Development of new reactions and reagents in carbene-catalyzed addition of carbon and nitrogen nucleophiles to unsaturated acyl azolium intermediates

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**Development of New Reactions and Reagents in Carbene-
Catalyzed Addition of Carbon and Nitrogen Nucleophiles to
Unsaturated Acyl Azolium Intermediates**

WU XINGXING

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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Catalyzed Addition of Carbon and Nitrogen Nucleophiles to
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TABLE OF CONTENTS

Chapter 1.	Introduction	1
1.1	Introduction to asymmetric organocatalysis	2
1.2	Introduction to N-heterocyclic carbene (NHC)	4
1.2.1	NHC catalysis involving umpolung acyl anion intermediate.	7
1.2.2	Catalysis involving homoenolate or more extended Breslow intermediate	11
1.2.3	Catalysis involving acyl zolium intermediates	15
1.3	Conclusion and our research design	26
1.4	References	28
Chapter 2.	Rapid access to bicyclic δ -lactones via carbene-catalyzed activation of unsaturated carboxylic esters	34
2.1	Introduction	35
2.2	Results and discussions	43
2.3	Summary	51
2.4	Experimental section	52
2.5	References	94
Chapter 3	Enantioselective Nucleophilic β -Carbon Amination of Enals: Carbene-Catalyzed Formal [3+2] Reactions to Access Pyrazolidinones	97
3.1	Introduction	98
3.2	Results and discussions	101
3.3	Summary	108
3.4	Experimental section	109

3.5	References	142
Chapter 4.	Construction of fused pyrrolidines and β -lactones via carbene-catalyzed C-N, C-C and C-O bond formations	146
4.1	Introduction	147
4.2	Results and discussions	152
4.3	Proposed reaction pathway and stereo-chemical modes	159
4.4	Summary	160
4.5	Experimental section	160
4.6	References	193
Chapter 5.	Polyhalides as efficient and mild oxidants for oxidative carbene organocatalysis by radical processes	198
5.1	Introduction	199
5.2	Results and discussions	204
5.3	Mechanistic study	210
5.4	Summary	214
5.5	Experimental section	215
5.6	References	241

ABSTRACT

This thesis focuses on development of efficient protocols for access to advanced complex molecules enabled by *N*-heterocyclic carbene (NHC) catalyzed LUMO activation of enal or its ester derivatives, and discovery of polyhalide as simple organic oxidant for oxidative carbene catalysis. It contains five parts:

Chapter 1 first gives a brief introduction to the history of asymmetric organocatalysis, followed by development of *N*-heterocyclic carbene (NHC) catalysis. This includes three main aspects, (a) catalysis involving umpolung acyl-anion, (b) homoenolate catalysis, (c) reactions involving acyl azolium intermediates. This chapter also illustrates the challenges and opportunities in NHC catalyzed reactions, especially in heteroatoms as nucleophiles for α , β -unsaturated acyl azolium and simple oxidants for oxidative NHC catalysis.

Chapter 2 describes a single-step, organocatalytic and enantioselective cascade process for access to a multi-cyclic lactone that constitutes the core structure of iridoids. This protocol shows the synthetic power of a NHC catalyst for the activation of a readily available and stable carboxylic ester to give the unsaturated acyl azolium intermediate.

Chapter 3 demonstrates an efficient protocol for the preparation of pyrazolidinone products via nucleophilic β -carbon amination of enals under oxidative NHC catalysis. The heterocycle adducts from the catalytic reaction can readily undergo further transformations to afford various useful functional molecules, such as pyrazolidines and β -amino acid derivatives.

Chapter 4 shows a novel and efficient cascade approach for the direct assembly of two privileged scaffolds (pyrrolidine and β -lactone) with good to excellent yield and enantioselectivity. This study sheds light on modulating the reactivity of nitrogen atom for challenging NHC-catalyzed asymmetric C-N bond formations.

Chapter 5 introduces polyhalide reagents as simple and inexpensive oxidants for oxidative NHC catalysis, providing efficient methods for functionalization of the α , β and γ atoms of aldehydes. The oxidative process involves multiple radical intermediates, and shall inspire new reaction development via NHC-catalyzed radical process.

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1. Construction of Fused Pyrrolidines and β -Lactones by Carbene-Catalyzed C–N, C–C, and C–O Bond Formations.

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ABBREVIATIONS

Ac	acetate
EWG	electron-withdrawing group
Glc	β -glucopyranosyl
HOBt	hydroxybenzotriazole
AIBN	2,2'-azo <i>bisisobutyronitrile</i>
Boc	<i>tert</i> -butyloxycarbonyl
Bu	butyl
Bn	benzyl
Bz	benzoyl
Ts	4-toluenesulfonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
CH ₂ Cl ₂	dichloromethane
DIBAL	diisobutylaluminum hydride
DIEA	N, N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
EA	ethyl acetate
EE	ethyl ether
equiv	equivalent
M.S.	molecular sieves
DQ	3,3',5,5'-tetra- <i>tert</i> -butyldiphenquinone

Mts	2,4,6-trimethylbenzenesulfonyl
Piv	pivaloyl
Boc	<i>tert</i> -butyloxycarbonyl
Ns	4-nitrobenzenesulfonyl
PMP	<i>p</i> -methoxyphenyl
ESI	electrospray ionization
ET	electron transfer
FG	functional group
GC	gas chromatography
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
IPA	isopropyl alcohol
<i>i</i> -Pr	isopropyl
IR	infrared
LC-MS	liquid chromatography-mass spectrometry
Mes	mesityl
mp	melting point
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
OAc	acetocy
RT	room temperature
SET	single-electron transfer
<i>t</i> Bu	<i>tert</i> -butyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
TPP	thiamine pyrophosphate
V-50	2,2'-azobis(2-methylpropionamidine)dihydrochloride
V-70	2,2'-azobis(4-methoxyl-2,4-dimethylvaleronitrile)
α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	Sigma

Chapter 1

Introduction

1.1 Introduction to Asymmetric Organocatalysis

Over the past two decades, the arena of asymmetric organo-catalysis has witnessed a thriving development in synthetic chemistry.^[1] Along with transition metal catalysis and bio-catalysis, organo-catalysis ubiquitously constitutes the three main pillars of the asymmetric catalysis. The utilization of small organic molecules (with carbon, hydrogen and other nonmetal elements) in chemical synthesis has a long history. The earliest example can be dated back to 1850, when Liebig demonstrated that acetaldehyde could promote the hydrolysis of cyanide to amide.^[2] However, this area was long ignored by chemists, though several cases were reported in the last century. The remarkable “turning point” was at the beginning of 21st century, when List and Barbas,^[3] MacMillan.^[4] reported their independent work on the secondary-amine catalysis (Scheme 1.1 and Scheme 1.2). These pioneering works greatly attract intensive interest from enormous research groups and since then, the field of organo-catalysis has become a highly active area in organic chemistry.

Scheme 1.1 L-Proline catalyzed asymmetric aldol reaction by List and Barbas.

Scheme 1.2 MacMillan's enantioselective Diels-Alder cycloaddition.

Significantly, organo-catalysis provides a practical and mild access to advanced functional molecules in high enantioselectivity. Compared with conventional transition-metal catalysis for asymmetric synthesis, it bears several advantages, such as: (a) inexpensive. Organic small molecules as catalysts are easy to prepare from naturally existing optically pure starting materials, such as amino acids and tartaric acid; (b) large chiral pool for elegant chirality control. Organo-catalysis provides a powerful method for various reactions with excellent enantioselectivity, e.g. aldol reaction, Diels-Alder reaction and Mannich reaction; (c) non-toxic and environmentally friendly. Organocatalysts are based on the small organic molecule, consisting of non-metal elements, such as C, H, O and S *etc.* Representative organocatalysts that have been widely used in synthetic chemistry are illustrated below (Scheme 1.3).^[1]

Scheme 1.3 Representative organocatalysts used in asymmetric catalysis.

1.2 Introduction to N-heterocyclic Carbene (NHC)

As one of the most developed organocatalysts, N-heterocyclic carbene (NHC) has witnessed rapid progress over the past two decades.^[5] The history of NHC can be dated back to 1943, when Ukai discovered that thiazolium salts could mediate the Benzoin condensation reaction.^[6] The mechanism of this transformation was later proposed by Breslow in 1958.^[7] He proposed that thiazolium salt was firstly deprotonated to form a free carbene (thiazolin-2-ylidene) as the true catalyst. The neutral enaminol intermediate was produced after nucleophilic addition of the carbene to the benzaldehyde and subsequent 1,2-proton transfer. And then, it attacked another aldehyde component to eventually give the benzoin condensation product (Scheme 1.4).

Scheme 1.4 Breslow's proposal on the benzoin condensation.

Since this hypothesis, the key enaminol species is known as Breslow intermediate. However, attempts to isolate the free carbene were unsuccessful until 30 years later, when seminal work was reported by Bertrand on the preparation of phosphinosilyl-based carbene.^[8a] To prevent the dimerization of the active free carbene, Arduengo^[8b]

used a bulky adamantyl group as the N-protecting group, and successfully obtained the first crystalline N-heterocyclic carbene (NHC) in 1991. These pioneering studies have greatly attracted extensive interest from chemists. To date, numerous reactions have been developed utilizing NHC for carbon-carbon or carbon-heteroatom bond formations, particularly in asymmetric organo-catalysis (Scheme 1.5).

Scheme 1.5 The history of N-heterocyclic carbene (NHC) organocatalysis.

Generally, there are four types of NHCs that have found wide applications in synthetic chemistry: imidazolylidene, imidazolinylidene, thiazolylidene and triazolylidene (Scheme 1.6). To conclude the literature, the imidazolylidene and imidazolinylidene are broadly used as elegant ligands in transition metal catalysis,^[9] though they also appear in some reports behaving as organocatalysts. The thiazolylidene, firstly developed by Ukai, are mostly explored in the Benzoin condensation and Stetter reaction (section 1.2.1). Today, the asymmetric organocatalysis are dominated not by these three kinds of NHCs, but by triazolylidene, which was firstly demonstrated by Enders and Teles independently in 1995.

Scheme 1.6 General types of N-heterocyclic carbenes.

Though a wide variety of NHC-catalyzed reactions have been reported, most of the substrates used are carbonyl compounds, such as aldehydes or carboxylic acid and their derivatives. With a series of NHC-bound reactive intermediates developed, amazing success has been achieved in the functionalization of the α , β , γ or remote carbon atoms, as well as the carbonyl carbon atom of the carbonyl compounds. According to the type of the generated intermediates, in this chapter we will discuss the NHC catalysis in three main aspects, (a) catalysis involving umpolung acyl-anion, (b) homoenolate catalysis, (c) reactions involving acyl azolium intermediates (Scheme 1.7).

Scheme 1.7 NHC-bound reactive intermediates.

1.2.1 NHC catalysis involving umpolung acyl anion intermediate.

The earliest studied reaction involving NHC is the benzoin reaction. In this catalytic cycle, the carbene catalyst can promote conversion of the aldehyde acyl carbon

from an electrophile to a nucleophilic species. This reactivity inversion is known widely as “umpolung”.^[10] The concept of umpolung is one of the most developed areas in NHC chemistry, particularly for Benzoin and Stetter reactions.

1.2.1.1 Benzoin condensation

Benzoin reaction is a powerful method for carbon-carbon bond construction. In 1832, Wohler and Liebig reported the first example of benzoin condensation with cyanide as the catalyst.^[11] After seminal work by Ukai who used the thiazolium salt, Sheehan and Hunneman focused their effort to achieve the asymmetric Benzoin reaction using a chiral thiazolium carbene catalyst.^[12] However, in their work, only moderate ee (~22% ee) was finally obtained. Since then, many groups began to develop more efficient catalytic systems to address the problem of enantioselectivity. In 2002, Enders reported a breakthrough work in the asymmetric benzoin reaction by evaluating triazolium pre-catalysts.^[13] The newly designed carbene catalyst readily furnished the desired product in excellent enantioselectivity (Scheme 1.8).

Scheme 1.8 Ender's enantioselective aromatic benzoin condensation

Recently, Cannon and Zeitler discovered an efficient catalyst with a H-bonding group (OH) (Scheme 1.9).^[14] The newly designed carbene provided the homo benzoin product of benzaldehyde in excellent yield and enantioselectivity (90% yield, >99% ee). The incorporation of the hydroxyl group significantly enhanced the selectivity control.

To date, this method remains to be the most powerful catalytic condition for the Benzoin reactions that have been reported.

Scheme 1.9 Cannon and Zeitler's enantioselective benzoin reactions.

The cross-benzoin reactions have also been reported with the C-C coupling of two aldehyde components. For example, Yang studied the cross-benzoin condensation of the aromatic aldehyde and alkyl aldehyde with thiazolium and triazolium catalyst (Scheme 1.10).^[15] They found an interesting result: when using the thiazolium carbene, it preferred to attack the aromatic aldehyde to form the corresponding Breslow intermediate, followed by coupling with the alkyl aldehyde; while the triazolium catalyst tended to form the Breslow intermediate with the alkyl aldehyde and subsequently reacted with the aromatic aldehyde to give the other benzoin product.

Scheme 1.10 Yang's cross-benzoin condensation.

1.2.1.2 Stetter reaction

The NHC-catalyzed Stetter reaction is another type of reaction involving the umpolung acyl-anion catalysis. It provides a general approach for the coupling of aldehydes and electron-deficient alkenes (Scheme 1.11). In 1973, Stetter demonstrated the first example of intermolecular 1,4-addition of acetaldehyde to the unsaturated enone with the thiazolium catalyst.^[16] Since then, this type of umpolung acyl-anion reaction has been widely known as Stetter reaction.^{[17][18]} Mechanistically, the Stetter reaction was initiated by the generation of Breslow intermediate through the reaction of free carbene and aldehyde. Subsequently, the umpolung acyl anion undergoes the 1,4-addition to the enone.

Scheme 1.11 General Stetter reaction and its reaction pathway.

In 1996, Enders reported the first enantioselective Stetter reaction in an intramolecular manner (Scheme 1.12).^[19] With a triazolium carbene, the cyclization product was obtained in 73% yield and 60% ee. Since then, the asymmetric Stetter reaction continues to be a hot area in synthetic chemistry. Interestingly, based on Enders' work, Law and McErlean^[20] significantly expanded the substrate scope to the extended unsaturated ester as the 1,6-Michael acceptor.

Scheme 1.12 Enders' enantioselective Stetter reaction.

Scheme 1.13 Extended Michael acceptor for Stetter reaction.

In addition to the extensive work on the intramolecular Stetter reaction, enantioselective intermolecular Stetter reaction was also developed by Enders, Rovis *et al.* For example, Rovis and co-workers discovered that a fluorinated catalyst showed much better reactivity and selectivity in the Stetter reaction of aryl aldehydes to nitroalkenes, compared to the non-fluorinated carbene catalyst (95% yield, 95% ee vs 90% yield, 88% ee) (eq. a, Scheme 1.14).^[21a] After this work, the Rovis group further demonstrated the coupling reaction of nitroalkenes with alkyl aldehydes. The fluorinated carbene again gave the product in good yield and excellent enantioselectivity (eq. b, Scheme 1.14).^[21b]

Scheme 1.14 Rovis' asymmetric Stetter reaction.

1.2.2 Catalysis involving homoenolate or more extended Breslow intermediate.

Employing α,β -unsaturated aldehyde as the competent substrate, the initially generated Breslow intermediate not only possess the acyl-anion reactivity, but also has another unique property. The Breslow intermediate can extend to β -carbon position, resulting in the inversion of β -carbon from typically electrophilic to nucleophilic property. The homoenolate equivalent can then react with other electrophiles to give diverse β -functionalized products (Scheme 1.15).

Scheme 1.15 NHC-catalyzed homoenolate reaction pathway.

The NHC-catalyzed homoenolate reactivity was first discovered by Bode and Glorius in 2004.^[22] Bode demonstrated annulations of a variety of enals with aryl aldehydes to form γ -lactone products in 41-87% yield and moderate diastereoselectivity (eq. a, Scheme 1.16).^[22a] Meanwhile, Glorius used enal to react with activated

trifluoromethyl ketones or aldehydes as electrophiles.^[22b] Similar γ -lactones were obtained in 32-70% yield and moderate diastereoselectivity (eq. b, Scheme 1.16).

Scheme 1.16 (a) Bode's [3+2] annulation of enal with aldehydes; (b) Glorius' annulation of enal with aldehydes or activated ketones.

Pioneered by these two reports, the homoenolate reactivity was largely explored, leading to numerous efficient approaches for access to complex functional molecules.^[23] In 2013, Ye group reported an enantioselective [4+3] annulation of enals with *o*-quinones.^[24] Under their conditions, both aromatic and alkyl enals gave the corresponding products in good yield (79-97%) and excellent enantioselectivity (up to 98% ee) (Scheme 1.17).

Scheme 1.17 Ye's [4+3] annulation via homoenolate.

With the cooperative Lewis acid/NHC catalysis strategy, Scheidt^[25] achieved the [3+2] annulation of enals with hydrazones via homoenolate intermediate. They proposed that Lewis acid catalyst, Mg(*O**t*Bu)₂, could coordinate to the nitrogen atom of hydrazone to increase its electrophilicity. With an indanol based NHC, the

cyclization products were obtained in 61-85% yield and 85-97% enantioselectivity (Scheme 1.18).

Scheme 1.18 Scheidt's enantioselective [3+2] annulations promoted by $\text{Mg}(\text{OtBu})_2$.

Despite extensive reports on the annulations or non-annulation reactions using homoenolate reactivity (via electron pair reaction mode), the extended Breslow intermediate was also reported to react through a single-electron-transfer pathway. The first example was demonstrated by Studer and his co-workers.^[26] They used TEMPO as the SET oxidant to oxidize the aldehyde to the corresponding TEMPO esters. Interestingly, the reaction involves two times of single-electron-transfer processes to give the desired esters (Scheme 1.19).

Scheme 1.19 Carbene catalyzed SET oxidation with TEMPO.

Rovis and Chi groups both reported seminal work on the carbene catalyzed radical activation.^[27] In 2014, they independently found that electron-deficient nitro

compounds readily served as competent SET oxidants to get one electron from the Breslow intermediate derived from the NHC and enal (Scheme 1.20 and Scheme 1.21). The generated NHC-bound radical intermediate then coupled with the nitro radical and subsequent N-O bond cleavage eventually afforded a β -hydroxyl ester in excellent enantioselectivity (Scheme 1.20). Seminal reports involving the radical activation have been demonstrated further by Rovis, Chi, Ye, and Sun in some other examples.^[28]

Scheme 1.20 Rovis' β -hydroxylation of enal via radical process.

Scheme 1.21 Chi's β -hydroxylation of enal.

1.2.3 Catalysis involving acyl azolium intermediates

Besides the umpolung chemistry, NHCs are also able to catalyze the non-umpolung reactions. For example, the NHC-bound acyl azolium as a significant intermediate has attracted extensive attention from chemists in these years. A set of active intermediates derived from acyl azoliums have been largely explored in α , β , γ or even remote carbon atom functionalization of aldehydes. In this section, we will discuss these studies in four parts based on the activated sites: (a) transesterification; (b) catalysis involving azolium enolate; (c) reactions through α,β -unsaturated acyl azolium; (d) γ -functionalization via vinyl azolium enolate.

1.2.3.1 Transesterification reactions

Saturated acyl azoliums have been widely used as precursor of transesterifications (eq. a, Scheme 1.22). This type of reactions was first discovered by Hedrick and Nolan in 2002.^[29] Soon after that, numerous reactions were reported by Hedrick, Nolan, Waymouth and other research groups.^[30] Using a chiral carbene as the catalyst, the transesterification reactions allow kinetic resolution of secondary alcohols. Seminal works were first independently reported by Suzuki and Maruoka (Scheme 1.22, eq. b and c).^[31a] Suzuki used vinyl acetate as the starting material and chiral imidazolium as

the catalyst. Under their conditions, the esters derived from the secondary alcohols were obtained in 9-58% ee. An improved approach was reported by Maruoka and his coworkers (eq. c, Scheme 1.22). By switching the simple vinyl acetate to the bulkier ester (vinyl diphenyl acetate), the corresponding esters were obtained in a higher enantioselectivity.^[31b]

Scheme 1.22 NHC catalyzed transesterification.

Aldehydes have also been applied in the NHC-catalyzed transesterifications. In 2004, Bode showed the internal redox reaction of epoxy or aziridinyl aldehyde. With thiazolium catalyst, β -hydroxy or amino esters were obtained in 53-89% yield (Scheme 1.23).^[32a] In the same year, Rovis and his coworkers used α -bromo or chloro aldehyde as the starting material. Under the NHC catalytic conditions, the facile conversion of the aldehydes to the corresponding esters could be achieved (Scheme 1.24).^[32b] In both

cases, the reactions were proposed to form an acyl azolium intermediate with an internal redox process initiated by the elimination of reducible α -functionality.

Scheme 1.23 Bode's self-redox reaction to form the ester.

Scheme 1.24 Rovis' NHC-catalyzed self-redox reaction.

1.2.3.2 Catalysis involving azolium enolate (α -carbon activation)

In 2006, Bode demonstrated the first [4+2] hetero-Diels-Alder reaction in high enantioselectivity via an enolate intermediate.^[33a] The key mechanism involved intramolecular proton transfer of the homoenolate to give the key NHC-bound enolate. The [4+2] reaction was proposed to proceed through a concerted step to yield the final products (eq. a, Scheme 1.25). A saturated aldehyde with a reducible functional group at the α position is also a competent substrate to give the same enolate intermediate. In the same year, Bode group further reported a [4+2] Diels-Alder reaction of an α -chloro aldehyde with an enone.^[33b] The corresponding lactone products were obtained with 75-95% yield and excellent enantioselectivity (up to 99% ee) (eq. b, Scheme 1.25).

Scheme 1.25 [4+2]-Hetero-Diels-Alder cycloaddition.

Since then, extensive studies have emerged using the NHC catalyzed enolate reactivity. Other significant approaches to give this key intermediate have been developed. In 2008, Ye^[34a] and Smith^[34b] groups both reported nucleophilic addition of a carbene to a ketene as an effective process to furnish an azolium enolate (Scheme 1.26). Subsequently, the reactive species was trapped by N-protected imines to form [2+2] annulated lactam products. In the same year, Ye also employed the ketene as the enolate precursor to react with enone as the electrophile, giving similar lactone products as reported by Bode in high enantioselectivity.^[35]

Scheme 1.26 [2+2] annulation of ketene by Ye.

As discussed above, the acyl azolium was readily trapped by alcohols to form ester products. With a “backward” pathway, Chi group successfully achieved generation of the acyl azolium from carboxylic esters (Scheme 1.27).^[36] Due to its enhanced acidity,

the acyl azolium could undergo facile deprotonation of the α -proton to form azolium enolate. The enolate was further demonstrated to react with chalcone imines to give the lactam products in good yield and excellent enantioselectivity.

Scheme 1.27 [4+2] cycloadditions of activated esters with chalcone imines.

Under oxidative conditions, saturated aldehydes were reported to provide acyl azoliums directly. In 2013, Rovis^[37] and Chi^[38] labs both independently achieved the [4+2] hetero-Diels-Alder reaction by employing simple alkyl aldehydes and α,β -unsaturated imines or enones as the substrates (Scheme 1.28). The key mechanistic process involved the generation of acyl azoliums by the oxidation of the Breslow intermediates and subsequent deprotonation of the α -proton to yield the azolium enolates. Under the optimal conditions, the corresponding lactam and lactone products were obtained in good yield and excellent enantioselectivity.

Scheme 1.28 Generation of azolium enolate from alkyl aldehydes.

In 2014, Sun^[39a] and Wang^[39b] groups independently described enantioselective α -fluorination of aldehydes using NFSI as the oxidant. In their work, the Breslow intermediate was oxidized by NFSI to finally give the enolate after deprotonation of the generated azolium. Then, the electrophilic NFSI was trapped by the azolium enolate to produce the α -fluoroester. Thus, NFSI not only behaved as a good internal oxidant, but also as a fluorine source (Scheme 1.29).

Scheme 1.29 Enolate generation for α -fluorination of aldehydes using NFSI.

1.2.3.3 NHC catalyzed reactions through α , β -unsaturated acyl azoliums (β -carbon reaction).

α , β -Unsaturated acyl azoliums remain to be among the most studied intermediates in NHC catalysis. This catalytic strategy provides a competent approach for the LUMO activation of α , β -unsaturated carbonyl compounds. To date, there have been several commonly used methods to generate NHC-bound unsaturated acyl azolium

intermediates, for example, smartly designed aldehydes with internal redox functionality (e.g. ynals, α -bromo enal), unsaturated acyl fluoride, activated esters, in-situ generated mixed anhydrides and the oxidative carbene catalysis (aldehyde combined with the external oxidants) (Scheme 1.30).

Scheme 1.30 Different precursors of unsaturated acyl azolium.

In 2006, Zeitler and her coworkers illustrated the utilization of ynals under NHC catalysis to form unsaturated acyl azoliums.^[40] The reaction proceeded through the addition of the carbene to the aldehyde group, furnishing the Breslow intermediate. After protonation of the intermediate **I** and tautomerization, the unsaturated acyl azolium was formed and finally trapped by the alcohol to give the unsaturated ester products (Scheme 1.31).

Scheme 1.31 Esterification of ynals.

With an α,β -unsaturated acyl fluoride as a precursor, Lupton and coworkers successfully achieved [4+2] cycloaddition with an enol ether (Scheme 1.32).^[41] They

Scheme 1.33 [3+3] Annulation via oxidative NHC catalysis.

A similar [3+3] annulation was also reported by Ye and co-workers. They used a different strategy to form the α,β -unsaturated acyl azolium with a bench-stable α -bromo enal as the precursor (Scheme 1.34).^[43] Coupled with 1,3-dicarbonyl compounds, the corresponding 3,4-dihydropyranones were obtained in excellent yields. The asymmetric transformation was also tested with chiral NHCs. The enantioselectivity of the product could be up to 95% ee.

Scheme 1.34 [3+3] Annulation using α -bromo enal to form the acyl azolium intermediate.

Recently, Ye group further developed a new strategy to form the key acyl azolium intermediate using a stable and inexpensive carboxylic acid (Scheme 1.35). The acid was activated in situ by PivCl to form a mixed anhydride. This strategy was successfully applied in different types of annulation reactions.^[44]

Scheme 1.35 Ye's protocol using carboxylic acid as the starting material.

1.2.3.4 Catalysis involving azolium dienolates (γ -carbon reaction)

When there is a β -methyl group on the α,β -unsaturated acyl azolium, its facile deprotonation would result in a the vinyl enolate intermediate. In 2011, Ye and co-workers described the first example of catalytic generation of this key intermediate from an in-situ formed α,β -unsaturated ketene.^[45] The reaction involved elimination of HCl to give the ketene intermediate, followed by the addition of NHC, leading to the vinyl azolium intermediate (Scheme 1.36). The subsequent [4+2] cycloaddition with an activated trifluoromethyl ketone would afford the dihydropyranones. However, the enantioselective control remains a challenge for the remote carbon with their conditions.

Scheme 1.36 [4+2] Annulations of ketenes with activated ketones.

In 2013, Chi lab reported an oxidative strategy for access to the vinyl azolium enolate intermediate (Scheme 1.37).^{[46][47]} They employed a γ -methyl enal as the substrate, instead of the acyl chloride in Ye's work. The oxidative process with the bisquinone oxidant, developed by Studer, and proton abstraction would eventually afford the key intermediate. Subsequent [4+2] formal cycloaddition with a trifluoromethyl ketone led to γ -lactone products. Interestingly, there was a significant increase in the enantioselectivity when a catalytic amount of a Lewis acid was added.

Scheme 1.37 Cooperative catalysis for enantioselective [4+2] reaction.

1.3 Conclusion and our research design

To date, carbene organocatalysis has been one of the most explored areas in asymmetric organocatalysis. Numerous chemists have made significant contributions to the development of NHCs in synthetic chemistry. With the discovery of diverse NHC activation modes, the unique activity of the generated NHC-bound intermediates allows for efficient protocols for access to advanced complex molecules from simple raw materials. Among them, synthetic methods based on the acyl azolium intermediate are most diverse and versatile for chemical bond construction.

However, there are still some problems in this research area. First, as discussed above, there are many protocols to generate the acyl azolium intermediate from different substrates. Our group first discovered that readily available esters can be applied as simple starting materials to provide the α,β -unsaturated acyl azoliums, which react with imines (as enamine precursors) to form the [3+3] annulation products. Further development of highly efficient processes to more complex molecular frameworks with the ester activation is depicted. Second, nearly all of the reported methods with unsaturated acyl azolium are explored for carbon-carbon bond formations. The typically used reagents are soft carbon nucleophiles, such as 1,3-dicarbonyl compounds, enamine, and ylide. Extension to the nitrogen as well as other heteroatom (S, O *etc.*) nucleophiles, which rarely studied, would provide a general approach for asymmetric C-N or other C-heteroatom bond constructions. Third, the oxidative NHC catalysis with an external oxidant is the most widely used method for the generation of acyl azoliums from various aldehydes. Pioneered by Studer, the 3,3',5,5'-tetra-*tert*-

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butyldiphenquinone has been recognized as the most powerful and efficient oxidant for this oxidative NHC strategy. However, the high price of the quinone and unavoidable generation of the reduced quinone greatly suppress its practical application, especially in large-scale synthesis. Thus, the development of a simple, efficient, and inexpensive oxidant is of great significance.

Therefore, in this thesis, we aim at developing new NHC catalytic reactions in these three aspects: (1) carboxylic ester activation for rapid access to bicyclic δ -lactones; (2) NHC-catalyzed aza-Michael addition for construction of bicyclic pyrrolidine fused β -lactones; (3) development of simple polyhalides as simple organic oxidants for oxidative carbene organocatalysis.

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Chapter 2

Rapid Access to Bicyclic δ -Lactones via Carbene-Catalyzed Activation of Unsaturated Carboxylic Esters

2.1 Introduction

Iridoids are a kind of phytonutrients, which are isolated from plants and animals.^[1] They exhibit widespread bioactivities, such as neuroprotective effect, anti-tumour, anti-bacteria, anti-cancer, anti-oxidant activities.^[2] Some representative iridoids and their analogues including natural products and bioactive molecules are shown in Scheme 2.1. For example, Nepetalactone, a bicyclic monoterpenoid with cyclopentane fused lactone structure, was isolated by steam distillation of catnip in 1941 by Johnson and showed antibacterial, antispasmodic activity.^[3] Ricciocarpin A^[4] is a furanosesquiterpene lactone bearing a furan ring, demonstrating strong molluscicidal activity against the *Biomphalaria glabrata*. Because of the interesting structural feature and biological activity of iridoids, many chemists have devoted considerable efforts towards their synthesis. Several synthetic methods for this class of molecules have been developed, including biosynthesis, metal catalysis and organocatalyst-catalyzed intramolecular or intermolecular cycloaddition.

Scheme 2.1 Natural products and bioactive compounds.

In 2012, Connor developed an elegant bio-synthetic approach to cyclic terpenes from the linear monoterpene 10-oxogeranial substrate, which was promoted by a plant-derived enzyme (Scheme 2.2).^[5] Initially, NAD(P)H promoted the 1,4-addition of the unsaturated aldehyde to form an enol intermediate, followed by two possible routes: one is a direct hetero-Diels-Alder reaction in an inverse-electron manner, the other is an intramolecular Michael addition pathway. Notably, the resulted products were in the equilibrium of *cis-trans*-nepetalactol/iridodial and the high efficiency of the enzyme enabled the large-scale preparation of the iridoids.

Scheme 2.2 Connor's bio-synthetic approach to cyclic terpenes.

Cycloaddition of TMM (trimethylenemethane) is a powerful method to construct five-membered carbocycles, either through thermal or metal-catalyzed cycloaddition pathway. Trost and his coworkers reported a Pd-catalyzed [3+2] cycloaddition of

methyl substituted TMM with coumarin in 1981 (Scheme 2.3).^[6] Under their conditions, the desired adduct was obtained in 82% yield, with 8:1 regioselectivity.

Scheme 2.3 Trost's Pd-catalyzed [3+2] cycloaddition using TMM.

With $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as a Lewis acid catalyst, Denmark achieved the construction of bicyclic fused five and six membered rings via hetero-Diels-Alder reactions (Scheme 2.4).^[7] Based on this work, they further completed a total synthesis of (+)-nepetalactone in 42% overall yield with 2 steps.

Scheme 2.4 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalyzed hetero-Diels-Alder reaction.

The cascade reaction catalyzed by organocatalyst is an efficient and economical way to construct a complex molecular framework from simple starting materials.^[8] Many elegant cascade synthetic approaches via organocatalysis have been reported in recent years with excellent stereoselectivities. With this concept, List in 2009 reported a three-step domino reaction towards a total synthesis of the natural product (+)-ricciocarpin A with high enantioselectivity (Scheme 2.5).^[9] This process involved reductive Michael addition/Tishchenko cascade from a simple enal. The MacMillan

catalyst was proved to show excellent reactivity and stereo-selectivity. This one-pot cascade reaction was quite general and was applied to the production of other analogues by adjusting the structure of the enal.

Scheme 2.5 List's total synthesis of natural product (+)-ricciocarpin A.

In Hofferberth's total synthesis of the ant-associated iridoids,^[10] the key step was achieved by using the enamine/iminium cascade concept (Scheme 2.6). From the commercially available citronellal, a linear aldehyde enal could be obtained after two times of oxidation, followed by the tandem cycloaddition promoted by N-methyl aniline. The iridoid skeleton was given in 84% yield after 24 h. Hydrolysis under TsOH/THF (wet) conditions afforded the desired nepetalactol in 84% yield.

Scheme 2.6 Hofferberth's enamine/iminium cascade.

The strategy to generate an enolate intermediate via organocatalysis receives great interest from chemists, because it provides facile access to chiral products. By using a chiral isothioureia as a Lewis base catalyst, Smith reported a highly stereospecific intramolecular Michael addition/lactonization domino reaction, leading to polycyclic lactones in excellent dr and ee values (Scheme 2.7).^[11] The enolate was generated by deprotonation of an acyl ammonium species, formed from the N-acylation of the catalyst with an in-situ formed mixed anhydride.

Scheme 2.7 Smith's Michael /lactonization domino reaction.

N-Heterocyclic carbene (NHC), a representative Lewis base catalyst, has emerged as a highly efficient tool in construction of complex organic frameworks.^[12] Scheidt in 2006 proposed to use the strategy of intramolecular conjugate addition of enolate to enone to build up the cyclopentane fused lactone ring (Scheme 2.8).^[13] With an NHC catalyst derived from indane-amino alcohol, enones that were linked with unsaturated aldehyde were efficiently transformed to the desired polycyclic lactones in

52-80% yield, with enantioselectivities ranging from 62-99% ee via the Michael addition/lactonization cascade reaction.

Scheme 2.8 Scheidt's NHC-catalyzed Michael/lactonization cascade reaction.

In 2009, You and his coworkers also reported the same cascade reaction by using their own designed NHC catalyst derived from camphor (Scheme 2.9).^[14] The catalyst was highly efficient for the intramolecular cascade process in terms of the catalyst loading (1-5 mol%) and high yield and ee.

Scheme 2.9 You's NHC catalyst derived from the camphor.

Our laboratory aims at using stable esters as key starting materials to develop new synthetic strategy to prepare important compounds such as bioactive compounds and natural products.^[15] Recently, we reported that N-heterocyclic carbene (NHC) could catalyze the [3+3] cycloaddition of unsaturated esters with N-tosyl imines derived from acetophenones via the LUMO activation of the esters (Scheme 2.10).^[16] Compared with

other methods to generate the unsaturated acyl azolium ion, the carboxylic esters are easily prepared and stable under the aerobic and moist conditions. It does not need to use relatively expensive oxidants, or preformed β -halo unsaturated aldehydes. Multi-substituted ester substrates are capable to give the unsaturated acyl azolium ions.

Scheme 2.10

Based on this work, we proposed to use NHC to catalyze the reaction of an unsaturated ester **2-1** with a β -enone malonate **2-2**, which would finally provide our desired product via cascade process including intermolecular Michael addition, intramolecular Michael addition and lactonization. In this transformation, two new rings (one cyclopentane or cyclohexane fused a six-membered lactone), three new bonds and four chiral centers could be formed in a single operation (Scheme 2.11). However, some potential undesired pathways may happen in the transformation, including hydrolysis of the key intermediate **I**, base-mediated background reaction, inter- or intra-molecular cyclization and the direct β -elimination of H-EWG. In this chapter, we developed a highly effective NHC-catalyzed intermolecular domino process for enantioselective access to iridoids from acyclic simple starting materials.

Scheme 2.11 Our strategy to synthesize iridoids.

It should be noted specially, during the preparation of our manuscript, Studer and Ye groups both independently reported similar annulation reaction to afford the iridoid type products (Scheme 2.12).^[17] In their work, they used oxidative approach with quinone oxidant to convert the enal to the unsaturated acyl azolium as the key intermediate. The authors also found that LiCl as a cooperative catalyst could help improve the enantioselectivity.

Scheme 2.12 Ye and Studer's annulation to iridoids.

2.2 Results and Discussions

The reaction of ester **2-1a** and β -enone malonate **2-2a** was chosen as the model reaction for conditions screening (Table 2-1). The iridoid **2-3a** was obtained in 90% yield when racemic NHC **A** was used under the standard conditions (Table 2.1, entry 1). LiCl improved the yield in this transformation, as only 46% NMR yield was obtained in the absence of LiCl (Table 2.1, entry 2).^[18] Then, we turned to achieve the asymmetric synthesis of the desired iridoid with chiral catalysts. Several chiral NHCs with N-Mes group were investigated (entries 3-4). We found that higher enantioselectivity was always combined with lower yield when we increased steric hindrance of NHC (from NHC **B** to **D**). This is probably because the big steric hinderance reduced the rate of the nucleophilic addition of NHC to the ester to give the NHC-bound α,β -unsaturated acyl azolium intermediate. To achieve an acceptable result in terms of yield and enantioselectivity, we proposed to enhance the reaction rate of NHC by increasing its nucleophilicity. With this in mind, NHC **E** with strong electron-donating group 2,6-diMeOC₆H₃ was used. To our delight, the desired **2-3a** was obtained in good yield and enantioselectivity (88% yield, 91:9 er) (entry 6). Furthermore, NHC

F with a slightly more sterically hindered Et group instead of Me (NHC **E**) gave the desired product with excellent enantioselectivity (96:4 er, entry 7). Considering the HOBt would help release the carbene catalyst from the acyl azolium intermediate, we finally found that the reaction with 0.2 equiv of HOBt as the additive and 1.2 equiv of **2-2a** afforded the desired iridoid **2-3a** in 85% isolated yield, 12:1 dr and 96:4 er (entry 8).^[19]

Table 2.1 Conditions screening for the reaction of **2-1a** with **2-2a**.^[a]

Entry	NHC	Yield [%] ^[b]	d.r. ^[c]	e.r.
1	A	90	20:1	-
2 ^[d]	A	46	20:1	-
3	B	55	20:1	57:43
4	C	43	10:1	77:23
5	D	25	12:1	90:10
6 ^[e]	E	88	11:1	91:9
7 ^[e]	F	74	12:1	96:4
8 ^[e,f]	F	92(85)	12:1	96:4

[a] NHC (20 mol%), **2-1a** (0.1 mmol, 1.0 equiv), **2-2a** (1.0 equiv), DBU (1.0 equiv), LiCl (1.0 equiv), THF (1.0 mL), 4Å MS, RT, 3 h. [b] NMR yield determined via ¹H NMR; isolated yield in parenthesis. [c] Determined via ¹H NMR analysis of reaction mixtures. [d] Without LiCl. [e] 0.3 equiv DABCO was added, followed by addition of 1.0 equiv DBU after 20 min. [f] 20 mol% HOBt was added and 1.2 equiv **2-2a** and 1.4 equiv DBU were used instead. HOBt= Hydroxybenzotriazole.

With the optimized conditions in hand (Table 2-1, entry 8), we next investigated the substrate generality of the cascade reaction using various unsaturated esters **2-1** with the β -enone malonate **2-2a** (Table 2-2). All the substrates illustrated in Table 2-2 could smoothly assemble the domino products **2-3**. Different substituents, such as F, Cl, Br, NO₂, Me at the para or meta position of the β -aromatic ring of the ester were all tolerated under the optimized conditions (**2-3c** to **2-3h**). However, unsaturated ester with a strong electron-donating group (MeO group) on the β -aryl group provided the product **2-3b** in a low yield (40%) due to the relatively poor electrophilicity of the β -carbon. Naphthyl substituted ester (**2-3i**) was effective in this transformation. Replacing the β -phenyl group of ester **2-3a** with heteroaryl, such as furyl (**2-3j**) or thienyl (**2-3k**) did not show obvious effect on the reaction yield, diastereoselectivity and enantioselectivity. It is worth noting that an alkenyl ester also realized the transformation and finally afforded the product **2-3l** bearing a convertible alkenyl group. Remarkably, β -ester substituted unsaturated ester was well tolerated under the standard conditions and gave the desired product **2-3m** in 50% yield, 10:1 dr and 94:6 er. We also studied the reaction scope with β -alkyl unsaturated ester substrates, and found that even simple acrylic ester could deliver the desired products in moderate yield (**2-3n** and **2-3o**). However, in these cases, the enantioselectivity of the products was much lower (75:25 er for **2-3n** and 53:47 er for **2-3o**).

Table 2.2 Substrate scope of unsaturated ester **2-1**. ^[a]

[a] Conditions: NHC **F** (20 mol%), **2-1** (0.1 mmol), **2-2a** (1.2 equiv), DBU (1.4 equiv), LiCl (1.0 equiv), HOBt (20 mol%), THF (1.0 mL), 4 Å MS, RT; Isolated yields based on ester **2-1**.

Then, the scope of β-enone malonates was investigated (Table 2-3). The aromatic unit of the enone part could be replaced with an electron-donating OMe (**2-4a**) or Me (**2-4b**) group at the para position. Installation of halogen substituents (F, Cl or Br) at the phenyl group of the enone was compatible to give the corresponding products **2-4c**,

4d and **2-4e** in excellent dr and er. Enones with heteroaryl groups reacted smoothly to afford the bicyclic products **2-4g** (49%, 20:1 dr, 94:6 er) and **2-4h** (52%, 20:1 dr, 95:5 er). Remarkably, the substituent at the α -carbon of the enone had no influence on the transformation and gave the desired product **2-4i** in 99% yield, 20:1 dr and 98:2 er. To our delight, a steroid derivative **2-4j** was also obtained by using our cascade strategy.^[20] Not surprisingly, the methyl unit of the enone could be replaced with ethyl (**2-4n**) or benzyl group (**2-4o**). The structure of the bicyclic products was confirmed by the X-ray analysis of the product **2-4p** (see section 2.4.3).

Table 2.3 Substrate scope of β -enone malonate **2-2**.^[a]

2-1a (Ar = 4-NO₂-C₆H₄)	2-2	2-4
	R=OMe; 2-4a; 72%; 20:1 d.r.; 94:6 e.r. R=Me; 2-4b; 82%; 20:1 d.r.; 96:4 e.r. R=F; 2-4c; 75%; 20:1 d.r.; 96:4 e.r. R=Cl; 2-4d; 58%; 20:1 d.r.; 96:4 e.r. R=Br; 2-4e; 56%; 19:1 d.r.; 96:4 e.r.	
2-4f; 78% 20:1 d.r.; 96:4 e.r.	2-4g; ^[b] 49% 20:1 d.r.; 94:6 e.r.	2-4h; 52% 20:1 d.r.; 95:5 e.r.
2-4i; 99% 20:1 d.r.; 98:2 e.r.	2-4j; 76% 10:1 d.r.; 97:3 e.r.	X=Br: 2-4k; 57% 20:1 d.r.; 99:1 e.r. X=Cl: 2-4l; 86% 12:1 dr, 95:5 e.r.

[a] Conditions: NHC **F** (20 mol%), **2-1** (0.1 mmol), **2-2** (1.2 equiv), DBU (1.4 equiv), LiCl (1.0 equiv), HOBT (20 mol%), THF (1.0 mL), 4 Å MS, RT; Isolated yields based on ester **2-1**. [b] 30 mol% NHC **F** and 1.6 equivalents of enone **2-2** were used.

We further tested a γ -malonate enone **2-5** to assemble a fused bicyclic six-membered ring products **2-6** (Table 2-4). When reacting with the unsaturated ester under the optimized conditions, product **2-6a** was formed with 99% yield, 1.2:1 dr and 96:4 er/94:6 er. Introducing substituents at the para position of ester's β -phenyl group did not affect the reaction outcome (**2-6b** and **2-6c**). The ester with a thienyl unit afforded the products **2-6d** in excellent yield (96%) and much better dr (10:1). The γ -nitro enones also furnished the products **2-6e-g** with a synthetic useful NO₂ group for further functionalization (Table 4). However, the product **2-6e** was obtained with low enantioselectivity (77:23 er). After careful investigation of reaction conditions, we could improve the enantioselectivity to 87:13 er by lowering temperature to -78 °C. After single recrystallization, the product **2-6e** could be obtained with up to 99:1 er.

In addition, we have also tried enones with other β -electron-withdrawing groups, such as β -Ts-enone (**2-2p**) and β -NO₂-enone (**2-2q**). After screening various conditions, we still could not get the corresponding products due to facile elimination of Ts and NO₂ under basic conditions (Eq. 1 and 2).

Table 2.4 Substrate scope of ester **2-1** and enone **2-5**.^[a]

[a] NHC **F** (20 mol%), **2-1** (0.1 mmol), **2-2a** (1.2 equiv), DBU (1.4 equiv), LiCl (1.0 equiv), HOBT (20 mol%), THF (1.0 mL), 4Å MS, RT; [b] Reactions performed at -78 °C. [c] After recrystallization. [d] 30 mol% NHC and 1.5 equivalents of ester were used. Yield based on enone **2-5**.

The proposed reaction pathway for the generation of product **2-3** is illustrated in Scheme 2.13. Addition of the carbene catalyst to the unsaturated ester **2-1** could give an NHC-bound acyl azolium intermediate **I**. Then an enolate **II** could be formed after deprotonation of the β -enone malonate **2-2** under basic conditions. Intermolecular

Michael addition of the intermediate **II** to the intermediate **I** could give an intermediate **III**, which underwent intramolecular Michael addition to generate an intermediate **IV**. Subsequent lactonization of the intermediate **IV** could form the final cascade product **2-3** and release the carbene catalyst. In our reaction, LiCl played a crucial role to provide high enantioselectivity. We propose that the coordination of the Li^+ with the malonate derived enolate and the acyl azolium would help to assemble the product to improve the yield, and assist the Michael addition of **II** to **III** in *Re* face manner (**TS A**) to give a better enantioselectivity. The subsequent intramolecular Michael addition proceeded through a chair-type transition state (**TS B**) to give the bicyclic lactone in high stereoselectivity. The reactions with γ -malonate enone **2-5** ($n = 2$) may not form the transition state (**TS B**) in a very good chair conformation, thus leading to the products in a lower diastereoselectivity.

Scheme 2.13 Proposed mechanism and stereochemical modes.

Last, we demonstrated further synthetic transformations as shown in Scheme 2.14. Ring-opening of **2-3a** with methanol, followed by reduction with NaBH₄ and intramolecular cyclization promoted by PTSA gave a compound **2-7** in 71% overall yield, 1:1 dr and 96:4 er/96:4 er. Epoxidation of the compound **2-3a** with *m*CPBA and then subsection to PTSA afforded cyclopenta[*c*]furan-1-one **2-8** in 65% yield, 2:1 dr and 96:4 er. The cyclopentyl fused γ -lactone is a core structure widely found in bioactive compounds^[21]. Ring-opening of the cascade product **2-6g** with MeOH, and then denitrogenation with AIBN/Bu₃SnH gave **2-9** in 40% yield.

Scheme 2.14 Synthetic transformations of cascade products.

2.3 Summary

In summary, we have achieved an organocatalytic and enantioselective single-step cascade process for access to multi-cyclic lactones from unsaturated esters and enone derivatives. Our protocol involves an NHC-bound unsaturated acyl azolium as the key intermediate, and subsequent Michael-Michael-lactonization process. Strong nucleophilicity of NHC (with N bonded 2,6-diMeOC₆H₃) greatly improves the

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efficiency of the reaction. This single-step cascade process could construct a five or six membered carbo-cycle fused with a six-membered lactone ring. Further transformations of the product have been demonstrated. Our study shows the synthetic power of NHC catalyst for the activation of the readily available ester, and shall inspire further development of NHC catalysis in ester activation.

2.4 Experimental Section

2.4.1 General Information

Commercially available materials were purchased from Alfa Aesar or Sigma-Aldrich. Toluene and CH_2Cl_2 was dried over Pure Solv solvent purification system. THF was distilled over sodium. Other solvents were dried over 4Å molecular sieve prior use. ^1H NMR spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded 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). ^{13}C NMR spectra were determined on a Bruker (400 MHz) (100 MHz) spectrometer. IR spectra were recorded on a Shimadzu FT-IR Spectrometer. High resolution mass spectral analysis (HRMS) was conducted on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of enantiomeric excess 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 on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c is in gm

per 100 mL solvent). Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 pre-coated silica gel plate. The TLC plate was visualized using a UV lamp or potassium permanganate stain.

2.4.2 General procedure for the catalytic reactions of ester (**2-1**) with enone (**2-2**) to synthesize product **2-3**:

To a dry Schlenk tube were added ester **2-1** (0.10 mmol, 1.0 equiv), NHC **F** (9.9 mg, 20 mol%), DABCO (3.4 mg, 30 mol%), HOBT (2.7 mg, 20 mol%), LiCl (5.0 mg, 1.0 equiv), and molecular sieves (50 mg). After evacuation and refilled with nitrogen, the enone **2-2** (1.2 equiv) was added and the mixture was dissolved with 1.0 mL of THF. After stirring at RT for 20 mins, DBU (21 μ L, 1.4 equiv) was added and the mixture was continued to stir at RT for another 3 h when the ester **2-1** was consumed completely (monitored by TLC). The mixture was concentrated and purified by column chromatography on silica gel (hexane/EtOAc) to afford the desired product **2-3**, which was confirmed by ^1H NMR, ^{13}C NMR spectra, and enantiomeric excess was determined by chiral HPLC.

Note: NHC **F** was prepared according to literature procedure.^[22]

2.4.3 Stereochemistry determination of **4o** via X-ray crystallographic analysis:

Product **2-4o** was crystallized as a colorless crystal *via* evaporation of a hexane/ethyl acetate solution, and its absolute configuration was determined by X-ray

structure analysis. CCDC 1404951 contains the supplementary crystallographic data that can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.4.4 Synthetic transformations of catalytic reaction products 2-3a and 2-6g.

To a dry round-bottom flask were added **2-3a** (0.1 mmol, 40.6 mg) and anhydrous MeOH (1 mL). The resulting mixture was allowed to stir overnight at 60 °C. After the completion of reaction, NaBH₄ (0.20 mmol, 2.0 equiv) was added and the mixture was stirred for 0.5 h at room temperature. After the completion of reaction, the 2N HCl aq was added and the reaction mixture was extracted with CH₂Cl₂ for three times. Then the combined organic layer was washed with saturated brine and dried over anhydrous

Na₂SO₄. CH₂Cl₂ was removed under reduced pressure, and then PTSA (0.09 mmol, 0.9 equiv) and CHCl₃ (3 mL) was added. The resulting mixture was allowed to stir for 4 h at 60 °C. After the completion of reaction, solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography to afford product **2-7** (29 mg), 71% yield, 1:1 dr and 96:4 er/96:4 er. (The relative stereochemistry of each isomer was established through NOESY spectrum).

To a stirred solution of **2-3a** (40.6 mg, 0.10 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C, was added *m*CPBA (51.8 mg, 55% purity, 0.15 mmol). The mixture was stirred at 0 °C for 12 h. After the reaction was completed, PTSA (1.9 mg, 0.01 mmol) was added, and the reaction was stirred for another 20 min at room temperature, followed by quench with aqueous NaHCO₃ solution and extraction with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified via SiO₂ flash chromatography (n-hexane/EtOAc) to afford **2-8** (27.5 mg, 65% yield, 2:1 dr and 96:4 er/96:4 er). (The relative stereochemistry of each isomer was established through NOESY spectrum).

To a dry round-bottom flask were added **2-6g** (0.1 mmol, 36.7 mg) and anhydrous MeOH (1 mL). The resulting mixture was allowed to stir overnight at 60 °C. After the completion of reaction, solvent was removed under reduced pressure, and then AIBN

(0.04 mmol, 0.4 equiv), Bu₃SnH (0.50 mmol, 5.0 equiv) and toluene (1 mL) was added. The resulting mixture was allowed to stir overnight at 110 °C. After the completion of reaction, solvent was removed, and the crude residue was purified by flash chromatography to afford product **2-9** in 40% yield.

2.4.5 Characterizations of substrates and products, reference

a) Preparations and characterizations of substrates

To a 100 mL of round bottom flask under N₂ atmosphere, aldehyde (10 mmol, 1 equiv) was added and dissolved in 50 mL of CH₂Cl₂, followed by the addition of the phosphorus ylide (10 mmol, 1 equiv). The reaction was kept stirring at RT for 12 h. Then, the mixture was concentrated under vacuum to remove the CH₂Cl₂ to give the crude product. Purification by the chromatograph on a silica gel column using hexane : ethyl acetate (3:1) as eluent gave the enone **2-2** as colorless oil.

Note: The β-aldehyde malonate was prepared according to previous report.^[23]

(E)-Dimethyl 2-(4-oxo-4-phenylbut-2-enyl)malonate: a yellow oil; ¹H NMR (400 MHz, CDCl₃): δ = 7.90 (d, *J* = 8.0 Hz, 2 H); 7.55 (t, *J* = 7.6 Hz, 1 H); 7.47 (t, *J* = 8.0 Hz, 2 H); 6.93–6.96 (m, 2 H); 3.76 (s, 6 H); 3.61 (t, *J* = 7.6 Hz, 1 H); 2.91 (dd, *J*₁ = 7.6 Hz, *J*₂ = 6.0 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 190.2, 168.8, 143.6, 137.5,

132.9, 128.6, 128.5, 128.1, 52.8, 50.5, 31.7 ppm. HRMS(ESI) calcd for C₁₅H₁₇O₅ (M+H)⁺: 277.1076, Found: 277.1078.

(E)-Dimethyl 2-(4-oxo-4-*p*-tolylbut-2-enyl)malonate: a yellow oil; ¹H NMR (400 MHz, CDCl₃): δ = 7.83 (d, *J* = 8.0 Hz, 2H); 7.27 (d, *J* = 8.0 Hz, 2H); 6.89–6.99 (m, 2H); 3.82 (s, 6H); 3.60 (t, *J* = 7.6 Hz, 2H); 2.91 (dd, *J* = 7.2, 6.0 Hz, 2H); 2.42 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 189.7, 168.8, 143.8, 143.1, 135.0, 129.3, 128.7, 128.2, 52.8, 50.6, 31.7, 21.7 ppm. HRMS(ESI) calcd for C₁₆H₁₉O₅ (M+H)⁺: 291.1232, Found: 291.1237.

(E)-Dimethyl 2-(4-(4-methoxyphenyl)-4-oxobut-2-enyl)malonate: a yellow oil; ¹H NMR (400 MHz, CDCl₃): δ = 7.91–7.95 (m, 2H); 6.87–7.00 (m, 4H); 3.88 (s, 3H); 3.76 (s, 6H); 3.60 (t, *J* = 7.6 Hz, 2H); 2.91 (t, *J* = 6.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 188.4, 168.8, 163.5, 142.5, 130.9, 130.4, 128.0, 113.8, 55.5, 52.8, 50.6, 31.7 ppm. HRMS(ESI) calcd for C₁₆H₁₉O₆ (M+H)⁺: 307.1182, Found: 307.1182.

(E)-Dimethyl 2-(4-(4-fluorophenyl)-4-oxobut-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.93–7.97 (m, 2H); 7.12–7.17 (m, 2H); 6.93–6.95 (m, 2H); 3.77 (s, 6H); 3.61 (t, J = 7.6 Hz, 2H); 2.90–2.93 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 188.5, 168.7, 166.9, 164.5, 143.8, 133.9, 133.8, 131.2, 131.1, 127.8, 115.8, 115.6, 52.8, 50.5, 31.7 ppm. HRMS(ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{FO}_5$ ($\text{M}+\text{H}$) $^+$: 295.0982, Found: 295.0984.

(E)-Dimethyl 2-(4-(4-chlorophenyl)-4-oxobut-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.84–7.88 (m, 2H); 7.43–7.56 (m, 2H); 6.89–6.95 (m, 2H); 3.76 (s, 6H); 3.61 (t, J = 7.6 Hz, 2H); 2.92 (dd, J = 7.2, 5.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 188.9, 168.7, 144.2, 139.4, 135.8, 130.0, 129.0, 127.7, 52.8, 50.4, 31.7 ppm. HRMS(ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{ClO}_5$ ($\text{M}+\text{H}$) $^+$: 311.0686, Found: 311.0692.

(E)-Dimethyl 2-(4-(4-bromophenyl)-4-oxobut-2-enyl)malonate: a white oil; ^1H NMR (500 MHz, CDCl_3): δ = 7.64-7.82 (m, 2 H); 7.58-7.65 (m, 2 H); 6.85-6.96 (m, 2 H); 3.77 (s, 6 H); 3.60 (t, J = 7.5 Hz, 1 H); 2.92 (dd, J_1 = 5.5 Hz, J_2 = 5.5 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 189.0, 168.2, 144.3, 136.2, 131.9, 130.1, 128.1, 127.7, 52.8, 50.4, 31.7 ppm. HRMS(ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{BrO}_5\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 377.0001, Found: 376.9999.

(E)-Dimethyl 2-(4-(naphthalen-2-yl)-4-oxobut-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 8.43 (s, 1H); 7.96–8.02 (m, 2H); 7.87–7.92 (m, 2H); 7.54–7.63 (m, 2H); 7.13 (d, J = 15.6 Hz, 1H); 6.96–7.03 (m, 1H); 3.78 (s, 6H); 3.65 (t, J = 7.6 Hz, 2H); 2.95–2.99 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 190.0, 168.8, 143.5, 135.5, 134.8, 132.5, 130.3, 129.6, 128.6, 128.5, 128.2, 127.8, 126.8, 124.4, 52.8, 50.6, 31.8 ppm. HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{19}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 327.1232, Found: 327.1242.

(E)-Dimethyl 2-(4-(furan-2-yl)-4-oxobut-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.62 (t, J = 0.8 Hz, 1H); 7.25 (d, J = 3.6 Hz, 1H); 6.99–7.06 (m, 1H); 6.87 (d, J = 19.6 Hz, 1H); 6.56 (dd, J = 3.6, 1.6 Hz, 1H); 3.76 (s, 6H); 3.60 (t, J =

7.2 Hz, 2H); 2.90 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 177.5, 168.8, 153.1, 146.8, 143.0, 127.3, 118.0, 112.5, 52.8, 50.5, 31.6$ ppm. HRMS(ESI) calcd for $\text{C}_{13}\text{H}_{15}\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 267.0863, Found: 267.0864.

(E)-Dimethyl 2-(4-oxo-4-(thiophen-2-yl)but-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.75$ (d, $J = 3.6$ Hz, 1H); 7.67 (d, $J = 4.8$ Hz, 1H); 7.15–7.17 (m, 1H); 6.95–7.03 (m, 1H); 6.87 (d, $J = 15.2$ Hz, 1H); 3.76 (s, 6H); 3.61 (t, $J = 7.2$ Hz, 2H); 2.91 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 181.7, 168.8, 144.8, 142.9, 134.1, 132.2, 128.3, 127.7, 52.8, 50.5, 31.6$ ppm. HRMS(ESI) calcd for $\text{C}_{13}\text{H}_{15}\text{O}_5\text{S}$ ($\text{M}+\text{H}$) $^+$: 283.0640, Found: 283.0644.

(E)-Dimethyl 2-(3-methyl-4-oxo-4-phenylbut-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.62$ –7.64 (m, 2H); 7.49–7.53 (m, 1H); 7.39–7.43 (m, 2H); 6.14–6.18 (m, 1H); 3.75 (s, 6H); 3.51 (t, $J = 7.6$ Hz, 2H); 2.88 (t, $J = 7.6$ Hz, 2H); 2.00 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 198.4, 168.9, 139.4, 138.8, 138.0, 131.8, 129.5, 128.1, 52.7, 50.7, 28.3, 12.8$ ppm. HRMS(ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 291.1232, Found: 291.1231.

(*E*)-Dimethyl 2-(2-(1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)ethyl)malonate:

a colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 8.05-8.15 (m, 1 H); 7.46-7.55 (m, 1 H); 7.30-7.40 (m, 1 H); 7.22-7.28 (m, 1 H); 6.74-6.82 (m, 1 H); 3.73 (s, 3 H); 3.58 (t, J = 7.6 Hz, 1 H); 2.92-3.02 (m, 2 H); 2.72-2.88 (m, 4 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 187.1, 169.0, 143.7, 137.6, 133.7, 133.3, 128.3, 128.2, 126.7, 52.7, 50.8, 29.0, 27.6, 25.8 ppm. HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 303.1232, Found: 303.1233.

(*E*)-Dimethyl 2-(4-oxopent-2-enyl)malonate:

a colorless oil; ^1H NMR (500 MHz, CDCl_3): δ = 6.73 (dt, J = 16.0, 7.0 Hz, 1 H), 6.13 (dt, J = 16.0, 1.4 Hz, 1 H), 3.76 (s, 6 H), 3.75 (d, J = 7.6 Hz, 1 H), 3.55 (t, J = 7.4 Hz, 1 H), 2.82 (td, J = 7.2, 1.5 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ = 197.9, 168.6 (x2), 142.4, 133.1, 52.7, 50.3, 31.2, 27.0 ppm. HRMS(ESI) calcd for $\text{C}_{10}\text{H}_{15}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 215.0919, Found: 215.0911.

(E)-Diethyl 2-(4-oxo-4-phenylbut-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.91 (d, J = 7.2 Hz, 2 H); 7.55 (t, J = 7.2, 1 H); 7.47 (t, J = 8.0 Hz, 2 H); 6.95–6.97 (m, 2 H); 4.18–4.25 (m, 4 H); 3.57 (t, J = 7.6 Hz, 1 H); 2.89–2.93 (m, 2 H); 1.27 (t, J = 7.2 Hz, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 190.2, 168.4, 143.9, 137.6, 132.9, 128.6, 128.5, 128.1, 61.7, 50.8, 31.7, 14.1 ppm. HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{21}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 305.1389, Found: 305.1390.

(E)-Dibenzyl 2-(4-oxo-4-phenylbut-2-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.85 (d, J = 7.2 Hz, 2 H); 7.55 (t, J = 7.6, 1 H); 7.44 (t, J = 8.0 Hz, 2 H); 7.36 (t, J = 4.8 Hz, 1 H); 7.26–7.32 (m, 9 H); 6.86–6.96 (m, 2 H); 5.12–5.19 (m, 4 H); 3.69 (t, J = 7.2 Hz, 1 H); 2.93 (dd, J_1 = 7.6 Hz, J_2 = 5.6 Hz, 2 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 190.1, 168.1, 143.5, 137.5, 135.1, 132.8, 128.6, 128.5, 128.4, 128.3, 128.1, 67.5, 50.8, 31.7 ppm. HRMS(ESI) calcd for $\text{C}_{27}\text{H}_{25}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 429.1702, Found: 429.1701.

(E)-Dimethyl 2-(5-oxo-5-phenylpent-3-enyl)malonate: a yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.92 (d, J = 7.2 Hz, 2 H); 7.57 (t, J = 7.2, 1 H); 7.47 (t, J = 7.6 Hz, 2 H); 6.89–7.04 (m, 2 H); 3.75 (s, 6 H); 3.43 (t, J = 7.6 Hz, 1 H); 2.38 (dd, J_1 = 14.4 Hz,

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$J_2 = 6.8$ Hz, 2 H); 2.15 (dd, $J_1 = 14.4$ Hz, $J_2 = 7.6$ Hz, 2 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 190.5, 169.4, 146.9, 137.7, 132.8, 128.6, 128.5, 126.9, 52.6, 50.9, 30.2, 27.2$ ppm. HRMS(ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 291.1232, Found: 291.1231.

(*E*)-6-Nitro-1-phenylhex-2-en-1-one: a yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.93\text{--}7.96$ (m, 2H); 7.56–7.60 (m, 1H); 7.47–7.50 (m, 2H); 6.94–7.03 (m, 2H); 4.45 (t, $J = 6.4$ Hz, 2H); 2.43–2.48 (m, 2H); 2.23–2.30 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 190.1, 145.5, 137.6, 133.0, 128.7, 128.6, 127.5, 74.6, 29.2, 25.8$ ppm. HRMS(ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 220.0974, Found: 220.0974.

(*E*)-1-(furan-3-yl)-4,4-Dimethyl-6-nitrohex-2-en-1-one: a yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 8.09$ (s, 1 H); 7.49 (t, $J = 3.2$ Hz, 1 H); 6.95 (d, $J = 15.6$ Hz, 1 H); 6.85–6.85 (m, 1H); 6.51 (d, $J = 15.6$ Hz, 1 H); 4.33–4.37 (m, 2 H); 2.21–2.25 (m, 2 H); 1.21 (s, 6 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 183.9, 153.5, 147.4, 144.4, 128.1, 124.3, 128.1, 124.3, 109.1, 72.4, 38.6, 36.0, 26.4$ ppm. HRMS(ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$: 238.1079, Found: 238.1079.

b) Characterizations of products

(4a*S*,7*R*,7a*R*)-Dimethyl 1-oxo-3,7-diphenyl-4a,5,7,7a-tetrahydrocyclo-

penta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 1.70, CHCl₃) = -16.8;

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 2 H); 7.24–7.39 (m, 8 H); 5.56 (d, J = 3.2 Hz, 1 H); 4.70 (d, J = 8.8 Hz, 1 H); 3.71 (s, 3 H); 3.52–3.61 (m, 2 H); 3.13 (m, 4 H); 2.27 (dd, J_1 = 12.0 Hz, J_2 = 4.0 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.6, 170.2, 168.4, 149.2, 137.3, 132.2, 129.2, 128.7, 128.5, 128.3, 127.8, 124.8, 102.2, 65.1, 53.7, 53.1, 52.3, 47.6, 41.3, 36.7 ppm. IR (film): $\nu_{\max}$ 2952, 1731, 1515, 1425, 1272, 1211, 1008 cm⁻¹. HRMS (ESI): C₂₄H₂₃O₆ [M+H]⁺ calcd: 407.1495, found: 407.1492; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 13.4 min, t_r (minor) = 16.6 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 7-(4-methoxyphenyl)-1-oxo-3-phenyl-4a,5,7,7a-tetra-

hydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 1.44, CHCl₃)

= -40.5; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2 H); 7.36–7.39 (m, 3 H); 7.25 (d, J = 9.2 Hz, 2 H); 6.83 (d, J = 8.0 Hz, 2 H); 5.53 (d, J = 3.2 Hz, 1 H); 4.61 (d, J = 9.6 Hz, 1 H); 3.77 (s, 3 H); 3.71 (s, 3 H); 3.49–3.59 (m, 2 H); 3.20 (s,

3 H); 3.11 (dd, $J_1 = 14.0$ Hz, $J_2 = 7.2$ Hz, 1 H); 2.68 (dd, $J_1 = 14.0$ Hz, $J_2 = 4.0$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.7, 170.4, 168.4, 159.1, 149.1, 132.2, 129.9, 129.2, 129.0, 128.5, 124.8, 113.6, 102.4, 64.8, 55.2, 53.1, 53.0, 52.4, 47.6, 41.1, 36.4$ ppm. IR (film): ν_{max} 2952, 1757, 1729, 1515, 1436, 1221, 1127, 1025, 929 cm^{-1} . HRMS (ESI): $\text{C}_{25}\text{H}_{25}\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd: 437.1600, found: 437.1613; 95:5 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 17.7 min, t_r (minor) = 21.5 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 7-(4-fluorophenyl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.90, CHCl_3) = -22.9; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.59$ (dd, $J_1 = 8.0$ Hz, $J_2 = 2.4$ Hz, 2 H); 7.34–7.41 (m, 3 H); 7.32 (dd, $J_1 = 8.8$ Hz, $J_2 = 5.2$ Hz, 2 H); 6.99 (t, $J = 8.8$ Hz, 2 H); 5.55 (d, $J = 3.2$ Hz, 1 H); 4.64 (d, $J = 10.0$ Hz, 1 H); 3.72 (s, 3 H); 3.56–3.62 (m, 1 H); 3.51 (t, $J = 8.8$ Hz, 1 H); 3.20 (s, 3 H); 3.11 (dd, $J_1 = 14.0$ Hz, $J_2 = 7.2$ Hz, 1 H); 2.27 (dd, $J_1 = 14.0$ Hz, $J_2 = 4.0$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.5, 170.3, 168.1, 149.2, 132.7, 132.6, 132.1, 130.5, 130.4, 129.3, 128.6, 124.8, 115.2, 115.0, 102.2, 64.8, 53.1, 52.9, 52.4, 47.5, 41.1, 36.5$ ppm. IR (film): ν_{max} 2954, 1762, 1729, 1515, 1437, 1275, 1215, 1016, 929 cm^{-1} . HRMS (ESI): $\text{C}_{24}\text{H}_{22}\text{FO}_6$ $[\text{M}+\text{H}]^+$ calcd: 425.1400, found: 425.1383; 95:5 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 13.0 min, t_r (minor) = 17.6 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 7-(4-chlorophenyl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 1.76, CHCl₃) = -41.2; ¹H NMR (400 MHz, CDCl₃): δ = 7.58 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 2 H); 7.35 – 7.39 (m, 3 H); 7.28 (s, 4 H); 5.55 (d, J = 3.2 Hz, 1 H); 4.62 (d, J = 9.6 Hz, 1 H); 3.72 (s, 3 H); 3.56–3.61 (m, 1 H); 3.50 (t, J = 8.8 Hz, 1 H); 3.21 (s, 3 H); 3.10 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1 H); 2.27 (dd, J_1 = 14.0 Hz, J_2 = 4.0 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.4, 170.2, 168.1, 149.1, 135.5, 133.7, 132.0, 130.2, 129.3, 128.6, 128.4, 124.8, 102.2, 64.8, 53.1, 53.0, 52.1, 47.3, 41.2, 36.5 ppm. IR (film): $\nu_{\max}$ 2953, 1762, 1729, 1526, 1436, 1255, 1015, 928 cm⁻¹. HRMS (ESI): C₂₄H₂₂ClO₆ [M+H]⁺ calcd: 441.1105, found: 441.1102; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 13.5 min, t_r (minor) = 18.7 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 7-(4-bromophenyl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 2.12, CHCl₃) = -47.3; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 2 H); 7.36–7.44 (m, 5 H); 7.22 (d, J = 8.4 Hz, 2 H); 5.55 (d, J = 3.2 Hz, 1 H); 4.60 (d, J = 10.0 Hz,

1 H); 3.72 (s, 3 H); 3.57–3.60 (m, 1 H); 3.50 (t, $J = 8.8$ Hz, 1 H); 3.22 (s, 3 H); 3.10 (dd, $J_1 = 14.0$ Hz, $J_2 = 7.2$ Hz, 1 H); 2.26 (dd, $J_1 = 14.0$ Hz, $J_2 = 4.4$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.4, 170.2, 168.0, 149.1, 136.1, 132.0, 131.4, 130.5, 129.3, 128.6, 128.4, 121.9, 102.2, 64.7, 53.1, 53.0, 52.5, 47.3, 41.2, 36.5$ ppm. IR (film): ν_{max} 2954, 1767, 1730, 1558, 1539, 1275, 1215, 1011, 929 cm^{-1} . HRMS (ESI): $\text{C}_{24}\text{H}_{22}\text{BrO}_6$ $[\text{M}+\text{H}]^+$ calcd: 485.0600, found: 485.0587; 97:3 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 14.1 min, t_r (minor) = 19.6 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 7-(4-nitrophenyl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (c 1.41, CHCl_3) = -58.9; ^1H NMR (400 MHz, CDCl_3): $\delta = 8.17$ (d, $J = 8.8$ Hz, 2 H); 7.59 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.4$ Hz, 2 H); 7.55 (d, $J = 8.8$ Hz, 2 H); 7.37–7.42 (m, 3 H); 5.59 (d, $J = 3.2$ Hz, 1 H); 4.72 (d, $J = 10.0$ Hz, 1 H); 3.75 (s, 3 H); 3.63–3.67 (m, 1 H); 3.58 (t, $J = 9.6$ Hz, 1 H); 3.22 (s, 3 H); 3.13 (dd, $J_1 = 14.0$ Hz, $J_2 = 7.6$ Hz, 1 H); 2.29 (dd, $J_1 = 14.0$ Hz, $J_2 = 4.8$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.0, 169.9, 167.7, 149.1, 147.4, 144.5, 131.9, 129.9, 129.4, 128.6, 124.8, 123.3, 101.9, 64.8, 53.3, 53.2, 52.6, 47.1, 41.4, 36.4$ ppm. IR (film): ν_{max} 2955, 1730, 1526, 1424, 1350, 1024, 925 cm^{-1} . HRMS (ESI): $\text{C}_{24}\text{H}_{22}\text{NO}_8$ $[\text{M}+\text{H}]^+$ calcd: 452.1345, found: 452.1348; 97:3 *er* as determined by HPLC

(Chiralcel IB, 85:15 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 23.4 min, t_r (minor) = 42.9 min.

**(4a*S*,7*R*,7a*R*)-Dimethyl 1-oxo-3-phenyl-7-*o*-tolyl-4a,5,7,7a-tetrahydrocyclopenta-
[c]pyran-6,6(1*H*)-dicarboxylate:** a yellow oil; $[\alpha]_D^{23}$ (c 1.25, CHCl_3) = +13.6; ^1H
NMR (400 MHz, CDCl_3): δ = 7.60 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2 H); 7.35–7.40 (m, 3
H); 7.08–7.17 (m, 3 H); 7.04 (d, J = 8.0 Hz, 1 H); 5.58 (d, J = 4.0 Hz, 1 H); 5.18 (d, J
= 6.8 Hz, 1 H); 3.67 (s, 3 H); 3.58–3.60 (m, 1 H); 3.36 (t, J = 7.6 Hz, 1 H); 3.14 (dd, J_1
= 13.6 Hz, J_2 = 6.8 Hz, 1 H); 3.08 (s, 3 H); 2.47 (s, 3 H); 2.67 (dd, J_1 = 14.0 Hz, J_2 =
5.6 Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.6, 169.9, 168.6, 149.7, 138.0, 137.9,
132.3, 130.4, 129.2, 128.5, 127.3, 126.8, 126.0, 124.8, 101.6, 65.6, 53.1, 52.2, 50.8,
48.8, 41.8, 37.3, 20.3 ppm. IR (film): ν_{max} 2952, 1734, 1434, 1260, 1216, 1125, 1046,
936, 884 cm^{-1} . HRMS (ESI): $\text{C}_{25}\text{H}_{25}\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd: 421.1646, found: 421.1646; 98:2
er as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major)
= 12.0 min, t_r (minor) = 14.5 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 7-(3-bromophenyl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydro-cyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.45, CHCl₃) = -21.6; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 2 H); 7.48 (s, 1 H); 7.36–7.40 (m, 3 H); 7.27 (d, J = 8.4 Hz, 2 H); 7.18 (t, J = 8.0 Hz, 1 H); 5.57 (d, J = 3.6 Hz, 1 H); 4.63 (d, J = 9.2 Hz, 1 H); 3.72 (s, 3 H); 3.59–3.62 (m, 1 H); 3.50 (t, J = 8.8 Hz, 1 H); 3.20 (s, 3 H); 3.10 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1 H); 2.24 (dd, J_1 = 14.0 Hz, J_2 = 4.8 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.2, 170.1, 168.0, 149.2, 139.7, 132.1, 131.9, 130.9, 129.8, 129.3, 128.6, 127.3, 124.8, 122.3, 102.0, 64.9, 53.2, 53.1, 52.4, 47.4, 41.3, 36.6 ppm. IR (film): ν_{max} 2952, 1761, 1729, 1525, 1436, 1215, 1124, 1024, 928 cm⁻¹. HRMS (ESI): C₂₄H₂₂BrO₆Na [M+Na]⁺ calcd: 485.0600, found: 485.0603; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 13.5 min, t_{r} (minor) = 17.5 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 7-(naphthalen-2-yl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydro-cyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.68, CHCl₃) = -71.8; ¹H NMR (400 MHz, CDCl₃): δ = 7.76–7.82 (m, 4 H); 7.61 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2 H); 7.36–7.47 (m, 5 H); 5.60 (d, J = 2.0 Hz, 1 H); 4.86 (d, J = 8.4 Hz, 1 H); 3.72 (s, 3 H); 3.67–3.70 (m, 2 H); 3.16 – 3.20 (m, 1 H); 3.02 (s, 3 H); 2.31 (dd, J_1 = 14.0 Hz, J_2 = 3.6 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.5, 170.3, 168.3, 149.2, 134.7, 133.2, 132.8, 132.2, 129.3, 128.5, 128.1, 128.0, 127.8, 127.5, 126.3, 126.1, 126.0,

124.8, 102.0, 65.0, 53.9, 53.1, 52.3, 47.8, 41.4, 36.7 ppm. IR (film): $\nu_{\max}$ 2954, 1761, 1725, 1525, 1436, 1124, 1024, 928 cm^{-1} . HRMS (ESI): $\text{C}_{28}\text{H}_{25}\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd: 457.1651, found: 457.1651; 96:4 *er* as determined by HPLC (Chiralcel IA, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 40.6 min, t_r (minor) = 22.5 min.

(4a*S*,7*S*,7a*R*)-Dimethyl 7-(furan-2-yl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.60, CHCl_3) = -11.0; ^1H NMR (400 MHz, CDCl_3): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 2 H); 7.33–7.40 (m, 4 H); 6.30 (s, 2 H); 5.55 (d, J = 2.4 Hz, 1 H); 4.73 (d, J = 7.6 Hz, 1 H); 3.69 (s, 3 H); 3.57–3.60 (m, 2 H); 3.44 (s, 3 H); 3.08–3.13 (m, 1 H); 2.19 (dd, J_1 = 14.0 Hz, J_2 = 4.0 Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 170.1, 169.8, 168.0, 151.0, 148.9, 142.3, 132.1, 129.2, 128.5, 124.7, 110.6, 108.8, 101.9, 63.3, 53.1, 53.0, 48.1, 46.1, 41.0, 36.0 ppm. IR (film): $\nu_{\max}$ 2954, 1734, 1554, 1527, 1424, 1215, 1013, 929 cm^{-1} . HRMS (ESI): $\text{C}_{22}\text{H}_{21}\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd: 397.1287, found: 397.1283; 96:4 *er* as determined by HPLC (Chiralcel ID, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 60.1 min, t_r (minor) = 72.5 min.

(4a*S*,7*S*,7a*R*)-Dimethyl 1-oxo-3-phenyl-7-(thiophen-2-yl)-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.95, CHCl₃) = -21.7; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 2 H); 7.34–7.39 (m, 3 H); 7.20 (dd, J_1 = 4.8 Hz, J_2 = 0.8 Hz, 1 H); 7.03 (d, J = 3.6 Hz, 1 H); 6.94 (dd, J_1 = 5.2 Hz, J_2 = 3.6 Hz, 1 H); 5.54 (d, J = 3.6 Hz, 1 H); 4.86 (d, J = 8.8 Hz, 1 H); 3.73 (s, 3 H); 3.56–3.59 (m, 2 H); 3.33 (s, 3 H); 3.10–3.15 (m, 1 H); 2.30 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.3, 170.1, 167.8, 149.0, 139.6, 132.0, 129.3, 128.6, 126.8, 126.6, 125.1, 124.8, 102.2, 64.8, 53.1, 52.7, 49.3, 48.8, 40.8, 36.1 ppm. IR (film): ν_{max} 2952, 1762, 1730, 1558, 1517, 1434, 1024, 929 cm⁻¹. HRMS (ESI): C₂₂H₂₁O₆S [M+H]⁺ calcd: 413.1059, found: 413.1059; 95:5 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 15.2 min, t_{r} (minor) = 19.2 min.

(4a*S*,7*S*,7a*R*)-Dimethyl 1-oxo-3-phenyl-7-styryl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.06, CHCl₃) = -38.7; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2 H); 7.20–7.40 (m, 8 H); 6.64 (d, J = 15.6 Hz, 1 H); 6.09 (dd, J_1 = 16.0 Hz, J_2 = 8.8 Hz, 1 H); 5.50 (d, J =

2.8 Hz, 1 H); 3.97 (t, $J = 9.2$ Hz, 1 H); 3.71 (s, 3 H); 3.65 (s, 3 H); 3.42–3.47 (m, 1 H); 3.24 (t, $J = 9.2$ Hz, 1 H); 2.97 (dd, $J_1 = 14.0$ Hz, $J_2 = 8.0$ Hz, 1 H); 2.37 (dd, $J_1 = 10.0$ Hz, $J_2 = 4.0$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.3, 170.5, 168.1, 148.6, 136.6, 134.4, 132.2, 129.2, 128.6, 128.5, 127.7, 126.6, 125.2, 124.8, 102.4, 63.5, 53.0, 52.8, 52.4, 47.6, 41.0, 36.0$ ppm. IR (film): ν_{max} 2954, 2321, 1734, 1558, 1517, 1424, 928 cm^{-1} . HRMS (ESI): $\text{C}_{26}\text{H}_{24}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd: 455.1471, found: 455.1475; 94:6 *er* as determined by HPLC (Chiralcel IA, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 17.3 min, t_r (minor) = 13.6 min.

(4a*S*,7*S*,7a*R*)-7-Ethyl-6,6-dimethyl 1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6,7(1*H*)-tricarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (c 1.25, CHCl_3) = +10.2; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.59$ (dd, $J_1 = 8.0$ Hz, $J_2 = 2.4$ Hz, 2 H); 7.34–7.40 (m, 3 H); 5.62 (d, $J = 4.4$ Hz, 1 H); 4.16–4.25 (m, 3 H); 3.73–3.76 (m, 3 H); 3.67–3.72 (m, 3 H); 3.31 – 3.39 (m, 1 H); 2.84 (dd, $J_1 = 13.2$ Hz, $J_2 = 7.2$ Hz, 1 H); 2.18 (dd, $J_1 = 13.2$ Hz, $J_2 = 8.4$ Hz, 1 H); 1.28 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.0, 170.4, 169.8, 168.3, 149.1, 132.0, 129.3, 128.5, 124.7, 100.6, 62.4, 61.7, 54.3, 53.3, 53.0, 43.8, 42.2, 35.8, 14.0$ ppm. IR (film): ν_{max} 2952, 2321, 1731, 1518, 1437, 1340, 1112, 928 cm^{-1} . HRMS (ESI): $\text{C}_{21}\text{H}_{22}\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd: 425.1212, found: 425.1211; 94:6 *er* as determined by HPLC (Chiralcel IA, 95:5 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 37.6 min, t_r (minor) = 22.5 min.

(4a*S*,7*S*,7a*R*)-Dimethyl

7-ethyl-1-oxo-3-phenyl-4a,5,7,7a-

tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.06, CHCl₃) = +17.5; ¹H NMR (400 MHz, CDCl₃): δ = 7.58 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 2 H); 7.34–7.39 (m, 3 H); 5.48 (d, J = 3.2 Hz, 1 H); 3.74 (s, 3 H); 3.66 (s, 3 H); 3.34–3.39 (m, 1 H); 3.13–3.19 (m, 1 H); 2.92 (t, J = 8.4 Hz, 1 H); 2.81 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz, 1 H); 2.23 (dd, J_1 = 10.0 Hz, J_2 = 5.2 Hz, 1 H), 1.52–1.62 (m, 2 H); 1.03 (t, J = 7.6 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.8, 171.0, 169.7, 148.6, 132.3, 129.1, 128.5, 124.7, 102.4, 62.6, 52.9, 52.6, 50.6, 47.1, 41.5, 35.7, 24.5, 12.4 ppm. IR (film): ν_{max} 2954, 1734, 1558, 1525, 1437, 1419, 1018, 928 cm⁻¹. HRMS (ESI): C₂₀H₂₃O₆ [M+H]⁺ calcd: 359.1495, found: 359.1497; 75:25 *er* as determined by HPLC (Chiralcel IA, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 14.1 min, t_{r} (minor) = 10.2 min.

(4a*S*,7a*S*)-Dimethyl

1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-

6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.34, CHCl₃) = -1.1; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 2 H); 7.34–7.40 (m, 3 H); 5.63 (d, J = 4.4 Hz, 1 H); 3.77 (s, 3 H); 3.70 (s, 3 H); 3.14–3.18 (m, 2 H); 2.78–2.90 (m, 2 H); 2.62

(dd, $J_1 = 13.6$ Hz, $J_2 = 7.2$ Hz, 1 H); 2.33 (dd, $J_1 = 13.6$ Hz, $J_2 = 8.0$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 172.0, 171.2, 169.4, 149.0, 132.2, 129.2, 128.5, 124.7, 101.5, 58.8, 53.1, 53.0, 41.5, 41.0, 36.8$ ppm. IR (film): ν_{max} 2952, 1734, 1549, 1525, 1437, 1023, 928 cm^{-1} . HRMS (ESI): $\text{C}_{18}\text{H}_{19}\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd: 331.1182, found: 331.1174; 53:47 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 15.0 min, t_r (minor) = 16.1 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(4-methoxyphenyl)-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 0.5, CHCl_3) = -80.3; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.53$ (dd, $J_1 = 6.8$ Hz, $J_2 = 1.6$ Hz, 2 H); 7.18–7.36 (m, 5 H); 6.89 (dd, 2 H, $J = 6.8, 2.0$ Hz, 2 H); 5.42 (d, $J = 3.2$ Hz, 1 H); 4.70 (d, $J = 8.8$ Hz, 1 H); 3.82 (s, 3 H); 3.71 (s, 3 H); 3.48–3.64 (m, 2 H); 3.13 (s, 3 H); 3.04–3.15 (m, 1 H); 2.26 (dd, $J = 14.0, 4.4$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.5, 170.2, 168.5, 160.4, 149.0, 137.4, 128.7, 128.2, 127.7, 126.2, 124.7, 113.9, 100.2, 65.1, 55.3, 53.6, 53.0, 52.2, 47.6, 41.3, 36.6$ ppm. IR (film): ν_{max} 2954, 2400, 1759, 1728, 1609, 1513, 1435, 1248, 1177, 1030, 928 cm^{-1} . HRMS (ESI): $\text{C}_{25}\text{H}_{25}\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd: 437.1600, found: 437.1602; 94:6 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 18.8 min, t_r (minor) = 21.2 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 1-oxo-7-phenyl-3-*p*-tolyl-4a,5,7,7a-tetrahydro-

penta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 0.5, CHCl₃) = -52.9;

¹H NMR (400 MHz, CDCl₃): δ = 7.48 (d, *J* = 8.0 Hz, 2 H); 7.20–7.35 (m, 5 H); 7.18

(d, *J* = 8.0 Hz, 2 H); 5.51 (d, *J* = 3.2 Hz, 1 H); 4.70 (d, *J* = 8.8 Hz, 1 H); 3.70 (s, 3 H);

3.49–3.64 (m, 2 H); 3.13 (s, 3 H); 3.02–3.13 (m, 3 H); 2.36 (s, 3 H); 2.26 (dd, *J* = 14.0,

4.4 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.5, 170.2, 168.4, 149.2, 139.2, 137.4,

129.3, 129.2, 128.7, 128.2, 127.7, 124.7, 101.2, 65.0, 53.6, 53.0, 52.2, 47.6, 41.2, 36.6,

21.2 ppm. IR (film): $\nu_{\max}$ 2952, 1730, 1570, 1533, 1272, 1126, 1042, 1017, 930 cm⁻¹.

HRMS (ESI): C₂₅H₂₅O₆ [M+H]⁺ calcd: 421.1651, found: 421.1652; 96:4 *er* as

determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) =

13.9 min, *t_r* (minor) = 16.1 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(4-fluorophenyl)-1-oxo-7-phenyl-4a,5,7,7a-tetrahydro-

cyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 1.00, CHCl₃) = -

19.9; ¹H NMR (400 MHz, CDCl₃): δ = 7.54–7.62 (m, 2 H); 7.21–7.38 (m, 5 H); 7.03 –

7.10 (m, 2 H); 5.49 (d, *J* = 3.2 Hz, 1 H); 4.69 (d, *J* = 8.8 Hz, 1 H); 3.71 (s, 3 H); 3.52 –

3.65 (m, 2 H); 3.08–3.16 (m, 4 H); 2.26 (dd, $J = 14.0, 4.4$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.5, 170.1, 168.1, 163.3$ ($J = 248$ Hz), 148.4, 137.2, 128.7, 128.39, 128.36, 128.2, 127.8, 126.8, 126.7, 115.7, 115.4, 101.9, 65.0, 53.6, 53.0, 52.3, 47.5, 41.2, 36.6 ppm. IR (film): ν_{max} 2952, 1767, 1730, 1558, 1510, 1272, 1159, 1024, 929 cm^{-1} . HRMS (ESI): $\text{C}_{24}\text{H}_{22}\text{O}_6\text{F}$ $[\text{M}+\text{H}]^+$ calcd: 425.1400, found: 425.1401; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 13.8 min, t_{r} (minor) = 15.7 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(4-chlorophenyl)-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (c 0.5, CHCl_3) = -56.7; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.53$ (dd, $J = 6.8, 1.6$ Hz, 2 H); 7.20–7.40 (m, 7 H); 5.56 (d, $J = 2.8$ Hz, 1 H); 4.68 (d, $J = 8.8$ Hz, 1 H); 3.71 (s, 3 H); 3.52–3.68 (m, 2 H); 3.06–3.18 (m, 4 H); 2.25 (dd, $J_1 = 14.0$ Hz, $J_2 = 4.4$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.5, 170.1, 168.0, 148.2, 137.2, 135.1, 130.6, 128.7, 128.6, 128.2, 127.8, 126.0, 102.6, 65.0, 53.6, 53.0, 52.3, 47.5, 41.2, 36.6$ ppm. IR (film): ν_{max} 2954, 1728, 1523, 1435, 1012, 928 cm^{-1} . HRMS (ESI): $\text{C}_{24}\text{H}_{22}\text{O}_6\text{Cl}$ $[\text{M}+\text{H}]^+$ calcd: 441.1105, found: 441.1096; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 15.3 min, t_{r} (minor) = 16.9 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(4-bromophenyl)-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.00, CHCl_3) = +29.2; ^1H NMR (400 MHz, CDCl_3): δ = 7.48 (dd, J = 18.8, 8.8 Hz, 4 H); 7.23–7.34 (m, 5 H); 5.57 (d, J = 3.2 Hz, 1 H); 4.68 (d, J = 8.4 Hz, 1 H); 3.71 (s, 3 H); 3.50–3.63 (m, 2 H); 3.13 (s, 3 H); 3.08–3.16 (m, 1 H); 2.25 (dd, J = 13.6, 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.5, 170.1, 168.0, 148.3, 137.2, 131.7, 131.1, 128.7, 128.3, 127.8, 126.3, 123.4, 102.7, 65.0, 53.7, 53.0, 52.3, 47.5, 41.1, 36.7 ppm. IR (film): ν_{max} 2954, 1762, 1729, 1515, 1437, 1275, 1215, 1016, 929 cm^{-1} . IR (film): ν_{max} 2952, 1728, 1523, 1425, 1008, 925 cm^{-1} . HRMS (ESI): $\text{C}_{24}\text{H}_{22}\text{O}_6\text{Br}$ $[\text{M}+\text{H}]^+$ calcd: 485.0600, found: 485.0602; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 20.7 min, t_{r} (minor) = 23.2 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(naphthalen-2-yl)-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.00, CHCl_3) = -62.5; ^1H NMR (400 MHz, CDCl_3): δ = 8.14–8.20 (m, 1 H); 7.78–7.90 (m, 3 H); 7.63 (dd, J = 8.8, 2.0 Hz, 1 H); 7.50 (dd, J = 6.0, 3.2 Hz, 2 H); 7.20–7.38 (m, 5 H); 5.72 (d,

$J = 3.2$ Hz, 1 H); 4.74 (d, $J = 8.8$ Hz, 1 H); 3.70 (s, 3 H); 3.56–3.68 (m, 2 H); 3.08–3.20 (m, 4 H); 2.32 (dd, $J_1 = 13.6$ Hz, $J_2 = 4.4$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.5, 170.0, 168.4, 149.1, 137.4, 133.5, 133.1, 129.1, 128.7, 128.6, 128.2, 127.7, 127.6, 126.7, 126.6, 124.3, 122.0, 102.6, 65.1, 53.7, 53.0, 52.2, 47.7, 41.3, 36.7$ ppm. IR (film): ν_{max} 2952, 1756, 1729, 1515, 1436, 1192, 1130, 1045, 929 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{28}\text{H}_{25}\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 457.1651, Found: 457.1649; 96:4 *er* as determined by HPLC (Chiralcel IC, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 26.8 min, t_r (minor) = 44.6 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(furan-2-yl)-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (c 0.5, CHCl_3) = -22.9; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.38\text{--}7.44$ (m, 1 H); 7.22 – 7.35 (m, 5 H); 6.59 (d, $J = 3.6$ Hz, 1 H); 6.44 (dd, $J = 3.6, 2.0$ Hz, 1 H); 5.54 (d, $J = 3.2$ Hz, 1 H); 4.66 (d, $J = 8.8$ Hz, 1 H); 3.71 (s, 3 H); 3.50–3.65 (m, 2 H); 3.05–3.18 (m, 4 H); 2.26 (dd, $J = 13.6, 4.0$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.5, 170.2, 167.6, 146.6, 143.2, 142.0, 137.1, 128.7, 128.2, 127.8, 111.5, 108.1, 100.3, 65.0, 53.7, 53.0, 52.3, 47.8, 41.1, 36.2$ ppm. IR (film): ν_{max} 2954, 1728, 1524, 1425, 1012, 928 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{22}\text{H}_{21}\text{O}_7$ ($\text{M}+\text{H}$) $^+$: 457.1651, Found: 457.1649; 96:4 *er* as determined by HPLC

(Chiralcel IB, 97:3 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 21.0 min, t_r (minor) = 24.9 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 1-oxo-7-phenyl-3-(thiophen-2-yl)-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 0.5, CHCl₃) = -111.5; ¹H NMR (400 MHz, CDCl₃): δ = 7.22–7.34 (m, 7 H); 7.02 (dd, *J* = 5.2, 4.0 Hz, 1 H); 5.44 (d, *J* = 3.2 Hz, 1 H); 4.69 (d, *J* = 8.8 Hz, 1 H); 3.73 (s, 3 H); 3.50–3.62 (m, 2 H); 3.13 (s, 3 H); 3.09 (dd, *J*₁ = 14.0 Hz, *J*₂ = 7.2 Hz, 1 H); 2.26 (dd, *J* = 13.6, 4.0 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.4, 170.1, 167.8, 145.0, 137.3, 135.6, 128.7, 128.2, 127.7, 127.6, 125.9, 124.9, 101.1, 65.0, 53.7, 53.0, 52.3, 47.7, 41.2, 36.6 ppm. IR (film): $\nu_{\max}$ 2954, 1728, 1518, 1437, 1022, 928 cm⁻¹. HRMS(ESI) calcd for C₂₂H₂₁O₆S (M+H)⁺: 413.1059, Found: 413.1057; 95:5 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 14.4 min, t_r (minor) = 18.2 min.

(4a*R*,7*R*,7a*R*)-Dimethyl 4-methyl-1-oxo-3,7-diphenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 1.00, CHCl₃) = +1.1;

^1H NMR (400 MHz, CDCl_3): δ = 7.34–7.45 (m, 5 H); 7.18–7.34 (m, 5 H); 4.84–4.93 (m, 1 H); 3.78 (s, 3 H); 3.42–3.55 (m, 4 H); 3.00–3.15 (m, 4 H); 2.24–2.33 (m, 1 H); 1.83 (s, 3 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.5, 170.2, 168.7, 144.9, 138.2, 133.1, 128.8, 128.7, 128.6, 128.2, 128.1, 127.5, 109.8, 65.0, 53.5, 53.0, 52.1, 48.4, 42.7, 39.4, 16.6 ppm. IR (film): ν_{max} 2954, 1739, 1539, 1437, 1262, 1100, 1010, 928 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 421.1651, Found: 421.1641; 98:2 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 11.4 min, t_{r} (minor) = 12.7 min.

(6a*R*,7*R*,9a*R*)-Dimethyl 6-oxo-7-phenyl-6a,7,9a,10,11-hexahydrobenzo[*h*]cyclopenta[*c*]chromene-8,8(6*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 0.5, CHCl_3) = -32.1; ^1H NMR (400 MHz, CDCl_3): δ = 7.50–7.56 (m, 1 H); 7.18–7.36 (m, 7 H); 7.08–7.18 (m, 1 H); 4.75 (d, J = 7.6 Hz, 1 H); 3.69 (s, 3 H); 3.53–3.61 (m, 2 H); 3.13 (s, 3 H); 2.98–3.12 (m, 1 H); 2.76–2.98 (m, 2 H); 2.33–2.46 (m, 2 H); 2.17–2.33 (m, 1 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.4, 170.2, 168.4, 142.6, 138.0, 135.3, 128.6, 128.23, 128.15, 127.6, 127.2, 126.6, 121.5, 110.7, 65.0, 54.1, 53.0, 52.2, 48.4, 40.6, 39.1, 27.5, 24.6 ppm. IR (film): ν_{max} 2954, 1750, 1729, 1524, 1436, 1093, 1020, 928 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{O}_6$ ($\text{M}+\text{H}$) $^+$: 433.1651, Found: 433.1649; 97:3 *er* as

determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 21.7 min, t_r (minor) = 32.3 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(4-bromophenyl)-7-(naphthalen-2-yl)-1-oxo-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 1.00, CHCl₃) = -79.8; ¹H NMR (400 MHz, CDCl₃): δ = 7.74–7.84 (m, 4 H); 7.36–7.54 (m, 7 H); 5.60 (d, *J* = 2.4 Hz, 1 H); 4.84 (d, *J* = 8.4 Hz, 1 H); 3.72 (s, 3 H); 3.60–3.70 (m, 2 H); 3.18 (dd, *J* = 13.6, 7.2 Hz, 1 H); 2.29 (dd, *J* = 14.0, 4.0 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.5, 170.2, 168.0, 148.3, 134.6, 133.1, 132.8, 131.7, 131.1, 128.03, 127.98, 127.8, 127.5, 126.31, 126.26, 126.10, 126.06, 123.4, 102.7, 64.9, 53.9, 53.1, 52.3, 47.6, 41.3, 36.7 ppm. IR (film): $\nu_{\max}$ 2954, 1728, 1523, 1425, 1008, 928 cm⁻¹. HRMS(ESI) calcd for C₂₈H₂₄BrO₆ (M+H)⁺: 535.0756, Found: 535.0749; 99:1 *er* as determined by HPLC (Chiralcel IC, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 18.9 min, t_r (minor) = 31.2 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-(4-chlorophenyl)-7-(naphthalen-2-yl)-1-oxo-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.67, CHCl₃) = -64.9; ¹H NMR (400 MHz, CDCl₃): δ = 7.79–7.82 (m, 4 H); 7.53–7.77 (m, 2H); 7.34–7.47 (m, 5H); 5.58–5.59 (m, 1H); 4.84 (d, *J* = 8.4 Hz, 1 H); 3.72 (s, 3 H); 3.66–3.70 (m, 1 H); 3.16–3.21 (m, 1H); 3.02 (s, 3H); 2.29 (dd, *J* = 13.6, 4.0 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.5, 170.2, 168.0, 148.3, 135.2, 134.6, 133.2, 132.9, 130.7, 128.8, 128.1, 128.0, 127.9, 127.5, 126.3, 126.1, 126.1, 102.6, 65.0, 53.9, 53.1, 52.3, 47.7, 41.4, 36.7. IR (film): ν_{max} 2954, 1757, 1729, 1601, 1527, 1437, 1424, 1017, 928 cm⁻¹. HRMS(ESI) calcd for C₂₈H₂₄ClO₆ (M+H)⁺: 491.1261, Found: 491.1263; 95:5 *er* as determined by HPLC (Chiralcel IA, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 47.5 min, *t_r* (minor) = 24.3 min.

(4a*S*,7*R*,7a*R*)-Dimethyl 3-methyl-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a colorless oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.61, CHCl₃) = -46.1; ¹H NMR (500 MHz, CDCl₃): δ = 7.20–7.38 (m, 5 H), 4.77 (d, *J* = 1.0 Hz, 1 H), 4.62 (d, *J* = 9.5 Hz, 1 H), 3.75 (s, 3 H), 3.34–3.52 (m, 2 H), 3.12 (s, 3 H), 3.01 (dd, *J* = 14.0 Hz, 7.5 Hz, 1 H), 2.13 (dd, *J* = 14 Hz, 4.5 Hz, 1 H), 1.88 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 171.7, 170.2, 168.8, 148.5, 137.3, 128.7, 128.2, 127.6, 102.2, 65.0, 53.5, 52.9, 52.2, 47.4, 41.1, 36.1, 18.7 ppm. IR (film): ν_{max} 2986, 1723, 1422, 1264, 1112,

896 cm⁻¹. HRMS(ESI) calcd for C₁₉H₂₁O₆ (M+H)⁺: 345.1338, Found: 345.1338; 95:5 *er* as determined by HPLC (Chiralcel ID, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 23.5 min, *t_r* (minor) = 26.9 min.

(4a*S*,7*R*,7a*R*)-Diethyl 1-oxo-3,7-diphenyl-4a,5,7,7a-tetrahydrocyclopenta-[c]pyran-6,6(1*H*)-dicarboxylate: a yellow oil; [α]_D²³ (*c* 2.01, CHCl₃) = -10.0; ¹H NMR (400 MHz, CDCl₃): δ = 7.58–7.61 (m, 2H); 7.23–7.39 (m, 8H); 5.56 (d, *J* = 3.2 Hz, 1H); 4.70 (d, *J* = 4.8 Hz, 1H); 4.18 (q, *J* = 6.8 Hz, 2H); 3.74 (dd, *J* = 14.0, 7.2 Hz, 1H); 2.29 (dd, *J* = 14.0, 4.0 Hz, 1H); 1.20 (t, *J* = 7.2 Hz, 3H); 0.75 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.1, 169.9, 168.5, 149.2, 137.5, 132.2, 129.2, 128.9, 128.5, 128.2, 127.7, 124.8, 102.3, 65.0, 61.9, 61.5, 53.5, 47.9, 41.3, 36.7, 13.9, 13.3. IR (film): ν_{max} 2954, 1766, 1722, 1520, 1423, 1075, 928 cm⁻¹. HRMS(ESI) calcd for C₂₆H₂₇O₆ (M+H)⁺: 435.1808, Found: 435.1805; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 10.0 min, *t_r* (minor) = 11.9 min.

(4a*S*,7*R*,7a*R*)-Dibenzyl 1-oxo-3,7-diphenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]-pyran-6,6(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.39, CHCl₃) = +26.2; ¹H NMR (400 MHz, CDCl₃): δ = 7.51–7.54 (m, 2H); 7.11–7.38 (m, 16H); 6.84–6.86 (m, 2H); 5.45–5.46 (m, 1H); 5.12 (d, *J* = 12.4 Hz, 1H); 4.96 (d, *J* = 12.0 Hz, 1H); 4.71–4.75 (m, 2H); 4.18 (d, *J* = 12.4 Hz, 1H); 3.55–3.58 (m, 2H); 3.15 (dd, *J* = 13.6, 7.2 Hz, 1H); 2.32 (dd, *J* = 13.6, 7.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 170.8, 169.7, 168.3, 149.3, 137.1, 135.1, 134.6, 132.2, 129.2, 128.9, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 124.9, 102.2, 67.8, 67.4, 65.2, 53.7, 47.9, 41.3, 36.7. IR (film): ν_{max} 2954, 1767, 1721, 1419, 1025, 928 cm⁻¹. HRMS(ESI) calcd for C₃₆H₃₁O₆ (M+H)⁺: 559.2121, Found: 559.2118; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 14.4 min, *t_r* (minor) = 16.5 min.

(4a*S*,7*R*,7a*R*)-Dibenzyl 7-(4-chlorophenyl)-1-oxo-3-phenyl-4a,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate: a white solid; $[\alpha]_{\text{D}}^{23}$ (*c* 1.55, CHCl₃) = +4.7; ¹H NMR (400 MHz, CDCl₃): δ = 7.50–7.53 (m, 2H); 7.34–7.37 (m, 3H); 7.22–7.32 (m, 8H); 7.15 (d, *J* = 8.4 Hz, 4H); 6.86 (d, *J* = 6.8 Hz, 2H); 5.45 (d, *J* = 3.2 Hz, 1H); 5.13 (d, *J* = 12.0 Hz, 1H); 5.01 (d, *J* = 12.0 Hz, 1H); 4.62 (d, *J* = 10.0 Hz, 1H); 4.37 (d, *J* = 12.0 Hz, 1H); 3.48–3.58 (m, 2H); 3.13 (dd, *J* = 14.0, 7.6 Hz, 1H); 2.32 (dd, *J* = 14.0, 4.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 170.7, 169.6, 168.0, 149.2, 135.3, 135.0, 134.3, 133.8, 132.0, 130.3, 129.3, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1,

124.8, 102.2, 67.9, 67.6, 64.9, 52.9, 47.6, 41.3, 36.5, 29.7. IR (film): $\nu_{\max}$ 2954, 1762, 1729, 1515, 1437, 1275, 1215, 1016, 929 cm^{-1} . IR (film): $\nu_{\max}$ 2954, 1724, 1525, 1424, 1015, 928 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{36}\text{H}_{30}\text{ClO}_6$ ($\text{M}+\text{H}$) $^+$: 597.1731, Found: 597.1730; 97:3 *er* as determined by HPLC (Chiralcel IA, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 16.7 min, t_r (minor) = 22.7 min.

(4a*S*,8*R*,8a*R*)-Dimethyl 1-oxo-3,8-diphenyl-5,6,8,8a-tetrahydro-1*H*-isochromene - 7,7(4a*H*)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 2.10, CHCl_3) = +15.6; ^1H NMR (400 MHz, CDCl_3): δ = 7.57–7.60 (m, 2H); 7.32–7.41 (m, 4H); 7.21–7.27 (m, 4H); 5.57 (dd, J = 2.0, 1.6 Hz, 1H); 4.03 (dd, J = 12.0, 4.8 Hz, 1H); 3.70 (s, 3H); 3.45 (d, J = 12.0 Hz, 1H); 3.33 (s, 3H); 3.27 (d, J = 2.4 Hz, 1H); 2.26–2.35 (m, 1H); 1.93–1.97 (m, 1H); 1.24–1.87 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.0, 170.2, 168.0, 150.7, 136.5, 132.0, 130.3, 129.1, 128.6, 127.9, 127.7, 124.6, 103.2, 59.5, 52.2, 45.9, 41.7, 31.6, 30.0, 25.3. IR (film): $\nu_{\max}$ 2954, 1773, 1731, 1543, 1420, 928 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{O}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 443.1471, Found: 443.1471; 96:4 *er* as determined by HPLC (Chiralcel IB, 95:5 hexanes/*i*-PrOH, 0.7 mL/min), t_{r1} (major) = 21.9 min, t_{r1} (minor) = 23.7 min t_{r2} (major) = 25.4 min, t_{r2} (minor) = 33.5 min.

(4a*S*,8*R*,8a*R*)-Dimethyl 8-(4-chlorophenyl)-1-oxo-3-phenyl-5,6,8,8a-tetrahydro-1*H*-isochromene-7,7(4a*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 0.5, CHCl₃) = -24.1; ¹H NMR (400 MHz, CDCl₃): δ = 7.57–7.60 (m, 2H); 7.38–7.39 (m, 5H); 7.22 (d, *J* = 8.8 Hz, 2H); 5.57 (dd, *J* = 2.0, 1.5 Hz, 1H); 3.96–4.01 (m, 1H); 3.72 (s, 3H); 3.39 (d, *J* = 8.4 Hz, 1H); 3.37 (s, 3H); 3.29 (d, *J* = 2.8 Hz, 1H); 2.27–2.33 (m, 2H); 1.93–1.98 (m, 1H); 1.80–1.86 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 170.8, 170.0, 167.7, 150.7, 134.8, 133.8, 131.8, 131.7, 129.2, 128.6, 127.9, 124.5, 103.0, 59.5, 52.3, 45.3, 41.6, 31.6, 29.9, 25.2. IR (film): ν_{max} 2954, 1767, 1730, 1517, 1424, 1016, 928 cm⁻¹. HRMS(ESI) calcd for C₂₅H₂₄ClO₆ (M+H)⁺: 455.1261, Found: 455.1242; 95:5 *er* as determined by HPLC (Chiralcel ID, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 18.4 min, *t_r* (minor) = 21.7 min.

(4a*S*,8*R*,8a*R*)-Dimethyl 8-(4-isopropylphenyl)-1-oxo-3-phenyl-5,6,8,8a-tetrahydro-1*H*-isochromene-7,7(4a*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.00, CHCl₃) = -65.8; ¹H NMR (400 MHz, CDCl₃): δ = 7.58–7.60 (m, 2H); 7.33–7.41 (m, 3H); 7.28 (s, 2H); 7.09 (d, *J* = 4.4 Hz, 2H); 5.56 (d, *J* = 0.8 Hz, 1H); 4.02 (dd, *J* = 12.0, 4.8 Hz, 1H); 3.70 (s, 3H); 3.43 (d, *J* = 12.0 Hz, 1H); 3.37 (s, 3H); 2.80–2.87 (m, 1H);

2.25–2.35 (m, 2H); 1.81–1.96 (m, 2H); 1.21 (s, 3H); 1.19 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.0, 170.2, 168.0, 150.6, 148.2, 133.7, 132.1, 130.1, 129.1, 128.5, 125.7, 124.6, 103.2, 59.6, 52.1, 52.0, 45.6, 41.7, 33.6, 31.7, 30.0, 25.4, 23.9, 23.8. IR (film): ν_{max} 2954, 2928 1514, 1435, 1021, 928 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{28}\text{H}_{31}\text{O}_6$ ($\text{M}+\text{H}$) $^{+}$: 463.2121, Found: 463.2121; 94:6 *er* as determined by HPLC (Chiralcel ODH, 98:2 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 28.9 min, t_{r} (minor) = 41.2 min.

(4a*S*,8*S*,8a*R*)-Dimethyl 1-oxo-3-phenyl-8-(thiophen-2-yl)-5,6,8,8a-tetrahydro-1*H*-isochromene-7,7(4a*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (c 1.00, CHCl_3) = +231.1; ^1H NMR (400 MHz, CDCl_3): δ = 7.55–7.57 (m, 2H); 7.31–7.37 (m, 3H); 7.19 (d, J = 4.8 Hz, 1H); 7.09–7.10 (m, 1H); 6.95 (d, J = 5.2, 3.6 Hz, 1H); 5.64 (s, 1H); 4.84 (d, J = 1.6 Hz, 1H); 3.78 (s, 3H); 3.49 (s, 3H); 3.19–3.21 (m, 2H); 2.50–2.58 (m, 1H); 2.38–2.42 (m, 1H); 2.17–2.22 (m, 1H); 1.23–1.33 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 170.9, 169.2, 167.4, 149.4, 137.8, 132.1, 129.9, 129.0, 128.4, 126.1, 125.0, 124.5, 105.2, 59.4, 53.1, 52.5, 44.1, 40.0, 30.3, 28.4, 26.3. IR (film): ν_{max} 2954, 1731, 1525, 1427, 1219, 1159, 1019, 928 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{23}\text{H}_{23}\text{O}_6\text{S}$ ($\text{M}+\text{H}$) $^{+}$: 427.1215, Found: 427.1206; 95:5 *er* as determined by HPLC (Chiralcel ODH, 92:8 hexanes/*i*-PrOH, 0.7 mL/min), t_{r} (major) = 23.1 min, t_{r} (minor) = 27.6 min.

(4a*S*,7*S*,8*R*,8a*R*)-7-Nitro-3,8-diphenyl-4a,5,6,7,8,8a-hexahydro-1*H*-isochromen-1-one: a white solid; $[\alpha]_D^{23}$ (*c* 1.20, CHCl₃) = -43.0; ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (dd, *J* = 7.2, 1.6 Hz, 2H); 7.43–7.47 (m, 3H); 7.28–7.34 (m, 3H); 7.18 (d, *J* = 7.2 Hz, 2H); 5.63 (s, 1H); 4.77–4.84 (m, 1H); 3.54 (t, *J* = 9.0 Hz, 1H); 3.28 (s, 1H); 3.01 (dd, *J* = 9.0, 0.9 Hz, 1H); 2.19–2.39 (m, 3H); 1.92–2.01 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.5, 151.2, 135.4, 131.7, 129.6, 129.1, 128.7, 128.6, 127.8, 124.7, 102.3, 88.7, 46.5, 43.8, 31.3, 27.7, 27.1. IR (film): $\nu_{\max}$ 2954, 1772, 1558, 1215, 1047, 1014, 928 cm⁻¹. HRMS(ESI) calcd for C₂₁H₂₀NO₄ (M+H)⁺: 350.1392, Found: 350.1391; 87:13 *er* as determined by HPLC (Chiralcel IA, *t_r* (major) = 37.6 min, *t_r* (minor) = 22.5 min hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 19.3 min, *t_r* (minor) = 21.2 min.

(4a*S*,7*S*,8*R*,8a*R*)-8-(4-chlorophenyl)-7-nitro-3-phenyl-4a,5,6,7,8,8a-hexahydro-1*H*-isochromen-1-one: a yellow solid; $[\alpha]_D^{23}$ (*c* 1.75, CHCl₃) = +0.8; ¹H NMR (400 MHz, CDCl₃): δ = 7.65 – 7.68 (m, 2 H); 7.42 – 7.47 (m, 3 H); 7.29 (d, *J* = 8.4 Hz, 2 H); 5.62 (t, *J* = 0.4 Hz, 1 H); 4.70 – 4.77 (m, 1 H); 3.82 (s, 3 H); 3.71 (s, 3 H); 3.48 – 3.64 (m, 2 H); 3.13 (s, 3 H); 3.04 – 3.15 (m, 1 H); 2.26 (dd, *J₁* = 14.0 Hz, *J₂* = 4.4 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.3, 151.2, 134.6, 134.0, 131.5, 129.7, 129.4, 129.2, 128.8, 124.6, 102.1, 88.6, 46.3, 43.2, 31.2, 27.6, 26.9 ppm. IR (film): $\nu_{\max}$ 2954, 2927,

2854, 1762, 1558, 1525, 1465, 1419, 928 cm⁻¹. HRMS(ESI) calcd for C₂₁H₁₉O₄NCl (M+ H)⁺: 384.1003, Found: 384.1004.

(4a*S*,7*S*,8*R*,8a*R*)-3-(furan-3-yl)-5,5-dimethyl-7-nitro-8-phenyl-4a,5,6,7,8,8a-

hexahydro-1*H*-isochromen-1-one: a yellow oil; [α]_D²³ (*c* 1.73, CHCl₃) = +3.6; ¹H NMR (400 MHz, CDCl₃): δ = 7.71 (s, 1H); 7.47 (s, 1H); 7.31–7.35 (m, 3H); 7.26–7.30 (m, 2H); 6.59 (d, *J* = 1.2 Hz, 1H); 5.50 (s, 1H); 4.97–5.04 (m, 1H); 3.53 (t, *J* = 12.0 Hz, 1H); 3.22–3.26 (m, 1H); 2.76 (d, *J* = 2.0 Hz, 1H); 2.14 (t, *J* = 4.4 Hz, 1H); 2.04 (dd, *J* = 12.0, 4.0 Hz, 1H); 1.22 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.7, 145.8, 144.1, 140.4, 135.4, 129.1, 128.7, 128.6, 127.8, 119.5, 107.0, 98.0, 86.8, 44.4, 43.6, 41.4, 39.9, 33.5, 29.7, 28.2, 26.1. IR (film): $\nu_{\max}$ 2927, 1768, 1558, 1517, 1419, 1018, 929 cm⁻¹. HRMS(ESI) calcd for C₂₁H₂₂NO₅ (M+H)⁺: 368.1498, Found: 368.14987; 89:11 *er* as determined by HPLC (Chiralcel IA, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), *t*_r (major) = 32.3 min, *t*_r (minor) = 19.8 min.

(3*R*,4*aS*,7*R*,7*aR*)-Dimethyl 1-oxo-3,7-diphenylhexahydrocyclopenta[*c*]pyran-6,6

(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.00, CHCl₃) = -10.3; ¹H NMR (400 MHz, CDCl₃): δ = 7.29–7.41 (m, 5H); 7.22–7.28 (m, 5H); 5.59 (dd, *J* = 7.6, 2.8 Hz, 1H); 4.34 (d, *J* = 10.4 Hz, 1H); 3.74 (s, 3H); 3.47 (t, *J* = 10.4 Hz, 1H); 3.33 (s, 3H); 3.19 (dd, *J* = 8.4, 2.0 Hz, 1H); 2.89 (dd, *J* = 14.0, 8.4 Hz, 1H); 2.31–2.38 (m, 1H); 1.91–1.99 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.8, 171.3, 170.5, 138.9, 137.3, 128.8, 128.6, 128.2, 128.1, 127.7, 125.5, 65.2, 54.8, 52.8, 52.1, 47.8, 41.6, 35.5, 32.6. IR (film): ν_{max} 2952, 1730, 1520, 1436, 1271, 1050, 928 cm⁻¹. HRMS(ESI) calcd for C₂₄H₂₃O₇ (M+ H)⁺: 423.1444, Found: 423.1440; 96:4 *er* as determined by HPLC (Chiralcel IA, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), *t*_r(major) = 32.2 min, *t*_r(minor) = 44.6 min.

(3*S*,4*aS*,7*R*,7*aR*)-Dimethyl 1-oxo-3,7-diphenylhexahydrocyclopenta[*c*]pyran-6,6

(1*H*)-dicarboxylate: a yellow oil; $[\alpha]_{\text{D}}^{23}$ (*c* 1.1, CHCl₃) = -11.0; ¹H NMR (400 MHz, CDCl₃): δ = 7.21–7.39 (m, 10H); 5.29 (dd, *J* = 11.2, 1.6 Hz, 1H); 4.73 (d, *J* = 7.2 Hz, 1H); 3.74 (s, 3H); 3.48–3.54 (m, 2H); 3.25 (s, 3H); 2.89 (dd, *J* = 13.6, 2.8 Hz, 1H); 2.37–2.41 (m, 1H); 1.77 (dd, *J* = 16.8, 8.8 Hz, 1H); 1.59–1.68 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 172.9, 171.3, 170.8, 139.3, 138.9, 128.7, 128.5, 128.2, 127.3, 126.0, 80.3, 65.5, 52.8, 52.6, 52.1, 48.8, 42.3, 38.1, 36.3. IR (film): ν_{max} 2952, 1730, 1520, 1436, 1271, 1050, 928 cm⁻¹. HRMS(ESI) calcd for C₂₄H₂₃O₇ (M+ H)⁺: 423.1444,

Found: 423.1440; 96:4 *er* as determined by HPLC (Chiralcel IA, 80:20 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 45.3 min, t_r (minor) = 25.2 min.

(1R,3aS,4R,6aR)-Dimethyl 1-benzoyl-3-oxo-4-phenyltetrahydro-1H-cyclopenta[c]furan-5,5(3H)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 0.5, CHCl₃) = -43.3; ¹H NMR (400 MHz, CDCl₃): δ = 7.98–8.00 (m, 2H); 7.67 (d, *J* = 7.6 Hz, 1H); 7.54–7.57 (m, 2H); 7.18–7.30 (m, 5H); 5.52 (d, *J* = 2.4 Hz, 1H); 4.53 (d, *J* = 4.0 Hz, 1H); 3.76–3.80 (m, 4H); 3.43 (dd, *J* = 9.2, 4.0 Hz, 1H); 3.22 (s, 3H); 3.10–3.15 (m, 1H); 2.29–2.33 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 193.9, 177.4, 170.8, 169.4, 138.8, 134.5, 133.5, 129.2, 128.8, 128.5, 128.2, 127.7, 81.7, 67.3, 54.1, 53.2, 52.3, 50.2, 42.9, 39.9, 29.7. IR (film): $\nu_{\max}$ 2954, 1786, 1730, 1599, 1433, 1216, 1022 cm⁻¹. HRMS(ESI) calcd for C₂₄H₂₃O₇ (M+H)⁺: 423.1444, Found: 423.1440; 96:4 *er* as determined by HPLC (Chiralcel OJH, 70:30 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 11.3 min, t_r (minor) = 15.6 min.

(1S,3aS,4R,6aR)-Dimethyl 1-benzoyl-3-oxo-4-phenyltetrahydro-1H-cyclopenta[c]furan-5,5(3H)-dicarboxylate: a yellow oil; $[\alpha]_D^{23}$ (*c* 0.5, CHCl₃) = -49.2; ¹H NMR (400 MHz, CDCl₃): δ = 8.02 (d, *J* = 7.6 Hz, 2H); 7.69 (d, *J* = 7.6 Hz, 1H); 7.54–7.66

(m, 2H); 7.22–7.32 (m, 5H); 5.94 (d, $J = 6.8$ Hz, 1H); 4.55 (d, $J = 4.8$ Hz, 1H); 4.23 (t, $J = 11.2$ Hz, 1H); 3.69 (s, 3H); 3.56 (dd, $J = 8.8, 4.4$ Hz, 1H); 3.11 (s, 3H); 2.41 (dd, $J = 14.4, 4.0$ Hz, 1H); 1.84 (dd, $J = 14.4, 6.4$ Hz, 1H);. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 192.3, 176.6, 170.1, 170.0, 138.9, 134.5, 134.2, 129.9, 128.4, 128.2, 128.1, 127.6, 79.6, 67.7, 53.0, 52.9, 52.7, 52.1, 44.2, 35.9$. IR (film): ν_{max} 2954, 1786, 1730, 1599, 1433, 1216, 1022 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}_7$ ($\text{M}+\text{H}$) $^+$: 423.1444, Found: 423.1440; 96:4 *er* as determined by HPLC (Chiralcel OJH, 70:30 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 40.0 min, t_r (minor) = 62.3 min.

(1R,2S,6R)-Methyl 2-(2-(furan-3-yl)-2-oxoethyl)-3,3-dimethyl-6-phenylcyclohexanecarboxylate: a white solid; $[\alpha]_{\text{D}}^{23}$ (c 0.5, CHCl_3) = -78; ^1H NMR (400 MHz, CDCl_3): $\delta = 8.09$ (dd, $J = 1.2, 0.8$ Hz, 1H); 7.43 (t, $J = 1.6$ Hz, 1H); 7.14–7.25 (m, 5H); 6.77 (q, $J = 0.8$ Hz, 1H); 3.33 (s, 3H); 3.28–3.21 (m, 1H); 3.11 (dd, $J = 18.4, 4.4$ Hz, 1H); 2.94 (dd, $J = 18.4, 6.0$ Hz, 1H); 2.80–2.84 (m, 2H); 1.52–1.72 (m, 3H); 1.31–1.35 (m, 1H); 1.25 (s, 3H); 0.88 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 193.4, 174.7, 146.7, 144.8, 144.0, 128.4, 127.6, 127.2, 126.3, 108.7, 51.4, 47.4, 40.9, 39.7, 36.9, 34.1, 33.2, 29.3, 26.4, 23.5$. HRMS(ESI) calcd for $\text{C}_{22}\text{H}_{27}\text{O}_4\text{NCl}$ ($\text{M}+\text{H}$) $^+$: 355.1904, Found: 355.1908. 90.5:9.5 *er* as determined by HPLC (Chiralcel ODH, 98:02 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 14.5 min, t_r (minor) = 11.9 min.

(S)-5-Benzyl-2-(2,6-dimethoxyphenyl)-6,6-diethyl-6,8-dihydro-5H-

[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate a yellow solid; $[\alpha]_D^{23}$ (c 1.06, CHCl_3) = +3.7; ^1H NMR (400 MHz, CDCl_3): δ = 8.44 (s, 1H); 7.43 (t, J = 8.8 Hz, 1H); 7.19–7.30 (m, 3H); 7.12 (d, J = 7.2 Hz, 2H); 6.62 (d, J = 8.8 Hz, 2H); 5.25 (dd, J = 10.8, 4.4 Hz, 1H); 5.11 (d, J = 17.2 Hz, 1H); 4.92 (d, J = 17.2 Hz, 1H); 3.80 (s, 6H); 3.43 (dd, J = 14.0, 4.4 Hz, 1H); 2.92 (dd, J = 14.0, 11.2 Hz, 1H); 1.78–2.04 (m, 3H); 1.58 (dd, J = 15.6, 7.2 Hz, 2H); 1.10 (t, J = 7.6 Hz, 3H); 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 155.4, 148.3, 144.9, 134.4, 133.5, 129.9, 129.2, 127.9, 112.0, 104.3, 78.9, 61.8, 56.5, 56.4, 36.8, 25.3, 21.9, 7.3, 6.9 ppm. IR (film): ν_{max} 1590, 1525, 1419, 1064, 1034, 928, 850 cm^{-1} . HRMS(ESI) calcd for $\text{C}_{24}\text{H}_{30}\text{O}_3\text{N}_3$ (M) $^+$: 408.2287, Found: 408.2287.

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Chapter 3

Enantioselective Nucleophilic β -Carbon Amination of Enals: Carbene-Catalyzed Formal [3+2] Reactions to Pyrazolidinones

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3.1 Introduction

Pyrazolidinones are an important class of *N*-containing heterocycles, owing to the fact that they are core structural units of numerous natural products, pharmaceuticals, biologically active compounds.^[1] Aside from their potential development in drug discovery, chiral pyrazolidinones have attracted particular attention in synthetic chemistry. For example, they serve as useful building blocks in organic synthesis as precursors of β -amino acid derivatives upon N-N bond cleavage.^[2] Interestingly, the optically pure pyrazolidinones have also demonstrated their reactivity as organocatalysts to promote the Diels-Alder reaction and kinetic resolution of alcohols.^[3] Despite their multifaceted applications, general synthetic methods for producing chiral pyrazolidinones from chiral materials or by optical resolution remain scarce,^[4] and thus the asymmetric synthesis of the pyrazolidinone core structure is highly desirable. The key challenge in the preparation of a chiral pyrazolidinone is the installation of the β -carbon stereocenter of the carbonyl group. In particular, construction of a C-N bond in an enantioselective manner can provide an efficient access to an amino substituted chiral carbon.

Over the last decade, *N*-heterocyclic carbenes (NHCs) have emerged as one of the most powerful organocatalysts demonstrating great versatility and selectivity to facilitate C-N bond formations through reactive intermediates such as homoenolate species.^[5] Scheidt^[6a] was the first to demonstrate a direct electrophilic amination of enals via the formal [3+2] annulation of diazenes with NHC-generated homoenolates.

The (+/-)-pyrazoline-3-ones were obtained in 61-84% yield (Scheme 3-1). Later, Ying,^[6b] Ma,^[6b] Zhong^[6c] and She^[6d] groups showed that nitrosobenzenes were also competent electrophiles for homoenolates to afford β -amination products. It is worth noting that in these reports, the nitrogen agents behaved as electrophiles to capture the nucleophilic homoenolate.

Scheme 3-1 Scheidt's electrophilic amination of enals.

On the other hand, an α,β -unsaturated acyl azolium is another representative intermediate in NHC catalysis generated by the oxidation of the homoenolate or other methods.^[7] The electrophilic β -carbon can react with various nucleophiles to provide a general approach for β -carbon functionalizations. To date, many types of nucleophiles have been utilized in the addition to this intermediate, such as enols (derived from the 1,3-dicarbonyl compounds, kojic acids, naphthols *etc*), enamines, or activated sulfur ylides (Scheme 3-2). These reports mainly involve soft carbon nucleophiles. Somewhat unfortunately, the N-containing agents as competent nucleophiles for a direct C-N bond construction via unsaturated acyl azolium **II** (nucleophilic amination process) have rarely been explored. The intrinsic problems are apparent: (1) the low electrophilicity of the β -carbon, making it a weak Michael acceptor; (2) the favorable acylation pathway, which would deliver the ester, or amide more easily (Scheme 3-3).^[7g]

Scheme 3-2 Carbon nucleophiles used to trap unsaturated acyl azolium.

Scheme 3-3 NHC-catalyzed β -carbon functionalizations.

Herein, in this chapter, we document our initial study on NHC-catalyzed nucleophilic β -amination of enals through a formal [3+2] annulation. The reaction is achieved through the aza-Michael addition of a nucleophilic nitrogen atom to the NHC-bound unsaturated acyl azolium as the key step, leading to pyrazolidinones in excellent

yield and enantioselectivity. In addition, the N-N bond of the pyrazolidinone adducts can easily be cleaved, affording β -amino acid derivatives highly efficiently.^[8]

Scheme 3-4 This work: nucleophilic β -carbon amination.

3.2 Results and Discussions

In our initial study, we chose a readily available N,N'-bistosylhydrazide (**3-2a**) as a model substrate to avoid the regioselectivity problem due to the different substituents on the hydrazines. The Ts protecting group would enhance the acidity of the N-H proton to assist the aza-Michael addition step under basic conditions.^[9] Firstly, the efficiency of several carbene precursors was examined in the presence of K_2CO_3 and quinone oxidant, as pioneered by Studer group.^[7a-c] 4 Å molecular sieves was used to remove the trace amount of water in the reactions. Gratifyingly, the triazolium salt **A** promoted the reaction and gave the desired product in 45% yield and 88:12 er using THF as the solvent (Table 3-1, entry 1). Replacing **A** with other pre-catalysts **B-E** also gave good results (entries 2-5), among which **B** proved to be the best in terms of yield and enantioselectivity (71% yield and 97:3 er respectively) (entry 2). Further screening of bases, including organic bases (DIEA, DBU, DABCO) and inorganic bases (Cs_2CO_3 and K_3PO_4), could not improve the enantioselectivity (88:12 to 96:4 er) and yield (25-53% yield) (entries 6-10). With strong bases, such as Cs_2CO_3 and DBU, the hydrazide

3-2a was easily consumed due to decomposition under basic conditions,^[10] resulting in lower yield (entries 6 and 9). Finally, increasing the amount of hydrazide to 2.0 equivalents under the same conditions as entry 2 gave the best result, with the product **3-3a** obtained in 88% yield and 97:3 er (entry 11). (For more condition optimization, please see Table 3-S1 and 3-S2 in the experimental section.)

Table 3-1 Conditions screening for the reaction of **3-1a** with **3-2a**.^[a]

Entry	NHC	Base	Yield [%] ^[b]	<i>E.r.</i>
1	A	K ₂ CO ₃	45	88:12
2	B	K ₂ CO ₃	71	97:3
3	C	K ₂ CO ₃	66	95:5
4	D	K ₂ CO ₃	61	96:4
5	E	K ₂ CO ₃	61	92:8
6	B	Cs ₂ CO ₃	45	88:12
7	B	K ₃ PO ₄	53	96:4
8	B	DIEA	51	94:6
9	B	DBU	25	92:8
10	B	DABCO	42	95:5
11 ^[c]	B	K ₂ CO ₃	92 (88) ^[d]	97:3

[a] Reaction conditions: **3-1a** (0.05 mmol, 1.0 equiv), **3-2a** (1.5 equiv), NHC (20 mol%), base (2 equiv) and oxidant (1.2 equiv), 4Å MS (50 mg) in 1 mL of THF. [b] NMR yield based on **3-1a** by using 1,3,5-trimethoxybenzene as an internal standard. [c] 2 equiv of **3-2a** was used. [d] Isolated yield in parenthesis.

With acceptable conditions in hand (Table 3-1, entry 11), the substrate scope of the reaction was explored (Table 3-2). The reaction could accommodate a broad range

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of aryl enals **3-1**. For example, installation of various electron-withdrawing (**3-1b-e**) or electron-donating substituents (**3-1f-g**) at the *para*-position of the aromatic ring was all tolerated, delivering the corresponding cycloadducts **3-3b-g** in 77-81% yield and excellent er. The absolute configuration of **3-3d** was established as *S* by X-ray crystallography analysis. Placing the substituents at the *meta* or *ortho* position on the phenyl ring of the enal had no significant effect on the enantioselectivities of the products (**3-3h-i**), albeit with slightly dropped yields (54-67%). To our delight, naphthyl (**3-1j**) and the heteroaromatic substituted enals, such as furyl (**3-1k**), thienyl (**3-1l**) or pyridinyl (**3-1m**) could also work well to give the corresponding products **3-3j-l** in moderate to excellent yield and er. Notably, enals with easily transformable functional groups such as 4-COOMe, and 4-OAllyl were also well tolerated, furnishing the corresponding products **3-3n-o** in good yields and high enantioselectivities (94%, 97:3 er and 74%, 97:3 er, respectively). Further expanding the reaction scope revealed that the protecting group of the hydrazine could be extended to other sulfonyl groups. For example, the phenyl sulfonyl protected hydrazide furnished the corresponding product **3-3p** in 76% yield and 95:5 er. We also tested other protecting groups, such as Boc (*t*-butyloxycarbonyl), while no desired product was obtained. In this case, most of the enal and hydrazide substrates remained unreacted in the reaction content. Hydrazide with Ns (4-nitrobenzenesulfonyl) as the protecting group was further examined. Under basic conditions, the Ns-substituted hydrazide was easily decomposed, and no desired amination product was observed (Table 3-2).

Table 3-2 Substrate scope of reactions of aromatic enals with hydrazide.^[a]

[a] Reaction conditions: **3-1** (0.05 mmol, 1.0 equiv), **3-2** (2.0 equiv), NHC **B** (20 mol%), K₂CO₃ (2 equiv) and oxidant **DQ** (1.2 equiv), MS (100 mg) in 2 mL of THF; Yields (after SiO₂ chromatography purification) based on enal **3-1** [b] PMP = *p*-methoxyphenyl.

Changing the β-aryl group of the enal to an alkyl substituent (Table 3-3), we observed a decrease in the enantioselectivity (**3-3r**, 87:13 er). We then turned to further optimization of the reaction conditions for **3-1r** and **3-2a** (Table 3-3). Gratifyingly, after examining various NHC catalysts and different solvents, we found that the reactions

performed with higher er (91:9 er) using triazolium salt **D** in toluene instead of the original conditions established in Table 3-1 (63%, 87:13 er), albeit in slightly decreased yield (59% isolated yield).

Table 3-3 Condition Optimization of the reaction between 3-1r and 3-2a.

[a] Conditions: **3-1r** (0.05 mmol, 1.0 equiv), **3-2a** (0.10 mmol, 2.0 equiv) NHC (20 mol%), K₂CO₃ (2 equiv) and **DQ** oxidant (1.2 equiv), MS (50 mg) in 1 mL of THF at RT for 16 h; [b] NMR yield based on **3-1r** by using 1,3,5-trimethoxybenzene as an internal standard.

The substrate scope with alkyl enals was then studied with the optimized conditions as in Table 3-4. Generally, the corresponding products can be obtained in moderate yields and good enantioselectivities (**3-3r-v**). Interestingly, enals containing the relative bulkier alkyl substituents led to better stereoselectivity (**3-3u-v**). For

example, the cyclohexyl substituted enal delivered the annulation product **3-3v** in 94:6 er. Finally, α,β -disubstituted enal **3-1w** was also examined. Under the standard reaction conditions with the NHC precursor **D**, a trace amount of the product was obtained. Careful investigation of the conditions revealed the superior performance of catalyst **E**, which afforded **3-3w** in 75% yield with 6:1 dr and 91:9 er. (For details, see Experimental section, Table 3-S4)

Table 3-4 Formal [3+2] annulations of the alkyl-enal with hydrazide **3-2a**.^[a]

[a] **3-1** (0.10 mmol), **3-2a** (0.20 mmol), NHC **D** (20 mol%), K_2CO_3 (0.2 mmol), **DQ** (1.2 equiv) and 4 Å MS (100 mg) in toluene (2 mL) at RT for 16 h; yields (after SiO_2 chromatography purification) based on enal **3-1**; [b] Conditions as in Table 3-1, entry 11; [c] Catalyst **E** was used instead of **D**.

Notably, the model reaction between **3-1a** and **3-2a** could be easily scaled up to gram-scale with a lower catalyst loading (12 mol%). The product **3-3a** (2.9 g) was

obtained in 78% yield and without erosion of the er value (97:3 er), demonstrating the synthetic utility of this approach (Scheme 3-5).

Scheme 3-5 Gram-scale reaction.

The optically active pyrazolidinone products are not only significant in drug discovery, but are also useful synthetic blocks in organic synthesis. The enantiomerically enriched product **3-3** obtained by our catalytic reaction underwent further transformations under simple conditions. For example, the pyrazolidinone **3-3a** could be reduced to access the pyrazolidine-3-ol **3-4** in 81% yield and 96:4 er. The alcohol **3-4** was further reduced with $BF_3 \cdot Et_2O$ and Et_3SiH to the pyrazolidine **3-5** in 83% yield without erosion of the er. It is worth noting that both the structures of **3-4** and **3-5** are privileged heterocycles in natural products and bioactive compounds. The Ts protecting group of **3-3a** could be removed by $Mg/MeOH$ to give the compound **3-6**. Subjection of **3-6** to Raney Ni/H_2 provided the β^3 -amino-acid derivative **3-7**, which was widely present in drugs,^[11] bioactive compounds^[12] and building units for peptidic foldamers.^[13]

Scheme 3-6 Synthetic transformations of pyrazolidinone **3-3a**.

3.3 Summary

In summary, we have developed a highly efficient approach for the enantioselective preparation of pyrazolidinone products. Our method involves a rarely explored aza-Michael addition of enals via oxidative NHC catalysis as the key step, which provides an efficient β -carbon amination protocol for unsaturated aldehyde via direct asymmetric C-N bond formation. Moreover, the heterocycle products obtained by our catalytic reaction can readily undergo further transformations to afford various useful functional molecules, such as pyrazolidines and β -amino acid derivatives. Considering most of the reported NHC-catalyzed reactions are focused on the C-C bond constructions, we expect this study on the C-N bond formations would inspire further reaction development in NHC organocatalysis. Further reaction development using tunable benzoyl group protected hydrazides, and N-heterocycle containing bisnucleophiles to synthesize useful functional molecules for bioactivity evaluation are in progress in our laboratory.

3.4 Experimental Section

3.4.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. HPLC grade CH₃CN (purchased from TEDIA) was dried over 4Å molecular sieve prior use. Toluene and CH₂Cl₂ was dried over Pure Solv solvent purification system. THF was distilled over sodium. Other solvents were dried over 4Å molecular sieve prior use. Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in 10 mL Schlenk tube.

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Bruker (400 MHz) spectrometer and JEOL-ECX-500 (500 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). 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 (¹³C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer and JEOL-ECX-500 (125 MHz) spectrometer. IR spectra were recorded on a Shimadzu IR IRAffinity-1 FT-IR Spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of enantiomeric excess 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: $[\alpha]_D^{rt}$ (c is in gm 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). The TLC plate was visualized using a UV lamp or potassium permanganate stain. Hydrazides were prepared according to literature procedures.^[14]

3.4.2 Experimental section.

a) Additional Condition Optimizations.

I. Condition optimization (additional results) of the model reaction.

Table 3-S1 NHC Catalysts^[a, b]

[a] Conditions: **3-1a** (0.05 mmol, 1.0 equiv), **3-2a** (1.5 equiv) NHC **B** (20 mol%), K₂CO₃ (2 equiv) and oxidant (1.2 equiv), MS (50 mg) in 1 mL of THF at RT for 16 h; [b] NMR yield based on **3-1a** by using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-S2 Bases and solvents^[a]

Entry	Base	Solvent	Yield (%) ^[b]	<i>E.r.</i>
1	Cs ₂ CO ₃	THF	45	88:12
2	DIEA	THF	51	94:6
3	Et ₃ N	THF	44	92:8
4	Na ₂ CO ₃	THF	35	95:5
5	K ₃ PO ₄	THF	53	96:4
6	DBU	THF	25	92:8
7	DABCO	THF	42	95:5
8	KHCO ₃	THF	N.R.	-
9	K ₂ HPO ₄	THF	N.R.	-
10	KH ₂ PO ₄	THF	N.R.	-
11	K₂CO₃	THF	71	97:3
11	K ₂ CO ₃	Toluene	51	96:4
12	K ₂ CO ₃	DCE	trace	-
13	K ₂ CO ₃	Et ₂ O	trace	-
14	K ₂ CO ₃	Dioxane	46	95:5
15	K ₂ CO ₃	CHCl ₃	trace	-

[a] Reaction conditions: **3-1a** (0.05 mmol, 1.0 equiv), **3-2a** (1.5 equiv) NHC **B** (20 mol%), Base (2 equiv) and oxidant (1.2 equiv), MS (50 mg) in 1 mL of solvent at RT for 16 h; [b] NMR yield based on **3-1a** by using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-S3 Screening of additives and equivalents of the hydrazide **3-2a**^[a]

Entry	Additives	Hydrazine (x equiv.)	Yield (%) ^[b]	E.r
1	LiCl	1.5	55	95:5
2	HOBt	1.5	41	95:5
3	Sc(OTf) ₃	1.5	44	92:8
4	-	1.5	71	97:3
5	-	1.2	56	97:3
6	-	2.0	92 (88)^[c]	97:3
7	-	3.0	89	97:3

[a] Conditions: **3-1a** (0.05 mmol, 1.0 equiv), **3-2a** (x equiv) NHC **B** (20 mol%), K₂CO₃ (2 equiv) and oxidant **DQ** (1.2 equiv), 4Å MS (50 mg) in 1 mL of THF at RT for 16 h. [b] NMR yield based on **3-1a** by using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield in parenthesis.

Table 3-S4 Condition Optimization of the reaction between **3-1w** and **3-2a**.

 trace	 N.R.	 73% yield	 61% yield, 2:1 d.r.(92:8; 93:7 e.r.)	
 69% yield 6:1 d.r., (91:9; 91:9 e.r.)	 72% (71% isolated) yield, 6:1 d.r., (91:9; 92:8 e.r.)	 65% yield, 3:1 d.r., (94:6; 96:4 e.r.)		

[a] Conditions: **3-1w** (0.05 mmol, 1.0 equiv), **3-2a** (0.10 mmol), NHC (20 mol%), K₂CO₃ (2 equiv) and oxidant **DQ** (1.2 equiv), 4Å MS (50 mg) in 1 mL of THF; [b] NMR yield based on **1w** by using 1,3,5-trimethoxybenzene as an internal standard.

b) General procedure for the catalytic reactions of enal (3-1) with *N*-tosyl hydrazide (3-2) to synthesize product 3-3

A dry 10 mL Schlenk tube with stir bar was charged with hydrazide **3-2** (0.20 mmol, 2.0 equiv), NHC **B** (7.6 mg, 20 mol%), K₂CO₃ (27.6 mg, 0.2 mmol, 2 equiv), **DQ** (48.9 mg, 0.12 mmol, 1.2 equiv.) and 4Å molecular sieves (100 mg). The tube was evacuated, and refilled with nitrogen. Then enal **3-1** (0.10 mmol, 1.0 equiv.) was added and the mixture was dissolved with newly distilled solvent THF (2.0 mL). Then the mixture was stirred at room temperature for 16 h when the substrate was consumed completely (monitored by TLC). The mixture was concentrated under vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate) to afford desired product **3**, which was confirmed by ¹H NMR, ¹³C NMR spectra, and the enantiomeric excess was determined by chiral HPLC.

Note: Racemic samples for chiral phase HPLC analysis were prepared using NHC below as the NHC precatalyst according to the procedure as above.

c) Stereochemistry determination of 3-3d via X-ray crystallographic analysis:

Product **3-3d** was crystallized as a colorless crystal *via* evaporation of a hexane/ethyl acetate solution, and its absolute configuration was determined by X-ray

structure analysis. CCDC 1480139 contains the supplementary crystallographic data that can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

d) Proposed reaction pathway and stereo-chemical modes.

Scheme 3-S1

Based on our work and previous study, we proposed a reaction pathway for the formation of product **3-3** as illustrated in Scheme 3-S1. First, the α,β -unsaturated acyl azolium **I** was generated via the oxidation of Breslow intermediate by **DQ** as the oxidant. Then an aza-Michael addition of hydrazide to **I** would afford intermediate **II**.

Subsequently, an intramolecular lactamization after proton transfer provided the final product **3-3** and released the carbene catalyst. The stereo-outcome of the reaction could be explained as the transient state **TS A** showed in Scheme 3-S1, considering the structure of the NHC-bound acyl azolium ion, in which the front face is shielded by the benzyl group of the catalyst.

e) Synthetic transformations of catalytic reaction product **3-3a**.

Gram-scale preparation of **3-3a**.

Under N_2 atmosphere, to a dry 2-neck flask equipped with a magnetic stir bar were added triazolium salt **B** (363.8 mg, 12 mol%), hydrazide **3-2a** (5.44 g, 16 mmol, 2 equiv), **DQ** (3.59 g, 1.1 equiv), K_2CO_3 (2.21 g, 2 equiv) and molecular sieves (500 mg). Then enal **3-1a** (1.06 g, 8.0 mmol, 1.0 equiv) was added and the mixture was dissolved with newly distilled THF (40.0 mL). The reaction mixture was stirred at room temperature until the enal **3-1a** was consumed completely (monitored by TLC). After concentrated under reduced pressure, the crude residue was purified via column chromatography to afford the desired product **3-3a** (2.93 g) with 78% yield and 97:3 er.

Reduction of **3-3a** to pyrazolidin-3-ol **3-4**:

Under N₂ atmosphere, a solution of **3-3a** (47.0 mg, 0.10 mmol) in CH₂Cl₂ (2.0 mL) was stirred at 0 °C, followed by the drop-wise addition of DIBAL-H (1.0 M in THF, 4.0 mL, 0.4 mmol). The mixture was then warmed to room temperature and continued to stir for 2 h until the consumption of **3-3a** (monitored by TLC). The reaction was quenched with brine and extracted with CH₂Cl₂ for 3 times. The combined organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The pure product **3-4** was obtained via SiO₂ flash chromatography (Hexane/Ethyl Acetate = 2:1) as a white solid (81% yield, >20:1 dr, 97:3 er).

Transformation of **3-4** to pyrazolidine **3-5**:

Under N₂ atmosphere, a solution of **3-4** (23.6 mg, 0.05 mmol, 1.0 equiv) in CH₂Cl₂ (2.0 mL) was stirred at 0 °C, followed by addition of BF₃·Et₂O (21 uL, 0.0165 mmol) and Et₃SiH (17.4 mg, 3 equiv). The mixture was then warmed to room temperature and continued to stir for 12h. The reaction was quenched with saturated NaHCO₃ and extracted with CH₂Cl₂ for 3 times. The combined organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified via SiO₂ flash chromatography (Hexane/Ethyl Acetate = 2:1) to afford **3-5** (19.2 mg, 83% yield, 97:3 er) as a white solid.

Deprotection of **3a** to **6**^[15]:

To a dry Schlenk tube equipped with a magnetic stir bar, were added **3-3a** (47.0 mg, 0.1 mmol) and Mg-powder (28.8 mg, 12 equiv). The tube was capped with a septum, evacuated, and refilled with Ar for 3 times. Then, absolute MeOH (4 mL) was added and the reaction was sonicated at room temperature until no more starting material remained monitored by TLC (around 25-30 min). The solution was cooled to 0 °C and slowly quenched with saturated NH₄Cl. The aqueous phases were extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with saturated brine (20 mL), then dried over MgSO₄, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 12:1) to afford **3-6**^[16] (10.4 mg, 65%) as a white solid.

N-N bond cleavage of **6** to **3-7**:

To a Schlenk tube equipped with a magnetic stir bar were added **3-6** (8.2 mg, 0.05 mmol), Raney Ni (150 mg, washed twice with EtOH before added) and EtOH (2 mL). The tube was filled with H₂ (~1 atm, balloon) and refluxed for 40 min. The reaction

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mixture was then passed through a short pad of celite, and then washed with EtOH extensively. The filtrate was concentrated under reduced pressure to afford the nearly pure product **3-7**^[17] (indicated from the crude ¹H NMR), which could further be purified by simple wash with cold Et₂O (7.8 mg, 94% yield, 97:3 er).

Product **3-7** was derivatized for HPLC analysis: To the solution of amide **3-7** (4.1 mg, 0.025 mmol, 1.0 equiv) in CH₂Cl₂ were added triethylamine (8 μL, 2 equiv), DMAP (cat) and the mixture was cooled in an ice bath. Tosyl chloride (5.2 mg, 1.1 equiv) was added and the mixture was stirred at 0 °C until TLC showed complete consumption of starting material. The mixture was diluted with CH₂Cl₂ and washed with water. The organic phase was dried with MgSO₄ and concentrated to give the crude product, which was purified by column to give the N-Ts protected amide **3-8**^[18].

HPLC analysis: 97 : 3 e.r. (Chiralcel IB, 20:80 *i*PrOH/Hexane, 0.5 mL/min), Rt (major) = 29.2 min, Rt (minor) = 48.2 min.

3.4.3 Characterization of Products

(S)-5-Phenyl-1,2-ditosylpyrazolidin-3-one (3-3a):

A white solid; M.p. 165-166 °C; **¹H NMR** (500 MHz, CDCl₃) δ = 7.80 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.33 – 7.24 (m, 3H), 7.18 (d, J = 7.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 5.43 (d, J = 8.5 Hz, 1H), 2.55 – 2.35 (m, 8H). **¹³C NMR** (126 MHz, CDCl₃) δ = 173.1, 146.3, 145.4, 136.6, 133.7, 131.2, 130.4, 129.5, 129.20, 129.16, 128.9, 128.5, 126.7, 61.7, 35.3, 21.8, 21.7 ppm.

IR (film): ν_{max} 2934, 2925, 2872, 1764, 1736, 1638, 1616, 1596, 1451, 1389, 1373, 1244, 1190, 1168, 1152, 1136, 1121, 1086 cm⁻¹.

HRMS (ESI): calculated for [C₂₃H₂₃N₂O₅S₂]⁺: m/z = 471.1048, found: m/z = 471.1044.

$[\alpha]_{\text{D}}^{25}$ = +92.5 (c = 1.0 in CHCl₃).

HPLC analysis: 97 : 3 e.r. (Chiralcel IA, 20:80 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 29.2 min, R_t (minor) = 48.2 min.

(S)-5-(4-Fluorophenyl)-1,2-ditosylpyrazolidin-3-one (3-3b):

A white solid; Mp 216-220 °C; **¹H NMR** (500 MHz, CDCl₃) δ = 7.78 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.19 – 7.11 (m, 4H), 6.94 (t, *J* = 8.5 Hz, 2H), 5.41 (d, *J* = 8.0 Hz, 1H), 2.52 – 2.45 (m, 4H), 2.44 – 2.37 (m, 4H). **¹³C NMR** (126 MHz, CDCl₃) δ = 173.0, 162.72 (d, *J* = 249.5 Hz), 146.5, 145.6, 133.7, 132.36 (d, *J* = 2.5 Hz), 131.0, 130.4, 129.4, 129.2, 129.1, 128.57 (d, *J* = 8.8 Hz), 115.83 (d, *J* = 12.7 Hz), 61.1, 35.3, 21.8, 21.7 ppm.

IR (film): ν_{max} 2953, 2927, 2859, 1760, 1638, 1617, 1604, 1597, 1509, 1385, 1375, 1341, 1171, 1187 cm⁻¹.

HRMS (ESI): calculated for [C₂₃H₂₂FN₂O₅S₂]⁺: *m/z* = 489.0954, found: *m/z* = 489.0951.

[α]_D²⁵ = +120.8 (*c* = 1.0, CHCl₃).

HPLC analysis: 97:3 e.r. (Chiralcel IA, 30:70 *i*PrOH/Hexane, 0.8 mL/min), *R*_t (major) = 10.6 min, *R*_t (minor) = 15.2 min.

(*S*)-5-(4-Chlorophenyl)-1,2-ditosylpyrazolidin-3-one (3-3c):

A white solid; Mp 208-211 °C; **¹H NMR** (500 MHz, CDCl₃) δ = 7.81 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 5.40 (d, *J* = 6.0 Hz, 1H), 2.49 – 2.43 (m, 5H),

2.42 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ = 173.1, 146.5, 145.7, 135.0, 134.7, 133.6, 131.0, 130.4, 129.5, 129.3, 129.03, 128.96, 128.1, 61.0, 34.9, 21.8, 21.7 ppm.

IR (film): ν_{max} 2977, 2954, 2926, 1759, 1638, 1617, 1595, 1492, 1403, 1385, 1375, 1306, 1296, 1214, 1191, 1189, 1155, 1086, 1012, 975 cm⁻¹.

HRMS (ESI): calculated for [C₂₃H₂₂ClN₂O₅S₂]⁺: m/z = 505.0659, found: m/z = 505.0656.

[α]_D²⁵ = +121.7 (c = 1.0, CHCl₃)

HPLC analysis: 95:5 e.r. (Chiralcel IA, 30:70 *i*PrOH/Hexane, 0.8 mL/min), Rt (major) = 11.5 min, Rt (minor) = 15.9 min.

(S)-5-(4-Bromophenyl)-1,2-ditosylpyrazolidin-3-one (3-3d):

A white solid; Mp 185-188 °C; **¹H NMR** (500 MHz, CDCl₃) δ = 7.82 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 5.38 (d, *J* = 6.0 Hz, 1H), 2.51 – 2.44 (m, 5H), 2.43 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ = 173.1, 146.5, 145.7, 135.5, 133.5, 132.0, 130.9, 130.4, 129.5, 129.3, 128.9, 128.4, 122.9, 61.0, 34.8, 21.9, 21.7 ppm.

IR (film): ν_{max} 2942, 2950, 1759, 1635, 1617, 1385, 1376, 1169 cm⁻¹.

HRMS (ESI): calculated for $[\text{C}_{23}\text{H}_{22}\text{BrN}_2\text{O}_5\text{S}_2]^+$: $m/z = 551.0133$, found: $m/z = 551.0128$.

$[\alpha]^{25}_{\text{D}} = +130.8$ ($c = 1.0$, CHCl_3).

HPLC analysis: 96:4 e.r. (Chiralcel IA, 30:70 i PrOH/Hexane, 0.8 mL/min), R_t (major) = 12.1 min, R_t (minor) = 16.6 min.

(S)-5-(4-Nitrophenyl)-1,2-ditosylpyrazolidin-3-one (3-3e):

A white solid; Mp 218-220 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) $\delta = 7.81$ (d, $J = 8.0$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.41 – 7.36 (m, 2H), 7.19 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 7.07 (d, $J = 8.5$ Hz, 2H), 5.40 (d, $J = 6.0$ Hz, 1H), 2.50 – 2.44 (m, 5H), 2.42 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) $\delta = 172.5, 147.9, 146.8, 146.1, 143.6, 133.9, 130.6, 130.5, 129.5, 129.4, 129.1, 127.7, 124.1, 61.0, 35.7, 21.9, 21.7$ ppm.

IR (film): ν_{max} 2923, 2855, 1768, 1636, 1617, 1521, 1375, 1121 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_7\text{S}_2]^+$: $m/z = 516.0899$, found: $m/z = 516.0901$.

$[\alpha]^{20}_{\text{D}} = +112.3$ ($c = 1.0$, CHCl_3).

HPLC analysis: 94:6 e.r. (Chiralcel IA, 30:70 i PrOH/Hexane, 0.8 mL/min), R_t (major) = 19.6 min, R_t (minor) = 29.4 min.

(S)-5-*p*-Tolyl-1,2-ditosylpyrazolidin-3-one (3-3f):

A white solid; Mp 184-186 °C; ¹H NMR (500 MHz, CDCl₃) δ = 7.79 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.90 – 7.10 (m, 4H), 5.37 (d, *J* = 8.0 Hz, 1H), 2.45 (s, 3 H), 2.31 – 2.43 (m, 8H). ¹³C NMR (126 MHz, CDCl₃) δ = 173.3, 146.3, 145.3, 138.3, 133.6, 133.4, 131.1, 130.3, 129.4, 129.3, 129.28, 129.04, 126.5, 61.5, 34.9, 21.7, 21.6, 21.0 ppm.

IR (film): ν_{max} 2924, 2853, 1764, 1638, 1617, 1377, 1170 cm⁻¹.

HRMS (ESI): calculated for [C₂₄H₂₅N₂O₅S₂]⁺: *m/z* = 485.1205, found: *m/z* = 485.1195.

[α]_D²⁵ = +125.8 (*c* = 1.0, CHCl₃).

HPLC analysis: 99:1 e.r. (Chiralcel IA, 30:70 ⁱPrOH/Hexane, 0.8 mL/min), Rt (major) = 11.7 min, Rt (major) = 17.3 min.

(S)-5-(4-Methoxyphenyl)-1,2-ditosylpyrazolidin-3-one (3-3g):

A white solid; Mp 186-190 °C; ¹H NMR (500 MHz, CDCl₃) δ = 7.80 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.05

(d, $J = 8.5$ Hz, 2H), 6.75 (d, $J = 9.0$ Hz, 2H), 5.38 (d, $J = 8.5$ Hz, 1H), 3.81 (s, 3H), 2.52 – 2.30 (m, 8H). **^{13}C NMR** (126 MHz, CDCl_3) $\delta = 173.3, 159.8, 146.3, 145.3, 133.6, 131.2, 130.4, 129.4, 129.14, 129.08, 128.4, 128.0, 114.2, 61.4, 55.3, 35.1, 21.8, 21.7$ ppm.

IR (film): ν_{max} 2925, 2842, 1760, 1636, 1613, 1594, 1514, 1387, 1374, 1251, 1288, 1178, 1169 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_6\text{S}_2]^+$: $m/z = 501.1154$, found: $m/z = 501.1151$.

$[\alpha]_{\text{D}}^{25} = +131.9$ ($c = 1.0$, CHCl_3).

HPLC analysis: 98:2 e.r. (Chiralcel IA, 30:70 i PrOH/Hexane, 0.8 mL/min), R_t (major) = 14.5 min, R_t (minor) = 21.3 min.

(S)-5-(*m*-Tolyl)-1,2-ditosylpyrazolidin-3-one (3-3h)

A white solid. Mp 195-198 °C; **^1H NMR** (500 MHz, CDCl_3) $\delta = 7.82$ (d, $J = 7.5$ Hz, 2H), 7.59 (d, $J = 7.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.22 – 7.04 (m, 4H), 7.04 – 6.86 (m, 2H), 5.39 (d, $J = 8.5$ Hz, 1H), 2.58 – 2.33 (m, 8H), 2.27 (s, 3H). **^{13}C NMR** (126 MHz, CDCl_3) $\delta = 173.2, 146.3, 145.3, 138.6, 136.4, 133.6, 131.1, 130.4, 129.5, 129.3, 129.2, 129.1, 128.8, 127.3, 123.9, 61.6, 35.0, 21.8, 21.7, 21.4$ ppm.

IR (film): ν_{max} 2924, 2853, 1754, 1648, 1619, 1387, 1170 cm^{-1} .

HRMS (ESI): calculated for $[C_{24}H_{25}N_2O_5S_2]^+$: $m/z = 485.1205$, found: $m/z = 485.1199$.

$[\alpha]_D^{25} = +111.4$ ($c = 0.5$, $CHCl_3$).

HPLC analysis: 96:4 e.r. (Chiralcel IA, 30:70 i PrOH/Hexane, 0.8 mL/min), R_t (major) = 9.5 min, R_t (minor) = 16.5 min.

(S)-5-(2-Bromophenyl)-1,2-ditosylpyrazolidin-3-one (3-3i):

A white solid; Mp 195-198 °C; ^1H NMR (500 MHz, $CDCl_3$) $\delta = 8.13$ (d, $J = 8.5$ Hz, 2H), 7.95 (d, $J = 7.5$ Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 3H), 7.46 – 7.35 (m, 3H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.21 (td, $J = 7.5, 1.5$ Hz, 1H), 5.52 (dd, $J = 8.5, 2.5$ Hz, 1H), 2.49 (s, 3H), 2.44 (s, 3H), 2.41 – 2.29 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 171.9, 146.5, 145.9, 137.1, 134.6, 133.3, 130.5, 130.4, 130.0, 129.5, 129.4, 129.1, 128.3, 127.5, 121.4, 62.0, 38.7, 21.8, 21.82, 21.76$ ppm.

IR (film): ν_{max} 2922, 2852, 1764, 1638, 1617, 1595, 1372, 1193, 1181, 1169, 1163 cm^{-1} .

HRMS (ESI): calculated for $[C_{23}H_{22}BrN_2O_5S_2]^+$: $m/z = 551.0133$, found: $m/z = 551.0129$.

$[\alpha]_D^{25} = +127.1$ ($c = 1.0$, $CHCl_3$).

HPLC analysis: 96:4 e.r. (Chiralcel IC, 30:70 *i*PrOH/Hexane, 0.8 mL/min), Rt (major) = 21.7 min, Rt (minor) = 28.3 min.

(S)-5-(Naphthalen-2-yl)-1,2-ditosylpyrazolidin-3-one (3-3j):

A white solid. Mp 241-243 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.84 (t, *J* = 8.8 Hz, 2H), 7.62 – 7.46 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 6.53 (d, *J* = 8.0 Hz, 2H), 5.61 (d, *J* = 8.4 Hz, 1H), 2.69 (d, *J* = 18.0 Hz, 1H), 2.56 (dd, *J* = 18.0, 8.0 Hz, 1H), 2.49 (s, 3H), 2.02 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.4, 146.4, 145.2, 133.8, 133.1, 132.8, 131.3, 130.4, 129.8, 129.0, 128.8, 128.7, 128.2, 127.6, 126.9, 126.5, 125.9, 124.8, 61.6, 34.1, 21.8, 21.4.

IR (film): ν_{max} 2947, 2924, 2862, 1774, 1957, 1489, 1434, 1373, 1165, 1087, 1018, 972, 910, 817.

HRMS (ESI): calculated for [C₂₇H₂₅N₂O₅S₂]⁺: *m/z* = 521.1205, found: *m/z* = 521.1203.

[α]_D²⁵ = +31.8 (*c* = 1.0, CHCl₃).

HPLC analysis: 98:2 e.r. (Chiralcel IA, 25:75 *i*PrOH/Hexane, 0.6 mL/min), Rt (major) = 27.4 min, Rt (minor) = 41.6 min.

(S)-5-(Pyridin-3-yl)-1,2-ditosylpyrazolidin-3-one (3-3k):

A white solid; Mp 205.2 – 205.7 °C; ^1H NMR (400 MHz, CDCl_3) δ = 8.57 (d, J = 4.4 Hz, 1H), 8.34 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 3H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.17 (d, J = 8.4 Hz, 2H), 5.47 (t, J = 4.8 Hz, 1H), 2.56 – 2.51 (m, 2H), 2.48 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ = 172.6, 149.8, 148.1, 146.7, 145.9, 134.4, 133.7, 132.5, 130.8, 130.5, 129.5, 129.4, 129.1, 123.7, 59.8, 35.3, 21.8, 21.7 ppm.

IR (film): ν_{max} 2920, 2854, 1778, 1593, 1431, 1365, 1296, 1168, 1141, 1083, 1014, 975, 910 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}_5\text{S}_2]^+$: m/z = 472.1001, found: m/z = 472.1004.

$[\alpha]_{\text{D}}^{25}$ = +107.8 (c = 1.0, CHCl_3).

HPLC analysis: 97:3 e.r. (Chiralcel IA, 25:75 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 48.1 min, R_t (minor) = 59.0 min.

(S)-5-(Furan-2-yl)-1,2-ditosylpyrazolidin-3-one (3-3l):

A white solid; Mp 101-102 °C; ^1H NMR (500 MHz, CDCl_3) δ = 7.80 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.24 (dd, J = 3.5, 2.0 Hz, 1H), 6.13 (d, J = 3.5 Hz, 1H), 5.44 (t, J = 5.0 Hz, 1H), 2.47 (s, 3H), 2.44 – 2.39 (m, 5H). ^{13}C NMR (126 MHz, CDCl_3) δ = 172.8, 149.1, 146.5, 145.4, 143.7, 133.7, 130.9, 130.3, 129.5, 129.3, 129.2, 110.7, 109.3, 56.5, 34.5, 21.8, 21.7 ppm.

IR (film): ν_{max} 2924, 2853, 1766, 1636, 1617, 1596, 1492, 1452, 1374, 1192, 1085 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_6\text{S}_2]^+$: m/z = 461.0841, found: m/z = 461.0841.

$[\alpha]_{\text{D}}^{25}$ = +78.2 (c = 1.0, CHCl_3).

HPLC analysis: 93:7 e.r. (Chiralcel IA, 30:70 i PrOH/Hexane, 0.8 mL/min), R_t (major) = 11.0 min, R_t (minor) = 14.1 min.

(S)-5-(Thiophen-2-yl)-1,2-ditosylpyrazolidin-3-one (3-3m):

A white solid; Mp 78-80 °C; ^1H NMR (500 MHz, CDCl_3) δ = 7.85 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.30 (dd, J = 5.0, 1.0 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 6.82 (dd, J = 5.0, 4.0 Hz, 1H), 6.75 – 6.66 (m, 1H), 5.59 (d, J = 8.5 Hz, 1H), 2.62 (dd, J = 18.0, 8.0 Hz, 1H), 2.53 – 2.45 (m, 4H), 2.39 (s, 3H). ^{13}C NMR

(126 MHz, CDCl₃) δ = 172.7, 146.5, 145.3, 140.4, 133.3, 131.0, 130.4, 129.6, 129.2, 129.0, 127.2, 127.1, 126.0, 58.4, 36.5, 21.8, 21.7 ppm.

IR (film): $\nu_{\max}$ 2957, 2853, 1773, 1637, 1617, 1384, 1365, 1194, 1180, 1166, 1085 cm⁻¹.

HRMS (ESI): calculated for [C₂₁H₂₂N₂O₅S₃]: m/z = 477.0613, found: m/z = 477.0606.

$[\alpha]_D^{25}$ = +72.3 (c = 1.0, CHCl₃).

HPLC analysis: 97:3 e.r. (Chiralcel IA, 30:70 *i*PrOH/Hexane, 0.8 mL/min), R_t (major) = 12.0 min, R_t (minor) = 15.3 min.

Methyl (*S*)-4-(5-oxo-1,2-ditosylpyrazolidin-3-yl)benzoate (3-3n):

A white solid. Mp 214-216 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.90 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.46 (d, J = 7.2 Hz, 1H), 3.95 (s, 3H), 2.60 – 2.42 (m, 5H), 2.39 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 172.9, 166.3, 146.6, 145.7, 141.4, 133.7, 131.0, 130.42, 130.35, 130.1, 129.5, 129.3, 129.1, 126.7, 61.3, 52.3, 35.2, 21.8, 21.6 ppm.

IR (film): $\nu_{\max}$ 2947, 2924, 2862, 1774, 1720, 1597, 1489, 1435, 1373, 1288, 1134, 1087, 1018, 972, 910, 879, 817.

HRMS (ESI): calculated for $[C_{25}H_{25}N_2O_7S_2]^+$: $m/z = 529.1103$, found: $m/z = 529.1101$.

$[\alpha]^{25}_D = +111.0$ ($c = 1.0$, $CHCl_3$).

HPLC analysis: 97:3 e.r. (Chiralcel IA, 25:75 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 34.3 min, R_t (minor) = 50.3 min.

(S)-5-(4-(Allyloxy)phenyl)-1,2-ditosylpyrazolidin-3-one (3-3o):

A white solid. Mp 111-113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, $J = 8.0$ Hz, 2H), 7.61 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 2H), 6.82 – 6.73 (m, 2H), 6.06 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H), 5.51 – 5.24 (m, 3H), 4.53 (dt, $J = 5.2, 1.6$ Hz, 2H), 2.56 – 2.31 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 158.8, 146.3, 145.3, 133.7, 132.9, 131.3, 130.3, 129.4, 129.13, 129.11, 128.6, 128.0, 117.8, 115.0, 68.8, 61.4, 35.2, 21.7, 21.6.

IR (film): ν_{max} 3070, 2924, 2877, 2252, 1982, 1766, 1597, 1512, 1427, 1365, 1131, 1234, 1165, 1087, 1010, 972, 910, 817.

HRMS (ESI): calculated for $[C_{26}H_{27}N_2O_6S_2]^+$: $m/z = 527.1311$, found: $m/z = 527.1315$.

$[\alpha]^{25}_D = +91.7$ ($c = 1.0$, $CHCl_3$).

HPLC analysis: 97:3 e.r. (Chiralcel IA, 25:75 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 32.9 min, R_t (minor) = 48.1 min.

(S)-5-Phenyl-1,2-bis(phenylsulfonyl)pyrazolidin-3-one (3-3p):

A white solid; Mp 197 – 198 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 7.93 (dd, J = 8.0, 1.0 Hz, 2H), 7.76 – 7.70 (m, 3H), 7.63 – 7.53 (m, 3H), 7.36 – 7.30 (m, 3H), 7.30 – 7.27 (m, 2H), 7.19 – 7.15 (m, 2H), 5.46 (d, J = 8.5 Hz, 1H), 2.55 (dd, J = 18.0, 1.0 Hz, 1H), 2.43 (dd, J = 18.0, 8.5 Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 173.0, 136.5, 136.3, 135.0, 134.3, 134.1, 129.8, 129.5, 129.13, 129.05, 128.7, 128.6, 126.6, 61.7, 35.2 ppm.

IR (film): ν_{max} 2923, 2850, 1764, 1638, 1617, 1492, 1448, 1357, 1192, 1181, 1163, 1156, 1083 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_5\text{S}_2]^+$: m/z = 443.0735, found: m/z = 443.0727.

$[\alpha]_{\text{D}}^{25}$ = +105.8 (c = 1.0, CHCl_3).

HPLC analysis: 95:5 e.r. (Chiralcel IA, 30:70 i PrOH/Hexane, 0.8 mL/min), R_t (major) = 10.7 min, R_t (minor) = 17.2 min.

(S)-1,2-Bis(4-methoxyphenylsulfonyl)-5-phenylpyrazolidin-3-one (3-3q):

A white solid; Mp 88-90 °C; **¹H NMR** (500 MHz, CDCl₃) δ = 7.86 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 5.42 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.53 (dd, *J* = 18.0, 1.0 Hz, 1H), 2.45 (dd, *J* = 18.0, 8.5 Hz, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ = 173.3, 164.8, 164.0, 136.7, 131.7, 131.5, 128.9, 128.5, 127.8, 126.7, 125.1, 114.9, 113.7, 61.6, 55.8, 55.6, 35.2 ppm.

IR (film): ν_{max} 2942, 2924, 2843, 1761, 1638, 1617, 1593, 1575, 1496, 1459, 1372, 1262, 1193, 1089, 1015 cm⁻¹.

HRMS (ESI): calculated for [C₂₃H₂₃N₂O₇S₂]⁺: *m/z* = 503.0947, found: *m/z* = 503.0938.

[α]_D²⁵ = +100.2 (*c* = 1.0, CHCl₃).

HPLC analysis: 95:5 e.r. (Chiralcel IA, 30:70 *i*PrOH/Hexane, 0.8 mL/min), Rt (major) = 17.6 min, Rt (minor) = 34.8 min.

(*R*)-5-Propyl-1,2-ditosylpyrazolidin-3-one (3-3r):

A white solid; Mp 113 – 116 °C; **¹H NMR** (400 MHz, CDCl₃) δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.22 (td, *J* = 8.8, 5.6 Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 2.06 (dd, *J* = 18.0, 8.0 Hz, 1H), 1.82 (d, *J* = 18.0 Hz, 1H), 1.54 (ddd, *J* = 18.0, 13.6, 6.4 Hz, 1H), 1.41 – 1.28 (m, 2H), 1.18 – 1.08 (m, 1H), 0.88 (t, *J* = 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 174.3, 146.0,

145.8, 134.4, 131.4, 130.2, 129.5, 129.31, 129.25, 60.1, 36.9, 36.5, 21.8, 21.7, 18.7, 13.2 ppm.

IR (film): $\nu_{\max}$ 2958, 2931, 2873, 1766, 1597, 1492, 1458, 1369, 1168, 1087, 918, 813 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_5\text{S}_2]^+$: $m/z = 437.1205$, found: $m/z = 437.1221$.

$[\alpha]_{\text{D}}^{25} = +148.1$ ($c = 1.0$, CHCl_3)

HPLC analysis: 91:9 e.r. (Chiralcel IB, 15:85 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 20.2 min, R_t (minor) = 16.8 min.

(R)-5-Ethyl-1,2-ditosylpyrazolidin-3-one (3-3s):

A white solid; Mp 145 – 147 °C **^1H NMR** (400 MHz, CDCl_3) $\delta = 8.00$ (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 7.6$ Hz, 2H), 4.19 – 4.02 (m, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 2.04 (dd, $J = 18.0, 8.0$ Hz, 1H), 1.85 (d, $J = 18.0$ Hz, 1H), 1.23 – 1.43 (m, 2H), 0.99 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (101 MHz, CDCl_3) $\delta = 174.2, 146.0, 145.8, 134.4, 131.4, 130.2, 129.5, 129.3, 129.2, 62.0, 36.7, 27.7, 21.77, 21.72, 10.2$ ppm.

IR (film): $\nu_{\max}$ 2974, 2935, 2877, 1747, 1666, 1593, 1454, 1373, 1292, 1188, 1168, 1083, 983, 925, 860, 817 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_5\text{S}_2]^+$: $m/z = 423.1048$, found: $m/z = 423.1064$.

$[\alpha]_D^{25} = +119.4$ ($c = 1.0$, CHCl_3).

HPLC analysis: 91:9 e.r. (Chiralcel IB, 15:85 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 20.9 min, R_t (minor) = 18.8 min.

(*R*)-5-Pentyl-1,2-ditosylpyrazolidin-3-one (3-3t):

A white solid; Mp 140 – 143 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 7.99$ (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 4.19 (td, $J = 8.8, 5.4$ Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 2.08 (dd, $J = 17.7, 7.9$ Hz, 1H), 1.83 (d, $J = 17.6$ Hz, 1H), 1.45 – 1.56 (m, 1H), 1.39 – 1.12 (m, 7H), 0.88 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) $\delta = 174.3, 146.0, 145.8, 134.4, 131.4, 130.2, 129.5, 129.31, 129.25, 60.4, 36.9, 34.4, 30.9, 22.4, 21.74, 21.71, 13.9$ ppm.

IR (film): ν_{max} 2954, 2866, 1766, 1597, 1492, 1377, 1361, 1292, 1180, 1153, 1087, 1002, 914, 844, 817 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_5\text{S}_2]^+$: $m/z = 465.1518$, found: $m/z = 465.1518$.

$[\alpha]_D^{25} = +97.8$ ($c = 1.0$, CHCl_3).

HPLC analysis: 93:7 e.r. (Chiralcel IB, 15:85 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 16.5 min, R_t (minor) = 14.6 min.

(S)-5-Isopropyl-1,2-ditosylpyrazolidin-3-one (3-3u):

A white solid; Mp 122 – 124 °C; **¹H NMR** (400 MHz, CDCl₃) δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.82 – 3.73 (m, 1H), 2.48 (s, 3H), 2.43 (s, 3H), 2.08 (dd, *J* = 18.0, 1.0 Hz, 1H), 1.95 (dd, *J* = 18.0, 8.0 Hz, 1H), 1.50 – 1.40 (m, 1H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 174.1, 146.0, 145.8, 134.7, 131.3, 130.2, 129.5, 129.3, 129.2, 66.4, 34.8, 31.5, 21.8, 21.7, 19.2, 18.4 ppm.

IR (film): ν_{max} 2962, 2924, 2850, 1766, 1597, 1492, 1454, 1361, 1168, 1087, 999, 918, 894, 821 cm⁻¹.

HRMS (ESI): calculated for [C₂₀H₂₅N₂O₅S₂]⁺: *m/z* = 437.1205, found: *m/z* = 437.1205.

[α]_D²⁵ = +136.5 (*c* = 1.0, CHCl₃).

HPLC analysis: 93:7 e.r. (Chiralcel IB, 10:90 *i*PrOH/Hexane, 0.6 mL/min), *R*_t (major) = 21.5 min, *R*_t (minor) = 20.1 min.

(S)-5-Cyclohexyl-1,2-ditosylpyrazolidin-3-one (3-3v):

A white solid; Mp 132 – 135 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.83 (t, J = 8.4 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 2.28 – 2.18 (m, 1H), 2.07 (d, J = 18.0 Hz, 1H), 1.93 (dd, J = 18.0, 8.0 Hz, 1H), 1.82 – 1.45 (m, 5H), 1.20 – 0.92 (m, 5H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.2, 145.9, 145.8, 134.6, 131.4, 130.2, 129.5, 129.3, 129.2, 65.3, 40.3, 34.3, 29.3, 28.9, 26.0, 25.6, 25.2, 21.8, 21.7 ppm.

IR (film): ν_{max} 2924, 2954, 2850, 1766, 1597, 1450, 1369, 1292, 1168, 1087, 914, 844, 813 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_5\text{S}_2]^+$: m/z = 499.1337, found: m/z = 499.1353.

$[\alpha]^{25}_{\text{D}} = +114.0$ (c = 1.0, CHCl_3).

HPLC analysis: 93:7 e.r. (Chiralcel IB, 15:85 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 17.2 min, R_t (minor) = 15.3 min.

(4R)-Ethyl 4-methyl-5-oxo-1,2-ditosylpyrazolidine-3-carboxylate (3-3w):

A white solid; Mp 125 – 127 °C; ^1H NMR (400 MHz, CDCl_3) δ (major isomer) = 8.09 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.90 (d, J = 8.8 Hz, 1H), 3.77 (s, 3H), 2.48 (s, 3H), 2.44 – 2.38 (m, 4H, *peaks overlap with those of the other isomer*), 0.95 (d, J = 7.2 Hz, 3H);

δ (minor isomer) = 7.82 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 7.2 Hz, 2H), 4.52 (b, 1H), 3.76 (s, 3H), 2.85 (dd, J = 7.6, 3.6 Hz, 1H); 2.45 – 2.52 (m, 6 H, *peaks overlap with those of the other isomer*), 2.28 – 2.37 (m, 1H, *peaks overlap with those of the other isomer*), 0.99 (t, J = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ = 175.8, 174.4, 166.2, 146.4, 146.2, 145.9, 145.6, 134.9, 133.9, 131.0, 130.4, 129.9, 129.8, 129.53, 129.46, 129.3, 129.2, 129.0, 64.9, 53.2, 52.5, 40.7, 38.4, 29.6, 21.7, 14.1, 10.3 ppm.

IR (film): ν_{max} 2954, 2924, 2854, 1751, 1597, 1492, 1454, 1373, 1168, 1087, 1018, 983, 914, 875, 813 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_7\text{S}_2]^+$: m/z = 481.1103, found: m/z = 481.1108.

$[\alpha]_{\text{D}}^{25}$ = +89.5 (c = 1.0, CHCl_3).

HPLC analysis: major isomer 1: 91:9 e.r. , minor isomer 2: 92:8 e.r. (Chiralcel IA, 30:70 *i*PrOH/Hexane, 0.6 mL/min), Rt_1 (major) = 18.0 min, Rt_1 (minor) = 34.8 min; Rt_2 (major) = 15.8 min, Rt_2 (minor) = 13.2 min.

(3R,5S)-5-Phenyl-1,2-ditosylpyrazolidin-3-ol (3-4):

A white solid. Mp 147-149 °C; **^1H NMR** (400 MHz, CDCl_3) δ 7.78 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.32 – 7.18 (m, 7H), 7.14 (d, J = 8.0 Hz, 2H), 5.80 (d, J = 4.8 Hz, 1H), 5.26 (dd, J = 9.2, 8.0 Hz, 1H), 3.41 (b, 1H), 2.46 – 2.28 (m, 7H), 2.12 – 2.02

(m, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ 145.21, 145.18, 139.2, 132.6, 131.9, 130.0, 129.5, 129.34, 129.30, 128.2, 127.4, 127.0, 86.6, 64.9, 42.1, 21.64, 21.57 ppm.

IR (film): ν_{max} 3456, 3070, 2970, 2924, 2862, 1597, 1489, 1450, 1357, 1242, 1165, 1056, 987, 925, 871, 817 cm⁻¹.

HRMS (ESI): calculated for [C₂₃H₂₅N₂O₅S₂]⁺: m/z = 473.1205, found: m/z = 473.1213.

[α]_D²⁵ = +30.8 (c = 1.0, CHCl₃).

HPLC analysis: 97:3 e.r. (Chiralcel IC, 25:75 *i*PrOH/Hexane, 0.5 mL/min), Rt (major) = 72.3 min, Rt (minor) = 60.0 min.

(S)-3-Phenyl-1,2-ditosylpyrazolidine (3-5):

A white solid. Mp 127-130 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.73 – 7.61 (m, 2H), 7.41 (d, *J* = 7.0 Hz, 2H), 7.37 – 7.22 (m, 5H), 7.11 (d, *J* = 8.0 Hz, 2H), 4.99 (t, *J* = 8.8 Hz, 1H), 3.96 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.66 (td, *J* = 12.8, 6.0 Hz, 1H), 2.45 (s, 3H), 2.35 (s, 3H), 2.33 – 2.21 (m, 1H), 1.95 – 2.05 (m, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ 145.1, 144.9, 139.8, 132.8, 131.8, 129.7, 129.5, 129.3, 128.2, 127.4, 127.0, 66.5, 49.6, 34.8, 21.7, 21.6 ppm.

IR (film): ν_{max} 3032, 2924, 2862, 1774, 1597, 1496, 1450, 1365, 1303, 1165, 1118, 1087, 1033, 956, 864, 810 cm⁻¹.

HRMS (ESI): calculated for [C₂₃H₂₅N₂O₄S₂]⁺: m/z = 457.1256, found: m/z = 457.1267.

$[\alpha]_D^{25} = +32.9$ ($c = 1.0$, CHCl_3).

HPLC analysis: 97:3 e.r. (Chiralcel IA, 25:75 *i*PrOH/Hexane, 0.6 mL/min), R_t (major) = 23.4 min, R_t (minor) = 21.3 min.

(S)-5-Phenylpyrazolidin-3-one (3-6):

A white solid. Mp 99-101 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.43 – 7.31 (m, 5H), 4.84 (t, $J = 8.4$ Hz, 1H), 4.38 (s, 1H), 2.85 (dd, $J = 16.2, 7.6$ Hz, 1H), 2.77 (dd, $J = 16.2, 9.4$ Hz, 1H), 1.69 (s, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 176.6, 138.5, 128.9, 128.3, 126.5, 61.7, 38.3 ppm.

IR (film): ν_{max} 3238, 3319, 3057, 2924, 2852, 1716, 1664, 1446, 1408, 1357, 1325, 1271, 1234, 111, 1078, 987, 941, 912, 881 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_9\text{H}_{11}\text{N}_2\text{O}]^+$: $m/z = 163.0871$, found: $m/z = 163.0873$.

$[\alpha]_D^{25} = -29.5$ ($c = 0.5$, CHCl_3).

HPLC analysis: 97:3 e.r. (Chiralcel ADH, 20:80 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 22.9 min, R_t (minor) = 16.8 min.

(S)-3-Amino-3-phenylpropanamide (3-7):

A white solid. Mp 127-129 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.38 – 7.30 (m, 4H), 7.29 – 7.21 (m, 1H), 6.97 (s, 1H), 5.99 (s, 1H), 4.35 (t, *J* = 6.8 Hz, 1H), 2.53 (d, *J* = 6.8 Hz, 2H), 1.90 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 174.1, 145.0, 128.7, 127.4, 125.8, 52.8, 44.9 ppm.

IR (film): ν_{max} 3336, 3282, 3203, 3061, 3026, 1660, 1606, 1494, 1415, 1369, 1269, 1166, 1072, 962, 883 cm⁻¹.

HRMS (ESI): calculated for [C₉H₁₃N₂O]⁺: *m/z* = 165.1028, found: *m/z* = 165.1030.

[α]_D²⁵ = -21.5 (*c* = 0.25, CHCl₃).

(S)-3-((4-Methylphenyl)sulfonamido)-3-phenylpropanamide (3-8):

A white solid. Mp 211-214 °C; **¹H NMR** (400 MHz, DMSO) δ 8.20 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.25 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.07 (m, 5H), 6.74 (s, 1H), 4.66 (dd, *J* = 8.4, 6.4 Hz, 1H), 2.47 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.39 – 2.26 (m, 4H). **¹³C NMR** (101 MHz, DMSO) δ 171.1, 142.5, 141.6, 139.1, 129.6, 128.3, 127.23, 127.18, 126.8, 54.9, 43.2, 21.3 ppm.

HPLC analysis: 97:3 e.r. (Chiralcel ADH, 20:80 *i*PrOH/Hexane, 0.5 mL/min), Rt (major) = 38.3 min, Rt (minor) = 44.7 min.

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Chapter 4

Construction of Fused Pyrrolidines and β -Lactones via Carbene-Catalyzed C-N, C-C and C-O Bond Formations

4.1 Introduction

As a class of structurally unique motif, β -lactones continue to receive tremendous attention from chemists with a focus on the development of their asymmetric synthetic methods and utility as versatile synthetic intermediates.^[1] In particular, fused β -lactones possessing bicyclic structure are interesting scaffolds as they are present in a vast array of bioactive natural products and drugs.^[2] Representative carbocycle- or heterocycle-fused β -lactones with significant biological activity, such as the pancreatic lipase inhibitor vibrallactone **A**^[2a] and proteasome inhibitor salinosporamide **A**,^[2b] are depicted in Scheme 4.1. More importantly, the cyclic fused β -lactones may also serve as versatile intermediates for complex structures and polymer synthesis.^[3] Considerable effort has been spent on the asymmetric preparation of these novel bicyclic scaffolds,^[4] mainly using optically active starting substrates^[5] or intramolecular aldol-lactonization process^[6]. In this respect, the development of catalytic cascade approach for rapid construction (ideally single-step) of structurally complex lactones from simple starting materials is of great interest.

Scheme 4.1 Representative natural products possessing carbo- (or hetero-) cycle fused β -lactone.

A seminal report by Romo group in 2013^[7a] illustrated an elegant domino process to assemble cyclopentane fused β -lactones by employing a chiral isothioureia as a chiral catalyst (Scheme 4.2). The reaction proceeded through the Michael addition of a malonate derivative to a HBTM-bound α,β -unsaturated acyl ammonium intermediate.^[7] This was followed by intramolecular aldol and lactonization process to give the final bicyclic β -lactone in excellent diastereoselectivity and enantioselectivity.

Scheme 4.2 Isothiourea-catalyzed cascade process to bicyclic β -lactone.

On the other hand, *N*-heterocyclic carbene (NHC) has also emerged as another valuable Lewis base catalyst for the synthesis of this complex molecule.^{[8][9]} Nair and Bode reported their pioneering works in 2006. They used an enal to form a homoenolate intermediate. With another unsaturated ketone as an electrophile, a cascade process could efficiently provide the bicyclic β -lactones (Scheme 4.3). However, due to the low stability, the products tended to undergo decarboxylation process to furnish cyclopentene derivatives.^[10]

Scheme 4.3 Nair's preparation of cyclopentene.

Since 2012, Lupton successively achieved both the racemic and asymmetric tandem routes to highly functionalized cyclopentane or cyclohexane fused β -lactones (Scheme 4.4). The reaction used an α,β -unsaturated acyl fluoride and a donor-acceptor cyclopropane as substrates. The key process involved the formation of an NHC-bound unsaturated acyl azolium ion via the nucleophilic attack of the carbene to the acyl fluoride and the generation of an enolate via ring-opening of the cyclopropane. 1,2-Addition of the enolate and subsequent Claisen rearrangement would furnish the products.^[11a-c]

Scheme 4.4 Lupton's work on the synthesis of bicyclic β -lactone.

Compared with the cyclopropane utilized in Lupton's work, very recently, Studer employed a modified ketone as a more readily accessible substrate to produce the bicyclic β -lactone with two fully substituted stereocenters (Scheme 4.5).^[11d] The key unsaturated acyl azolium intermediate was produced through oxidation of the NHC/enal derived Breslow intermediate by quinone oxidant. The desired bicyclic adduct was obtained in 95% yield, >20:1 dr and 98% ee.

Scheme 4.5 Studer's synthesis of bicyclic β -lactone via oxidative NHC catalysis.

It should be noted that all of these elegant reports focused on the construction of all carbon cycle fused β -lactones. However, to the best of our knowledge, the

development of a novel organocascade reaction for the rapid assembly of complex heterocycle fused β -lactones, which involves unsaturated acyl ammonium (or azolium) ion from readily prepared starting materials, has not been achieved so far (Scheme 4.6).

Scheme 4.6

Nitrogen-containing heterocycles, especially multi-substituted pyrrolidines are widely found in natural products, pharmaceutical compounds and commonly used platforms in synthetic chemistry.^[12] In this chapter, we describe a novel and efficient cascade approach for the direct assembly of the two privileged scaffolds (pyrrolidine and β -lactone). The resulting sophisticated pyrrolidine fused β -lactones, bearing up to three contiguous stereocenters including one quaternary carbon, are obtained in good yields and excellent diastereoselectivities and enantioselectivities. Our proposed organocascade process initiates with an aza-Michael addition^[13] of an α -amino ketone to a catalytically generated α,β -unsaturated acyl azolium intermediate^[14] (Scheme 4.7, a). This was followed by an intramolecular aldol- β -lactonization sequence to give the final bicyclic product.^[15] Some of intrinsic problems for this highly challenging transformation should be noted here: 1) the competing [3+2] lactam pathway due to the reactivity of α -carbon as reported in Ye's work^[16] (Scheme 4.7, b); 2) amide bond formation between the nitrogen nucleophile and the acyl azolium ion.

Scheme 4.7 (a) Our proposed strategy to prepare heterocycle fused β -lactone via carbene-catalyzed intermolecular cascade reaction; (b) Possible side reaction pathway.

4.2 Results and Discussions

We started our investigation by using enal **4-1a** as the model substrate and quinone (**DQ**) as the oxidant to generate the α,β -unsaturated acyl azolium intermediate. Key results of our initial reaction screening are summarized in Table 4-1. Achiral catalyst **A**^[17a] in the presence of K_2CO_3 as the base mediated the cascade process to afford the bicyclic adduct in 40% yield, albeit with a small amount of Ye's [3+2] product^[16] (entry 1). We deemed the difference between our result with Ye's work was mainly due to the different substituents on the amino ketone (**4-2a**). The relatively lower acidity of the α -carbon C-H of **4-2a** compared with aryl amino ketones in Ye's work, would decrease the side reaction rate to form **4-4a**. To our delight, chiral aminoindanol-derived NHC precatalysts **B-D** and triazolium salt **E** significantly improved the ratio of **4-3a**: **4-4a** owing to the steric hindrance between the α -carbon of the amino ketone with the bulky substituent on the catalyst (entries 2-5).^[17b-d] In terms of enantioselectivity, **D** proved

to be superior, giving an encouraging 87:13 er (entry 4). In all cases, only a single diastereoisomer of **4-3a** was observed by NMR. We then chose **D** for further examination of the effects of different solvents and bases (entries 6-9), and found that the reaction using Cs₂CO₃ and CHCl₃ gave a more satisfactory result (64% yield, 93:7 er, entry 9). Encouraged by this outcome, the effect of additives was screened extensively to further improve the enantioselectivity of the product **4-3a**. Unexpectedly, the reaction of **4-2a** containing a trace amount of TsNH₂ displayed a slightly increased er (95:5 er, entry 10). We then found that the use of 2,4,6-triisopropyl benzenesulfonyl amide (Ar'SO₂NH₂) improved the e.r. value to 96:4 (entry 11). Inspired from the previous literature that the sulfonyl amide may play as a Brønsterd acid additive to improve the enantioselectivity, we screened other acid additives, such as HOAc, PivCOOH, benzoic acid.^[18] However, we did not find a consistent improvement on the selectivity. Therefore, at this point we cannot ascertain the exact role of this additive played in the reaction. Finally, we were pleased to find that a slight increase of the amount of **4-1a** and **DQ** furnished **4-3a** in 74% yield, >20:1 dr and 96:4 er (entry 12).

Table 4.1 Conditions Optimization^[a]

Entry	Cat.	Base	Solvent	4-3a [%] ^[b]	Yield e.r.	4-3a: 4a ^[b]	4-
1	A	K ₂ CO ₃	CH ₂ Cl ₂	40	-	4:1	
2	B	K ₂ CO ₃	CH ₂ Cl ₂	43	71:29	12:1	
3	C	K ₂ CO ₃	CH ₂ Cl ₂	50	83:17	>20:1	
4	D	K ₂ CO ₃	CH ₂ Cl ₂	48	87:13	>20:1	
5	E	K ₂ CO ₃	CH ₂ Cl ₂	85	34:66	10:1	
6	D	DIEA	CH ₂ Cl ₂	trace	n.d.	n.d.	
7	D	DBU	CH ₂ Cl ₂	trace	n.d.	n.d.	
8	D	Cs ₂ CO ₃ ^[c]	CH ₂ Cl ₂	61	90:10	>20:1	
9	D	Cs ₂ CO ₃ ^[c]	CHCl ₃	64	93:7	>20:1	
10 ^[d]	D	Cs ₂ CO ₃ ^[c]	CHCl ₃	61	95:5	>20:1	
11 ^[e]	D	Cs ₂ CO ₃ ^[c]	CHCl ₃	65	96:4	>20:1	
12 ^[f]	D	Cs ₂ CO ₃ ^[c]	CHCl ₃	76 (74) ^[g]	96:4	>20:1	

[a] Reaction conditions: **4-1a** (0.065 mmol, 1.3 equiv), **4-2a** (0.05 mmol, 1.0 equiv), NHC (15 mol%), base (1.5 equiv) and **DQ** (1.2 equiv), 4 Å MS (50 mg) in solvent (0.05 M) at RT for 20 h. [b] Yield and ratio of **4-3a**: **4-4a** determined by NMR spectroscopy. Yield based on **4-2a** using 1,3,5-trimethoxybenzene as an internal standard. [c] 1.0 equiv of Cs₂CO₃ was used. [d] 10 mol% of TsNH₂ was added. [e] 10 mol% of Ar'SO₂NH₂ was added. [f] 10 mol% of Ar'SO₂NH₂, 1.5 equiv of **4-1a** and 1.4 equiv of **DQ** were used instead. [g] Isolated yield given within parentheses. Ts = 4-methylbenzenesulfonyl, Ar'SO₂NH₂ = 2,4,6-triisopropylbenzenesulfonyl.

With the optimized reaction conditions in hand, we next studied the generality of the reaction. We first examined the effect of varying β -aryl or alkyl enals in the cascade process by using α -amino ketone **4-2a** as the model substrate (Table 4.2). Various substituents at different positions of the β -phenyl ring of enals, such as *p*-F, *p*-Cl, *p*-Br or *p*-Me, *p*-OMe and *o*-OMe, were all well tolerated. The introduction of a strong electron-withdrawing NO₂ group (**4-1e**) resulted in a slight decrease in enantioselectivity (74%, 90:10 er). Enals with convertible functional groups, such as ester and allyl groups, performed very well to furnish the corresponding bicyclic adducts in excellent er (**4-3k** and **4-3l**). The β -phenyl ring of **4-1** could be replaced with heteroaryl substituents (**4-3m** and **4-3n**). Moreover, alkyl enals were also good substrates to provide desired products, albeit with relatively moderate yield and er (**4-**

3o-q). Notably, replacement of N-Ts group with a bulky N-Mts group led to a slightly higher er (**4-3p** vs **4-3o**).

Table 4.2 Substrate scope with respect of enal **4-1**^[a]

[a] Reaction conditions: **4-1a** (1.5 equiv), **4-2a** (0.10 mmol, 1.0 equiv), **D** (15 mol%), Ar'SO₂NH₂ (10 mol%), Cs₂CO₃ (1.0 equiv) and **DQ** (1.4 equiv), 4 Å MS (100 mg) in CHCl₃ (0.05 M) at RT for 20 h. Yields (after SiO₂ chromatography purification) based on **4-2**. [b] 2.0 equiv of **4-1a** was used, and reaction was conducted at 40 °C. Mts = 2,4,6-trimethylbenzenesulfonyl.

Subsequently, the scope of the amino ketone **4-2** with alkyl groups was studied (Table 4.3). Different alkyl substituents of ketones, such as Me, Bu, Bn or even Cy (**4-2r**, **4-2t-v**) were all compatible with the standard conditions. Ketone **4-2s** with bulky *i*Pr group showed relatively low reactivity under the same conditions (trace amount of product was observed), while a modification of the catalyst to **D** led to product **4-3s** in 81% yield and 93:7 er. Remarkably, a substituent with an acetal unit were tolerant in the current transformation, providing the lactone **4-3w** in 73% and 97:3 er.

Table 4.3 Substrate scope with respect to α -amino ketone **4-2**.^[a]

[a] **4-1a** (1.5 equiv), **4-2a** (0.10 mmol, 1.0 equiv), **D** (15 mol%), Ar'SO₂NH₂ (10 mol%), Cs₂CO₃ (1.0 equiv) and **DQ** (1.4 equiv), 4 Å MS (100 mg) in CHCl₃ (0.05 M) at RT for 20 h. Isolated yields based on **4-2**. [b] Catalyst **E** was used.

The results of ketones with aryl substituents under the standard conditions produced pyrrolines **4-5a-d** as the main products, along with [3+2] lactam products in

Ye's previous work (Scheme 4.8 a and b). It was apparent that the pyrrolines were derived through decarboxylation of the corresponding β -lactones. After additional investigations, we were pleased to find that the precatalyst *ent*-**B** (used in Ye's work) at 0 °C greatly suppressed the undesired competing [3+2] lactam pathway (selectivity >20:1), leading to **4-5a-d** in good yields and excellent er. Notably, the resulting pyrroline structure is one of typical N-containing heterocycles and our cascade reaction provides a complementary approach for asymmetric construction of this significant motif.

Scheme 4.8 (a) Substrate scope with respect to α -amino ketone **4-2**; (b) Ye's [3+2] example.

The cascade reaction could be easily scaled-up with the optimized conditions, providing **4-3a** (1.18 g) in 64% yield and 96:4 er. The optically enriched pyrrolidine

fused β -lactone products readily underwent further manipulations, as depicted in Scheme 4.9. The lactone unit of **4-3** was easily reduced to the corresponding diol **4-6** in 83% yield without erosion of the er value. The N-Ts group could be readily removed with Mg/MeOH after mild alcoholysis to afford a β -proline methyl ester **4-7**. Notably, the β -proline derivative **4-7** behaved as an organocatalyst to catalyze the Michael addition^[19] of aldehyde **4-11** to nitro styrene **4-12**. The corresponding product **4-13** was afforded in good yield and 89:11 er. Decarboxylation of **4-3a** at 110 °C in DMF, followed by epoxidation using *m*-CPBA furnished a bicyclic epoxide **4-8** in 81% yield and 96:4 er. The oxabicyclic structure of **4-8** could be widely found as a core structure in various antibiotic molecules and natural products, such as (+)-epogymnolactam.^[20]

Scheme 4.9 Synthetic transformations of bicyclic lactone **4-3a** (a) and its catalytic application (b).

4.3 Proposed reaction pathway and stereo-chemical modes

Scheme 4.10 Proposed reaction mechanism and stereo-chemical modes.

Based on our work and previous study, we proposed a reaction pathway for the generation of product **4-3** as described in Scheme 4.10. First, the Breslow intermediate generated from the aldehyde and free NHC was oxidized by **DQ** to provide an unsaturated acyl azolium intermediate **I**. Then an aza-Michael addition of the amino ketone **4-2** to **I** occurred to afford an intermediate **II**. Subsequently, an intramolecular aldol reaction would form an intermediate **III**. Finally, the following lactonization of the intermediate **III** would provide the final product **4-3** and release the carbene catalyst. The stereochemical-outcome of the cascade reaction could be explained as shown in **TS A** and **TS B**. For the process of aza-Michael addition, the back face of the intermediate **I** is well shielded by the indanol backbone. The NO_2 substituent on the phenyl ring of the catalyst **D** likely behaves as a hindered group to extend the chiral

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environment for a better enantioselectivity control of the aza-Michael addition. The subsequent intramolecular aldol reaction proceeded through the envelope-type confirmation (as in **TS B**), thus giving the bicyclic products in excellent diastereoselectivity (>20:1).

4.4 Summary.

In summary, we have developed a highly efficient approach for the preparation of complex pyrrolidine- fused β -lactone in good to excellent yield and enantioselectivity. Our reaction proceeds through the asymmetric aza-Michael addition to the catalytically generated α,β -unsaturated acyl azolium ion, followed by a selective aldol-lactonization tandem process. The bicyclic β -lactone products are versatile platforms and readily undergo further transformation to other useful molecules such as bicyclic epoxides. The present methodology exhibits high synthetic efficiency for advanced functionalized products from readily prepared amino ketone substrates via an extremely short route. Further biological investigation of the prepared pyrrolidine fused lactone derivatives is underway in our lab.

4.5 Experimental Section

4.5.1 General Information.

Commercially available materials were purchased from Alfa Aesar or Sigma-Aldrich. HPLC grade CH_3CN (purchased from TEDIA) was dried over 4Å molecular sieve prior use. Toluene and CH_2Cl_2 was dried over Pure Solv solvent purification system. THF was distilled over sodium, and CHCl_3 was newly distilled over CaH_2 .

Other solvents were dried over 4Å molecular sieve prior use. Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in 10 mL Schlenk tube.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker (400 MHz) spectrometer and JEOL-ECX-500 (500 MHz) spectrometer. Chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer and JEOL-ECX-500 (125 MHz) spectrometer. IR spectra were recorded on a Shimazu IR IRAffinity-1 FT-IR Spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of enantiomeric excess 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 on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_{\text{D}}^{\text{rt}}$ (c is in gm per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate. The TLC plate was visualized using a UV lamp or potassium permanganate stain. Catalyst **D** was prepared according to literature procedures.^[20]

4.5.2 General Procedure for the Catalytic Reactions of Enal (4-1) with *N*-Tosyl Amino Ketone (4-2).

(1) Reactions of Enal (4-1) with *N*-Tosyl Amino Ketone (4-2) to Synthesize Bicyclic β -Lactone 4-3.

An oven dried 10 mL Schlenk tube was charged with α -amino ketone **4-2** (0.10 mmol, 1.0 equiv), NHC **D** (7.0 mg, 15 mol%), anhydrous Cs₂CO₃ (32.4 mg, 0.1 mmol, 1 equiv), **DQ** (57.1 mg, 0.14 mmol, 1.4 equiv), TPSNH₂ **4-4** (2.8 mg, 10 mol%) and 4 Å molecular sieves (100 mg). After evacuated, and refilled with nitrogen, the tube was added with the enal **4-1** (0.15 mmol, 1.5 equiv) and the mixture was dissolved with 2.0 mL of CHCl₃. The reaction was stirred at room temperature for 20 h when the α -amino ketone was consumed completely (monitored by TLC). The mixture was concentrated and purified by column chromatography on silica gel (hexane/ethyl acetate) to afford the desired product **4-3**. The characterization was performed by ¹H NMR, ¹³C NMR spectra, and the enantiomeric excess was determined by chiral HPLC.

Note: Racemic samples for chiral phase HPLC analysis were prepared as the using racemic catalyst **B**.

(2) Reactions of Enal (**4-1**) with *N*-Tosyl Amino Ketone (**4-2**) to Synthesize Pyrroline **4-5**.

Under N_2 atmosphere, to an oven dried 10 mL Schlenk tube with a magnetic stir bar, were added α -amino ketone **4-2** (0.10 mmol, 1.0 equiv), NHC **D** (6.3 mg, 15 mol%), anhydrous Cs_2CO_3 (32.4 mg, 0.1 mmol, 1 equiv), **DQ** (57.1 mg, 0.14 mmol, 1.4 equiv), TPSNH_2 **4-4** (2.8 mg, 10 mol%) and 4 Å molecular sieves (100 mg). Then the enal **4-1** (0.15 mmol, 1.5 equiv) was added and the mixture was dissolved with 2.0 mL of CHCl_3 . The reaction mixture was stirred at 0 °C for 3 days when the ketone **4-2** was consumed completely (monitored by TLC). After concentrated under reduced pressure, the crude residue was purified via column chromatography to afford the desired product **4-5**.

Note: Racemic samples for chiral phase HPLC analysis were prepared by using racemic NHC **B** as the catalyst.

(3) Stereochemistry Determination of **4-3j** and **4-5c** via X-ray Crystallographic Analysis.

Product **4-3j** and **4-5c** were crystallized as colorless crystals *via* evaporation of a hexane/ethyl acetate solution, and their absolute configurations were determined by X-ray structure analysis. CCDC 1518922 (**4-3j**) and CCDC 1518923 (**4-5c**) contain the

supplementary crystallographic data that can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

(4) Synthetic Transformations of Product 4-3a.

Under N_2 atmosphere, to a dry 2-neck flask equipped with a magnetic stir bar, were added triazolium salt **D** (349.5 mg, 15 mol%), α -amino ketone **4-2a** (1.21 g, 5 mmol, 1.0 equiv), **DQ** (2.86 g, 1.4 equiv), TPS-NH₂ **4-4** (140.1 mg, 10 mol%), Cs_2CO_3 (1.63 g, 1.0 equiv) and 4 Å molecular sieves (1.0 g). Then the mixture was dissolved with CHCl_3 (40.0 mL) and the enal **4-1a** (0.99 g, 7.5 mmol, 1.5 equiv) was added. The mixture was stirred at room temperature until the ketone **4-2a** was consumed completely (monitored by TLC). After concentrated under vacuum, the crude residue was purified via column chromatography to afford the desired product **4-3a** (1.18 g) with 64% yield and 96:4 er.

Under N_2 atmosphere, a solution of bicyclic fused lactone **4-3a** (18.6 mg, 0.05 mmol) in CH_2Cl_2 (2.0 mL) was cooled to 0 °C, followed by the drop-wise addition of DIBAL-H (1.0 M in THF, 0.25 mL, 0.25 mmol). The reaction was then warmed to room temperature and continued to stir for 12 h until the consumption of the **4-3a** (monitored by TLC). The reaction was quenched with saturated Rochelle salt and extracted with CH_2Cl_2 for 3 times. The combined organic layer was dried over MgSO_4 ,

filtered and concentrated under reduced pressure. The pure product **4-6** (15.4 mg) was given via flash chromatography (Hexane/Ethyl Acetate = 1:1) as a colorless oil (83% yield, 96:4 er).

Under N₂ atmosphere, a solution of **3a** (18.6 mg, 0.05 mmol, 1.0 equiv) and K₂CO₃ (10.3 mg, 1.5 equiv) in MeOH (1.0 mL) was stirred at RT for 2 h. Then reaction mixture was then passed through a short pad of silica gel and concentrated under reduced pressure to afford the ring-open product, which was pure enough determined by NMR analysis and could be used directly for the next step without further purification.

Under Ar atmosphere, to an oven-dried Schlenk tube equipped with a magnetic stir bar, was added the ring-open product in the above step and Mg-powder (18.0 mg, 15 equiv). Absolute MeOH (1.4 mL) was added and the reaction was capped with a septum, then sonicated at room temperature until no more starting material remained monitored by TLC (around 40 min). After cooled to 0 °C, the reaction mixture was slowly quenched with saturated NH₄Cl. The aqueous phases were extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with saturated brine (20 mL), then dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 12:1) to afford **4-7** (9.3 mg, overall 74% yield).

Product **4-7** was derivatized for HPLC analysis: To the CH₂Cl₂ solution of amino ester **4-7** (5.0 mg, 0.02 mmol, 1.0 equiv) were added triethylamine (2 equiv) and DMAP (10 mol%). After the mixture was cooled to 0 °C, tosyl chloride (4.2 mg, 1.1 equiv) was added and the mixture was stirred at 0 °C until complete consumption of **4-7**. The mixture was diluted with CH₂Cl₂ and washed with water. The organic phase was dried with Na₂SO₄ and concentrated to give the crude product. After purification by column (Hexane:EA = 2:1), the N-Ts protected pyrrolidine ester was obtained.

HPLC analysis: 96: 4 e.r. (Chiralcel ADH, 30:70 iPrOH/Hexane, 0.7 mL/min), Rt (major) = 31.3 min, Rt (minor) = 12.2 min.

Under N₂ atmosphere, a solution of **4-3a** (18.6 mg, 0.05 mmol, 1.0 equiv) in DMF (1.0 mL) was heated at 110 °C for 12 h. Then reaction mixture was diluted with Et₂O (60 mL), followed by washing with H₂O (20 mL) for 3 times. The organic layer was separated, dried with Na₂SO₄ and concentrated under reduced pressure to give the crude residue, which was pure enough (indicated from the crude ¹H NMR) and used directly in the next step.

Under N₂ atmosphere, the crude product obtained in the last step was added to a Schlenk tube and dissolved in CH₂Cl₂ (2 mL). After the solution was cooled to 0 °C, *m*-CPBA (50%, 1.8 equiv) was added in one portion and continued to stir for 10 h at rt. Then the reaction mixture was concentrated and purified by silica gel column

chromatography (Hexane/Ethyl Acetate = 3:1) to provide the desired epoxide **4-8** (13.8 mg) in 81% yield and 96:4 e.r. (dr>20:1)

Under N₂ atmosphere, a solution of **4-9** (20 μ L), **4-10** (11.4 mg, 0.05 mmol, 1.0 equiv), product **4-7** (1.9 mg, 15 mol%) and benzoic acid (1.3 mg, 20 mol%) in hexane (1.0 mL) was stirred at rt for 24 h. Then reaction mixture was then passed through a short pad of silica gel and concentrated under reduced pressure to afford the crude product, and purified by silica gel column chromatography (Hexane/Ethyl Acetate = 5:1) to provide the desired product **4-11** (10.4 mg) in 70% yield (syn:anti = 6:1) and 90:10 e.r. (major *syn* isomer).^[19]

4.5.3 Characterizations of substrates and products.

a) Characterizations of substrates.

Note: α -Amino ketones were prepared according to previous literature procedures.^[23]

4-Methyl-N-(2-oxobutyl)benzenesulfonamide:

A white solid; M.p. 101.7-102.2 $^{\circ}$ C; ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.32 (s, 1H), 3.84 (d, *J* = 4.8 Hz, 2H), 2.42 (s, 3H), 2.37 (q, *J* = 7.2 Hz, 2H), 1.03 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 204.1, 143.8, 136.1, 129.8, 127.2, 51.0, 33.4, 21.5, 7.4 ppm.

IR (film): $\nu_{\max}$ 3279, 2976, 2941, 2877, 1716, 1598, 1483, 1444, 1411, 1332, 1163, 1093, 1031, 902, 815 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{11}\text{H}_{16}\text{NO}_3\text{S}]^+$: $m/z = 242.0851$, found: $m/z = 242.0850$.

2,4,6-Trimethyl-N-(2-oxobutyl)benzenesulfonamide:

A white solid; M.p. 77.0-78.1 °C; **^1H NMR** (400 MHz, CDCl_3) δ 6.95 (s, 2H), 5.44 (s, 1H), 3.78 (d, $J = 4.4$ Hz, 2H), 2.64 (s, 6H), 2.38 (q, $J = 7.2$ Hz, 2H), 2.29 (s, 3H), 1.04 (td, $J = 7.2, 1.0$ Hz, 3H). **^{13}C NMR** (101 MHz, CDCl_3) δ 204.2, 142.4, 139.2, 132.9, 132.0, 50.5, 33.4, 22.8, 20.9, 7.4 ppm.

IR (film): $\nu_{\max}$ 3273, 2983, 2943, 2917, 1718, 1448, 1404, 1294, 1155, 1103, 1055, 1031, 991, 894, 856, 819 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{13}\text{H}_{20}\text{NO}_3\text{S}]^+$: $m/z = 270.1164$, found: $m/z = 270.1165$.

4-Methyl-N-(2-oxopropyl)benzenesulfonamide:

A white solid; M.p. 97.0-98.8 °C; **^1H NMR** (400 MHz, CDCl_3) δ 7.74 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 5.34 (s, 1H), 3.85 (d, $J = 4.4$ Hz, 2H), 2.42 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (101 MHz, CDCl_3) δ 201.1, 143.8, 136.1, 129.8, 127.1, 52.0, 27.1, 21.5 ppm.

IR (film): $\nu_{\max}$ 3280, 3037, 2970, 1716, 1597, 1448, 1408, 1363, 1325, 1163, 1093, 989, 815 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{10}\text{H}_{14}\text{NO}_3\text{S}]^+$: $m/z = 228.0694$, found: $m/z = 228.0691$.

4-Methyl-N-(3-methyl-2-oxobutyl)benzenesulfonamide:

A white solid; M.p. 74.5-75.0 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.35 (s, 1H), 3.89 (d, $J = 4.8$ Hz, 2H), 2.53 (dt, $J = 13.6$, 6.8 Hz, 1H), 2.42 (s, 3H), 1.03 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 207.3, 143.7, 136.0, 129.7, 127.2, 49.4, 38.7, 21.5, 17.9 ppm.

IR (film): $\nu_{\max}$ 3292, 2962, 2875, 1714, 1705, 1558, 1409, 1350, 1328, 1161, 1093, 1029, 964, 923, 891, 810 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{12}\text{H}_{18}\text{NO}_3\text{S}]^+$: $m/z = 256.1007$, found: $m/z = 256.1002$.

4-Methyl-N-(2-oxohexyl)benzenesulfonamide:

A white solid; M.p. 72.5-74.1 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.34 (s, 1H), 3.82 (d, $J = 4.8$ Hz, 2H), 2.42 (s, 3H), 2.33 (t, $J = 7.6$ Hz, 2H), 1.54 – 1.44 (m, 2H), 1.20 (dt, $J = 9.2$, 7.6 Hz, 2H), 0.85 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 203.8, 143.8, 136.1, 129.8, 127.2, 51.3, 39.8, 25.6, 22.1, 21.5, 13.7 ppm.

IR (film): $\nu_{\max}$ 3280, 2985, 2937, 2873, 1720, 1600, 1408, 1321, 1159, 1114, 1091, 1045, 1001, 852, 813 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{13}\text{H}_{20}\text{NO}_3\text{S}]^+$: $m/z = 270.1164$, found: $m/z = 270.1161$.

4-Methyl-*N*-(2-oxo-3-phenylpropyl)benzenesulfonamide:

A white solid; M.p. 107.0-108.5 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 8.4$ Hz, 2H), 7.35 – 7.20 (m, 6H), 7.12 – 7.03 (m, 2H), 5.34 (s, 1H), 3.87 (d, $J = 4.8$ Hz, 2H), 3.62 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 201.5, 143.7, 135.9, 132.4, 129.7, 129.2, 128.9, 127.5, 127.1, 50.8, 47.2, 21.5 ppm.

IR (film): ν_{max} 3269, 3059, 3028, 2976, 2872, 1720, 1598, 1506, 1496, 1452, 1411, 1355, 1321, 1288, 1247, 1120, 1093, 1055, 916, 862, 813 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{16}\text{H}_{18}\text{NO}_3\text{S}]^+$: $m/z = 304.1007$, found: $m/z = 304.0998$.

***N*-(2-cyclohexyl-2-oxoethyl)-4-methylbenzenesulfonamide:**

A white solid; M.p. 80.1-81.9 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.36 (s, 1H), 3.87 (d, $J = 4.4$ Hz, 2H), 2.42 (s, 3H), 2.32 – 2.18 (m, 1H), 1.77 – 1.61 (m, 5H), 1.28 – 1.13 (m, 5H). ^{13}C NMR (101 MHz, CDCl_3) δ 206.5, 143.7, 136.1, 129.7, 127.2, 49.7, 48.4, 28.2, 25.5, 25.3, 21.5 ppm.

IR (film): ν_{max} 3284, 2922, 2856, 1716, 1598, 1448, 1409, 1375, 1342, 1321, 1307, 1288, 1161, 1132, 1093, 1062, 1002, 918, 887, 860, 815 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{15}\text{H}_{21}\text{NO}_3\text{SNa}]^+$: $m/z = 318.1140$, found: $m/z = 318.1140$.

***N*-(4-(1,3-Dioxolan-2-yl)-2-oxobutyl)-4-methylbenzenesulfonamide:**

A white solid; M.p. 82.9-84.1 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.34 (t, $J = 4.4$ Hz, 1H), 4.84 (t, $J = 4.0$ Hz, 1H), 3.96 – 3.71 (m, 6H), 2.53 – 2.35 (m, 5H), 1.95 (td, $J = 7.2, 4.0$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 203.0, 143.7, 136.1, 129.7, 127.2, 102.6, 65.0, 51.3, 33.6, 27.3, 21.5 ppm.

IR (film): $\nu_{\max}$ 3261, 2972, 2887, 1718, 1597, 1452, 1436, 1406, 1388, 1344, 1315, 1288, 1163, 1139, 1087, 1062, 1039, 1008, 948, 938, 931, 864, 813 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{14}\text{H}_{19}\text{NO}_5\text{SNa}]^+$: $m/z = 336.0882$, found: $m/z = 336.0885$.

4-Methyl-N-(2-oxo-2-phenylethyl)benzenesulfonamide:

A white solid; M.p. 108.5-109.8 $^{\circ}\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 7.85 (d, $J = 8.0$ Hz, 2H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 5.69 (s, 1H), 4.46 (d, $J = 4.4$ Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (101 MHz, CDCl_3) δ 192.5, 143.7, 136.1, 134.4, 133.7, 129.8, 128.9, 127.8, 127.1, 48.6, 21.5 ppm.

IR (film): $\nu_{\max}$ 3280, 2972, 1685, 1597, 1492, 1450, 1411, 1346, 1325, 1305, 1290, 1236, 1159, 1118, 1091, 997, 914, 817 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{15}\text{H}_{16}\text{NO}_3\text{S}]^+$: $m/z = 290.0851$, found: $m/z = 290.0852$.

4-Methyl-N-(2-oxo-2-(p-tolyl)ethyl)benzenesulfonamide:

A white solid; M.p. 109.3-110.7 $^{\circ}\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.4$ Hz, 2H), 7.74 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 5.66 (s, 1H), 4.42 (s, 4H), 2.41 (s, 3H), 2.39 (s, 3H). **^{13}C NMR** (101 MHz, CDCl_3) δ 192.0, 145.6, 143.7, 136.2, 131.3, 129.8, 129.6, 128.0, 127.2, 48.5, 21.8, 21.5 ppm.

IR (film): $\nu_{\max}$ 3282, 2970, 2914, 2860, 1689, 1598, 1448, 1404, 1348, 1321, 1290, 1242, 1188, 1159, 1109, 1093, 999, 927, 812 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{16}\text{H}_{18}\text{NO}_3\text{S}]^+$: $m/z = 304.1007$, found: $m/z = 304.1001$.

4-Methyl-N-(2-(naphthalen-2-yl)-2-oxoethyl)benzenesulfonamide:

A white solid; M.p. 169.5-171.2 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.36 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.91 – 7.85 (m, 3H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.68 – 7.53 (m, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 5.73 (s, 1H), 4.60 (s, 2H), 2.38 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 192.4, 143.8, 136.2, 136.1, 132.3, 131.1, 129.9, 129.8, 129.6, 129.2, 128.9, 127.9, 127.3, 127.2, 123.0, 48.7, 21.5 ppm.

IR (film): ν_{max} 3278, 3062, 2945, 1680, 1627, 1597, 1471, 1417, 1325, 1282, 1159, 1111, 1091, 1020, 989, 941, 893, 862, 815 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{18}\text{NO}_3\text{S}]^+$: $m/z = 340.1007$, found: $m/z = 340.1010$.

b). Characterization of Products

(1S,2R,5S)-5-Ethyl-2-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3a):

A white solid; M.p. 109.3-111.9 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.39 – 7.29 (m, 3H), 7.28 – 7.22 (m, 4H), 5.50 (s, 1H), 4.07 (d, $J = 13.6$ Hz, 1H), 3.72 (d, $J = 0.4$ Hz, 1H), 3.55 (d, $J = 13.2$ Hz, 1H), 2.42 (s, 3H), 1.95 (q, $J = 7.2$ Hz, 2H), 0.96 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.5, 143.9, 138.1, 135.8, 129.6, 129.1, 128.2, 127.2, 125.8, 89.1, 64.7, 63.3, 53.3, 26.2, 21.6, 8.4 ppm.

IR (film): ν_{max} 2974, 2926, 2850, 1820, 1739, 1597, 1494, 1456, 1404, 1344, 1240, 1166, 1159, 1139, 1089, 1014, 950, 864, 819 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{22}\text{NO}_4\text{S}]^+$: $m/z = 372.1270$, found: $m/z = 372.1266$.

$[\alpha]_{\text{D}}^{25} = -68.9$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 96: 4 e.r. (Chiralcel ID, 20:80 $i\text{PrOH}$ /Hexane, 0.6 mL/min), R_t (major) = 56.4 min, R_t (minor) = 66.1 min.

(1*S*,2*R*,5*S*)-5-Ethyl-2-(4-fluorophenyl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3b):

A colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.32 – 7.25 (m, 2H), 7.25 – 7.19 (m, 2H), 7.03 (t, $J = 8.4$ Hz, 2H), 5.47 (s, 1H), 4.06 (d, $J = 13.6$ Hz, 1H), 3.69 (s, 1H), 3.53 (d, $J = 13.2$ Hz, 1H), 2.42 (s, 3H), 1.95 (q, $J = 7.6$ Hz, 2H), 0.96 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.2, 162.4 (d, $J = 242.4$ Hz), 144.1, 135.6, 134.0 (d, $J = 3.03$ Hz), 129.7, 127.7 (d, $J = 8.08$ Hz), 127.2, 116.0 (d, $J = 22.2$ Hz), 89.0, 64.7, 62.7, 53.2, 26.2, 21.5, 8.4 ppm.

IR (film): ν_{max} 3066, 2991, 2978, 2931, 2877, 1828, 1598, 1508, 1406, 1342, 1328, 1280, 1232, 1207, 1157, 1089, 1051, 1035, 1014, 968, 952, 871, 823, 812 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{21}\text{NO}_4\text{SF}]^+$: $m/z = 390.1175$, found: $m/z = 390.1183$. $[\alpha]_{\text{D}}^{25} = -53.6$ ($c = 2.0$ in CHCl_3).

HPLC analysis: 95: 5 e.r. (Chiralcel ID, 30:70 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 26.5 min, R_t (minor) = 29.7 min.

(1*S*,2*R*,5*S*)-2-(4-Chlorophenyl)-5-ethyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3c):

A white solid; M.p. 140.9-142.4 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 5.45 (s, 1H), 4.06 (d, $J = 13.2$ Hz, 1H), 3.67 (s, 1H), 3.52 (d, $J = 13.6$ Hz, 1H), 2.43 (s, 3H), 1.94 (q, $J = 7.6$ Hz, 2H), 0.96 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.1,

144.2, 136.7, 135.6, 134.2, 129.7, 129.2, 127.3, 127.2, 89.0, 64.6, 62.7, 53.3, 26.1, 21.6, 8.4 ppm.

IR (film): $\nu_{\max}$ 2972, 2931, 2868, 1832, 1816, 1598, 1492, 1460, 1404, 1344, 1307, 1276, 1242, 1188, 1159, 1097, 1056, 1012, 974, 960, 864, 845, 829, 817 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{21}\text{NO}_4\text{SCl}]^+$: $m/z = 406.0880$, found: $m/z = 406.0877$. $[\alpha]^{25}_{\text{D}} = -66.3$ ($c = 2.0$ in CHCl_3).

HPLC analysis: 96: 4 e.r. (Chiralcel IB, 10:90 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 42.3 min, R_t (minor) = 46.4 min.

(1S,2R,5S)-2-(4-bromophenyl)-5-ethyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3d):

A white solid; M.p. 144.8-145.9 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 5.43 (s, 1H), 4.06 (d, $J = 13.6$ Hz, 1H), 3.67 (s, 1H), 3.52 (d, $J = 13.6$ Hz, 1H), 2.43 (s, 3H), 1.93 (q, $J = 7.2$ Hz, 2H), 0.96 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.1, 144.2, 137.2, 135.6, 132.2, 129.7, 127.6, 127.2, 122.3, 89.0, 64.5, 62.8, 53.3, 26.2, 21.6, 8.4 ppm.

IR (film): $\nu_{\max}$ 2980, 1927, 1862, 1820, 1735, 1597, 1460, 1404, 1340, 1251, 1157, 1089, 1010, 954, 862, 823 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{21}\text{NO}_4\text{SBr}]^+$: $m/z = 450.0375$, found: $m/z = 450.0374$. $[\alpha]^{25}_{\text{D}} = -59.6$ ($c = 2.3$ in CHCl_3).

HPLC analysis: 95: 5 e.r. (Chiralcel ID, 30:70 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 31.2 min, R_t (minor) = 34.4 min.

(1S,2R,5S)-5-Ethyl-2-(4-nitrophenyl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3e):

A white solid; M.p. 149.8-152.1 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 5.56 (s, 1H), 4.10 (d, $J = 14.0$ Hz, 1H), 3.71 (s, 1H), 3.59 (d, $J = 13.6$ Hz, 1H), 2.45 (s, 3H), 1.93 (q, $J = 7.6$ Hz, 2H), 0.95 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 165.6, 147.7, 145.4, 144.6, 135.2, 129.9, 127.2, 126.8, 124.4, 89.0, 64.6, 62.7, 53.5, 26.1, 21.6, 8.5 ppm.

IR (film): ν_{max} 3278, 2991, 1976, 1924, 1879, 1828, 1716, 1597, 1521, 1494, 1460, 1411, 1348, 1307, 1280, 1209, 1159, 1089, 1051, 1033, 1016, 968, 954, 812 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_6\text{S}]^+$: $m/z = 417.1120$, found: $m/z = 417.1118$.

$[\alpha]_{\text{D}}^{25} = -60.1$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 90: 10 e.r. (Chiralcel IB, 20:80 $i\text{PrOH}$ /Hexane, 0.6 mL/min), R_t (major) = 38.7 min, R_t (minor) = 47.8 min.

(1S,2R,5S)-5-Ethyl-2-(p-tolyl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3f):

A white solid; M.p. 122.8-124.1 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.18 – 7.06 (m, 4H), 5.45 (s, 1H), 4.05 (d, J = 13.2 Hz, 1H), 3.70 (s, 1H), 3.53 (d, J = 13.2 Hz, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 1.95 (q, J = 7.6 Hz, 2H), 0.97 (t, J = 7.6 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.6, 143.9, 138.1, 135.9, 135.2, 129.7, 129.6, 127.2, 125.8, 89.1, 64.7, 63.1, 53.3, 26.2, 21.6, 21.0, 8.4 ppm.

IR (film): ν_{max} 2960, 2926, 2854, 1820, 1732, 1674, 1622, 1602, 1463, 1344, 1280, 1262, 1159, 1120, 1089, 1072, 821, 804 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{24}\text{NO}_4\text{S}]^+$: m/z = 386.1426, found: m/z = 386.1423. $[\alpha]^{25}_{\text{D}} = -55.2$ (c = 1.0 in CHCl_3).

HPLC analysis: 96: 4 e.r. (Chiralcel ID, 20:80 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 53.5 min, R_t (minor) = 56.4 min.

(1S,2R,5S)-5-Ethyl-2-(4-methoxyphenyl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3g):

A white solid; M.p. 119.9-121.5 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.45 (s, 1H), 4.04 (d, J = 13.6 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 1H), 3.51 (d, J = 13.2 Hz, 1H), 2.42 (s, 3H), 1.96 (q, J = 7.6 Hz, 2H), 1.00 (t, J = 7.6 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.6, 159.5, 143.9, 135.9, 130.1, 129.6, 127.3, 127.2, 114.4, 89.0, 64.6, 62.9, 55.3, 53.2, 26.2, 21.6, 8.4 ppm.

IR (film): ν_{max} 3278, 3043, 3021, 2972, 2953, 2841, 1820, 1739, 1614, 1597, 1514, 1463, 1452, 1400, 1340, 1259, 1240, 1205, 1139, 1089, 1010, 974, 952, 860, 815 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{24}\text{NO}_5\text{S}]^+$: m/z = 402.1375, found: m/z = 402.1382. $[\alpha]^{25}_{\text{D}} = -58.0$ (c = 1.2 in CHCl_3).

HPLC analysis: 98: 2 e.r. (Chiralcel ID, 30:70 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 53.1 min, Rt (minor) = 71.2 min.

(1*S*,2*R*,5*S*)-5-Ethyl-2-(2-methoxyphenyl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3h):

A colorless oil; **¹H NMR** (400 MHz, CDCl₃) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.32 – 7.21 (m, 3H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.51 (s, 1H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.73 (s, 3H), 3.68 – 3.62 (m, 2H), 2.42 (s, 3H), 1.98 – 1.75 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 167.4, 155.9, 143.7, 135.9, 129.7, 129.5, 127.8, 127.2, 126.3, 120.9, 110.6, 89.1, 64.0, 61.4, 55.1, 54.4, 26.1, 21.6, 8.4 ppm.

IR (film): ν_{max} 3053, 2976, 2931, 2841, 1822, 1681, 1589, 1454, 1346, 1265, 1161, 1095, 1053, 1022, 975, 894, 813 cm⁻¹.

HRMS (ESI): calculated for [C₂₁H₂₄NO₅S]⁺: *m/z* = 402.1375, found: *m/z* = 402.1375.

[α]_D²⁵ = -69.8 (*c* = 1.0 in CHCl₃).

HPLC analysis: 96: 4 e.r. (Chiralcel ID, 30:70 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 56.2 min, Rt (minor) = 71.1 min.

4-((1*S*,2*R*,5*S*)-5-Ethyl-7-oxo-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-2-yl)-2-methoxyphenyl acetate (4-3i):

A colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 1.6$ Hz, 1H), 6.74 (dd, $J = 8.4$, 2.0 Hz, 1H), 5.48 (s, 1H), 4.08 (d, $J = 13.6$ Hz, 1H), 3.81 (s, 3H), 3.73 (s, 1H), 3.51 (d, $J = 13.2$ Hz, 1H), 2.43 (s, 3H), 2.31 (s, 3H), 1.95 (q, $J = 7.6$ Hz, 2H), 0.99 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 168.8, 166.4, 151.5, 144.1, 139.5, 136.9, 135.6, 129.7, 127.2, 123.2, 117.5, 110.4, 89.1, 64.5, 63.1, 55.9, 53.4, 26.2, 21.5, 20.6, 8.4 ppm. **IR** (film): ν_{max} 3024, 2972, 2939, 1828, 1770, 1606, 1510, 1463, 1346, 1338, 1199, 1159, 1124, 1093, 1055, 1033, 1012, 977, 904, 817 cm^{-1} . **HRMS** (ESI): calculated for $[\text{C}_{23}\text{H}_{26}\text{NO}_7\text{S}]^+$: $m/z = 460.1430$, found: $m/z = 460.1432$. $[\alpha]^{25}_{\text{D}} = -36.1$ ($c = 2.0$ in CHCl_3). **HPLC** analysis: 95: 5 e.r. (Chiralcel IB, 20:80 i PrOH/Hexane, 0.5 mL/min), R_t (major) = 27.1 min, R_t (minor) = 38.5 min.

4-3j

(1*S*,2*R*,5*S*)-5-Ethyl-2-(naphthalen-2-yl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3j):

A white solid; M.p. 152.8-154.6 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.86 – 7.77 (m, 3H), 7.71 (s, 1H), 7.65 (d, $J = 8.0$ Hz, 2H), 7.56 – 7.47 (m, 2H), 7.25 – 7.17 (m, 2H), 5.66 (s, 1H), 4.16 (d, $J = 13.2$ Hz, 1H), 3.81 (s, 1H), 3.66 (d, $J = 13.6$ Hz, 1H), 2.39 (s, 3H), 1.95 (q, $J = 7.6$ Hz, 2H), 0.96 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.5, 144.0, 135.8, 135.3, 133.1, 132.9, 129.7, 129.2, 128.1, 127.6, 127.3, 126.7, 126.6, 124.9, 123.3, 89.1, 64.8, 63.5, 53.6, 26.3 21.5, 8.5 ppm. **IR** (film): ν_{max} 3055, 2955, 2972, 2922, 2854, 1820, 1739, 1597, 1508, 1460, 1359, 1340, 1284, 1249, 1159, 1193, 1089, 956, 813 cm^{-1} . **HRMS** (ESI): calculated for $[\text{C}_{24}\text{H}_{24}\text{NO}_4\text{S}]^+$: $m/z = 422.1426$, found: $m/z = 422.1422$. $[\alpha]^{25}_{\text{D}} = -53.1$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 96: 4 e.r. (Chiralcel IB, 20:80 *i*PrOH/Hexane, 0.6 mL/min), Rt (major) = 32.9 min, Rt (minor) = 22.7 min.

(1*S*,2*R*,5*S*)-2-(4-(allyloxy)phenyl)-5-ethyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3k):

A white solid; M.p. 104.5-105.4 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.04 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.48 – 5.24 (m, 3H), 4.60 – 4.44 (m, 2H), 4.03 (d, *J* = 13.2 Hz, 1H), 3.69 (s, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 2.41 (s, 3H), 1.96 (q, *J* = 7.6 Hz, 2H), 0.98 (t, *J* = 7.6 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 166.6, 158.5, 143.8, 135.8, 132.9, 130.2, 129.6, 127.22, 127.20, 117.8, 115.2, 89.0, 68.8, 64.6, 62.9, 53.2, 26.2, 21.5, 8.4 ppm.

IR (film): ν_{max} 2983, 2926, 2854, 1816, 1739, 1612, 1514, 1456, 1406, 1340, 1290, 1251, 1159, 1089, 1024, 966, 920, 862, 823 cm⁻¹.

HRMS (ESI): calculated for [C₂₃H₂₆NO₅S]⁺: *m/z* = 428.1532, found: *m/z* = 428.1538. [α]_D²⁵ = -57.4 (*c* = 2.0 in CHCl₃).

HPLC analysis: 99: 1 e.r. (Chiralcel IB, 10:90 *i*PrOH/Hexane, 0.6 mL/min), Rt (major) = 35.5 min, Rt (minor) = 38.8 min.

Methyl 4-((1*S*,2*R*,5*S*)-5-ethyl-7-oxo-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-2-yl)benzoate (4-3l):

A colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.03 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 5.53 (s, 1H), 4.09 (d, $J = 13.6$ Hz, 1H), 3.93 (s, 3H), 3.70 (s, 1H), 3.57 (d, $J = 13.6$ Hz, 1H), 2.43 (s, 3H), 1.93 (q, $J = 7.2$ Hz, 2H), 0.94 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.4, 166.1, 144.3, 143.1, 135.6, 130.4, 130.1, 129.8, 127.2, 125.8, 89.0, 64.7, 63.0, 53.4, 52.2, 26.1, 21.6, 8.4 ppm.

IR (film): ν_{max} 3280, 3039, 2991, 2924, 2879, 1820, 1720, 1614, 1597, 1438, 1413, 1336, 1282, 1247, 1220, 1192, 1159, 1120, 1093, 1020, 958, 902 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{22}\text{H}_{24}\text{NO}_6\text{S}]^+$: $m/z = 430.1324$, found: $m/z = 430.1330$. $[\alpha]_{\text{D}}^{25} = -42.7$ ($c = 1.5$ in CHCl_3).

HPLC analysis: 98: 2 e.r. (Chiralcel IB, 20:80 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 26.5 min, R_t (minor) = 30.0 min.

(1S,2R,5S)-5-Ethyl-2-(furan-2-yl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3m):

A white solid; M.p. 120.9-122.9 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.52 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 1.2$ Hz, 1H), 6.37 (d, $J = 3.2$ Hz, 1H), 6.28 (dd, $J = 3.2, 2.0$ Hz, 1H), 5.44 (s, 1H), 3.92 (d, $J = 12.0$ Hz, 1H), 3.72 (s, 1H), 3.42 (d, $J = 12.0$ Hz, 1H), 2.40 (s, 3H), 2.15 – 1.99 (m, 2H), 1.06 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.3, 150.7, 143.7, 142.8, 135.2, 129.5, 127.3, 110.5, 109.0, 88.6, 61.8, 56.7, 53.0, 26.1, 21.5, 8.3 ppm.

IR (film): ν_{max} 2983, 2924, 2881, 1840, 1734, 1598, 1494, 1452, 1371, 1340, 1327, 1294, 1259, 1246, 1165, 1147, 1093, 1055, 1022, 1010, 977, 925, 821, 808 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{18}\text{H}_{20}\text{NO}_5\text{S}]^+$: $m/z = 362.1062$, found: $m/z = 362.1068$. $[\alpha]_{\text{D}}^{25} = -63.2$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 98: 2 e.r. (Chiralcel ID, 30:70 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 44.3 min, Rt (minor) = 49.0 min.

(1*S*,2*R*,5*S*)-5-Ethyl-2-(pyridin-3-yl)-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3n):

A colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.57 (dd, J = 4.8, 1.6 Hz, 1H), 8.49 (d, J = 2.4 Hz, 1H), 7.72 – 7.62 (m, 3H), 7.34 – 7.26 (m, 3H), 5.51 (s, 1H), 4.09 (d, J = 13.6 Hz, 1H), 3.74 (s, 1H), 3.53 (d, J = 13.6 Hz, 1H), 2.43 (s, 3H), 1.98 (q, J = 7.6 Hz, 2H), 0.99 (t, J = 7.6 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 165.8, 149.7, 147.4, 144.3, 135.4, 134.1, 133.8, 129.8, 127.2, 123.8, 89.0, 64.1, 61.3, 53.3, 26.1, 21.6, 8.4 ppm.

IR (film): ν_{max} 3037, 2978, 2868, 1816, 1598, 1479, 1456, 11435, 1404, 1344, 1246, 1166, 1097, 975, 952, 866, 819 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_4\text{S}]^+$: m/z = 373.1222, found: m/z = 373.1228. $[\alpha]_{\text{D}}^{25}$ = -61.2 (c = 1.5 in CHCl_3).

HPLC analysis: 92: 8 e.r. (Chiralcel OJH, 30:70 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 55.3 min, Rt (minor) = 36.7 min.

(1*S*,2*S*,5*S*)-5-Ethyl-2-propyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3o):

A colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.71 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.31 (t, J = 6.4 Hz, 1H), 3.87 (d, J = 13.6 Hz, 1H), 3.43 (d, J = 13.6 Hz, 1H), 3.35 (s, 1H), 2.43 (s, 3H), 1.96 (q, J = 7.6 Hz, 2H), 1.70 – 1.62 (m, 1H), 1.50 – 1.34 (m, 3H), 1.03 (t, J = 7.6 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz,

CDCl₃) δ = 167.2, 143.9, 136.1, 129.7, 127.3, 88.6, 61.8, 60.8, 52.2, 36.3, 26.3, 21.6, 19.0, 13.7, 8.6 ppm.

IR (film): $\nu_{\max}$ 2960, 2927, 2873, 1824, 1598, 1460, 1348, 1301, 1251, 1186, 1155, 1093, 1058, 1026, 960, 813 cm⁻¹.

HRMS (ESI): calculated for [C₁₇H₂₄NO₄S]⁺: m/z = 338.1426, found: m/z = 338.1434.

$[\alpha]^{25}_{\text{D}}$ = -25.3 (c = 1.0 in CHCl₃).

HPLC analysis: 86: 14 e.r. (Chiralcel ID, 20:80 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 26.3 min, R_t (minor) = 28.1 min.

(1S,2S,5S)-5-Ethyl-3-(mesitylsulfonyl)-2-propyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3p):

A white solid; M.p. 108.5-109.7-166 °C; **¹H NMR** (400 MHz, CDCl₃) δ 6.95 (s, 2H), 4.31 (dd, J = 10.0, 4.4 Hz, 1H), 3.58 – 3.42 (m, 2H), 3.35 (d, J = 12.0 Hz, 1H), 2.59 (s, 6H), 2.30 (s, 3H), 2.09 – 1.96 (m, 2H), 1.93 – 1.83 (m, 1H), 1.54 – 1.41 (m, 1H), 1.29 – 1.23 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 167.8, 143.0, 140.4, 132.1, 132.0, 87.0, 60.7, 60.6, 50.6, 33.9, 26.5, 22.7, 20.9, 19.1, 13.7, 8.6.

IR (film): $\nu_{\max}$ 2960, 2935, 2883, 1809, 1604, 1564, 1456, 1379, 1327, 1253, 1155, 1058, 1028, 966, 935, 852, 812 cm⁻¹.

HRMS (ESI): calculated for [C₁₉H₂₈NO₄S]⁺: m/z = 366.1739, found: m/z = 366.1733.

$[\alpha]^{25}_{\text{D}}$ = -21.2 (c = 2.0 in CHCl₃).

HPLC analysis: 91: 9 e.r. (Chiralcel ID, 20:80 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 20.1 min, R_t (minor) = 18.9 min.

(1*S*,2*S*,5*S*)-5-Ethyl-3-(mesitylsulfonyl)-2-pentyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3q):

A colorless oil; **¹H NMR** (400 MHz, CDCl₃) δ 6.95 (s, 2H), 4.28 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.62 – 3.47 (m, 2H), 3.35 (d, *J* = 12.4 Hz, 1H), 2.59 (s, 6H), 2.29 (s, 3H), 2.06 – 1.95 (m, 2H), 1.94 – 1.81 (m, 1H), 1.54 – 1.39 (m, 1H), 1.32 – 1.22 (m, 6H), 1.06 (t, *J* = 7.6 Hz, 3H), 0.92 – 0.83 (m, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 167.8, 143.0, 140.4, 132.2, 132.0, 87.7, 61.0, 60.8, 50.6, 31.8, 31.2, 26.5, 25.5, 22.7, 22.4, 20.9, 13.8, 8.7 ppm.

IR (film): $\nu_{\max}$ 2951, 2926, 2858, 1805, 1604, 1566, 1460, 1381, 1340, 1247, 1209, 1157, 1091, 1058, 1008, 925, 854, 812 cm⁻¹.

HRMS (ESI): calculated for [C₂₁H₃₁NO₄SN_a]⁺: *m/z* = 416.1872, found: *m/z* = 416.1869.

[α]_D²⁵ = -16.1 (*c* = 1.7 in CHCl₃).

HPLC analysis: 88: 12 e.r. (Chiralcel ID, 20:80 *i*PrOH/Hexane, 0.7 mL/min), *R*_t (major) = 19.4 min, *R*_t (minor) = 17.4 min.

(1*S*,2*R*,5*S*)-5-Methyl-2-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3r):

A white solid; M.p. 127.3-129.1 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.26 – 7.20 (m, 4H), 5.49 (s, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 3.71 (s, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 2.41 (s, 3H), 1.68 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 166.2, 143.9, 138.0, 135.8, 129.6, 129.1, 128.3, 127.3, 126.0, 85.5, 66.5, 63.6, 54.6, 21.6, 19.3 ppm.

IR (film): $\nu_{\max}$ 2970, 2924, 2873, 1828, 1824, 1653, 1598, 1494, 1456, 1494, 1456, 1398, 1361, 1340, 1286, 1259, 1240, 1209, 1159, 1141, 1093, 1078, 1037, 1016, 974, 823, 812 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{20}\text{NO}_4\text{S}]^+$: $m/z = 358.1113$, found: $m/z = 358.1112$.
 $[\alpha]^{25}_{\text{D}} = -61.1$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 95: 5 e.r. (Chiralcel ID, 20:80 i PrOH/Hexane, 0.6 mL/min), R_t (major) = 69.7 min, R_t (minor) = 83.0 min.

(1*R*,2*S*,5*R*)-5-Isopropyl-2-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3s):

A colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.68 (d, $J = 8.0$ Hz, 2H), 7.40 – 7.32 (m, 2H), 7.32 – 7.24 (m, 5H), 5.51 (s, 2H), 4.01 (d, $J = 13.6$ Hz, 2H), 3.71 (s, 2H), 3.64 (d, $J = 13.2$ Hz, 2H), 2.43 (s, 3H), 2.09 (dt, $J = 13.6, 6.8$ Hz, 1H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.7, 144.0, 138.2, 135.8, 129.7, 129.1, 128.1, 127.2, 125.6, 92.0, 64.2, 63.2, 51.9, 31.0, 21.6, 17.3, 16.9 ppm.

IR (film): $\nu_{\max}$ 3034, 2981, 2864, 1816, 1739, 1473, 1450, 1344, 1255, 1242, 1155, 1103, 1093, 1085, 1056, 1039, 1016, 975, 864, 815 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{24}\text{NO}_4\text{S}]^+$: $m/z = 386.1426$, found: $m/z = 386.1429$.
 $[\alpha]^{25}_{\text{D}} = +53.1$ ($c = 1.5$ in CHCl_3).

HPLC analysis: 93: 7 e.r. (Chiralcel ID, 20:80 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 42.7 min, R_t (minor) = 37.7 min.

(1*R*,2*S*,5*R*)-5-Isopropyl-2-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3t):

A colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, $J = 8.4$ Hz, 2H), 7.38 – 7.28 (m, 3H), 7.24 (dd, $J = 10.8, 4.0$ Hz, 4H), 5.48 (s, 1H), 4.07 (d, $J = 13.6$ Hz, 1H), 3.71 (d, $J = 0.4$ Hz, 1H), 3.54 (d, $J = 13.6$ Hz, 1H), 2.42 (s, 3H), 1.89 (t, $J = 7.6$ Hz, 2H), 1.39 – 1.21 (m, 4H), 0.86 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.6, 143.9, 138.1, 135.8, 129.7, 129.1, 128.2, 127.2, 125.9, 88.6, 65.2, 63.3, 53.6, 32.9, 26.3, 22.5, 21.6, 13.7 ppm.

IR (film): ν_{max} 3030, 2958, 2931, 2864, 1842, 1828, 1687, 1598, 1494, 1454, 1338, 1305, 1286, 1253, 1180, 1157, 1091, 1041, 1018, 972, 914, 862, 815 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{22}\text{H}_{26}\text{NO}_4\text{S}]^+$: $m/z = 400.1583$, found: $m/z = 400.1586$. $[\alpha]^{25}_{\text{D}} = -50.4$ ($c = 2.0$ in CHCl_3).

HPLC analysis: 96: 4 e.r. (Chiralcel ID, 30:70 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 26.0 min, R_t (minor) = 29.6 min.

(1*S*,2*R*,5*S*)-5-Benzyl-2-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3u):

A white solid; M.p. 157.0-158.9 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.60 (d, $J = 8.4$ Hz, 2H), 7.32 – 7.20 (m, 8H), 7.14 – 7.04 (m, 4H), 5.44 (s, 1H), 3.98 (d, $J = 13.6$ Hz, 1H), 3.73 (s, 1H), 3.63 (d, $J = 13.6$ Hz, 1H), 3.19 (s, 2H), 2.41 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.0, 143.9, 137.9, 135.8, 133.6, 129.64, 129.57, 129.0, 128.9, 128.2, 127.7, 127.2, 125.8, 88.0, 65.1, 63.3, 53.3, 39.1, 21.6 ppm.

IR (film): ν_{max} 3064, 3030, 2939, 2927, 1840, 1598, 1494, 1456, 1336, 1309, 1265, 1247, 1188, 1159, 1147, 1091, 1068, 1055, 985, 970, 812 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{25}\text{H}_{24}\text{NO}_4\text{S}]^+$: $m/z = 434.1426$, found: $m/z = 434.1434$. $[\alpha]^{25}_{\text{D}} = -42.3$ ($c = 1.5$ in CHCl_3).

HPLC analysis: 91: 9 e.r. (Chiralcel ID, 30:70 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 37.4 min, Rt (minor) = 47.5 min.

(1*S*,2*R*,5*S*)-5-Cyclohexyl-2-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3v):

A colorless oil; **¹H NMR** (400 MHz, CDCl₃) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.22 (m, 7H), 5.49 (s, 1H), 4.01 (d, *J* = 13.2 Hz, 1H), 3.74 (s, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 2.42 (s, 3H), 1.80 – 1.61 (m, 5H), 1.45 – 1.35 (m, 1H), 1.24 – 0.95 (m, 5H). **¹³C NMR** (101 MHz, CDCl₃) δ 166.9, 143.9, 138.3, 135.8, 129.7, 129.0, 128.1, 127.2, 125.6, 91.5, 63.8, 63.1, 52.1, 40.5, 27.4, 27.0, 25.6, 25.5, 25.4, 21.6 ppm.

IR (film): ν_{max} 2929, 2865, 1828, 1822, 1651, 1454, 1346, 1305, 1265, 1203, 1161, 1091, 1056, 995, 972, 815 cm⁻¹.

HRMS (ESI): calculated for [C₂₄H₂₈NO₄S]⁺: *m/z* = 426.1739, found: *m/z* = 426.1739. $[\alpha]_{\text{D}}^{25}$ = -38.2 (*c* = 2.0 in CHCl₃).

HPLC analysis: 98: 2 e.r. (Chiralcel ID, 20:80 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 47.0 min, Rt (minor) = 52.5 min.

(1*S*,2*R*,5*S*)-5-(2-(1,3-dioxolan-2-yl)ethyl)-2-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one (4-3w):

A colorless oil; **¹H NMR** (400 MHz, CDCl₃) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.20 (m, 7H), 5.49 (s, 1H), 4.83 (t, *J* = 4.0 Hz, 1H), 4.07 (d, *J* = 13.6 Hz, 1H), 3.95 – 3.74 (m,

5H), 3.53 (d, $J = 13.6$ Hz, 1H), 2.42 (s, 3H), 2.12 – 1.97 (m, 2H), 1.84 – 1.72 (m, 1H), 1.72 – 1.63 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.3, 143.9, 138.0, 135.8, 129.6, 129.1, 128.3, 127.2, 125.9, 102.7, 88.0, 65.3, 65.0, 63.3, 53.6, 28.2, 26.8, 21.6 ppm.

IR (film): ν_{max} 2958, 2926, 2887, 1828, 1681, 1598, 1504, 1494, 1454, 1346, 1305, 1286, 1249, 1157, 1138, 1091, 1076, 1029, 1016, 964, 914, 864, 817 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{23}\text{H}_{26}\text{NO}_6\text{S}]^+$: $m/z = 444.1481$, found: $m/z = 444.1485$.

$[\alpha]_{\text{D}}^{25} = -38.2$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 97: 3 e.r. (Chiralcel ID, 40:60 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 52.5 min, R_t (minor) = 72.3 min.

(S)-2,4-Diphenyl-1-tosyl-2,5-dihydro-1H-pyrrole (4-5a):

A white solid; M.p. 168.0–170.1 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.4$ Hz, 2H), 7.37 – 7.25 (m, 10H), 7.18 (d, $J = 8.0$ Hz, 2H), 6.01 (dd, $J = 4.0, 2.0$ Hz, 1H), 5.66 (dt, $J = 5.2, 2.4$ Hz, 1H), 4.79 – 4.52 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.2, 140.6, 136.3, 135.4, 132.3, 129.5, 128.7, 128.6, 128.5, 127.9, 127.4, 127.3, 125.6, 124.0, 71.0, 55.4, 21.4 ppm.

IR (film): ν_{max} 3028, 2956, 2927, 2854, 1732, 1593, 1492, 1448, 1348, 1290, 1271, 1095, 1062, 912, 866, 800 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{23}\text{H}_{22}\text{NO}_2\text{S}]^+$: $m/z = 376.1371$, found: $m/z = 376.1368$.

$[\alpha]_{\text{D}}^{25} = +101.7$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 97: 3 e.r. (Chiralcel IA, 20:80 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 29.2 min, R_t (minor) = 48.2 min.

(S)-2-Phenyl-4-(*p*-tolyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (4-5b):

A white solid; M.p. 169.5-171.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.24 (m, 5H), 7.24 – 7.10 (m, 6H), 6.04 – 5.87 (m, 1H), 5.64 (dt, *J* = 5.2, 2.4 Hz, 1H), 4.80 – 4.49 (m, 2H), 2.36 (s, 3H), 2.33 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 143.2, 140.7, 138.6, 136.2, 135.4, 129.5, 129.4, 128.5, 127.8, 127.4, 127.2, 125.5, 123.0, 71.0, 55.5, 21.4, 21.2 ppm.

IR (film): ν_{max} 3028, 2956, 2926, 2854, 1735, 1597, 1456, 1338, 1278, 1261, 1157, 1112, 1016, 810 cm⁻¹.

HRMS (ESI): calculated for [C₂₄H₂₄NO₂S]⁺: *m/z* = 390.1528, found: *m/z* = 390.1526. [α]_D²⁵ = +104.5 (*c* = 2.0 in CHCl₃).

HPLC analysis: 99.5: 0.5 e.r. (Chiralcel ID, 20:80 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 26.2 min, Rt (minor) = 35.2 min.

(S)-2-(4-Chlorophenyl)-4-(*p*-tolyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (4-5c):

A white solid; M.p. 182.9-184.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.18 (m, 8H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.90 (dd, *J* = 4.0, 2.0 Hz, 1H), 5.60 (dt, *J* = 5.2, 2.4 Hz, 1H), 4.75 – 4.53 (m, 2H), 2.38 (s, 3H), 2.34 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 143.4, 139.3, 138.9, 136.7, 135.3, 133.7, 129.6, 129.4, 129.3, 128.8, 128.6, 127.2, 125.5, 122.4, 70.2, 55.5, 21.5, 21.2 ppm.

IR (film): ν_{max} 3024, 2956, 2922, 2868, 1597, 1516, 1489, 1413, 1336, 1276, 1155, 1080, 1016, 873, 852, 810 cm⁻¹.

HRMS (ESI): calculated for [C₂₄H₂₃NO₂SCl]⁺: *m/z* = 424.1138, found: *m/z* = 424.1138. [α]_D²⁵ = +98.7 (*c* = 2.0 in CHCl₃).

HPLC analysis: 98: 2 e.r. (Chiralcel ID, 20:80 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 24.2 min, Rt (minor) = 33.9 min.

(S)-4-(Naphthalen-2-yl)-2-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (4-5d):

A white solid; M.p. 179.5-180.6 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.86 – 7.74 (m, 3H), 7.66 (s, 1H), 7.58 (d, $J = 7.2$ Hz, 2H), 7.54 – 7.43 (m, 3H), 7.37 – 7.27 (m, 5H), 7.19 (d, $J = 8.0$ Hz, 2H), 6.13 (s, 1H), 5.83 – 5.63 (m, 1H), 4.97 – 4.65 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.2, 140.5, 136.3, 135.4, 133.2, 133.1, 129.6, 129.5, 128.5, 128.4, 128.1, 127.9, 127.7, 127.4, 127.3, 126.7, 126.6, 124.9, 124.7, 123.2, 71.1, 55.5, 21.4 ppm.

IR (film): ν_{max} 3051, 2956, 2926, 2854, 1735, 1593, 1490, 1454, 1346, 1278, 1159, 1141, 1093, 1066, 1016, 850, 819 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{27}\text{H}_{24}\text{NO}_2\text{S}]^+$: $m/z = 426.1528$, found: $m/z = 426.1531$. $[\alpha]_D^{25} = +97.7$ ($c = 1.0$ in CHCl_3).

HPLC analysis: 95: 5 e.r. (Chiralcel ID, 20:80 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 33.1 min, R_t (minor) = 45.4 min.

(3R,4S,5S)-3-Ethyl-4-(hydroxymethyl)-5-phenyl-1-tosylpyrrolidin-3-ol (4-6):

A colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, $J = 8.0$ Hz, 2H), 7.32 – 7.18 (m, 7H), 4.93 (d, $J = 10.0$ Hz, 1H), 3.86 (dd, $J = 12.0, 1.6$ Hz, 1H), 3.69 (d, $J = 12.0$ Hz, 1H), 3.57 (d, $J = 12.4$ Hz, 1H), 3.54 – 3.42 (m, 1H), 2.78 – 2.65 (m, 2H), 2.38 (s, 3H), 1.89 – 1.78 (m, 2H), 1.59 – 1.46 (m, 1H), 0.97 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.4, 141.4, 135.0, 129.3, 128.4, 127.8, 127.5, 126.7, 81.2, 63.7, 60.4, 57.6, 29.7, 21.5, 8.5 ppm.

IR (film): $\nu_{\max}$ 3344, 3030, 2964, 2926, 2858, 1598, 1494, 1336, 1219, 1153, 1091, 1043, 1018, 987, 929 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{20}\text{H}_{26}\text{NO}_4\text{S}]^+$: $m/z = 376.1583$, found: $m/z = 376.1582$.

$[\alpha]^{25}_{\text{D}} = -74.6$ ($c = 1.5$ in CHCl_3).

HPLC analysis: 96: 4 e.r. (Chiralcel ID, 15:85 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 60.7 min, R_t (minor) = 74.7 min.

Methyl (2*S*,3*R*,4*R*)-4-ethyl-4-hydroxy-2-phenylpyrrolidine-3-carboxylate (4-7):

A colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.26 (m, 5H), 4.73 (d, $J = 9.6$ Hz, 1H), 3.68 (s, 3H), 3.27 – 3.05 (m, 2H), 2.77 (d, $J = 9.6$ Hz, 1H), 2.27 (s, 2H), 1.86 – 1.66 (m, 2H), 0.99 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 173.5, 142.9, 128.6, 127.4, 126.4, 83.4, 64.8, 60.9, 58.8, 52.0, 31.7, 8.6 ppm.

IR (film): $\nu_{\max}$ 3307, 2924, 2850, 1730, 1660, 1498, 1458, 1434, 1377, 1357, 1309, 1170, 1014, 962, 910 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{14}\text{H}_{20}\text{NO}_3]^+$: $m/z = 250.1443$, found: $m/z = 250.1443$.

$[\alpha]^{25}_{\text{D}} = +11.2$ ($c = 1.5$ in CHCl_3).

Methyl (2*S*,3*R*,4*R*)-4-ethyl-4-hydroxy-2-phenyl-1-tosylpyrrolidine-3-carboxylate:

^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, $J = 8.4$ Hz, 2H), 7.31 – 7.23 (m, 7H), 5.02 (d, $J = 10.0$ Hz, 1H), 3.79 (d, $J = 12.0$ Hz, 1H), 3.66 – 3.55 (m, 4H), 2.91 (d, $J = 10.0$ Hz, 1H), 2.77 (s, 1H), 2.40 (s, 3H), 1.81 – 1.67 (m, 1H), 1.63 – 1.59 (m, 1H), 0.93 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.8, 143.6, 140.6, 134.7, 129.4, 128.5, 127.9, 127.8, 126.5, 78.0, 65.8, 62.1, 60.3, 52.3, 30.1, 21.5, 8.5 ppm.

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{26}\text{NO}_5\text{S}]^+$: $m/z = 404.1532$, found: $m/z = 404.1527$.

(1S,4R,5R)-1-Ethyl-4-phenyl-3-tosyl-6-oxa-3-azabicyclo[3.1.0]hexane (4-8):

A white solid; M.p. 106.1-108.2 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, $J = 8.4$ Hz, 2H), 7.41 – 7.25 (m, 7H), 4.96 (s, 1H), 3.74 (d, $J = 12.4$ Hz, 1H), 3.59 (d, $J = 12.4$ Hz, 1H), 3.35 (s, 1H), 2.42 (s, 3H), 1.93 – 1.68 (m, 2H), 0.90 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 143.4, 137.7, 135.6, 129.5, 128.9, 128.1, 127.5, 126.6, 67.5, 64.3, 63.6, 50.9, 22.0, 21.6, 9.1 ppm.

IR (film): ν_{max} 3032, 2974, 2924, 2887, 2854, 1598, 1494, 1462, 1340, 1290, 1234, 1163, 1145, 1111, 1089, 1053, 989, 925 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{22}\text{NO}_3\text{S}]^+$: $m/z = 344.1320$, found: $m/z = 344.1321$. $[\alpha]_{\text{D}}^{25} = -85.0$ ($c = 2.0$ in CHCl_3).

HPLC analysis: 96: 4 e.r. (Chiralcel ID, 20:80 i -PrOH/Hexane, 0.7 mL/min), R_t (major) = 39.0 min, R_t (minor) = 50.2 min.

(2R,3S)-3-(4-Bromophenyl)-2-ethyl-4-nitrobutanal (4-11):

A colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) *Syn* isomer: δ 9.71 (d, $J = 2.4$ Hz, 1 H), 7.48 (d, $J = 8.4$ Hz, 2 H), 7.07 (d, $J = 8.4$ Hz, 2 H), 4.68 – 4.76 (m, 1 H), 4.60 (dd, $J_1 = 10.0$ Hz, $J_2 = 10.0$ Hz, 1 H), 3.72 – 3.86 (m, 1 H), 2.62 – 2.75 (m, 1 H), 1.45 – 1.60 (m, 2 H), 0.84 (t, $J = 7.6$ Hz, 3 H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 202.7, 135.9, 132.3, 129.7, 122.1, 78.2, 54.6, 42.0, 20.3, 10.5 ppm.

Anti isomer: δ 9.49 (d, $J = 2.4$ Hz, 1 H), 7.46 (d, $J = 8.4$ Hz, 2 H), 7.07 (d, $J = 8.4$ Hz, 2 H), 4.68 – 4.76 (m, 2 H), 3.72 – 3.86 (m, 1 H), 2.56 – 2.62 (m, 1 H), 1.68 – 1.80 (m,

2 H), 1.00 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (101 MHz, CDCl_3) δ 202.7, 135.4, 132.2, 129.9, 122.2, 77.6, 54.8, 43.3, 20.5, 11.4 ppm.

IR (film): ν_{max} 3057, 2987, 1637, 1560, 1640, 1422, 1158, 1033, 992, 904 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{12}\text{H}_{15}\text{NO}_3\text{Br}]^+$: $m/z = 300.0235$, found: $m/z = 300.0233$. $[\alpha]_{\text{D}}^{25} = +5.4$ ($c = 1.0$ in CHCl_3).

HPLC analysis (*syn* isomer): 90:10 e.r. (Chiralcel ADH, 2:98 i PrOH/Hexane, 1.0 mL/min), R_t (major) = 19.4 min, R_t (minor) = 28.1 min.

(5a*S*,10b*R*)-2-Mesityl-9-nitro-5a,10b-dihydro-4*H*,6*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium:

A white solid; M.p. 289.1 °C (decomposed); ^1H NMR (400 MHz, CDCl_3) δ 10.24 (s, 1H), 8.30 – 8.12 (m, 2H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.03 (s, 2H), 6.31 (d, $J = 3.5$ Hz, 1H), 5.27 – 4.94 (m, 3H), 3.45 (dd, $J = 17.9, 4.4$ Hz, 1H), 3.28 (d, $J = 17.6$ Hz, 1H), 2.42 (s, 3H), 2.07 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 149.8, 148.1, 147.7, 143.4, 142.2, 137.9, 135.0, 130.9, 129.9, 126.4, 125.1, 119.3, 77.7, 61.6, 60.3, 37.7, 21.3, 17.2 ppm.

IR (film): ν_{max} 3122, 3091, 3049, 2951, 1060, 1581, 1529, 1479, 1452, 1402, 1317, 1273, 1207, 1174, 1161, 1097, 1033, 974, 912 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_3\text{BF}_4]^+$: $m/z = 465.1721$, found: $m/z = 465.1718$.

$[\alpha]_{\text{D}}^{25} = -108.6$ ($c = 0.9$ in CHCl_3).

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Chapter 5

Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis by Radical Processes

5.1 Introduction

Thiamine pyrophosphate (TPP), a thiamine derivative, occurs in biological systems to mediate the oxidative decarboxylation of pyruvate to form acetyl-CoA. These enzymatic reactions enabled by the pyruvate ferredoxin oxidoreductase (PFOR) are believed to proceed via an acyl azolium intermediate (Scheme 5.1).^[1] Inspired by this oxidative process, catalytically generated acyl azoliums and their derived azolium enolates, conjugated acyl azoliums or vinylogous enolates have received great attention in synthetic chemistry. These intermediates are fascinating with unique reactivity and they have been explored in annulation reactions with a large set of nucleophiles and electrophiles (Scheme 5.2).^[2]

Scheme 5.1 TPP-mediated SET process in biological systems.

Scheme 5.2 Acyl azolium and its derived active intermediates.

5.1.1 Oxidative NHC catalysis

One way to provide acyl azoliums is the smart design of the substrates bearing redox active functionality, as described by Bode and Rovis.^[3] Meanwhile, extensive studies have been conducted to find efficient oxidants that can furnish the desired acyl azolium intermediates by oxidizing the respective Breslow intermediate. 3,3',5,5'-tetra-*tert*-Butyldiphenoquinone (**DQ**) is the most popular stoichiometric oxidant for this function due to its inherent two-electron acceptor property.^[4a-b] **DQ** ($E_{\text{THF}} = -1.3 \text{ V}$ vs SCE) is able to produce various azolium intermediates, which can undergo annulation reactions with appropriate partners to form numerous high value complex products.^[4] However, wide application of **DQ** is hindered due to its relatively high cost. This is particularly true for large-scale synthesis, that requires large amount of **DQ**. Furthermore, using **DQ** leads to complications when obtaining the final product via chromatography, since equimolar amount of the generated phenol, as the reductant, needs to be removed before isolation of the final product (Scheme 5.3a).

Scheme 5.3 Representative oxidants used in the literatures.

On the other hand, other common oxidants, such as organic oxidants like nitrobenzene,^[5] TEMPO and related N-oxyl radical *etc.*,^[6-8] transition metal (TM)/terminal oxidants and atmospheric O₂,^[9,10] have also been explored albeit with limited application (Scheme 5.3b). Mechanistically, these oxidative processes are usually initiated by generation of the Breslow intermediate, which is formed after the addition of a carbene to an aldehyde and 1,2-proton transfer. In contrast, when MnO₂ is used as the oxidant, it is likely to oxidize the alcoholate intermediate directly before 1,2-proton transfer to give the Breslow ion (Scheme 5.4).^[7]

Scheme 5.4 Oxidative NHC catalysis.

Recently, some new reagents and approaches have been discovered to efficiently oxidize the Breslow intermediates. In 2015, Sun^[11a] and Wang^[11b] groups both independently demonstrated that N-fluorobenzenesulfonimide (NFSI) was an efficient oxidant in the NHC-catalyzed asymmetric α -fluorination of aliphatic aldehyde. In Sun's work, NFSI played two roles: (1) oxidant for the generation of azolium enolates from aldehyde/NHC, (2) electrophilic fluorine source. With their approach, various α -fluoro esters, amides, and thioesters could be obtained in excellent enantioselectivities (Scheme 5.5).

Scheme 5.5 NFSI as oxidant in asymmetric α -fluorination of aldehydes.

Electrochemistry is a powerful method for transformation of functional groups while it remains less developed. In 2012, Boydston reported an electro-synthetic route to achieve the oxidation of Breslow intermediate (Scheme 5.6). Their method has broad applicability with various aromatic aldehydes and unsaturated aldehydes to give the corresponding esters in excellent yields under mild conditions (with low potential).^[12]

Scheme 5.6 Oxidative NHC catalysis via electrochemistry.

Despite the exciting success, these oxidants and oxidative approaches are limited to oxidation of aldehydes to carboxylic acids and related ester derivatives. Their application as efficient oxidants in the functionalization of aldehydes at the α , β , and γ carbon atoms is rarely explored, due to some limitations such as the high cost and side reaction pathway. For example, as reported by Zhong in 2016, when atmospheric O₂ was chosen as the oxidant to give the α,β -unsaturated acyl azolium from enal, an unavoidable side pathway proceeded to consume the aldehyde to carboxylic acid.

Therefore, the discovery of effective and versatile oxidants with low cost is still highly desired in oxidative NHC catalysis.^[10e]

5.1.2 Motivation of our proposal

Our group is interested in oxidative NHC catalysis through single-electron-transfer (SET) process for the discovery of new methodologies.^[13] In 2013, we discovered that nitroalkenes could serve as SET oxidants for the conversion of aldehydes to corresponding esters.^[13a] Later, we, as well as Rovis *et al.*, showed β -carbon C-O bond formation via radical pathway where the NO₂ group also behaved as a SET oxidant (Scheme 5.7).^[14]

Scheme 5.7 Newly developed SET oxidant for oxidative NHC catalysis.

These reports greatly motivate us to screen structurally simple, readily available feedstock polyhalides for a practical and broadly applicable oxidant to generate acyl azoliums through SET oxidation of the Breslow intermediate. Herein, in this chapter we propose to employ simple polyhalides directly in NHC-catalyzed annulation reactions, including the activation of the α , β or γ carbon of the acyl azolium intermediate (Scheme 5.8). Our method takes advantage of the fact that polyhalides (eg. CCl₄) are good SET oxidants to form polyhalo carboradicals.^[15a] Furthermore, they are simple and inexpensive reagents in synthetic chemistry.^[15b] Finally, the stoichiometrically generated reductant, after oxidizing the Breslow intermediate, is

volatile, making it very easy to be removed under reduced pressure. Thus, our newly developed polyhalide oxidant is extremely useful for the generation of acyl azolium ion in both small and large scale by saving time and money.

Scheme 5.8 Our proposed simple polyhalides as oxidants via 2 steps of SET process.

5.2 Results and Discussions

We began our study by choosing enal **5-1a** and acetoacetate **5-2a** as model reaction substrates for the formal [3+3] annulation.^[16a] Initially, BrCCl_3 , which was extensively utilized as a SET oxidant in photocatalysis,^[17] was tested as the oxidant to generate the α,β -unsaturated acyl azolium from enal **5-1a** with triazolium salt **A**^[18] as the pre-catalyst (Table 1, entry 1). Gratifyingly, the desired lactone product **5-3a** was readily afforded in 43% yield. Encouraged by this result, we turned to investigate other simple polyhalide compounds with the hope of finding an inexpensive and more efficient oxidant for oxidative NHC catalysis. Interestingly, carbon tetrachloride (CCl_4 , 4 equiv) also promoted the reaction to furnish **5-3a** in 41% yield (Table 1, entry 2). Further screening of other common halides, including CBr_4 , CHCl_3 , 1,2-dichloroethane (DCE), and 1,1,2,2-tetrachloroethane (TCE) did not produce the desired adduct **5-3a** (entries 3-6). We then optimized the model reaction using CCl_4 as the oxidant. After examining

various solvents, bases as well as NHC catalysts at different temperatures, we could not achieve a yield higher than 46%. Surprisingly, we found that in most cases, the conversion of the enal was very high (no aldehyde remained from crude NMR analysis), while all the reaction yields were still less than 50%.

Table 5.1 Condition optimization for the annulation of **5-1a** with **5-2a**.

5-1a + **5-2a** $\xrightarrow[\text{Polyhalide as oxidant}]{\text{NHC A conditions}}$ **5-3a** + **NHC A**

Entry	Halide	Base	<i>T</i> [°C]	Yield [%] ^[b]
1	BrCCl ₃	Cs ₂ CO ₃	40	43
2	CCl ₄	Cs ₂ CO ₃	40	41
3	CHCl ₃	Cs ₂ CO ₃	40	N.R.
4	CBr ₄	Cs ₂ CO ₃	40	N.R.
5	CH ₂ ClCH ₂ Cl	Cs ₂ CO ₃	40	N.R.
6	CHCl ₂ CHCl ₂	Cs ₂ CO ₃	40	N.R.
7	CCl ₄	K ₂ CO ₃	40	30
8	CCl ₄	DABCO	40	7
9	CCl ₄	(other solvents, bases and NHCs)	40	<46
10	CCl ₃ CCl ₃	Cs ₂ CO ₃	40	61
11	CCl ₃ CCl ₃ (1.2 equiv)	Cs ₂ CO ₃	rt	72
12	CCl ₃ CCl ₃ (1.2 equiv)	Cs ₂ CO ₃ /DABCO ^[c]	rt	83
13 ^[d]	CCl ₃ CCl ₃ (1.2 equiv)	Cs ₂ CO ₃ /DABCO ^[c]	rt	93 (89) ^[e]

[a] Unless otherwise noted, reaction conditions: pre-catalyst **A** (10 mol%), **5-1a** (0.05 mmol), **5-2a** (0.075 mmol), base (2.0 equiv), halide (4.0 equiv), THF (1.0 mL), 4 Å MS, 12 h. [b] NMR yield based on **5-1a** by using 1,3,5-trimethoxybenzene as an internal standard. [c] Cs₂CO₃ (1.2 equiv) and DABCO (1.2 equiv) were used. [d] THF/*t*BuOH (20:1, 1 mL) as the solvent. [e] Isolated yield in parenthesis.

Previous literatures revealed that the low yield was due to unproductive consumption of the enal, caused by in situ generated trichloride methyl anion ([−]CCl₃).^[19] We envisaged this undesired pathway could be avoided if the anion was quenched fast enough. Thus, hexachloride ethane (CCl₃CCl₃, or C₂Cl₆) was explored, as we thought

that the resulting reactive carbanion would quickly give inert tetrachloroethylene (**5-4**) via elimination of the β -chloride (Scheme 5.9). Further conditions screening indeed proved the validity of our proposal (tetrachloroethylene was confirmed by NMR and GC, see part 5.3 for mechanistic study) (entries 11-13).^[20] Finally, we found that 1.2 equivalents of C_2Cl_6 in the presence of CS_2CO_3 and DABCO as the base, with **A** and molecular sieves in THF/*t*BuOH (20:1), provided the best result (89% isolated yield, entry 13).

Scheme 5.9

With the optimized protocol in hand, we next explored the generality of the reaction (Table 5.2). The transformation accommodated a broad range of 1,3-diketones and β -keto esters, providing the corresponding adducts **5-3d-f** in 76-89% yields. It was noteworthy that the unsymmetrical 1,3-diketone also underwent the transformation smoothly, yielding product **5-3g** in 77% yield. Moreover, the electronic nature of the substituent on the phenyl ring of enals (**5-3b** and **5-3c**) had no significant impact on the reaction outcome. Gratifyingly, other Michael donors like activated imines could equally work well to produce the corresponding lactam products **5-6a-c** in moderate to good yields.

Table 5.2 β -Carbon atom reaction: Scope of the reactions of enals **5-1** with either 1,3-dicarbonyls **5-2**^[a] or imines **5-5**^[b].

[a] Conditions 1: enal **5-1** (0.10 mmol), **5-2** (0.15 mmol), **A** (10 mol%), Cs₂CO₃ (1.2 equiv), DABCO (1.2 equiv), C₂Cl₆ (1.2 equiv), 4 Å MS (80 mg), THF/*t*BuOH (20:1, 2 mL), RT for 12 h. [b] Conditions 2: enal **5-1** (0.10 mmol), **5-5** (0.15 mmol), **A** (10 mol%), Cs₂CO₃ (1.5 equiv), DABCO (1.2 equiv), C₂Cl₆ (1.2 equiv), THF (4 mL), RT for 12 h.

We further extended our approach to produce the vinyl enolate intermediate by introducing a methyl group at the β position of unsaturated acyl azolium intermediate (Table 5.3).^[21] First, the [4+2] reaction between enals (**5-7**) and hydrazones (**5-8**) was tested to give the δ -lactam products, which were important precursors of bioactive piperidine derivatives.^[21a,b] The scope of the substrates was broad. Various carboxylic ester substituents of the hydrazones worked well, furnishing products with good yields (**5-8a-c**). Both electron-withdrawing (**5-9d**) and electron-donating (**5-9e**) substituents on the β -phenyl group were tolerated. Additionally, the electrophiles could also be

extended to activated trifluoromethyl ketones under similar conditions, affording the corresponding unsaturated δ -lactones **5-11a-d** in 72-76% yield.^[21c]

Table 5.3 γ -Carbon atom reactions: Scope of the reactions of enals (**5-7**) with either hydrazones (**5-8**)^[a] or activated ketones (**5-10**)^[b].

[a] Conditions 3: enal **5-7** (1.3 equiv), **5-8** (1.0 equiv), **A** (10 mol%), Cs₂CO₃ (1.1 equiv), DABCO (1.2 equiv), C₂Cl₆ (1.2 equiv), THF/*t*BuOH = 20:1 (0.025 M), and 4 Å MS (80 mg) at RT for 12 h. [b] Conditions 4: enal **5-7** (1.3 equiv), **5-10** (1.0 equiv), **A** (10 mol%), Cs₂CO₃ (1.5 equiv), DABCO (1.2 equiv), C₂Cl₆ (1.5 equiv), THF/*t*BuOH = 20:1 (4 mL), and 4 Å MS (80 mg) at RT for 12 h

Aliphatic aldehydes, as stable and readily available substrates, have been previously reported by Rovis^[8f] and our group^[22a] independently to serve as enolate precursors via oxidative NHC catalysis. Not surprisingly, our approach using CCl₃CCl₃ as the oxidant was able to directly provide the NHC-bound azolium enolate from alkyl aldehydes. As shown in Table 5.4, a formal [4+2] cycloaddition of simple aldehydes with chalcone imines occurred smoothly to give the lactams **5-14a-e** in good yields.

Switching the electrophile to unsaturated ketones under similar conditions also afforded six-membered lactones **5-16a-b** in 72-89% yields.^[22]

Table 5.4 α -Carbon activation: Scope of the reactions of aliphatic aldehydes **5-11** with chalcone imines **5-13**^[a] and enones **5-15**^[b].

[a] Conditions 5: aldehyde **5-12** (0.22 mmol), **5-13** (0.10 mmol, 1.0 equiv), **A** (10 mol%), Cs_2CO_3 (2.0 equiv), DABCO (1.2 equiv), C_2Cl_6 (2.2 equiv), THF and 4 Å MS at RT for 18 h. Combined isolated yields based on **5-13**. [b] **5-12** (0.30 mmol), **5-15** (0.10 mmol, 1.0 equiv), **A** (10 mol%), Cs_2CO_3 (2.0 equiv), DABCO (1.2 equiv), C_2Cl_6 (2.2 equiv), THF and 4 Å MS at RT for 18 h. Combined isolated yields based on **5-15**.

Gratifyingly, preliminary experiments showed that the asymmetric transformations of these annulations could be readily achieved by the application of chiral NHC catalysts (Scheme 5.10). Replacing racemic **A** with amino-indanol-derived **B** as the precatalyst, dihydropyranone **5-3a-b** and **5-3f** were obtained in excellent yield and ee. This pre-catalyst **B** continued to show superior performance in furnishing the

lactam products **5-9a** and **5-9e** in excellent enantioselectivity.^[23] Notably, the asymmetric [3+3] annulation could easily be scaled-up to gram-scale, with the formation of chiral lactone **5-3b** in 82% yield and 95:5 er.

Scheme 5.10 Examples in asymmetric version.

5.3 Mechanistic study.

5.3.1 Verification of the generated tetrachloroethylene (**5-4**) as reduced product.

The reaction was performed according to the conditions as above with THF-*d*₈ as the solvent. After stirring at RT for 18 h, the crude mixture was simply filtered to remove the insoluble material and later transferred into a NMR tube for analysis. The crude ¹³C spectrum indicated the existence of CCl₂=CCl₂ (**5-4**) from the peak at 120.98 ppm (Figure 5.1).

The generation of tetrachloroethylene (**5-4**) was further verified from GC spectrum of the reaction mixture. The desired peak could be found at 4.578 min, which matched well with the retention time of the standard sample (Figure 5.2).

Figure 5.1 ^{13}C NMR spectra (in d_8 -THF). (a) ^{13}C NMR of the standard tetrachloroethylene; (b) ^{13}C NMR of the crude reaction residue

Figure 5.2 GC spectra. (a) spectrum 1: Standard sample from Sigma-Aldrich; (b) spectrum 2: Sample from reaction mixture; (c) Mixed sample of the reaction mixture and tetrachloroethylene (TCE).

5.3.2 Proposed reaction pathway.

Scheme 5.11 Proposed reaction pathway.

A proposed reaction pathway is illustrated in Scheme 5.11.^[20] Breslow intermediate **I** is produced upon addition of the carbene to the aldehyde, which is then oxidized by the activated polyhalide (C_2Cl_6) through a single-electron-transfer pathway. The generated polyhalide carbon radical ($\cdot\text{CCl}_2\text{-CCl}_3$) is highly reactive and undergoes a subsequent radical oxidation with intermediate **I'** to give C_2Cl_5^- . Tetrachloroethylene (TCE) is finally generated via a fast intramolecular elimination of the β -chloride. On the other hand, the acyl azolium intermediate **II** is formed and could readily undergo further reactions with the nucleophiles/electrophiles (Table 5-2, 3 and 4). Interestingly, when the model reaction in Table 5-1 was performed without **5-2a**, dimerization product **5-16** was isolated, which was in accordance with previous work reported by Rovis. They had reported the radical intermediate **I'** could couple together with **I** and

eventually afforded product **5-16**. This result proved that polyhalide C_2Cl_6 indeed served as a single electron oxidant in the reaction.^[14b]

Scheme 5.12 Experiment indicating the presence of radical intermediates.

5.4 Summary

In conclusion, we have developed an efficient oxidative approach in NHC organo catalysis. The method, using C_2Cl_6 as a highly efficient oxidant, can readily provide various acyl azolium derived intermediates from aldehydes. It is a rare and practical oxidation pathway through two times of single-electron-transfer processes. In our study, the α , β and γ carbons could be readily activated and react with the appropriate nucleophiles/electrophiles through the generated azolium intermediates. The low cost of the polyhalide oxidant and easily removable reduced byproduct in purification process are attractive for large-scale industrial applications. We expect the SET processes and various radical intermediates in this method shall inspire further novel reaction design and development.

5.5 Experimental Section

5.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. HPLC grade CH₃CN (purchased from TEDIA) was dried over 4Å molecular sieve prior use. Toluene and CH₂Cl₂ was dried over Pure Solv solvent purification system. THF was distilled over sodium. Other solvents were dried over 4Å molecular sieve prior use. Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in 10 mL Schlenk tube.

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Bruker (400 MHz) spectrometer and JEOL-ECX-500 (500 MHz) spectrometer. Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer and JEOL-ECX-500 (125 MHz) spectrometer. IR spectra were recorded on a Shimadzu IR IRAffinity-1 FT-IR Spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of enantiomeric excess 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: [α]_D^r (*c* is in gm 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). The TLC plate was visualized using a UV lamp or potassium permanganate stain.

5.5.2 Experimental section

a) General procedure 1 for the [3+3] annulation of enals **5-1** with 1,3-dicarbonyls **5-2** (Conditions 1 in Table 5-2).

To a dry 10 mL Schlenk tube with stir bar were added with NHC **A** (3.2 mg, 10 mol%), Cs₂CO₃ (38.7 mg, 1.2 equiv), DABCO (13.6 mg, 1.2 equiv), C₂Cl₆ (28.4 mg, 1.2 equiv) and molecular sieves (80 mg). After evacuation, the tube was refilled with nitrogen. Then the nucleophile **5-2** (0.15 mmol, 1.5 equiv) and THF/*t*BuOH (2.0 mL, 20:1, v/v) was added, followed by the addition of enal **5-1** (0.10 mmol, 1.0 equiv). The reaction was stirred at room temperature for 12 h when enal **5-1** was consumed (monitored by TLC). The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (hexane/EtOAc) to afford desired product **5-3**, which was confirmed by ¹H NMR, ¹³C NMR spectrum.

b) General procedure 2 for the [3+3] annulation of enals **5-1** with imines **5-5** (Conditions 2 in Table 5-2).

To a dry 10 mL Schlenk tube with stir bar were added with NHC **A** (3.2 mg, 10 mol%), Cs₂CO₃ (48.4 mg, 1.5 equiv), DABCO (13.6 mg, 1.2 equiv), C₂Cl₆ (28.4 mg, 1.2 equiv) and molecular sieves (80 mg). After evacuation, the tube was refilled with nitrogen. Then **5-5** (0.15 mmol, 1.5 equiv) and 4.0 mL of THF were added, followed by the addition of enal **5-1** (0.10 mmol, 1.0 equiv). The mixture was stirred at room temperature for 12 h when enal **5-1** was consumed (monitored by TLC). The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (hexane/EtOAc) to afford desired product **5-6**, which was confirmed by ¹H NMR, ¹³C NMR spectrum.

c) General procedure (3) for the [4+2] annulation of β-methyl enals 5-7 with hydrazones 5-8 (Conditions 3 in Table 5-3).

Under N₂ atmosphere, to a dry 10 mL Schlenk tube with stir bar, were added NHC **A** (3.2 mg, 10 mol%), Cs₂CO₃ (35.4 mg, 1.1 equiv), DABCO (13.6 mg, 1.2 equiv), C₂Cl₆ (28.4 mg, 0.12 mmol, 1.2 equiv), hydrazones **5-8** (0.10 mmol, 1.0 equiv) and molecular sieves (80 mg). Then enal **5-7** (0.13 mmol, 1.3 equiv) was added and the mixture was dissolved with THF/*t*BuOH (4.0 mL, 20:1, v/v). The reaction mixture was stirred at room temperature for 12 h when enal **5-7** was consumed completely (monitored by TLC). After concentrated under reduced pressure, the crude residue was purified via column chromatography to afford the desired product **5-9**.

d) General procedure (4) for the [4+2] annulation of β -methyl enals **5-6 with trifluoromethyl ketones **5-10** (Conditions 4 in Table 5-3).**

Under N₂ atmosphere, to a dry 10 mL Schlenk tube with stir bar, were added NHC **A** (3.2 mg, 10 mol%), Cs₂CO₃ (48.4 mg, 1.5 equiv), DABCO (13.6 mg, 1.2 equiv), C₂Cl₆ (35.5 mg, 0.15 mmol, 1.5 equiv), activated ketone **5-10** (0.10 mmol, 1.0 equiv) and molecular sieves (80 mg). Then enal **5-7** (0.13 mmol, 1.3 equiv) was added and the mixture was dissolved with THF/*t*BuOH (20:1, 4.0 mL). The reaction mixture was stirred at room temperature for 12 h when enal **5-7** was consumed completely (monitored by TLC). After concentrated under reduced pressure, the crude residue was purified via column chromatography to afford the desired product **5-11**.

e) General procedure (5) for the [4+2] annulation of alkyl aldehyde **5-12 with chalcone imines **5-13** (Conditions 5 in Table 5-4).**

To a dry 10 mL Schlenk tube with stir bar were added with NHC **A** (3.2 mg, 10 mol%), Cs₂CO₃ (64.5 mg, 2.0 equiv), DABCO (13.6 mg, 1.2 equiv), C₂Cl₆ (47.4 mg, 0.22 mmol, 2.2 equiv), chalcone imine **5-13** (0.10 mmol, 1.0 equiv) and molecular sieves (80 mg). After evacuation, the tube was refilled with nitrogen. Then aldehyde **5-12** was added and the reaction was dissolved with THF (2.0 mL). The mixture was

stirred at room temperature for 18 h when chalcone imine **5-13** was consumed completely (monitored by TLC). The mixture was concentrated under reduced pressure (d.r. was determined via the ^1H NMR analysis of crude mixture) and purified by column chromatography on silica gel (hexane/EtOAc) to afford desired product **5-14**.

f) General procedure for the [4+2] annulation of alkyl aldehyde **5-12 with chalcones **5-14** (Conditions 6 in Table 5-4).**

To a dry 10 mL Schlenk tube with stir bar were added with NHC **A** (3.2 mg, 10 mol%), Cs_2CO_3 (64.5 mg, 2.0 equiv), DABCO (13.6 mg, 1.2 equiv), C_2Cl_6 (47.4 mg, 0.22 mmol, 2.2 equiv), chalcone **5-15** (0.10 mmol, 1.0 equiv) and molecular sieves (80 mg). After evacuation, the tube was refilled with nitrogen. Then aldehyde **5-12** (0.30 mmol) was added and the mixture was dissolved in THF (2.0 mL). The mixture was stirred at room temperature for 18 h when chalcone **5-15** was consumed (monitored by TLC). The mixture was concentrated under vacuum (d.r. was determined via the ^1H NMR analysis of crude mixture) and purified by column chromatography on silica gel (hexane/EtOAc) to give the desired product **5-16**.

g) Asymmetric reactions.

Optical catalytic generated products **5-3a-b**, **5-3f** were prepared using chiral NHC **B** as the precatalyst (replace of NHC **A**) according to Procedure 2 (For **5-3f**, additional 50 mol% of LiCl was added as the additive). The enantiomeric excess was determined by chiral HPLC and absolute conformation was confirmed by comparison with previous reports.

Chiral **5-9a** and **5-9c** were synthesized using chiral NHC **B** as the triazolium salt (replace of NHC **A**) following Procedure 4. The enantiomeric excess was determined by chiral HPLC and absolute conformation was confirmed by comparison with previous reports.^[14b]

h) Gram-scale synthesis of chiral **5-3b**.

Under N_2 atmosphere, to a dry 2-neck flask equipped with a magnetic stir bar were added triazolium salt **B** (720.1 mg, 10 mol%), C_2Cl_6 oxidant (5.68 g, 1.2 equiv), Cs_2CO_3 (7.76 g, 1.2 equiv), DABCO (2.72 g, 1.2 equiv), and molecular sieves (1.0 g). Then **5-2a** (3.90 g, 30 mmol, 1.5 equiv) was added and the mixture was dissolved with newly distilled THF (120 mL) and $t\text{BuOH}$ (6 mL), followed by addition of enals **5-1b** (3.34 g,

20.0 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature until the enal **5-1b** was consumed completely (monitored by TLC). After concentrated under reduced pressure, the crude residue was purified via column chromatography to afford the desired product **5-3b** (4.76 g) with 82% yield and 95:5 er.

i) Experiment indicating the presence of radical intermediates.

Under Ar atmosphere, to a dry 10 mL Schlenk tube with stir bar were added NHC **A** (12.8 mg, 20 mol%), Cs_2CO_3 (39.1 mg, 0.6 equiv), C_2Cl_6 (112.0 mg, 0.4 mmol, 2.0 equiv) and molecular sieves (50 mg). Subsequently, enal **5-1a** (27.2 mg, 0.2 mmol, 1.0 equiv) and newly distilled THF (4 mL) were added. The reaction mixture was stirred at 40 °C for 24 h when **5-1a** was consumed completely. After concentrated under reduced pressure, the crude residue was purified via column chromatography to afford the desired product **5-4** in 18% yield. ^1H and ^{13}C NMR spectra of **5-4** matched that of the previously reported compound.^{[14b][23]}

j) Determination of the reductive potential of DQ (3,3',5,5'-tetra-*tert*-butyldiphenylquinone).

Glassy carbon working electrode, Platinum wire counter electrode, and SCE reference electrode in THF at room temperature.

5.5.3 Characterization of Products

Ethyl 6-methyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (5-3a):

A white solid. Mp 81-83 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.22 (m, 3H), 7.17 – 7.09 (m, 2H), 4.26 (d, J = 7.2 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.95 (dd, J = 16.0, 7.2 Hz, 1H), 2.83 (dd, J = 16.0, 2.4 Hz, 1H), 2.47 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.1, 165.9, 161.3, 140.6, 129.0, 127.5, 126.6, 110.0, 60.8, 37.8, 36.3, 18.9, 14.0 ppm.

IR (film): ν_{max} 2993, 2978, 1782, 1705, 1651, 1612, 1489, 1450, 1365, 1288, 1180, 1157, 1080, 1026, 979, 864.

HRMS (ESI): calculated for $[\text{C}_{15}\text{H}_{17}\text{O}_4]^+$: m/z = 261.1127, found: m/z = 261.1126.

$[\alpha]_{\text{D}}^{21}$ = - 127.7 (c = 1.5 in CHCl_3).

HPLC analysis: 94:6 e.r. (Chiralcel ODH, 5:95 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 23.7 min, Rt (minor) = 11.8 min.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (5-3b):

A white solid. Mp 95-97 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.05 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.21 (d, *J* = 6.8 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 2.92 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.80 (dd, *J* = 16.0, 2.4 Hz, 1H), 2.46 (d, *J* = 0.4 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 166.3, 166.0, 161.0, 158.9, 132.6, 127.7, 114.4, 110.4, 60.8, 55.2, 37.0, 36.6, 18.9, 14.1 ppm.

IR (film): ν_{max} 2993, 2939, 2846, 2067, 1712, 1612, 1512, 1435, 1365, 1249, 1180, 1157, 1111, 1033, 941, 825 cm⁻¹.

HRMS (ESI): calculated for [C₁₆H₁₉O₅]⁺: *m/z* = 291.1232, found: *m/z* = 291.1230.

[α]_D²¹ = - 139.6 (*c* = 1.0 in CHCl₃).

HPLC analysis: 95:5 e.r. (Chiralcel ODH, 5:95 *i*PrOH/Hexane, 0.7 mL/min), Rt (major) = 28.4 min, Rt (minor) = 16.3 min.

Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (5-3c):

A white solid. Mp 105-109 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.11 (dd, $J = 8.8, 5.6$ Hz, 2H), 6.99 (t, $J = 8.8$ Hz, 2H), 4.25 (d, $J = 7.2$ Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 2.94 (dd, $J = 16.0, 7.6$ Hz, 1H), 2.80 (dd, $J = 16.0, 2.0$ Hz, 1H), 2.48 (s, 3H), 1.20 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 165.9, 165.8, 162.1 (d, $J = 246.4$ Hz), 161.5, 136.3 (d, $J = 4.0$ Hz), 128.2 (d, $J = 8.1$ Hz), 115.9 (d, $J = 21.2$ Hz), 109.9, 60.9, 37.2, 36.4, 18.9, 14.0 ppm.

IR (film): ν_{max} 3317, 2978, 2931, 2854, 2337, 1735, 1064, 1512, 1411, 1365, 1311, 1242, 1157, 1095, 1018, 941, 825 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{15}\text{H}_{16}\text{O}_4\text{F}]^+$: $m/z = 279.1033$, found: $m/z = 279.1031$.

Ethyl 2-oxo-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carboxylate (5-3d):

A white solid. Mp 132-135 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.56 – 7.38 (m, 5H), 7.37 – 7.21 (m, 5H), 4.41 (dd, $J = 7.6, 2.4$ Hz, 1H), 3.93 (q, $J = 7.2$ Hz, 2H), 3.11 (dd, $J = 16.0, 7.6$ Hz, 1H), 2.94 (dd, $J = 16.0, 2.4$ Hz, 1H), 0.88 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.4, 166.0, 158.5, 139.9, 133.1, 130.1, 129.2, 128.6, 128.0, 127.7, 126.7, 111.7, 61.0, 38.9, 36.3, 13.4 ppm.

IR (film): ν_{max} 3348, 2985, 2924, 2299, 1959, 1735, 1681, 1597, 1450, 1141, 1288, 1265, 1157, 1080, 1026, 979, 802 cm^{-1} .

HRMS (ESI): calculated for $[C_{20}H_{19}O_4]^+$: $m/z = 323.1283$, found: $m/z = 323.1278$.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-2-one (5-3e):

A white solid. Mp 115-118 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.27 (m, 3H), 7.19 – 7.11 (m, 2H), 4.15 (d, $J = 6.0$ Hz, 1H), 2.97 (dd, $J = 15.6, 7.2$ Hz, 1H), 2.84 (dd, $J = 16.0, 2.8$ Hz, 1H), 2.43 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.9, 165.6, 160.3, 139.7, 129.4, 128.0, 126.7, 117.3, 38.9, 37.2, 29.8, 19.1 ppm.

IR (film): ν_{max} 3024, 2924, 2854, 2360, 1774, 1689, 1627, 1489, 1442, 1357, 1249, 1172, 1111, 1026, 948, 864 cm^{-1} .

HRMS (ESI): calculated for $[C_{14}H_{15}O_3]^+$: $m/z = 231.1021$, found: $m/z = 231.1020$.

5-Benzoyl-4,6-diphenyl-3,4-dihydro-2H-pyran-2-one (5-3f):

A white solid. Mp 158-160 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.49 (d, $J = 7.2$ Hz, 2H), 7.40 – 7.34 (m, 2H), 7.32 – 7.03 (m, 11H), 4.56 (dd, $J = 7.6, 2.4$ Hz, 1H), 3.21 (dd, $J = 16.0, 8.0$ Hz, 1H), 3.06 (dd, $J = 16.0, 2.4$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 195.9, 166.7, 154.8, 139.7, 137.1, 132.6, 132.0, 130.3, 129.25, 129.23, 129.0, 128.1, 127.99, 127.79, 126.9, 118.3, 40.4, 35.9 ppm.

IR (film): $\nu_{\max}$ 3024, 2924, 2854, 2360, 1959, 1766, 1627, 1489, 1442, 1334, 1303, 1195, 1126, 1072, 1026, 987, 894 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{24}\text{H}_{19}\text{O}_3]^+$: $m/z = 355.1334$, found: $m/z = 355.1339$.

$[\alpha]_D^{21} = -12.1$ ($c = 1.5$ in CHCl_3).

HPLC analysis: 96:4 e.r. (Chiralcel ODH, 5:95 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 24.6 min, R_t (minor) = 29.1 min.

5-Benzoyl-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-2-one (5-3g):

A white solid. Mp 101-105 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.59 (m, 2H), 7.52 (t, $J = 7.4$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 2H), 7.29 – 7.19 (m, 3H), 7.17 – 7.10 (m, 2H), 4.32 (dd, $J = 7.2, 3.2$ Hz, 1H), 3.07 (dd, $J = 16.0, 7.2$ Hz, 1H), 2.93 (dd, $J = 16.0, 3.6$ Hz, 1H), 1.90 (d, $J = 0.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 195.8, 166.5, 154.8, 140.0, 138.4, 133.1, 129.2, 128.8, 128.7, 127.6, 126.8, 117.8, 39.4, 36.2, 19.0 ppm.

IR (film): $\nu_{\max}$ 3032, 2916, 2854, 1774, 1720, 1627, 1489, 1442, 1342, 1311, 1273, 1226, 1172, 1118, 1033, 987, 964, 894, 864 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{17}\text{O}_3]^+$: $m/z = 293.1178$, found: $m/z = 293.1183$.

4,6-Diphenyl-1-tosyl-3,4-dihydropyridin-2(1*H*)-one (5-6a):

A white solid. Mp 188-190 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.20 (m, 12H), 5.98 (d, *J* = 4.0 Hz, 1H), 3.86 (td, *J* = 8.0, 4.4 Hz, 1H), 2.82 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 144.9, 141.0, 140.4, 137.2, 136.4, 129.13, 129.10, 129.0, 128.4, 127.4, 127.1, 126.0, 123.2, 42.9, 37.2, 21.7 ppm.

IR (film): ν_{max} 3039, 2993, 2978, 2862, 1712, 11597, 1496, 1450, 1411, 1357, 1296, 1249, 1165, 1111, 1087, 1033, 1010, 972, 887 cm⁻¹.

HRMS (ESI): calculated for [C₂₄H₂₂NO₃S]⁺: *m/z* = 404.1320, found: *m/z* = 404.1319.

6-(Benzo[*d*][1,3]dioxol-4-yl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2(1*H*)-one (5-6b):

A white solid. Mp 185-188 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.16 (m, 7H), 6.91 – 6.84 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.98 (s, 2H), 5.90 (d, *J* = 4.4 Hz, 1H), 3.82 (td, *J* = 7.6, 4.4 Hz, 1H), 2.80 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 171.6, 147.8, 147.7, 144.9, 140.6, 140.5, 136.5, 131.3, 129.1, 129.0, 127.3, 127.0, 122.1, 119.7, 108.1, 106.8, 101.3, 42.9, 37.1, 21.7 ppm.

IR (film): ν_{max} 3062, 3030, 2980, 2900, 2781, 2254, 1957, 1728, 1714, 1597, 1494, 1487, 1454, 1359, 1294, 1247, 1172, 1141, 1087, 1039, 931, 910 cm⁻¹.

HRMS (ESI): calculated for [C₂₅H₂₂NO₅S]⁺: m/z = 448.1219, found: m/z = 448.1219.

Methyl 4-(6-(benzo[*d*][1,3]dioxol-4-yl)-2-oxo-1-tosyl-1,2,3,4-tetrahydropyridin-4-yl)benzoate (5-6c):

A white solid. Mp 156-159 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.25 (dd, *J* = 16.0, 8.0 Hz, 4H), 6.94 – 6.81 (m, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.00 (s, 2H), 5.90 (d, *J* = 4.4 Hz, 1H), 3.92 (s, 3H), 3.89 – 3.83 (m, 1H), 2.83 (d, *J* = 7.6 Hz, 2H), 2.43 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 171.1, 166.6, 148.0, 147.8, 145.6, 145.1, 141.2, 136.3, 131.1, 130.3, 129.3, 129.2, 129.1, 127.1, 120.8, 119.8, 108.2, 106.9, 101.4, 52.1, 42.4, 36.9, 21.6 ppm.

IR (film): ν_{max} 3024, 2953, 2902, 2781, 2254, 1957, 1722, 1714, 1612, 1504, 1487, 1435, 1417, 1361, 1284, 1246, 1215, 1171, 1143, 1112, 1087, 1039, 1020, 964, 935 cm⁻¹.

HRMS (ESI): calculated for [C₂₇H₂₄NO₇S]⁺: m/z = 506.1273, found: m/z = 506.1266.

Ethyl 1-benzamido-6-oxo-4-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (5-9a):

A white solid. Mp 203-206 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.79 (s, 1H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.62 – 7.36 (m, 8H), 6.35 (d, *J* = 2.8 Hz, 1H), 4.80 (dd, *J* = 6.8, 2.0 Hz, 1H), 4.23 (qd, *J* = 7.2, 0.8 Hz, 2H), 3.61 (ddd, *J* = 17.5, 7.1, 2.5 Hz, 1H), 3.39 (dd, *J* = 17.6, 2.3 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 166.2, 164.3, 149.6, 136.7, 132.4, 132.0, 130.2, 128.9, 128.7, 127.5, 126.0, 118.5, 62.2, 61.1, 30.1, 14.2 ppm.

IR (film): ν_{max} 3317, 3070, 2939, 2839, 2314, 1728, 1666, 1612, 1573, 1496, 1450, 1435, 1404, 1373, 1296, 1273, 1249, 1219, 1049, 995, 902, 864 cm⁻¹.

HRMS (ESI): calculated for [C₂₁H₂₁N₂O₄]⁺: *m/z* = 365.1501, found: *m/z* = 365.1501.

[α]_D²¹ = - 22.8 (*c* = 2.0 in CHCl₃).

HPLC analysis: 99:1 e.r. (Chiralcel IB, 35:65 *i*PrOH/Hexane, 0.4 mL/min), *R*_t (major) = 19.4 min, *R*_t (minor) = 16.5 min.

Benzyl 1-benzamido-6-oxo-4-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (5-9b):

A white solid. Mp 140-143 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.88 (s, 1H), 7.87 – 7.75 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.37 (m, 7H), 7.30 – 7.22 (m, 5H), 6.32 (d, *J* = 2.4 Hz, 1H), 5.29 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 4.85 (dd, *J* = 7.2, 2.0 Hz, 1H), 3.60 (ddd, *J* = 17.6, 7.2, 2.4 Hz, 1H), 3.36 (dd, *J* = 17.2, 2.0 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.6, 166.2, 164.3, 149.5, 136.6, 134.9, 132.3, 131.9, 130.1, 128.9, 128.7, 128.62, 128.60, 128.2, 127.5, 126.1, 118.5, 67.7, 61.2, 30.1 ppm. **IR** (film): ν_{max} 3317, 3070, 2939, 2839, 2314, 1728, 1666, 1612, 1573, 1496, 1450, 1435, 1404, 1396, 1249, 1219, 1049, 995, 902, 864 cm⁻¹.

HRMS (ESI): calculated for [C₂₆H₂₃N₂O₄]⁺: *m/z* = 427.1658, found: *m/z* = 427.1653.

Isopropyl 1-benzamido-6-oxo-4-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate

(5-9c):

A white solid. Mp 187-189 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.85 (s, 1H), 7.86 (d, *J* = 6.4 Hz, 2H), 7.59 – 7.38 (m, 8H), 6.34 (d, *J* = 2.4 Hz, 1H), 5.07 (dt, *J* = 12.4, 6.4 Hz, 1H), 4.76 (dd, *J* = 6.4, 2.4 Hz, 1H), 3.58 (ddd, *J* = 17.6, 7.2, 2.4 Hz, 1H), 3.38 (dd, *J* = 17.6, 2.4 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.2, 166.2, 164.3, 149.6, 136.8, 132.3, 132.0, 130.1, 128.9, 128.6, 127.5, 126.0, 118.6, 70.1, 61.2, 30.2, 21.72, 21.66 ppm. **IR** (film): ν_{max} 3302, 3024, 2985, 1720, 1666, 1612, 1519, 1489, 1411, 1365, 1226, 1095, 995, 910, 864 cm⁻¹.

HRMS (ESI): calculated for $[C_{22}H_{23}N_2O_4]^+$: $m/z = 379.1658$, found: $m/z = 379.1660$.

Ethyl 1-benzamido-4-(4-chlorophenyl)-6-oxo-1,2,3,6-tetrahydropyridine-

2-carboxylate (5-9d):

A white solid. Mp 127-129 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.97 (s, 1H), 7.85 (d, $J = 7.2$ Hz, 2H), 7.59 – 7.49 (m, 1H), 7.49 – 7.36 (m, 6H), 6.32 (d, $J = 2.4$ Hz, 1H), 4.78 (dd, $J = 6.8, 2.0$ Hz, 1H), 4.22 (qd, $J = 7.2, 2.0$ Hz, 2H), 3.58 (ddd, $J = 17.6, 6.8, 2.4$ Hz, 1H), 3.33 (dd, $J = 17.6, 2.4$ Hz, 1H), 1.24 (t, $J = 7.2$ Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.6, 166.2, 163.9, 148.2, 136.3, 135.1, 132.4, 131.8, 129.2, 128.6, 127.5, 127.3, 118.9, 62.2, 61.0, 30.0, 14.2 ppm.

IR (film): $\nu_{\max}$ 3271, 2978, 2924, 2245, 1743, 1658, 1612, 1512, 1489, 1365, 1288, 1242, 1195, 1095, 1010, 918, 825 cm⁻¹.

HRMS (ESI): calculated for $[C_{21}H_{20}N_2O_4Cl]^+$: $m/z = 399.1112$, found: $m/z = 399.1112$.

Ethyl 1-benzamido-4-(3-methoxyphenyl)-6-oxo-1,2,3,6-tetrahydropyridine-2-
carboxylate (5-9e):

A white solid. Mp 148-151 °C; **¹H NMR** (400 MHz, CDCl₃) δ 9.02 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 6.97 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 4.78 (dd, *J* = 6.8, 2.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.59 (ddd, *J* = 17.6, 7.2, 2.4 Hz, 1H), 3.36 (dd, *J* = 17.6, 2.4 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.7, 166.2, 164.2, 159.9, 149.4, 138.1, 132.3, 131.9, 129.9, 128.6, 127.5, 118.7, 118.5, 115.6, 111.7, 62.2, 61.1, 55.3, 30.2, 14.2 ppm.

IR (film): ν_{max} 3302, 3055, 2924, 2839, 2222, 1913, 1728, 1651, 1581, 1512, 1427, 1373, 1288, 1257, 1226, 1172, 1095, 1049, 1026, 856 cm⁻¹.

HRMS (ESI): calculated for [C₂₂H₂₃N₂O₄]⁺: *m/z* = 395.1607, found: *m/z* = 395.1606.

[α]_D²¹ = - 29.1 (*c* = 1.5 in CHCl₃).

HPLC analysis: 97: 3 e.r.. (Chiralcel IB, 35:65 *i*-PrOH/Hexane, 0.4 mL/min), *R*_t (major) = 22.3 min, *R*_t (minor) = 20.4 min.

4,6-Diphenyl-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-2-one (5-11a):

A colorless oil; **¹H NMR** (400 MHz, CDCl₃) δ 7.59 – 7.43 (m, 7H), 7.42 – 7.34 (m, 3H), 6.25 (d, *J* = 2.4 Hz, 1H), 3.62 (d, *J* = 17.6 Hz, 1H), 3.52 (dd, *J* = 17.6, 2.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8, 152.0, 135.6, 133.8, 131.2, 129.7, 129.2, 128.8, 126.5, 126.0, 123.3 (d, *J* = 284.8 Hz), 115.0, 82.5 (q, *J* = 30.3 Hz), 29.68 ppm.

IR (film): $\nu_{\max}$ 3062, 2924, 1735, 1597, 1489, 1450, 1365, 1234, 1087, 987, 864, 810 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{18}\text{H}_{14}\text{O}_2\text{F}_3]^+$: $m/z = 319.0946$, found: $m/z = 319.0946$.

4-(4-Chlorophenyl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-2-one (5-11b):

A white solid. Mp 117-119 °C; **^1H NMR** (400 MHz, CDCl_3) δ 7.57 – 7.48 (m, 2H), 7.47 – 7.35 (m, 7H), 6.23 (d, $J = 2.0$ Hz, 2H), 3.66 – 3.41 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 161.5, 150.5, 137.5, 133.9, 133.6, 129.8, 129.5, 128.9, 127.3, 126.5, 123.2 (d, $J = 284.8$ Hz), 115.3, 82.5 (q, $J = 30.3$ Hz), 29.7 ppm.

IR (film): $\nu_{\max}$ 3099, 3034, 2922, 2852, 1724, 1616, 1593, 1566, 1496, 1454, 1434, 1409, 1311, 1274, 1259, 1236, 1197, 1166, 1093, 1082, 1051, 1035, 993, 956, 923 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{18}\text{H}_{13}\text{O}_2\text{F}_3\text{Cl}]^+$: $m/z = 353.0574$, found: $m/z = 353.0558$.

4-(3-Methoxyphenyl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-2-one (5-11c):

A white solid. Mp 150-152 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.60 – 7.49 (m, 2H), 7.42 – 7.37 (m, 3H), 7.35 (d, J = 8.0 Hz, 1H), 7.10 – 7.05 (m, 1H), 7.03 – 6.94 (m, 2H), 6.24 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 3.59 (d, J = 17.6 Hz, 1H), 3.50 (dd, J = 17.6, 2.4 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.8, 160.0, 151.8, 136.9, 133.7, 130.2, 129.7, 128.8, 126.5, 123.3 (d, J = 284.8 Hz), 118.3, 116.4, 115.2, 111.8, 82.5 (q, J = 30.3 Hz), 55.4, 29.8 ppm.

IR (film): ν_{max} 3070, 2939, 2839, 2314, 1720, 1573, 1496, 1450, 1435, 1373, 1296, 1273, 1188, 1049, 995, 964 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{16}\text{O}_3\text{F}_3]^+$: m/z = 349.1052, found: m/z = 349.1050.

4-(3-Methoxyphenyl)-6-(thiophen-2-yl)-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-2-one (5-11d):

A white solid. Mp 107-108 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.33 (m, 2H), 7.25 (dd, J = 3.6, 0.8 Hz, 1H), 7.14 – 7.08 (m, 1H), 7.04 – 6.97 (m, 3H), 6.28 (dd, J = 2.0, 0.4 Hz, 1H), 3.85 (s, 3H), 3.58 – 3.39 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.2, 160.1, 151.7, 136.8, 130.3, 128.4, 127.44, 127.40, 122.7 (d, J = 284.8 Hz), 118.5, 116.5, 114.9, 112.0, 81.4 (q, J = 32.3 Hz), 55.4, 31.3 ppm.

IR (film): ν_{max} 3070, 3016, 2939, 2839, 2314, 1728, 1573, 1496, 1450, 1435, 1373, 1296, 1273, 1257, 1103, 1049, 1033, 995, 979, 864 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{17}\text{H}_{14}\text{O}_3\text{F}_3\text{S}]^+$: $m/z = 355.0616$, found: $m/z = 355.0617$.

5-14a

3-Methyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (5-14a):

A white solid. Mp 70-72 °C; Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.88 – 7.78 (m, 2H), 7.42 – 7.23 (m, 10H), 7.18 (d, $J = 7.6$ Hz, 2H), 5.90 (d, $J = 3.6$ Hz, 1H), 3.45 (dd, $J = 11.9, 3.1$ Hz, 1H), 2.81 – 2.64 (m, 1H), 2.45 (s, 3H), 0.94 (d, $J = 6.8$ Hz, 3H).

Minor isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.88 – 7.78 (m, 2H), 7.42 – 7.23 (m, 10H), 7.18 (d, $J = 7.6$ Hz, 2H), 5.99 (d, $J = 6.0$ Hz, 1H), 3.88 (t, $J = 5.6$ Hz, 1H), 2.99 – 2.86 (m, 1H), 2.45 (s, 3H), 1.03 (d, $J = 7.2$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.7, 174.4, 145.0, 144.9, 140.6, 140.5, 139.6, 137.7, 137.2, 136.8, 136.7, 136.5, 129.5, 129.11, 129.07, 128.7, 128.39, 128.35, 128.3, 128.2, 127.8, 127.4, 126.03, 125.95, 124.4, 120.9, 46.4, 44.9, 44.6, 42.3, 30.3, 21.7, 13.6, 11.5 ppm.

IR (film): ν_{max} 3062, 2978, 2939, 2870, 2252, 1720, 1643, 1597, 1496, 1450, 1303, 1165, 1087, 910, 810 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{25}\text{H}_{24}\text{NO}_3\text{S}]^+$: $m/z = 418.1477$, found: $m/z = 418.1477$.

5-14b

3-Ethyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (5-14b):

A colorless oil ; Major isomer: **¹H NMR** (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.11 (m, 12H), 5.86 (d, *J* = 4.4 Hz, 1H), 3.64 (dd, *J* = 10.4, 4.4 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.42 (s, 3H), 1.76 – 1.59 (m, 1H), 1.44 – 1.20 (m, 1H), 0.72 (t, *J* = 7.2 Hz, 3H).

Minor isomer: **¹H NMR** (400 MHz, CDCl₃) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.11 (m, 12H), 6.02 (d, *J* = 6.0 Hz, 1H), 3.93 (t, *J* = 5.6 Hz, 1H), 2.65 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.45 (s, 3H), 1.76 – 1.59 (m, 1H), 1.44 – 1.20 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 173.8, 173.5, 145.0, 144.8, 140.4, 140.3, 139.4, 137.9, 137.3, 137.0, 136.64, 136.56, 129.4, 129.2, 129.1, 129.0, 128.9, 128.7, 128.4, 128.3, 128.2, 128.1, 127.7, 127.32, 127.28, 125.9, 125.8, 123.1, 121.2, 51.9, 51.7, 41.0, 40.9, 21.7, 21.6, 20.9, 18.8, 12.0, 10.0 ppm.

IR (film): ν_{max} 3061, 3030, 2968, 2935, 2877, 2254, 1712, 1598, 1494, 1454, 1361, 1305, 1265, 1234, 1168, 1122, 1087, 1029, 1002, 987, 910 cm⁻¹.

HRMS (ESI): calculated for [C₂₆H₂₆NO₃S]⁺: *m/z* = 432.1633, found: *m/z* = 432.1639.

3-Ethyl-6-phenyl-4-(*p*-tolyl)-1-tosyl-3,4-dihydropyridin-2(1*H*)-one (5-14c):

A colorless oil; Major isomer: **¹H NMR** (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.46 – 7.32 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 – 7.00 (m, 4H), 5.86 (d, *J* = 4.4 Hz,

1H), 3.60 (dd, $J = 10.4, 4.4$ Hz, 1H), 2.71 (ddd, $J = 10.4, 6.0, 4.4$ Hz, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 1.73 – 1.59 (m, 1H), 1.41 – 1.28 (m, 1H), 0.70 (t, $J = 7.2$ Hz, 3H).

Minor isomer: **¹H NMR** (400 MHz, CDCl₃) δ 7.86 (d, $J = 8.4$ Hz, 2H), 7.46 – 7.32 (m, 5H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.16 – 7.00 (m, 4H), 6.00 (d, $J = 6.0$ Hz, 1H), 3.89 (t, $J = 5.6$ Hz, 1H), 2.65 – 2.58 (m, 1H), 2.45 (s, 3H), 2.31 (s, 3H), 1.73 – 1.59 (m, 1H), 1.41 – 1.28 (m, 1H), 0.91 (t, $J = 7.2$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 173.9, 173.6, 144.9, 144.7, 140.1, 139.2, 137.9, 137.3, 137.0, 136.9, 136.6, 136.5, 133.8, 129.6, 129.4, 129.2, 129.1, 129.0, 128.4, 128.3, 128.2, 128.1, 127.5, 126.8, 125.8, 123.5, 121.5, 51.8, 51.7, 40.5, 40.4, 21.6, 21.0, 20.8, 18.7, 11.9, 9.9 ppm.

IR (film): $\nu_{\max}$ 3062, 2970, 2877, 2252, 1712, 1597, 1489, 1450, 1365, 1296, 1087, 1010, 910 cm⁻¹.

HRMS (ESI): calculated for [C₂₇H₂₈NO₃S]⁺: $m/z = 446.1790$, found: $m/z = 446.1782$.

4-(4-Bromophenyl)-3-ethyl-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (5-14d):

A colorless oil; Major isomer: **¹H NMR** (400 MHz, CDCl₃) δ 7.75 (d, $J = 8.4$ Hz, 2H), 7.45 – 7.32 (m, 7H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 5.82 (d, $J = 4.8$

Hz, 1H), 3.60 (dd, $J = 9.2, 4.8$ Hz, 1H), 2.77 – 2.67 (m, 1H), 2.43 (s, 3H), 1.69 – 1.59 (m, 1H), 1.46 – 1.34 (m, 1H), 0.75 (t, $J = 7.2$ Hz, 3H).

Minor isomer: **^1H NMR** (400 MHz, CDCl_3) δ 7.83 (d, $J = 8.4$ Hz, 2H), 7.45 – 7.32 (m, 7H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 5.96 (d, $J = 6.0$ Hz, 1H), 3.86 (t, $J = 6.0$ Hz, 1H), 2.67 – 2.60 (m, 1H), 2.45 (s, 3H), 1.76 – 1.70 (m, 1H), 1.26 – 1.21 (m, 1H), 0.91 (d, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.3, 173.2, 145.1, 144.9, 140.7, 139.9, 139.4, 137.6, 137.1, 136.3, 135.9, 132.0, 131.8, 129.9, 129.4, 129.3, 129.2, 129.1, 129.0, 128.41, 128.39, 128.3, 128.2, 125.8, 121.8, 121.3, 121.1, 120.6, 51.7, 51.2, 40.2, 40.1, 21.6, 21.1, 18.9, 11.9, 10.1 ppm.

IR (film): ν_{max} 3062, 2877, 2252, 1712, 1643, 1597, 1489, 1450, 1365, 1165, 1080, 1010, 910, 817 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{26}\text{H}_{25}\text{NO}_3\text{SBr}]^+$: $m/z = 510.0739$, found: $m/z = 510.0741$.

5-14e

3-Pentyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (5-14e):

A colorless oil; Major isomer: **^1H NMR** (400 MHz, CDCl_3) δ 7.78 (d, $J = 8.4$ Hz, 2H), 7.45 – 7.12 (m, 12H), 5.87 (d, $J = 4.4$ Hz, 1H), 3.60 (dd, $J = 9.6, 4.8$ Hz, 2H), 2.81 – 2.64 (m, 1H), 2.41 (s, 3H), 1.55 – 1.45 (m, 1H), 1.42 – 1.31 (m, 1H), 1.24 – 1.02 (m, 5H), 1.02 – 0.91 (m, 1H), 0.84 – 0.73 (m, 3H).

Minor isomer: **¹H NMR** (400 MHz, CDCl₃) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.12 (m, 12H), 6.02 (d, *J* = 6.0 Hz, 1H), 3.91 (t, *J* = 6.0 Hz, 1H), 2.81 – 2.64 (m, 1H), 2.45 (s, 3H), 1.71 – 1.59 (m, 1H), 1.42 – 1.31 (m, 1H), 1.24 – 1.02 (m, 6H), 0.84 – 0.73 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 173.8, 173.7, 144.9, 144.7, 140.4, 140.3, 139.6, 137.9, 137.4, 137.0, 136.59, 136.55, 129.4, 129.2, 129.1, 129.0, 128.9, 128.7, 128.4, 128.32, 128.28, 128.2, 128.1, 127.7, 127.3, 127.2, 125.81, 125.77, 122.7, 121.2, 50.9, 50.0, 41.4, 41.0, 31.63, 31.56, 28.0, 26.9, 25.4, 25.3, 22.3, 21.7, 21.6, 13.9, 13.8 ppm.

IR (film): ν_{max} 3062, 2954, 2929, 2858, 2256, 1957, 1714, 1643, 1597, 1494, 1454, 1361, 1305, 1170, 1107, 1085, 1031, 910 cm⁻¹.

HRMS (ESI): calculated for [C₂₉H₃₂NO₃S]⁺: *m/z* = 474.2103, found: *m/z* = 474.2110.

3-Ethyl-4,6-diphenyl-3,4-dihydro-2H-pyran-2-one (5-16a):

A white solid. Mp 82-85 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.45 – 7.34 (m, 3H), 7.34 – 7.21 (m, 3H), 7.17 (d, *J* = 7.6 Hz, 2H), 6.06 (d, *J* = 6.4 Hz, 1H), 3.84 (t, *J* = 6.8 Hz, 1H), 2.84 (q, *J* = 6.8 Hz, 1H), 1.89 – 1.67 (m, 1H), 1.35 – 1.16 (m, 1H), 1.02 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.4, 150.1, 138.0, 132.3, 129.1, 128.9, 128.5, 128.1, 127.6, 124.6, 104.7, 46.0, 41.3, 19.8, 12.0 ppm.

IR (film): $\nu_{\max}$ 3032, 2970, 2931, 2360, 1759, 1666, 1489, 1450, 1373, 1280, 1149, 1080, 956, 871, 810 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{19}\text{O}_2]^+$: $m/z = 279.1385$, found: $m/z = 279.1389$.

4,6-Bis(4-chlorophenyl)-3-ethyl-3,4-dihydro-2H-pyran-2-one (5-16b):

A colorless oil; Major isomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 – 7.54 (m, 2H), 7.40 – 7.24 (m, 4H), 7.08 (d, $J = 7.6$ Hz, 2H), 6.01 (d, $J = 6.4$ Hz, 1H), 3.82 (t, $J = 6.6$ Hz, 1H), 2.84 (q, $J = 6.8$ Hz, 1H), 1.80 – 1.68 (m, 1H), 1.27 – 1.17 (m, 1H), 1.02 (t, $J = 7.2$ Hz, 3H).

Minor isomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 – 7.54 (m, 2H), 7.40 – 7.24 (m, 4H), 7.16 (d, $J = 7.8$ Hz, 2H), 5.78 (d, $J = 4.4$ Hz, 4H), 3.73 – 3.65 (m, 1H), 2.69 (dd, $J = 12.8, 6.4$ Hz, 1H), 1.80 – 1.68 (m, 1H), 1.27 – 1.17 (m, 1H), 1.09 – 0.99 (m, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 169.7, 169.3, 149.5, 148.9, 139.7, 136.3, 135.2, 133.6, 133.4, 130.5, 130.4, 129.4, 129.3, 129.1, 128.8, 128.7, 126.0, 125.9, 104.6, 103.4, 47.8, 45.7, 41.8, 40.7, 22.7, 19.8, 12.0, 11.3 ppm.

IR (film): $\nu_{\max}$ 3070, 2970, 2877, 2252, 1090, 1766, 1589, 1489, 1401, 1365, 1265, 1141, 1010, 956, 910, 825 cm^{-1} .

HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{17}\text{O}_2\text{Cl}_2]^+$: $m/z = 347.0606$, found: $m/z = 347.0609$.

(3*S*,4*S*)-3,4-Diphenylcyclopentan-1-one (5-4):

¹H NMR (300 MHz, CDCl₃) δ 7.30 – 7.06 (m, 10H), 3.60 – 3.35 (m, 2H), 2.94 – 2.74 (m, 2H), 2.68 – 2.40 (m, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 215.8, 140.9, 128.6, 127.2, 126.9, 50.2, 47.2 ppm. Spectra matched that of the previously reported compound.

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