Carbene-catalyzed dynamic kinetic resolutions and cycloaddition reactions via acylazolium intermediates

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**Carbene-Catalyzed Dynamic Kinetic Resolutions and
Cycloaddition Reactions via Acylazolium Intermediates**

SONG RUNJIANG

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2022

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Cycloaddition Reactions via Acylazolium Intermediates**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2022

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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A handwritten signature in black ink, appearing to read 'Robin', is written over a background of faint, repeating 'NTU' text.

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Chi Yonggui Robin

Authorship Attribution Statement

This thesis contains material from 1 paper(s) published in the following peer-reviewed journal(s) / from papers accepted at conferences in which I am listed as an author.

Chapter 2 is published as Bin Liu, Runjiang Song, Jun Xu, Pankaj Kumar Majhi, Xing Yang, Song Yang, Zhichao Jin, and Yonggui Robin Chi. Access to Optically Enriched α -Aryloxycarboxylic Esters via Carbene-Catalyzed Dynamic Kinetic Resolution and Transesterification. *Organic Letters*. **22**, 3335-3338 (2020). DOI: 10.1021/acs.orglett.0c00748.

The contributions of the co-authors are as follows:

- Prof. Chi conceptualized the project and revised the manuscript draft.
- Dr. Bin Liu started this project.
- I optimized the reaction condition and conducted the substrate scope as well as manuscript draft.
- Dr. Jun Xu analyzed the data regarding HRMS.
- Dr. Pankaj Kumar Majhi, Dr. Xing Yang, Prof. Song Yang and Prof. Zhichao Jin contributed to the discussion and manuscript revision.
- All authors contributed to discussions and manuscript preparation.

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Abstract

This thesis focuses on exploring the reactivity of N-heterocyclic carbene (NHC) catalyst-derived acylazolium intermediates. In particular, the thesis is mainly focused on NHC-catalyzed dynamic kinetic resolution (DKR) and cycloaddition reactions through formation of acylazolium intermediates. It contains three chapters:

Chapter 1 provides a brief review on the history and development of NHCs in organic catalysis. A number of classical reactive intermediates and key reaction modes in NHC catalysis are summarized. Literature studies closely related to the thesis work are introduced.

Chapter 2 describes an NHC-catalyzed DKR and transesterification reaction for asymmetric synthesis of optically enriched α -aryloxy-carboxylic esters with up to 99% yield and 99:1 er value. The facile interconversion between two NHC-activated diastereomeric acylazolium intermediates allows for highly efficient DKR to occur. The products from our strategy can readily undergo further transformations to produce chiral herbicides and other functional molecules.

Chapter 3 presents a highly chemo- and enantioselective organocatalytic tandem reaction between hydroxylamines and bromoenals. The reaction provides access to isoxazolidin-5-ones in good yields and satisfactory enantioselectivities.

Chapter 4 provides the conclusion and perspective of this thesis, including potential scientific and real-world applications derived from our study.

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Abbreviations

Ac	acetyl
Ar	aryl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
Bn	benzyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	<u>1,8-diazabicyclo[5.4.0]undec-7-ene</u>
DIPEA	N,N-Diisopropylethylamine
DMSO	dimethylsulfoxide
KR	kinetic resolution
DKR	dynamic kinetic resolution
NHC	N-heterocyclic carbene
r.t.	room temperature
ee	enantiomeric excess
e.r.	enantiomeric ratio
ESI	electrospray ionization
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
<i>i</i> Pr	isopropyl
Mes	mesityl
OTBS	trifluoromethanesulfonate
TLC	thin layer chromatography
α	alpha

β

beta

γ

gamma

δ

delta

Chapter 1

Introduction

1.1 General introduction to NHC organic catalysis

The carbon–carbon bond formation and the construction of chiral carbon centers behave to be great tasks in research. Besides, compounds with optical activities usually displayed unique biological activities, the area of organic catalysis has thus attracted much attention, as remarkable giants in this research area, MacMillan¹ shared the 2021 Nobel Prize in chemistry with List². In particular, since the pioneering work of successful isolation of structurally stable carbene by Arduengo³ and co-workers (Figure 1.1a), the N-heterocyclic carbenes (NHCs) have been developed as remarkable organic catalysts to promote many organocatalytic transformations.⁴

In chemistry, an NHC is defined as a cyclic molecule containing a divalent carbon atom that bound to one nitrogen atom with two unshared valence electrons. The ring size and the substituent groups of an NHC typically lead to various NHCs exhibiting a broad range of electronic properties. Generally, categorizes these NHCs into four typical types based on the ring configurations which includes imidazolylidene, imidazolinylidene, triazolylidene and thiazolylidene (Figure 1.1b).

Figure 1.1 First isolation of stable NHC and common types of NHCs

1.2 Common intermediates in NHC catalysis

Nowadays, NHC-catalyzed reactions have been widely reported, most of which reported researches involved key intermediates.⁵ NHCs can activate substrates through the addition reaction to form a variety of reactive adduct intermediates. Based on the type of the generated intermediates, these intermediates could be classified as: a) acyl anions, b) homoenolates, c) acylazoliums; d) enolates, e) α , β -unsaturated acylazoliums, f) vinyl enolates (Figure 1.2). These reactive intermediates could participate in further transformations.

Figure 1.2 Common NHC-bound intermediates in catalysis

1.2.1 NHC catalysis involving acyl anions

In NHC catalysis, aldehydes are one of the most commonly used substrates with high reactivities. Through the addition of NHC to aldehydes, generating acyl anion equivalents is the most direct and effective strategy.⁶ Furthermore, acyl anion equivalents play a significant role in benzoin reaction, Stetter reaction and hydroacylation.

1.2.1.1 Benzoin reaction

Benzoin reaction is one of the most important condensation reactions widely used in chemical industry, agrichemical production, and material sciences. This reaction can be traced back to the year 1832, when Wohler and Liebig first discovered that certain aromatic aldehydes or glyoxals could be converted to benzoin in the presence of cyanide ions (Scheme 1.1).⁷ In this pathway, cyanide ion promoted the conversion of an electrophilic aldehyde carbonyl carbon to a nucleophilic species, which phenomenon is the so-called “umpolung”. However, considering the notoriety of cyanide ion, in 1943, Ukai and co-workers initially found that treatment of aldehydes with a catalytic amount of thiazolium salts also allows the generation of benzoin products.⁸

The most widely accepted mechanism for thiazolium salts catalyzed benzoin reaction was firstly proposed by Breslow in 1958 (Scheme 1.2).⁹ According to his mechanism, the initial addition of deprotonated thiazolium salt to aldehyde forms the resulting adduct **1** followed by proton transfer leads to the Breslow intermediate, which then reacts with another molecule of aldehyde to produce the corresponding benzoin product. Umpolung phenomenon played a crucial role during this reaction as reactivity of the aldehyde was reversed from an electrophilic

acyl carbon to a nucleophile. Thus, Breslow intermediates could be considered as acyl anion equivalents.

Scheme 1.2 Mechanism of thiazolium-catalyzed benzoin reaction by Breslow

After Breslow established a reasonable mechanism, the NHC-catalyzed benzoin reactions have been intensively studied involving asymmetric benzoin reactions and cross-benzoin reactions. The first case of asymmetric benzoin condensation was reported by Sheehan and Hunneman (Scheme 1.3), who used chiral thiazolium salt **2** as the precatalyst. Although a lower optical purity (up to 22%) of the product was obtained, their work proved that chiral NHC-catalyzed asymmetric benzoin reaction is promising.¹⁰ Since this pioneering research was reported, many chemists began to focus on the development of efficient NHC-catalyzed benzoin reactions for access to optically enriched products. As a remarkable example, Enders and co-workers designed and synthesized a chiral bicyclic triazolium salt **3**, which was then applied to catalyze benzoin reactions.¹¹ By using this NHC catalyst **3**, they were able to achieve both quantitative yield and excellent enantioselectivity (>99% yield, up to 95% ee).

Sheehan and Hunneman (1966)

Enders et al. (2002)

Scheme 1.3 Asymmetric benzoin condensations by Sheehan, Hunneman and Enders

Later, Connon and Zeitler developed a unique NHC catalyst **4** bearing a hydroxyl group that can provide hydrogen bond interactions between the substrate and catalyst to achieve significant improvement of selectivity (up to >99% ee) (Scheme 1.4).¹²

selected examples

Scheme 1.4 Development of novel NHC catalyst for benzoin reaction

Benzoin reaction could also be applied to the C-C bond formation of two different aldehyde units, which is known as a cross-benzoin reaction. Cookson and Lane initially started working

with this area and demonstrated the first cross-coupling of two aldehyde units in 1976, though this method is only suitable for intramolecular reactions (Scheme 1.5).¹³ Since then, this area has received great attention from researchers, with a huge number of works reported to date. Some of them included intermolecular cross-benzoin reactions, aldehyde-ketone cross-benzoin reactions, and cross-coupling of aldehyde and imine.¹⁴ The development of cross-benzoin condensation has greatly expanded the application of benzoin reactions.

Scheme 1.5 Intramolecular cross-benzoin reaction by Cookson and Lane

1.2.1.2 Stetter reaction

Stetter reaction is another kind of reaction containing acyl anion intermediates. Similarly, the earliest Stetter reaction was catalyzed by cyanide ion as well.¹⁵ Later, in 1976, Stetter utilized thiazolium salt instead of sodium cyanide and achieved good results.¹⁶ The initial step of the NHC-catalyzed Stetter reaction has the same process with benzoin condensation that creates Breslow intermediate, followed by 1,4-addition of Breslow intermediate to Michael acceptor to generate nucleophilic addition products (Scheme 1.6). It is worth noting that the second step of the Stetter reaction would not be interfered with by the formation of benzoin products due to the reversibility of the benzoin reaction. In contrast, the addition of Breslow intermediate to Michael acceptor is irreversible.

Scheme 1.6 The difference between benzoin reaction and Stetter reaction

Stetter reactions are also applied to intramolecular reactions. For example, in 1995, Ciganek¹⁷ reported the first NHC-catalyzed intramolecular Stetter reaction for rapid access to the ester compounds of 2,3-dihydro-3-oxo-benzofuran-2-acetic acid and 3,4-dihydro-4-oxo-2H-1-benzopyran-3-acetic acid (depends on the number of “n”) (Scheme 1.7a). Soon later, Enders¹⁸ and co-workers were able to prepare 3,4-dihydro-4-oxo-2H-1-benzopyran-3-acetic compounds in an asymmetric manner using **7** as the pre-catalyst (Scheme 1.7b). In this transformation, the aldehyde group was firstly activated by free carbene and converted to a nucleophilic species, followed by the intramolecular Michael addition of a nucleophile to the C=C bond, leading to the formation of corresponding acetates. Later, a dramatic enhancement of product optical purities of this type of reaction was achieved by Rovis¹⁹ and colleagues (Scheme 1.7c). Through adjusting the structures of substrate and NHC catalysts, they were able to obtain 3,4-dihydro-4-oxo-2H-1-benzopyran-3-acetates with good yields and high enantioselectivities (up to 95% yield and 97% ee).

a) Ciganek (1995)

b) Enders et al. (1995)

c) Rovis et al. (2002)

Scheme 1.7 Stetter reactions developed by Ciganek, Enders, and Rovis

1.2.1.3 Hydroacylation

In 2006, the laboratory of She and Pan firstly discovered the extended reactivity of NHC-bounded acyl anion and demonstrated the first case of NHC-catalyzed intramolecular hydroacylation of olefin compounds (Scheme 1.8).²⁰ Later, the mechanism of this reaction was confirmed to be occurred with the enol ester **11** (generated through elimination reaction of tethered alkyl tosylate substrates).²¹ In this reaction, NHC catalyst **10** was firstly deprotonated by base to form free carbene. Then, the free carbene added to enol ester **11** to give adduct **12** followed by proton transfer to produce Breslow intermediate **13**. The key step in this reaction mechanism was deprotonation of conjugated enol ether to hydroxyl group, which process generated the intermediate **14** and subsequent formation of final product with release of free carbene.

Scheme 1.8 Reaction and mechanism of hydroacylation of olefins

Soon after this, Glorius' group intensively studied this type of reaction and extended the reactivity to intermolecular version. Besides, they also found this hydroacylation could work with alkynes (Scheme 1.9).²² Since then, the NHC-catalyzed hydroacylations involving acyl anion equivalents have been widely studied with a number of publication and application. The studies on NHC-catalyzed hydroacylations not only extended the reactivity of acyl anion equivalents in addition to benzoin and Stetter reactions, but also implicated the potential of NHC-bounded intermediate for development of novel active mode.

Scheme 1.9 Hydroacylation of alkynes developed by Glorius' group

1.2.2 NHC catalysis involving homoenolates

Besides acyl anions, homoenolates are also essential intermediates in NHC catalysis with high reactivities. Homoenolates are conventionally generated through the reaction between α , β -unsaturated aldehydes and free carbenes. The adduct intermediate **16** from the first step undergoes a proton transfer process to form homoenolate equivalent **17**, which has a resonance structure **18** (Scheme 1.10). Notably, NHC catalysis involving acyl anions, such as benzoin reaction and Stetter reaction, belongs to a¹-d¹ Umpolung. However, in the case of NHC-activated α , β -unsaturated aldehydes, the homoenolate equivalent **17** allows a nucleophilic shift of α -carbon to β -carbon, classifies as a³-d³ Umpolung. Thus, homoenolates can be considered as extended Breslow intermediates.

Scheme 1.10 Generation of homoenolates through enals

1.2.2.1 Annulation reaction and β -Functionalization

NHC-bound homoenolates are widely used in various kinds of chemical conversions, such as annulation reactions and β -functionalizations due to high β -carbon reactivities. The groups

of Bode²³ and Glorius²⁴ pioneered the annulation involving homoenolates at the same time, respectively. Furthermore, their works are the first example of the generation of homoenolates by combining NHCs and unsaturated aldehydes as well. The proposed mechanism showed that NHC-derived homoenolate **19** containing a nucleophilic β -carbon that can add to the carbonyl group of another aldehyde substrate to afford enol intermediate **20**, which then tautomerized to intermediate **21**. Followed by the intramolecular cycloaddition to give corresponding γ -lactone **22** (Scheme 1.11).

Scheme 1.11 Proposed pathway for NHC-catalyzed β -functionalizations

Besides, NHC-bounded homoenolates also played a significant role in β -functionalizations reactions. As a remarkable example, in 2009, Nair's group demonstrated a case of NHC-catalyzed activation of enals for β -nitrostyrene functionalizations.²⁵ The key step of this reaction is the conversion of nitronate intermediate **23** to acyl azolium **25**. In this case, intermediate **23** could attract a proton from the solvent, resulting in the formation of protonated intermediate **24** rather than undergoes a direct annulation to produce cyclization products. Then, the enol **24** became the keto intermediate **25** based on the enol-keto tautomerism. Subsequently, the acyl azolium **25** was replaced by methanol to afford ester product **26** with releasing of free carbene (Scheme 1.12).

Scheme 1.12 Proposed mechanism for β -nitrostyrene functionalizations

Since Bode and Glorius established the NHC-catalyzed version of homoenolates generation, many researchers have already made a great contribution to the exploration and application of this field. Various kinds of electrophiles such as ketones, imines, and amides (Figure 1.3) were extensively designed to incorporate NHC-bounded homoenolates to prepare useful molecules.²⁶

Figure 1.3 Selected examples for NHC-catalyzed homoenolate reactions

1.2.2.2 Access to homoenolates with non-formaldehyde substances

Homoenolates are not only prepared through enals but also by other non-formaldehyde substances such as hydroxyenones and esters. As a pioneering example, Bode and co-workers reported the first NHC-catalyzed formation of homoenolate equivalents through using α' -hydroxyenones as the starting materials.²⁷ The retro-benzoin process played an inventive step in this method. Intermediate **27** was easily released acetone due to benzoin reaction is reversible, resulting in the production of homoenolates to participate in further transformations (Scheme 1.13).

Scheme 1.13 Access to homoenolates through retro-benzoin reactions

In 2013, our laboratory intensively explored the potential property of aromatic esters and established the first NHC-induced two-steps deprotonation of saturated carboxylic esters for access to homoenolates.²⁸ Mechanically, ester was initially attacked by NHC to give acylazolium **28**. Then, the α -CH was deprotonated by base and led to the formation of NHC-bounded enol intermediate **29**, followed by the second deprotonation of β -CH resulted in a homoenolate equivalent. It is worth noting that the β -carbon of saturated ester is normally difficult to activate. In this case, they firstly activated the α -carbon by NHC, which allowed to form intermediate **29** and increased the acidity of β -CH (Scheme 1.14). Bound triazolium promoted the enol to go through intramolecular deprotonation of β -CH. Thus, the β -carbon was able to be activated.

Scheme 1.14 Our previous work on the generation of homoenolates

1.2.3 NHC catalysis involving acylazoliums

Unlike the previous examples, NHC-catalyzed acylazolium reactions belong to non-umpolung chemistry, thus the acylazolium intermediate remains an electrophilic species. In particular, the most crucial type of these intermediates is α , β -unsaturated acylazolium, which was firstly discovered in the biomimetic synthesis of Clavulanic acid. In this case, Townsend²⁹

and colleagues demonstrated that thiazolium-bounded D-glyceraldehyde3-phosphate could undergo two eliminations to form α , β -unsaturated acylazolium (Scheme 1.15). Since then, α , β -unsaturated acylazolium have received continuous attention from chemists.

Scheme 1.15 First NHC-catalyzed generation of α , β -unsaturated acylazolium

Upon treating enals with NHCs and oxidant, α , β -unsaturated acylazoliums are produced in a reaction, which is the most general strategy to generate α , β -unsaturated acylazoliums. In addition to this method, access to α , β -unsaturated acylazoliums through esters, acyl fluorides, carboxylic acids, ynals, and other substrates (Scheme 1.16) were also explored by chemists.³⁰ Besides, the NHC-based acylazoliums have played an important role in various kinds of chemical transformations due to their significant reactivities. Some of these reactions involving transesterification, amidation of esters, [3 + 3] annulation, [3 + 2] annulation, and etc.

Scheme 1.16 Access to α , β -unsaturated acylazoliums from different substrates

1.2.3.1 Transesterification

Catalytic transesterification is one of the most important applications of saturated acylazolium. Hedrick³¹ and co-workers pioneered the use of this type of intermediate for polymerization of lactides and lactones (Scheme 1.17a). Since that, the research groups of Hedrick, Nolan, and others were focused on study of NHC-catalyzed transesterification. In 2002, Nolan³² and colleagues demonstrated imidazolium salts **30** and **31** were versatile NHC precatalysts that could promote transesterification and prepare various kinds of primary alcohols with almost quantitative yields (Scheme 1.17b). The same year, Hedrick³³ indicated that this type of reaction is applicable not only for primary alcohols but secondary alcohols, even tertiary species as well (Scheme 1.17c). The result showed **32** induced transesterification of methyl benzoate with isopropyl alcohol gave product ester with up to 72% yield. However, only trace yield of tertiary alcohols product was obtained.

Scheme 1.17 Investigations of NHC-catalyzed transesterifications by Hedrick and Nolan

1.2.3.2 Amidation

When NHC-bound acylazolium was attacked by amines, amide compounds are produced in a reaction called amidation. This type of conversion could be regarded as the extended application of transesterification. As a remarkable example, in 2007, Rovis³⁴ and co-workers reported an NHC and HOAt co-catalyzed reaction for the efficient construction of C-N bonds (Scheme 1.18). The selected examples showed that different kinds of substituents on amines including EWG and EDG as well as disubstituted amides were tolerated in the reaction, with corresponding amide products generated in good yields (72 – 89% yield).

Scheme 1.18 Amidation induced by NHC and HOAt

Mechanistically, this cascade reaction consists of two steps. The first step was initialized with the nucleophilic addition of free carbene **33** to α, α -dichlorobenzene propanal, followed by the release of chloride to form acylazolium **34**. The intermediate **34** was then converted to the carboxylate **35**, which was a HOAt-activated intermediate and readily to be attacked by amines to afford correspond amides and regenerated HOAt catalyst to participate in the reaction cycle (Scheme 1.19).

Scheme 1.19 Catalytic process for NHC and HOAt co-catalysis

1.2.3.3 [3 + 3] annulation

The NHC-catalyzed [3 + 3] annulation involving α , β -unsaturated acylazoliums has been extensively studied in recent ten years. Intramolecular version, for instance, Lupton³⁵ and co-workers investigated the reactivity of unsaturated acylazoliums in detail and disclosed the first intramolecular [3+3] addition of enol esters for direct access to pyranone compounds (Scheme 1.20a). In this reaction pathway, the ester substrate was firstly attacked by NHC to afford acylazolium **37** with the lease of enolate **36**. Thus, the substrate was split into two parts, the enolate **36** acts as a 1,3-bisnucleophile that can conjugate to electrophilic species **37**, followed by cyclization to form final products. Besides, they also studied the intermolecular reaction by using unsaturated acid fluorides as the acylazolium precursors to react TMS enol ethers in the presence of imidazolium salts **38** (Scheme 1.20b). The resulted dihydropyranone products could be obtained with up to 76% yield.

Scheme 1.20 Pioneered [3 + 3] annulations induced by NHCs

Our group was able to generate enantiomerically enriched lactams by activating α , β -unsaturated esters (Scheme 1.21).³⁶ The formation of NHC-bound acylazolium **40** and the isomerization of imine to enamide **41** played significant steps in this transformation. Enamide behaved as 1,3-donor that can occur cyclization with NHC-activated intermediate **40** to afford the desired lactams and liberated the free carbene. Moreover, the optical purities of products could be effectively controlled by loading chiral triazolium salt **39**, resulting in the asymmetric preparation of lactam compounds in good yields and excellent ee values (up to 83% yield, 99% ee).

Scheme 1.21 Our previous report on [3 + 3] annulations

The [3 + 3] annulation starting from enals has been widely studied as well. Normally, this type of reaction often requires adding oxidative agents for the generation of acylazoliums. Studer's group pioneered in-situ oxidation of NHC-derived intermediate **43**, which allowed the direct generation of α , β -unsaturated acylazolium **44** (Scheme 1.22).³⁷ Meanwhile, the dione substrate was deprotonated by the base and converted to enolate, which then undergoes [3+3] reaction with **44** to form corresponding dihydropyranones. It is important to note that adduct **43** could also go through a proton transfer process to become Breslow intermediate. However, since the reaction rate of DQ-promoted oxidation was much faster than the generation of the Breslow intermediate, acylazolium played the key role in the reaction pathway.

Scheme 1.22 Formation of α , β -unsaturated acylazolium through in-situ oxidation

1.2.3.4 [3 + 2] annulation

The acylazolium-participated [3 + 2] annulations have been frequently used in the synthesis of five-membered compounds. The pioneering work in this area was reported by Ye³⁸ and co-workers. In their methodology, carboxylic acids were used as one of the starting materials to react with pivaloyl chloride (PivCl) to give anhydrides **45**, which were then intercepted by NHC to form acylazoliums **46**. On the other hand, the α -amino ketones were initially deprotonated to afford enolates **47**, followed by [3+2] cyclization with acylazoliums **46** to give the lactam products (Scheme 1.23). Selected examples showed that different substitutes on the aromatic ring involving EDG and EWG were tolerated in this reaction, and most lactams could be obtained in acceptable yields and high enantioselectivities. Since then, the potential reactivity of acylazolium in [3 + 2] annulations has received much attention.

Scheme 1.23 First NHC-catalyzed [3 + 2] annulation by Ye' group

In 2016, our group reported an NHC-catalyzed activation of enals for β -amination, which not only allows the installation of a nitrogen atom at the β -position of enals but also promotes the reaction to undergo a [3 + 2] annulation process, resulting in the asymmetric generation of five-membered heterocycles (Scheme 1.24).³⁹ Treatment of the 1,2-donors **48** with α , β -unsaturated acylazoliums generated from enals with catalysts **49** or **50** under oxidative conditions led to the enantioselective synthesis of pyrazolidinones with up to 94% yield and 99:1 er value.

Scheme 1.24 NHC-induced β -Aminations reported by us

1.3 NHC-catalyzed KR and DKR

Besides the utilities of N-Heterocyclic carbenes in organocatalysis, NHCs have also been employed as powerful tools to promote kinetic resolutions and dynamic kinetic resolutions. The first NHC-catalyzed KR was achieved by Suzuki⁴⁰ and co-workers, chiral NHC catalysts **51** and vinyl acetate were used in the kinetic resolution of racemic secondary alcohols (Scheme 1.25). Even though only 58% enantiomeric excess was obtained as the best result, this pioneering work has successfully demonstrated the potential of N-Heterocyclic carbenes in kinetic resolutions.

Scheme 1.25 First KR induced by NHC

The breakthrough came when Maruoka⁴¹ and colleagues introduced larger steric groups on the vinyl substrates to cooperate with imidazolium salts **52** (Scheme 1.26). Through this approach, they were able to improve the enantioselectivity of this reaction dramatically. The recovered alcohol substrates were isolated in satisfactory selectivity (up to 96% ee) but low yield (up to 39%), which indicated that the increase of steric hindrance favors the enantioselectivity. However, too much steric hindrance could deactivate the NHC catalyst, leading to a significant drop of the product yield. Thus, the development of more efficient methods addressing both conversion rate and selectivity for NHC-catalyzed KR is of profound importance.

Scheme 1.26 Maruoka's work on NHC-catalyzed KR

In addition to the separation of alcohol substrates, NHC-promoted kinetic resolutions were widely used to resolve amines, atropisomers, and other compounds as well. Notably, acylazoliums could not directly undergo acylations with amines, and the additives are required for this reaction. As a remarkable example, Bode⁴² and co-workers developed a cascade reaction for the kinetic resolution of racemic amines (Scheme 1.27). In their approach, a chiral hydroxamic acid **53** was designed as the cocatalyst with NHC **54** used as the reaction catalyst,

resulting in recovery of (*R*)-amine substrates and the formation of (*S*)-amides in high enantioselectivities (both up to 96:4 er).

Scheme 1.27 KR catalyzed by NHC and chiral additives

The proposed mechanism showed that this KR process consists of two independent steps. The catalytic cycle 1 was mediated by NHC **56** through which the saturated acylazolium **57** was generated (Scheme 1.28). In this pathway, α' -hydroxyenone substrate went through three procedures to form the intermediate **57**: retro-benzoin, β -protonation, and tautomerization. The chiral additive **55** played a significant role in cycle 2, which not only behaved as an acylating reagent but also controlled the enantioselectivity of this reaction. Moreover, the afforded intermediate **58** only allowed reaction with particular (*R*)-amines, resulting in the kinetic resolution of racemic substrates.

Scheme 1.28 Catalytic pathway of NHC and additives co-catalysis

Recently, NHCs have also been used in the KRs of axially biaryl compounds. For example, in 2014, Zhao^{43a} and co-workers reported the first enantioselective kinetic resolution of BINOLs and N-protected NOBINs, with optically pure atropisomers obtained as the products in up to >99% ee (Scheme 1.29). Besides, several works in this area have been subsequently reported by Zhao, Wang and others.⁴³

Scheme 1.29 Access to axially chiral biaryls through NHC-catalyzed KRs.

Comparing with KR, the dynamic kinetic resolution has a great advantage that up to quantitative yield of the enantiomerically enriched product could be achieved. Scheidt's group

pioneered the study in this field and reported an NHC-catalyzed asymmetric preparation of multi substituted β -lactones, which involved a DKR process induced by chiral NHC (Scheme 1.30).⁴⁴ The racemic enal substrate ($\pm$)-**59** was firstly attacked by free carbene to generate homoenolate **62**, which then underwent a β -protonation to give azolium enolates (*R*)-**63** and (*S*)-**63**. Since the two enantiomers of the starting material could rapidly interconvert into each other in the presence of a mild base, the reaction favored to consume (*R*)-**63** and generated (+)-**60a** as the major product under the catalysis of the chiral NHC **61**.

Scheme 1.30 First NHC-catalyzed DKR by Scheidt's group

Our group reported an NHC-catalyzed DKR and acylation of hydroxyphthalides in 2019 (Scheme 1.31a).⁴⁵ The reaction gave a series of enantiomerically enriched phthalides in high yields and excellent optical purities (up to 96% yield, 99:1 e.r.). Besides, aldehydes bearing various substituents and substitution patterns were tolerant in this reaction. The formylbenzoic acid substrate could undergo an intramolecular reaction and converted to racemic hydrophthalide **65** in the presence of the solvent. Due to steric inhibition, the chiral NHC-bound acylazolium **66** preferred to react with (*S*)-**65** and generate corresponding product (*S*)-**67** in most cases (Scheme 1.31b).

Scheme 1.31 One of our previous works on NHC-induced DKR

1.4 Conclusion and Research Design

Nowadays, N-heterocyclic carbene has been developed as a versatile organocatalyst with great potential in the area of organocatalysis. In addition to benzoin reactions and Stetter reactions, the extended Breslow intermediates such as homoenolates and acylazoliums are widely appeared in many significant chemical transformations: transesterifications, amidations, cyclizations, kinetic resolutions, etc. However, to date, though many research directions of NHC-catalyzed reactions have been extensively explored, the development of novel catalytic modes and new chemical methodologies with efficient activation of various kinds of substrates remains challenging.

Compounds bearing optically active α -aryloxycarboxylic acid skeletons are frequently found to have bioactivities in many critical functional molecules. For another, the NHC-catalyzed DKR reactions have proven to be powerful tools to resolve various kinds of valuable substances in recently 10 years. Therefore, our research group aims to find more optically enriched molecules with unique bioactivities that can be efficiently isolated or prepared by NHC-catalyzed DKR reactions.

We design a chiral NHC-catalyzed dynamic kinetic resolution of α -aryloxycarboxylic esters through transesterification reaction, which allows the isolation of α -aryloxycarboxylic esters in high optical purities. In addition, isoxazolidin-5-ones are valuable motifs frequently found in bioactive compounds and they have emerged as crucial chiral building blocks that are readily converted into the corresponding amino alcohols and β -amino acids. Besides, the α , β -unsaturated acylazolium intermediates are widely used in β -functionalizations. However, the β -aminations involving this intermediate are less studied. Consequently, we intend to develop more catalytic modes for the construction of the C-N bond. Here we design an NHC-catalyzed enantioselective cycloaddition of hydroxylamines to bromoenals. Our method can not only

establish C-N bonds in asymmetric fashion but also give chiral isoxazolidin-5-ones with promising biological activities as the products.

1.5 References

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Chapter 2

Access to Optically Enriched α -Aryloxycarboxylic Esters via Carbene-Catalyzed Dynamic Kinetic Resolution and Transesterification

2.1 Introduction

The α -aryloxy-carboxylic acids and their derivatives play significant roles in organic chemistry. They are biologically important functional molecules and have been applied in plant protections and chiral drug discoveries. For example, fenoxaprop-p and dichlorprop (Figure 2.1) contain α -aryloxy-carboxylic acids skeleton and are used for crop protection.¹ Furthermore, α -aryloxy-carboxylic acids or esters are also useful building blocks with broad applications in organic synthesis.² Thus, it is important to develop highly efficient approaches for the generation of optically enriched α -aryloxy-carboxylic acids and related compounds.

Figure 2.1 Some examples of bioactive α -aryloxy-carboxylic acids and their derivative

In the past twenty years, numerous reports have been documented regarding the generation of this kind of compound. One frequently used method is transition-metal catalyzed formation of chiral bonds. For example, in 2004, Humphrey's group reported a catalytic hydrogenation reaction of α -aryloxy α,β -unsaturated acids to α -aryloxy-carboxylic acids using a chiral ruthenium catalyst, which allows direct access to α -aryloxy acids with high conversion rates and enantioselectivities. (Scheme 2.1)³

Scheme 2.1 Humphrey's work on hydrogenation of α -aryloxy α,β -unsaturated acids

Later, Zhou and co-workers developed a rapid approach for the formation of α -aryloxy-carboxylic esters through insertion of carbenoids into phenol O–H bonds under the catalysis of copper complexes (Scheme 2.2).⁴ In this reaction, the α -diazoester first reacts with the copper complex to form the carbenoid intermediate, which then reacts with the alcohol substrates through asymmetric insertion processes to give the target products with good yields and enantioselectivities.

Scheme 2.2 The formation of α -aryloxy-carboxylic esters copper complexes

Another method involves the kinetic resolution (KR) of racemic α -aryloxy-carboxylic acids for the separation of the two optical isomers. In 2011, a KR process of α -aryloxy-carboxylic acids was developed by Birman and co-workers (Scheme 2.3).⁵ The carboxylic acid substrates can react with the homobenzotetramisole (HBTM) catalyst to give the N-acylated intermediate. Then, the reaction rate of the esterification process is determined by the two configurations of the N-acylated intermediate.

Scheme 2.3 Birman's kinetic resolution of α -aryloxycarboxylic acids.

Dynamic kinetic resolution (DKR) is a special type of kinetic resolution since it has extended the scope of methodology for the preparation of enantio-enriched compounds from racemic starting materials.⁶ Besides, different from kinetic resolution, in the DKR process, a racemic compound could be completely transformed into an enantiopure compound.

Before 2010, most of the methods for the generation of α -aryloxycarboxylic acids are focused on enzyme-catalytic DKR. Based on this approach, in 1998, Drueckhammer and co-workers reported an enzyme-catalytic DKR of thioesters to give α -aryloxycarboxylic acids as the final products with lipase used as the catalyst (Scheme 2.4).⁷

Scheme 2.4 Dynamic enzymatic resolution of thioesters

Later, Ohta's group reported that the chirality of one enantiomer of a racemic substrate can be transformed to the other enantiomer through a novel deracemization process promoted by *Nocardia diaphanozonaria* (Scheme 2.5).⁸ Notably, this method is different from the normal DKR process as the substrate and the product are the same substance but with different optical properties.

Scheme 2.5 Ohta's work on deracemization of α -aryloxycarboxylic acids

Recently, N-heterocyclic carbene (NHC) has emerged as a promising small organic molecule catalyst and has been widely used in the dynamic kinetic resolution.⁹ For example, in 2012, Scheidt and co-workers disclosed the first NHC-catalyzed DKR of β -ketoesters for enantioselective access to β -lactone compounds in good yields and with up to 99% ee values (Scheme 2.6).¹⁰

Scheme 2.6 The first NHC-catalyzed dynamic kinetic resolution by Scheidt

Later, the KR of racemic ketones or imines through Breslow intermediates or dienolate intermediates has been developed by Johnson, Wang, and us.¹¹

The mechanism of the NHC-catalyzed DKR process is believed to be initiated by the addition of the chiral carbene catalyst to the carbonyl carbon of the α -aryloxycarboxylic esters (Figure 2.2). The diastereo-isomeric intermediates (*R*)-**1a** and (*S*)-**1a** were formed through this process. The intermediates (*R*)-**1a** and (*S*)-**1a** can be easily converted to each other through an enolization process. Intermediate (*R*)-**1a** can react with the alcohol substrate in a more efficient fashion, since the reactions between (*S*)-**1a** and the alcohol were suppressed due to steric reasons caused by the chiral NHC and the starting materials. As a result, the racemic esters could be successfully converted to a large amount of the chiral product (*R*)-**2a**.

Figure 2.2 General pathway of NHC-induced DKR

Our group is interested in the development of activation modes with useful synthetic applications for the preparation of functional molecules for agricultural use such as plant fungicides and pesticides.¹² We have previously demonstrated the unique power of carbene-catalyzed reactions to efficiently prepare optically pure α , α -disubstituted carboxylic esters via a DKR process (Scheme 2.7 a).¹³ In order to extend the scope of this method, here we report an NHC-mediated DKR reaction for the synthesis of α -aryloxycarboxylic esters with high yields and excellent enantioselectivities (Scheme 2.7 b). The corresponding products could be further transformed to bioactive molecules through simple protocols.

Scheme 2.7 Our works on DKR of α, α -disubstituted carboxylic esters and α -aryloxy carboxylic esters

2.2 Results and discussion

The results of our initial attempts to optimize the reaction condition are summarized in Table 2.1. We first used 4-nitrophenyl 2-phenoxypropanoate and diphenylmethanol as the model substrates in the presence of the achiral NHC (Table 2.1, entries 9 and 10) to test the feasibility of this reaction. Gratifyingly, the corresponding ester **4a** can be obtained with a satisfactory yield. Subsequently, we evaluated the effects of different types of chiral NHCs on the enantioselectivities of the products. To our great delight, most of chiral NHCs (Table 2.1, entries 1 to 8) promoted the reaction well and gave the desired product with promising optical purities. The use of **NHC-D** and **NHC-H** can lead to the formation of the target product with excellent yields (Table 2.1, entries 4 and 8). Additionally, the desired product **3a** can be obtained with the best enantioselectivity without much erosion on the product yield when **NHC-B** was used as the reaction catalyst (Table 2.1, entry 2). Therefore, **NHC-B** was selected as the optimal reaction catalyst for this DKR process for further condition optimizations.

Table 2.1 Screening of Catalysts ^a

entry	NHC	base	solvent	yield% ^b	er ^c
1	A	Cs ₂ CO ₃	THF	89	83:17
2	B	Cs ₂ CO ₃	THF	94	94:6
3	C	Cs ₂ CO ₃	THF	96	90:10
4	D	Cs ₂ CO ₃	THF	97	25:75
5	E	Cs ₂ CO ₃	THF	94	23:77
6	F	Cs ₂ CO ₃	THF	93	93:7
7	G	Cs ₂ CO ₃	THF	95	25:75
8	H	Cs ₂ CO ₃	THF	97	13:87
9	I	Cs ₂ CO ₃	THF	91	--
10	J	Cs ₂ CO ₃	THF	94	--

^a General conditions (unless otherwise specified): **1a** (0.10 mmol), **2** (0.20 mmol), **NHC** (0.02 mmol), base (0.15 mmol), solvent (1.0 mL), 4 Å MS (100 mg), RT, 24 h. ^b Isolated yield. ^c Er values were determined via HPLC on chiral stationary phase.

Different diarylmethanols (**2a** to **2f**) were then examined in this DKR process to test their effects on the reaction yields and enantioselectivities (Table 2.2, entries 1 to 6). Diarylmethyl alcohols bearing various substituents and substitution patterns worked well in this DKR reaction, with the desired products afforded in excellent yields and good to excellent enantioselectivities (Table 2.2, entries 1 to 4). It is worth noting that the di(naphthalen-1-

yl)methanol **2b** can give the target product in almost quantitative yield with an excellent optical purity (entry 2). Diarylmethyl alcohol **2e** giving severe steric hindrance was not effective in this trans-esterification process, with only trace amount of the desired product formed (entry 5). Moreover, benzyl alcohol **2f** with little steric effects gave the target product in a poor enantioselectivity, although in an excellent yield. As a result, the di(naphthalen-1-yl)methanol **2b** was chosen as the alcohol substrate for this enantioselective transesterification DKR process.

Table 2.2 Screening of Alcohols ^a

entry	2	base	solvent	yield% ^b	er ^c
1	2a	Cs ₂ CO ₃	THF	94	94:6
2	2b	Cs ₂ CO ₃	THF	99	97:3
3	2c	Cs ₂ CO ₃	THF	98	97:3
4	2d	Cs ₂ CO ₃	THF	97	94:6
5	2e	Cs ₂ CO ₃	THF	trace	--
6	2f	Cs ₂ CO ₃	THF	98	61:39

^a General conditions (unless otherwise specified): **1a** (0.10 mmol), **2** (0.20 mmol), **NHC** (0.02 mmol), base (0.15 mmol), solvent (1.0 mL), 4 Å MS (100 mg), RT, 24 h. ^b Isolated yield. ^c Er values were determined via HPLC on chiral stationary phase.

Having got an optimized reaction catalyst and substrate, we proceeded to examine the effects of solvents and bases on this DKR reaction (Table 2.3). The uses of K_2CO_3 and Et_3N as the base can give the products with satisfactory enantioselectivities (Table 2.3, entries 2 and 4). The use of chloroform, dichloromethane and dichloroethane as the reaction solvents led to drops on the product er values (entries 6 to 8). Both of the reaction yields and enantioselectivities dropped when a decreased amount of the NHC catalyst (**NHC-B**) was used (entries 10 to 11). Therefore, we chose Cs_2CO_3 as the base, **2b** as the alcohol substrate, THF as the solvent with the catalysis of 20 mol% **NHC-B** for this enantioselective trans-esterification DKR reaction in our further investigations (entry 1).

Table 2.3 Condition Optimization ^a

entry	base	solvent	yield% ^b	er ^c
1	Cs_2CO_3	THF	99	97:3
2	K_2CO_3	THF	91	97:3
3	DBU	THF	97	57:43
4	Et_3N	THF	76	97:3
5	Cs_2CO_3	DCM	99	79:21
6	Cs_2CO_3	$CHCl_3$	92	86:14
7	Cs_2CO_3	DCE	96	83:17
8	Cs_2CO_3	EtOAc	99	93:7
9	Cs_2CO_3	THF	93	95:5
10 ^d	Cs_2CO_3	THF	91	93:7
11 ^e	Cs_2CO_3	THF	91	93:7

^a General conditions (unless otherwise specified): **1a** (0.10 mmol), **2b** (0.20 mmol), **NHC-B** (0.02 mmol), base (0.15 mmol), solvent (1.0 mL), 4 Å MS (100 mg), RT, 24 h. ^b Isolated yield. ^c Er values were determined via HPLC on chiral stationary phase. ^d 10 mol% **NHC-B**. ^e 5 mol% **NHC-B**.

With an optimal reaction condition at hand, we proceeded to investigate the substrate scope of this DKR process. As shown in table 2.4, introduction of a board range of both electron-

donating and electron-withdrawing groups at the α -aryloxy group of the substrate **1** was well tolerated, with the corresponding products formed in good to excellent yields and enantioselectivities. For example, products **3j** and **3k** bearing 4-Cl and 4-Br groups were isolated in almost quantitative yields and excellent optical purities. Esters with electron-donating substituents such as 4-Me and 4-OMe installed on the α -aryloxy group led to the corresponding products **3e** and **3h** in excellent yields and optical purities as well. Besides, α -aryloxycarboxylic ester substrates with functional groups installed at different positions of the benzene ring has little influence on the reaction results (**3j** to **3s**).

When the phenyl moiety on the substrate **1** was replaced with a naphthyl group, the reaction proceeded smoothly and gave the desired products with good yields and excellent er values (**3t**, **3u**). Notably, α -methyl group on the ester **1** can also be switched to an α -ethyl group, although a longer time (48h) is needed to obtain an optimal reaction outcome (**3v**, 94% yield, 94:6 er). Furthermore, the products **3w** and **3x** bearing steric bulkier n-propyl and isopropyl substituents can also be obtained in excellent yields and good optical purities, although a slight alteration of the catalytic condition is needed.

Table 2.4 Scope of Reactions ^a

^a General conditions (unless otherwise specified): **1** (0.10 mmol), **2b** (0.20 mmol), **NHC-B** (0.02 mmol), Cs₂CO₃ (0.15 mmol), THF (1.0 mL), 4 Å MS (100 mg), RT, 24 h. ^c 48 h. ^d **NHC-D** (0.02 mmol), 48 h. ^e **NHC-D** (0.02 mmol), K₂CO₃ (0.15 mmol), 24 h.

To our great delight, the α -methyl group in the substrate **1a** can even be switched to an α -phenyl group, although the product yield and er value were slightly dropped (**3y**). It is worth noting that when the α -aryloxy moiety of the ester substrate was replaced with an alkoxyl group (**3z**), the target product can also be obtained in a good yield with acceptable optical purity. It is worth noting that when the α -aryloxy group on the ester **1a** was replaced with an α -ArS group, the corresponding product (**3aa**) can be formed in a poor yield without optical activity. When

the α -aryloxy group was replaced with an α -imido group, the target product (**3ab**) can only be afforded in trace amount.

Figure 2.3 Investigation of the application of our approach

In order to show the practical utilities of this strategy, we synthesized some human drugs and bioactive molecules through our approach. To our delight, the chiral products we prepared could be readily transformed to other building blocks or bioactive molecules without erosion on the optical purities (Figure 2.3). For example, upon treating di(naphthalen-1-yl)methyl (*R*)-2-phenoxypropanoate **3a** with reducing reagents such as LAH under -78°C , the chiral primary alcohol **4** was generated in 89% yield. The chiral primary alcohol **4** can be used as an important building block in the synthesis of mGlu3 inhibitor¹⁴ and (*R*)-N-(2-phenoxypropyl)acetamide (activator for MT1 and MT2 melatonin receptors).^{15a} Furthermore, after removing the di(naphthalen-1-yl)methyl moiety of **3s** through a Pd/C catalyzed hydrogenation process, we were able to obtain chiral dichlorprop **5** that has been frequently used as a herbicide in crop protection. Amide **6** has played significant roles in the mediation process of type III secretion

system (T3SS) in Gram-negative bacteria.^{15b} Transformation of compound **3s** to **6** could be achieved in a two-step process without erosions on the product optical purities.

2.3 Conclusion

In summary, we have developed an efficient approach for the asymmetric synthesis of α -aryloxycarboxylic ester compounds. A carbene-catalyzed transesterification reaction and an enantioselective dynamic kinetic resolution process are involved in our approach. The developed methodology is featured with mild reaction conditions, convenient operations, and good functional group tolerance. Through this method, not only can α -aryloxycarboxylic esters be efficiently isolated in quantitative yields and excellent optical purities, but also can α -alkyloxycarboxylic esters be obtained in good yields and enantioselectivities. The α -aryloxycarboxylic ester products from our approach are important building blocks that can be applied to prepare chiral bioactive molecules such as herbicides. In our future study, we will explore and evaluate the applicability of these chiral carboxylic acid derivatives in the agricultural and medicinal research.

2.4 Experimental and methods section

2.4.1 Materials and Instrumentation

In addition to aldehyde substrate (purified before used) other commercially available materials were purchased from TCI or Sigma-Aldrich. Tetrahydrofuran (THF) was distilled from Na and used immediately. Other used solvents were dried through 4Å molecular sieve. Unless otherwise indicated, all reactions were set up in Schlenk tube (10 mL size) using N₂ as the atmosphere.

The ¹H NMR spectra data of the sample were recorded on a Bruker BBFO (400 MHz) spectrometer. Unit of parts per million (ppm, δ) was used to record chemical shift and referred to TMS (δ 0.00) or CH₃Cl (δ = 7.26, singlet). The different splitting patterns of ¹H NMR

spectrum are assigned as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned based on the appearance of the multiplet. Some patterns that are difficult to interpret are designated as multiplet (m) or broad (br). The ^{13}C NMR spectra data of substances were recorded on a Bruker BBFO (101 MHz) spectrometer. High-resolution mass spectral analysis (HRMS) was carried out on a Finnigan MAT 95 XP mass spectrometer. A Shimadzu LC-20AD HPLC workstation was to determine the enantiomeric excess of the product. Crystalline structure of 3s was determined on a Bruker X8 APEX X-ray diffractometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL solvent). The thin-layer chromatography (TLC) analysis was performed on Merck 60 F254 pre-coated silica gel plate (thickness 0.2 mm). UV lamp was employed as the visualization.

Preparation of 4-nitrophenyl esters 1

The 2-phenoxy acid and 4-nitrophenyl ester were prepared according to the reported procedure.¹⁶ A typical procedure for the synthesis of starting material is shown below.

To a stirred solution of sodium hydroxide (20 mmol) in ethanol (30 mL) was added phenol (10 mmol) and 2-bromopropionic acid (10 mmol). The reaction mixture was refluxed for 24 hours. The mixture was after cooling to room temperature, the ethanol was removed under reduced pressure and the resulting solid was dissolved in 50 mL of water and acidified with 6.0 M HCl. The acidified mixture was extracted with EtOAc. The combined EtOAc layers were then extracted with saturated NaHCO_3 . The aqueous layers were combined and then acidified

with 6.0 M HCl and extracted again with EtOAc. The final combined EtOAc layers were washed with brine, then dried over Na₂SO₄, and filtered. The solvent was evaporated under reduced pressure to give the crude product.

To a 50 mL round bottom flask provided with a magnetic stir bar was added 2-phenoxy acid (10 mmol), 4-nitrophenol (10 mmol), DCC (12 mmol) and DCM (30 mL). The reaction mixture was stirred overnight at rt. Then the reaction mixture was filtered, and the filtrate was concentrated and evaporated under reduced pressure and the residue was purified by column chromatography utilizing hexane/EtOAc (10:1) as eluent to obtain the desired product **1a** as a white solid.

Preparation of alcohols 2

The alcohol **2a** was purchased from Sigma-Aldrich and other alcohols were prepared according to the reported procedure.¹⁷ A typical procedure for the synthesis of starting alcohol **2b** is shown below.

To a stirred solution of 1-naphthylmagnesium bromide (prepared from 1-bromonaphthalene (20 mmol), magnesium (25 mmol) and iodine (3 mmol) in 25 mL of THF) 1-naphthaldehyde (20 mmol) was added dropwise under nitrogen atmosphere. The solution was stirred for 2-3 h at room temperature, obtaining a grayish white precipitate. A 2.0 M HCl solution was added slowly and the mixture was extracted with EtOAc. The organic phases were washed with brine and dried over Na₂SO₄, evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using hexane/EtOAc (5:1) as eluent to afford the desired product **2b** as a white solid.

General catalytic method for access to products 3

To a 10 mL flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was added eaters **1** (0.1 mmol), alcohol **2b** (0.2 mmol, 56.8 mg), **NHC-B** (0.02 mmol, 8.4 mg), Cs₂CO₃ (0.15 mmol, 49.0 mg) and 4 Å molecular sieves (100 mg, Note: activation by high temperature before used). The reaction tube was sealed with a septum, evacuated the original gas, and refilled with N₂ (3 cycles). THF (1.0 mL) was then added and the reaction mixture was allowed to stir for 24 hours at room temperature (23-26 °C). After the reaction was completed (determined by TLC plate), the mixture was concentrated under reduced pressure to give the residue, which was then subjected to SiO₂ column chromatography using hexane/EtOAc (most use 8/1) as eluent to obtain the desired product **3**.

General catalytic method for access to products 3w, 3x and 3y

To a 10 mL flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was added eaters **1** (0.1 mmol), alcohol **2b** (0.2 mmol, 56.8 mg), **NHC-D** (0.02 mmol, 8.2 mg), Cs₂CO₃ (0.15 mmol, 49.0 mg) and 4 Å molecular sieves (100 mg, Note: activation by high temperature before used). The Schlenk tube was sealed with a septum, evacuated and refilled with N₂ (5 cycles). THF (1.0 mL) was then added and the reaction mixture was allowed to stir for 48 hours at room temperature (23-26 °C). After the reaction was completed (determined by TLC plate),

the mixture was concentrated under reduced pressure to give the residue, which was then subjected to SiO₂ column chromatography using hexane/EtOAc (most use 8/1) as eluent to obtain the desired products **3x** and **3y**. (Note: **3y** condition: K₂CO₃ instead Cs₂CO₃)

Transformations of product and proposed pathway

Reduction of **3a** to form (*R*)-2-Phenoxypropan-1-ol **4**

To a 25 mL round bottom flask equipped with a magnetic stir bar was added **3a** (121.6 mg, 0.28 mmol, 97:3 er) in dry THF (2.0 mL) cooled to -78 °C, LiAlH₄ (16 mg, 0.42 mmol) was added slowly. After the addition, kept at that temperature for 1 h, the mixture was warmed to 0 °C, kept at that temperature for 2 h, and then stirred at room temperature. The reaction was quenched by EtOAc at 0 °C and added 1.0 M HCl solution, next extracted with EtOAc. The combined organic phases were dried with anhydrous Na₂SO₄, and the reaction mixture was concentrated to afford residue, which was then subjected to SiO₂ column chromatography using hexane/ EtOAc (4/1) as eluent to provide the desired product **4** as a colorless oil (37.9 mg, 89% yield, 97:3 er).

Transformation of ester **3s** to **6**

To a 25.0 mL round bottom flask equipped with a magnetic stir bar, was added the ester **3s** (220.0 mg, 0.439 mmol, 98:2 er), wet 10% Pd/C (22.0 mg), and EtOH/THF (1:1, 6.0 mL). The

tube was filled with reducing gas with a balloon equipped with H₂. The mixture was then allowed to stir at room temperature for 18 hours followed by the filtration of mixture with a short pad of celite and methanol. The obtained filtrate was concentrated to give the residual, which was purified by column chromatography using hexane/EtOAc = 10/1 to pure EA (0.1 % HCOOH) as eluent to afford the acid **5** (89.1 mg, 86%).

To the solution of acid **5** (0.1 mmol) in DMF (0.5 mL) was cooled to -15 °C, added HATU (0.15 mmol) and DIPEA (0.2 mmol) and stirred for an additional 5 min. Piperonylamine (0.15 mmol) was added and the reaction was stirred at -15 °C for 2 h. After reaction complete the solution was directly subjected to column chromatography using hexane/ EtOAc = 3/1 as eluent to afford **6** (34.8 mg, 93%, 98:2 er) as a white solid.

2.4.2 Structure determination **3s** via X-ray crystallographic analysis

Product **3s** was crystallized as a colorless crystal via vaporization of CHCl₃ solvent, and its absolute configuration was determined by X-ray structure analysis. CCDC **1973614** includes the supplementary crystallographic data that can be obtained free of charge from the web of Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

2.4.3 Characterization of Products

(R)-di(naphthalen-1-yl)methyl-2-phenoxypropanoate (3a): White solid, 42.8 mg;

[α]²¹_D = -13.7 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.89-7.79 (m, 4H), 7.57-7.42 (m, 3H), 7.39-7.20 (m, 5H), 7.16 (t, *J* = 8.0 Hz, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.87 (q, *J* = 6.8 Hz, 1H), 1.63 (d, *J* = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 171.5, 157.5, 134.4, 134.2, 134.0, 133.8, 131.3, 130.9, 129.5, 129.4, 129.1, 129.0, 128.8, 126.9, 126.6, 126.4, 126.0, 125.8, 125.6, 125.2, 125.1, 123.4, 123.4, 121.6, 115.2, 72.7, 71.8, 18.6;

HRMS (ESI, *m/z*): calcd. for C₃₀H₂₅O₃⁺ 433.1798, found 433.1797;

HPLC analysis: 97:3 *er* (CHIRALPAK IB column, 254 nm, 90:10 hexanes/*i*PrOH, 0.5 mL/min), *R*_t (major) = 9.7 min, *R*_t (minor) = 13.3 min.

(R)-di(naphthalen-1-yl)methyl-2-(4-fluorophenoxy)propanoate (3b): White solid, 44.5 mg;

[α]¹⁹_D = + 0.9 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.90-7.80 (m, 4H), 7.57-7.44 (m, 3H), 7.41-7.20 (m, 5H), 6.84-6.76 (m, 2H), 6.75-6.68 (m, 2H), 4.79 (q, *J* = 6.8 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 171.4, 157.7 (d, *J* = 239.3 Hz), 153.6, 134.3, 134.1, 134.0, 133.9, 131.2, 130.9, 129.4, 129.2, 129.0, 128.9, 126.9, 126.7, 126.3, 126.0, 125.9, 125.7, 125.2, 125.1, 123.4, 123.3, 116.5 (d, *J* = 8.0 Hz), 115.8 (d, *J* = 23.2 Hz), 73.6, 72.0, 18.6;

HRMS (ESI, m/z): calcd. for $C_{30}H_{24}FO_3^+$ 451.1704, found 451.1704;

HPLC analysis: 96:4 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),

Rt (major) = 29.5 min, Rt (minor) = 16.9 min.

(R)-di(naphthalen-1-yl)methyl-2-(4-chlorophenoxy)propanoate (3c): White solid, 47.1 mg;

$[\alpha]^{19}_D = +7.1$ ($c = 1.0$ in $CHCl_3$);

1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 7.90-7.79 (m, 4H), 7.54 (t, $J = 7.0$ Hz, 1H), 7.51-7.44 (m, 2H), 7.40-7.27 (m, 4H), 7.21 (d, $J = 7.1$ Hz, 1H), 7.08-7.01 (m, 2H), 6.73-6.65 (m, 2H), 4.81 (q, $J = 6.8$ Hz, 1H), 1.63 (d, $J = 6.8$ Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 156.1, 134.2, 134.0, 134.0, 133.8, 131.2, 130.9, 129.4, 129.3, 129.2, 129.0, 128.9, 126.9, 126.6, 126.5, 126.3, 126.0, 125.9, 125.7, 125.2, 125.1, 123.3, 123.3, 116.5, 73.1, 72.0, 18.5;

HRMS (ESI, m/z): calcd. for $C_{30}H_{24}ClO_3^+$ 467.1408, found 467.1408;

HPLC analysis: 96:4 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),

Rt (major) = 25.6 min, Rt (minor) = 16.9 min.

(R)-di(naphthalen-1-yl)methyl-2-(4-bromophenoxy)propanoate (3d): White solid, 50.5 mg;

$[\alpha]^{19}_D = +6.1$ ($c = 1.0$ in $CHCl_3$);

1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 7.90-7.79 (m, 4H), 7.57-7.44 (m, 3H), 7.40-7.26 (m, 4H), 7.23-7.15 (m, 3H), 6.70-6.60 (m, 2H), 4.81 (q, $J = 6.8$ Hz, 1H), 1.63 (d, $J = 6.8$ Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 171.1, 156.6, 134.2, 134.0, 133.8, 132.3, 131.2, 130.9, 129.4, 129.2, 129.0, 128.9, 126.9, 126.6, 126.3, 126.0, 125.9, 125.7, 125.2, 125.1, 123.3, 123.3, 117.0, 113.9, 73.0, 72.0, 18.5;

HRMS (ESI, m/z): calcd. for C₃₀H₂₄BrO₃⁺ 511.0903, found 511.0906;

HPLC analysis: 96:4 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),
Rt (major) = 25.7 min, Rt (minor) = 17.7 min.

(R)-di(naphthalen-1-yl)methyl-2-(p-toloxo)propanoate (3e): White solid, 44.3 mg;

[α]_D¹⁹ = -1.2 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 7.88-7.78 (m, 4H), 7.56-7.41 (m, 3H), 7.39-7.31 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.24-7.19 (m, 1H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 4.83 (q, *J* = 6.8 Hz, 1H), 2.26 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 171.7, 155.5, 134.5, 134.2, 134.0, 133.9, 131.3, 131.0, 130.8, 130.0, 129.4, 129.1, 129.0, 128.8, 126.8, 126.6, 126.4, 126.0, 125.8, 125.7, 125.2, 125.1, 123.5, 123.4, 115.1, 72.9, 71.8, 20.5, 18.6;

HRMS (ESI, m/z): calcd. for C₃₁H₂₇O₃⁺ 447.1955, found 447.1953;

HPLC analysis: 97:3 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),
Rt (major) = 29.6 min, Rt (minor) = 18.7 min.

(R)-di(naphthalen-1-yl)methyl-2-(4-ethylphenoxy)propanoate (3f): White solid, 43.1 mg;

[α]_D¹⁹ = -2.6 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.89-7.76 (m, 4H), 7.57-7.41 (m, 3H), 7.39-7.32 (m, 2H), 7.31-7.20 (m, 3H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.1 Hz, 2H), 4.84 (q, *J* = 6.7 Hz, 1H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.61 (d, *J* = 6.7 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 171.7, 155.6, 137.3, 134.4, 134.2, 134.0, 133.8, 131.3, 130.9, 129.4, 129.0, 129.0, 128.8, 128.7, 126.8, 126.6, 126.4, 126.0, 125.8, 125.7, 125.2, 125.1, 123.4, 123.4, 115.1, 72.9, 71.8, 28.0, 18.6, 15.7;

HRMS (ESI, *m/z*): calcd. for C₃₂H₂₉NO₃⁺ 461.2111, found 461.2113;

HPLC analysis: 96:4 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),
Rt (major) = 27.3 min, Rt (minor) = 20.5 min.

(*R*)-di(naphthalen-1-yl)methyl-2-(4-(tert-butyl)phenoxy)propanoate (3g): White solid, 45.2 mg;

[α]_D¹⁹ = -0.5 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.84-7.78 (m, 4H), 7.57-7.41 (m, 3H), 7.39-7.32 (m, 2H), 7.31-7.22 (m, 3H), 7.19-7.12 (m, 2H), 6.77-6.69 (m, 2H), 4.83 (q, *J* = 6.8 Hz, 1H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.29 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 171.7, 155.3, 144.2, 134.4, 134.2, 134.0, 133.8, 131.3, 130.9, 129.4, 129.0, 129.0, 128.8, 126.8, 126.6, 126.5, 126.3, 125.9, 125.8, 125.6, 125.2, 125.1, 123.5, 123.4, 114.5, 72.7, 71.8, 34.1, 31.5, 18.6;

HRMS (ESI, *m/z*): calcd. for C₃₄H₃₂NaO₃⁺ 511.2244, found 511.2249;

HPLC analysis: 99:1 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),
Rt (major) = 14.0 min, Rt (minor) = 18.0 min.

(R)-di(naphthalen-1-yl)methyl-2-(4-methoxyphenoxy)propanoate (3h): White solid, 42.1 mg;

[α]¹⁹_D = +7.9 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.88-7.79 (m, 4H), 7.55-7.42 (m, 3H), 7.41-7.19 (m, 5H), 6.75 (dd, *J* = 9.0, 1.1 Hz, 2H), 6.70-6.63 (m, 2H), 4.79 (q, *J* = 6.6 Hz, 1H), 3.74 (s, 3H), 1.61 (d, *J* = 6.7 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 171.7, 154.5, 151.7, 134.4, 134.2, 134.0, 133.8, 131.2, 130.9, 129.3, 129.1, 129.0, 128.8, 126.8, 126.6, 126.3, 125.9, 125.8, 125.7, 125.2, 125.1, 123.4, 123.4, 116.5, 114.7, 73.7, 71.8, 55.7, 18.6;

HRMS (ESI, *m/z*): calcd. for C₃₁H₂₇O₄⁺ 463.1904, found 463.1900;

HPLC analysis: 96:4 *er* (CHIRALPAK ID column, 254 nm, 90:10 hexanes/*i*-PrOH, 0.5 mL/min), *R*_t (major) = 39.0 min, *R*_t (minor) = 25.5 min.

(R)-di(naphthalen-1-yl)methyl-2-(4-nitrophenoxy)propanoate (3i): White solid, 41.6 mg;

[α]¹⁹_D = +44.5 (*c* = 1.2 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.99-7.78 (m, 8H), 7.58-7.51 (m, 1H), 7.50-7.34 (m, 5H), 7.33-7.23 (m, 2H), 6.79-6.70 (m, 2H), 4.93 (q, *J* = 6.8 Hz, 1H), 1.70 (d, *J* = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 170.3, 162.3, 142.0, 134.0, 134.0, 133.9, 133.8, 131.0, 130.8, 129.6, 129.4, 129.1, 129.0, 126.9, 126.7, 126.1, 126.1, 126.0, 125.9, 125.7, 125.2, 125.0, 123.2, 115.0, 73.2, 72.5, 18.4;

HRMS (ESI, m/z): calcd. for $C_{30}H_{24}NO_5^+$ 478.1649, found 478.1640;

HPLC analysis: 94:6 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/*i*PrOH, 0.5 mL/min), Rt (major) = 29.7 min, Rt (minor) = 32.9 min.

(R)-di(naphthalen-1-yl)methyl-2-(3-chlorophenoxy)propanoate (3j): White solid, 46.1 mg;

$[\alpha]^{19}_D = +12.5$ ($c = 1.0$ in $CHCl_3$);

1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.97 (d, $J = 8.1$ Hz, 1H), 7.93-7.80 (m, 5H), 7.55-7.43 (m, 3H), 7.38 (t, $J = 7.7$ Hz, 2H), 7.34-7.28 (m, 2H), 7.26-7.21 (m, 1H), 7.02 (t, $J = 8.1$ Hz, 1H), 6.93-6.87 (m, 1H), 6.86-6.81 (m, 1H), 6.69-6.62 (m, 1H), 4.83 (q, $J = 6.7$ Hz, 1H), 1.62 (d, $J = 6.8$ Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 158.3, 135.0, 134.2, 134.1, 134.0, 133.9, 131.2, 130.9, 130.2, 129.4, 129.2, 129.0, 128.9, 126.9, 126.7, 126.2, 126.0, 125.9, 125.8, 125.2, 125.2, 123.3, 123.2, 121.8, 115.8, 113.4, 72.9, 72.1, 18.5;

HRMS (ESI, m/z): calcd. for $C_{30}H_{24}ClO_3^+$ 467.1408, found 467.1406;

HPLC analysis: 95:5 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/*i*PrOH, 0.5 mL/min), Rt (major) = 18.1 min, Rt (minor) = 13.3 min.

(R)-di(naphthalen-1-yl)methyl-2-(3-bromophenoxy)propanoate (3k): White solid, 50.3 mg;

$[\alpha]^{19}_D = +15.4$ ($c = 1.0$ in $CHCl_3$);

1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.81-7.93 (m, 5H), 7.55-7.44 (m, 3H), 7.39 (dd, $J = 10.5, 4.7$ Hz, 2H), 7.35-7.29 (m, 2H), 7.23 (d, $J = 6.9$ Hz, 1H), 7.08-

7.03 (m, 1H), 7.02-6.93 (m, 2H), 6.73-6.67 (m, 1H), 4.84 (q, $J = 6.8$ Hz, 1H), 1.62 (d, $J = 6.8$ Hz, 3H);

^{13}C NMR (101 MHz, CDCl_3) δ 171.0, 158.3, 134.2, 134.1, 134.0, 133.9, 131.1, 130.9, 130.5, 129.4, 129.2, 129.0, 128.9, 126.9, 126.7, 126.2, 126.0, 125.9, 125.8, 125.3, 125.2, 124.8, 123.3, 123.2, 122.9, 118.7, 113.9, 72.9, 72.1, 18.5;

HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{23}\text{BrO}_3\text{Na}^+$ 533.0723, found 533.0726;

HPLC analysis: 96:4 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ i PrOH, 0.5 mL/min), R_t (major) = 18.9 min, R_t (minor) = 14.0 min.

(*R*)-di(naphthalen-1-yl)methyl-2-(m-tolyloxy)propanoate (3l): White solid, 42.6 mg;

$[\alpha]_D^{19}$ = +0.5 ($c = 1.0$ in CHCl_3);

^1H NMR (400 MHz, CDCl_3) δ 8.47 (s, 1H), 8.01 (d, $J = 8.3$ Hz, 1H), 7.94-7.78 (m, 5H), 7.56-7.42 (m, 3H), 7.40-7.33 (m, 2H), 7.32-7.26 (m, 2H), 7.25-7.19 (m, 1H), 7.07-7.00 (m, 1H), 6.75 (d, $J = 7.7$ Hz, 1H), 6.61 (d, $J = 6.5$ Hz, 2H), 4.86 (q, $J = 6.8$ Hz, 1H), 2.18 (s, 3H), 1.62 (d, $J = 6.8$ Hz, 3H);

^{13}C NMR (101 MHz, CDCl_3) δ 171.6, 157.6, 139.6, 134.5, 134.2, 134.0, 133.9, 131.3, 131.0, 129.4, 129.3, 129.1, 129.0, 128.8, 126.9, 126.6, 126.4, 126.0, 125.9, 125.8, 125.2, 125.2, 123.4, 123.4, 122.4, 115.9, 112.1, 72.6, 71.8, 21.4, 18.7;

HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{27}\text{O}_3^+$ 447.1955, found 447.1959;

HPLC analysis: 96:4 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ i PrOH, 0.5 mL/min), R_t (major) = 25.7 min, R_t (minor) = 14.2 min.

(R)-di(naphthalen-1-yl)methyl-2-(3-methoxyphenoxy)propan-oate (3m): White solid, 39.5 mg;

$[\alpha]^{19}_D$ = -13.4 (c = 1.0 in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.46 (s, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.94-7.79 (m, 5H), 7.56-7.42 (m, 3H), 7.40-7.20 (m, 5H), 7.04 (t, J = 8.2 Hz, 1H), 6.51 (dd, J = 8.3, 1.8 Hz, 1H), 6.44-6.34 (m, 2H), 4.87 (q, J = 6.8 Hz, 1H), 3.66 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.5, 160.9, 158.8, 134.4, 134.2, 134.0, 133.8, 131.2, 130.9, 129.9, 129.4, 129.1, 129.0, 128.8, 126.9, 126.6, 126.4, 126.0, 125.8, 125.7, 125.2, 125.2, 123.4, 123.4, 107.8, 106.9, 101.6, 72.7, 71.9, 55.2, 18.6;

HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{27}\text{O}_4^+$ 463.1904, found 463.1906;

HPLC analysis: 96:4 v/v (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ i PrOH, 0.5 mL/min), R_t (major) = 38.1 min, R_t (minor) = 19.3 min.

(R)-di(naphthalen-1-yl)methyl-2-(3-(trifluoromethyl)phenoxy) propanoate (3n): White solid, 46.7 mg;

$[\alpha]^{19}_D$ = +11.3 (c = 1.0 in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.46 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.89-7.79 (m, 4H), 7.54-7.42 (m, 3H), 7.41-7.26 (m, 4H), 7.24-7.15 (m, 3H), 7.10 (s, 1H), 6.93-6.88 (m, 1H), 4.90 (q, J = 6.8 Hz, 1H), 1.65 (d, J = 6.8 Hz, 3H);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.9, 157.7, 134.2, 134.0, 134.0, 133.9, 132.0 (q, J = 32.5 Hz), 131.1, 130.9, 130.0, 129.5, 129.3, 129.0, 128.9, 126.9, 126.7, 126.1, 126.0, 125.9, 125.8, 125.2, 125.1, 123.8 (q, J = 272.7 Hz), 123.3, 123.2, 118.3 (q, J = 3.8 Hz), 118.1, 112.6 (q, J = 3.9 Hz), 73.0, 72.2, 18.5;

HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{24}\text{F}_3\text{O}_3^+$ 501.1672, found 501.1667;

HPLC analysis: 95:5 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),

Rt (major) = 12.4 min, Rt (minor) = 11.8 min.

(R)-di(naphthalen-1-yl)methyl-2-(2-chlorophenoxy)propanoate (3o): White solid, 45.1 mg;

[α]_D¹⁹ = -7.1 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.95-7.79 (m, 5H), 7.55-7.43 (m, 3H), 7.43-7.26 (m, 6H), 6.95-6.81 (m, 2H), 6.69 (dd, *J* = 8.0, 1.4 Hz, 1H), 4.87 (q, *J* = 6.8 Hz, 1H), 1.69 (d, *J* = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 170.9, 153.3, 134.3, 134.1, 134.0, 133.9, 131.2, 130.9, 130.5, 129.4, 129.2, 129.0, 128.9, 127.5, 126.8, 126.7, 126.3, 126.0, 125.9, 125.8, 125.2, 125.2, 123.8, 123.4, 123.4, 122.5, 115.2, 74.1, 72.0, 18.4;

HRMS (ESI, *m/z*): calcd. for C₃₀H₂₃ClO₃Na⁺ 489.1228, found 489.1222;

HPLC analysis: 98:2 er (CHIRALPAK ID column, 220 nm, 90:10 hexanes/*i*PrOH, 0.5 mL/min), Rt (major) = 25.3 min, Rt (minor) = 12.6 min.

(R)-di(naphthalen-1-yl)methyl-2-(2-bromophenoxy)propanoate (3p): White solid, 51.3 mg;

[α]_D¹⁹ = -16.0 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.95-7.79 (m, 5H), 7.56-7.44 (m, 4H), 7.43-7.26 (m, 5H), 6.95 (ddd, *J* = 9.1, 7.8, 1.6 Hz, 1H), 6.78 (td, *J* = 7.7, 1.4 Hz, 1H), 6.66 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.87 (q, *J* = 6.8 Hz, 1H), 1.69 (d, *J* = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 170.8, 154.2, 134.3, 134.1, 134.0, 133.9, 133.6, 131.2, 130.9, 129.4, 129.2, 129.0, 128.9, 128.2, 126.8, 126.7, 126.3, 126.0, 125.9, 125.9, 125.2, 125.2, 123.4, 122.9, 114.9, 113.0, 74.1, 72.0, 18.4;

HRMS (ESI, m/z): calcd. for C₃₀H₂₄BrO₃⁺ 511.0903, found 511.0902;

HPLC analysis: 97:3 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/*i*PrOH, 0.5 mL/min), Rt (major) = 28.8 min, Rt (minor) = 13.0 min.

(R)-di(naphthalen-1-yl)methyl-2-(2-iodophenoxy)propanoate (3q): White solid, 55.1 mg;

[α]_D¹⁹ = -32.4 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.94-7.78 (m, 5H), 7.71 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.56-7.43 (m, 3H), 7.43-7.34 (m, 3H), 7.33-7.26 (m, 2H), 6.98 (td, *J* = 8.2, 1.6 Hz, 1H), 6.64 (td, *J* = 7.6, 1.2 Hz, 1H), 6.57 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.88 (q, *J* = 6.7 Hz, 1H), 1.70 (d, *J* = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 170.8, 156.4, 139.8, 134.3, 134.1, 134.0, 133.9, 131.2, 130.9, 129.4, 129.2, 129.2, 129.0, 128.9, 126.8, 126.7, 126.3, 126.0, 125.9, 125.3, 125.2, 123.4, 123.4, 123.4, 113.4, 87.2, 74.1, 72.0, 18.5;

HRMS (ESI, m/z): calcd. for C₃₀H₂₄IO₃⁺ 559.0765, found 559.0760;

HPLC analysis: 98:2 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min), Rt (major) = 33.8 min, Rt (minor) = 15.4 min.

(R)-di(naphthalen-1-yl)methyl-2-(2-methoxyphenoxy)propanoate (3r): White solid, 37.3 mg;

$[\alpha]^{19}_D$ = +4.6 ($c = 0.5$ in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.45 (s, 1H), 7.98 (d, $J = 8.3$ Hz, 1H), 7.93-7.79 (m, 5H), 7.54-7.42 (m, 3H), 7.41-7.25 (m, 5H), 6.95-6.88 (m, 1H), 6.84 (dd, $J = 8.1, 1.3$ Hz, 1H), 6.75 (dd, $J = 8.0, 1.4$ Hz, 1H), 6.67 (td, $J = 7.8, 1.5$ Hz, 1H), 4.88 (q, $J = 6.8$ Hz, 1H), 3.74 (s, 3H), 1.66 (d, $J = 6.8$ Hz, 3H);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.5, 150.1, 147.2, 134.5, 134.4, 133.9, 133.9, 131.2, 131.0, 129.3, 129.1, 128.9, 128.8, 126.8, 126.6, 126.2, 125.9, 125.9, 125.8, 125.2, 125.2, 123.5, 123.4, 122.7, 120.9, 116.4, 112.7, 74.3, 71.7, 56.0, 18.7;

HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{27}\text{O}_4^+$ 463.1904, found 463.1907;

HPLC analysis: 94:6 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ i PrOH, 0.5 mL/min), R_t (major) = 13.6 min, R_t (minor) = 27.9 min.

(*R*)-di(naphthalen-1-yl)methyl-2-(2,4-dichlorophenoxy)propan-oate (3s): White solid, 51.1 mg;

$[\alpha]^{19}_D$ = +15.4 ($c = 1.0$ in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.45 (s, 1H), 8.00-7.78 (m, 6H), 7.57-7.34 (m, 6H), 7.31 (t, $J = 7.6$ Hz, 1H), 7.24 (dd, $J = 8.1, 5.6$ Hz, 2H), 6.75 (dd, $J = 8.8, 2.5$ Hz, 1H), 6.54 (d, $J = 8.8$ Hz, 1H), 4.82 (q, $J = 6.8$ Hz, 1H), 1.68 (d, $J = 6.8$ Hz, 3H);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.6, 152.0, 134.1, 133.9, 133.8, 131.0, 130.9, 130.2, 129.4, 129.3, 129.1, 129.0, 127.3, 126.9, 126.8, 126.7, 126.1, 126.0, 125.9, 125.2, 125.1, 124.5, 123.3, 123.2, 115.7, 74.3, 72.1, 18.4;

HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{23}\text{Cl}_2\text{O}_3^+$ 501.1019, found 501.1017;

HPLC analysis: 98:2 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ i PrOH, 0.5 mL/min), R_t (major) = 12.9 min, R_t (minor) = 11.1 min.

(R)-di(naphthalen-1-yl)methyl-2-(naphthalen-1-yloxy)propanoate (3t): White solid, 48.1 mg;

$[\alpha]^{19}_D$ = -62.3 (c = 1.0 in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.47 (s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.96-7.89 (m, 1H), 7.88-7.75 (m, 5H), 7.57-7.38 (m, 6H), 7.36-7.29 (m, 2H), 7.28-7.18 (m, 3H), 7.11 (t, J = 8.0 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 5.06 (q, J = 6.7 Hz, 1H), 1.76 (d, J = 6.7 Hz, 3H);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.4, 153.4, 134.7, 134.4, 134.1, 134.0, 133.8, 131.3, 130.9, 129.4, 129.0, 129.0, 128.8, 127.4, 126.9, 126.6, 126.6, 126.5, 126.0, 125.8, 125.8, 125.6, 125.5, 125.3, 125.2, 125.1, 123.4, 123.4, 122.3, 121.3, 106.0, 73.2, 71.9, 18.6.

HRMS (ESI, m/z): calcd. for $\text{C}_{34}\text{H}_{27}\text{O}_3^+$ 483.1955, found 483.1960;

HPLC analysis: 97:3 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ i PrOH, 0.5 mL/min), R_t (major) = 17.5 min, R_t (minor) = 15.9 min.

(R)-di(naphthalen-1-yl)methyl-2-(naphthalen-2-yloxy)propanoate (3u): White solid, 47.5 mg;

$[\alpha]^{19}_D$ = +105.7 (c = 1.0 in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.47 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.87 – 7.64 (m, 6H), 7.53 – 7.46 (m, 1H), 7.43 – 7.28 (m, 7H), 7.27 – 7.20 (m, 1H), 7.19 – 7.03 (m, 3H), 6.94 (d, J = 2.5 Hz, 1H), 5.01 (q, J = 6.7 Hz, 1H), 1.70 (d, J = 6.8 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 155.5, 134.4, 134.3, 134.1, 134.0, 133.8, 131.3, 130.9, 129.7, 129.5, 129.4, 129.0, 129.0, 128.8, 127.6, 127.1, 127.0, 126.5, 126.4, 126.3, 126.0, 125.8, 125.7, 125.2, 125.0, 124.0, 123.3, 123.3, 118.9, 107.9, 72.9, 72.0, 18.7.

HRMS (ESI, m/z): calcd. for C₃₄H₂₇O₃⁺ 483.1955, found 483.1957;

HPLC analysis: 96:4 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),
Rt (major) = 40.9 min, Rt (minor) = 26.8 min.

(R)-di(naphthalen-1-yl)methyl-2-phenoxybutanoate (3v): White solid, 41.8 mg;

[α]_D¹⁹ = -5.8 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.95-7.89 (m, 1H), 7.84 (dt, *J* = 16.5, 6.4 Hz, 4H), 7.57-7.41 (m, 3H), 7.38-7.31 (m, 2H), 7.31-7.20 (m, 3H), 7.19-7.12 (m, 2H), 6.97-6.90 (m, 1H), 6.85-6.78 (m, 2H), 4.67 (dd, *J* = 7.0, 5.5 Hz, 1H), 2.06-1.94 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 171.0, 157.9, 134.5, 134.2, 134.0, 133.8, 131.2, 130.9, 129.5, 129.4, 129.0, 129.0, 128.8, 126.8, 126.6, 126.5, 126.0, 125.8, 125.7, 125.2, 125.1, 123.4, 123.4, 121.5, 115.2, 77.9, 71.7, 26.2, 9.7;

HRMS (ESI, m/z): calcd. for C₃₁H₂₇O₃⁺ 447.1955, found 447.1967;

HPLC analysis: 94:6 er (CHIRALPAK ID column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min),
Rt (major) = 15.2 min, Rt (minor) = 12.7 min.

(S)-di(naphthalen-1-yl)methyl-2-phenoxybutanoate (3w): White solid, 44.1 mg;

$[\alpha]^{19}_D$ = +8.4 (c = 1.0 in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.46 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.96-7.89 (m, 1H), 7.89-7.77 (m, 4H), 7.57-7.40 (m, 3H), 7.37-7.31 (m, 2H), 7.31-7.20 (m, 3H), 7.19-7.11 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.85-6.76 (m, 2H), 4.73 (dd, J = 7.8, 4.8 Hz, 1H), 2.03-1.83 (m, 2H), 1.53-1.42 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.2, 157.9, 134.5, 134.2, 134.0, 133.8, 131.3, 130.9, 129.5, 129.4, 129.0, 129.0, 128.8, 126.8, 126.6, 126.5, 126.0, 125.8, 125.7, 125.2, 125.1, 123.5, 123.4, 121.5, 115.2, 71.8, 34.7, 18.5, 13.6, 1.0;

HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{29}\text{O}_3^+$ 461.2111, found 461.2117;

HPLC analysis: 88:12 er (9:91 er) (CHIRALPAK IB column, 254 nm, 95:5 hexanes/ i -PrOH, 0.5 mL/min), R_t (major) = 9.9 min, R_t (minor) = 9.0 min (R_t (major) = 9.1 min, R_t (minor) = 10.1 min.)

(S)-di(naphthalen-1-yl)methyl-3-methyl-2-phenoxybutanoate (3x): White solid, 41.9 mg;

$[\alpha]^{19}_D$ = +4.9 (c = 1.0 in CHCl_3);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.51 (s, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.94-7.88 (m, 1H), 7.87-7.82 (m, 3H), 7.78 (dd, J = 5.8, 3.6 Hz, 1H), 7.55-7.40 (m, 3H), 7.39-7.29 (m, 3H), 7.27-7.21 (m, 2H), 7.17-7.10 (m, 2H), 6.92 (t, J = 7.3 Hz, 1H), 6.81 (d, J = 7.8 Hz, 2H), 4.49 (d, J = 5.4 Hz, 1H), 2.36-2.23 (m, 1H), 1.01 (dd, J = 6.8, 2.1 Hz, 6H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.6, 158.3, 134.6, 134.3, 134.0, 133.8, 131.2, 130.9, 129.5, 129.3, 129.0, 129.0, 128.8, 126.8, 126.6, 126.5, 126.0, 125.8, 125.8, 125.2, 125.1, 123.5, 123.4, 121.5, 115.3, 81.7, 71.5, 31.5, 18.9, 17.5;

HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{29}\text{O}_3^+$ 461.2111, found 461.2109;

HPLC analysis: 91:9 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ⁱPrOH, 0.5 mL/min), Rt (major) = 11.1 min, Rt (minor) = 12.5 min.

(S)-di(naphthalen-1-yl)methyl-2-phenoxy-2-phenylacetate (3y): White solid, 47.2 mg;

[α]¹⁹_D = +79.0 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.38 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.85-7.78 (m, 2H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.58-7.49 (m, 4H), 7.48-7.42 (m, 1H), 7.40-7.14 (m, 8H), 7.08 (dd, *J* = 15.6, 7.6 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 7.1 Hz, 1H), 5.73 (s, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 169.2, 157.4, 135.0, 134.2, 134.0, 133.8, 133.7, 131.4, 130.8, 129.6, 129.5, 129.1, 129.0, 128.8, 128.8, 128.7, 127.7, 126.9, 126.8, 126.4, 126.0, 125.7, 125.2, 125.1, 125.0, 123.4, 123.3, 121.8, 115.5, 78.7, 72.3;

HRMS (ESI, *m/z*): calcd. for C₃₅H₂₇O₃⁺ 495.1955, found 495.1961;

HPLC analysis: 86:14 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/ⁱPrOH, 0.5 mL/min), Rt (major) = 24.6 min, Rt (minor) = 20.9 min.

(R)-di(naphthalen-1-yl)methyl-2-methoxypropanoate (3z): White solid, 32.3 mg;

[α]¹⁹_D = +25.7 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 7.98 (t, *J* = 9.4 Hz, 2H), 7.93-7.82 (m, 4H), 7.55-7.43 (m, 4H), 7.43-7.34 (m, 4H), 4.00 (d, *J* = 6.8 Hz, 1H), 3.35 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 172.4, 134.7, 134.6, 133.9, 131.1, 131.1, 129.2, 129.2, 128.9, 126.7, 126.7, 126.0, 126.0, 125.9, 125.7, 125.2, 125.2, 123.4, 71.4, 57.8, 18.5;

HRMS (ESI, m/z): calcd. for C₂₅H₂₃O₃⁺ 371.1642, found 371.1637;

HPLC analysis: 89:11 er (CHIRALPAK ID column, 254 nm, 90:10 hexanes/*i*PrOH, 0.5 mL/min), Rt (major) = 15.8 min, Rt (minor) = 14.2 min.

(R)-2-phenoxypropan-1-ol (4): Colorless oil, 37.9 mg;

[α]_D¹⁹ = -46.2 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 7.28 (m, 2H), 7.01-6.90 (m, 3H), 4.50 (m, 1H), 3.82-3.64 (m, 2H), 2.18-2.04 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 157.8, 129.6, 121.3, 116.2, 74.8, 66.4, 15.9;

HRMS (ESI, m/z): calcd. for C₉H₁₃O₂⁺ 153.0910, found 153.0916;

HPLC analysis: 97:3 er (CHIRALPAK IA column, 254 nm, 95:5 hexanes/*i*PrOH, 0.5 mL/min), Rt (major) = 17.0 min, Rt (minor) = 15.1 min.

(R)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-2-(2,4-dichlorophen-oxy)propenamide: White solid, 34.8 mg;

[α]_D¹⁹ = +5.8 (*c* = 1.0 in CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J* = 2.5 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.93 (br, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.76-6.66 (m, 3H), 5.94 (s, 2H), 4.72 (q, *J* = 6.7 Hz, 1H), 4.45-4.31 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.9, 151.4, 148.0, 147.1, 131.6, 130.3, 128.0, 127.6, 124.7, 120.9, 116.3, 108.3, 108.2, 101.1, 76.9, 43.0, 18.5;

HRMS (ESI, m/z): calcd. for $C_{17}H_{15}Cl_2NO_4Na^+$ 390.0270, found 390.0269;

HPLC analysis: 98:2 *er* (CHIRALPAK IC column, 254 nm, 90:10 hexanes/*i*PrOH, 0.8 mL/min), *Rt* (major) = 22.0 min, *Rt* (minor) = 35.4 min.

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Chapter 3

N-Heterocyclic Carbene-Catalyzed Enantioselective Cycloaddition of *N*- protected Hydroxylamines with Bromo-enals: Access to Chiral isoxazolidin-5-ones

3.1 Introduction

Isoxazolidin-5-ones are special types of heterocyclic compounds. They are commonly existed in natural products and often display unique bioactivities.¹ For example, the derivatives of isoxazolidin-5-ones **I** and **II** have been proved to be anti-inflammatory and herbicidal activity respectively (Figure 3.1). Besides, isoxazolidin-5-ones are also crucial building blocks in organic synthesis, which are readily converted to the corresponding amino alcohols or β -amino acids.² Thus, the development of efficient and stereoselective approaches for direct access to isoxazolidin-5-one compounds is of great value and has attracted much attention.

Figure 3.1 Structures of isoxazolidin-5-one and its derivatives

In the last decade, a great number of methods have been developed for the stoichiometric or indirect construction of isoxazolidin-5-ones. Some of them involved the base-catalyzed cycloaddition of hydroxylamines to give unsaturated esters. For example, in 1984, Baldwin's group reported the first cycloaddition of methyl 3-(benzyl(hydroxy)amino)propanoate **III** (Scheme 3.1), which provided rapid access to 2-benzylisoxazolidin-5-one **IV** in 91% yield.³ This method consists of two steps: a conjugate addition of N-benzylhydroxylamine to unsaturated ester, followed by cyclization of the adduct **III** in the presence of LDA. The products could be further converted to the corresponding amino acids **V** through catalytic hydrogenation.

Scheme 3.1 Generation of isoxazolidin-5-ones via cycloaddition

The addition-rearrangement of N-substituted hydroxylamines to α , β -unsaturated δ -lactones represents another useful approach for the preparation of isoxazolidin-5-ones. Chmielewski⁴ and co-workers disclosed the pioneering work in this direction. Starting from chiral sugar lactones, they were able to synthesize optically enriched isoxazolidin-5-one derivatives. Mechanically, the lactone **VI** first reacted with N-substituted hydroxylamine to give the adduct **VII**, which then underwent a ring shrinking rearrangement to give the product **VIII** (Scheme 3.2). Notably, this transformation cannot directly control the selectivity of the product, the configuration of the sugar material played a crucial role in the process.

Scheme 3.2 Access to isoxazolidin-5-ones via addition-rearrangement

Preparation of isoxazolidin-5-ones through cycloaddition of ynolates with nitrones has proven to be a promising method as well. In 2002, Shindo⁵ and co-workers reported the first example of stereoselective synthesis of isoxazolidin-5-ones via inverse electron-demand [3+2] cycloaddition (Scheme 3.3). In this strategy, electron-rich ynolate **IX** was required to be prepared and used at low temperature due to its high reactivity. After the formation of intermediate **X**, the following quenching step determined the *trans* or *cis* selectivity of the

product **XI**. The best *trans*-selectivity (up to 99:1 *trans:cis*) can be achieved when *tert*-butanol was used as the quenching reagent.

Scheme 3.3 First case of asymmetric synthesis of isoxazolidin-5-ones

Although stoichiometric or indirect synthetic approaches to isoxazolidin-5-one structures have been documented, the one step catalytic and enantioselective construction of this heterocyclic framework is still challenging. Sibi⁶ and co-workers reported a unique asymmetric version based on the addition of N-benzylhydroxylamine to activated acrylamides **XII** in the presence of chiral magnesium Lewis acid complexes (Scheme 3.4). However, an additional auxiliary must be incorporated into Michael acceptors to achieve satisfactory enantioselectivity.

Scheme 3.4 Sibi's work on preparation of isoxazolidin-5-ones

Zhang and Ying developed an N-heterocyclic carbene organocatalyzed reaction of nitrosobenzene to enals, giving rise to the formation of unstable N-phenylisoxazolidin-5-ones.⁷ Only one enantioselective example was described with moderate selectivity (44.5% ee).

Besides, the substrate scope suffered from limitation owing to the inaccessibility of nitrosobenzene (Scheme 3.5).

Scheme 3.5 NHC-catalyzed generation of N-phenylisoxazolidin-5-ones

Moreover, in 2013, Brière group disclosed that Meldrum's acid turned out to be a useful ketene equivalent, facing to nitron dipoles to form various isoxazolidin-5-one derivatives under Brønsted base organocatalytic conditions (Scheme 3.6).⁸ Although the asymmetric version was demonstrated by means of quinine-based organocatalysts, the moderate selectivity and unatomeconomic procedure were not satisfactory. Despite these advances, the development of a general and practical protocol toward chiral isoxazolidin-5-ones entities starting from readily available substrates under mild conditions, is still highly desirable.

Scheme 3.6 Generation of isoxazolidin-5-ones via ketene equivalent

Over the past decade, N-heterocyclic carbenes (NHCs) have emerged as powerful organocatalysts for a large number of chemical transformations that cannot be achieved by traditional strategies.⁹ Particularly, the application of α , β -unsaturated acyl azoliums as versatile 1,3-bielectrophilic synthons in annulation reactions has attracted much attention.¹⁰ The formal $[3 + 3]$ ¹¹ and $[3 + 4]$ ¹² annulations of α , β -unsaturated acyl azoliums have been

intensively investigated respectively for the synthesis of diverse six- or seven-membered heterocyclic compounds. In contrast, the formal [3 + 2] annulations of α , β -unsaturated acyl azoliums for the synthesis of five-member ring systems are less explored. The reported work is limited to enolizable carbonyl substrate with a heteroatom at α -position.¹³ Later, the Yao and our groups successfully demonstrated pyrazolidinone skeletons could be easily constructed through the annulation of α , β -unsaturated acylazoliums with protected hydrazines.¹⁴

Figure 3.2 The challenges in this work

Encouraged by these advances, we envisaged that the target chiral isoxazolidin-5-ones could be accessible through the reaction of NHC-bound α , β -unsaturated acylazolium intermediates with proper protected hydroxylamines. It is remarkable that several challenges are associated with this [3+2] annulation strategy (Figure 3.2), such as: i) the relatively weak electrophilicity of the β -carbon atom of α , β -unsaturated acyl azoliums might favor the direct N-acylation or O-acylation; ii) the enantioselectivity control might be challenging for this [3+2] process; and iii) the initial O-Michael addition at β position of α , β -unsaturated acyl azoliums would give another heterocycle product. Hydroxylamine with suitable protecting group might favor the

expected pathway. Herein we disclose the enantioselective addition of N-protected hydroxylamine to bromoenal catalyzed by triazolium-derived NHC, which provided an access to chiral isoxazolidin-5-ones in a direct and efficient manifold.

3.2 Results and discussion

We commenced our study with the reaction of α -bromoenal **1a** with various N-protected hydroxylamines in the presence of 20 mol% of carbene precursor **A** and 1.5 equiv of Na₂CO₃ (Table 3.1). Ts- or Boc- protected hydroxylamine proved to be unsuitable for this annulation, with only α , β -unsaturated esters obtained. Although the reaction with N-benzylhydroxylamine could afford the desired corresponding isoxazolidin-5-ones **3** with good yield, the er value was unsatisfactory.

To achieve high enantioselectivity, more steric N-(1-phenylethyl)hydroxylamine was introduced into this [3+2] cycloaddition reaction. The expected higher er value was observed, but the O-acylation side reaction leading to unsaturated ester reduced the yield of desired product. N-(1,1'-diphenylethyl)hydroxylamine turned out to be more effective and the desired product could be obtained in a good yield with a moderate er value. This promising result confirmed our hypothesis and encouraged us to further investigate the effect of different NHC catalysts on the reactivity and enantioselectivity. Piperazine-derived triazolium **B** was ultimately found to be the best (Table 3.1, entry 5-10). Further screening of the bases and solvents in the presence of catalyst **B** reveals that DABCO and Et₂O are the optimal base and solvent, respectively, affording product **3a** in 67% yield with 95:5 er (Table 3.1, Entry 17).

With the optimal reaction conditions in hand, we next explored the generality of the reaction. As briefed in table 3.2, a broad range of bromoenal could readily participate in this transformation, affording the corresponding isoxazolidin-5-ones in acceptable yields and good enantioselectivities. This catalytic system exhibited high compatibility with various substituents.

Table 3.1 Optimization of the Reaction Conditions ^a

entry	R	NHC	base	solvent	yield% ^b	er ^c
1	Ts	A	Na ₂ CO ₃	THF	--	--
2	Boc	A	Na ₂ CO ₃	THF	--	--
3	Bn	A	Na ₂ CO ₃	THF	87	61:39
4	PhCHCH ₃	A	Na ₂ CO ₃	THF	30	80:20
5	Ph ₂ CH	A	Na ₂ CO ₃	THF	73	79:21
6	Ph ₂ CH	B	Na ₂ CO ₃	THF	66	86:14
7	Ph ₂ CH	C	Na ₂ CO ₃	THF	54	52:48
8	Ph ₂ CH	D	Na ₂ CO ₃	THF	38	76:24
9	Ph ₂ CH	E	Na ₂ CO ₃	THF	46	83:17
10 ^d	Ph ₂ CH	F	Na ₂ CO ₃	THF	59	85:15
11 ^d	Ph ₂ CH	B	Na ₂ CO ₃	THF	65	88:12
12 ^d	Ph ₂ CH	B	DABCO	THF	63	89:11
13 ^d	Ph ₂ CH	B	DABCO	dioxane	71	92:8
14 ^d	Ph ₂ CH	B	DABCO	DCE	54	77:23
15 ^d	Ph ₂ CH	B	DABCO	EA	58	90:10
16 ^d	Ph ₂ CH	B	DABCO	toluene	75	92:8
17 ^d	Ph ₂ CH	B	DABCO	Et ₂ O	67	95:5
18 ^d	Ph ₂ CH	B	DABCO	hexane	36	97:3

^a General conditions (unless otherwise specified): **1a** (0.12 mmol), **2** (0.1 mmol), **NHC** (0.02 mmol), base (0.15mmol), solvent (1.5 mL), 4 Å MS (100 mg), RT, 20 h. ^b Isolated yield. ^c er values were determined via HPLCon chiral stationary phase. ^d The reaction was conducted with 10 mol % NHC catalyst **B**.

ester-, nitro-, trifluoromethyl and halide group were amenable in this catalytic system. Substitution electron patterns affected the yields of the products to some extent. In general, bromoenal with electron-withdrawing substituents afforded the desired heterocycles in better selectivity compared to those with donating groups (**3d-3i** vs **3a-3c**). As indicated by the results of steric hindrance investigation, the reaction of enal with substituent at *para*- or *meta*- position proceeded better than the *ortho*- ones (**3e-3f** vs **3g**). To demonstrate the synthetic utility of this method, two scale-up experiments were performed, and no obvious loss of yield or er value was observed (**3d** and **3e**).

Table 3.2 Examples of substituted aryl bromoenals ^a

^a Unless otherwise noted, all reactions were carried out with **1** (0.12 mmol), **N-(1,1'-diphenylethyl)hydroxylamine** (0.1 mmol), **NHC** (0.01 mmol), **DABCO** (1.5 equiv.) and 100mg of 4 Å MS in anhydrous Et₂O (1.5 ml) under N₂ at room temperature. All yields are isolated yields and enantiomeric ratios (er) were determined by HPLC analysis.

Besides, the scope of hydroxylamines and aliphatic bromoenals was also examined under the optimal reaction conditions. The annulations of various substituted benzylhydroxylamines proceeded smoothly, affording the corresponding heterocycle products in acceptable results (**3j-3r**). Unfortunately, there was no desired products could be obtained with furan-derived or aliphatic bromoenals.

Table 3.3 Scope of bromoenals and hydroxylamines ^a

^a Unless otherwise noted, all reactions were carried out with **1** (0.24 mmol), **2** (0.2 mmol), **NHC** (0.01 mmol), DABCO (1.5 equiv.) and 100mg of 4 Å MS in anhydrous Et₂O (1.5 ml) under N₂ at room temperature. All yields and are isolated yields and enantiomeric ratios (er) were determined by HPLC analysis.

3.3 Proposed reaction mechanism

Figure 3.3 Postulated reaction pathway

As illustrated in Figure 3.3, a brief mechanism showed that this reaction was happened with the nucleophilic addition of free carbene to bromoenal **1a**, resulting the formation of acyl azolium intermediate **S1**. This intermediate was then undergone an N-Michael addition by hydroxylamine substrate **2** to give adduct intermediate **S2** followed by the intermolecular cycloaddition to form final product **3** with release of free NHC to re-participate in the reaction cycle. Notably, this reaction has two other side reactions with three by-products (observed in early experiments). Through our optimization to reaction condition, these side products could be successfully controlled as trace amounts.

3.4 Conclusion

In summary, a direct and efficient method for synthesis of chiral isox-azalidin-5-ones was developed, enabled by the cycloaddition of NHC-bound α , β -unsaturated acyl azoliums with N-protected hydroxylamines. The chiral NHC-mediated N-Michael addition of hydroxylamines to acyl azoliums stood out in two competitive side reactions, resulting in both chemoselectivity and enantioselectivity were achieved. Moreover, a broad range of substituted hydroxylamines and enal substrates can react smoothly under mild and metal-free conditions and lead to the asymmetric access to isox-azalidin-5-one compounds in satisfactory yields and good optical purities. This new organocatalytic protocol is attractive in terms of both mechanistic and synthetic aspects, in addition to its simplicity and advantages over the current approaches. Future research development will focus on employing of this strategy to synthesize useful drugs and bioactive molecules containing chiral isox-azalidin-5-one moieties, as well as exploration of the conversion of isox-azalidin-5-ones to other varied substances.

3.5 Experimental and methods section

3.5.1 Materials and Instrumentation

In addition to aldehyde substrate (purified before used) other commercially available materials were purchased from TCI or Sigma-Aldrich. Tetrahydrofuran (THF) was distilled from Na and used immediately. Other used solvents were dried through 4Å molecular sieve. Unless otherwise indicated, all reactions were set up in Schlenk tube (10 mL size) using N₂ as the atmosphere.

The ¹H NMR spectra data of the sample were recorded on a Bruker BBFO (400 MHz) spectrometer. Unit of parts per million (ppm, δ) was used to record chemical shift and referred to TMS (δ 0.00) or CH₃Cl (δ = 7.26, singlet). The different splitting patterns of ¹H NMR spectrum are assigned as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets);

m (multiplets), and etc. All first-order splitting patterns were assigned based on the appearance of the multiplet. Some patterns that are difficult to interpret are designated as multiplet (m) or broad (br). The ^{13}C NMR spectra data of substances were recorded on a Bruker BBFO (101 MHz) spectrometer. High-resolution mass spectral analysis (HRMS) was carried out on a Finnigan MAT 95 XP mass spectrometer. A Shimadzu LC-20AD HPLC workstation was to determine the enantiomeric excess of the product. Crystalline structure of 3s was determined on a Bruker X8 APEX X-ray diffractometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL solvent). The thin-layer chromatography (TLC) analysis was performed on Merck 60 F254 pre-coated silica gel plate (thickness 0.2 mm). UV lamp was employed as the visualization.

Preparation of α -bromoenal substrates 1

The α -bromo enals were prepared based on the literature reported procedure.¹⁵ The general process is shown below.

To a stirred solution of α,β -unsaturated aldehyde (5 mmol) in dried DCM (10 mL) was added Br_2 (7.5 mmol) at $0\text{ }^\circ\text{C}$. After the reaction mixture was stirred for 10 min, the triethylamine (10 mmol) was added. The mixture was then stirred for additional 15 min, monitored by TLC plate, followed by quenched by 10% NaHSO_3 solution moderate. Then the mixture was washed by water, and brine. The organic layer was isolated by extraction, dried over sodium sulfate, and concentrated under vacuum. The obtained residue was purified

through SiO₂ column chromatography using hexane/EtOAc (5:1) to give α -bromoenal substrates **1** as a yellow solid.

Preparation of hydroxylamines **2**

The hydroxylamines **2** was synthesized via two main steps according to the previous reported method.¹⁶ Typical pathway is shown below.

To a solution of benzoyl compounds (5 mmol) in 15 ml solvent (EtOH:H₂O = 1:1) was added sodium hydroxide (5.5 mmol) and NH₂OH·HCl (5.5 mmol). The mixture was then stirred for 20 min followed by concentration to remove ethanol. After extraction, the organic layer was dried over sodium sulfate and concentrated in vacuo again to afford crude oximes that can be directly used in next step without further purification.

The obtained oxime was dissolved in 10 ml MeOH and adjusted the pH of solution to maintain around 2 by adding 2 N HCl. Then the NaBH₃CN (11 mmol) was added in small portions at rt. After stirred for 3 hours, the 6 N NaOH was added to adjust the pH of mixture to 9. Concentrated the mixture in vacuo and extracted it with ethyl acetate (3 x 20 ml). The organic layer was dried over Na₂SO₄ and concentrated again to remove solvent. The crude hydroxylamine was purified by flash SiO₂ column chromatography using hexane/EtOAc as eluent to afford the substrate **2**.

General procedure for access to products **3a – 3i**

To a 10 mL flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was added α -bromoenal **1** (0.12 mmol), Ph_2CHNHOH (0.1 mmol), **NHC-B** (0.01 mmol), DABCO (0.15 mmol) and 4 Å molecular sieves (100 mg, Note: activation by high temperature before used). The reaction tube was sealed with a septum, evacuated and refilled with N_2 (5 cycles). Et_2O (1.5 mL) was then added, and the reaction mixture was allowed to stir at room temperature until the reaction was completed (observed by TLC plate). The mixture was concentrated under reduced pressure and the residue was purified by column chromatography directly using hexane/EtOAc (most use 10/1) as eluent to give the products **3a – 3i**.

General catalytic method for synthesis of products **3j – 3r**

To a 10 mL flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was added substrate **1** (0.24 mmol), hydroxylamine **2** (0.2 mmol), **NHC-B** (0.01 mmol), base-DABCO (0.3 mmol) and 4 Å molecular sieves (100 mg, activation by high temperature before used). Then, the reaction tube was sealed followed by evacuated in vacuum and refilled with N_2 (5 cycles). Et_2O (1.5 mL) was then added as the solvent, and the reaction mixture was allowed to stir at rt until the reaction was finished (determined by TLC plate). The mixture was concentrated under reduced pressure and the residue was flashed by SiO_2 column chromatography using hexane/EtOAc (most use 10/1) as eluent to afford the pure products **3j – 3r**.

3.5.2 Structure determination 3a via X-ray crystallographic analysis

Product **3a** was crystallized as a colorless crystal via vaporization of CHCl₃ solvent, and its absolute configuration was determined by X-ray structure analysis. CCDC **1986298** includes the supplementary crystallographic data that can be obtained free of charge from the web of Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

3.5.3 Characterization of Products

(R)-2-benzhydryl-3-phenylisoxazolidin-5-one (3a): White solid, 43.4 mg (0.2 mmol scale);

¹H NMR (400 MHz, CDCl₃) δ 7.31 (dd, *J* = 15.7, 8.8 Hz, 12H), 7.26 – 7.08 (m, 3H), 5.08 (s, 1H), 4.41 (t, *J* = 8.9 Hz, 1H), 2.91 (d, *J* = 9.6 Hz, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 172.90 (s), 139.81 (s), 137.58 (d, *J* = 11.2 Hz), 130.05 (s), 129.02 (s), 128.55 (d, *J* = 6.1 Hz), 128.17 (d, *J* = 11.6 Hz), 127.44 (d, *J* = 8.7 Hz), 77.41 (s), 77.10 (s), 76.78 (s), 72.62 (s), 66.32 (s), 39.62 (s);

[α]_D²² = 150.2 (c = 0.21 in CHCl₃);

HRMS: C₂₂H₂₀NO₂ for [M+H]⁺, calculated 330.1494, found 330.1501;

HPLC analysis: 94:6 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 12.8 min, Rt (major) = 17.9 min.

(R)-2-benzhydryl-3-(4-methoxyphenyl)isoxazolidin-5-one (3b): White solid, 21.9 mg;

¹H NMR (400 MHz, CDCl₃) δ 7.48-7.13 (m, 13H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.09 (s, 1H), 4.38 (t, *J* = 8.9 Hz, 1H), 3.82 (s, 3H), 2.91 (d, *J* = 8.9 Hz, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 173.2, 140.2, 137.3, 130.4, 129.4, 128.8, 128.6, 128.4, 127.5, 114.6, 71.6, 65.8, 55.6, 44.0 ppm;

[α]_D²² = 144.5 (c = 0.46 in CHCl₃);

HRMS: C₂₃H₂₂NO₃ for [M+H]⁺, calculated 360.1600, found 360.1590;

HPLC analysis: 94:6 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 17.0 min, Rt (major) = 20.8 min.

(R)-2-benzhydryl-3-(p-tolyl)isoxazolidin-5-one (3c): Colorless oil, 22.2 mg;

¹H NMR (500 MHz, CDCl₃) δ 7.30-7.13 (m, 9H), 7.13-7.01 (m, 5H), 4.98 (s, 1H), 4.28 (t, *J* = 8.9 Hz, 1H), 2.79 (d, *J* = 8.8 Hz, 2H), 2.24 (s, 3H);

¹³C NMR (125 MHz, CDCl₃) δ 173.1, 140.1, 138.6, 137.3, 134.4, 130.4, 129.8, 128.6, 128.0, 127.4, 72.0, 66.0, 39.6, 21.3 ppm;

[α]_D²² = 81.6 (c = 0.40 in CHCl₃);

HRMS: C₂₃H₂₂NO₂ for [M+H]⁺, calculated 344.1651, found 344.1652;

HPLC analysis: 93:7 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 13.4 min, Rt (major) = 15.9 min.

(R)-2-benzhydryl-3-(4-bromophenyl)isoxazolidin-5-one (3d): White solid, 27.3 mg, 285.6 mg (1 mmol scale);

¹H NMR (500 MHz, CDCl₃) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.40 – 7.28 (m, 7H), 7.20 (dt, *J* = 12.3, 5.6 Hz, 5H), 5.07 (s, 1H), 4.50 – 4.28 (m, 1H), 2.97 (dd, *J* = 17.1, 7.4 Hz, 1H), 2.86 (dd, *J* = 17.2, 10.0 Hz, 1H);

¹³C NMR (126 MHz, CDCl₃) δ 171.02 (s), 146.54 (s), 144.52 (s), 137.46 (s), 137.26 (s), 127.60 (d, *J* = 2.0 Hz), 127.38 (d, *J* = 5.6 Hz), 127.26 – 126.90 (m), 122.94, 76.24, 75.99, 75.73, 73.95, 64.89, 38.25 ppm;

[α]_D²² = 128.1 (c = 0.27 in CHCl₃);

HRMS: C₂₂H₁₉BrNO₂ for [M+H]⁺, calculated 408.0599, found 408.0587;

HPLC analysis: 95:5 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 18.6 min, Rt (major) = 22.3 min.

(R)-2-benzhydryl-3-(4-chlorophenyl)isoxazolidin-5-one (3e): White solid, 22.8 mg, 211.0 mg (1 mmol scale);

¹H NMR (500 MHz, CDCl₃) δ 7.45-7.27 (m, 11H), 7.19 (t, *J* = 6.7 Hz, 3H), 5.09 (s, 1H), 4.54-4.36 (m, 1H), 2.98 (dd, *J* = 17.1 Hz, 7.4 Hz, 1H), 2.87 (dd, *J* = 17.2 Hz, 10.0 Hz, 1H);

¹³C NMR (125 MHz, CDCl₃) δ 172.7, 139.5, 137.8, 136.4, 134.4, 130.2, 129.7, 129.2, 128.7, 128.4, 128.2, 127.8, 73.3, 65.8, 39.5 ppm;

[α]²²_D = 63.2 (c = 0.20 in CHCl₃);

HRMS: C₂₂H₁₉ClNO₂ for [M+H]⁺, calculated 364.1121, found 344.1104;

HPLC analysis: 95:5 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 15.9 min, Rt (major) = 19.1 min.

(R)-2-benzhydryl-3-(3-chlorophenyl)isoxazolidin-5-one (3f): White solid, 24.5 mg;

¹H NMR (400 MHz, CDCl₃) δ 7.41- 7.23 (m, 8H), 7.23-7.08 (m, 6H), 5.07 (s, 1H), 4.51-4.26 (m, 1H), 2.94 (dd, *J* = 17.3 Hz, 7.8 Hz, 1H), 2.81 (dd, *J* = 17.3 Hz, 9.8 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 172.6, 140.2, 139.2, 138.2, 134.8, 130.3, 129.3, 128.6, 128.3, 128.1, 127.9, 127.5, 125.4, 74.0, 66.0 , 39.4;

[α]²²_D = 121.3 (c = 0.37 in CHCl₃);

HRMS: C₂₂H₁₉ClNO₂ for [M+H]⁺, calculated 364.1104, found 364.1111;

HPLC analysis: 95:5 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 14.0 min, Rt (major) = 22.2 min.

(R)-2-benzhydryl-3-(2-chlorophenyl)isoxazolidin-5-one (3g): White solid, 20.5 mg;

¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.84 (m, 1H), 7.51 – 7.32 (m, 9H), 7.31 – 7.20 (m, 4H), 5.26 (s, 1H), 5.04 (t, *J* = 8.3 Hz, 1H), 3.13 (dd, *J* = 17.5, 8.2 Hz, 1H), 2.76 (dd, *J* = 17.5, 8.4 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 173.3, 139.2, 138.2, 136.6, 132.4, 129.7, 129.3, 128.0, 74.4, 62.4, 37.7 ppm;

[α]_D²² = 18.9 (c = 0.70 in CHCl₃);

HRMS: C₂₂H₁₉ClNO₂ for [M+H]⁺, calculated 364.1104, found 364.1096;

HPLC analysis: 89:11 er (Chiralcel OD, 20:80 iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 13.0 min, Rt (major) = 18.9 min.

(R)-2-benzhydryl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-5-one (3h): Colorless oil, 25.7 mg;

¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.54 – 7.28 (m, 10H), 7.17 (dd, *J* = 5.1, 1.9 Hz, 3H), 5.12 (s, 1H), 4.63 – 4.47 (m, 1H), 3.04 (dd, *J* = 17.3, 7.8 Hz, 1H), 2.89 (dd, *J* = 17.3, 9.8 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 172.5, 142.35, 139.1, 138.3, 130.7, 130.4, 130.1, 129.1, 128.6, 128.4 128.0, 126.34 – 125.59 (m), 125.31 (s), 122.61 (s), 77.38 (d, *J* = 11.5 Hz), 77.12 (s), 76.80 (s), 74.30 (s), 66.08 (s), 39.34 (s);

[α]_D²² = 77.3 (c = 0.40 in CHCl₃);

HRMS: C₂₃H₁₉F₃NO₂ for [M+H]⁺, calculated 398.1368, found 398.1367;

HPLC analysis: 95:5 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 15.2 min, Rt (major) = 17.5 min.

(R)-2-benzhydryl-3-(4-nitrophenyl)isoxazolidin-5-one (3i): White solid, 28.0 mg;

¹H NMR (500 MHz, CDCl₃) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.26 (t, *J* = 4.6 Hz, 2H), 7.18 – 7.08 (m, 3H), 5.10 (s, 1H), 4.59 (t, *J* = 8.8 Hz, 1H), 3.09 (dd, *J* = 17.4, 8.0 Hz, 1H), 2.87 (dd, *J* = 17.4, 9.5 Hz, 1H);

¹³C NMR (126 MHz, CDCl₃) δ 172.08 (s), 147.61 (s), 145.58 (s), 138.53 (s), 138.32 (s), 128.66 (d, *J* = 2.0 Hz), 128.45 (d, *J* = 5.6 Hz), 128.32 – 127.96 (m), 124.01 (s), 77.31 (s), 77.05 (s), 76.80 (s), 75.01 (s), 65.95 (s), 39.31 (s), 1.04 (s);

[α]_D²² = 128.0 (c = 0.20 in CHCl₃);

HRMS: C₂₂H₁₉N₂O₄ for [M+H]⁺, calculated 375.1345, found 375.1346;

HPLC analysis: 94:6 (Chiralcel IA, 10:90= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 23.9 min, Rt (major) = 25.6 min.

(R)-2-benzyl-3-phenylisoxazolidin-5-one (3j): Colorless oil, 48.6 mg (0.2 mmol scale);

¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 6.8 Hz, 2H), 7.52 – 7.42 (m, 3H), 7.43 – 7.27 (m, 5H), 4.41 (t, *J* = 9.5 Hz, 1H), 4.23 (d, *J* = 14.6 Hz, 1H), 4.01 (d, *J* = 14.6 Hz, 1H), 3.05 (d, *J* = 9.7 Hz, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 171.33 (s), 135.24 (s), 134.32 (s), 128.05 (d, *J* = 11.5 Hz), 127.39 (s), 126.82 (s), 126.53 (s), 76.35 (s), 76.03 (s), 75.71 (s), 69.14 (s), 59.90 (s), 39.27 (s), 0.00 (s);

[α]_D²² = 72.6 (c = 0.37 in CHCl₃);

HRMS: C₁₆H₁₆NO₂ for [M+H]⁺, calculated 254.1181, found 254.1180;

HPLC analysis: 95:5 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 15.9 min, Rt (major) = 19.1 min.

(R)-2-(4-methylbenzyl)-3-phenylisoxazolidin-5-one (3k): White solid, 39.0 mg (0.2 mmol scale);

¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.40 (dq, *J* = 14.0, 6.9 Hz, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.35 (t, *J* = 9.5 Hz, 1H), 4.16 (d, *J* = 14.5 Hz, 1H), 3.92 (d, *J* = 14.5 Hz, 1H), 2.98 (d, *J* = 9.7 Hz, 2H), 2.35 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 172.57 (s), 137.72 (s), 136.53 (s), 132.32 (s), 129.23 (t, *J* = 13.3 Hz), 127.69 (s), 77.52 (s), 77.20 (s), 76.88 (s), 69.97 (s), 60.72 (s), 40.44 (s), 21.25 (s);

[α]_D²² = 237.3 (c = 0.36 in CHCl₃);

HRMS: C₁₇H₁₈NO₂ for [M+H]⁺, calculated 268.1338, found 268.1335;

HPLC analysis: 93:7 er (Chiralcel AD, 10:90= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 16.6 min, Rt (major) = 20.3 min.

(R)-2-(4-methoxybenzyl)-3-phenylisoxazolidin-5-one (3l): Colorless oil, 36.0 mg (0.2 mmol scale);

¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, *J* = 7.0 Hz, 2H), 7.45 – 7.35 (m, 3H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.33 (t, *J* = 9.5 Hz, 1H), 4.13 (d, *J* = 14.5 Hz, 1H), 3.89 (d, *J* = 14.5 Hz, 1H), 3.79 (s, 3H), 2.97 (d, *J* = 9.7 Hz, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 172.63 (s), 159.46 (s), 136.43 (s), 130.73 (s), 129.18 (d, *J* = 17.4 Hz), 127.70 (s), 127.36 (s), 113.98 (s), 77.45 (s), 77.20 (s), 76.95 (s), 69.87 (s), 60.34 (s), 55.41 (s), 40.48 (s);

[α]_D²² = 173.8 (c = 0.55 in CHCl₃);

HRMS: C₁₇H₁₈NO₃ for [M+H]⁺, calculated 284.1287, found 284.1294;

HPLC analysis: 92:8 er (Chiralcel OD, 30:70= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 17.0 min, Rt (major) = 19.9 min.

(R)-2-(4-bromobenzyl)-3-phenylisoxazolidin-5-one (3m): White solid, 40.7 mg (0.2 mmol scale);

¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.31 (m, 7H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.33 (t, *J* = 9.6 Hz, 1H), 4.09 (d, *J* = 14.7 Hz, 1H), 3.89 (d, *J* = 14.7 Hz, 1H), 3.00 (d, *J* = 9.9 Hz, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 172.24 (s), 136.07 (s), 134.63 (s), 131.70 (s), 130.66 (d, *J* = 37.8 Hz), 129.35 (d, *J* = 4.4 Hz), 128.99 (s), 127.70 (s), 122.02 (s), 77.52 (s), 77.20 (s), 76.88 (s), 70.61 (s), 60.39 (s), 40.41 (s);

[α]_D²² = 180.6 (c = 0.30 in CHCl₃);

HRMS: C₁₆H₁₅BrNO₂ for [M+H]⁺, calculated 332.0286, found 332.0287;

HPLC analysis: 96:4 er (Chiralcel IC, 10:90= iPrOH/Hexane, 0.5 mL/min), Rt (major) = 36.7 min, Rt (minor) = 38.2 min.

(R)-2-(3-bromobenzyl)-3-phenylisoxazolidin-5-one (3m): White solid, 54.0 mg (0.2 mmol scale);

¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.35 (m, 7H), 7.26 – 7.21 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 4.34 (t, *J* = 9.6 Hz, 1H), 4.10 (d, *J* = 14.7 Hz, 1H), 3.90 (d, *J* = 14.7 Hz, 1H), 3.02 (d, *J* = 9.6 Hz, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 172.21 (s), 138.00 (s), 135.96 (s), 132.02 (s), 131.10 (s), 130.11 (s), 129.39 (s), 127.70 (d, *J* = 4.9 Hz), 122.66 (s), 77.52 (s), 77.20 (s), 76.88 (s), 70.87 (s), 60.48 (s), 40.43 (s);

[α]_D²² = 130.7 (c = 0.44 in CHCl₃);

HRMS: C₁₆H₁₅BrNO₂ for [M+H]⁺, calculated 332.0286, found 332.0283;

HPLC analysis: 92:8 er (Chiralcel OD, 10:90= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 28.3 min, Rt (major) = 45.9 min.

(R)-2-(2-bromobenzyl)-3-phenylisoxazolidin-5-one (3o): Colorless oil, 49.0 mg (0.2 mmol scale);

¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.51 (dd, *J* = 7.4, 2.7 Hz, 3H), 7.44 – 7.34 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.13 (td, *J* = 7.8, 1.6 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.25 – 4.07 (m, 2H), 3.07 (s, 1H), 3.05 (d, *J* = 3.4 Hz, 1H);

¹³C NMR (126 MHz, CDCl₃) δ 172.46 (s), 135.84 (s), 135.25 (s), 132.76 (s), 131.08 (s), 129.46 – 129.12 (m), 127.88 (s), 127.60 (s), 123.84 (s), 77.45 (s), 77.20 (s), 76.95 (s), 71.28 (s), 61.06 (s), 40.36 (s);

[α]_D²² = 153.5 (c = 0.80 in CHCl₃);

HRMS: C₁₆H₁₅BrNO₂ for [M+H]⁺, calculated 332.0286, found 332.0285;

HPLC analysis: 93:7 er (Chiralcel IC, 10:90= iPrOH/Hexane, 0.5 mL/min), Rt (major) = 32.1 min, Rt (minor) = 37.8 min.

(R)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-phenylisoxazolidin-5-one (3p): Colorless oil, 45.3 mg (0.2 mmol scale);

¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.31 (m, 5H), 6.81 (s, 1H), 6.74 (s, 2H), 5.93 (s, 2H), 4.33 (t, *J* = 9.5 Hz, 1H), 4.07 (d, *J* = 14.5 Hz, 1H), 3.85 (d, *J* = 14.5 Hz, 1H), 2.98 (d, *J* = 10.5 Hz, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 172.45 (s), 147.88 (s), 147.46 (s), 136.38 (s), 129.22 (d, *J* = 12.4 Hz), 127.69 (s), 122.79 (s), 109.80 (s), 108.24 (s), 101.19 (s), 77.52 (s), 77.30 (d, *J* = 20.4 Hz), 76.88 (s), 70.07 (s), 60.79 (s), 40.46 (s);

[α]_D²² = 150.3 (c = 0.75 in CHCl₃);

HRMS: C₁₇H₁₆NO₄ for [M+H]⁺, calculated 298.1079, found 298.1075;

HPLC analysis: 93:7 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 24.1 min, Rt (major) = 32.9 min.

(R)-2-(naphthalen-2-ylmethyl)-3-phenylisoxazolidin-5-one (3q): White solid, 50.9 mg (0.2 mmol scale);

¹H NMR (500 MHz, CDCl₃) δ 7.90 – 7.76 (m, 4H), 7.46 (ddt, *J* = 36.7, 22.2, 7.3 Hz, 8H), 4.39 (t, *J* = 9.5 Hz, 1H), 4.33 (d, *J* = 14.6 Hz, 1H), 4.10 (d, *J* = 14.6 Hz, 1H), 3.02 (d, *J* = 9.7 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 172.54 (s), 136.26 (s), 133.34 (s), 133.04 (d, *J* = 12.4 Hz), 129.23 (d, *J* = 12.0 Hz), 128.25 (d, *J* = 1.6 Hz), 128.02 (s), 127.75 (d, *J* = 8.6 Hz), 126.98 (s), 126.22 (d, *J* = 15.0 Hz), 77.46 (s), 77.20 (s), 76.95 (s), 70.40 (s), 61.17 (s), 40.42 (s).

[α]_D²² = 178.2 (c = 0.45 in CHCl₃);

HRMS: C₂₀H₁₈NO₂ for [M+H]⁺, calculated 304.1338, found 304.1339.

HPLC analysis: 93:7 er (Chiralcel OD, 10:90= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 36.9 min, Rt (major) = 52.4 min.

methyl (*R*)-4-((5-oxo-3-phenylisoxazolidin-2-yl)methyl)benzoate (3r): Colorless oil, 34.0 mg (0.2 mmol scale);

¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.41 (dd, *J* = 18.1, 8.3 Hz, 5H), 4.35 (t, *J* = 9.6 Hz, 1H), 4.18 (d, *J* = 14.9 Hz, 1H), 3.99 (d, *J* = 14.9 Hz, 1H), 3.91 (s, 3H), 3.02 (d, *J* = 9.6 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 172.22 (s), 166.97 (s), 140.84 (s), 136.03 (s), 129.88 (s), 129.41 (s), 128.96 (s), 127.74 (s), 77.52 (s), 77.20 (s), 76.88 (s), 70.90 (s), 60.79 (s), 52.23 (s), 40.42 (s);

[α]_D²² = 123.3 (c = 0.50 in CHCl₃);

HRMS: C₁₈H₁₈NO₄ for [M+H]⁺, calculated 312.1236, found 312.1241;

HPLC analysis: 93:7 er (Chiralcel OD, 20:80= iPrOH/Hexane, 0.5 mL/min), Rt (minor) = 31.4 min, Rt (major) = 41.8 min.

3.6 References

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Chapter 4

Summary and Perspective

4.1 Summary and Perspective

The main focus of this thesis study concerns reactivities of NHC catalyst-derived acyl azolium intermediates and their analogs and derivatives such as α,β -unsaturated acyl azolium intermediates. Among multiple types of reactions performed during my Ph.D. studies, two of them are presented in this study. The first one, as documented in chapter 2, mainly focuses on direct nucleophilic addition of a nucleophile to the carbonyl carbon of the acyl azolium intermediates. In particular, this addition step forms a new ester adduct with simultaneous dynamic kinetic resolution of the α -aryloxy-carboxylic esters with excellent yields and enantioselectivities. The second type of reaction, as documented in chapter 3, concerns formation of new heterocycles via formal cycloaddition reactions involving (α,β -unsaturated) acyl azolium intermediates. Briefly, a highly intermolecular chemo-selective addition of hydroxyl amine (selectivity of the “N” over the “O” atom) to the β -carbon of the (α,β -unsaturated) acyl azolium intermediates in an enantio-selective manner forms a new carbon-nitrogen (C-N) bond. This C-N bond formation is followed by an intramolecular ester bond formation to eventually provide the final lactone-type products bearing a nitrogen-oxygen bond within the ring. One immediate application of our reactions documented in chapters 2 lies on the preparation of chiral aryloxy-carboxylic acids that have found proven applications as herbicides.¹ The reactions described in chapter 3 can be directly used to prepare heterocyclic molecules for potential antimicrobial and other activities.

Further development and application from this thesis work can likely lead to broad and highly important applications. This is because carboxylic esters and related functional groups are nearly everywhere in pharmaceuticals and other functional molecules. Our study on NHC catalyst-bound acyl azolium intermediates, as a catalytic and asymmetric strategy to control the reactivities and selectivities of esters and their derivatives, shall bring broad impacts on both basic science and practical applications.

Currently, in the research laboratory of Prof. Robin Chi (my supervisor), exploration of similar acyl azolium intermediates has led to site-specific functionalization of complex molecules such as saccharides, paving the road for concise construction of a large site of molecules (such as low molecular weight heparins) for applications in medicines.

The impact of our research may also be reflected in a relatively obvious manner by a potential drug for covid-19 (**PF-07321332**) developed by Pfizer (Figure 4.1). **PF-07321332** exhibits strong antiviral activities against covid-19 (inhibitor of 3CL protease) and can be used via oral intake.² The information released by Pfizer indicated very promising curative effects with a reduction of hospitalization or death by 89%. If this candidate was later proven to be safe with efficiency at this level, it may become one of the major game-changing bombs to end this pandemic that has had caused big losses and disruptions.

Figure 4.1 PF-07321332 and its properties

An analysis on the structure of **PF-07321332** indicates that one straightforward method is to prepare this molecule from three amino acid derivatives (**A**, **B**, and **C**) as the building blocks (Figure 4.2). NHC catalysis method, based on understanding of the acyl azolium reactivities, can likely be designed to prepare these building blocks in a metal-free and catalytic manner. For example, the chirality of the building block **A** may be established starting from the corresponding racemic substrate (that itself can be made easily via many methods) by using an

NHC-catalyzed dynamic kinetic resolution process similar to that developed in our chapter 2. On the other side, controlling the reactivity of acyl azalium for β -sp³-carbon activation³ may lead to the development of a formal [3+2] process to prepare building block C.

Figure 4.2 Possible strategy to prepare building blocks for PF-07321332 via further development of our NHC-catalyzed approach

In short, we believe that there are many possible further developments from this thesis work. This thesis and its further development shall have broad impacts on the scientific community and human society in general. On the scientific level, access to functional molecules enabled by our NHC catalysis approach shall provide powerful molecular tools for the studies of many fundamental problems in chemistry, biology, materials, and beyond. The potential real-world applications derived from this study, such as those in the medicinal field, shall benefit the wellbeing of humankind. When challenges such as covid-19 arrive, most rational individuals recognize the importance of science. Molecular science, including asymmetric catalysis and molecule constructions, shall likely have its irreplaceable significance in future civilizations, as far as intelligent species still live on this planet.

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