, $J = 1.4$ Hz, 1H), 3.11-3.04 (m, 1H), 2.99-2.89 (m, 2H), 2.81-2.75 (m, 1H), 1.08 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.4, 139.0, 135.3, 131.6, 131.4, 128.5, 127.4, 127.2, 126.2, 120.9, 53.3, 49.4, 42.1, 19.8; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{18}\text{Br}^+$ 313.0586, found 313.0595; $[\alpha]^{20}_{\text{D}} = 3$ ($c = 2.6$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), Rt (minor) = 18.4 min, Rt (major) = 25.8 min.

1-chloro-4-((1*R*,2*R*)-2-methyl-4-phenylcyclopent-3-en-1-yl)benzene (3-7c)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 7.4$ Hz, 2H), 7.37-7.16 (m, 7H), 6.10 (d, $J = 1.5$ Hz, 1H), 3.22-3.16 (m, 1H), 3.01 (dd, $J = 15.8, 7.8$ Hz, 1H), 2.96-2.92 (m, 1H), 2.86-2.80 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.2, 140.0, 136.2, 131.8, 130.5, 128.8, 128.5, 128.4, 127.2, 125.6, 52.6, 49.4, 42.1, 19.9; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{18}\text{Cl}^+$ 269.1092, found 269.1085; $[\alpha]^{20}_{\text{D}} = 7$ ($c = 1.5$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), Rt (minor) = 31.0 min, Rt (major) = 35.3 min.

4,4'-((1*R*,5*R*)-5-methylcyclopent-3-ene-1,3-diyl)bis(chlorobenzene) (3-7d)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.15 (m, 8H), 6.08 (d, $J = 1.2$ Hz, 1H), 3.17-3.11 (m, 1H), 3.01 (dd, $J = 15.6, 7.7$ Hz, 1H), 2.96-2.92 (m, 1H), 2.83-2.77 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.9, 138.9, 134.6, 132.9, 131.9, 131.2, 128.7, 128.6, 128.5, 126.8, 52.6, 49.4, 42.0, 19.7; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{17}\text{Cl}_2^+$ 303.0702, found 303.0701; $[\alpha]_D^{20} = 6$ ($c = 1.6$ in CH_2Cl_2); HPLC analysis: 91:9 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 24.7 min, R_t (major) = 26.4 min.

2-((3*R*,4*R*)-3-methyl-4-phenylcyclopent-1-en-1-yl)furan (3-7e)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.37 (br s, 1H), 7.33-7.28 (m, 4H), 7.24-7.19 (m, 1H), 6.37 (dd, $J = 3.1, 1.9$ Hz, 1H), 6.18 (d, $J = 3.2$ Hz, 1H), 6.00 (s, 1H), 3.12-3.06 (m, 1H), 3.04-2.98 (m, 2H), 2.82-2.78 (m, 1H), 1.50 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.0, 145.4, 141.8, 130.6, 129.4, 128.5, 127.4, 126.2, 111.0, 106.4, 53.2, 49.3, 41.3, 19.9; HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{17}\text{O}^+$ 225.1274, found 225.1272; $[\alpha]_D^{20} = -16$ ($c = 2.1$ in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 13.4 min, R_t (major) = 19.1 min.

2-((3*R*,4*R*)-4-phenyl-3-propylcyclopent-1-en-1-yl)furan (3-7f)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.20 (m, 6H), 7.02-7.00 (m, 1H), 6.97-6.96 (m, 1H), 6.08 (d, $J = 1.8$ Hz, 1H), 3.28-3.12 (m, 2H), 2.97-2.83 (m, 2H), 1.59-1.30 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.5, 140.9, 134.8, 128.6, 128.5, 127.4, 127.3, 126.1, 124.0, 123.7, 55.0, 51.0, 43.2, 37.6, 21.0, 14.3; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{21}\text{O}^+$ 253.1587, found 253.1587; $[\alpha]_D^{20} = -25$ ($c = 1.9$ in CH_2Cl_2); HPLC analysis: 98:2 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 11.6 min, R_t (major) = 14.5 min.

((1R,5R)-5-propylcyclopent-3-ene-1,3-diyl)dibenzene (3-7g)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.52-7.50 (m, 2H), 7.39-7.21 (m, 8H), 6.26 (d, $J = 1.8$ Hz, 1H), 3.29-3.23 (m, 1H), 3.20-3.14 (m, 1H), 3.00-2.96 (m, 1H), 2.92-2.85 (m, 1H), 1.60-1.31 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.9, 140.4, 136.4, 129.0, 128.5, 128.4, 127.4, 127.1, 126.0, 125.6, 54.9, 50.9, 42.3, 37.8, 21.1, 14.4; HRMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{23}^+$ 263.1794, found 263.1791; $[\alpha]_D^{20} = -4$ ($c = 2.2$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 11.6 min, R_t (major) = 14.6 min.

1-bromo-4-((3R,4R)-4-phenyl-3-propylcyclopent-1-en-1-yl)benzene (3-7h)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.48-7.45 (m, 2H), 7.35-7.22 (m, 7H), 6.24 (d, $J = 1.4$ Hz, 1H), 3.23-3.12 (m, 2H), 2.97-2.90 (m, 1H), 2.85-2.79 (m, 1H), 1.56-1.28 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.5, 139.4, 135.3, 131.4,

129.9, 128.5, 127.3, 127.2, 126.1, 120.9, 54.9, 50.8, 42.2, 37.6, 21.0, 14.3; HRMS (ESI, m/z): calcd. for $C_{20}H_{22}Br^+$ 341.0899, found 341.0891; $[\alpha]_D^{20} = 20$ ($c = 0.1$ in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 15.5 min, R_t (major) = 22.3 min.

1-methoxy-4-((1*R*,2*R*)-4-phenyl-2-propylcyclopent-3-en-1-yl)benzene (3-7i)

Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.37-7.33 (m, 2H), 7.28-7.23 (m, 3H), 6.90-6.86 (m, 2H), 6.24 (d, $J = 1.8$ Hz, 1H), 3.83 (s, 3H), 3.25-3.18 (m, 1H), 3.13-3.08 (m, 1H), 2.93-2.87 (m, 1H), 2.85-2.79 (m, 1H), 1.55-1.32 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 140.4, 138.9, 136.4, 129.0, 128.3, 128.2, 127.1, 125.6, 113.8, 55.3, 54.9, 50.1, 42.4, 37.7, 21.1, 14.4; HRMS (ESI, m/z): calcd. for $C_{21}H_{25}O^+$ 293.1900, found 293.1903; $[\alpha]_D^{20} = -14$ ($c = 1.2$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 23.0 min, R_t (major) = 42.9 min.

1-bromo-3-((1*R*,2*R*)-4-phenyl-2-propylcyclopent-3-en-1-yl)benzene (3-7j)

Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.46 (m, 3H), 7.38-7.34 (m, 3H), 7.29-7.17 (m, 3H), 6.23 (d, $J = 1.8$ Hz, 1H), 3.27-3.21 (m, 1H), 3.14-3.08 (m, 1H), 2.96-2.89 (m, 1H), 2.85-2.79 (m, 1H), 1.55-1.30 (m, 4H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 140.2, 136.1, 130.4, 130.0, 129.1, 128.8, 128.4, 127.2, 126.0, 125.6, 122.5, 54.9, 50.4, 42.2, 37.7, 21.0, 14.3; HRMS (ESI, m/z): calcd. for $C_{20}H_{22}Br^+$

341.0899, found 341.0891; $[\alpha]_D^{20} = 1.3$ ($c = 1.8$ in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 12.5 min, R_t (major) = 15.8 min.

2-((3R,4R)-4-phenyl-3-propylcyclopent-1-en-1-yl)naphthalene (3-7k)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.86-7.77 (m, 5H), 7.52-7.45 (m, 2H), 7.39-7.34 (m, 4H), 7.29-7.24 (m, 1H), 6.40 (d, $J = 1.4$ Hz, 1H), 3.42-3.36 (m, 1H), 3.25-3.20 (m, 1H), 3.06-2.98 (m, 2H), 1.65-1.31 (m, 4H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.8, 140.4, 133.8, 133.6, 132.7, 129.9, 128.5, 128.1, 127.8, 127.6, 127.4, 126.1, 125.7, 124.3, 124.1, 55.0, 50.9, 42.4, 37.8, 21.1, 14.4; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{25}^+$ 313.1951, found 313.1950; $[\alpha]_D^{20} = 14$ ($c = 1.9$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel IA, 100% Hexane, 0.5 mL/min), R_t (minor) = 23.3 min, R_t (major) = 30.1 min.

(2S,3S)-3-methyl-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (3-9a)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.42 (m, 6H), 7.31-7.23 (m, 11H), 7.05-6.98 (m, 2H), 6.34 (dd, $J = 7.1, 1.6$ Hz, 1H), 2.99-2.88 (m, 2H), 2.75-2.64 (m, 1H), 1.09 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.4, 174.5, 144.6, 141.4, 129.6, 129.4, 129.2, 127.8, 127.8, 127.2, 125.2, 123.7, 123.0, 116.5, 85.7, 75.1, 40.9, 35.1, 13.0; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{26}\text{NO}_3^+$ 460.1907, found 460.1899; $[\alpha]_D^{20} = 4$ ($c = 2.4$ in CH_2Cl_2); HPLC analysis: >99:1 er (Chiralcel IA, Hexane/2-PrOH = 95/5, 0.7 mL/min), R_t (minor) = 13.9 min, R_t (major) = 14.8 min.

(2*S*,3*S*)-3,5'-dimethyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (3-9b)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.41 (m, 6H), 7.31-7.22 (m, 10H), 7.12 (d, $J = 1.6$ Hz, 1H), 6.80 (dd, $J = 8.3, 1.1$ Hz, 1H), 6.21 (d, $J = 8.3$ Hz, 1H), 2.99-2.86 (m, 2H), 2.70-2.66 (m, 1H), 2.26 (s, 3H), 1.10 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.5, 174.5, 142.1, 141.5, 132.7, 130.1, 129.4, 129.2, 127.8, 127.7, 127.1, 125.2, 124.4, 116.2, 85.8, 75.0, 40.9, 35.1, 20.7, 13.0; HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{28}\text{NO}_3^+$ 474.2064, found 474.2066; $[\alpha]^{20}_{\text{D}} = 2$ ($c = 3.9$ in CH_2Cl_2); HPLC analysis: >99:1 er (Chiralcel IA, Hexane/2-PrOH = 95/5, 0.7 mL/min), R_t (minor) = 11.3 min, R_t (major) = 12.3 min.

(2*S*,3*S*)-5'-methoxy-3-methyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (3-9c)

Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.42 (m, 6H), 7.31-7.23 (m, 10H), 6.88 (d, $J = 2.6$ Hz, 1H), 6.54 (dd, $J = 8.9, 2.6$ Hz, 1H), 6.24 (d, $J = 8.9$ Hz, 1H), 3.73 (s, 3H), 2.99-2.85 (m, 2H), 2.71-2.65 (m, 1H), 1.10 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.5, 174.4, 155.9, 141.5, 137.6, 129.4, 129.2, 127.8, 127.8, 127.2, 126.5, 117.2, 114.9, 109.7, 85.9, 75.1, 55.6, 41.1, 35.1, 13.0; HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{28}\text{NO}_4^+$ 490.2013, found 490.2017; $[\alpha]^{20}_{\text{D}} = 3$ ($c = 4.1$ in CH_2Cl_2); HPLC

analysis: >99:1 er (Chiralcel IB, Hexane/2-PrOH = 95/5, 0.7 mL/min), Rt (minor) = 23.7 min, Rt (major) = 28.2 min.

(2*S*,3*S*)-5'-fluoro-3-methyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (3-9d)

Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.40 (m, 6H), 7.32-7.24 (m, 11H), 7.04 (dd, $J = 7.2, 2.7$ Hz, 1H), 6.71 (td, $J = 8.9, 2.7$ Hz, 1H), 6.29 (dd, $J = 9.0, 4.2$ Hz, 1H), 2.98-2.85 (m, 2H), 2.69 (dd, $J = 15.0, 6.5$ Hz, 1H), 1.12 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.0, 174.4, 160.2, 157.7, 141.2, 140.4, 129.3, 127.9, 127.3, 117.5, 117.4, 116.4, 116.1, 111.5, 111.3, 85.4, 75.3, 41.1, 34.9, 12.9; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{25}\text{FNO}_3^+$ 478.1813, found 478.1811; $[\alpha]_D^{20} = 5.5$ ($c = 1.2$ in CH_2Cl_2); HPLC analysis: 98:2 er (Chiralcel IA, Hexane/2-PrOH = 95/5, 0.7 mL/min), Rt (minor) = 11.5 min, Rt (major) = 12.5 min.

(2*S*,3*S*)-5'-chloro-3-methyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (3-9e)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.39 (m, 6H), 7.32-7.24 (m, 10H), 6.97 (dd, $J = 8.8, 2.2$ Hz, 1H), 6.27 (d, $J = 8.8$ Hz, 1H), 3.00-2.81 (m, 2H), 2.76-2.63 (m, 1H), 1.12 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.9, 174.1, 143.1, 141.0, 129.6, 129.3, 129.1, 128.8, 127.9, 127.9, 127.4, 127.0, 124.1, 117.5, 85.2, 75.3, 41.0, 34.9, 13.0;

HRMS (ESI, m/z): calcd. for $C_{31}H_{25}ClNO_3^+$ 494.1517, found 494.1509; $[\alpha]^{20}_D = 1$ ($c = 1.1$ in CH_2Cl_2); HPLC analysis: 98:2 er (Chiralcel IC, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 25.0 min, R_t (major) = 27.0 min.

(2*S*,3*S*)-5'-bromo-3-methyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (3-9f)

White solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.39 (m, 6H), 7.33-7.25 (m, 9H), 7.13 (dd, $J = 8.7, 2.1$ Hz, 1H), 6.22 (d, $J = 8.7$ Hz, 1H), 2.98-2.84 (m, 2H), 2.76-2.68 (m, 1H), 1.13 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 174.0, 143.7, 141.0, 132.5, 129.3, 129.1, 127.9, 127.4, 127.0, 117.9, 116.1, 85.1, 75.4, 41.0, 34.9, 13.0; HRMS (ESI, m/z): calcd. for $C_{31}H_{25}BrNO_3^+$ 538.1012, found 538.1031; $[\alpha]^{20}_D = -0.4$ ($c = 1.3$ in CH_2Cl_2); HPLC analysis: 99:1 er (Chiralcel IB, Hexane/2-PrOH = 95/5, 0.7 mL/min), R_t (minor) = 15.3 min, R_t (major) = 16.9 min.

(2*S*,3*S*)-3-propyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (3-9g)

White solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.44 (m, 6H), 7.33-7.23 (m, 10H), 7.05-7.00 (m, 2H), 6.35-6.33 (m, 1H), 2.93 (dd, $J = 15.6, 12.0$ Hz, 1H), 2.83-2.75 (m, 1H), 2.70 (dd, $J = 15.6, 7.9$ Hz, 1H), 1.46-1.39 (m, 1H), 1.31-1.15 (m, 2H), 1.12-1.01 (m, 1H), 0.83 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.3, 144.5, 141.4, 129.6, 129.3, 127.8, 127.2, 125.7, 123.8, 123.0, 116.4, 85.1, 75.1, 46.0, 33.9, 30.7, 21.5, 14.0;

HRMS (ESI, m/z): calcd. for $C_{33}H_{30}NO_3^+$ 488.2220, found 488.2224; $[\alpha]^{20}_D = 19$ ($c = 0.9$ in CH_2Cl_2); HPLC analysis: 99:1 er (Chiralcel IC, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (major) = 22.3 min, R_t (minor) = 33.6 min.

(2*S*,3*S*)-5'-methoxy-3-propyl-1'-trityl-3,4-dihydro-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (3-9h)

White solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 6H), 7.31-7.23 (m, 10H), 6.88 (d, $J = 2.6$, 1H), 6.55 (dd, $J = 8.9$, 2.6, 1H), 6.24 (d, $J = 8.9$, 1H), 3.75 (s, 3H), 2.93 (dd, $J = 15.0$, 11.4 Hz, 1H), 2.80-2.66 (m, 2H), 1.47-1.04 (m, 4H), 0.84 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.2, 155.9, 141.5, 137.5, 129.3, 129.2, 127.7, 127.1, 127.0, 117.1, 114.8, 109.9, 85.3, 75.0, 55.6, 46.3, 33.9, 30.7, 21.5, 14.0; HRMS (ESI, m/z): calcd. for $C_{34}H_{32}NO_4^+$ 518.2326, found 518.2339; $[\alpha]^{20}_D = 10$ ($c = 1.6$ in CH_2Cl_2); HPLC analysis: 99:1 er (Chiralcel IC, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (major) = 24.5 min, R_t (minor) = 34.8 min.

(4-bromophenyl)((1*S*,4*R*,5*S*)-2-(4-bromophenyl)-5-(3-methoxyphenyl)-4-methylcyclopent-2-en-1-yl)methanone (3-10)

White solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, $J = 8.6$ Hz, 2H), 7.36 (dd, $J = 14.1$, 8.6 Hz, 4H), 7.10 (d, $J = 8.5$ Hz, 2H), 6.98 (t, $J = 7.9$ Hz, 1H), 6.73 (d, $J = 7.6$ Hz, 1H),

6.67 (t, $J = 2.4$ Hz, 1H), 6.55-6.31 (m, 2H), 5.12 (dd, $J = 8.3, 2.2$ Hz, 1H), 3.65 (s, 3H), 3.52-3.45 (m, 2H), 1.15 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.3, 159.3, 139.8, 139.1, 136.5, 134.1, 131.6, 131.4, 129.7, 129.3, 127.8, 127.1, 121.4, 121.2, 114.8, 112.4, 58.9, 58.2, 55.1, 45.1, 18.5; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{Br}_2\text{O}_2^+$ 525.0059, found 525.0059; $[\alpha]^{20}_{\text{D}} = -134$ ($c = 10.0$ in CH_2Cl_2); HPLC analysis: 94:6 er (Chiralcel OD-H, Hexane/2-PrOH = 90/10, 0.75 mL/min), R_t (minor) = 7.3 min, R_t (major) = 8.3 min.

(4-bromophenyl)((1S,2S,3S,4S,5S)-1-(4-bromophenyl)-3-(3-methoxyphenyl)-4-methyl-6-oxabicyclo[3.1.0]hexan-2-yl)methanone (3-11)

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.35 (m, 6H), 7.16-7.14 (m, 2H), 7.00 (t, $J = 7.8$ Hz, 1H), 6.68 (d, $J = 7.6$ Hz, 1H), 6.62 (br s, 1H), 6.56 (d, $J = 8.2$ Hz, 1H), 4.69 (d, $J = 7.8$ Hz, 1H), 4.07 (s, 1H), 3.68 (s, 3H), 3.21 (dd, $J = 10.4, 8.0$ Hz, 1H), 3.10-3.03 (m, 1H), 1.16 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.7, 159.5, 137.8, 136.5, 134.7, 131.5, 131.4, 129.4, 129.3, 122.4, 121.3, 114.9, 112.3, 67.7, 67.6, 55.1, 54.5, 51.4, 37.4, 13.3; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{Br}_2\text{O}_3^+$ 541.0008, found 541.0002; $[\alpha]^{20}_{\text{D}} = -191$ ($c = 1.2$ in CH_2Cl_2); HPLC analysis: >99:1 er (Chiralcel OD-H, Hexane/2-PrOH = 90/10, 0.75 mL/min), R_t (minor) = 9.3 min, R_t (major) = 10.4 min.

(2*S*,3*R*)-4-(4-bromobenzoyl)-5-(4-bromophenyl)-3-(3-methoxyphenyl)-2-methyl-5-oxopentanoic acid (3-12)

White solid. ^1H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 8.14 (d, $J = 6.5$ Hz, 1H), 7.93 (d, $J = 6.7$ Hz, 1H), 7.76 (d, $J = 6.7$ Hz, 1H), 7.62 (d, $J = 7.0$ Hz, 1H), 7.06 (t, $J = 7.9$ Hz, 1H), 6.93 (s, 1H), 6.88 (d, $J = 7.6$ Hz, 1H), 6.65 (dd, $J = 8.1, 2.0$ Hz, 1H), 6.53 (br s, 1H), 4.21 (br s, 1H), 3.66 (s, 3H), 2.75-2.68 (m, 1H), 0.91 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.6, 175.9, 159.2, 140.6, 135.8, 132.5, 132.2, 131.3, 131.1, 129.3, 122.3, 115.5, 112.5, 55.3, 49.0, 42.1, 13.9; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{Br}_2\text{O}_5^+$ 572.9907, found 572.9906; $[\alpha]^{20}_{\text{D}} = -1$ ($c = 2.6$ in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel IC, Hexane/2-PrOH = 70/30, 0.8 mL/min), R_t (minor) = 8.7 min, R_t (major) = 30.7 min.

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Chapter 4

*Enantioselective [3+2] Cyclizations of Propionic Acid and Active Ketones through β -Activation of Carboxylic Acid Enabled by *N*-Heterocyclic Carbenes*

4.1 Introduction

4.1.1 Generation of Acyl Anions in NHC Catalysis.

During the last decade of the “gold rush” in NHC organocatalysis, various carbonyl compounds have been intensively studied within this field and several unique catalytic modes have been well developed.¹ Among the most important and widely used substrates are aldehyde compounds, including simple aldehydes, α,β -unsaturated aldehydes and various modified aldehydes.² Corresponding NHC catalyzed reaction modes such as the Benzoin condensation,³ Stetter reaction,⁴ homoenolate⁵ and enolate activations,⁶ and esterification⁷ or nucleophilic additions of acyl azoliums⁸ have been developed with exceptional chemo- and stereo-selectivities. Besides the aldehyde derived starting materials, carboxylic derivatives such as carboxylic halides,⁹ esters¹⁰ and anhydrides¹¹ have appeared recently in the NHC based organocatalysis and showed some unique and unexpected reactivities. For example, Lupton and co-workers initiated the application of α,β -unsaturated acyl fluoride in the 1,4-addition with various nucleophiles (Scheme 4.1).⁹ Our group recently published the acyl anion activations in the 4-nitrophenol carboxylic esters involving both enolate reactions and 1,4-addition of α,β -unsaturated acyl azoliums (Scheme 4.1).^{10b} Specifically, the β -activation of a saturated ester as the nucleophilic carbon was realized in our group in 2013 (Scheme 4.2).^{10c} Since then, we have also successfully extended this strategy to simple carboxylic anhydrides with various electrophiles to overcome the low efficiencies and selectivities of aliphatic substrates that existed in the previous ester strategy as well as the well established homoenolate activation with α,β -unsaturated aldehydes (Scheme 4.2, as described in Chapter 3).¹¹

Lupton's pioneering work:

Our work on ester activations:

Scheme 4.1 NHC Catalyzed Carboxylic Acid Derivatives Activation.

Our previous work:

Scheme 4.2 β -Activation of Carboxylic Acid Derivatives.

We have demonstrated the generality of this strategy through reactions of different electrophiles in good reaction yields and stereoselectivities. However, several drawbacks remained. For example, substitution on the β -carbon is necessary and the carbonyl group needs to be pre-activated by an electron-withdrawing group in the form of either 4-nitrophenol ester or carboxylic anhydride (Scheme 4.2). Therefore, terminal β -carbon activation remains challenging and a direct β -functionalization of a carboxylic acid is still of great interest.

4.1.2 Our Proposal.

As a continuity of our β -activation work through NHC catalysis, we went on to explore catalytic pathways to furnish the β -functionalization of simple carboxylic acid. We assumed that one way to achieve this goal would be a cascade activation pathway that involves an acid activation followed by the β -functionalization process in a single

reaction system. It should be noted that the α -carbon functionalization of a carboxylic acid has been previously studied by Romo¹² and Smith¹³ with either tertiary amines or isothioureas as the organocatalysts. More recently, Scheidt reported the NHC catalyzed α -functionalization of carboxylic acids through a one-pot process.¹⁴ Ye and co-workers reported the 1,4-additions of α,β -unsaturated acyl azoliums that are generated by the one-pot cascade activation of α,β -unsaturated carboxylic acid enabled by NHC catalysts.¹⁵ However, to the best of our knowledge, no report on the β -activation of carboxylic acid by organocatalysts has been presented (Scheme 4.3).

Here we report the β -activation of propionic acid—one of the smallest 3-carbon synthon with a terminal β -carbon. As a note, the current study also represents the first successful example of the [3+2] cyclizations of the smallest C-3 carbonyl synthons with activated ketones in asymmetric organocatalysis (Scheme 4.3).

Scheidt's work

Use CDI as the acid-preactivation reagent.

Ye's work

Use PivCl as the acid-preactivation reagent.

This work:

Scheme 4.3 Activation of Carboxylic Acid in NHC Organocatalysis.

4.2 Results and Discussions

Trityl (Trt) protected isatin **4-2a** was first chosen as the model electrophile (Table 4.1).¹⁶ To our great delight, with the commonly used NHC precursor **4-4a** as the catalyst and stoichiometric amount of DBU in THF, the desired product could be formed in quantitative yield when EDCI was applied to pre-activate the carboxylic acid (Entry 1). Other pre-activating reagents such as DCC, MsCl or TsCl resulted in no product formation (Entries 2-4). Different NHC precursors were then tested, which revealed that an electron rich N-aromatic substituent on the triazolium ring would favor this process (Entries 5-7). NHC precursor **4-4c** afforded the product **4-3a** in a quantitative yield with the highest enantioselectivity (Entry 6). Screening of different solvents revealed that the reaction could take place in a variety of organic media such as ethers and esters (Entries 8-11). DCM or solvents with high polarities such as alcohols and acetonitrile were not suitable for this transformation (Entries 12-14). The reaction also showed good tolerance to organic and inorganic bases (Entries 15-22). The amount of propionic acid **4-1a** could be reduced to 4 equivalents without affecting the reaction yield, while a little decrease in the *er* value was observed (Entry 23). However, further decreasing the amount of the propionic acid **4-1a**, EDC·HCl or the base would result in lower product yield (Entries 24-25).

Table 4.1 Conditional Optimization.^[a]

Entry	NHC	Additive	Base	Solvent	Yield (%)	er
1	4-4a	EDC·HCl	DBU	THF	99	94:6
2	4-4a	DCC	DBU	THF	0	-
3	4-4a	MsCl	DBU	THF	0	-
4	4-4a	TsCl	DBU	THF	0	-
5	4-4b	EDC·HCl	DBU	THF	99	94:6
6	4-4c	EDC·HCl	DBU	THF	99	96:4
7	4-4d	EDC·HCl	DBU	THF	0	-
8	4-4c	EDC·HCl	DBU	Et ₂ O	79	92:8
9	4-4c	EDC·HCl	DBU	Dioxane	99	94:6
10	4-4c	EDC·HCl	DBU	EtOAc	99	94:6
11	4-4c	EDC·HCl	DBU	MTBE	47	92:8
12	4-4c	EDC·HCl	DBU	EtOH	0	-
13	4-4c	EDC·HCl	DBU	MeCN	38	85:15
14	4-4c	EDC·HCl	DBU	DCM	51	91:9
15	4-4c	EDC·HCl	DIEA	THF	52	96:4
16	4-4c	EDC·HCl	TEA	THF	99	95:5
17	4-4c	EDC·HCl	K ₂ CO ₃	THF	89	95:5
18	4-4c	EDC·HCl	Cs ₂ CO ₃	THF	99	94:6
19	4-4c	EDC·HCl	KOtBu	THF	77	95:5
20	4-4c	EDC·HCl	K ₃ PO ₄	THF	99	94:6
21	4-4c	EDC·HCl	DABCO	THF	99	95:5
22	4-4c	EDC·HCl	DMAP	THF	27	95:5
23 ^[b]	4-4c	EDC·HCl	DBU	THF	99	95:5
24 ^[c]	4-4c	EDC·HCl	DBU	THF	54	95:5
25 ^[d]	4-4c	EDC·HCl	DBU	THF	46	96:4

[a] Unless otherwise noted, the reactions were carried out using 5 eq of **4-1a**, 1 eq of **4-2a** (0.1 mmol), 10 mol% of NHC, 2 eq of base, 4 eq of additive and 1 mL of solvent for 12h. Yields are isolated yields. Ers were determined by HPLC. [b] 4 Eq of **4-1a** was used. [c] 3 Eq of **4-1a** was used. [d] 1 eq of DBU was used.

With the optimized reaction conditions in hand, we next examined the substrate scope using various substituted isatin derivatives (Table 4.2). Both electron-donating and electron withdrawing substituents on the aromatic ring of the isatin substrate generally afforded the lactone products in good to quantitative yields with excellent enantioselectivities (**4-3a** to **4-3i**). Strong electron withdrawing group on the 5-position deteriorated the reaction outcome (**4-3j**). Simple aliphatic carboxylic acid other than propionic acid also worked under the current reaction conditions to afford the corresponding products in good yields with excellent enantioselectivities, although the diastereoselectivities were not satisfactory (**4-3k**, **4-3l**). The electron-rich and sterically bulky trityl (Trt) group was critical to the asymmetric induction. Protecting groups other than Trt gave the products with poor er values, but still in satisfactory yields (**4-3m** to **4-**

3o).

Table 4.2 Reaction Scope^[a]

[a] 5 eq of **4-1**, 1 eq of **4-2** (0.1 mmol), 10 mol% of **4-4c**, 2 eq of DBU, 4 eq of EDCI and 1 mL of THF for 12h. Yields were isolated yields. Ers were determined *via* chiral HPLC.

Having examined various substituted isatin substrates, we then sought to further expand the scope of this transformation to other type of electrophiles to prove the synthetic utility of this methodology. α -Ketoester **4-5a** was found as another suitable reactant¹⁷ in this process, which afforded the corresponding lactone **4-6a** in a moderate yield and encouraging enantioselectivity (Table 4.3, entry 1). After modification of reaction conditions including the solvent and the base (Entries 5 to 11), excellent yield and er could be reached with the same NHC precursor **4-4c** (Entry 11).

Table 4.3 Conditional Optimization.^[a]

Entry	NHC	Additive	Base	Solvent	Yield (%) ^[b]	ee ^[c]
1	4-4a	EDCI	DBU	THF	35	80:20
2	4-4b	EDCI	DBU	THF	28	79:21
3	4-4c	EDCI	DBU	THF	35	86:14
4	4-4d	EDCI	DBU	THF	0	-
5	4-4c	EDCI	DBU	Toluene	78	91:9
6	4-4c	EDCI	DBU	<i>p</i> -Xylene	90	93:7
7	4-4c	EDCI	DBU	Mesitylene	86	94:6
8	4-4c	EDCI	TEA	Mesitylene	88	94:6
9	4-4c	EDCI	K ₂ CO ₃	Mesitylene	99	95:5
10	4-4c	EDCI	Cs ₂ CO ₃	Mesitylene	58	92:8
11 ^[d]	4-4c	EDCI	K ₂ CO ₃	Mesitylene	98	95:5

[a] 5 eq of **4-1a**, 1 eq of **4-5a** (0.1 mmol), 20 mol% of NHC, 2 eq of base, 4 eq of additive and 1 mL of solvent at rt (24 °C) for 24 h. [b] Yield was isolated yield after column chromatography. [c] Er was determined *via* chiral HPLC. [d] 4 Eq of **4-1a** was used.

Then the scope of various substituted α -ketoesters **4-5** was tested as summarized in Table 4.4. Electron-withdrawing substituents on the aromatic ketone group favoured this transformation very well to afforded the corresponding products in excellent yields and er values (**4-6b**, **4-6c**, **4-6e**, **4-6f**, **4-6j** to **4-6l**). However, substituents on the 2'-position of the aromatic ketone group seriously decreased the product yields (**4-6d**, **4-6g**), which would probably due to the steric hindrance against the nucleophilic attack in the lactone formation. Evidence that supports this was that product **4-6j** with a much smaller F atom on the 2'-position could be afforded in satisfactory yield. Electron-donating substituents also decreased the corresponding product yields (**4-6h**, **4-6i**), presumably due to the deactivation of the electrophilic ketone moiety. The aromatic group of the ketone motif could also be replaced with a methyl group, although the product could only be afforded in moderate yield and er value (**4-6m**). α -Ketoesters with different ester groups afforded the corresponding products in somewhat lower yields and er values.

Table 4.4 Reaction Scope^[a]

[a] 4 eq of **4-1a**, 1 eq of **4-5** (0.1 mmol), 20 mol% of **4-4c**, 2 eq of K_2CO_3 , 4 eq of EDCI and 1 mL of mesitylene. Yield was isolated yield. Ers were determined via chiral HPLC.

The Trt protecting group on the product **4-3** could easily be removed under weakly acidic conditions to give product **4-7** in a good yield without erosion of the optical purity. The deprotected chiral isatin derivative **4-7** could be transformed to various synthetic intermediates through reported procedures.¹⁸ Transesterification of the lactone motif on **4-3a** under weakly basic conditions afforded the corresponding hydroxyl ester **4-8** in a quantitative yield with an excellent er. The benzhydryl group on the product **4-6** could also be easily removed under strongly acidic conditions to afford the corresponding chiral acid **4-9** in a good yield. The acid product **4-9** could be found in the synthesis of various bioactive molecules as a versatile starting material,¹⁹ and the carboxylic acid group on **4-9** was also easily modified to afford various carbonyl compounds such as amides and other

esters (eg. **4-10**). Some of their applications in the literatures were also shown in Scheme 4.4.

Scheme 4.4 Synthetic Applications of Final Products.

4.3 Mechanistic Study.

4.3.1 Reaction Pathway.

We assumed two most possible pathways for the activation of propionic acid activation mode (Scheme 4.5). **Pathway A**: EDC-bounded propionic acid ester pathway; **Pathway B**: Anhydride activation pathway. We did comparison experiment by ^1H NMR in THF-d_8 to check the activation pathway of propionic acid **4-1a** by EDCI, as shown in Figure 4.1.

Scheme 4.5 Two Reaction Pathways for the Activation of Propionic Acid.

Figure 4.1 Comparison Experiment by ^1H NMR in THF-d_8

The NMR experiments indicated immediate formation of “B” upon mixing A and EDC·HCl (see the spectrum C). In the experiment using DBU as the base, propionic acid disappeared completely, while a considerable amount of propionic anhydride was observed (spectrum D). When a catalytic amount of the NHC catalyst **4-4c** was added, the spectrum did not change much (spectrum E), which indicated that propionic anhydride was dominant during the catalytic procedure. Therefore, we assume that pathway B is operating in this acid- β -activation process.

One of the most plausible pathway of our one-pot acid- β -functionalization process would begin with an anhydride formation step, which is summarized in Scheme 4.6. Propionic acid **4-1a** is first activated by EDC·HCl to form propionic anhydride **I**, which would then be attacked by an NHC catalyst to form an intermediate **II**. The intermediate **II** would then undergo an α -CH deprotonation to form an enolate intermediate **III**, which then go through a deprotonation / proton transfer process to form the key intermediate **IV**.

bearing a reactive nucleophilic β -carbon. Nucleophilic addition of the β -carbon of intermediate **IV** to the electrophile **4-2** or **4-5** followed by a lactone formation process gives the product **4-3** or **4-6**, while releasing the NHC catalyst to complete the catalytic cycle.

Scheme 4.6 Proposed Reaction Pathway.

It is also important to note that the acid activation process is crucial to both of the product yield and the enantioselectivity. The product **4-3a** would be formed in much lower yield and er value from the corresponding anhydride process (Table 4.5, entry 1). However, the product yield could be improved when corresponding propionic acid was

added as the additive (Entries 2, 3), which indicates that side reactions such as enolate reaction, polymerization of isatin under basic conditions and decomposition of the product could be suppressed under acidic conditions. But the enantioselectivities were not improved. When EDC·HCl derived urea was added, er values were improved to some extent, while the product yield remained moderate (Entries 4, 5). When the propionic acid and urea additives were added simultaneously, the er value was further improved (Entry 6), which indicates cooperation of the acid and the urea. Although the exact roles of these additives are unclear, the enhancement of the NHC-induced facial selectivity by hydrogen bonding may account for this improvement. This cooperating effect could be further strengthened when the urea additive was generated in situ from the acid and EDC·HCl (Entry 7). And the best results could be obtained from our acid activation pathway (Entry 8).

Table 4.5 Comparison of the Acid with the Anhydride Activation Approach.^[a]

Entry	4-1a (eq)	urea (eq)	Yield (%)	er
1	0	0	67	89:11
2	1	0	83	89:11
3	2	0	81	89:11
4	0	1	69	90:10
5	0	2	61	91:9
6	2	2	66	93:7
7	2	[b]	84	94:6
8	acid approach (Table 4.1 entry 1)		99	94:6

[a] 2 eq of **1**, 1 eq of **4-2a** (0.1 mmol), 10 mol% of **4-4a**, 2 eq of DBU and 1 mL of THF for 12 h. Yield was isolated yield. Ers were determined via chiral HPLC. [b] 2 Eq of EDCI was used instead of corresponding urea additive.

When it comes to the α -keto ester substrates **4-5**, our current acid activation approach again showed obvious advantages over the previously reported anhydride approach (Table 4.6). The direct use of an anhydride in this transformation afforded the product in much

lower yield and enantioselectivity (Entry 1). The addition of propionic acid into the anhydride activation reaction system dramatically improved the er value, but seriously decreased the reaction yield (Entries 2 to 3). A similar phenomenon was observed when applying urea as the additive (Entries 4 to 6). EDCI·HCl was effective only when used together with certain amount of propionic acid (Entries 7 to 9). And the highest yield and er value could only be obtained under the established acid activation approach.

Table 4.6 Comparison of the Acid with the Anhydride Activation Approach.^[a]

Entry	Propionic acid (eq)	urea (eq)	yield (%)	er
1	0	0	68	92:8
2	1	0	49	96:4
3	2	0	21	96:4
4	0	2	23	95:5
5	0	4	32	95:5
6	2	2	10	95:5
7	2	_[b]	59	95:5
8	0	_[b]	0	-
9	0	_[c]	0	-
10	acid approach (Table 5.3, entry 11)		98	95:5

[a] 2 eq of **I**, 1 eq of **4-5a** (0.1 mmol), 20 mol% of **4-4c**, 2 eq of K_2CO_3 and 1 mL of mesitylene at rt (24 °C) for 24 h. Yield was isolated yield after column chromatography. Er was determined *via* chiral HPLC. [b] 2 Eq of EDCI was used instead of corresponding urea additive. [c] 1 Eq of EDCI was used instead of corresponding urea additive.

4.3.2 Chiral Induction.

Based on literature works and our final product structure, we proposed the chiral induction pathway, which is illustrated in Scheme 4.7.

Scheme 4.7 Proposed Chiral Induction.

4.4 Summary.

In summary, we have disclosed the first β -functionalization of simple carboxylic acid. As one of the smallest C-3 synthons, propionic acid worked well to afford various lactone products in generally good yields and enantioselectivities. The one-pot strategy also represents an important new example of inert bond activation in the field of organocatalysis.

4.5 Experimental Section

4.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich 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.

4.5.2 General Procedures.

General Procedure for the Synthesis of Substrate 4-5.

To a stirred solution of **S1** (5 mmol), **S2** (6 mmol) in DCM (30 mL) was added one drop of DMF. After the bubbling was finished the solution was stirred for another 2h, and then concentrated to remove all the volatiles to afford crude **S3**, which was used without further purification.

The above residue was then dissolved in DCM (30 mL) and benzhydrol **S4** (6 mmol) was added. Then the solution was cooled to 0 °C and pyridine (6 mmol) was added. The reaction was allowed to warm to rt and stirred overnight. After that the reaction mixture was washed with water, dried over MgSO_4 and concentrated. Then the residue was subjected to column chromatography using hexane/EtOAc = 20/1 as eluent to yield the desired product **4-5a** as a white solid.

General Procedure for the Asymmetric Reaction of Aliphatic Acid 4-1 and Trt-Protected Isatin 4-2.

To a 4 mL vial equipped with a magnetic stir bar was added NHC precursor **4-4c** (0.01

mmol), **4-2a** (0.1 mmol), and EDCI (0.4 mmol). Then freshly distilled THF (1 mL), propionic acid (0.4 mmol), and DBU (0.2 mmol) was subsequently added. The vial was then capped and the biphasic mixture was stirred vigorously (1500 rpm) for 12h. Then the reaction mixture was concentrated and directly subjected to column chromatography using hexane/EtOAc = 7/1 as eluent to yield the desired product **4-3a** in 99% yield as a white solid.

General Procedure for the Asymmetric Reaction of Propionic Acid **4-1a** and Benzhydrol α -Ketoester **4-5**.

To a 4 mL vial equipped with a magnetic stir bar was added NHC precursor **4-4c** (0.01 mmol), **4-5a** (0.1 mmol), EDCI (0.4 mmol), and partial formed K_2CO_3 (0.2 mmol). Then Mesitylene (1 mL) and propionic acid (0.4 mmol) was subsequently added. The vial was then capped and the biphasic mixture was stirred vigorously (1500 rpm) for 48h. Then the reaction mixture was directly subjected to column chromatography using hexane/EtOAc = 8/1 as eluent to yield the desired product **4-6a** in 98% yield as a white solid.

Removal of Trt group on **4-3a**.

AcOH (3 mL) and PhOMe (0.5 mL) were added to **4-3a** (0.1 mmol). The mixture was stirred under reflux for 48h. Then the homogeneous solution was concentrated and subjected to column chromatography using hexane/EtOAc = 1/1 as eluent to yield the

desired product **4-7** in 90% yield as a colorless oil.

Transesterification of **4-3a**.

DMAP (0.11 mmol) were added to the solution of **4-3a** (0.1 mmol) in MeOH (0.5 mL). The mixture was stirred at rt for 24h. Then the mixture was concentrated and subjected to column chromatography using hexane/EtOAc = 3/1 as eluent to yield the desired product **4-8** in 99% yield as a colorless oil.

Removal of benzhydryl group on **4-6e**.

Trifluoroacetic acid (1 mL) was added to a solution of **4-6e** (0.2 mmol) in anisole (1 mL). The mixture was stirred for 4h at rt and concentrated and purified by column chromatography using hexane/EA = 5/1 to pure EA as eluent to afford **4-9** in 79% yield as a white powder.

Synthesis of amide **4-10** from carboxylic acid **4-9**.

To the solution of acid **4-9** (0.1 mmol) in DCM (1 mL) was added (COCl)₂ and a drop of DMF. After the bubbling was ceased the solution was stirred for an additional 30 min.

After that diphenyl amine (0.12 mmol) was added and the solution was cooled to 0 °C. Et₃N (30 μL) was then slowly added and the solution was warmed to rt and stirred overnight. After concentration the residue was directly subjected to column chromatography using hexane/EA = 5/1 as eluent to afford **4-10** in 80% yield as a white foam solid.

4.5.3 Stereochemistry Determination via X-Ray Crystallographic Analysis.

Absolute configuration of the product **4-6** was assigned based on the single crystal X-ray structures of **4-6e**. CCDC 1026847 (**4-6e**, obtained as colorless needles *via* evaporation of a hexane/CH₂Cl₂ solution) contains the supplementary X-ray crystallographic data.

4.5.4 Characterization of catalysts and products.

(S)-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3a)

White solid. M.P. 215-216 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.43 (m, 6H), 7.33-7.23 (m, 10H), 7.05-6.98 (m, 2H), 6.34-6.32 (m, 1H), 3.16 (ddd, $J = 9.9, 10.9, 17.6$ Hz, 1H), 2.75 (ddd, $J = 2.7, 9.6, 17.6$ Hz, 1H), 2.58 (ddd, $J = 2.6, 9.8, 13.2$ Hz, 1H), 2.46 (ddd, $J = 9.7, 10.9, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.1, 175.3, 143.9, 141.4, 129.3, 127.8, 127.2, 126.5, 123.7, 123.1, 116.5, 82.4, 74.6, 31.4, 28.4; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{24}\text{NO}_3^+$ 446.1751, found 446.1741; $[\alpha]_{\text{D}}^{20} = -3.2$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel IC, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (major) = 28.9 min, R_t (minor) = 36.3 min.

(S)-5'-fluoro-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3b)

White solid. M.P. 199-200 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.42 (m, 6H), 7.34-7.24 (m, 9H), 7.07 (dd, $J = 4.5, 7.3$ Hz, 1H), 6.72 (dt, $J = 2.7, 8.9$ Hz, 1H), 6.28 (dd, $J = 4.1, 9.0$ Hz, 1H), 3.16 (ddd, $J = 10.0, 10.9, 17.7$ Hz, 1H), 2.74 (ddd, $J = 2.4, 9.7, 17.6$ Hz, 1H), 2.60 (ddd, $J = 2.5, 9.8, 13.2$ Hz, 1H), 2.44 (ddd, $J = 9.9, 11.0, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.7, 175.2, 160.2, 157.8, 141.1, 139.7 (d, $J = 2.8$ Hz), 129.3, 128.1 (d, $J = 8.0$ Hz), 127.9, 127.3, 117.6 (d, $J = 7.5$ Hz), 116.3 (d, $J = 22.8$ Hz), 111.5 (d, $J = 24.7$ Hz), 82.1, 74.8, 31.5, 28.2; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{23}\text{FNO}_3^+$ 464.1656, found 464.1658; $[\alpha]_{\text{D}}^{20} = -17.8$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 94:6 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 6.8 min, R_t (major) = 7.7 min.

(S)-5'-chloro-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3c)

White solid. M.P. 204-206 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.41 (m, 6H), 7.34-7.25 (m, 10H), 6.98 (dd, $J = 2.3, 8.7$ Hz, 1H), 6.26 (d, $J = 8.7$ Hz, 1H), 3.15 (ddd, $J = 10.1, 10.8, 17.6$ Hz, 1H), 2.74 (ddd, $J = 2.5, 9.6, 17.6$ Hz, 1H), 2.59 (ddd, $J = 2.6, 9.8, 13.1$ Hz, 1H), 2.45 (ddd, $J = 9.9, 10.8, 13.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.6, 174.9, 142.4, 141.0, 129.7, 129.2, 128.8, 128.2, 127.9, 127.4, 124.2, 117.6, 81.9, 74.9, 31.4, 28.2; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{23}\text{ClNO}_3^+$ 480.1361, found 480.1353; $[\alpha]_D^{20} = 0.7$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 92:8 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 6.7 min, R_t (major) = 7.3 min.

(S)-5'-bromo-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3d)

White solid. M.P. 211-215 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.41 (m, 6H), 7.34-7.25 (m, 10H), 7.13 (dd, $J = 2.1, 8.7$ Hz, 1H), 6.21 (d, $J = 8.7$ Hz, 1H), 3.15 (dt, $J = 10.1, 17.7$ Hz, 1H), 2.74 (ddd, $J = 2.4, 9.6, 17.6$ Hz, 1H), 2.59 (ddd, $J = 2.4, 9.8, 13.0$ Hz, 1H), 2.45 (dt, $J = 10.1, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.6, 174.8, 142.9, 141.0, 132.6, 129.3, 129.2, 128.6, 128.0, 127.8, 127.4, 127.2, 127.0, 118.0, 116.1, 81.8, 74.9, 31.4, 28.2; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{23}\text{BrNO}_3^+$ 524.0856, found 524.0883; $[\alpha]_D^{20} = 0.8$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 92:8 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 6.8 min, R_t (major) = 7.5 min.

(S)-5'-iodo-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3e)

White solid. M.P. 197-200 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, $J = 1.8$ Hz, 1H), 7.42-7.39 (m, 6H), 7.33-7.25 (m, 10H), 6.09 (d, $J = 8.7$ Hz, 1H), 3.13 (ddd, $J = 9.9, 10.8, 17.6$ Hz, 1H), 2.73 (ddd, $J = 2.6, 9.6, 17.6$ Hz, 1H), 2.58 (ddd, $J = 2.6, 9.8, 13.2$ Hz, 1H), 2.44 (ddd, $J = 9.9, 10.8, 13.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.6, 174.6, 143.7, 141.0, 138.4, 132.6, 129.2, 128.8, 127.9, 127.8, 127.4, 118.4, 86.0, 81.7, 74.8, 31.4, 28.2; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{23}\text{INO}_3^+$ 572.0717, found 572.0712; $[\alpha]^{20}_{\text{D}} = 1.4$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel IA, Hexane/2-PrOH = 90/10, 0.75 mL/min), R_t (minor) = 9.0 min, R_t (major) = 10.2 min.

(S)-5'-methoxy-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3f)

White solid. M.P. 207-208 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.44 (m, 6H), 7.33-7.24 (m, 9H), 6.91 (d, $J = 2.7$ Hz, 1H), 6.54 (dd, $J = 2.7, 8.9$ Hz, 1H), 6.23 (d, $J = 8.9$ Hz, 1H), 3.74 (s, 3H), 3.17 (ddd, $J = 10.0, 11.0, 17.6$ Hz, 1H), 2.73 (ddd, $J = 2.4, 9.6, 17.6$ Hz, 1H), 2.58 (ddd, $J = 2.4, 9.8, 13.1$ Hz, 1H), 2.44 (ddd, $J = 9.8, 11.0, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.2, 175.2, 155.9, 141.5, 136.8, 129.3, 127.8, 127.7, 127.2, 117.3, 114.8, 109.9, 82.6, 74.6, 55.6, 31.6, 28.4; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{26}\text{NO}_4^+$ 476.1856, found 476.1856; $[\alpha]^{20}_{\text{D}} = 0.4$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 94:6 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 8.6 min, R_t (major) =

9.4 min.

(S)-5'-methyl-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3g)

White solid. M.P. 234-237 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.43 (m, 6H), 7.32-7.24 (m, 9H), 7.15 (d, $J = 1.1$ Hz, 1H), 6.81 (dd, $J = 1.1, 8.4$ Hz, 1H), 6.21 (d, $J = 8.3$ Hz, 1H), 3.16 (ddd, $J = 10.0, 10.8, 17.6$ Hz, 1H), 2.73 (ddd, $J = 2.7, 9.6, 17.6$ Hz, 1H), 2.57 (ddd, $J = 2.7, 9.8, 13.1$ Hz, 1H), 2.45 (ddd, $J = 9.7, 10.9, 13.2$ Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.2, 175.3, 141.5, 141.4, 132.8, 130.1, 129.3, 127.8, 127.2, 126.5, 124.4, 116.3, 82.6, 74.6, 31.4, 28.5, 20.7; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{26}\text{NO}_3^+$ 460.1907, found 460.1921; $[\alpha]_D^{20} = 1.0$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 95:5 *er* (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 6.9 min, R_t (major) = 7.9 min.

(S)-7'-fluoro-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3h)

White solid. M.P. 121-122 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.40 (m, 6H), 7.32-7.24 (m, 9H), 7.22 (dd, $J = 1.1, 7.4$ Hz, 1H), 7.08 (ddd, $J = 3.9, 7.5, 8.3$ Hz, 1H), 6.82 (ddd, $J = 1.1, 8.4, 12.1$ Hz, 1H), 3.15 (ddd, $J = 10.0, 10.7, 17.6$ Hz, 1H), 2.80-2.66 (m, 2H), 2.51 (ddd, $J = 9.8, 10.6, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.7, 174.8, 148.0, 145.5, 142.9 (d, $J = 2.5$), 130.8 (d, $J = 8.5$), 129.3 (d, $J = 2.3$), 128.8 (d, $J = 2.0$), 127.7, 127.0, 125.1 (d, $J = 7.1$), 120.3 (d, $J = 24.0$), 120.0 (d, $J = 3.3$), 82.1 (d, $J = 2.2$),

75.2, 31.7, 28.3; HRMS (ESI, m/z): calcd. for $C_{30}H_{23}FNO_3^+$ 464.1656, found 464.1668; $[\alpha]_D^{20} = -4.1$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel IA, Hexane/2-PrOH = 90/10, 0.75 mL/min), R_t (minor) = 10.6 min, R_t (major) = 11.5 min.

(S)-5'-(trifluoromethoxy)-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3i)

White solid. M.P. 138-139 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 6H), 7.34-7.26 (m, 9H), 7.21 (d, $J = 1.4$ Hz, 1H), 6.87 (dd, $J = 1.7, 8.9$ Hz, 1H), 6.32 (d, $J = 9.0$ Hz, 1H), 3.16 (ddd, $J = 9.9, 10.9, 17.6$ Hz, 1H), 2.74 (ddd, $J = 2.3, 9.7, 12.0$ Hz, 1H), 2.60 (ddd, $J = 2.3, 9.8, 13.1$ Hz, 1H), 2.45 (ddd, $J = 9.9, 10.9, 13.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 175.1, 144.9, 142.4, 141.0, 129.2, 128.1, 128.0, 127.4, 122.5, 117.2 (d, $J = 12.6$), 81.8, 74.9, 31.5, 28.2; HRMS (ESI, m/z): calcd. for $C_{31}H_{23}FNO_4^+$ 530.1574, found 530.1564; $[\alpha]_D^{20} = -2.9$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel IA, Hexane/2-PrOH = 90/10, 0.75 mL/min), R_t (minor) = 6.9 min, R_t (major) = 7.7 min.

(S)-5'-nitro-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3j)

White solid. M.P. 222-224 °C; 1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 2.4$ Hz, 1H), 7.94 (dd, $J = 2.4, 9.1$ Hz, 1H), 7.42-7.39 (m, 6H), 7.37-7.27 (m, 9H), 6.45 (d, $J = 9.1$ Hz, 1H), 3.16 (dt, $J = 10.3, 17.7$ Hz, 1H), 2.81 (ddd, $J = 2.5, 9.5, 17.7$ Hz, 1H), 2.64 (ddd, $J =$

2.4, 9.8, 13.0 Hz, 1H), 2.54 (ddd, $J = 10.2, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.2, 175.0, 149.6, 143.4, 140.5, 129.1, 128.1, 127.7, 127.6, 125.9, 119.6, 116.3, 81.1, 75.5, 31.2, 28.0; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{23}\text{N}_2\text{O}_5^+$ 491.1601, found 491.1606; $[\alpha]^{20}_{\text{D}} = -0.4$ ($c = 1.5$ in CH_2Cl_2); HPLC analysis: 87:13 er (Chiralcel IA, Hexane/2-PrOH = 90/10, 0.75 mL/min), R_t (minor) = 12.8 min, R_t (major) = 14.8 min.

3-methyl-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3k)

White solid. M.P. 228-231 °C; ^1H NMR (400 MHz, CDCl_3) major diastereomer: δ 7.44-7.42 (m, 6H), 7.31-7.23 (m, 11H), 7.05-6.98 (m, 2H), 6.34 (dd, $J = 7.1, 1.6$ Hz, 1H), 2.99-2.88 (m, 2H), 2.75-2.64 (m, 1H), 1.09 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) major diastereomer: δ 175.4, 174.5, 144.6, 141.4, 129.6, 129.4, 129.2, 127.8, 127.8, 127.2, 125.2, 123.7, 123.0, 116.5, 85.7, 75.1, 40.9, 35.1, 13.0; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{26}\text{NO}_3^+$ 460.1907, found 460.1906; $[\alpha]^{20}_{\text{D}} = -0.6$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: Major diastereomer 98:2 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 7.1 min, R_t (major) = 7.5 min; Minor diastereomer 90:10 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 8.4 min, R_t (major) = 14.3 min.

(2S,3S)-3-(3-bromopropyl)-1'-trityl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3l)

White solid. M.P. 193-194 °C; ^1H NMR (400 MHz, CDCl_3) major + minor diastereomers:

δ 7.45-7.41 (m, 6H), 7.30-7.20 (m, 11H), 7.02-7.00 (m, 2H), 6.38-6.31 (m, 1H), 3.55-3.19 (m, 2H), 2.99-2.89 (m, 1H), 2.80-2.36 (m, 2H), 1.71-1.33 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) major + minor diastereomers: δ 175.0 (d, $J = 2.8$ Hz), 174.1 (d, $J = 2.5$ Hz), 144.5, 141.4, 129.8, 129.6, 129.3, 129.1, 127.8, 127.2, 127.1, 125.4, 125.4, 124.7, 123.8, 123.2, 116.5, 84.8, 75.1, 45.5, 45.4, 44.3, 33.9, 32.7, 30.9, 30.9, 29.7, 27.4, 26.1; HRMS (ESI, m/z): calcd. for $\text{C}_{33}\text{H}_{29}\text{BrNO}_3^+$ 566.1325, found 566.1320; $[\alpha]^{20}_{\text{D}} = 11.3$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: Major diastereomer 98:2 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 7.6 min, R_t (major) = 8.8 min; Minor diastereomer 60:40 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 9.3 min, R_t (major) = 11.6 min.

(S)-1'-methyl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3m)

White solid. M.P. 123-124 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (td, $J = 1.2, 7.8$ Hz, 1H), 7.38 (dd, $J = 0.6, 7.5$ Hz, 1H), 7.16 (td, $J = 0.8, 7.6$ Hz, 1H), 6.89 (d, $J = 7.8$ Hz, 1H), 3.28-3.18 (m, 4H), 2.79 (ddd, $J = 3.2, 9.5, 17.6$ Hz, 1H), 2.60 (ddd, $J = 3.2, 9.7, 13.3$ Hz, 1H), 2.48 (ddd, $J = 9.5, 10.6, 13.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.0, 174.2, 143.9, 131.2, 126.4, 124.2, 123.6, 108.9, 82.3, 31.3, 28.3, 26.3; HRMS (ESI, m/z): calcd. for $\text{C}_{12}\text{H}_{12}\text{NO}_3^+$ 218.0812, found 218.0813; $[\alpha]^{20}_{\text{D}} = 7.7$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 63:37 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 13.4 min, R_t (major) = 15.4 min.

(S)-1'-allyl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3n)

White solid. M.P. 107-108 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.36 (m, 2H), 7.15 (td, $J = 0.8, 7.6$ Hz, 1H), 6.89-6.87 (m, 1H), 5.90-5.80 (m, 1H), 5.30-5.29 (m, 1H), 5.27-5.23 (m, 1H), 4.35-4.32 (m, 2H), 3.23 (ddd, $J = 9.8, 10.7, 17.7$ Hz, 1H), 2.80 (ddd, $J = 3.1, 9.5, 17.6$ Hz, 1H), 2.61 (ddd, $J = 3.1, 9.7, 13.2$ Hz, 1H), 2.50 (ddd, $J = 9.5, 10.7, 13.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.0, 174.0, 143.1, 131.1, 130.6, 126.4, 124.3, 123.6, 118.2, 109.8, 82.2, 42.4, 31.4, 28.3; HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{14}\text{NO}_3^+$ 244.0968, found 244.0980; $[\alpha]_D^{20} = 10.8$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 65:35 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 10.8 min, R_t (major) = 13.2 min.

(S)-1'-benzyl-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-3o)

White solid. M.P. 113-114 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.28 (m, 7H), 7.12 (td, $J = 0.8, 7.6$ Hz, 1H), 6.77 (d, $J = 7.8$ Hz, 1H), 4.90 (s, 2H), 3.27 (ddd, $J = 9.7, 10.7, 17.6$ Hz, 1H), 2.82 (ddd, $J = 3.0, 9.5, 17.6$ Hz, 1H), 2.66 (ddd, $J = 3.0, 9.7, 13.3$ Hz, 1H), 2.53 (ddd, $J = 9.6, 10.7, 13.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.0, 174.4, 143.0, 134.9, 131.1, 129.0, 128.0, 127.3, 126.4, 124.3, 123.6, 109.9, 82.3, 43.9, 31.5, 28.3; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}_3^+$ 294.1125, found 294.1123; $[\alpha]_D^{20} = 15.2$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 73:27 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 13.8 min, R_t (major) = 19.8 min.

benzhydryl 2-oxo-2-phenylacetate (4-5a)

White solid. M.P. 64-65 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.92-7.89 (m, 2H), 7.62 (tt, J = 1.2, 7.4 Hz, 1H), 7.47-7.30 (m, 12H), 7.15 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 186.0, 163.1, 139.0, 135.0, 132.5, 130.0, 128.9, 128.7, 128.4, 127.2, 78.8; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{17}\text{O}_3^+$ 317.1172, found 317.1173.

benzhydryl 2-(3-chlorophenyl)-2-oxoacetate (4-5b)

Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (t, J = 1.8 Hz, 1H), 7.80 (dt, J = 1.2, 7.9 Hz, 1H), 7.60 (dq, J = 1.0, 8.0 Hz, 1H), 7.43-7.31 (m, 11H), 7.13 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 184.5, 162.3, 138.7, 135.3, 134.8, 134.0, 130.2, 129.9, 128.8, 128.5, 128.2, 127.2, 79.2; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{ClO}_3^+$ 351.0782, found 351.0782.

benzhydryl 2-(4-chlorophenyl)-2-oxoacetate (4-5c)

Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 8.5 Hz, 2H), 7.48-7.35 (m, 12H), 7.16 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 184.5, 162.5, 141.7, 138.8, 131.4, 130.9, 129.3, 128.7, 128.5, 128.4, 127.3, 127.2, 79.0; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{ClO}_3^+$ 351.0782, found 351.0786.

benzhydryl 2-(2-chlorophenyl)-2-oxoacetate (4-5d)

White solid. M.P. 72-73 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 7.4$ Hz, 1H), 7.45-7.26 (m, 13H), 7.10 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 186.2, 162.3, 138.8, 134.5, 134.0, 133.1, 131.8, 130.6, 128.7, 128.4, 127.4, 127.3, 79.2; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{ClO}_3^+$ 351.0782, found 351.0786.

benzhydryl 2-(3-bromophenyl)-2-oxoacetate (4-5e)

Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.06 (t, $J = 1.6$ Hz, 1H), 7.84 (dt, $J = 1.4$, 7.8 Hz, 1H), 7.84 (dq, $J = 0.8$, 8.0 Hz, 1H), 7.43-7.31 (m, 11H), 7.13 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 184.4, 162.2, 138.7, 137.7, 134.2, 132.8, 130.4, 128.8, 128.6, 128.5, 127.9, 127.2, 127.1, 79.2; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{BrO}_3^+$ 395.0277, found 395.0284.

benzhydryl 2-(4-bromophenyl)-2-oxoacetate (4-5f)

Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.80-7.77 (m, 2H), 7.62-7.59 (m, 2H), 7.43-7.31 (m, 10H), 7.13 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 184.7, 162.5, 138.8, 132.3, 131.4, 131.3, 130.6, 128.7, 128.5, 128.4, 127.3, 127.2, 79.1; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{BrO}_3^+$ 395.0277, found 395.0280.

benzhydryl 2-(2-bromophenyl)-2-oxoacetate (4-5g)

Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.62 (m, 1H), 7.59-7.57 (m, 1H), 7.42-7.29 (m, 12H), 7.09 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 186.9, 161.6, 138.7, 135.4, 134.0, 133.8, 131.9, 128.7, 128.6, 128.5, 128.4, 127.7, 127.4, 127.2, 126.6, 121.6, 79.2; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{BrO}_3^+$ 397.0257, found 397.0276.

benzhydryl 2-(3-methoxyphenyl)-2-oxoacetate (4-5h)

White solid. M.P. 87-88 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.53-7.35 (m, 13H), 7.23-7.21 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 186.0, 163.2, 160.0, 139.0, 133.7, 130.0, 128.7, 128.4, 127.3, 123.1, 122.2, 113.1, 78.9, 55.5; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{19}\text{O}_4^+$ 347.1278, found 347.1290.

benzhydryl 2-oxo-2-(p-tolyl)acetate (4-5i)

White solid. M.P. 58-59 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.87-7.83 (m, 2H), 7.47-7.29 (m, 12H), 7.21-7.19 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 185.7, 163.3, 146.3, 139.1, 130.2, 130.0, 129.7, 128.7, 128.5, 128.4, 127.2, 78.7, 21.9; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{19}\text{O}_3^+$ 331.1329, found 331.1343.

benzhydryl 2-(2-fluorophenyl)-2-oxoacetate (4-5j)

White solid. M.P. 67-68 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (td, $J = 1.8, 7.6$ Hz, 1H), 7.65-7.59 (m, 1H), 7.41-7.26 (m, 11H), 7.14-7.10 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 183.6, 163.5 (d, $J = 91.5$ Hz), 161.4, 138.8, 136.8 (d, $J = 8.9$ Hz), 131.0, 128.7, 128.6, 128.5, 128.4, 128.3, 127.6, 127.3, 127.2, 126.5, 124.8 (d, $J = 3.4$ Hz), 79.0; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{FO}_3^+$ 335.1078, found 335.1087.

benzhydryl 2-(3-fluorophenyl)-2-oxoacetate (4-5k)

White solid. M.P. 56-57 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 7.7$ Hz, 1H), 7.64 (d, $J = 9.0$ Hz, 1H), 7.45-7.31 (m, 12H), 7.14 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 184.5 (d, $J = 2.6$ Hz), 163.2 (d, $J = 163.9$ Hz), 161.5, 138.8, 134.4 (d, $J = 7.0$ Hz), 130.6 (d, $J = 7.9$ Hz), 128.7, 128.5, 127.2, 126.0 (d, $J = 3.2$ Hz), 122.1 (d, $J = 21.3$ Hz), 116.4 (d, $J = 23.0$ Hz), 79.1; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{FO}_3^+$ 335.1078, found 335.1081.

benzhydryl 2-(3-nitrophenyl)-2-oxoacetate (4-5l)

Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.82 (t, $J = 1.8$ Hz, 1H), 8.47 (ddd, $J = 0.9, 2.1, 8.2$ Hz, 1H), 8.29 (dt, $J = 1.3, 7.9$ Hz, 1H), 7.68 (t, $J = 8.0$ Hz, 1H), 7.45-7.24 (m, 10H), 7.16 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 183.2, 161.5, 148.5, 143.8, 138.5, 135.4, 133.9, 130.2, 128.9, 128.8, 128.6, 128.5, 127.6, 127.2, 126.5, 125.0, 79.7; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{NO}_5^+$ 362.1023, found 362.1030.

benzhydryl 2-oxopropanoate (4-5m)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.30 (m, 10H), 6.95 (s, 1H), 2.48 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 191.5, 159.9, 139.0, 128.7, 128.4, 127.2, 79.0, 26.8;

HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{15}\text{O}_3^+$ 255.1016, found 255.1017.

benzhydryl (R)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (4-6a)

White solid. M.P. 94-95 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.38 (m, 2H), 7.30-7.24 (m, 3H), 7.18-7.12 (m, 6H), 7.08-7.06 (m, 4H), 6.72 (s, 1H), 2.95-2.85 (m, 1H), 2.50-2.34 (m, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 169.2, 139.3, 139.3, 137.8, 128.9, 128.7, 128.6, 128.6, 128.2, 126.8, 125.3, 87.0, 79.0, 33.0, 28.2; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{21}\text{O}_4^+$ 373.1434, found 373.1440; $[\alpha]_D^{20} = 11.6$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis:

95:5 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 10.7 min, R_t (major) = 30.9 min.

benzhydryl (R)-2-(3-chlorophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6b)

White solid. M.P. 106-107 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.51-7.50 (m, 1H), 7.39-7.24 (m, 9H), 7.21-7.17 (m, 4H), 6.82 (s, 1H), 3.05-2.99 (m, 1H), 2.59-2.46 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 168.7, 139.7, 139.0, 139.0, 134.8, 130.0, 129.1, 128.7,

128.6, 128.3, 126.8, 125.7, 123.4, 86.3, 79.3, 33.1, 28.0; HRMS (ESI, m/z): calcd. for

$C_{24}H_{20}ClO_4^+$ 407.1045, found 407.1053; $[\alpha]^{20}_D = 13.0$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 9.6 min, R_t (major) = 28.6 min.

benzhydryl (R)-2-(4-chlorophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6c)

White solid. M.P. 131-133 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.31-7.25 (m, 6H), 7.19-7.16 (m, 4H), 6.81 (s, 1H), 3.05-2.99 (m, 1H), 2.59-2.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 168.9, 139.0, 139.0, 136.3, 135.0, 128.9, 128.6, 128.6, 128.3, 126.8, 126.7, 86.5, 79.2, 33.1, 28.1; HRMS (ESI, m/z): calcd. for $C_{24}H_{20}ClO_4^+$ 409.1016, found 409.1028; $[\alpha]^{20}_D = 12.8$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 9.5 min, R_t (major) = 28.5 min.

benzhydryl (R)-2-(2-chlorophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6d)

Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 1H), 7.31-7.11 (m, 11H), 7.03-7.00 (m, 2H), 6.78 (s, 1H), 3.37 (ddd, $J = 4.8, 10.0, 13.4$ Hz, 1H), 2.78 (ddd, $J = 8.3, 10.1, 18.1$ Hz, 1H), 2.48 (ddd, $J = 4.9, 10.0, 17.9$ Hz, 1H), 2.33 (ddd, $J = 8.2, 9.9, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 167.6, 139.1, 139.0, 137.1, 131.1, 130.4, 129.9, 128.5, 128.4, 128.1, 127.1, 127.1, 126.7, 126.3, 87.0, 79.1, 31.0, 28.0; HRMS (ESI, m/z): calcd. for $C_{24}H_{20}ClO_4^+$ 407.1045, found 407.1053; $[\alpha]^{20}_D = 46.6$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 92:8 er (Chiralcel AS-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t

(major) = 15.6 min, Rt (minor) = 20.8 min.

benzhydryl (R)-2-(3-bromophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6e)

White solid. M.P. 118-119 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.66 (t, J = 1.8 Hz, 1H), 7.50 (dq, J = 0.9, 7.9 Hz, 1H), 7.42 (ddd, J = 0.9, 1.4, 7.8 Hz, 1H), 7.31-7.23 (m, 7H), 7.20-7.17 (m, 4H), 6.82 (s, 1H), 3.04-2.98 (m, 1H), 2.63-2.46 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 168.7, 139.9, 139.0, 139.0, 132.0, 130.2, 128.7, 128.6, 128.5, 128.3, 126.8, 126.8, 123.9, 122.8, 86.2, 79.3, 33.1, 28.0; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{BrO}_4^+$ 451.0539, found 451.0545; $[\alpha]_D^{20}$ = 11.9 (c = 1.0 in CH_2Cl_2); HPLC analysis: 96:4 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), Rt (minor) = 10.3 min, Rt (major) = 27.7 min.

benzhydryl (R)-2-(4-bromophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6f)

White solid. M.P. 137-138 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.56-7.54 (m, 2H), 7.41-7.39 (m, 2H), 7.33-7.29 (m, 6H), 7.23-7.21 (m, 4H), 6.85 (s, 1H), 3.09-3.02 (m, 1H), 2.62-2.48 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 168.8, 139.0, 139.0, 136.8, 131.8, 128.7, 128.6, 128.3, 128.3, 127.0, 126.8, 123.2, 86.5, 79.2, 33.1, 28.1; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{BrO}_4^+$ 451.0539, found 451.0583; $[\alpha]_D^{20}$ = 12.5 (c = 1.0 in CH_2Cl_2); HPLC analysis: 94:6 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), Rt (minor) = 10.0 min, Rt (major) = 30.1 min.

benzhydryl (R)-2-(2-bromophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6g)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.62 (dd, $J = 1.6, 7.9$ Hz, 1H), 7.48 (dd, $J = 1.0, 7.9$ Hz, 1H), 7.35-7.12 (m, 10H), 7.03-7.01 (m, 2H), 6.79 (s, 1H), 3.45 (ddd, $J = 4.9, 10.0, 13.3$ Hz, 1H), 2.78 (ddd, $J = 8.1, 10.3, 18.0$ Hz, 1H), 2.48 (ddd, $J = 5.1, 10.0, 17.9$ Hz, 1H), 2.34 (ddd, $J = 7.8, 10.0, 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.3, 167.5, 139.1, 138.9, 138.7, 133.9, 130.0, 128.6, 128.5, 128.4, 128.1, 128.1, 127.6, 127.6, 127.4, 127.2, 126.8, 126.7, 126.6, 120.2, 88.0, 79.2, 31.1, 28.0; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{BrO}_4^+$ 451.0539, found 451.0564; $[\alpha]^{20}_{\text{D}} = 38.5$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 91:9 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (major) = 10.7 min, R_t (minor) = 11.4 min.

benzhydryl (R)-2-(3-methoxyphenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6h)

White solid. M.P. 105-106 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.18 (m, 11H), 7.07-7.02 (m, 2H), 6.92-6.90 (m, 1H), 6.81 (s, 1H), 3.76 (s, 3H), 3.04-3.01 (m, 1H), 2.58-2.52 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.0, 169.1, 159.8, 139.2, 139.2, 139.1, 129.8, 128.6, 128.5, 128.2, 126.8, 126.8, 117.4, 114.8, 110.6, 87.0, 79.0, 55.4, 33.0, 28.2; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{23}\text{O}_5^+$ 403.1540, found 403.1520; $[\alpha]^{20}_{\text{D}} = 18.7$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 93:7 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 10.6 min, R_t (major) = 26.4 min.

benzhydryl (R)-5-oxo-2-(p-tolyl)tetrahydrofuran-2-carboxylate (4-6i)

White solid. M.P. 111-113 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.29 (m, 2H), 7.20-7.17 (m, 6H), 7.12-7.10 (m, 6H), 6.73 (s, 1H), 2.95-2.87 (m, 1H), 2.51-2.43 (m, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 169.4, 139.3, 139.2, 138.8, 134.7, 129.3, 128.6, 128.5, 128.1, 128.1, 126.8, 125.2, 87.1, 78.9, 33.0, 28.2, 21.1; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{23}\text{O}_4^+$ 387.1591, found 387.1592; $[\alpha]_D^{20} = 6.6$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 94:6 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 8.6 min, R_t (major) = 21.3 min.

benzhydryl (R)-2-(2-fluorophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6j)

White solid. M.P. 101-102 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.63 (td, $J = 1.7, 7.7$ Hz, 1H), 7.44-7.39 (m, 1H), 7.34-7.19 (m, 11H), 7.13 (ddd, $J = 1.0, 8.2, 11.1$ Hz, 1H), 6.88 (s, 1H), 3.20-3.15 (m, 1H), 2.83-2.73 (m, 1H), 2.65-2.53 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 168.1, 160.8, 158.3, 139.2 (d, $J = 3.2$ Hz), 130.7 (d, $J = 8.4$ Hz), 128.6 (d, $J = 4.1$ Hz), 128.1, 126.7 (d, $J = 9.5$ Hz), 126.0 (d, $J = 13.0$ Hz), 124.3 (d, $J = 3.2$ Hz), 116.0 (d, $J = 21.5$ Hz), 85.0, 79.1, 32.0, 27.9; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{FO}_4^+$ 391.1340, found 391.1372; $[\alpha]_D^{20} = 28.2$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 8.8 min, R_t (major) = 11.9 min.

benzhydryl (R)-2-(3-fluorophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6k)

White solid. M.P. 88-90 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.16 (m, 13H), 7.06 (tdd, J = 0.9, 2.6, 8.3 Hz, 1H), 6.82 (s, 1H), 3.05-2.99 (m, 1H), 2.61-2.47 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 168.8, 164.0, 161.5, 140.2 (d, J = 7.3 Hz), 139.0 (d, J = 5.1 Hz), 130.4 (d, J = 8.3 Hz), 128.6 (d, J = 4.7 Hz), 128.3 (d, J = 2.6 Hz), 126.7, 120.9 (d, J = 3.0 Hz), 115.8 (d, J = 21.0 Hz), 112.8 (d, J = 23.3 Hz), 86.4 (d, J = 1.9 Hz), 79.2, 33.1, 28.0; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{FO}_4^+$ 391.1340, found 391.1355; $[\alpha]^{20}_{\text{D}}$ = 17.6 (c = 1.0 in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 9.1 min, R_t (major) = 31.2 min.

benzhydryl (R)-2-(3-nitrophenyl)-5-oxotetrahydrofuran-2-carboxylate (4-6l)

White solid. M.P. 149-150 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.38 (t, J = 1.9 Hz, 1H), 8.23 (ddd, J = 1.0, 2.2, 8.2 Hz, 1H), 7.85 (ddd, J = 1.0, 1.7, 7.9 Hz, 1H), 7.57 (t, J = 8.2 Hz, 1H), 7.31-7.27 (m, 6H), 7.22-7.19 (m, 4H), 6.85 (s, 1H), 3.13-3.07 (m, 1H), 2.65-2.51 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 168.4, 148.4, 139.9, 138.7, 138.7, 131.3, 129.8, 128.7, 128.4, 128.4, 126.8, 123.8, 120.7, 85.9, 79.7, 33.4, 28.0; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{NO}_6^+$ 418.1285, found 418.1294; $[\alpha]^{20}_{\text{D}}$ = 13.1 (c = 1.0 in CH_2Cl_2); HPLC analysis: 91:9 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 17.4 min, R_t (major) = 42.7 min.

benzhydryl (S)-2-methyl-5-oxotetrahydrofuran-2-carboxylate (4-6m)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.26 (m, 10H), 6.91 (s, 1H), 2.58-2.53 (m, 2H), 2.47 (ddd, $J = 3.9, 8.4, 16.7$ Hz, 1H), 2.12 (dt, $J = 9.4, 12.7$ Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.8, 170.6, 143.8, 139.3, 139.2, 128.7, 128.7, 128.5, 128.4, 128.2, 127.6, 127.0, 126.8, 126.6, 83.9, 78.6, 33.0, 28.5, 23.6; HRMS (ESI, m/z): calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_4^+$ 311.1278, found 311.1276; $[\alpha]_D^{20} = 6.3$ ($c = 2.6$ in CH_2Cl_2); HPLC analysis: 87:13 er (Chiralcel AS-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 16.7 min, R_t (major) = 19.8 min.

methyl (R)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (4-6n)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.51-7.50 (m, 2H), 7.43-7.37 (m, 3H), 3.76 (s, 3H), 3.10-3.07 (m, 1H), 2.68-2.54 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.9, 170.9, 138.0, 128.8, 128.7, 125.0, 86.9, 53.4, 33.5, 28.1; HRMS (ESI, m/z): calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_4^+$ 221.0808, found 221.0808; $[\alpha]_D^{20} = 15.5$ ($c = 1.5$ in CH_2Cl_2); HPLC analysis: 82:18 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 10.4 min, R_t (major) = 11.9 min.

ethyl (R)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (4-6o)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.52-7.50 (m, 2H), 7.42-7.35 (m, 3H), 4.21

(dd, $J = 7.2, 14.2$ Hz, 2H), 3.11-3.05 (m, 1H), 2.70-2.51 (m, 3H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.0, 170.3, 138.1, 128.8, 128.6, 125.0, 86.9, 62.6, 33.4, 28.1, 13.9; HRMS (ESI, m/z): calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_4^+$ 235.0965, found 235.0971; $[\alpha]^{20}_{\text{D}} = 11.1$ ($c = 1.5$ in CH_2Cl_2); HPLC analysis: 85:15 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 8.8 min, R_t (major) = 10.0 min.

isopropyl (R)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (4-6p)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.51-7.49 (m, 2H), 7.41-7.33 (m, 3H), 5.03 (dt, $J = 6.3, 12.5$ Hz, 1H), 3.07-3.03 (m, 1H), 2.65-2.52 (m, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 1.19 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 169.8, 138.1, 128.7, 128.6, 125.1, 87.0, 70.5, 33.4, 28.2, 21.5, 21.4; HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{17}\text{O}_4^+$ 249.1121, found 249.1125; $[\alpha]^{20}_{\text{D}} = 8.5$ ($c = 1.4$ in CH_2Cl_2); HPLC analysis: 91:9 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 7.4 min, R_t (major) = 8.1 min.

phenyl (R)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (4-6q)

White solid. M.P. 119-120 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.63-7.60 (m, 2H), 7.48-7.33 (m, 5H), 7.23 (t, $J = 7.3$ Hz, 1H), 7.01-6.99 (m, 2H), 3.27-3.22 (m, 1H), 2.80-2.62 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 168.8, 150.3, 137.6, 129.5, 129.1, 128.9, 126.4, 125.1, 120.9, 86.9, 33.3, 28.1; HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{15}\text{O}_4^+$ 283.0965, found 283.0961; $[\alpha]^{20}_{\text{D}} = 28.6$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 91:9 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 10.9 min, R_t (major) = 11.8 min.

benzyl (R)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (4-6r)

White solid. M.P. 79-80 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.51-7.49 (m, 2H), 7.41-7.36 (m, 3H), 7.34-7.30 (m, 3H), 7.22-7.20 (m, 2H), 5.18 (s, 2H), 3.08-3.01 (m, 1H), 2.64-2.51 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.9, 170.1, 137.8, 134.9, 128.9, 128.7, 128.6, 128.5, 127.8, 125.1, 86.9, 67.9, 33.3, 28.1; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_4^+$ 297.1121, found 297.1136; $[\alpha]^{20}_{\text{D}} = 18.7$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 91:9 er (Chiralcel OD-H, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 11.6 min, R_t (major) = 22.9 min.

(S)-3,4-dihydro-5H-spiro[furan-2,3'-indoline]-2',5-dione (4-7)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.98 (br s, 1H), 7.29-7.26 (m, 2H), 7.05 (t, $J = 7.5$ Hz, 1H), 6.85 (d, $J = 7.8$ Hz, 1H), 3.11 (dt, $J = 9.9, 17.7$ Hz, 1H), 2.71 (ddd, $J = 3.0, 9.6, 17.6$ Hz, 1H), 2.56 (ddd, $J = 3.0, 9.7, 13.2$ Hz, 1H), 2.40 (ddd, $J = 9.7, 10.6, 13.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.1, 176.0, 140.9, 131.2, 126.7, 124.7, 123.7, 110.7, 82.5, 31.4, 28.2; HRMS (ESI, m/z): calcd. for $\text{C}_{11}\text{H}_{10}\text{NO}_3^+$ 204.0655, found 204.0661; $[\alpha]^{20}_{\text{D}} = 16.9$ ($c = 1.6$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel IC, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (minor) = 30.3 min, R_t (major) = 33.7 min.

methyl (S)-3-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)propanoate (4-8)

Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.43 (m, 6H), 7.35-7.21 (m, 11H), 7.00-6.91 (m, 2H), 6.34 (d, $J = 7.5$ Hz, 1H), 3.66 (s, 3H), 2.90 (br s, 1H), 2.51-2.29 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.8, 173.5, 142.8, 141.8, 130.0, 129.3, 129.2, 128.2, 127.8, 127.8, 127.0, 123.4, 122.6, 116.3, 75.1, 74.5, 51.8, 34.2, 28.1; MS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{28}\text{NO}_4^+$ 478.2013, found 478.2053; $[\alpha]^{20}_{\text{D}} = -9.8$ ($c = 1.8$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel IA, Hexane/2-PrOH = 80/20, 0.75 mL/min), R_t (major) = 7.0 min, R_t (minor) = 9.8 min.

(R)-2-(3-bromophenyl)-5-oxotetrahydrofuran-2-carboxylic acid (4-9)

White solid. M.P. 137-138 $^{\circ}\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.9 (br s, 1H), 7.61-7.56 (m, 2H), 7.49-7.47 (m, 1H), 7.42-7.38 (m, 1H), 2.98-2.92 (m, 1H), 2.72-2.52 (m, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 175.8, 171.7, 141.9, 131.8, 131.2, 128.5, 125.0, 122.1, 86.2, 32.9, 28.3; MS (ESI, m/z): calcd. for $\text{C}_{11}\text{H}_9\text{BrO}_4^+$ 284.9757, found 284.9757; $[\alpha]^{20}_{\text{D}} = 13.6$ ($c = 0.5$ in CH_2Cl_2).

(R)-2-(3-bromophenyl)-5-oxo-N,N-diphenyltetrahydrofuran-2-carboxamide (4-10)

Light yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.32-6.97 (m, 14H), 3.48 (ddd, $J = 5.1$, 9.0, 12.9 Hz, 1H), 2.68 (dt, $J = 8.9$, 17.7 Hz, 1H), 2.38 (ddd, $J = 5.1$, 8.9, 17.7 Hz, 1H), 2.07 (dt, $J = 8.8$, 12.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.2, 168.6, 142.4, 131.1, 130.2, 128.9, 126.5, 122.9, 121.8, 88.5, 36.1, 28.3; MS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{19}\text{BrNO}_3^+$ 436.0543, found 435.0536; $[\alpha]^{20}_{\text{D}} = 83.8$ ($c = 1.0$ in CH_2Cl_2); HPLC analysis: 95:5 er (Chiralcel IA, Hexane/2-PrOH = 90/10, 0.7 mL/min), R_t (minor) = 11.3 min, R_t (major) = 13.0 min.

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Chapter 5

Enantioselective Intramolecular Aza [4+2]

Annulation Catalyzed by Simple

Organic Phosphine Catalysts

5.1 Introduction

5.1.1 Organocatalytic Diels-Alder Reactions

Of readily available synthetic methods in the formation of six-membered rings, the Diels-Alder reactions have always been the most common and efficient ones (Scheme 5.1).¹ During the last few decades, asymmetric inverse-electron-demand Diels-Alder (IEDDA) reactions, initiated by Kobayashi and coworkers,² have been intensively developed in both the fields of Lewis acid³ catalysis and organocatalysis⁴ through lowering the LUMO energy of dienes. Since the first report of iminium catalysis from MacMillan's group,⁵ asymmetric Diels-Alder reactions in organocatalysis have attracted much attention.⁶ On the other hand, by raising HOMO energy of the dienophiles, Jørgensen and co-workers disclosed another activation mode of IEDDA reaction through enamine catalysis.⁷ Great success has also been achieved by Jacobsen, Chen and Wang's research groups in recent years.^{8,9} Moreover, besides the marvelous progress in asymmetric Diels-Alder and IEDDA reactions achieved with Lewis acid, amine and multi-functional catalysis, organophosphine catalysis would also provide potential alternatives to these [4+2] annulation reactions. However, to the best of our knowledge, there has been only one example regarding this type of annulations under the catalysis of organophosphine catalyst,¹⁰ and no asymmetric version has yet to be reported.

5.1.2 Phosphine Catalyzed Annulation Reactions

Phosphine catalysis has been investigated for quite a long time since Rauhut and Currier's pioneering work in 1963.¹¹ Among various reactions catalyzed by different phosphines, Lu's [3+2] annulation represents one of the most excellent works,¹² which has been intensively studied in the last decade in both racemic and asymmetric settings (Scheme 5.1).¹³ Besides this type of cycloadditions, Kwon reported a series of [4+2] annulation reactions using simple phosphines as catalysts to synthesize substituted

tetrahydropyridines as well as functionalized cyclohexenes and other cyclic products.¹⁴ Similar process has also been reported by Ye and coworkers in the synthesis of 3,6-dihydropyrans.¹⁵ Kumar and coworkers have disclosed the first phosphine catalyzed [4+2] cyclization between alkyne and oxa-diene in the synthesis of dehydropyran.¹⁰ With the rapid development in chiral phosphine catalysts, especially those readily derived from amino acids, highly enantio- and diastereo-selective variants of most of these cycloadditions, together with various Morita-Baylis-Hillman and Rauhut-Currier reactions, have been realized with elegant designs.^{16,17} Beyond these excellent examples, annulations other than these types of pathways are still of great importance and interests. Herein, we describe the first chiral phosphine-catalyzed aza-IEDDA-type cycloaddition, with which a series of multi-functionalized fused heterocyclic compounds could be synthesized in good yields with exceptional diastereo- and enantio-selectivities. Potential synthetic applications of these functionalized multi-cyclic molecules have also been demonstrated through some simple transformations.

5.1.3 Our proposal

We assume that by using our rationally designed multifunctional acrylates, the Rauhut-Currier reaction might first take place under the catalysis of suitable simple molecules, and a nucleophilic annulation step might be followed to afford our desired fused tricyclic compound (Scheme 5.1).

Scheme 5.1 Recent Development in Diels-Alder / IEDDA Activations and Phosphine Catalysed Annulation Reactions.

5.2 Results and discussion

Initial trials were performed using a modified chalcone in the presence of various catalysts. The experimental results showed that the process would only stop at the first Rauhut-Currier reaction and then undergo a proton transfer to yield a substituted coumarin derivatives in a moderate yield. No desired product was obtained. However, by simply switching the chalcone motif into α,β -unsaturated amide, the cascade process proceeded smoothly with various organocatalysts. Moreover, all the products from these reactions were obtained as single diastereomers in moderate to good yields (Scheme 5.2).

Scheme 5.2 Initial Design and Trials on the Postulated [4+2] Annulation Reactions.

Having demonstrated the feasibility of the cascade process, we then paid our attention to the identification of an enantioselective catalytic system (Table 5.1). Some typical chiral molecules bearing tertiary amino motifs were firstly tested, but they turned out to be ineffective in this process (Entries 3 to 4). Trials of the carbene catalysts also afforded no desired product (Entry 5). In contrast, simple chiral phosphine catalysts that derived from naturally existing amino acids showed excellent catalytic activities and exceptional stereoselectivities (Entries 6 to 9). Substituents on the amino acid scaffold exhibited slight differences in the product yield and enantiomeric purity. The protecting group on the amino motif is crucial to both the reactivity and the selectivity (Entry 10), but it could be typical ones such as Ts, Boc and benzoyl groups. Strong hydrogen bond donating groups such as thiorurea seriously decreased the reaction efficiency (Entry 11), which is probably due to competitive interactions of multiple functional groups with the starting material. Having identified **5-5b** as the most effective catalyst, a survey of solvent effects showed that this catalytic system is effective in various reaction media except those with either too strong or too weak polarities (Entries 12 to 19). The product yield turned out to be affected by the catalyst loading. Finally, by lowering the amount of the catalyst to 5 mol%, the target product could be isolated in a good yield with excellent enantioselectivity (Entry 20).

Table 5.1 Primary Screening Results.^[a]

Entry	Cat.	Solvent	Yield (%) ^[b]	ee (%) ^[c]
1	DABCO	CH ₂ Cl ₂	62	--
2	PPh ₃	CH ₂ Cl ₂	51	--
3	5-3a	CH ₂ Cl ₂	0	--
4	5-3b	CH ₂ Cl ₂	0	--
5	5-4 ^[d]	CH ₂ Cl ₂	0	--
6	5-5a	CH ₂ Cl ₂	49	97
7	5-5b	CH ₂ Cl ₂	55	99
8	5-5c	CH ₂ Cl ₂	62	93
9	5-5d	CH ₂ Cl ₂	61	98
10	5-5e	CH ₂ Cl ₂	10	64
11	5-5f	CH ₂ Cl ₂	22	75
12	5-5b	THF	43	97
13	5-5b	Dioxane	39	97
14	5-5b	Toluene	61	99
15	5-5b	Et ₂ O	50	98
16	5-5b	MeCN	70	93
17	5-5b	EtOH	14	77
18	5-5b	Hexane	6	93
19	5-5b	DMF	50	88
20	5-5b ^[e]	Toluene	80	99
21	5-5b ^[f]	Toluene	66	99

[a] Unless otherwise noticed, all the reactions were carried out at r.t. using 1.0 equiv of **5-1a** (0.10 mmol), 0.1 equiv of catalyst and 0.5 mL of solvent. [b] Isolated yield, followed by ¹H NMR for confirmation. [c] Enantiomeric excess of **5-2a**, determined by chiral HPLC. [d] 20 Mol% of Et₃N was added. [e] 5.0 Mol% of catalyst was used, and the reaction was stirred for 24h. [f] 20 Mol% of catalyst was used.

With the optimized reaction conditions in hand, the scope of this aza-IEDDA-type [4+2] annulation reaction was then examined to illustrate the substrate generality of this reaction (Table 5.2). To our great delight, the present reaction is applicable to a large variety of substituents on each aromatic ring of the substrates involving both electron-

donating and electron-withdrawing groups. All the resulting fused cyclic compounds could be obtained in moderate to excellent yields with excellent enantio- and diastereoselectivities. Notably, the aromatic ring B in the model substrate could even be replaced with a vinylogous aromatic motif (Scheme 5.3, **5-6**), which would afford another diene product **5-7** that is ready for further transformations. Some of its interesting transformations have been carried out as examples, as shown in Scheme 5.3. Although replacement of the aromatic ring B with aliphatic groups was unsuccessful in this process, the protecting group of R₃ could be switched to a methyl group without erosion of the product yield and ee value (Table 5.2, **5-2q**).

Table 5.2 Reaction Scope.^[a]

[a] Isolated yields via SiO₂ column chromatography. Ee was determined via chiral phase HPLC. Absolute configurations of the products were established via X-ray structure of **5-2d**.

Scheme 5.3 Catalytic Enantioselective Synthesis of Diene and Its Further Transformations.

Having successfully demonstrated the generality of this reaction, we were then interested in its potential applications in organic synthesis (Scheme 5.4). Transformations of the optically pure model product **5-2a** through some simple protocols were carried out as examples. Both the ester group and the enamide motifs within the tricyclic system could be hydrolysed or transesterified in different conditions and the released free functional groups of phenol, ester, ketone and amide could be further modified if needed. Aromatization of the piperidine cycle by Pd/C and sodium formate could afford the fused pyridine compound **5-12** in a good yield. The double bond in the piperidine cycle could be stereoselectively reduced through a one-pot step wise reduction by $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{Et}_3\text{SiH}$ in DCE.

Scheme 5.4 Synthetic Transformations of **5-2a**.

5.3 Mechanistic Study.

Single crystals of the bromine-containing product **5-2d** were subjected to an X-ray analysis to verify the absolute structure, which is in accordance with our postulated reaction pathways. Based on this result and previous works, a plausible catalytic mechanism has been summarized and shown in Scheme 5.5.

Scheme 5.5 Proposed Reaction Pathway.

We propose that the catalytic process goes through a tandem Rauhut–Currier/ $\text{S}_{\text{N}}2$ -substitution sequence. First of all, nucleophilic attack of the phosphine catalyst to the acrylate moiety would result in an activated enolate **5-14**, which goes through a Rauhut–Currier reaction through transition states **TS1** and **TS2**, as described in numerous literatures.¹⁷ A kinetic resolution of the steric match (**TS1**) and mismatch (**TS2**) transition state in the subsequent $\text{S}_{\text{N}}2$ -substitution would result in the exclusive diastereoselectivity in the final product (**5-2a**) formation.

The Rauhut–Currier product **5-15** could be isolated in about 20% yield at the very beginning (1 h) of the reaction when using PPh_3 as the catalyst, and it could go on to form the final product **5-2a** when mixing again with the phosphine catalyst in various solvents. During the exploration of the catalytic pathway, an imine compound **5-16** was isolated in a low yield as a side product. Therefore, a second catalytic cycle probably exist which might be reasonable for both of the by-product formation and the kinetic resolution of the final product.

When applying DABCO instead of phosphines as the catalyst, the other diastereomer of the final product **5-2a'** could be obtained in an excellent yield (88%) when heating the reaction to 70 °C for 24 h in THF. This result could further indicate that the exclusive diastereoselectivity in our methodology is kinetically controlled rather than thermodynamically controlled.

5.4 Summary

In summary, the first chiral phosphine-catalyzed aza-IEDDA-type [4+2] annulation has been described. All the functionized multi-heterocyclic compounds could be obtained in moderate to excellent yields with exceptional diastereo- and enantio-selectivities. Moreover, all the enantio enriched products obtained through this approach would have potential synthetic applications due to their highly functionalized structure and might be useful in both organic synthesis and pharmaceutical research.

5.5 Experimental section

5.5.1 General Information

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were

used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (300 or 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); 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.

5.5.2 General procedure for the preparation of substrates 5-1

Synthesis of B (5-1g to 5-1o):

To a stirred solution of phenol derivative **A** (20 mmol) in freshly distilled THF (100 mL) in a 250 mL two neck round bottom flask, was added anhydrous magnesium chloride (30 mmol), paraformaldehyde (135 mmol) and triethylamine (75 mmol) at room temperature. The reaction mixture was stirred at reflux for 24 h. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and quenched with 1M aqueous HCl solution. The organic layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to afford the crude salicylaldehyde derivative **B**, which was used directly in the next step without further purifications.

Synthesis of C:

The corresponding acetophenone (20 mmol) was added to an ice-cooled suspension of KOH (15 g) in $\text{MeOH}/\text{H}_2\text{O} = 5/1$ (15 mL) in a 100 mL two neck round bottom flask. After stirring vigorously for 10 min, salicylaldehyde **B** (20 mmol) was added and the reaction mixture was allowed to attain the room temperature and stirred at this temperature for 12 h. After completion of the reaction, the reaction mixture was acidified

with 4M aqueous HCl solution under ice bath to around pH 2. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄. The solvent was removed under vacuum and the residue was either purified via recrystallization from dichloromethane/hexane or column chromatography to give the desired chalcone **C**.

Synthesis of D:

Acrylic acid was added to a solution of the corresponding chalcone **C** (10 mmol), DCC (20 mmol) and DMAP (0.8 mmol) in toluene (200 mL) in a 250 ml two neck round bottom flask and the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The resulting residue was purified via column chromatography to give acrylate product **D**.

Synthesis of substrates 5-1:

Titanium tetrachloride (20 mmol) was added drop-wise to an ice-cooled solution of the corresponding acrylate **D** (10 mmol), sulfonyl amide (10 mmol) and triethylamine (20 mmol) in dichloromethane in a 100 mL two neck round bottom flask. The reaction mixture was heated to reflux for 24 h. Then the reaction mixture was cooled to room temperature and diluted with water. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was subjected to column chromatography followed by recrystallization from dichloromethane/hexane to give the desired products (**5-1**) as fine crystals or powder.

5.5.3 General procedure for the asymmetric [2+4] reaction.

To a 10 mL Schlenk tube equipped with a magnetic stir bar, was added **5-1a** (0.1 mmol) and chiral phosphine catalyst **5-5b** (0.005 mmol). The tube was closed with a septum; evacuated and refilled with nitrogen ($\times 3$ cycles). Toluene (0.5 mL) was added and the reaction mixture was allowed to stir for 24 h at room temperature. The reaction mixture was directly subjected to column chromatography using hexane/EtOAc = 9/1 as eluent to yield the desired product **5-2a** in 80% yield as a white solid. The corresponding racemic products (for HPLC analysis) were prepared using PPh_3 as the catalyst.

5.5.4 Synthetic transformations of **5-7** and **5-2a**.

To a solution of lactone **5-7** (0.05 mmol) in CH_2Cl_2 (1 mL) in a 10 mL Schlenk tube, was added ethene-1,1,2,2-tetracarbonitrile (0.2 mmol). The mixture was stirred at room temperature for 0.5 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was subjected to column chromatography with hexane/EtOAc = 4/1 as eluent to give product **5-8** in 63% yield as a white solid.

To a solution of lactone **5-7** (0.05 mmol) in toluene (1 mL) in a 10 mL Schlenk tube, was added *N*-phenylmaleimide (0.2 mmol). The reaction mixture was stirred at 120 °C for 24 h. After completion of the reaction, the mixture was cooled to room temperature and directly subjected to column chromatography with hexane/EtOAc = 4/1 as eluent to give product **5-9** in 65% yield as a white solid. [3]

A solution of lactone **5-2a** (0.1 mmol) in wet toluene (1.5 mL) in a 10 mL Schlenk tube was stirred at 80 °C for 36 h. After complete consumption of the starting material, the reaction mixture was cooled to room temperature and directly subjected to column chromatography with hexane/EtOAc = 4/1 as eluent to give product **5-10** in 79% yield as a white solid.

Lactone **5-2a** (0.05 mmol) was added to a solution of methanol (1.0 mL) and H₂SO₄ (0.1 μL) in a 10 mL Schlenk tube. The reaction mixture was stirred at room temperature for 20 h. After completion of the reaction, the reaction mixture was concentrated under vacuum. The crude residue was purified by column chromatography with hexane/EtOAc = 4/1 as eluent to give product **5-11** in 51% yield as a colorless oil.

To a mixture of **5-2a** (0.1 mmol) and HCOONa (0.5 mmol, 32.9 mg) in DMF (0.5 mL) in a 10 mL Schlenk tube, was added Pd/C (12.9 mg). The reaction mixture was then stirred at 60 °C for 24 h. Then the reaction mixture was cooled to room temperature, diluted water, and extracted with EtOAc. The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography with hexane/EtOAc = 10/1 as eluent to give product **5-12** in 79% yield as a white solid.^[4]

Et₃SiH (0.2 mmol, 34 μL) and BF₃·Et₂O (0.2 mmol, 24 μL) were added into a solution of **5-2a** (0.066 mmol) in DCE (0.5 mL) in a 10 mL Schlenk tube. The mixture was heated to 70 °C and stirred for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature and purified by column chromatography with hexane/EtOAc = 8/1 as eluent to give **5-13** in 85% yield as a white solid.^[4]

5.5.5 Stereochemistry determination *via* X-ray crystallographic analysis.

Absolute configurations of the products **5-2** and **5-8** were assigned based on the crystal X-ray structures of **5-2d** and **5-8**. CCDC 874967 (**5-2d**, obtained as colorless needles *via* evaporation of a hexane/EtOAc/trace CH₂Cl₂ solution) and CCDC 874968 (**5-8**, obtained as colorless needles *via* evaporation of a hexane/EtOAc solution) contain the supplementary X-ray crystallographic data.

5.5.6 Characterization of substrates and products.

2-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1a): 46% yield. White solid. mp 122-123 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.15-7.95 (m, 3H), 7.87-7.83 (m, 1H), 7.66-7.66 (m, 2H), 7.56-7.48 (m, 2H), 7.43-7.34 (m, 5H), 7.22-7.14 (m, 2H), 6.55 (d, $J = 17.2$ Hz, 1H), 6.26 (dd, $J = 10.8, 16.0$ Hz, 1H), 6.01 (d, $J = 10.4$ Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 149.5, 143.6, 142.0, 138.6, 133.3, 131.9, 130.3, 129.7, 129.5, 128.3, 127.5, 127.2, 127.1, 126.7, 126.5, 122.9, 21.6; LCMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{21}\text{NO}_4\text{SH}^+$ 432.13, found 432.01.

2-(3-(4-methoxyphenyl)-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1b): 22% yield. Yellow solid. mp 102-103 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.02-7.91 (m, 3H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 2H), 7.46 (td, $J = 1.6, 8.0$ Hz, 1H), 7.38-7.30 (m, 3H), 7.18 (dd, $J = 0.8, 8.0$ Hz, 1H), 7.09 (d, $J = 16.0$ Hz, 1H), 6.89-6.86 (m, 2H), 6.57 (d, $J = 17.6$ Hz, 1H), 6.27 (dd, $J = 10.4, 17.6$ Hz, 1H), 6.00 (dd, $J = 0.8, 10.4$ Hz, 1H), 3.84 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.1, 149.3, 143.3, 142.4, 138.9, 133.3, 132.7, 131.5, 129.4, 128.3, 127.7, 127.3, 127.2, 126.7, 122.9, 113.8, 55.5, 21.6; LCMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_5\text{SH}^+$ 462.14, found 462.02.

2-(3-(p-tolyl)-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1c): 45% yield. White

solid. mp 124-125 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.04-7.91 (m, 3H), 7.80 (d, $J = 7.2$ Hz, 1H), 7.55-7.54 (m, 2H), 7.45 (td, $J = 1.6, 8.0$ Hz, 1H), 7.35-7.30 (m, 3H), 7.18 (d, $J = 8.0$ Hz, 3H), 7.12 (d, $J = 16.0$ Hz, 1H), 6.54 (d, $J = 17.2$ Hz, 1H), 6.25 (dd, $J = 10.4, 17.2$ Hz, 1H), 5.98 (d, $J = 10.8$ Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 149.4, 143.4, 141.4, 138.8, 133.2, 131.7, 129.4, 129.1, 127.6, 127.3, 127.2, 126.7, 122.9, 21.6; LCMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_4\text{SH}^+$ 446.14, found 446.09.

2-(3-(4-bromophenyl)-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1d): 49% yield. Colorless crystal. mp 88-89 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.12-7.85 (m, 4H), 7.57-7.49 (m, 5H), 7.40-7.35 (m, 3H), 7.10 (d, $J = 16.4$ Hz, 1H), 6.57 (d, $J = 17.2$ Hz, 1H), 6.29 (dd, $J = 10.4, 16.0$ Hz, 1H), 6.07 (d, $J = 10.4$ Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 149.5, 143.8, 142.0, 138.4, 133.5, 132.1, 131.8, 131.6, 129.5, 128.3, 127.3, 127.1, 126.8, 124.0, 123.0, 21.6; LCMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{20}\text{NO}_4\text{SBrH}^+$ 512.04, found 511.97.

2-(3-(4-chlorophenyl)-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1e): 43% yield. White solid. mp 89-90 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.13-7.84 (m, 4H), 7.61-7.49 (m, 3H), 7.40-7.35 (m, 5H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.10 (d, $J = 16.0$ Hz, 1H), 6.58 (d, $J = 16.4$ Hz, 1H), 6.29 (dd, $J = 10.4, 16.0$ Hz, 1H), 6.06 (d, $J = 10.4$ Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 149.5, 143.7, 141.9, 138.4, 133.5, 132.1, 131.7,

131.6, 130.0, 129.5, 128.7, 128.3, 128.0, 127.3, 127.1, 126.8, 123.0, 21.6; LCMS (ESI, m/z): calcd. for $C_{25}H_{20}NO_4SClH^+$ 466.09, found 465.97.

2-(3-(3-bromophenyl)-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1f): 59% yield.

White solid. mp 144-146 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.15-7.80 (m, 5H), 7.67-7.65 (d, $J = 8.0$ Hz, 1H), 7.55-7.49 (m, 2H), 7.40-7.32 (m, 3H), 7.29 (t, $J = 5.2$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 16.4$ Hz, 1H), 6.58 (d, $J = 16.4$ Hz, 1H), 6.29 (dd, $J = 10.0, 15.6$ Hz, 1H), 6.04 (d, $J = 10.8$ Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 149.6, 143.8, 142.3, 139.0, 138.2, 134.8, 133.6, 132.8, 132.2, 129.8, 129.6, 128.9, 128.4, 127.3, 127.2, 127.0, 126.7, 123.9, 123.0, 122.4, 21.6; LCMS (ESI, m/z): calcd. for $C_{25}H_{20}NO_4SBrH^+$ 512.04, found 511.99.

5-methoxy-2-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1g): 28%

yield. Yellow solid. mp 91-93 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.78 (m, 4H), 7.61-7.50 (m, 3H), 7.42-7.33 (m, 4H), 7.11 (d, $J = 16.0$ Hz, 1H), 6.92 (dd, $J = 2.0, 8.8$ Hz, 1H), 6.74 (d, $J = 2.4$ Hz, 1H), 6.52 (d, $J = 16.8$ Hz, 1H), 6.23 (dd, $J = 10.4, 16.8$ Hz, 1H), 6.00 (d, $J = 10.4$ Hz, 1H), 3.88 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 162.8, 151.0, 143.4, 142.7, 138.8, 133.4, 129.4, 128.2, 127.2, 127.0, 120.0, 113.1, 108.4, 55.8, 21.6; LCMS (ESI, m/z): calcd. for $C_{26}H_{23}NO_5SH^+$ 462.14, found 462.05.

5-bromo-2-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1h): 30% yield.

Yellow solid. mp 102-103 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.14-7.95 (m, 3H), 7.72-7.65 (m, 3H), 7.56-7.50 (m, 2H), 7.43-7.35 (m, 5H), 7.07 (d, $J = 16.0$ Hz, 1H), 6.56 (d, $J = 16.8$ Hz, 1H), 6.225 (dd, $J = 10.4, 16.4$ Hz, 1H), 6.03 (d, $J = 10.4$ Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.6, 149.6, 143.7, 140.7, 138.4, 134.2, 134.0, 130.3, 130.0, 129.5, 128.4, 127.2, 126.7, 126.6, 126.4, 125.2, 21.6; LCMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{20}\text{NO}_4\text{SBrH}^+$ 512.04, found 511.98.

4-methyl-2-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1i): 38% yield.

Yellow solid. mp 112-113 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.13-7.96 (m, 3H), 7.64-7.51 (m, 4H), 7.43-7.35 (m, 4H), 7.30-7.29 (m, 1H), 7.15-7.07 (m, 2H), 6.53 (d, $J = 17.2$ Hz, 1H), 6.24 (dd, $J = 10.4, 16.8$ Hz, 1H), 5.99 (d, $J = 10.8$ Hz, 1H), 2.46 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.2, 147.4, 143.5, 142.4, 138.7, 136.5, 133.1, 132.8, 130.4, 130.3, 129.5, 128.5, 128.3, 127.2, 127.0, 122.6, 21.6, 21.0; LCMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_4\text{SH}^+$ 446.14, found 446.01.

4-(tert-butyl)-2-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1j): 33%

yield. White solid. mp 120-121 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.15-7.94 (m, 3H), 7.75-7.65 (m, 3H), 7.55-7.50 (m, 2H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.14-7.11 (m, 2H), 6.54 (d, $J = 16.8$ Hz, 1H), 6.27 (t, $J = 10.8$ Hz, 1H), 5.99 (d, $J = 10.4$ Hz, 1H), 2.45 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.2, 149.6, 147.2, 143.5, 143.1, 133.2, 129.5, 129.3, 128.3, 127.2, 126.5, 122.4, 34.7, 31.3; LCMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{29}\text{NO}_4\text{SH}^+$ 488.19, found 488.07.

2-isopropyl-6-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1k): 42% yield. White solid. mp 114-115 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.11-7.96 (m, 3H), 7.72-7.64 (m, 3H), 7.56-7.34 (m, 7H), 7.07 (d, $J = 16.0$ Hz, 1H), 6.58 (d, $J = 17.2$ Hz, 1H), 6.26 (dd, $J = 10.0, 15.2$ Hz, 1H), 6.01 (d, $J = 10.4$ Hz, 1H), 3.02-2.95 (m, 1H), 2.46 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.2, 147.0, 143.5, 142.8, 141.5, 138.7, 137.1, 133.4, 131.9, 130.3, 129.5, 128.3, 127.9, 127.2, 126.9, 125.6, 124.2, 27.5, 23.0, 21.6; LCMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{27}\text{NO}_4\text{SH}^+$ 474.17, found 474.06.

2-(tert-butyl)-6-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1l): 48% yield. White solid. mp 126-127 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.11-7.96 (m, 3H), 7.78-7.64 (m, 3H), 7.58-7.49 (m, 2H), 7.40-7.31 (m, 5H), 6.99 (d, $J = 15.6$ Hz, 1H), 6.60 (d, $J = 9.2$ Hz, 1H), 6.26 (dd, $J = 10.4, 16.0$ Hz, 1H), 6.03 (d, $J = 10.4$ Hz, 1H), 3.02-2.95 (m, 1H), 2.46 (s, 3H), 1.36(s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.4, 148.3, 143.5, 142.9, 142.5, 138.7, 133.6, 130.4, 130.2, 129.5, 129.1, 128.4, 127.5, 127.2, 126.5, 126.1,

124.3, 34.8, 30.4, 21.6; LCMS (ESI, m/z): calcd. for $C_{29}H_{27}NO_4SH^+$ 488.19, found 488.14.

2-allyl-6-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)phenyl acrylate (5-1m): 41% yield.

White solid. mp 105-106 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.12-7.96 (m, 3H), 7.76-7.64 (m, 3H), 7.52 (t, J = 7.2 Hz, 1H), 7.41-7.34 (m, 6H), 7.08 (d, J = 16.0 Hz, 1H), 6.58 (d, J = 17.2 Hz, 1H), 6.25 (dd, J = 10.0, 15.2 Hz, 1H), 6.01 (d, J = 10.4 Hz, 1H), 5.94-5.84 (m, 1H), 5.12-5.06 (m, 2H), 3.30 (d, J = 6.8 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 147.9, 143.5, 142.4, 138.6, 135.2, 133.4, 133.3, 132.9, 130.4, 129.5, 128.3, 128.1, 127.2, 126.8, 126.3, 124.3, 116.9, 34.6, 21.6; LCMS (ESI, m/z): calcd. for $C_{29}H_{27}NO_4SH^+$ 472.16, found 472.11.

2-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)-5,6,7,8-tetrahydronaphthalen-1-yl acrylate

(5-1n): 35% yield. White solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.09-7.76 (m, 3H), 7.62-7.49 (m, 4H), 7.41-7.29 (m, 4H), 7.12-7.06 (m, 2H), 6.56 (d, J = 17.2 Hz, 1H), 6.24 (dd, J = 10.4, 16.8 Hz, 1H), 5.99 (d, J = 10.4 Hz, 1H), 2.85 (s, 2H), 2.55 (s, 2H), 2.45 (s, 3H), 1.80 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 148.2, 143.4, 143.2, 143.1, 138.8, 133.2, 130.6, 129.5, 128.2, 127.7, 127.2, 126.9, 124.8, 29.8, 29.7, 23.3, 22.3, 22.2, 21.6; LCMS (ESI, m/z): calcd. for $C_{29}H_{27}NO_4SH^+$ 486.17, found 486.84.

3-(3-phenyl-3-(tosylimino)prop-1-en-1-yl)-5,6,7,8-tetrahydronaphthalen-2-yl acrylate (5-1o): 20% yield. Yellow solid. mp 121-122 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.09-7.95 (m, 3H), 7.62-7.50 (m, 4H), 7.45-7.34 (m, 4H), 7.11 (d, $J = 16.0$ Hz, 1H), 6.89 (s, 1H), 6.52 (d, $J = 17.2$ Hz, 1H), 6.23 (dd, $J = 10.4, 17.2$ Hz, 1H), 5.97 (d, $J = 10.4$ Hz, 1H), 2.84-2.82 (m, 4H), 2.46 (s, 3H), 1.85-1.78 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.4, 147.2, 143.4, 143.0, 142.6, 138.8, 135.9, 133.0, 129.5, 129.4, 128.2, 127.2, 127.2, 124.4, 122.9, 29.7, 28.9, 22.9, 22.6, 21.6; ; LCMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{27}\text{NO}_4\text{SH}^+$ 486.1739, found 486.07.

2-(3-phenyl-3-((phenylsulfonyl)imino)prop-1-en-1-yl)phenyl acrylate (5-1p): 36% yield. Colorless crystal. mp 90-92 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.09-7.86 (m, 4H), 7.66-7.38 (m, 10H), 7.23-7.16 (m, 2H), 6.56 (d, $J = 17.2$ Hz, 1H), 6.26 (dd, $J = 10.4, 16.4$ Hz, 1H), 6.01 (d, $J = 10.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 149.5, 142.3, 141.5, 133.4, 132.7, 132.0, 130.4, 130.3, 128.9, 128.4, 127.4, 127.2, 127.1, 126.7, 123.0; LCMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{NO}_4\text{SH}^+$ 418.11, found 418.50.

2-(3-((methylsulfonyl)imino)-3-phenylprop-1-en-1-yl)phenyl acrylate (5-1q): 28% yield. Yellow solid. mp 85-86 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 16.0$ Hz,

1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.70 (d, $J = 6.8$ Hz, 2H), 7.58 (t, $J = 7.2$ Hz, 1H), 7.51-7.44 (m, 3H), 7.36 (t, $J = 7.6$ Hz, 1H), 7.21-7.15 (m, 2H), 6.55 (d, $J = 17.2$ Hz, 1H), 6.26 (dd, $J = 10.4, 17.2$ Hz, 1H), 6.01 (d, $J = 10.8$ Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 149.5, 142.4, 133.3, 132.0, 130.2, 128.4, 127.3, 127.1, 126.7, 124.1, 122.9, 43.2; LCMS (ESI, m/z): calcd. for $\text{C}_{19}\text{H}_{17}\text{NO}_4\text{SH}^+$ 356.10, found 355.97.

2-(3-(((4-nitrophenyl)sulfonyl)imino)-3-phenylprop-1-en-1-yl)phenyl acrylate (5-1r):

33% yield. White solid. mp 112-114 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, $J = 8.8$ Hz, 2H), 8.26 (d, $J = 8.4$ Hz, 2H), 8.04 (br s, 1H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 6.8$ Hz, 2H), 7.59 (t, $J = 7.2$ Hz, 1H), 7.53 (td, $J = 1.2, 7.8$ Hz, 1H), 7.47-7.38 (m, 3H), 7.27-7.22 (m, 2H), 6.57 (d, $J = 17.2$ Hz, 1H), 6.27 (dd, $J = 10.4, 17.2$ Hz, 1H), 6.03 (d, $J = 10.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 150.1, 149.7, 147.1, 143.6, 133.5, 132.4, 130.2, 128.5, 127.2, 127.1, 126.8, 124.1, 123.1; LCMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_6\text{SH}^+$ 463.10, found 462.96.

2-(3-(((4-methoxyphenyl)sulfonyl)imino)-3-phenylprop-1-en-1-yl)phenyl acrylate (5-1s):

33% yield. White solid. mp 107-109 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.16-7.86 (m, 4H), 7.66 (br s, 2H), 7.55-7.47 (m, 2H), 7.43-7.36 (m, 3H), 7.22-7.13 (m, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.55 (d, $J = 17.2$ Hz, 1H), 6.26 (dd, $J = 10.4, 15.2$ Hz, 1H), 6.01 (d, $J = 10.4$ Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.0, 163.02, 162.3, 149.4,

141.9, 133.3, 131.8, 130.3, 129.4, 128.3, 127.5, 127.1, 126.7, 122.9, 114.1, 55.6; LCMS (ESI, m/z): calcd. for $C_{25}H_{21}NO_5SH^+$ 448.12, found 448.01.

2-(5-phenyl-3-(tosylimino)penta-1,4-dien-1-yl)phenyl acrylate (5-6): 44% yield.

Yellow foam solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.21 (m, 17H), 6.60 (d, J = 17.2 Hz, 1H), 6.31 (dd, J = 10.0, 14.0 Hz, 1H), 5.97 (d, J = 10.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.4, 145.0, 143.4, 138.8, 137.3, 134.7, 133.5, 131.5, 130.8, 129.7, 129.5, 129.0, 128.6, 128.0, 127.6, 127.2, 126.6, 126.5, 123.1, 21.6; LCMS (ESI, m/z): calcd. for $C_{27}H_{23}NO_4SH^+$ 458.1426, found 458.08.

2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2a): 80%

yield. White solid. mp 128-131 °C. 1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2H), 7.39-7.24 (m, 8H), 7.21-7.19 (m, 1H), 7.11 (td, J = 1.2, 7.5 Hz, 1H), 7.03 (dd, J = 0.9, 8.1 Hz, 1H), 5.66 (d, J = 4.2 Hz, 1H), 4.32 (dd, J = 4.2, 13.5 Hz, 1H), 3.77 (dd, J = 8.4, 13.5 Hz, 1H), 3.61 (dd, J = 5.1, 10.2 Hz, 1H), 2.99-2.92 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 149.9, 144.3, 141.0, 137.9, 135.8, 129.8, 129.0, 128.5, 128.0, 127.8, 127.7, 127.6, 125.1, 123.1, 117.3, 115.8, 45.1, 38.7, 33.0, 21.7; HRMS (ESI, m/z): calcd. for $C_{25}H_{21}NO_4SH^+$ 432.1270, found 432.1268; $[\alpha]_D^{29}$ = - 50.7° (c = 1.38 in $CHCl_3$); HPLC analysis: 99% ee (Chiralcel OD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), R_t (minor) = 24.5 min, R_t (major) = 28.8 min.

2-(4-methoxyphenyl)-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one

(5-2b): 58% yield. White solid. mp 87-89 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.61-7.59 (m, 2H), 7.34-7.24 (m, 5H), 7.20-7.18 (m, 1H), 7.11 (td, $J = 1.2, 7.5$ Hz, 1H), 7.03 (dd, $J = 0.9, 8.1$ Hz, 1H), 6.84-6.81 (m, 2H), 5.59 (d, $J = 4.2$ Hz, 1H), 4.33 (dd, $J = 4.5, 13.5$ Hz, 1H), 3.84 (s, 3H), 3.76 (dd, $J = 8.4, 13.5$ Hz, 1H), 3.57 (dd, $J = 4.5, 10.5$ Hz, 1H), 2.98-2.91 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.1, 159.8, 149.8, 144.1, 140.5, 135.8, 130.2, 129.7, 128.9, 128.9, 127.9, 127.6, 125.0, 123.1, 117.2, 114.6, 113.2, 55.3, 45.1, 38.7, 32.9, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_5\text{SH}^+$ 462.1375, found 462.1373; $[\alpha]^{29}_{\text{D}} = -52.3^\circ$ ($c = 1.32$ in CHCl_3); HPLC analysis: 98% ee (Chiralcel OD-H, Hexane/*i*PrOH = 4/1, 0.75 mL/min), R_t (minor) = 27.2 min, R_t (major) = 33.1 min.

2-(p-tolyl)-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2c): 70%

yield. White solid. mp 114-117 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.63-7.61 (m, 2H), 7.35-7.24 (m, 5H), 7.20-7.17 (m, 1H), 7.14-7.08 (m, 3H), 7.03 (dd, $J = 0.6, 8.1$ Hz, 1H), 5.66 (d, $J = 4.2$ Hz, 1H), 4.32 (dd, $J = 4.5, 13.8$ Hz, 1H), 3.72 (dd, $J = 8.7, 13.5$ Hz, 1H), 3.57 (dd, $J = 5.1, 5.4$ Hz, 1H), 2.94-2.88 (m, 1H), 2.47 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 149.8, 144.2, 140.8, 138.4, 135.6, 135.1, 129.8, 128.9, 128.5, 128.0, 127.7, 127.4, 125.0, 123.1, 117.2, 115.2, 45.0, 38.6, 32.9, 21.6, 21.3; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_4\text{SH}^+$ 446.1426, found 446.1429; $[\alpha]^{29}_{\text{D}} = -53.1^\circ$ ($c = 1.28$ in CHCl_3); HPLC analysis: 99% ee (Chiralcel OD-H, Hexane/*i*PrOH = 4/1, 0.75 mL/min), R_t (minor) = 18.7 min, R_t (major) = 22.3 min.

2-(4-bromophenyl)-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2d): 65% yield. White solid. mp 184-186 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.61-7.59 (m, 2H), 7.44-7.42 (m, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.30-7.22 (m, 3H), 7.19-7.17 (m, 1H), 7.12 (td, J = 1.2, 7.2 Hz, 1H), 7.04 (dd, J = 0.8, 8.0 Hz, 1H), 5.66 (d, J = 4.0 Hz, 1H), 4.28 (dd, J = 4.4, 13.6 Hz, 1H), 3.77 (dd, J = 8.4, 13.6 Hz, 1H), 3.58 (dd, J = 4.4, 6.0 Hz, 1H), 2.96-2.91 (m, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 149.8, 144.5, 139.9, 136.8, 135.4, 131.0, 129.9, 129.1, 129.0, 127.8, 127.6, 125.1, 122.8, 122.6, 117.3, 116.2, 45.0, 38.6, 33.0, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{20}\text{NO}_4\text{SBrH}^+$ 512.0354, found 512.0359; $[\alpha]_D^{29} = -61.3^\circ$ (c = 6.82 in CHCl_3); HPLC analysis: 98% ee (Chiralcel OD-H, Hexane/*i*PrOH = 4/1, 0.75 mL/min), R_t (minor) = 23.5 min, R_t (major) = 29.5 min.

2-(4-chlorophenyl)-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2e): 64% yield. White solid. mp 168-170 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.62-7.60 (m, 2H), 7.36-7.27 (m, 7H), 7.20-7.18 (m, 1H), 7.13 (td, J = 0.8, 8.0 Hz, 1H), 7.05 (dd, J = 0.8, 8.4 Hz, 1H), 5.65 (d, J = 4.4 Hz, 1H), 4.29 (dd, J = 4.4, 13.2 Hz, 1H), 3.79 (dd, J = 8.4, 13.6 Hz, 1H), 3.59 (dd, J = 4.4, 5.6 Hz, 1H), 2.98-2.93 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 149.9, 144.5, 139.9, 136.3, 135.5, 134.4, 129.9, 129.0, 128.8, 128.0, 127.8, 127.6, 125.1, 122.9, 117.3, 116.2, 45.0, 38.6, 33.0, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{20}\text{NO}_4\text{SClH}^+$ 466.0880, found 466.0879; $[\alpha]_D^{29} = -80.4^\circ$ (c = 5.78 in CHCl_3); HPLC analysis: 98% ee (Chiralcel OD-H, Hexane/*i*PrOH = 4/1, 0.75 mL/min),

Rt (minor) = 22.6 min, Rt (major) = 28.6 min.

2-(3-bromophenyl)-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2f):

55% yield. White solid. mp 196-198 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.60-7.57 (m, 2H), 7.45-7.43 (m, 1H), 7.36-7.27 (m, 5H), 7.22-7.18 (m, 2H), 7.14 (td, $J = 1.2, 7.2$ Hz, 1H), 7.05 (dd, $J = 0.8, 8.0$ Hz, 1H), 5.65 (d, $J = 4.0$ Hz, 1H), 4.30 (dd, $J = 4.4, 13.6$ Hz, 1H), 3.83 (dd, $J = 8.0, 13.2$ Hz, 1H), 3.67 (dd, $J = 4.4, 5.6$ Hz, 1H), 3.07-3.02 (m, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 149.9, 144.5, 139.6, 139.5, 135.7, 131.4, 130.4, 129.9, 129.4, 129.0, 127.8, 127.6, 126.5, 125.1, 122.9, 121.8, 117.3, 116.5, 44.9, 38.8, 33.1, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{20}\text{NO}_4\text{SBrH}^+$ 512.0354, found 512.0355; $[\alpha]_D^{29} = -62.8^\circ$ ($c = 5.54$ in CHCl_3); HPLC analysis: 97% ee (Chiralcel OD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), Rt (minor) = 27.7 min, Rt (major) = 39.0 min.

8-methoxy-2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2g):

52% yield. White foam solid. ^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, $J = 8.0$ Hz, 2H), 7.38-7.28 (m, 7H), 7.08 (d, $J = 8.4$ Hz, 1H), 6.67-6.65 (m, 1H), 6.57 (br s, 1H), 5.66 (d, $J = 3.6$ Hz, 1H), 4.31 (dd, $J = 3.6, 13.2$ Hz, 1H), 3.78 (s, 3H), 3.72 (dd, $J = 8.8, 14.0$ Hz, 1H), 3.54 (m, 1H), 2.89 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 159.9, 150.5, 144.2, 140.6, 138.0, 135.6, 129.8, 128.5, 128.4, 127.8, 127.7, 127.5, 116.3, 114.8, 111.3, 102.5, 55.5, 45.0, 38.6, 32.3, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_5\text{SH}^+$ 462.1375, found 462.1378; $[\alpha]_D^{29} = -76.3^\circ$ ($c = 4.00$ in CHCl_3); HPLC

analysis: 98% ee (Chiralcel OD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), Rt (major) = 21.1 min, Rt (minor) = 24.3 min.

8-bromo-2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2h): 46% yield. White solid. mp 98-100 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.60-7.58 (m, 2H), 7.37-7.32 (m, 7H), 7.25 (dd, J = 2.0, 8.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 5.61 (d, J = 4.4 Hz, 1H), 4.32 (dd, J = 4.4, 13.6 Hz, 1H), 3.75 (dd, J = 16.8, 21.6 Hz, 1H), 3.60 (dd, J = 4.8, 5.6 Hz, 1H), 2.99-2.94 (m, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.2, 150.3, 144.3, 141.3, 137.6, 135.6, 129.8, 129.3, 128.6, 128.1, 127.8, 127.6, 122.2, 121.8, 120.5, 114.7, 44.9, 38.4, 32.7, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{20}\text{NO}_4\text{SBrH}^+$ 512.0354, found 512.0355; $[\alpha]_D^{29}$ = - 29.8° (c = 1.68 in CHCl_3); HPLC analysis: 99% ee (Chiralcel OD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), Rt (major) = 22.1 min, Rt (minor) = 28.9 min.

9-methyl-2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2i): 75% yield. White foam solid. ^1H NMR (300 MHz, CDCl_3) δ 7.62-7.59 (m, 2H), 7.41-7.30 (m, 7H), 7.06-7.04 (m, 1H), 6.98 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.68 (d, J = 4.2 Hz, 1H), 4.32 (dd, J = 4.5, 13.8 Hz, 1H), 3.72 (dd, J = 8.7, 13.5 Hz, 1H), 3.56 (dd, J = 4.8, 5.4 Hz, 1H), 2.92-2.86 (m, 1H), 2.47 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 147.7, 144.2, 140.7, 138.0, 135.6, 134.8, 129.8, 129.4, 128.5, 128.2, 127.8, 127.7,

127.6, 122.5, 117.0, 115.9, 45.1, 38.5, 32.9, 21.6, 20.8; HRMS (ESI, m/z): calcd. for $C_{26}H_{23}NO_4SH^+$ 446.1426, found 446.1426; $[\alpha]^{29}_D = -77.8^\circ$ ($c = 3.06$ in $CHCl_3$); HPLC analysis: 99% ee (Chiralcel AD-H, Hexane/*i*PrOH = 9/1, 0.50 mL/min), R_t (minor) = 65.0 min, R_t (major) = 77.7 min.

9-(tert-butyl)-2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2j): 73% yield. White foam solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.37-7.27 (m, 8H), 7.15 (d, $J = 2.4$ Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 5.60 (d, $J = 3.6$ Hz, 1H), 4.29 (dd, $J = 4.8, 13.2$ Hz, 1H), 4.00 (dd, $J = 6.8, 13.2$ Hz, 1H), 3.53 (dd, $J = 4.0, 6.4$ Hz, 1H), 3.09-3.05 (m, 1H), 2.48 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 148.1, 147.9, 144.1, 141.0, 137.6, 136.0, 129.7, 128.4, 127.7, 127.7, 127.6, 126.0, 124.4, 122.5, 116.7, 116.5, 45.3, 39.5, 34.5, 33.7, 31.3, 26.9, 21.6; HRMS (ESI, m/z): calcd. for $C_{29}H_{29}NO_4SH^+$ 488.1896, found 488.1903; $[\alpha]^{29}_D = -43.2^\circ$ ($c = 7.5$ in $CHCl_3$); HPLC analysis: 91% ee (Chiralcel AD-H, Hexane/*i*PrOH = 9/1, 0.50 mL/min), R_t (major) = 43.4 min, R_t (minor) = 54.4 min.

7-isopropyl-2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2k): 99% yield. Colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.38-7.28 (m, 7H), 7.21 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.08 (t, $J = 7.6$ Hz, 1H), 6.99 (d, $J = 7.2$ Hz, 1H), 5.64 (d, $J = 4.0$ Hz, 1H), 4.29 (dd, $J = 4.8, 13.2$ Hz, 1H), 3.89 (dd, $J = 7.6, 13.6$ Hz,

1H), 3.51 (dd, $J = 4.4, 5.6$ Hz, 1H), 3.42-3.35 (m, 1H), 3.02-2.97 (m, 1H), 2.47 (s, 3H), 1.22 (d, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 147.1, 144.2, 140.8, 137.9, 137.0, 135.7, 129.7, 128.4, 127.8, 127.6, 127.5, 126.0, 125.2, 124.8, 123.1, 116.6, 45.0, 39.0, 33.4, 26.5, 22.8, 22.7, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{27}\text{NO}_4\text{SH}^+$ 474.1739, found 474.1733; $[\alpha]_D^{29} = +2.3^\circ$ ($c = 8.8$ in CHCl_3); HPLC analysis: 94% ee (Chiralcel AS-H, Hexane/ i PrOH = 9/1, 0.40 mL/min), R_t (minor) = 79.1 min, R_t (major) = 92.7 min.

7-(tert-butyl)-2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2l): 99% yield. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.63-7.61 (m, 2H), 7.39-7.28 (m, 8H), 7.07-6.99 (m, 2H), 5.64 (d, $J = 4.0$ Hz, 1H), 4.29 (dd, $J = 5.2, 13.6$ Hz, 1H), 3.93 (dd, $J = 7.2, 13.6$ Hz, 1H), 3.46 (dd, $J = 4.4, 6.0$ Hz, 1H), 3.02-2.98 (m, 1H), 2.48 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 148.8, 144.1, 141.0, 138.4, 137.8, 135.7, 129.7, 128.4, 127.8, 127.6, 127.5, 126.5, 125.9, 124.4, 124.1, 117.0, 44.9, 39.1, 34.9, 33.6, 29.9, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{27}\text{NO}_4\text{SH}^+$ 488.1896, found 488.1894; $[\alpha]_D^{29} = -13.9^\circ$ ($c = 9.74$ in CHCl_3); HPLC analysis: 96% ee (Chiralcel AS-H, Hexane/ i PrOH = 4/1, 0.60 mL/min), R_t (major) = 25.4 min, R_t (minor) = 34.7 min.

7-allyl-2-phenyl-3-tosyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2m): 79% yield. White foam solid. ^1H NMR (400 MHz, CDCl_3) δ 7.62-7.60 (m, 2H), 7.38-7.28 (m, 7H), 7.14 (dd, $J = 2.4, 6.8$ Hz, 1H), 7.08-7.03 (m, 2H), 6.00-5.90 (m, 1H), 5.63 (d, $J = 4.4$ Hz, 1H), 5.09-5.04 (m, 2H), 4.29 (dd, $J = 4.4, 13.2$ Hz, 1H), 3.85 (dd, $J =$

7.6, 13.2 Hz, 1H), 3.54 (dd, $J = 4.4, 6.0$ Hz, 1H), 3.44 (d, $J = 6.8$ Hz, 2H), 3.00-2.95 (m, 1H), 2.47(s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 147.7, 144.2, 140.9, 137.8, 135.7, 135.6, 129.7, 129.6, 128.6, 128.4, 127.8, 127.6, 127.5, 125.9, 124.7, 123.2, 116.4, 116.3, 45.0, 38.9, 33.6, 33.3, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{27}\text{NO}_4\text{SH}^+$ 472.1583, found 472.1586; $[\alpha]^{29}_{\text{D}} = -57.1^\circ$ ($c = 7.50$ in CHCl_3); HPLC analysis: 98% ee (Chiralcel AS-H, Hexane/iPrOH = 4/1, 0.60 mL/min), R_t (major) = 50.4 min, R_t (minor) = 57.5 min.

3-phenyl-2-tosyl-4a,7,8,9,10,12a-hexahydro-1H-benzo[7,8]chromeno[3,4-c]pyridin-12(2H)-one (5-2n): 68% yield. White solid. mp 150-152 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.59-7.57 (m, 2H), 7.34-7.26 (m, 7H), 6.84 (dd, $J = 7.6, 25.2$ Hz, 2H), 5.61 (d, $J = 4.0$ Hz, 1H), 4.26 (dd, $J = 4.8, 13.6$ Hz, 1H), 3.80 (dd, $J = 8.0, 13.2$ Hz, 1H), 3.47 (dd, $J = 4.8, 5.2$ Hz, 1H), 2.93-2.88 (m, 1H), 2.72-2.67 (m, 4H), 2.44 (s, 3H), 1.76-1.74 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 147.7, 144.1, 140.6, 138.6, 138.0, 135.8, 129.7, 128.4, 127.8, 127.7, 127.5, 125.9, 125.3, 124.2, 119.7, 116.7, 45.1, 38.8, 33.0, 29.3, 22.9, 22.4, 22.2, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{27}\text{NO}_4\text{SH}^+$ 486.1739, found 486.1740; $[\alpha]^{29}_{\text{D}} = -2.2^\circ$ ($c = 5.82$ in CHCl_3); HPLC analysis: >99% ee (Chiralcel AS-H, Hexane/iPrOH = 4/1, 0.60 mL/min), R_t (major) = 63.0 min, R_t (minor) = 70.6 min.

2-phenyl-3-tosyl-4a,8,9,10,11-hexahydro-3H-benzo[6,7]chromeno[3,4-c]pyridin-5(12bH)-one (5-2o): 80% yield. White foam solid. ^1H NMR (300 MHz, CDCl_3) δ 7.63-7.60 (m, 2H), 7.41-7.30 (m, 7H), 6.85 (s, 1H), 6.72 (s, 1H), 5.69 (d, $J = 4.2$ Hz, 1H), 4.31

(dd, $J = 4.2, 13.5$ Hz, 1H), 3.68 (dd, $J = 9.0, 13.5$ Hz, 1H), 3.53 (dd, $J = 4.8, 5.4$ Hz, 1H), 2.87-2.80 (m, 1H), 2.72-2.67 (m, 4H), 2.47 (s, 3H), 1.78-1.74 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.3, 162.3, 147.4, 144.2, 140.5, 138.1, 135.6, 134.0, 129.8, 128.4, 128.1, 127.8, 127.7, 127.6, 119.9, 117.0, 116.2, 45.1, 38.5, 32.6, 29.0, 28.7, 22.9, 22.7, 21.6; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{27}\text{NO}_4\text{SH}^+$ 486.1739, found 486.1735; $[\alpha]^{29}_{\text{D}} = -80.2^\circ$ ($c = 3.18$ in CHCl_3); HPLC analysis: 90% ee (Chiralcel AS-H, Hexane/ i PrOH = 4/1, 0.60 mL/min), R_t (major) = 77.8 min, R_t (minor) = 88.8 min.

2-phenyl-3-(phenylsulfonyl)-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2p): 67% yield. White solid. mp 164-166 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ 7.72-7.69 (m, 2H), 7.63-7.60 (m, 1H), 7.55-7.50 (m, 2H), 7.35-7.25 (m, 6H), 7.20-7.18 (m, 1H), 7.11 (td, $J = 1.2, 7.2$ Hz, 1H), 7.04 (dd, $J = 1.2, 8.1$ Hz, 1H), 5.64 (d, $J = 3.9$ Hz, 1H), 4.33 (dd, $J = 4.5, 13.5$ Hz, 1H), 3.85 (dd, $J = 8.1, 13.5$ Hz, 1H), 3.60 (dd, $J = 4.2, 5.7$ Hz, 1H), 3.01-2.95 (m, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 149.9, 140.8, 138.7, 137.6, 133.2, 129.1, 129.0, 128.5, 127.9, 127.8, 127.7, 127.6, 125.1, 123.1, 117.3, 116.0, 45.1, 38.9, 33.1; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{NO}_4\text{SH}^+$ 418.1113, found 418.1114; $[\alpha]^{29}_{\text{D}} = -91^\circ$ ($c = 1.00$ in CHCl_3); HPLC analysis: 99% ee (Chiralcel OD-H, Hexane/ i PrOH = 4/1, 0.75 mL/min), R_t (minor) = 20.7 min, R_t (major) = 25.7 min.

3-(methylsulfonyl)-2-phenyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-5(10bH)-one (5-2q): 60% yield. White solid. mp 228-230 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.35

(m, 5H), 7.33-7.32 (m, 2H), 7.19 (td, $J = 1.2, 7.6$ Hz, 1H), 7.12-7.10 (m, 1H), 5.42 (d, $J = 3.2$ Hz, 1H), 4.19 (dd, $J = 3.2, 5.6$ Hz, 2H), 4.03 (dd, $J = 3.6, 6.8$ Hz, 1H), 3.50-3.46 (m, 1H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 150.2, 140.3, 137.2, 129.0, 128.8, 128.0, 125.1, 123.4, 117.2, 114.5, 45.2, 42.1, 39.4, 34.0; HRMS (ESI, m/z): calcd. for $\text{C}_{19}\text{H}_{17}\text{NO}_4\text{SH}^+$ 356.0957, found 356.0957; $[\alpha]^{29}_{\text{D}} = -64.8^\circ$ ($c = 3.44$ in CHCl_3); HPLC analysis: >99% ee (Chiralcel OD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), R_t (major) = 44.4 min, R_t (minor) = 58.3 min.

3-((4-nitrophenyl)sulfonyl)-2-phenyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-

5(10bH)-one (5-2r): 69% yield. White solid. mp 233-235 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.26 (d, $J = 9.2$ Hz, 2H), 7.75 (d, $J = 8.8$ Hz, 2H), 7.33-7.30 (m, 2H), 7.25-7.13 (m, 6H), 7.07 (d, $J = 8.0$ Hz, 1H), 5.45 (d, $J = 3.6$ Hz, 1H), 4.30 (dd, $J = 4.4, 12.8$ Hz, 1H), 4.22 (dd, $J = 6.4, 13.2$ Hz, 1H), 3.83 (dd, $J = 3.6, 6.0$ Hz, 1H), 3.26-3.21 (m, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 150.1, 150.0, 145.2, 140.0, 136.3, 129.2, 128.9, 128.8, 128.6, 127.9, 127.8, 125.3, 124.0, 123.1, 117.3, 115.7, 45.4, 39.2, 33.7; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_6\text{SH}^+$ 463.0970, found 463.0962; $[\alpha]^{29}_{\text{D}} = -128.0^\circ$ ($c = 0.75$ in CHCl_3); HPLC analysis: >99% ee (Chiralcel OD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), R_t (minor) = 58.1 min, R_t (major) = 67.0 min.

3-((4-methoxyphenyl)sulfonyl)-2-phenyl-4,4a-dihydro-3H-chromeno[3,4-c]pyridin-

5(10b*H*)-one (5-2s): 70% yield. White foam solid. ^1H NMR (300 MHz, CDCl_3) δ 7.66-7.63 (m, 2H), 7.38-7.30 (m, 5H), 7.24-7.20 (m, 2H), 7.12 (td, $J = 0.6, 7.5$ Hz, 1H), 7.05-7.02 (m, 1H), 7.00-6.97 (m, 2H), 5.66 (d, $J = 4.2$ Hz, 1H), 4.30 (dd, $J = 4.2, 13.5$ Hz, 1H), 3.91 (s, 3H), 3.75 (dd, $J = 8.7, 13.5$ Hz, 1H), 3.65 (t, $J = 5.1$ Hz, 1H), 2.99-2.93 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 163.3, 149.8, 140.9, 137.9, 130.2, 129.8, 128.9, 128.5, 128.0, 127.8, 127.6, 125.1, 123.0, 117.3, 115.5, 114.3, 55.7, 45.0, 38.5, 33.0; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{22}\text{NO}_5\text{SH}^+$ 448.1219, found 448.1219; $[\alpha]^{29}_{\text{D}} = -59.8^\circ$ ($c = 1.12$ in CHCl_3); HPLC analysis: 99% ee (Chiralcel OD-H, Hexane/ i PrOH = 4/1, 0.75 mL/min), R_t (minor) = 34.9 min, R_t (major) = 42.9 min.

(E)-2-styryl-3-tosyl-4,4a-dihydro-3*H*-chromeno[3,4-*c*]pyridin-5(10b*H*)-one (5-7): 48% yield. White solid. mp 165-168 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.77-7.75 (m, 2H), 7.44-7.26 (m, 9H), 7.16 (td, $J = 1.2, 7.6$ Hz, 1H), 7.05 (dd, $J = 0.8, 8.0$ Hz, 1H), 6.99 (d, $J = 15.6$ Hz, 1H), 6.70 (d, $J = 15.6$ Hz, 1H), 5.62 (d, $J = 3.6$ Hz, 1H), 4.14 (dd, $J = 3.6, 13.6$ Hz, 1H), 3.91 (dd, $J = 8.0, 13.6$ Hz, 1H), 3.65 (t, $J = 5.2$ Hz, 1H), 2.86-2.81 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 149.9, 144.2, 138.7, 136.4, 136.1, 130.8, 129.8, 128.9, 128.7, 128.2, 128.0, 127.7, 126.8, 125.9, 125.1, 123.3, 117.2, 110.1, 60.4, 44.6, 38.0, 33.2, 21.6, 21.0, 14.2; HRMS (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{23}\text{NO}_4\text{SH}^+$ 458.1426, found 458.1425; $[\alpha]^{29}_{\text{D}} = -14.8^\circ$ ($c = 3.30$ in CHCl_3); HPLC analysis: 95% ee (Chiralcel OD-H, Hexane/ i PrOH = 4/1, 0.75 mL/min), R_t (minor) = 37.1 min, R_t (major) = 39.7 min.

(6a*R*,10*R*,12a*S*,12b*R*)-6-oxo-10-phenyl-8-tosyl-7,8-dihydro-6*H*-chromeno[3,4-*c*]quinoline-11,11,12,12(6a*H*,10*H*,12a*H*,12b*H*)-tetracarbonitrile (5-8): 63% yield. White solid. mp 171-176 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.84-7.50 (m, 9H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.27-7.21 (m, 2H), 6.71 (dd, *J* = 1.6, 5.2 Hz, 1H), 5.30 (br s, 1H), 4.37 (d, *J* = 3.2 Hz, 1H), 3.79-3.66 (m, 2H), 3.38 (s, 1H), 2.71 (d, *J* = 11.2 Hz, 1H), 2.45(s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.9, 150.9, 145.7, 133.8, 132.0, 132.0, 131.2, 130.7, 130.2, 128.8, 128.4, 125.7, 119.9, 118.3, 110.4, 109.6, 109.6, 108.5, 46.8, 43.3, 43.2, 42.5, 21.6; HRMS (ESI, *m/z*): calcd. for C₃₃H₂₃N₅O₄SH⁺ 586.1549, found 586.1547; [α]_D²⁹ = + 62.5° (*c* = 1.92 in CHCl₃); HPLC analysis: 82% ee (Chiralcel AD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), Rt (major) = 37.6 min, Rt (minor) = 84.2 min.

(2a*R*,6*S*,6a*S*,9a*R*,9b*S*,9c*R*)-6,8-diphenyl-4-tosyl-3,4,6,6a,9b,9c-hexahydrochromeno[3,4-*c*]pyrrolo[3,4-*f*]quinoline-2,7,9(2a*H*,8*H*,9a*H*)-trione (5-9): 65% yield. Yellow solid. mp 266-267 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.85-7.83 (m, 2H), 7.77 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.46-7.15 (m, 14H), 7.09-7.07 (m, 2H), 4.78 (dd, *J* = 3.2, 12.4 Hz, 1H), 4.16-4.15 (m, 1H), 3.81 (dd, *J* = 3.6, 12.4 Hz, 1H), 3.53 (d, *J* = 9.2 Hz, 1H), 3.42-3.38 (m, 1H), 3.36-3.33 (m, 1H), 3.09-2.90 (m, 3H), 2.42(s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 174.6, 167.3, 150.9, 144.3, 139.2, 137.5, 137.3, 131.3, 130.8, 130.0, 129.6, 129.0, 128.7, 128.3, 127.6, 127.0, 126.9, 126.4, 124.9, 123.3, 117.4, 109.1, 45.6, 44.4, 42.9, 40.2, 38.6, 36.3, 30.0, 21.6; HRMS (ESI, *m/z*): calcd. for C₃₇H₃₀N₂O₆SH⁺ 631.1903, found 631.1907; [α]_D²⁹ = - 105.3° (*c* = 2.82 in CHCl₃); HPLC analysis: >99% ee (Chiralcel AS-H, Hexane/iPrOH = 7/3, 0.80 mL/min), Rt (major) = 87.6 min, Rt (minor) = 123.6 min.

4-methyl-N-(((3R,4R)-2-oxo-4-(2-oxo-2-phenylethyl)chroman-3-

yl)methyl)benzenesulfonamide (5-10): 76% yield. White solid. mp 100-101 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.79-7.75 (m, 4H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 8.8$ Hz, 2H), 7.28-7.24 (m, 4H), 7.11-7.04 (m, 2H), 5.68 (t, $J = 6.8$ Hz, 1H), 3.96 (dd, $J = 6.0$, 12.0 Hz, 1H), 3.51-3.44 (m, 1H), 3.23-2.97 (m, 4H), 2.37(s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.4, 169.3, 150.6, 143.6, 136.6, 135.9, 133.8, 129.8, 129.0, 128.7, 128.2, 128.1, 127.0, 126.9, 125.0, 117.0, 44.4, 40.8, 39.7, 32.4, 21.5; LCMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{23}\text{NO}_5\text{SH}^+$ 450.14, found 450.05; $[\alpha]_D^{29} = +36.0^\circ$ ($c = 12.72$ in CHCl_3); HPLC analysis: 94% ee (Chiralcel AD-H, Hexane/iPrOH = 4/1, 0.75 mL/min), R_t (major) = 41.7 min, R_t (minor) = 50.1 min.

(3R,4R)-methyl 4-(2-hydroxyphenyl)-6-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine-3-carboxylate (5-11): 51% yield. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.4$ Hz, 2H), 7.43-7.41 (m, 2H), 7.31-7.26 (m, 5H), 7.09 (td, $J = 1.6$, 8.4 Hz, 1H), 6.96 (dd, $J = 0.8$, 7.6 Hz, 1H), 6.85-6.80 (m, 2H), 6.10 (s, 1H), 5.37 (d, $J = 4.0$ Hz, 1H), 4.45 (dd, $J = 3.2$, 14.4 Hz, 1H), 4.18 (dd, $J = 4.4$, 7.2 Hz, 1H), 3.59 (dd, $J = 12.0$, 14.4 Hz, 1H), 3.48 (s, 3H), 2.96-2.91 (m, 1H), 2.45(s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.9, 153.5, 144.1, 139.8, 138.6, 136.3, 130.7, 129.7, 128.7, 128.1, 127.8, 127.5, 127.4, 127.3, 121.2, 119.9, 118.0, 52.2, 43.3, 43.2, 33.6, 31.5, 22.6, 21.6, 14.1; LCMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{25}\text{NO}_5\text{SH}^+$ 464.15, found 464.09; $[\alpha]_D^{29} = -166.2^\circ$ ($c = 1.36$ in CHCl_3); HPLC

analysis: 99% ee (Chiralcel AD-H, Hexane/iPrOH = 4/1, 0.60 mL/min), Rt (minor) = 32.1 min, Rt (major) = 51.6 min.

2-phenyl-5H-chromeno[3,4-c]pyridin-5-one (5-12): 79% yield. White solid. mp 193-194 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.64 (s, 1H), 8.33 (s, 7H), 8.23-8.17 (m, 3H), 7.67-7.63 (m, 1H), 7.61-7.56 (m, 3H), 7.47-7.43 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.1, 160.0, 153.1, 152.8, 142.1, 138.0, 132.7, 130.5, 129.0, 127.6, 124.9, 123.4, 118.2, 116.3, 114.7, 111.1; HRMS (ESI, m/z): calcd. for C₁₈H₁₁NO₂H⁺ 274.0868, found 274.0857.

(2R,4aR,10bR)-2-phenyl-3-tosyl-2,3,4,4a-tetrahydro-1H-chromeno[3,4-c]pyridin-5-one (5-13): 85% yield. White solid. mp 181-182 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.47 (m, 2H), 7.31-7.27 (m, 1H), 7.21-7.01 (m, 10H), 4.90 (dd, *J* = 6.0, 11.2 Hz, 1H), 4.25 (dd, *J* = 6.4, 14.4 Hz, 1H), 3.87 (dd, *J* = 6.4, 14.0 Hz, 1H), 3.38 (dd, *J* = 6.4, 13.2 Hz, 1H), 3.22-3.16 (m, 1H), 2.40(s, 3H), 2.24-2.18 (m, 1H), 1.88-1.78 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 168.2, 150.4, 143.2, 139.7, 137.4, 129.3, 128.9, 128.2, 128.1, 127.6, 127.2, 127.1, 124.9, 123.6, 117.0, 59.5, 42.9, 38.3, 37.9, 34.7, 21.4; HRMS (ESI, m/z): calcd. for C₂₅H₂₃NO₄SH⁺ 434.1426, found 434.1420; [α]_D²⁹ = + 15.2° (c = 2.9 in CHCl₃); HPLC analysis: 99% ee (Chiralcel IA, Hexane/iPrOH = 4/1, 0.60 mL/min), Rt (minor) = 32.5 min, Rt (major) = 52.0 min.

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