N-heterocyclized carbene catalyzed enolate generation from aldehydes, esters and anhydrides

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**NANYANG
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**N-HETEROCYCLIC CARBENE CATALYZED ENOLATE
GENERATION FROM ALDEHYDES, ESTERS AND
ANHYDRIDES**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2014

**N-HETEROCYCLIC CARBENE CATALYZED ENOLATE
GENERATION FROM ALDEHYDES, ESTERS AND
ANHYDRIDES**

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ABSTRACT

N-heterocyclic carbenes have been proved to be powerful organocatalysts in asymmetric reactions. Despite the well established homoenolate-type addition reactions, the enolate-type reactions using efficient condition-control protocol or simple substrates are still under development. My study is mainly focused on the *N*-heterocyclic carbenes catalyzed enantioselective enolate reactions with various electrophiles.

At the beginning, we discovered that α,β -unsaturated aldehydes undergo enolate addition with unactivated chalcones under chiral NHC catalysis, when weak bases was used instead of strong ones, as shown in appendix. The chemoselectivity between enolte and homoenolate is quite good and the desired lactones were obtained in good yields and excellent enantioselectivities. Thus, we applied this method to other electrophiles, including isatins and β -nitrostyrenes. However, the enolate intermediate was failed to be trapped by these substrates. Then, we introduced activated ester as the enolate precursor in chapter 2. Under chiral NHC catalysis, [4+2] cycloaddition of acetic esters with chalcones was realized in good yield and excellent enantioselectivity. Acetic ester shows great advantages compared to other enolate precursors, such as acetyl chloride and acetaldehyde. Then, we employed this method to other useful electrophiles, and still could not get the desired products through enolate intermediate. In chapter 3, we introduced aliphatic anhydrides as azolium enolate precursors in *N*-heterocyclic carbene catalysis. The Diels-Alder reaction of acetic anhydride and other 2-aliphatic anhydrides with α,β -unsaturated ketone esters was developed. Compared to the previous activated esters, aliphatic anhydrides are proved to be ideal enolate precursor because they are commerical available or easily prepared and most importantly, they have good reactivity with electrophiles. Finally, we employed this method to other electrophiles and a direct aldol reaction of acetic anhydride with isatins was developed under NHC catalysis, as presented

in chapter 4. Various bioactive 3-hydroxy oxindoles could be efficiently obtained with good yield and high enantioselectivity. This work provided a new strategy for direct activation of less reactive aldol donors in carboxylic acid oxidation state without installing specific groups on carbonyl group or α carbon.

PUBLICATIONS

1. “Controlled β -protonation and [4+2] cycloaddition of enals and chalcones via N-heterocyclic carbene/acid catalysis: toward substrate independent reaction control” Fu, Z.; Sun, H.; **Chen, S.**; Tiwari, B.; Li, G.; Chi, Y. R. *Chem. Commun.* **2013**, 49, 261-263.
2. “Organocatalytic activation of alkylacetic esters as enolate precursors to react with α , β -unsaturated imines” Hao, L.; **Chen, S.**; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, 15, 4956-4959.
3. “Asymmetric access to the smallest enolate intermediate via organocatalytic activation of acetic ester” **Chen, S.**; Hao, L.; Zhang, Y.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2013**, 15, 5822-5825.
4. “Access to pyridines via DMAP-catalyzed activation of α -chloro acetic ester to react with unsaturated imines” Hao, L.; Chen, X.; **Chen, S.**; Jiang, K.; Torres, J.; Chi, Y. R. *Org. Chem. Front.* **2014**, 1, 148-150.
5. “NHC-catalyzed enolate generation from aliphatic anhydrides: enantioselective reaction with unsaturated ketone esters” **Chen, S.**; Zhang, Y.; Chi, Y. R. (submitted)
6. “N-heterocyclic carbene catalyzed asymmetric aldol reaction with acetic anhydrides” **Chen, S.**; Jin, Z.; Wang, Y.; Wang, M.; Chi, Y. R. (submitted)
7. β -sp³ C-H activation of carboxylic anhydrides bearing β -alkyl substituents *via* carbene organocatalysis” Jin, Z.;* **Chen, S.**;* Wang, Y.; Zheng, P.; Yang, S.; Chi, Y. R. *Angew. Chem. Int. Ed* DOI: 10.1002/ange.201408604. (* equal contribution)

ABBREVIATIONS

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

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

TMS	trimethylsilyl
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α	alpha
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β	beta
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γ	gamma
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μ	micro
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π	pi
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η	eta
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ω	omega
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σ	sigma
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Chapter 1. *N*-Heterocyclic Carbenes Catalysis

1.1 Introduction

N-heterocyclic carbenes have emerged as powerful and efficient synthetic tools in organocatalysis during last decades, besides as ligands in various metal-based catalytic reactions.¹ In 1960s, Wanzlick performed a significant amount of work on NHC and its dimmers.² Since then, various NHC catalysts have been disclosed, including several main types: thiazolium salts, imidazolium salts and triazolium salts. In 1991, the first stable carbene was isolated by Arduengo, which was substituted by steric Adamantyl groups at nitrogen atoms.³ The pioneering research has constructed steady pillars for the future application of NHC in organic synthesis.

Scheme 1.1 Mechanism of benzoin condensation

As the most basic synthetic blocks in organic chemistry, aldehydes have been utilized in NHC catalyzed reaction for the C-C Bond formation. In 1943, Ukai and co-workers reported that thiazolium salts in the presence of base could catalyze the benzoin reaction similarly as cyanide.⁴ In 1958, Breslow proposed a mechanism for the thiazolium salts catalyzed benzoin condensation.⁵ As shown in scheme 1.1, thiazolyliidene carbene could be generated after the deprotonation of thiamine salt **1**. The in situ generated free carbene **2** was nucleophilic enough to the carbonyl group of aldehyde, generating polarity

reversed nucleophile **4**, which could be trapped by another molecular of aldehyde to afford the benzoin product **6** (Scheme 1.1). The adduct **4** of carbene with aldehyde is typically referred to as “Breslow intermediate”.

The first asymmetric example of benzoin reaction with benzaldehyde was reported by Sheehan in 1966, forming the benzoin product in 22% *ee*.⁶ Subsequently, Sheehan reported that using thiazolium salt as NHC catalyst afforded the product in 51% *ee*, but yield is very low.⁷ The attempts for high enantioselective benzoin reaction remained unsuccessful for over 20 years. In 1998, Leeper and co-workers employed amino alcohol derived triazolium salt in the benzoin reaction and the desired product was obtained in moderate yield and 80% *ee*.⁸ Finally, Enders and co-workers achieved 90% *ee* with good yield in this reaction by using a more reactive triazolium salt (Scheme 1.2).⁹

Scheme 1.2 Asymmetric Benzoin Reactions

In the 1970s, Stetter and co-workers found that thiazolium salts could catalyze the intermolecular addition of aldehyde to Michael accepters in the presence of base.¹⁰ The first asymmetric intramolecular Stetter reaction was reported by Enders using thiazolium salts, giving 1,4-diketone products in 39% enantioselectivity with low yield.¹¹ Rovis and co-workers also developed various intramolecular Stetter reactions using aminoindanol or phenylalanine derived triazolium salts, providing different chromanones and their analogues in good yield and high enantioselectivity (Scheme 1.3).¹²

Scheme 1.3 Asymmetric Intramolecular Stetter Reactions

Compared to the intramolecular reactions, the asymmetric intermolecular Stetter reaction is less successful because of the self condensation of donor aldehydes.¹³ Although β -unsubstituted Michael acceptors could be efficiently converted, reactions with β -substituted Michael acceptors could only give products in low yields. Rovis and co-workers elegantly resolved this problem by utilizing phenylalanine derived triazolium catalyst and developed a highly enantioselective intermolecular Stetter reaction.¹⁴ The 1,4-dicarbonyl products could be obtained in good yield and high enantioselectivity (Scheme 1.4).

Scheme 1.4 Asymmetric Intermolecular Stetter Reactions **1.2 N-Heterocyclic Carbenes Catalyzed Homoenolate Formation**

Saturated aldehydes have been the major substrates for umpolung in *N*-heterocyclic carbene catalysis for a long time, until Glorius and Bode independently extended the scope to α,β -unsaturated aldehydes.¹⁵ Nucleophilic addition of NHC to α,β -unsaturated

aldehydes could form extended Breslow intermediates, which are analogous to the Breslow intermediates from saturated aldehydes. Because of the extended conjugation system, electron could transfer from the carbonyl carbon (acyl anion intermediate) to β -carbon, rendering the β -position significant nucleophilicity, and the corresponding intermediate is named as homoenolate (Scheme 1.5).

Scheme 1.5 Generation of homoenolate in NHC catalysis

Scheme 1.6 Homoenolate addition reactions with aldehyde

Bode's Conditions:

enal: aldehyde= 1 equiv. : 2 equiv.

8 mol% cat. 7 mol% DBU

10:1 THF/tBuOH

rt, 15h

79% yield, 4:1 *cis/trans*

Glorius's Conditions:

enal: aldehyde= 1 equiv. : 1 equiv.

5 mol% cat. 10 mol% KOtBu

THF

rt, 16h

49% yield, 4:1 *cis/trans*

In 2004, Glorius and Bode independently developed the addition reaction of α,β -unsaturated aldehydes to aromatic aldehydes *via* homoenolate intermediate (Scheme 1.6).¹⁵ Although their reaction conditions are slightly different, γ -butyrolactones products were obtained in both reactions with similar diastereoselectivity and *cis* configuration was preferred. Glorius further expanded the substrates scope to ketones, and γ -butyrolactones with one quaternary stereocenter were formed in good yields with low diastereo ratios.¹⁶

Scheme 1.7 Homoenoate addition reaction with chalcone

In 2006, Michael accepters were introduced into the racemic homoenoate addition reactions by Nair (Scheme 1.7).¹⁷ In their initial proposal, chalcones could undergo Michael addition with homoenoate generated from enals, and following annulations could lead to acyl cyclopentanones. However, unexpected 3,4-trans-disubstituted-1-aryl cyclopentenes were obtained instead of the proposed 1,3-diketone products. Analysis of the reaction pathways leads to a reasonable explanation for this result. Instead of the nucleophilic addition of α -carbon of chalcone to carbonyl group of acyl triazolium, the enolate intermediate on enal component generated after the homoenoate addition could undergo an intramolecular aldol reaction, followed by β -lactone formation and decarboxylation to cyclopentenes. Other Michael accepters, such as β -nitrostryenes, could also be employed in this homoenoate reactions.¹⁸ The acyclic γ -nitrocarboxylates products, which can be further transformed to biological compounds such as δ -lactams and δ -amino acid derivatives, were formed in good yield and stereoselectivity.

Later, Bode and co-workers reported several asymmetric Michael addition reactions of homoenoate (Scheme 1.8). Aminoindanol derived chiral carbene was proved to be very efficient and various cyclopentene products were obtained from chalcones in good yield with high enantioselectivity and diastereoselectivity.¹⁹ Beside chalcone type substrates,

α,β -unsaturated *N*-sulfonyl ketimines could also trap the homoenolates to furnish bicyclic β -lactams.²⁰

Scheme 1.8 Homoenolate addition reactions with α,β -unsaturated ketones and ketimines

Besides aldehydes and Michael acceptors, proton could also be used to trap the homoenolate intermediate. Scheidt reported that homoenolate generated from α,β -unsaturated aldehyde could be protonated in presence of phenol to form activated carboxylates, which could undergo esterification with benzyl alcohol (Scheme 1.9).²¹

Scheme 1.9 Protonation of homoenolate

Later, Scheidt extended the scope of homoenolate trappers to 1, 3-dipoles, and developed a series of formal [3+3] cycloaddition reactions (Scheme 1.10). Using *N*-mesityl benzimidazolium salts as carbene precursors, α,β -unsaturated aldehydes could react with azomethine imines *via* homoenolate intermediates, and various pyridazinones products were formed in good yield with high diastereoselectivity (>20:1). Ring opening of the

pyridazinones with alcohols or amines could lead to corresponding esters and amides.²² Similarly, nitrones could undergo cycloaddition reactions with homoenolate intermediates to furnish morpholinone heterocycles, which could be tapped by methanol to afford γ -hydroxy amino esters.²³ With a chiral *N*-heterocyclic carbene (NHC) as the catalyst, the amino esters were generated in high diastereoselectivity and enantioselectivity. Synthetic application of amino esters to γ -lactams was achieved by reduction cleavage of N-O bond and following acid-catalyzed amide formation.

Scheme 1.10 Homoenolate addition reactions with 1,3-dipoles

In 2009, Bode developed a new strategy for homoenolate formation, using α' -hydroxyenones as surrogates of α,β -unsaturated aldehydes (Scheme 1.11).²⁴ The hydroxyenones substrates are easily prepared from aldol reaction of aromatic aldehyde and commercially available 3-hydroxy-3-methylbutanones. Considering the labor and time consumed in α,β -unsaturated aldehydes synthesis, this method shows significant advantage in substrates preparation. Addition of the NHC catalyst to the carbonyl group of α' -hydroxyenone, followed by a retro-benzoin-type reaction, provided the same Breslow intermediate as the one from α,β -unsaturated aldehydes.

Scheme 1.11 Breslow intermediate from α' -hydroxyenones

Similar to α,β -unsaturated aldehydes, α' -hydroxyketone could react with several previous electrophiles in NHC catalysis, such as aromatic aldehydes, chalcones and imines, leading to cyclopentenones, lactams and lactones respectively (Scheme 1.12). The main problem associated with this strategy is that chiral NHC catalysts are less efficient than the racemic ones due to the steric hinderance on α' -carbon.

Scheme 1.12 Reactions of α' -hydroxyketones with electrophiles

1.3 N-Heterocyclic Carbenes Catalyzed Enolate Formation

Analysis the reaction pathway of the above mentioned homoenolate interception by electrophiles reveals that an enolate intermediate could be formed if the homoenolate intermediate is protonated at the β -position (Scheme 1.13). This inherent reactivity of Breslow intermediate provides a new possibility for reaction design. Generation of

homoenolate and enolate from the same intermediate provides a new strategy for selectively formation of C-C bond at β or α carbon of enals.

Scheme 1.13 Enolate Generation from α,β -unsaturated aldehydes

In 2006, Bode and co-workers reported the reaction of enals activated by electron-withdrawing group with α,β -unsaturated imines *via* enolate intermediate (Scheme 1.14).²⁵ Various lactams were obtained in good yield and excellent enantioselectivity. In the same year, Glorius group extended the scope of electrophiles to activated ketones. However, the β -lactones were formed in low yields with poor diastereoselectivity.¹⁶ In 2010, Bode and co-workers reported another [4+2] annulations of enolate intermediate with activated enones, and lactones were obtained under weak basic condition.²⁶ Nair and co-workers disclosed that annulation of β -unsubstituted vinyl ketones with enals provide lactones instead of cyclopentenones in the cases of chalcones.²⁷ Our group also reported that enolate intermediates from enals could be trapped by modified chalcones (alkylidene diketones) in the presence of strong bases, affording lactones in good yield and excellent diastereo- and enantioselectivity.²⁸

Scheme 1.14 Enolate Reaction of α,β -unsaturated aldehydes with electrophiles

Ye²⁹ and Smith³⁰ group concurrently developed enolate reactions of ketenes under NHC catalysts (Scheme 1.15). Initially, they both investigated the reaction of ketenes with imines, and established a formal [2+2] cycloaddition approach for synthesis of β -lactams. In Ye's work, *N*-Boc imines were employed in the cycloaddition with unsymmetrical alkylarylketenes, affording β -lactams in good yield with excellent diastereo- and enantioselectivity.²⁹ Smith's strategy utilized the *N*-tosyl imines, and β -lactams were formed in moderate enantioselectivity (75% *ee*), which could be increased to >99% by a crystallization process.³⁰ Later, Ye and co-workers reported dimerization reactions of alkylarylketenes, providing γ -lactones in regioselective pure form with good yield and enantioselectivity.³¹ Based on these research, various aldehydes and ketones, such as 2-oxo aldehydes, trifluoromethyl ketones and isatins, were investigated.³² Various γ -lactones, including biologically useful spirocyclic oxindoles, were obtained in good yield and enantioselectivity with moderate diastereoselectivity. In 2009, diazenedicarboxylates was employed in the cycloaddition process, and highly enantioselective aza β -lactams were obtained, providing a new method for synthesis of multisubstituted amino acids.³³ In 2011,

N-sulfinylanilines were disclosed to be an efficient interceptor of azolium enolate, and thiazetidinone oxides were obtained in both enantiomers.³⁴ The products could be further transformed to synthetically useful compounds, such as sultams, sulfonimides and mercapto amides, with high enantioselectivity remained.

Scheme 1.15 Enolate reaction of ketenes with 1, 2-dipolar electrophiles

Besides the well established [2+2] cycloaddition, formal [2+3] and [2+4] type reactions were also developed (Scheme 1.16). In 2010, Ye and co-workers reported the annulations of ketenes with oxaziridines, and oxazolidinones were formed in good yield and enantioselectivity.³⁵ It is surprising that the opposite stereoisomers could be accessed by simply using an NHC catalyst with *N*-benzyl instead of the *N*-aryl substitution. Similar to the cases of α,β -unsaturated aldehyde, enones and their azadiene analogues could be

Scheme 1.16 Enolate reactions of ketenes with 1, 3- dipolar electrophiles and enones

employed in the [4+2] cycloaddition reactions with ketenes, affording 2,2-disubstituted δ -lactones and lactams in good yields with high diastereo- and enantioselectivity.³⁶ Enones derived from oxindoles were also successfully employed in the corresponding reactions, and dihydropyranones bearing indole moiety were obtained in good yields and *ee* values, which are in accordance with previous reactions.³⁷ It is interesting to find that *N*-benzoyldiazenes underwent [4+2] cycloaddition with ketenes instead of [2+2] cycloaddition as diazenedicarboxylates.³⁸ The reaction proceeded well with various alkylarylketenes, affording azalatonones in good yields with high enantioselectivity. Dihydrocoumarins, an important type of biological molecule, could also be obtained *via* cycloaddition of ketenes and *o*-quinone methides, and moderate to good yields with high diastereo- and enantioselectivity could be achieved.³⁹

Beside the above mentioned α,β -unsaturated aldehydes and ketenes, α -chloroaldehydes have also been employed in NHC catalysis to generate enolate intermediates. In 2008, Bode introduced α -chloroaldehyde bisulfite adducts as analogue of α -chloroaldehyde in the chiral NHC-catalyzed annulations with various oxodienes, providing lactones with high enantioselectivity (Scheme 1.17).⁴⁰

Scheme 1.17 Enolate reaction of α -chloroaldehyde with enones

Later, Ye and co-workers reported an NHC-catalyzed Diels-Alder reaction of α -chloroaldehydes with azadienes (Scheme 1.18).⁴¹ Various dihydropyridinones were obtained in good yields with excellent diastereo- and enantioselectivity. Further hydrogenation of the lactam products could provide biologically important piperidinones with high enantioselectivity remained.

Scheme 1.18 Enolate reaction of α -chloroaldehyde with ketimines

Recently, Enders reported a [2+3] annulation of nitrovinylindoles and α -chloroaldehydes catalyzed by NHC *via* the generation of azolium enolate (Scheme 1.19).⁴² Various

pyrroloindolones were formed in good yields and excellent diastereo- and enantioselectivities. The lactam products could be further transformed to tetracyclic pyrrolo-[1,2- α]indoles, which are potentially bioactive molecule.

Scheme 1.19 Enolate reactions of α -chloroaldehydes with nitrovinylindoles

In 2009, Scheidt reported that α -aryloxyacetaldehyde could be utilized as an alternative precursor for enolate generation in NHC catalysis (Scheme 1.20). The Mannich reactions of this new enolate precursor with imines could afford β -amino acid derivatives in good yield with high enantioselectivity.⁴³

Scheme 1.20 Enolate reactions of α -aryloxyacetaldehyde with imines

In 2012, Rovis and our group independently developed a similar NHC/[O] system to generate azolium enolate from simple saturated aldehydes (Scheme 1.21).⁴⁴ In Rovis' work, both *trans* lactams and *cis* lactones could be obtained in high yield with high level of diastereo- and enantiocontrol.

Scheme 1.21 Enolate reactions of simple aldehydes with enones and ketimines

1.4 Research Design and Summary of Thesis Work

In this thesis, we present that azolium enolate could be generated with NHC catalysis from α,β -unsaturated aldehydes through efficient control of reaction conditions or from simple substrates, such as activated esters or anhydrides. The later strategy provides a new route to develop synthetically useful reactions, with significant advantages in saving synthetic efforts compared to previous methods.

In chapter 2, we introduce activated acetic ester as the enolate precursor in chiral NHC catalyzed [4+2] cycloaddition with chalcones. Acetic ester shows great advantages in stability compared to acetaldehyde. In chapter 3, we employ aliphatic anhydrides as azolium enolate precursor in the Diels-Alder reaction with α,β -unsaturated ketone esters under chiral NHC catalysis. Aliphatic anhydrides are proved to be ideal enolate precursor because they are commercial available or easily prepared and most importantly, they have good reactivity with electrophiles. In chapter 4, an NHC catalyzed direct aldol reaction of acetic anhydride with isatins is developed, providing bioactive 3-hydroxy oxindoles with good yield and high enantioselectivity. This work provides a new strategy for direct activation of less reactive aldol donors in carboxylic acid oxidation state without installing specific groups on carbonyl group or α carbon. In appendix, we disclose that

α,β -unsaturated aldehydes undergo asymmetric [4+2] annulation with chalcones under chiral NHC catalysis. Under weak basic condition, α,β -unsaturated aldehydes react with electrophiles through enolate instead of homoenolate intermediate.

1.5 References

(1) For selected NHC reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534-541; (b) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 5130-5135; (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655; (d) Marion, N.; Diez-Gonzalez, S.; Nolan, I. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000; (e) Arduengo, A. J.; Iconaru, L. I. *Dalton Trans.* **2009**, 6903-6914; (f) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichim. Acta* **2009**, *43*, 55-66; (g) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77-144; (h) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; Cesar, V. *Chem. Rev.* **2011**, *111*, 2705-2733; (i) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182-1195; (j) Chiang, P. C.; Bode, J. W. *TCI Mail* **2011**, *149*, 2-17; (k) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336-5346; (l) Chiang, P. C.; Bode, J. W. *Science of Synthesis: Asymmetric Organocatalysis*; Vol. 1, Georg Thieme Verlag, **2012**, pp. 639-672; (m) Grossman, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314-325; (n) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522; (o) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11686-11698; (p) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906-4917.

(2) (a) Wanzlick, H. W.; Schikora, E. *Angew. Chem.* **1960**, *72*, 494-495; (b) Wanzlick, H. W.; Schonherr, H. J. *Angew. Chem. Int. Ed.* **1968**, *7*, 141-142; (c) Wanzlick, H. W.; Schonherr, H. J. *Justus Liebigs Ann. Chem.* **1970**, *731*, 176-179.

(3) Arduengo III, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361-363.

(4) Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296-300. (Chem. Abstr. **1951**, *45*, 5148).

-
- (5) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726.
- (6) Sheehan, J.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666-3667.
- (7) Sheehan, J.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196-1199.
- (8) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 1891-1893.
- (9) Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743-1745.
- (10) Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639-712.
- (11) (a) Tiebes, J. Diploma Thesis, RWTH Aachen, Aachen, Germany, 1990; (b) Enders, D. In *Stereoselective Synthesis*; Springer-Verlag: Heidelberg, Germany, 1993; p 63; (c) Enders, D.; Bockstiegel, B.; Dyker, H.; Jegelka, U.; Kipphardt, H.; Kownatka, D.; Kuhlmann, H.; Mannes, D.; Tiebes, J.; Papadopoulos, K. In *Dechema-Monographs*; VCH: Weinheim, Germany, 1993; Vol. 129, p 209.
- (12) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298-10299.
- (13) (a) Stetter, H.; Lorenz, G. *Chem. Ber.* **1985**, *118*, 1115-1125; (b) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314-2315; (c) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715-5724; (d) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932-4933.
- (14) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066-14067.
- (15) (a) Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205-6208; (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370-14371.
- (16) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418-2439.
- (17) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736-8737.
- (18) Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E. *Org. Lett.* **2009**, *11*, 5570-5573.

- (19) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520-3521.
- (20) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418-419.
- (21) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905-908.
- (22) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334-5335.
- (23) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416-2417.
- (24) Chiang, P.C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714-8718.
- (25) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420.
- (26) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A* **2010**, *107*, 20661-20665.
- (27) Nair, V.; Paul, R. R.; Lakshmi, K. C. S.; Menon, R. S.; Jose, A.; Sinu, C. R. *Tetrahedron Lett.* **2011**, *52*, 5992-5994.
- (28) Fang, X. Q.; Chen, X. K.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708-4711.
- (29) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2007**, *10*, 277-280.
- (30) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108-1113.
- (31) Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715-2718.
- (32) (a) He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. *J. Org. Chem.* **2008**, *73*, 8101-8103; (b) Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029-4031; (c) Wang, X.-N.; Zhang, Y.-Y.; Ye, S. *Adv. Synth. Catal.* **2010**, *352*, 1892-1895.
- (33) Huang, X.-L.; Chen, X.-Y.; Ye, S. *J. Org. Chem.* **2009**, *74*, 7585-7587.
- (34) Jian, T.-Y.; He, L.; Tang, C.; Ye, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9104-9107.
- (35) Shao, P.-L.; Chen, X.-Y.; Ye, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 8412-8416.

- (36) (a) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem. Eur. J.* **2008**, *14*, 8473-8476; (b) Jian, T.-Y.; Shao, P.-L.; Ye, S. *Chem. Commun.* **2011**, *47*, 2381-2383.
- (37) Lv, H.; Chen, X.-Y.; Sun, L.-H.; Ye, S. *J. Org. Chem.* **2010**, *75*, 6973-6976.
- (38) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 192-195.
- (39) Lv, H.; You, L.; Ye, S. *Adv. Synth. Catal.* **2009**, *351*, 2822-2826.
- (40) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817-3820.
- (41) Jian, T.-Y.; Sun, L.-H.; Ye, S. *Chem. Commun.* **2012**, *48*, 10907-10909.
- (42) Ni, Q.; Zhang, H.; Grossmann, A.; Loh, C. C. J.; Merkens, C.; Enders, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 13562-13566.
- (43) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098-10099.
- (44) (a) Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 12330-12333; (b) Mo, J.; Yang, R.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 50-53.

Chapter 2. *N*-Heterocyclic Carbenes Catalyzed Enolate

Formation from Activated Acetic Ester

2.1 Introduction

Carboxylate esters are widely spread synthetic blocks and functional group in organic synthesis. While these substrates and their derivatives have been successfully utilized for generation of enolates in metal¹ or organic molecule-based catalysts², they are rarely investigated in *N*-heterocyclic carbene catalysis. In 2002, Nolan³ and Hedrick⁴ simultaneously reported an NHC catalyzed transesterification reaction. Numerous alcohols could react with methyl esters under the catalysis of alkyl-substituted carbene, furnishing the corresponding esters in very short time. The scope of substrates was further expanded to secondary alcohols and phosphorus esters. It is noteworthy that polymerization of long chain alcohol esters was also realized, providing an efficient route to biodegradable and commodity polymers and dendrimer precursors.⁴ Besides these transesterification reactions, NHC catalyzed activation of carboxylate esters for generation of enolate is still undeveloped.⁵

As the main target of our research is to develop a general strategy of enolate formation under *N*-heterocyclic carbene catalysis, and its application in synthesis of biologically useful organic compounds, we focused on the NHC catalyzed activation of carboxylate esters. Based on the previous study, we envisioned that with a suitable base and reactive leaving group, enolate might be generated after the addition of carbene to carboxylic ester. Compared to previously used α,β -unsaturated aldehydes, using activated esters could avoid the competing reactions *via* homoenolate intermediates. Thus, we introduced electron deficient phenol as the leaving group on the activated ester and the desired enolate intermediate could be successfully trapped by α,β -unsaturated ketimines to provide various six-membered lactam products.⁶ In this chapter, we want to use activated

acetic ester as an enolate precursor. After addition of NHC to acetic ester and the following deprotonation process, the smallest enolate intermediate could be generated, which could be a powerful two-carbon nucleophile in organic synthesis.

Scheme 2.1 Amines and quindines catalyzed nucleophilic addition reactions of acetaldehyde and acetyl chloride.

Simple two-carbon enolate precursors have attracted much attention for their utility in synthesis of bioactive molecules, since organocatalysts emerged as powerful synthetic tools (Scheme 2.1). Acetaldehyde, a representative type of two-carbon nucleophiles, has been successfully employed in chiral amine catalysis, as reported by List, Hayashi, Maruoka and other groups.⁷ Various biologically useful targets could be obtained through the reaction of acetaldehyde with N -protected imines, aldehydes, nitrostyrenes. Another important type of two-carbon nucleophile is acetyl chloride, which could undergo [2+2] reactions with aldehydes *via* ketene intermediates under cinchona alkaloid catalysis, as

reported by the groups of Wynberg and Nelson.⁸ Although various synthetically important transformations have been established, the unstability of these two-carbon enolate precursors and big equivalent excess needed in reactions remain two major problems needed to be resolved for further synthetic application. Among the well established enolate formation in NHC catalysis from α,β -unsaturated aldehydes,⁹ α -functionalized aldehydes,¹⁰ and ketenes,¹¹ only few examples of two-carbon nucleophiles have been developed (scheme 2.2). For example, α -chloroacetaldehyde bisulfite adducts has been investigated by Bode and co-workers for enantioselective reactions with enones to afford lactones.¹² Scheidt developed α -aryloxyacetaldehyde for Mannich reactions through an internal formation of enolate *via* redox process.¹³ In both reactions, activation at α -position of acetaldehyde is essential for enolate generation, which may require additional synthetic steps. Compared to those two-carbon nucleophiles in literature, our method using acetic ester as substrates shows significant advantages in atom economy, considering the less amount of ester substrates needed in the reaction and the simply preparation of the ester starting material.

Scheme 2.2 Two-carbon enolate precursors in NHC catalysis.

2.2 Results and Discussion

Table 2.1 Screening of solvents in annulation of acetic ester with chalcone ^a

Entry	Cat.	solvent	yield (%) ^b	ee (%) ^c
1	A	THF	40	-
2	B	THF	23	-
3	C	THF	69	94
4	C	toluene	76	98
5	C	CH ₂ Cl ₂	80	99
6	C	EtOAc	80	94
7	C	CHCl ₃	74	99
8	C	MeCN	99	96
9^d	C	MeCN	98	98

^a Reaction conditions: **2-1a** (0.10 mmol), **2-2a** (0.05 mmol), Cat. (30 mol%), DBU (0.10 mmol), solvent (0.5 mL), rt. ^b Yield of **2-3a** was estimated *via* ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxy benzene as an internal standard. ^c The *ee* of **2-3a** was determined *via* chiral phase HPLC analysis. ^d 0.075 mmol of DBU was used.

In this chapter, we present that 4-nitrophenyl acetic ester could be used as a powerful two-carbon enolate precursor in NHC catalysis. This new substrate could be readily synthesized from condensation of acetic acid with 4-nitrophenol, and it is stable toward moisture and air. At the outset, we employed acetic ester **2-1a** and chalcone **2-2a** as the

model substrates. Under the catalysis of racemic triazolium salts, the desired product could be obtained in acceptable yield with DBU as base in THF (Table 2.1, entry 1). With 30 mol% of chiral aminoindanol-derived catalyst **C**,¹⁴ we are delighted to found that lactone product **2-3a** was obtained in 69% yield and 94% *ee* (Entry 3). Other solvents were then investigated, and toluene was also a suitable solvent as well as ethyl acetate (entries 4 and 6). Excellent enantioselectivity could be obtained with halogenated solvents, such as dichloromethane and chloroform, with good yields remained (entries 5 and 7). When acetonitrile was used for this reaction, the lactone **2-3a** was obtained in nearly quantitative yield with 96% *ee* (entries 8). Decreasing the amount of base could lead to even higher enantioratio with almost the same yield (entries 9).

Table 2.2 Screening of bases in annulation of acetic ester with chalcone ^a

2-1a + **2-2a** $\xrightarrow[\text{MeCN, 24 h}]{\text{C, base}}$ **2-3a**

R = 4-NO₂C₆H₄

Entry	base	yield (%) ^b	<i>ee</i> (%) ^c
1	Cs ₂ CO ₃	30	98
2	K ₂ CO ₃	27	n.d.
3	KOtBu	57	n.d.
4	Et ₃ N	trace	n.d.
5^d	DBU	92	98
6 ^e	DBU	88	96

^a Reaction conditions: **2-1a** (0.10 mmol), **2-2a** (0.05 mmol), **C** (30 mol%), base (0.10 mmol), MeCN (0.5 mL), rt. ^b Yield of **2-3a** was estimated *via* ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxy benzene as an internal standard. ^c The *ee* of **2-3a** was determined *via* chiral phase HPLC analysis. ^d 0.075 mmol of DBU and 20 mol% catalyst **C** was used. ^e 0.075 mmol of DBU and 10 mol% catalyst **C** was used.

Table 2.3 Scope of the α,β -unsaturated ketones ^a

^a Reaction conditions: **2-1a** (0.20 mmol), **2-2** (0.10 mmol), **C** (0.02 mmol), DBU (0.15 mmol), MeCN (1.0 mL). Reported yields are isolated yields based on **2-2**. Enantiomeric excesses were determined *via* chiral phase HPLC.

After acetonitrile has been identified as the best solvent, the effect of different bases was studied. While weak inorganic bases could only give low yield (Table 2.2, entry 1 and 2), strong inorganic bases provided the product in moderate yield (Entry 3). Weak organic base, such as triethylamine, provided only trace of the product (Entry 4). Due to the inherently low reactivity of the α proton on the acetic ester, inorganic bases and weak organic bases could not promote this annulation reaction efficiently. With DBU as base, the catalyst loading could be decreased to 20 mol%, furnishing the lactone in good yield and *ee* (Entry 5). Further decreasing the catalyst loading to 10 mol% leads to slightly lower yield and *ee* value (Entry 6).

Having identified the optimal reaction condition, the scope of the enone substrate was then explored. Various chalcone-type enones were tolerated under the standard reaction condition, giving the corresponding lactone products with good yields and excellent *ee* (Table 2.3). Substrates with naphthyl group at either side of enones were smoothly converted to the corresponding lactones in good yield and *ee* (**2-3b, c**). Methyl substitution at *ortho*, *meta* and *para* position on the β -phenyl group of chalcone were all well tolerated (**2-3d, e, f**). Dimethyl substituted chalcone was also suitable substrates (**2-3g**). Enones with Br or Cl substituent on the carbonyl phenyl group could also be converted to the desired products in good reaction outcome (**2-3h, i**), while those with electron withdrawing substituent on β -phenyl group provided lactones with decreased enantioselectivity (**2-3j, k**). Heteroaryl substituents also worked well, except enone with furan group at β -position, providing product (**2-3n**) in both decreased yield and *ee* (62% yield, 90% *ee*). Beside the aryl enones, the alkyl enone were also investigated under the standard reaction condition. With methyl group substituted at β -position of enone, the lactone product could be provided with excellent *ee*, albeit with low yield (**2-3o**, 36% yield).¹⁴ Unfortunately, enone with methyl group at the carbonyl side could not give any

desired product (**2-3p**). The absolute configurations of the lactone products were determined based on X-ray crystal structure analysis of **2-3j**.¹⁵

The proposed mechanism for lactone formation is shown in Scheme 2.3. The triazolium salt is deprotonated by a base to generate a free carbene, which reacts with the acetic ester to form the acyl azolium **I**. Deprotonation of **I** under the basic condition gives enolate **II**, which reacts with α,β -unsaturated ketone to eventually form the lactone product *via* intermediate **III**. To shed insightful lights on the reaction mechanism, preliminary kinetic studies were performed. By adopting Bode's procedure for kinetic studies in NHC-catalyzed reactions of ynals,¹⁶ we studied the rate orders with respect to ester, NHC catalyst, and chalcone (Figure 2.1). Under the concentrations (0.1-0.3 M for ester and chalcone, 0.015-0.035 M for catalyst) and conditions evaluated, the concentration of all three components can influence the reaction rates, with chalcone having the biggest effect.

Scheme 2.3 Proposed mechanism for lactone formation

Figure 2.1 Kinetic studies of annulations of acetic ester and chalcone.

With the strategy for the asymmetric [4+2] cycloaddition reaction realized, we then explored the synthetic utility of the six-membered lactone products (Scheme 2.4). When lactone **2-3a** was treated under weak oxidant such as *meta*-chloroperoxybenzoic acid (mCPBA), an unstable epoxide product could be obtained and further rearranged under acidic condition to butyrolactones **2-4** (and **2-4'**), which possess an important core structure found in many biologically active natural products.¹⁷

Scheme 2.4 Synthetic utility of the lactone products

2.3 Conclusion

In summary, we disclosed an NHC-catalyzed annulation reaction of acetic ester with chalcones, providing α -unsubstituted δ -lactones which were difficult to access using other

methods. The acetic ester is quite stable and easily available, possessing significant synthetic advantage to the previous enolate precursors. Further investigation of this smallest ester enolate precursor involved addition with other electrophiles are under progress.

2.4 Experimental Section

General Information

Commercially available materials were used as received. 4-Nitrophenyl acetate **2-1a** and chalcones **2-2** were synthesized following literature reported methods.⁶ Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Bruker AV400 (400 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Bruker AV400 (400 MHz) (100 MHz) spectrometers. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *ee* was performed by chiral phase HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 0.5 mL cell with a 10 mm path length on a PerkinElmer Model 341 digital polarimeter and are reported as follows: $[\alpha]_{\text{D}}^{\text{rt}}$ (*c* in mmol per mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

Typical procedure for NHC-catalyzed reactions of esters with α,β -unsaturated ketones to give lactones **2-3**.

A dry 10 mL Schlenk tube, equipped with a stir bar, was charged with ester **2-1a** (0.20 mmol), α,β -unsaturated ketone **2-2** (0.10 mmol) and chiral triazolium salt **C** (0.02 mmol). The flask was then evacuated and refilled with Argon. To this mixture was added

anhydrous CH_3CN (1.0 mL) and DBU (0.15 mmol). The mixture was stirred at rt for 24 h. After complete consumption of the enone **2-2** (monitored by TLC), the mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (15:1, hexanes/EtOAc) to afford the desired lactones **2-3**. The lactone products were characterized by ^1H NMR, ^{13}C NMR and high-resolution mass spectrometry (HRMS), and the enantiomeric excesses were determined by chiral HPLC analysis.

Note: Racemic products for the chiral phase HPLC analysis were synthesized *via* similar procedure using achiral triazolium salt **A**.

Stereochemistry determination *via* X-ray crystallographic analysis:

Good quality crystals of **2-3j** (colorless needle crystals) were obtained by vaporization of hexane/ CH_2Cl_2 (1:1) solutions of compounds **2-3j**. CCDC 921945 (**2-3j**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

R^2	0.92	0.96	0.83	0.88	0.94
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Rate order for catalyst: A solution of 1,3,5-trimethoxybenzene (0.25 mmol; 5.0 equiv as internal standard), chalcone (0.25 mmol; 5.0 equiv) and 4-nitrophenyl acetate (0.25 mmol; 5.0 equiv) was prepared using 2.5 mL CDCl₃. The final solution was quickly transferred to dried NMR tubes (0.5 mL of the final solution to each tube) containing varied amounts of NHC catalyst: 0.15, 0.20, 0.25, 0.30, and 0.35 equiv. DBU (0.05 mmol, 1.0 equiv) was added to each NMR tube at room temperature before the percentage conversions were measured using ¹H NMR (Bruker 400 MHz) by the disappearance of the chalcone, from the integration of the peak at 7.81 ppm (1H) against the internal standard peak at 6.08 ppm (3H). The plots of molar concentration of the chalcone versus time (min) were generated; the rates were determined from the slope of each plot. The rate order was calculated from the plot of ln(rate) against ln(chalcone concentration) to be 0.27 ($R^2 = 0.89$). Below, the table reports raw data; the plots shows [chalcone] vs. time, and the ln[rate] vs. ln[chalcone].

time/min	conc.of chalcone for reactions (varying catalyst equiv.)				
	0.15eq	0.20eq	0.25eq	0.3 eq	0.35eq
0	0.1002	0.0992	0.1007	0.1000	0.1008
20	0.0980	0.0980	0.0985	0.0965	0.0980
40	0.0964	0.0951	0.0957	0.0945	0.0945
60	0.0946	0.0928	0.0944	0.0926	0.0932
80	0.0936	0.0919	0.0927	0.0915	0.0925
Rate [M/min]	-8.36×10^{-5}	-9.89×10^{-5}	-9.98×10^{-5}	-1.04×10^{-4}	-1.08×10^{-4}
R^2	0.98	0.97	0.98	0.95	0.93

Rate order for chalcone: A solution of 1,3,5-trimethoxybenzene (0.25 mmol; 5.0 equiv as internal standard), 4-nitrophenyl acetate (0.25 mmol; 5.0 equiv) and the NHC catalyst (0.075 mmol; 1.5 equiv) was prepared using 2.5 mL CDCl_3 . The final solution was quickly transferred to dried NMR tubes (0.5 mL of the final solution to each tube) containing varied amounts of chalcone: 1.0, 1.7, 2.1, 2.7, and 3.2 equiv. DBU (0.05 mmol, 1.0 equiv) was added to each NMR tube at room temperature before the percentage conversions were measured using ^1H NMR (Bruker 400 MHz) by the disappearance of the chalcone, from the integration of the peak at 7.81 ppm (1H) against the internal standard peak at 6.08 ppm (3H). The plots of molar concentration of the chalcone versus time (min) were generated; the rates were determined from the slope of each plot. The rate order was calculated from the plot of $\ln(\text{rate})$ against $\ln(\text{chalcone concentration})$ to be 0.73 ($R^2 = 0.98$). Below, the table reports raw data; the plots shows [chalcone] vs. time, and the $\ln[\text{rate}]$ vs. $\ln[\text{chalcone}]$.

time/min	conc.of chalcone for reactions (varying chalcone equiv.)				
	1.0 eq	1.7 eq	2.1 eq	2.7 eq	3.2 eq
0	0.0977	0.1696	0.2104	0.2660	0.3171
20	0.0958	0.1672	0.2067	0.2629	0.3114
40	0.0945	0.1654	0.2046	0.2599	0.3087
60	0.0936	0.1644	0.2030	0.2577	0.3068
80	0.0930	0.1635	0.2024	0.2569	0.3059
Rate [M/min]	-5.81×10^{-5}	-7.51×10^{-5}	-9.86×10^{-5}	-1.17×10^{-4}	-1.34×10^{-4}
R^2	0.96	0.96	0.92	0.96	0.90

Characterization Data

(R)-4,6-Diphenyl-3,4-dihydro-2H-pyran-2-one (2-3a). 92% yield; yellowish solid; ν_{max} (KBr)/ cm^{-1} 1759, 1377, 1279, 1138, 1018, 770; $[\alpha]_{\text{D}}^{20} = +56$ (0.09 M in CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.67 (m, 2H), 7.34-7.41 (m, 5H), 7.24-7.30 (m, 3H), 5.95 (d, $J = 4.4$ Hz, 1H), 3.93-3.98 (m, 1H), 3.02 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.79 (dd, $J = 16.0, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 150.8, 141.6, 132.2, 129.3, 129.2, 128.6, 127.6, 127.0, 124.7, 104.3, 37.3, 36.9; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{17}\text{H}_{15}\text{O}_2$, 251.1072; found, 251.1072; **HPLC** analysis: 98% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 42.8 min, R_t (minor) = 65.8 min.

(R)-4-(Naphthalen-2-yl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (2-3b). 95% yield; white solid; $[\alpha]_{\text{D}}^{20} = +60$ (0.07 M in CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.79-7.83 (m, 3H), 7.69-7.71 (m, 3H), 7.45-7.51 (m, 2H), 7.35-7.43 (m, 4H), 6.03 (d, $J = 4.4$ Hz, 1H), 4.09-4.14 (m, 1H), 3.09 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.89 (dd, $J = 16.0, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 151.0, 138.8, 133.6, 132.8, 132.2, 129.3, 129.1, 128.6, 127.8, 127.7, 126.5, 126.1, 125.6, 125.1, 124.8, 104.1, 37.5, 36.8; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{21}\text{H}_{17}\text{O}_2$, 301.1229; found, 301.1231; **HPLC** analysis: 95% *ee* (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 43.0 min, R_t (minor) = 52.4 min.

(R)-6-(Naphthalen-2-yl)-4-phenyl-3,4-dihydro-2H-pyran-2-one (2-3c). 99% yield; orange solid; $[\alpha]_{\text{D}}^{20} = +79$ (0.07 M in CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.21 (s, 1H), 7.86-7.88 (m, 1H), 7.82 (d, $J = 8.4$ Hz, 2H), 7.68 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.49-7.51 (m, 2H), 7.35-7.39 (m, 2H), 7.27-7.31 (m, 3H), 6.08 (d, $J = 4.4$ Hz, 1H), 3.97-4.02 (m, 1H), 3.06 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.83 (dd, $J = 16.0, 8.4$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.8, 150.7, 141.5, 133.5, 133.2, 129.2, 128.7, 128.4, 127.7, 127.6, 127.1, 126.8, 126.7, 124.2, 122.0, 104.9, 37.5, 36.9; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{21}\text{H}_{17}\text{O}_2$, 301.1229; found, 301.1229; **HPLC** analysis: 98% *ee* (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 49.3 min, R_t (minor) = 41.4 min.

(R)-6-Phenyl-4-(p-tolyl)-3,4-dihydro-2H-pyran-2-one (2-3d). 99% yield; yellowish solid; $[\alpha]_{\text{D}}^{20} = +54$ (0.08 M in CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.66 (dd, $J = 8.0, 1.6$ Hz, 2H), 7.37-7.39 (m, 3H), 7.15 (s, 4H), 5.94 (d, $J = 4.0$ Hz, 1H), 3.90-3.94 (m, 1H), 3.00 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.77 (dd, $J = 16.0, 8.4$ Hz, 1H), 2.34 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.8, 150.6, 138.5, 137.3, 132.3, 129.8, 129.2, 128.6, 126.9, 124.7, 104.6, 37.0, 36.9, 21.1; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_2$, 265.1229; found, 265.1222; **HPLC** analysis: >99% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 37.7 min, R_t (minor) = 46.7 min.

(R)-6-Phenyl-4-(o-tolyl)-3,4-dihydro-2H-pyran-2-one (2-3e). 82% yield; white solid; $[\alpha]_D^{20} = +32$ (0.06 M in CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.67 (dd, $J = 8.0, 1.6$ Hz, 2H), 7.36-7.42 (m, 3H), 7.19-7.23 (m, 4H), 5.92 (d, $J = 4.0$ Hz, 1H), 4.18-4.23 (m, 1H), 3.00 (dd, $J = 16.0, 6.4$ Hz, 1H), 2.73 (dd, $J = 16.0, 9.2$ Hz, 1H), 2.39 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.8, 151.1, 139.4, 135.3, 132.3, 131.0, 129.2, 128.6, 127.5, 126.9, 124.7, 104.4, 35.7, 33.4, 19.3; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_2$, 265.1229; found, 265.1229; **HPLC** analysis: >99% *ee* (Chiralcel OJ-H, 8:92 i PrOH/Hexane, 0.7 mL/min), R_t (major) = 24.7 min, R_t (minor) = 68.7 min.

(R)-6-Phenyl-4-(m-tolyl)-3,4-dihydro-2H-pyran-2-one (2-3f). 87% yield; white solid; $[\alpha]_D^{20} = +53$ (0.06 M in CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.67 (dd, $J = 8.0, 1.8$ Hz, 2H), 7.36-7.42 (m, 3H), 7.25 (dd, $J = 8.8, 7.2$ Hz, 1H), 7.10 (d, $J = 7.2$ Hz, 1H), 7.06 (s, 2H), 5.95 (d, $J = 4.4$ Hz, 1H), 3.90-3.97 (m, 1H), 3.01 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.79 (dd, $J = 16.0, 8.4$ Hz, 1H), 2.35 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.8, 150.7, 141.5, 138.9, 132.2, 129.2, 129.0, 128.6, 128.3, 127.7, 124.7, 124.1, 104.5, 37.3, 36.9, 21.5; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_2$, 265.1229; found, 265.1229; **HPLC** analysis: 98%

ee (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 25.8 min, R_t (minor) = 38.2 min.

(R)-4,6-Di-p-tolyl-3,4-dihydro-2H-pyran-2-one (2-3g). 92% yield; white solid; $[\alpha]_D^{20} = +52$ (0.09 M in CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.14 (s, 4H), 5.87 (d, $J = 4.4$ Hz, 1H), 3.87-3.92 (m, 1H), 2.98 (dd, $J = 15.6, 6.8$ Hz, 1H), 2.75 (dd, $J = 15.6, 8.8$ Hz, 1H), 2.36 (s, 3H), 2.33 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.9, 150.7, 139.3, 138.7, 137.2, 129.8, 129.5, 129.3, 126.9, 124.6, 103.7, 37.1, 36.9, 21.3, 21.1; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_2$, 279.1385; found, 279.1382; **HPLC** analysis: 99% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 36.8 min, R_t (minor) = 59.5 min.

(R)-4-(4-Chlorophenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (2-3h). 96% yield; yellowish solid; $[\alpha]_D^{20} = +40$ (0.06 M in CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65-7.68 (m, 2H), 7.38-7.40 (m, 3H), 7.33 (dd, $J = 6.4, 2.0$ Hz, 2H), 7.20 (dd, $J = 6.4, 2.0$ Hz, 2H), 5.91 (d, $J = 4.4$ Hz, 1H), 3.92-3.97 (m, 1H), 3.01 (dd, $J = 15.6, 6.8$ Hz, 1H), 2.76 (dd, $J = 16.0, 8.0$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.2, 151.2, 139.9, 133.4, 132.0, 129.4, 129.3, 128.6, 128.4, 124.7, 103.5, 36.8, 36.7; **HRMS** (m/z): $[\text{M}]^+$ calcd. for

$C_{17}H_{14}ClO_2$, 285.0682; found, 285.0682; **HPLC** analysis: 93% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 59.5 min, R_t (minor) = 66.9 min.

(R)-4-(4-Bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (2-3i). 88% yield; yellowish solid; $[\alpha]_D^{20} = +43$ (0.06 M in CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.68 (m, 2H), 7.48 (dd, $J = 6.4, 2.0$ Hz, 2H), 7.38-7.40 (m, 3H), 7.14 (d, $J = 8.4$ Hz, 2H), 5.91 (d, $J = 4.4$ Hz, 1H), 3.91-3.96 (m, 1H), 3.01 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.76 (dd, $J = 16.0, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 151.2, 140.5, 132.3, 132.0, 129.4, 128.8, 128.6, 124.7, 121.5, 103.5, 36.8, 36.7; **HRMS** (m/z): $[M]^+$ calcd. for $C_{17}H_{14}BrO_2$, 329.0177; found, 329.0173; **HPLC** analysis: 92% *ee* (Chiralcel OD-H, 13:87 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 26.6 min, R_t (minor) = 27.9 min.

(R)-6-(4-Bromophenyl)-4-phenyl-3,4-dihydro-2H-pyran-2-one (2-3j). 88% yield; white solid; $[\alpha]_D^{20} = +32$ (0.07 M in CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 4H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.30 (d, $J = 7.2$ Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 5.95 (d, $J = 4.0$ Hz, 1H), 3.92-3.97 (m, 1H), 3.02 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.79 (dd, $J = 16.0, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 149.9, 141.2, 131.8, 131.1, 129.2, 127.7, 127.0,

126.2, 123.4, 104.9, 37.3, 36.7; **HRMS** (m/z): $[M]^+$ calcd. for $C_{17}H_{14}BrO_2$, 331.0157; found, 331.0160; **HPLC** analysis: 97% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 42.0 min, R_t (minor) = 50.6 min.

(R)-6-(4-Chlorophenyl)-4-phenyl-3,4-dihydro-2H-pyran-2-one (2-3k). 87% yield; white solid; $[\alpha]_D^{20} = +51$ (0.07 M in CH_2Cl_2); **1H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, $J = 8.4$ Hz, 2H), 7.35-7.38 (m, 4H), 7.29-7.32 (m, 1H), 7.24-7.28 (m, 2H), 5.94 (d, $J = 4.4$ Hz, 1H), 3.93-3.98 (m, 1H), 3.02 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.79 (dd, $J = 16.0, 8.4$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.3, 149.8, 141.3, 135.2, 130.7, 129.2, 128.8, 127.7, 127.0, 126.0, 104.8, 37.3, 36.8; **HRMS** (m/z): $[M]^+$ calcd. for $C_{17}H_{14}ClO_2$, 285.0682; found, 285.0679; **HPLC** analysis: 98% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 36.0 min, R_t (minor) = 44.7 min.

(R)-6-(Furan-2-yl)-4-phenyl-3,4-dihydro-2H-pyran-2-one (2-3l). 89% yield; yellow oil; $[\alpha]_D^{20} = +20$ (0.08 M in CH_2Cl_2); **1H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, $J = 1.2$ Hz, 1H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.25-7.30 (m, 3H), 6.65 (d, $J = 3.6$ Hz, 1H), 6.46 (dd, $J = 3.6, 1.6$ Hz, 1H), 5.92 (d, $J = 4.4$ Hz, 1H), 3.94-3.99 (m, 1H), 3.03 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.79 (dd, $J = 16.0, 8.4$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 146.8, 143.7,

143.2, 141.4, 129.1, 127.6, 127.0, 111.5, 107.9, 102.5, 37.1, 37.0; **HRMS** (m/z): $[M]^+$ calcd. for $C_{15}H_{13}O_3$, 241.0865; found, 241.0868; **HPLC** analysis: 97% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.7 mL/min), R_t (major) = 29.0 min, R_t (minor) = 32.6 min.

(R)-6-Phenyl-4-(thiophen-2-yl)-3,4-dihydro-2H-pyran-2-one (2-3m). 77% yield; colorless solid; $[\alpha]_D^{20} = +45$ (0.06 M in CH_2Cl_2); **1H NMR** (400 MHz, $CDCl_3$) δ 7.65-7.68 (m, 2H), 7.37-7.40 (m, 3H), 7.22 (dd, $J = 5.2, 1.2$ Hz, 1H), 6.93-6.98 (m, 2H), 6.02 (d, $J = 4.8$ Hz, 1H), 4.23-4.27 (m, 1H), 3.08 (dd, $J = 15.6, 6.4$ Hz, 1H), 2.91 (dd, $J = 16.0, 8.0$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 150.8, 144.6, 132.0, 129.4, 128.6, 127.2, 124.8, 124.6, 124.3, 103.9, 37.4, 32.5; **HRMS** (m/z): $[M]^+$ calcd. for $C_{15}H_{13}O_2S$, 257.0636; found, 257.0634; **HPLC** analysis: >99% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 66.6 min, R_t (minor) = 105.8 min.

(R)-4-(Furan-2-yl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (2-3n). 62% yield; yellow solid; $[\alpha]_D^{20} = +76$ (0.05 M in CH_2Cl_2); **1H NMR** (400 MHz, $CDCl_3$) δ 7.65 (dd, $J = 7.6, 2.0$ Hz, 2H), 7.37-7.39 (m, 4H), 6.32 (dd, $J = 2.8, 2.0$ Hz, 1H), 6.15 (d, $J = 3.2$ Hz, 1H), 5.96 (d, $J = 4.8$ Hz, 1H), 4.04 (dd, $J = 11.6, 6.8$ Hz, 1H), 2.92-3.04 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.3, 153.6, 151.1, 142.4, 132.1, 129.4, 128.6, 124.8, 110.4, 105.7, 101.2, 33.7, 31.0; **HRMS** (m/z): $[M]^+$ calcd. for $C_{15}H_{13}O_3$, 241.0865; found, 241.0860;

HPLC analysis: 89% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 47.0 min, R_t (minor) = 77.2 min.

(R)-4-Methyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (2-3o). 36% yield; colorless oil; $[\alpha]_D^{20} = +55$ (0.03 M in CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.61 (dd, $J = 8.0, 1.6$ Hz, 2H), 7.34-7.39 (m, 3H), 5.75 (d, $J = 4.0$ Hz, 1H), 2.75-2.80 (m, 2H), 2.37-2.44 (m, 1H), 1.21 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 168.7, 149.7, 132.4, 129.0, 128.5, 124.5, 106.7, 36.5, 26.2, 20.3; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_2$, 189.0916; found, 189.0916; **HPLC** analysis: 99% *ee* (Chiralcel OJ-H, 8:92 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 25.7 min, R_t (minor) = 27.4 min.

Procedure for synthesis of 5-Benzoyl-4-phenyldihydrofuran-2(3H)-one (2-4 and 2-4').

To a stirred solution of **2-3a** (25.0 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C, was added mCPBA (51.8 mg, 55% purity, 0.15 mmol). The mixture was stirred at 0 °C for 12 h. After the reaction finished, *p*-toluene-sulfonic acid (1.9 mg, 0.01 mmol) was added, and the reaction was stirred for another 20 min at room temperature, quenched with aqueous NaHCO_3 solution and extracted with CH_2Cl_2 . The combined organic layers were washed

with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified via SiO₂ flash chromatography (*n*-hexane/EtOAc 10:1-4:1) to afford **2-4** (18.0 mg, 67% yield, 98% *ee*) as a white solid and **2-4'** (6.0 mg, 22% yield, 98% *ee*) as a white solid.

(4S, 5R)-5-Benzoyl-4-phenyldihydrofuran-2(3H)-one (2-4). 67% yield; white solid; $[\alpha]_{\text{D}}^{20} = +148$ (0.06 M in CH₂Cl₂); **¹H NMR** (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.23-7.27 (m, 2H), 7.02-7.07 (m, 5H), 6.12 (d, *J* = 8.0 Hz, 1H), 4.22 (q, *J* = 8.8 Hz, 1H), 3.10 (dd, *J* = 17.2, 9.6 Hz, 1H), 2.93 (dd, *J* = 17.2, 8.8 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 195.2, 175.7, 135.3, 134.6, 133.6, 128.7, 128.4, 128.1, 127.9, 81.2, 45.6, 33.1; **HRMS** (*m/z*): [M]⁺ calcd. for C₁₇H₁₅O₃, 267.1021; found, 267.1018; **HPLC** analysis: 99% *ee* (Chiralcel OD, 20:80 *i*PrOH/Hexane, 0.5 mL/min), *R*_t (major) = 32.2 min, *R*_t (minor) = 54.6 min.

(4S, 5S)-5-Benzoyl-4-phenyldihydrofuran-2(3H)-one (2-4'). 22% yield; white solid; $[\alpha]_{\text{D}}^{20} = -75$ (0.03 M in CH₂Cl₂); **¹H NMR** (400 MHz, CDCl₃) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.61-7.65 (m, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.33-7.42 (m, 3H), 7.27-7.29 (m, 2H), 5.78 (d, *J* = 4.0 Hz, 1H), 3.87-3.91 (m, 1H), 3.08 (dd, *J* = 17.6, 9.2 Hz, 1H), 2.70 (dd, *J* = 18.0,

4.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.5, 175.5, 140.6, 134.5, 133.6, 129.5, 129.0, 128.9, 128.1, 126.7, 84.3, 43.1, 35.2; **HRMS** (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{17}\text{H}_{15}\text{O}_3$, 267.1021; found, 267.1014; **HPLC** analysis: 99% *ee* (Chiralcel OD, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 41.1 min, R_t (minor) = 45.5 min.

2.5 References

(1) For selected examples, see: (a) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2404-2406; (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168-4178; (c) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003-12004; (d) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240-11241; (e) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706-8707.

(2) For selected examples, see: (a) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396; (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267; (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799; (d) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790-1793; (e) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3677-3680; (f) Tang, Z.; Jiang, F.; Yu, L.; Cui, X.; Gong, L.; Mi, A.; Jiang, Y.; Wu, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5262-5263; (g) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *44*, 861-863; (h) Rueping, M.; Sundén, H.; Hubener, L.; Sugiono, E. *Chem. Commun.* **2012**, *48*, 2201-2203.

(3) (a) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583-3586; (b) Grasa, G. A.; Guveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812-2819.

(4) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587-3590.

(5) Lupton has studied NHC-catalyzed activation of enol ether to generate substituted enol as nucleophile, see: (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176-14177; (b) Candish, L.; Lupton, D. W. *Org. Lett.* **2010**, *11*, 4836-4839.

(6) (a) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154-2157; (b) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956-4959.

(7) (a) Yang, J.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453-455; (b) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 4719-4721; (c) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2082-2084; (d) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4722-4724; (e) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1838-1840.

(8) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166-168; (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977-1979; (c) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352-5353; (d) Xu, X.; Wang, K.; Nelson, S. G. *J. Am. Chem. Soc.* **2007**, *129*, 11690-11691.

(9) α,β -Unsaturated enals are not suitable substrates for the generation of α -unsubstituted enolates (e.g., acetic enolates). (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420; (b) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418-2439; (c) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3107-3110; (d) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098-10099; (e) Li, Y.; Wang, X. Q.; Zheng, C.; You, S. L. *Chem. Commun.* **2009**, 5823-5825; (f) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20661-20665; (g) Fang, X. Q.; Chen, X. K.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708-4711; (h) Fu, Z.; Sun, H.; Chen, S.; Tiwari, B.; Li, G.; Chi, Y. R. *Chem. Commun.* **2013**, *49*, 261-263.

(10) NHC-catalyzed activation of α -chloroaldehydes: (a) Reynolds, N. T.; deAlaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518-9519; (b) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406-16407; (c) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem.*

Soc. **2006**, *128*, 15088-15089; (d) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860-2861; (e) Yang, L.; Wang, F.; Chua, P. J.; Lv, Y.; Zhong, L.; Zhong, G. *Org. Lett.* **2012**, *14*, 2894-2897; (f) Jian, T. Y.; Sun, L. H.; Ye, S. *Chem. Commun.* **2012**, *48*, 10907-10909.

(11) NHC-catalyzed activation of ketenes: (a) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108-1113; (b) Huang, X. L.; He, L.; Shao, P. L.; Ye, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 192-195; (c) Jian, T. Y.; He, L.; Tang, C.; Ye, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9104-9107. For examples of acid activation: (d) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714-2720; (e) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088-2093; (f) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 3653-3657; (g) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146-4155.

(12) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817-3820.

(13) (a) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028-18029; (b) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105-108.

(14) For selected reactions using this type of catalyst: (a) Kerr, M. S.; deAlaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298-10299; (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876-8877; (c) Chiang, P. C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520-3521.

(15) CCDC 921945 (**2-3j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

(16) The kinetic study was set up according to Bode and coworker's report: Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem. Int. Ed.* **2011**, *50*, 1673-1677.

(17) (a) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, 66, 1818-1826; (b) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, 243, 43-72; (c) Kitson, R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem. Int. Ed.* **2009**, 48, 9426-9451; (d) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, 28, 429-440; (e) Lee, S.; Jang, J. H.; Hwang, G.-S.; Ryu, D. H. *J. Org. Chem.* **2013**, 78, 770-775.

Chapter 3. *N*-Heterocyclic Carbenes Catalyzed [4+2]

Cycloaddition Reaction with Aliphatic Anhydrides

3.1 Introduction

N-heterocyclic carbene catalyzed generation of enolates has emerged as a powerful strategy for construction of chiral C-C bond.¹ As well documented in literature, enals², α -prefunctionalized aldehydes³, ketenes⁴ and simple saturated aldehydes⁵ have been elegantly employed as enolate precursors (scheme 3.1). Through addition reactions of these substrates with electrophiles, various molecule with bioactive interest could be efficiently obtained, such as lactones, lactams and amino acids. In these known enolate precursors, several problems related to synthetic application need to be addressed. The major one is prefunctionalization or an additional organic oxidant needed for aldehydes, which requires extra synthetic efforts, and another one is the unstable character of ketenes. Thus, a readily available, stable and general enolate precursor is still in demand.

As mentioned in chapter 2, we have developed activated ester as enolate precursor under NHC catalysis.⁶ Although the cycloaddition reactions with chalcones and α,β -unsaturated imines has been successfully realized, other electrophiles are still not effective with this strategy. The major reasons are 1) strong basic condition needed which could decompose various electrophiles and 2) low electrophilicity of activated esters to form acyl azolium with free carbene catalysts. Thus, a new enolate precursor is needed, which should be electrophilic enough to be easily deprotonated under weak basic reaction condition. After detailed comparison of several common activation substituents for carbonyl group, including HOAt and HOBt, simple aliphatic anhydrides appear to be a suitable choice as enolate precursor.

Anhydrides are readily available and stable substrates, typically used as acylation reagents for functionalization or chiral resolution of amines and alcohols. Compared to

their abundance in organic synthesis, aliphatic anhydrides have rarely been successfully employed for enolate formation in asymmetric organocatalysis.

Scheme 3.1 Generation of enolate intermediate under NHC catalysis

Romo reported that aldehyde- and keto-acids could undergo intramolecular cyclization through *in situ* formation of mixed anhydride with either cinchona alkaloids or 4-pyrrolidiny pyridine as promoter, furnishing β -lactones in good yields and stereoselectivities.⁷ This method has been elegantly extended to catalytic intramolecular desymmetrizing aldol-lactonization reactions with high enantioselectivity.⁸ Since 2011, Smith has reported a series of [4+2] cycloaddition reactions of enolate intermediate from 2-aryl acetic acids under chiral isothioureas catalysts.⁹ In their system, additional acylation reagents such as acyl chlorides are needed, which provide pivalic anhydride as unwanted byproduct, arising purification problem. Recently, Smith group reported an improved protocol for enolate formation using 2-aryl acetic anhydrides.¹⁰ Connon group has also disclosed that cyclic enolisable 2-arylacetic anhydrides could undergo cycloaddition with aldehydes using bifunctional squaramides.¹¹ At this stage, direct activation of 2-aliphatic acetic anhydrides in intermolecular reactions remains challenging, mainly because of the low acidity of proton on α -carbon. Herein, we proposed that NHC catalysts may provide a solution for this problem, because of their strongly electron deficient character after addition to the carbonyl group. As shown in scheme 3.2, *in situ*

generated free NHC catalyst could intercept into the carbonyl group of anhydrides to provide the azolium intermediate, followed by deprotonation to generate an enolate intermediate. Finally, nucleophilic addition to electrophiles could afford the desired products. The acid byproduct generated could be easily removed from the reaction mixture.

Scheme 3.2 Proposed reaction pathway of anhydride with electrophiles

3.2 Results and Discussion

In preliminary study, we treated acetic anhydride (**3-1a**) with unsaturated ketone ester (**3-2a**) in the presence of catalyst **A**, using THF as solvent (Table 3.1). Under strong basic condition, such as in presence of Cs_2CO_3 , K_3PO_4 and DBU, the desired product was not observed. When weak bases were used, such as Et_3N and NaOAc , the lactone product was obtained in moderate yields (Table 3.1, entries 3-5). Detailed examination of the byproducts revealed that the lactone product could be easily deprotonated at β -position under basic condition, forming an analogue with δ -postion protonated.¹² Thus, the pK_a value of bases is crucial to this lactone formation. After the racemic reaction condition established, several chiral catalysts were tested. It is quite surprising that the reaction proceeded very fast and finished in five minutes with catalyst **B**, providing the desired product in good yield and *ee* value (Entry 6). Further screening disclosed that catalyst **C** could afford nearly optical pure product in 89% yield (Entry 7). With catalyst **D** bearing a

Table 3.1 Screening of bases in annulation of acetic anhydride with ketone ester^a

Entry	NHC	Base	Yield (%) ^b	e.e (%) ^c	time
1	30% A	2eq K ₃ PO ₄	0	n.d.	15 min
2	30% A	2eq DMAP	0	n.d.	1.3 h
3	30% A	2eq Et ₃ N	19	n.d.	1.5 h
4	30% A	2eq DIEA	34	n.d.	3.5 h
5	30% A	4eq NaOAc	54	n.d.	24 h
6	30% B	4eq NaOAc	88	90	5 min
7	30% C	4eq NaOAc	89	>99	5 min
8	30% D	4eq NaOAc	52	>99	23 h
9	10% D	2eq KOAc	76	96	15 min
10	10% C	2eq KOAc	80	95	10 min
11	10% C	4eq NaOAc	89	>99	10 min
12	10% C	2eq NaOAc	82	>99	20 min
13	5% C	2eq NaOAc	65	>99	2 h

^a Reaction condition: **3-1a** (0.1 mmol), **3-2a** (0.05 mmol), catalyst (5-30 mol%), base (0.1-0.2 mmol), THF (1.0 ml), r.t., under air. ^b Determined by crude ¹H NMR using 1,3,5-trimethoxybenzene as internal standard based on **3-2a**. ^c The *ee* value was determined by chiral HPLC.

Table 3.2 Screening of solvents in annulation of acetic anhydride with ketone ester^a

Entry	solvent	yield (%) ^b	e.e (%) ^c	time
1	1,4-dioxane	61	65	1.5 h
2	CH ₃ CN	22	85	20 h
3	DCM	15	65	20 h
4	DCE	19	51	20 h
5	toluene	26	96	20 h

^a Reaction condition: **3-1a** (0.1 mmol), **3-2a** (0.05 mmol), catalyst **C** (10 mol%), NaOAc (0.1 mmol), solvent (0.5 ml), r.t, under air. ^b Determined by crude ¹H NMR using 1,3,5-trimethoxybenzene as internal standard based on **3-2a**. ^c The *ee* value was determined by chiral HPLC.

tetrafluoroboron counteranion instead of chloro, the reaction became much slower, providing the product in moderate yield with high enantioselectivity remained (Entry 8).

As the reaction is very efficient with 30 mol% of catalyst, lower catalyst loading was then investigated. We are delighted to observe that 10 mol% of catalyst is enough for good reaction outcome (Entry 12). Further decreasing catalyst loading to 5 mol% could also provide the product in moderate yield with high enantioselectivity (Entry 13).

Next, the effect of solvents was examined using sodium acetate as base and trazolium salt **C** as catalyst (Table 3.2). These solvents were not better than THF, and significant

Table 3.3 Optimization of NHC catalyzed annulation of acetic anhydride with ketone ester.^[a]

^a Reaction conditions: **3-1a** (0.10 mmol), **3-2** (0.05 mmol), **Cat. C** (10 mol %), NaOAc (0.10 mmol), THF (0.5 mL), rt. The *ee* values were determined *via* chiral phase HPLC analysis. ^b 10 mol% of **D** and 1 mol% NaOAc used. ^c 10 mol% of **D** without NaOAc.

influence of solvents on enantio control was observed, with toluene providing the highest *ee* value. The yields were also decreased dramatically in these solvents.

Table 3.4 Optimization of NHC catalyzed annulation of butyl anhydride with ketoester^a

Entry	Solvent	Conversion (%) ^b	Yield (%) ^b
1	THF	66	14
2	Ether	70	13
3	EtOAc	53	22
4	Hexane	31	6
5	Toluene	60	9
6	1,4-Dioxane	94	26
7	CH ₃ CN	n.d.	trace
8	DMSO	n.d.	trace

^a Reaction condition: **3-1b** (0.1 mmol), **3-2a** (0.05 mmol), catalyst **C** (10 mol%), NaOAc (0.1 mmol), solvent (0.5 ml), r.t, under air. ^b Determined by crude ¹H NMR using 1,3,5-trimethoxybenzene as internal standard based on **3-2a**.

With optimized reaction conditions obtained, the scope of α -ketone esters was tested (Table 3.3). Methyl, iso-propyl and tert-butyl ketone ester were all suitable substrates (**3-3b**, **3-3d**). Both electron-donating and electron-withdrawing group on phenyl ring were tolerated, providing the corresponding lactones in moderate to good yield with excellent *ee* (**3-3e-3-3h**). Thiophenyl and naphthyl group substituted ketone esters gave only trace

Table 3.5 Optimization of NHC catalyzed annulation of butyl anhydride with ketoester

Entry	base	solvent	Conversion (%) ^b	Yield (%) ^b
1	Cs ₂ CO ₃	EtOAc	n.d.	0
2	K ₃ PO ₄	EtOAc	86	8
3	K ₂ CO ₃	EtOAc	86	5
4	CsOAc	EtOAc	n.d.	trace
5	DIEA	EtOAc	83	23
6	DMAP	EtOAc	n.d.	trace
7	PhCO ₂ Na	EtOAc	56	25
8	PhCO ₂ Na	1,4-Dioxane	58	48
9 ^c	PhCO ₂ Na	1,4-Dioxane	78	63
10 ^{c,d}	PhCO ₂ Na	1,4-Dioxane	64	63
11 ^{c,e}	PhCO₂Na	1,4-Dioxane	100	78

^a Reaction condition: **3-1b** (0.1 mmol), **3-2a** (0.05 mmol), catalyst **C** (10 mol%), base (0.1 mmol), solvent (0.5 ml), r.t, under air. ^b Determined by crude ¹H NMR using 1,3,5-trimethoxybenzene as internal standard based on **3-2a**. ^c 30 mol% of catalyst **C** was used. ^d 10 mg of 4Å MS was added. ^e 20 mg of 4Å MS was added.

products, due to the instability of the lactone products under basic condition. Further decreasing the amount of base to only 1 mol% could provide higher yield (**3-3i**, **3-3j**). It is interesting that these lactones could also be obtained even without base, albeit in low yield. Besides the aromatic substrates, branched and linear alkyl groups were also well

tolerated (**3-3k-3-3m**). The enone derived from cinnamaldehyde could not provide the desired product under the standard condition.¹³

Having proven that acetic anhydride was a feasible enolate precursor, other 2-aliphaticacetic anhydrides were examined (Table 3.4). Under the standard condition, butyric anhydride **3-1b** could undergo cycloaddition reaction with ketone ester **3-2a**, affording the desired lactone in low yield (Entry 1). Screening of solvents showed that 1,4-dioxane and ethyl acetate were better than THF (Entry 2-6). Acetonitrile and DMSO could not afford any product under the catalytic system (Entry 7 and 8).

Table 3.6 Optimization of NHC catalyzed annulation of acetic anhydride with ketone ester.^[a]

^a Reaction conditions: **3-1** (0.10 mmol), **3-2a** (0.05 mmol), Cat. **C** (30 mol %), PhCO₂Na (0.10 mmol), 4Å MS (20 mg), 1,4-dioxane (0.5 mL), rt. The *ee* values were determined by chiral phase HPLC analysis. The *d.r.* values were determined by ¹H NMR analysis of the crude reaction mixture.

Then, the effect of bases was investigated (Table 3.5). With ethyl acetate as solvent, only weak bases could provide the lactone and the yield is poor. Due to the high electrophilicity of butyric anhydride and the unstability of the product, these substrates could be easily decomposed under strong basic conditions, which leads to only trace of product. Significant improvement was achieved when sodium benzoate was used with 1,4-dioxane as solvent, and the desired product was afforded in 48% yield with >99% *ee* (Entry 8). When the catalyst loading was increased to 30 mol% of catalyst **C**, moderate yield was obtained (Entry 9). Further improvement was achieved with 4Å MS as additive to protect anhydride substrates from hydrolysis by removing the trace water from the solvent, furnishing the lactone in 78% yield with excellent *ee* (Entry 10 and 11).

Under this optimized condition, several aliphatic anhydrides were investigated (Table 3.6). While the linear anhydrides provided the corresponding lactones in moderate yield, high *d.r.* and excellent *ee* value (**3-3o-3-3q**),¹⁴ the α - or β -branched anhydrides could not deliver any desired product, mainly due to the steric effect.

Scheme 3.3 One pot synthesis of 2-ketone-1,6-diester.

To further demonstrate the utility of this reaction, a domino lactonization followed by ring opening of ethanol was realized (Scheme 3.3). Both aromatic and aliphatic lactones prepared under standard conditions, could undergo ring opening through addition of ethanol into the crude reaction mixture, furnishing 1,6-diester compounds in good yields and excellent enantioselectivity (**3-3r**, **3-3s**, **3-3t**).¹⁵

The proposed catalytic cycle for these transformations was shown in scheme 3.4. The reaction was triggered by the interception of free carbene generated by deprotonation of NHC precursor to acid anhydride to form the acyl azolium **I**. Deprotonation of the acyl azolium delivered the enolate intermediate **II**, which underwent [4+2] cycloaddition reaction with α -ketone ester to form an adduct **III**, then the lactone product was generated with free carbene released.

Scheme 3.4 Proposed mechanism for lactone formation.

3.3 Conclusion

In summary, we have realized an NHC-catalyzed generation of enolate intermediates from simple aliphatic anhydride substrates, which could undergo highly enantioselective reactions with unsaturated α -ketone esters. Various lactones could be obtained in good yield, high *d.r.* and excellent *ee* values. As relatively stable and commercially available compounds, 2-aliphaticacetic anhydrides have obvious advantages compared to the

previous enolate precursors. Further studies in identifying effective catalysts and conditions for other electrophiles are in progress.

3.4 Experimental Section

General Information

Commercially available materials were used as received. Starting materials were synthesized according to the procedure in literature.^{15,16} Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Bruker AV400 (400 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Bruker AV400 (400 MHz) (100 MHz) spectrometers. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *ee* was performed by chiral phase HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 0.5 mL cell with a 10 mm path length on a PerkinElmer Model 341 digital polarimeter and are reported as follows: $[\alpha]_D^{rt}$ (*c* in mmol per mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

Synthesis of starting materials: γ -aryl- β,γ -unsaturated α -ketoesters

Following the procedure outlined by Smith *et al.*¹⁵

Step 1: To a solution of pyruvic acid (1.0 equiv.), arylaldehyde (1.0 equiv.) and MeOH at 0 °C was added a solution of potassium hydroxide (1.5 equiv.) in MeOH. The first 1.0 equiv. of the potassium hydroxide solution was added dropwise over 30 min. The last third was added as one portion and the reaction stirred at 40 °C for 1 h followed by 0 °C overnight. The precipitate was collected by filtration, washed twice with cold MeOH, once with ether and dried under vacuum to furnish the potassium salt which was used as an intermediate without further purification.

Step 2: Acetyl chloride (11.5 equiv.) was added to the desired alcohol at 0 °C to generate hydrochloric acid. Potassium salt from step 1 (1.0 equiv.) was added and the mixture stirred at 0 °C for 30 minutes then warmed to rt for 2 hours before heating at reflux overnight. Concentration in vacuo gave a solid which was dissolved in water and extracted with DCM. The combined organics were washed with saturated aqueous solution of NaHCO₃, water and brine before being dried (MgSO₄), filtered and concentrated in vacuo to give the crude mixture. The mixture was purified by flash column chromatography to give the desired ketoester.

Synthesis of starting materials: γ -alkyl- β,γ -unsaturated α -ketoesters

Following the procedure outlined by Alexakis *et al.*¹⁶

Step 1: A solution of aldehyde (1.0 equiv.), *p*-toluenesulfonic acid monohydrate (5 mol %) and trimethyl orthoformate (10.0 equiv.) in dry methanol was heated to reflux for 24 h. A part of the solvent was evaporated in vacuo, Et₂O was added to the residue, and the mixture was washed with saturated solution of NaHCO₃. After drying (MgSO₄), the organic layer was concentrated in vacuo and the residue was purified by flash chromatography to give alkyl acetal.

Step 2: To a mixture of acetal (1.0 equiv.) and ethyl 2-((trimethylsilyl)oxy) -acrylate (1.2 equiv.) in dry dichloromethane under argon at -78°C was added dropwise boron trifluoridediethyl ether 48% (1.1 equiv.). The reaction mixture was warmed to 0°C for over 1h and stirred at the same temperature for 2h. Saturated NaHCO₃ was added, and the mixture was extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated under reduced pressure to afford crude γ -alkoxy- α -oxo esters, which were dissolved in toluene. Then, silica gel was added and the mixture was heated at reflux with vigorous stirring for 24h. After being cooled to room temperature, the mixture was filtered and the residual solid was washed with ether several times. The filtrate was combined, concentrated and dried with NaHCO₃ to give the crude β,γ -unsaturated- α -ketoester. The crude ketoester was purified by flash column chromatography.

The lactone product **3-3g** generated from 4-bromophenyl ketonester **3-2g** is unstable under the standard condition, and three byproducts (**3-3g-1**, **3-3g-2**, **3-3g-3**) could be observed (Scheme 3.5). These byproducts could be readily formed *via* isomerization or oxidation of **3-3g** in the presence of base and air, due to the high acidity of proton at β -position.

Scheme 3.5 Formation of byproducts in annulations of acetic anhydride and ketone ester Characterization Data of **3-3g-1**, **3-3g-2**, **3-3g-3** **3-3g-1**

^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.64 (m, 2H), 7.52 – 7.48 (m, 2H), 7.40 (d, $J = 1.6$ Hz, 1H), 6.69 (d, $J = 1.6$ Hz, 1H), 4.43 (q, $J = 7.2$ Hz, 2H), 1.42 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.4, 159.5, 152.4, 149.4, 133.4, 132.7, 128.2, 126.0, 115.9, 109.5, 62.7, 14.1.

3-3g-2

^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.51 (m, 2H), 7.27 – 7.23 (m, 2H), 6.34 (dd, $J = 4.8$, 2.4 Hz, 1H), 5.53 – 5.50 (m, 1H), 4.32 – 4.21 (m, 2H), 3.60 (dt, $J = 20.8$, 2.4 Hz, 1H), 3.50 (dd, $J = 20.8$, 2.0 Hz, 1H), 1.31 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 167.5, 135.3, 135.2, 132.1, 126.7, 123.3, 115.9, 76.7, 62.5, 32.2, 14.1.

3-3g-3

^1H NMR (400 MHz, CDCl_3) δ 7.61 – 7.56 (m, 2H), 7.42 – 7.38 (m, 2H), 6.36 (t, $J = 1.2$ Hz, 1H), 5.15 (t, $J = 5.6$ Hz, 1H), 4.30 – 4.24 (m, 2H), 3.17 (dd, $J = 5.6$, 1.2 Hz, 2H), 1.28 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 162.8, 151.5, 134.4, 132.3, 127.5, 125.5, 115.4, 73.9, 62.4, 28.5, 14.1.

Characterization of products

(R)-Ethyl 2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate (3-3a): 82% yield; $[\alpha]_D^{23}$ (c 1.61, CH_2Cl_2): + 55; ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.35 (m, 2H), 7.33 – 7.29 (m, 1H), 7.21 – 7.19 (m, 2H), 6.65 (d, $J = 4.4$ Hz, 1H), 4.36 – 4.30 (m, 2H), 3.97 – 3.91 (m, 1H), 2.99 (dd, $J = 16.0, 7.2$ Hz, 1H), 2.76 (dd, $J = 16.0, 8.4$ Hz, 1H), 1.35 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 160.3, 142.9, 139.6, 129.3, 127.9, 126.9, 117.7, 61.9, 37.2, 35.8, 14.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{15}\text{O}_4$, 247.0970 found, 247.0972; > 99% *ee* (*R*)- isomer as determined by HPLC (IA, 90:5:5 hexanes/*i*-PrOH/MeOH, 0.5 ml/min) $tr(S) = 26.5$ min, $tr(R) = 29.1$ min.

(R)-Methyl 2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate (3-3b): 68% yield; $[\alpha]_D^{23}$ (c 1.53, CH_2Cl_2): + 142; ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.34 (m, 2H), 7.33 – 7.31 (m, 1H), 7.21 – 7.18 (m, 2H), 6.66 (d, $J = 4.4$ Hz, 1H), 3.98 – 3.93 (m, 1H), 3.87 (s, 3H), 3.02 – 2.96 (m, 1H), 2.77 (dd, $J = 16.0, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 160.8, 142.7, 139.5, 129.3, 127.9, 126.9, 118.0, 52.76, 37.2, 35.8; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{13}\text{O}_4$, 233.0814 found, 233.0814; > 99% *ee* (*R*)- isomer as determined by HPLC (IA, 90:5:5 hexanes/*i*-PrOH/MeOH, 0.5 ml/min) $tr(S) = 35.0$ min, $tr(R) = 36.7$ min.

(R)-Isopropyl 2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate (3-3c): 64% yield; $[\alpha]_D^{23}$ (c 0.32, CH_2Cl_2): + 2; ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.35 (m, 2H), 7.33 – 7.29 (m, 1H), 7.21 – 7.19 (m, 2H), 6.62 (d, $J = 4.4$ Hz, 1H), 5.23–5.13 (m, 1H), 3.96 – 3.89 (m, 1H), 2.98 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.76 (dd, $J = 16.0, 8.8$ Hz, 1H), 1.33 (d, $J = 6.0$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 159.9, 143.1, 139.7, 129.3, 127.9, 126.9, 117.4, 69.9, 37.2, 35.8, 21.7; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_4$, 261.1127 found, 261.1122; > 99% *ee* (*R*)- isomer as determined by HPLC (IA, 90:5:5 hexanes/*i*-PrOH/MeOH, 0.5 ml/min) $tr(S) = 17.5$ min, $tr(R) = 18.8$ min.

(R)-tert-Butyl 2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate (3-3d): 68% yield; $[\alpha]_D^{23}$ (c 0.14, CH_2Cl_2): + 10; ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 7.21 – 7.19 (m, 2H), 6.53 (d, $J = 4.4$ Hz, 1H), 3.93 – 3.87 (m, 1H), 2.96 (dd, $J = 16.0, 7.2$ Hz, 1H), 2.74 (dd, $J = 16.0, 8.8$ Hz, 1H), 1.54 (s, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.1, 159.3, 143.6, 139.9, 129.3, 127.9, 126.9, 116.7, 83.0, 37.2, 35.8, 28.0; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{19}\text{O}_4$, 275.1283 found, 275.1281; > 99% *ee* (*R*)- isomer as determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.5 ml/min) $tr(R) = 32.3$ min, $tr(S) = 38.4$ min.

(R)-Ethyl 4-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (3-3e):

80% yield; $[\alpha]_D^{23}$ (c 1.10, CH_2Cl_2): + 85; ^1H NMR (400 MHz, CDCl_3) δ 7.13 – 7.09 (m, 2H), 6.91 – 6.86 (m, 2H), 6.62 (d, $J = 4.4$ Hz, 1H), 4.36 – 4.29 (m, 2H), 3.92–3.86 (m, 1H), 3.80 (s, 3H), 2.95 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.73 (dd, $J = 16.0, 8.0$ Hz, 1H), 1.35 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 166.0, 160.4, 159.2, 142.6, 131.6, 128.0, 118.1, 114.6, 61.9, 55.3, 36.4, 36.0, 14.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_5$, 277.1076 found, 277.1075; > 99% *ee* (*R*)- isomer as determined by HPLC (OD-H, 88:12 hexanes/*i*-PrOH, 0.5 ml/min) $tr(S) = 41.3$ min, $tr(R) = 50.1$ min.

(R)-Ethyl 4-(3-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (3-3f):

72% yield; $[\alpha]_D^{23}$ (c 0.28, CH_2Cl_2): + 10; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (t, $J = 8.0$ Hz, 1H), 6.84 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.72 (t, $J = 2.0$ Hz, 1H), 6.63 (d, $J = 4.4$ Hz, 1H), 4.36 – 4.30 (m, 2H), 3.94 – 3.87 (m, 1H), 3.81 (s, 3H), 2.97 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.76 (dd, $J = 16.1, 8.8$ Hz, 1H), 1.35 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 160.3, 160.2, 142.9, 141.2, 130.4, 119.1, 117.6, 113.0, 112.9, 62.0, 55.3, 37.2, 35.7, 14.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_5$, 277.1076 found, 277.1074; 99% *ee* (*R*)- isomer as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.5 ml/min) $tr(S) = 18.4$ min, $tr(R) = 19.9$ min.

(R)-Ethyl 4-(4-bromophenyl)-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (3-3g): 58% yield; $[\alpha]_D^{23}$ (c 0.85, CH_2Cl_2): - 8; ^1H NMR (400 MHz, CDCl_3) δ 7.51 – 7.48 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 4.4 Hz, 1H), 4.37 – 4.30 (m, 2H), 3.94 – 3.88 (m, 1H), 2.97 (dd, J = 16.0, 6.8 Hz, 1H), 2.72 (dd, J = 16.0, 8.4 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.4, 160.2, 143.2, 138.6, 132.5, 128.6, 121.9, 116.8, 62.1, 36.7, 35.6, 14.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{14}\text{BrO}_4$, 327.0055 found, 327.0051; 98% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.5 ml/min) $tr(S)$ = 45.0 min, $tr(R)$ = 47.0 min.

(R)-Ethyl 4-(2-fluorophenyl)-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (3-3h): 75% yield; $[\alpha]_D^{23}$ (c 0.49, CH_2Cl_2): + 5; ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.27 (m, 1H), 7.20 – 7.07 (m, 3H), 6.62 (d, J = 4.4 Hz, 1H), 4.37 – 4.30 (m, 2H), 4.28 – 4.22 (m, 1H), 3.00 (dd, J = 16.4, 7.2 Hz, 1H), 2.82 (dd, J = 16.0, 7.6 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 161.6, 160.2, 159.1, 143.3, 129.7 (d, J = 8.3 Hz), 128.0 (d, J = 3.7 Hz), 126.4 (d, J = 14.0 Hz), 124.9 (d, J = 3.6 Hz), 116.0 (d, J = 22.9 Hz), 62.0, 34.1, 30.8 (d, J = 3.1 Hz), 14.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{14}\text{FO}_4$,

265.0876 found, 265.0872; > 99% *ee* (*R*)- isomer as determined by HPLC (IA, 98:2 hexanes/i-PrOH, 0.5 ml/min) *tr*(*S*) = 36.9 min, *tr*(*R*) = 46.8 min.

(*R*)-Ethyl 2-oxo-4-(thiophen-2-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3i): 30% yield; $[\alpha]_D^{23}$ (c 0.56, CH₂Cl₂): + 17; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.92 – 6.90 (m, 1H), 6.68 (d, *J* = 4.4 Hz, 1H), 4.36 – 4.30 (m, 2H), 4.25 – 4.20 (m, 1H), 3.04 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.88 (dd, *J* = 16.0, 7.6 Hz, 1H), 1.35 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.3, 160.2, 142.7, 142.1, 127.3, 125.0, 124.7, 117.0, 62.1, 36.2, 32.4, 14.1; HRMS (ESI) [M+H]⁺ calcd. for C₁₂H₁₃O₄S, 253.0535 found, 253.0535; > 99% *ee* (*R*)- isomer as determined by HPLC (OD-H, 88:12 hexanes/i-PrOH, 0.5 ml/min) *tr*(*S*) = 35.7 min, *tr*(*R*) = 43.0 min.

(*R*)-Ethyl 4-(naphthalen-2-yl)-2-oxo-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3j): 53% yield; $[\alpha]_D^{23}$ (c 0.70, CH₂Cl₂): + 63; ¹H NMR (400 MHz, CDCl₃) δ 7.87 – 7.77 (m, 3H), 7.64 (s, 1H), 7.52 – 7.48 (m, 2H), 7.30 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.73 (d, *J* = 4.0 Hz, 1H), 4.39 – 4.31 (m, 2H), 4.13 – 4.07 (m, 1H), 3.06 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.87 (dd, *J* = 16.0, 8.4 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 160.4, 143.0, 136.9, 133.5, 132.8, 129.3, 127.8, 127.7, 126.7, 126.4, 125.6, 124.8, 117.5, 62.0,

37.3, 35.7, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{18}H_{17}O_4$, 297.1127 found, 297.1129; > 99% *ee* (*R*)- isomer as determined by HPLC (OD-H, 92:8 hexanes/*i*-PrOH, 0.5 ml/min) $tr(R) = 97.1$ min, $tr(S) = 102.9$ min.

(*S*)-Ethyl 4-isopropyl-2-oxo-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3k): 71% yield; $[\alpha]_D^{23}$ (c 1.01, CH_2Cl_2): + 31; 1H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, $J = 3.6$ Hz, 1H), 4.34 – 4.28 (m, 2H), 2.67 (dd, $J = 18.4, 9.2$ Hz, 1H), 2.56 – 2.48 (m, 2H), 1.84 – 1.75 (m, 1H), 1.35 (t, $J = 7.2$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 160.4, 142.6, 117.5, 61.8, 37.5, 31.4, 31.0, 19.3, 19.1, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{11}H_{17}O_4$, 213.1127 found, 213.1126; > 99% *ee* (*S*)- isomer as determined by HPLC (IC, 92:8 hexanes/*i*-PrOH, 0.5 ml/min) $tr(R) = 124.7$ min, $tr(S) = 130.5$ min.

(*R*)-Ethyl 2-oxo-4-phenethyl-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3l): 83% yield; $[\alpha]_D^{23}$ (c 1.21, CH_2Cl_2): + 27; 1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, $J = 7.6$ Hz, 2H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 7.2$ Hz, 2H), 6.50 (d, $J = 4.4$ Hz, 1H), 4.31 (q, $J = 7.2$ Hz, 2H), 2.77 – 2.62 (m, 4H), 2.47 (dd, $J = 15.2, 7.6$ Hz, 1H), 1.90 – 1.71 (m, 2H), 1.34 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 160.4, 142.3, 140.4, 128.6, 128.2, 126.3, 118.6, 61.8, 35.4, 33.5, 32.5, 30.4, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{16}H_{19}O_4$,

275.1283 found, 275.1288; > 99% *ee* (*R*)- isomer as determined by HPLC (IA, 95:5 hexanes/*i*-PrOH, 0.5 ml/min) *tr*(*S*) = 23.4 min, *tr*(*R*) = 25.3 min.

(*R*)-Ethyl 2-oxo-4-pentyl-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3m): 63% yield; $[\alpha]_D^{23}$ (c 0.98, CH₂Cl₂): + 20; ¹H NMR (400 MHz, CDCl₃) δ 6.48 (d, *J* = 4.4 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 2.75–2.62 (m, 2H), 2.43 (dd, *J* = 15.2, 7.6 Hz, 1H), 1.53 – 1.44 (m, 2H), 1.42 – 1.28 (m, 9H), 0.89 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 160.5, 142.1, 119.2, 61.8, 33.8, 33.6, 31.5, 31.1, 26.0, 22.4, 14.1, 13.9; HRMS (ESI) [M+H]⁺ calcd. for C₁₃H₂₁O₄, 241.1440 found, 241.1436; > 99% *ee* (*R*)- isomer as determined by HPLC (IA, 98:2 hexanes/*i*-PrOH, 0.5 ml/min) *tr*(*S*) = 20.5 min, *tr*(*R*) = 22.8 min.

(3*R*, 4*S*)-Ethyl 3-ethyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3n): 78% yield; $[\alpha]_D^{23}$ (c 0.35, CH₂Cl₂): + 58; ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.28 (m, 3H), 7.12 – 7.09 (m, 2H), 6.71 (d, *J* = 6.4 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.83 (t, *J* = 6.8 Hz, 1H), 2.75 (q, *J* = 6.8 Hz, 1H), 1.80 – 1.68 (m, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.26 – 1.16 (m, 1H), 0.99 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 160.6, 142.3, 136.0, 129.1, 128.1, 128.0, 118.0, 61.9, 45.1, 41.3, 19.6, 14.1, 11.9; HRMS (ESI) [M+H]⁺

calcd. for $C_{16}H_{19}O_4$, 275.1283 found, 275.1280; > 99% *ee* (major)- isomer as determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.5 ml/min) *tr*(minor) = 23.4 min, *tr*(major) = 43.4 min; dr > 20:1.

(3*R*,4*S*)-Ethyl 3-methyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3o):

44% yield; $[\alpha]_D^{23}$ (c 0.64, CH_2Cl_2): + 11; 1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 3H), 7.10 – 7.07 (m, 2H), 6.71 (d, J = 6.4 Hz, 1H), 4.33 (q, J = 6.8 Hz, 2H), 3.73 (t, J = 6.8 Hz, 1H), 3.05 (p, J = 6.8 Hz, 1H), 1.36 (t, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 160.6, 142.5, 135.7, 129.1, 128.2, 117.8, 61.9, 43.1, 38.2, 14.1, 12.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{17}O_4$, 261.1127 found, 261.1125; > 99% *ee* (major)- isomer as determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.5 ml/min) *tr*(minor) = 33.0 min, *tr*(major) = 58.1 min; dr > 20:1.

(3*R*, 4*S*)-Ethyl 3-butyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3p):

57% yield; $[\alpha]_D^{23}$ (c 0.92, CH_2Cl_2): + 187; 1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 3H), 7.12 – 7.07 (m, 2H), 6.70 (d, J = 6.4 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.81 (t, J = 6.8 Hz, 1H), 2.83 (q, J = 7.2 Hz, 1H), 1.73 – 1.64 (m, 1H), 1.41 – 1.31 (m, 4H), 1.30 – 1.23 (m, 3H), 1.22 – 1.14 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 168.9, 160.6, 142.3, 136.0, 129.1, 128.1, 128.0, 118.0, 61.9, 43.4, 41.5, 29.3, 25.9, 22.4, 14.1, 13.8; HRMS (ESI) $[M+H]^+$ calcd. for $C_{18}H_{23}O_4$, 303.1596 found, 303.1598; > 99% *ee* (major)- isomer as determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.5 ml/min) $tr(\text{minor}) = 19.2$ min, $tr(\text{major}) = 30.7$ min; *dr* > 20:1.

(3*R*, 4*S*)-Ethyl 3-benzyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (3-3q):

52% yield; $[\alpha]_D^{23}$ (c 0.51, CH_2Cl_2): + 207; 1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 7.25 – 7.21 (m, 1H), 7.08 – 7.01 (m, 4H), 6.65 (d, $J = 6.8$ Hz, 1H), 4.31 (q, $J = 7.2$ Hz, 2H), 3.63 (t, $J = 6.8$ Hz, 1H), 3.30 – 3.24 (m, 2H), 2.41 (dd, $J = 15.6, 10.8$ Hz, 1H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 160.5, 142.1, 138.1, 135.8, 129.2, 128.9, 128.6, 128.4, 128.3, 126.7, 118.4, 61.9, 44.8, 40.6, 32.0, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{21}H_{21}O_4$, 337.1440 found, 337.1434; > 99% *ee* (major)- isomer as determined by HPLC (IA, 98:2 hexanes/*i*-PrOH, 0.5 ml/min) $tr(\text{minor}) = 34.9$ min, $tr(\text{major}) = 39.6$ min; *dr* = 10:1.

(*S*)-Diethyl 2-oxo-4-phenylhexanedioate (3-3r): 61% yield; $[\alpha]_D^{23}$ (c 1.59, CH_2Cl_2): + 5;

1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 4.26 (q, $J = 7.2$ Hz, 2H), 4.07 – 4.01 (m, 2H), 3.74 (p, $J = 7.2$ Hz, 1H), 3.28 (dd, $J = 17.6, 7.2$ Hz, 1H),

3.21 (dd, $J = 17.6, 7.2$ Hz, 1H), 2.71 (dd, $J = 15.6, 7.6$ Hz, 1H), 2.64 (dd, $J = 15.6, 7.6$ Hz, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.15 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.4, 171.5, 160.6, 142.4, 128.6, 127.3, 126.9, 62.4, 60.5, 45.0, 40.5, 36.8, 14.0, 13.9; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{21}\text{O}_5$, 293.1389 found, 293.1385; > 99% *ee* (*S*)- isomer as determined by HPLC (OD-H, 98:2 hexanes/*i*-PrOH, 0.5 ml/min) $tr(R) = 38.3$ min, $tr(S) = 43.4$ min.

(*S*)-Diethyl 4-(4-fluorophenyl)-2-oxohexanedioate (3-3s): 64% yield; $[\alpha]_{\text{D}}^{23}$ (c 0.93, CH_2Cl_2): + 19; ^1H NMR (400 MHz, CDCl_3) δ 7.24 – 7.18 (m, 2H), 7.01 – 6.94 (m, 2H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.08 – 4.00 (m, 2H), 3.73 (p, $J = 7.2$ Hz, 1H), 3.26 (dd, $J = 18.0, 7.6$ Hz, 1H), 3.19 (dd, $J = 18.0, 6.8$ Hz, 1H), 2.69 (dd, $J = 15.6, 7.6$ Hz, 1H), 2.61 (dd, $J = 15.6, 8.0$ Hz, 1H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.16 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.3, 171.3, 162.9, 160.6 (d, $J = 11.2$ Hz), 138.1 (d, $J = 3.2$ Hz), 128.9 (d, $J = 8.0$ Hz), 115.5 (d, $J = 21.4$ Hz), 62.6, 60.6, 45.1, 40.6, 36.1, 14.1, 13.9; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{20}\text{FO}_5$, 311.1295 found, 311.1295; 93% *ee* (*S*)- isomer as determined by HPLC (IA, 99:1 hexanes/*i*-PrOH, 0.5 ml/min) $tr(S) = 41.7$ min, $tr(R) = 49.9$ min.

(S)-Diethyl 2-oxo-4-phenethylhexanedioate (3-3t): 64% yield; $[\alpha]_{\text{D}}^{23}$ (c 2.08, CH_2Cl_2): -3.6; ^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.25 (m, 2H), 7.20 – 7.15 (m, 3H), 4.31 (q, J = 7.2 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.01 – 2.90 (m, 2H), 2.67 – 2.61 (m, 2H), 2.54 – 2.34 (m, 3H), 1.74 – 1.67 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.5, 172.3, 160.9, 141.5, 128.4, 128.3, 125.9, 62.5, 60.5, 43.2, 38.1, 35.9, 33.1, 30.5, 14.2, 13.9; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{25}\text{O}_5$, 321.1702 found, 321.1711; > 99% *ee* (*S*)- isomer as determined by HPLC (IA, 98:2 hexanes/*i*-PrOH, 0.5 ml/min) $tr(S)$ = 18.9 min, $tr(R)$ = 20.8 min.

3.5 References

- (1) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis*, **2012**, *44*, 2295-2309.
- (2) (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420; (b) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418-2439; (c) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3107-3110; (d) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098-10099; (e) Li, Y.; Wang, X. Q.; Zheng, C.; You, S. L. *Chem. Commun.* **2009**, 5823-5825; (f) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20661-20665; (g) Fang, X. Q.; Chen, X. K.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708-4711; (h) Fu, Z.; Sun, H.; Chen, S.; Tiwari, B.; Li, G.; Chi, Y. R. *Chem. Commun.* **2013**, *49*, 261-263.
- (3) (a) Reynolds, N. T.; deAlaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518-9519; (b) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406-16407; (c) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088-15089; (d) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860-2861; (e) Yang, L.; Wang, F.; Chua, P. J.; Lv, Y.; Zhong, L.; Zhong, G. *Org. Lett.* **2012**, *14*, 2894-2897; (f) Jian, T. Y.; Sun, L. H.; Ye, S. *Chem. Commun.* **2012**, *48*, 10907-10909; (g) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028-18029; (h) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105-108.
- (4) NHC-catalyzed activation of ketenes: (a) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108-1113; (b) Huang, X. L.; He, L.; Shao, P. L.; Ye, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 192-195; (c) Jian, T. Y.; He, L.; Tang, C.; Ye, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9104-9107.
- (5) (a) Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 12330-12333; (b) Mo, J.; Yang, R.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 50-53.

(6) (a) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154-2157; (b) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956-4959.

(7) (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946; (b) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731-1736; (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835-2838; (d) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363-4366; (e) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143-2146; (f) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun* **2010**, *46*, 4803-4805; (g) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764-3767; (h) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, *76*, 2-12.

(8) (a) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478-10479; (b) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 9479-9483.

(9) (a) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714-2720; (b) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088-2093; (c) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 3653-3657; (d) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146-4155.

(10) Morrill, L. C.; Ledingham, L. A.; Couturier, J.; Bickel, J.; Harper, A. D.; Fallan, C.; Smith, A. D. *Org. Biomol. Chem.*, **2014**, *12*, 624-636.

(11) Manoni, F.; Cornaggia, C.; Murray, J.; Tallon, S.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 6502-6504.

(12) For a similar proton transfer process, see: Leckie, S. M.; Brown, T. B.; Pryde, D.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2013**, *11*, 3230-3246.

(13) The absolute stereochemistry of product **3-3a** is preliminarily assigned by the comparison to a previous related reaction: He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817-3820.

(14) The relative configuration within **3-3q** was assigned by ¹H NMR spectroscopic analysis in comparison to a previous report: Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373-375.

(15) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714-2720.

(16) Gremaud, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 794-797.

Chapter 4. *N*-Heterocyclic Carbene Catalyzed Asymmetric

Aldol Reaction with Acetic Anhydrides

4.1 Introduction

The aldol reaction is a powerful and widely used method for converting carbonyl compounds to β -hydroxy carbonyl units.¹ For the efficient carbon-carbon bond formation, aldol donors are typically pre-activated to more reactive species, such as metal enolates or enol silyl ethers. Since the first report of the intermolecular direct catalytic asymmetric aldol reaction, a great deal of effort has been taken for *in situ* or direct generation of active aldol donors using metal catalysts or organocatalysts.² In most cases, the scope of aldol donors is limited to carbonyl substrates with highly acidic α protons, such as aldehydes and ketones.³ Direct aldol reactions using less acidic carbonyl compounds, such as ester equivalents, have been much less developed because of the intrinsic difficulty of deprotonation activation.⁴ Current methods for direct aldol reactions of ester equivalents either need elegantly designed auxiliary substituent installed on carbonyl group⁵, additional electron-withdrawing group⁶ or specific substituent on α carbon⁷ to lower the energy for deprotonation (scheme 4.1). For example, Kobayashi group reported a direct aldol reaction of amide-based aldol donors with moderate *ee* values.^{5b} Shibasaki group also developed a series of asymmetric aldol reactions of thioamides^{5c} or α -sulfanyl aldol donors.^{7c} At this stage, simple ester equivalents without specific modification have not yet been successfully employed in organocatalyzed intermolecular aldol reactions. Herein, we report a new method to overcome the low reactivity of simple esters through the combination of acetic anhydride and ethanol under the catalysis of *N*-heterocyclic carbenes.

Scheme 4.1 Direct Aldol Reactions of ester equivalents with relatively inert α proton.**Previous methods** **This Work**

Recently, *N*-heterocyclic carbenes have emerged as efficient catalysts for many useful transformations,⁸ including chiral enolate reactions, which open the access to direct ester activation. Based on our previous work on [4+2] cycloaddition *via N*-heterocyclic carbene catalyzed ester activation^{9,10} and anhydride activation in chapter 3, we envisioned that acetic anhydride may act as efficient enolate precursor in some other type of reactions, such as direct asymmetric aldol reactions. In this chapter, we proposed that acetic anhydride may be activated by free carbene, forming acyl azolium intermediate, following deprotonation and aldol addition to carbonyl substrates lead to β -hydroxy carbonyl units, which could be *in situ* trapped by alcohols to form the desired products. To realize this protocol, the reaction rate of the aldol addition process is of most importance, which should be competent to the fast alcoholysis of anhydride or acyl azolium intermediate.

4.2 Results and Discussion

Figure 4.1 Natural products containing 3-hydroxyindole units **Table 4.1** Optimization of NHC catalyzed aldol reaction of acetic anhydride with isatin.^a

Entry	Cat.	R	Solvent	Yield [%] ^b	er [%] ^c
1	A	Bn	THF	10	-
2	B	Bn	THF	38	83 : 17
3	B	Bn	EtOAc	35	83 : 17
4	B	Bn	DCM	40	53 : 47
5	B	Bn	Et ₂ O	47	88 : 12
6 ^d	B	Bn	Et ₂ O	66	80 : 20
7 ^d	B	Trt	Et ₂ O	60	90 : 10
8 ^d	C	Trt	Et ₂ O	66	95 : 5
9 ^{d,e}	C	Trt	Et ₂ O	78	95 : 5
10 ^{d,e,f}	C	Trt	Et ₂ O	84	95 : 5

^a Reaction conditions: acetic anhydride (0.20 mmol), ethanol (0.20 mmol), isatin (0.10 mmol), Cat. (20 mol%), CsOAc (200 mol%), 3 Å MS (100 mg), solvent (1.0 mL), rt. ^b Estimated *via* ¹H NMR analysis of the crude reaction mixture by using 1,3,5-trimethoxybenzene as an internal standard. ^c Determined *via* chiral phase HPLC analysis. ^d 0.60

mmol ethanol was used. ^e 30 mol% of **D** used. ^f 30 mol% of HOBt and 2 eq. of KOAc was used.

In the initial investigation, we selected isatins as the carbonyl counterpart in the aldol reaction to generate 3-hydroxyindole moiety, which is widely spread in biologically useful natural products (Figure 4.1).^{11,12} We began our study on the reaction of *N*-Benzyl isatin with acetic anhydride and ethanol under the NHC catalysts. Although only trace product was obtained with the racemic catalyst **A**, the desired product could be successfully obtained with chiral catalyst **B** derived from phenylalanine, albeit in low yield and moderate enantioselectivity (Table 4.1, entry 2). Further screening of reaction condition revealed that solvents have a significant influence on the enantio ratio of the product, and ether was found to be the best choice, while halogenated solvent such as dichloromethane gave nearly racemic product (entries 4 and 5). Efforts to improve the reaction yield *via* screening of other bases proved to be not efficient, and the yield remained less than 50%. After carefully examination of the byproducts, we noticed that the hydroxyl group on the product was readily acylated by acetic anhydride and β -acetoxy ester would be generated, and easily undergo elimination to unsaturated ester byproduct. Thus, more ethanol was added into the reaction mixture, and the yield could be improved to 66% with *ee* value slightly decreased (entry 6). With a more bulky protecting group on isatin, the *ee* value was significantly improved to 90:10 without much decreasing the yield (entry 7). With a branched alkyl substituent on the NHC catalyst skeleton, excellent enantio ratio of the product was achieved, with some starting material remained (entry 8). To solve this conversion problem, the catalyst loading was increased to 30 mol%, and the yield was improved to 78% with excellent *ee* value (entry 9). Based on the screening of several additives, HOBt emerged as the best choice and the yield was further improved with high *ee* value remained (entry 10).

Table 4.2 Substrates scope of the NHC catalyzed aldol reaction with isatins.^a

^a Reaction conditions: acetic anhydride (0.20 mmol), ethanol (0.60 mmol), isatin (0.10 mmol), Cat. (30 mol%), KOAc (200 mol%), HOBt (30 mol%), 3Å MS (100 mg), ether (1.0 mL), rt. The *ee* values were determined *via* chiral phase HPLC analysis.

Having established the optimized reaction condition, the substrates scope of this direct aldol reaction was explored (Table 4.2). Using methanol or benzyl alcohol instead of ethanol, the reactions could proceed in good yield, although the enantioselectivity is slightly decreased (**4-2b**, **4-2c**). Sterically bulky alcohols such as isopropyl or tert-butyl alcohol could not give any desired product. Isatins substrates bearing electron-donating or electron-withdrawing groups at 5-position typically showed good reactivity and good enantioselectivity (**4-2d-4-2k**). With fluoro substituent at 7-position, the isatin substrate was also well tolerated (**4-2l**). With bulky groups such as Me-, Cl- and Br- at 7-position, protecting isatins with trt-group could not be realized and benzyl group was used instead. These substrates could also afford the products in moderate to good yield, albeit with decreased enantioselectivity (**4-2m-4-2o**).¹³

Scheme 4.2 Proposed reaction pathway of aldol reaction with isatin.

The catalytic cycle for the asymmetric aldol reaction was shown in Scheme 4.2. The initial addition of the NHC catalyst to acetic anhydride furnishes acyl azolium intermediate **I**, which was then deprotonated by base to give the chiral enolate **II**. Due to the steric effect of the bulky substituent on NHC catalyst, the isatin substrate **4-1a** was attacked preferentially from the back face to generate the quaternary chiral center. The aldol addition gave azolium intermediate **III**, which could be trapped by ethanol or alternatively HOBt as a activating agent followed by ethanol to release the free cabene and generate the desired β -hydroxy ester product **4-2a**.

4.3 Conclusion

In summary, we have developed a new strategy for direct aldol reaction of ester equivalent *via* the combination of simple acetic anhydride and ethanol. A variety of isatin substrates could be employed in this reaction, affording biologically useful 3-hydroxyindole products in good yield and high enantioselectivity. This strategy could expand the scope of synthetically useful transformations involving ester equivalent in organo catalysis.

4.4 Experimental Section

General Information

Commercially available materials were used as received. Trt protected isatins were synthesized according to the procedure in literature.^{12c} Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Bruker AV400 (400 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Bruker AV400 (400 MHz) (100 MHz) spectrometers. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *ee* was performed by chiral phase HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 0.5 mL cell with a 10 mm path length on a PerkinElmer Model 341 digital polarimeter and are reported as follows: $[\alpha]_{\text{D}}^{25}$ (*c* in mmol per mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

General procedure for NHC catalyzed asymmetric aldol reaction with acetic anhydride

To a dry 10 mL Schlenk tube, equipped with a stir bar, was added isatin **4-1** (0.10 mmol), potassium acetate (0.20 mmol), HOBt (0.03 mmol), 3 Å MS (100 mg) and chiral triazolium salt **C** (0.03 mmol). The flask was then evacuated and refilled with Argon. To this mixture was added acetic anhydride (0.05 mmol) and ethanol (0.15 mmol) in

anhydrous ether (1.0 mL). The mixture was stirred at room temperature. Acetic anhydride (0.05 mmol) and ethanol (0.15 mmol) in anhydrous ether (0.2 mL) was added followed by potassium acetate (0.10 mmol) in every 6 hs until complete consumption of the isatin **4-1** (monitored by TLC). The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (4:1, hexanes/EtOAc) to afford the desired product.

The racemic product was obtained using the same protocol with catalyst **A**.

Characterization of products

(R)-ethyl 2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2a): 84% yield; $[\alpha]_D^{23} = -29$ (c 1.92, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.46 (m, 6H), 7.35-7.33 (m, 1H), 7.26-7.17 (m, 9H), 6.97-6.89 (m, 2H), 6.30 (d, $J = 8.8$ Hz, 1H), 4.12 (dd, $J = 14.0, 7.2$ Hz, 2H), 3.83 (s, 1H), 2.96 (dd, $J = 23.2, 15.2$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.9, 170.0, 143.3, 141.9, 129.4, 129.3, 128.5, 127.7, 126.9, 123.3, 122.6, 116.3, 74.5, 73.4, 61.1, 42.2, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for C₃₁H₂₈NO₄, 478.2018 found, 478.2012; HPLC analysis: 95:5 er (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 14.1 min, R_t (minor) = 19.0 min.

(R)-methyl 2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2b): 75% yield; $[\alpha]_D^{23} = -42$ (c 1.43, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.45 (m, 6H), 7.34-7.32 (m,

1H), 7.27-7.17 (m, 9H), 6.97-6.90 (m, 2H), 6.31-6.29 (m, 1H), 3.75 (br, 1H), 3.64 (s, 3H), 2.98 (dd, $J = 25.6, 15.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.8, 170.3, 143.3, 141.8, 129.3, 128.6, 127.7, 126.9, 123.2, 122.7, 116.3, 74.5, 73.3, 52.1, 42.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{30}\text{H}_{26}\text{NO}_4$, 464.1862 found, 464.1865; HPLC analysis: 93.5:6.5 er (Chiralcel OD-H, 10:90 i PrOH/Hexane, 0.5 mL/min), R_t (major) = 18.0 min, R_t (minor) = 23.2 min.

(R)-benzyl 2-(3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2c): 69% yield; $[\alpha]_{\text{D}}^{23} = -16$ (c 1.91, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.44 (m, 6H), 7.32-7.30 (m, 4H), 7.24-7.18 (m, 11H), 6.94-6.89 (m, 2H), 6.32-6.28 (m, 1H), 5.10 (s, 2H), 3.73 (br, 1H), 3.03 (dd, $J = 19.2, 15.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.9, 169.7, 143.4, 141.8, 135.4, 129.3, 129.2, 128.6, 128.3, 128.2, 127.7, 126.9, 123.3, 122.7, 116.4, 74.6, 73.4, 66.8, 42.3; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{36}\text{H}_{30}\text{NO}_4$, 540.2175 found, 540.2180; HPLC analysis: 90:10 er (Chiralcel OD-H, 10:90 i PrOH/Hexane, 0.5 mL/min), R_t (major) = 30.9 min, R_t (minor) = 26.3 min.

(R)-ethyl 2-(3-hydroxy-5-methoxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2d): 84% yield; $[\alpha]_{\text{D}}^{23} = -45$ (c 3.36, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.45 (m, 6H), 7.26-7.16 (m, 9H), 6.93 (d, $J = 2.4$ Hz, 1H), 6.45 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.18 (d, $J = 8.8$ Hz, 1H), 4.13 (dd, $J = 14.4, 7.2$ Hz, 2H), 3.88 (s, 1H), 3.68 (s, 3H), 2.94 (dd, $J = 24.4$,

15.2 Hz, 2H), 1.18 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.7, 169.9, 155.6, 141.9, 136.3, 130.7, 129.3, 127.7, 126.9, 117.0, 113.6, 109.7, 74.5, 73.7, 61.1, 55.6, 42.3, 14.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{32}\text{H}_{30}\text{NO}_4$, 508.2124 found, 508.2124; HPLC analysis: 93:7 er (Chiralcel OD-H, 10:90 i PrOH/Hexane, 0.5 mL/min), R_t (major) = 16.1 min, R_t (minor) = 21.1 min.

(R)-ethyl 2-(3-hydroxy-5-methyl-2-oxo-1-tritylindolin-3-yl)acetate (4-2e): 93% yield; $[\alpha]_{\text{D}}^{23} = -41$ (c 3.34, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.45 (m, 6H), 7.25-7.15 (m, 10H), 6.71 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.16 (d, $J = 8.4$ Hz, 1H), 4.12 (dd, $J = 14.4, 7.2$ Hz, 2H), 3.82 (s, 1H), 2.95 (dd, $J = 26.4, 15.2$ Hz, 2H), 2.21 (s, 3H), 1.17 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.9, 170.0, 142.0, 140.8, 132.2, 129.4, 129.3, 129.0, 127.7, 126.9, 124.0, 116.1, 74.5, 73.5, 61.1, 42.3, 20.8, 14.1; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{32}\text{H}_{30}\text{NO}_4$, 492.2175 found, 492.2168; HPLC analysis: 94.5:5.5 er (Chiralcel OD-H, 10:90 i PrOH/Hexane, 0.5 mL/min), R_t (major) = 12.9 min, R_t (minor) = 16.8 min.

(R)-ethyl 2-(5-bromo-3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2f): 63% yield; $[\alpha]_{\text{D}}^{23} = -49$ (c 3.58, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.45-7.43 (m, 7H), 7.27-7.18 (m, 9H), 7.03 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.17 (d, $J = 8.8$ Hz, 1H), 4.14 (dd, $J = 14.0, 6.8$ Hz, 2H), 3.86 (s, 1H), 2.95 (dd, $J = 20.8, 15.2$ Hz, 2H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.3, 169.7, 142.5, 141.5, 131.5, 131.4, 129.3, 127.8, 127.1,

126.6, 117.7, 115.7, 74.7, 73.2, 61.3, 42.1, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{31}H_{27}BrNO_4$, 558.1103 found, 558.1115; HPLC analysis: 94:6 er (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 13.1 min, R_t (minor) = 20.5 min.

(R)-ethyl 2-(5-fluoro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2g): 60% yield; $[\alpha]_D^{23} = -24$ (c 2.58, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 6H), 7.27-7.20 (m, 9H), 7.08 (dd, $J = 7.2, 2.4$ Hz, 1H), 6.65-6.59 (m, 1H), 6.23 (dd, $J = 8.8, 4.0$ Hz, 1H), 4.16-4.11 (m, 2H), 3.87 (s, 1H), 2.94 (dd, $J = 18.0, 15.2$ Hz, 2H), 1.19 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 169.7, 160.0, 157.6, 141.6, 139.1 (d, $J = 3.0$ Hz), 131.1 (d, $J = 8.0$ Hz), 129.3, 127.8, 127.1, 117.1 (d, $J = 8.0$ Hz), 115.0 (d, $J = 22.0$ Hz), 111.2 (d, $J = 24.0$ Hz), 74.7, 73.4 (d, $J = 1.0$ Hz), 61.2, 42.2, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{31}H_{27}FNO_4$, 496.1924 found, 496.1935; HPLC analysis: 93:7 er (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 13.2 min, R_t (minor) = 19.1 min.

(R)-ethyl 2-(5-chloro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2h): 63% yield; $[\alpha]_D^{23} = -42$ (c 3.19, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 6H), 7.31 (d, $J = 2.0$ Hz, 1H), 7.27-7.18 (m, 9H), 6.89 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.22 (d, $J = 8.8$ Hz, 1H), 4.14 (dd, $J = 14.4, 7.2$ Hz, 2H), 3.86 (s, 1H), 2.95 (dd, $J = 19.6, 15.2$ Hz, 2H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 169.7, 141.9, 141.5, 131.1, 129.3,

128.5, 128.3, 127.8, 127.1, 123.8, 117.3, 74.7, 73.3, 61.3, 42.1, 14.1; HRMS (ESI)

$[M+H]^+$ calcd. for $C_{31}H_{27}ClNO_4$, 512.1629 found, 512.1631; HPLC analysis: 94:6 er

(Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 13.1 min, R_t (minor) = 20.5 min.

(R)-ethyl 2-(3-hydroxy-2-oxo-5-(trifluoromethoxy)-1-tritylindolin-3-yl) acetate (4-2i):

60% yield; $[\alpha]_D^{23} = -36$ (c 2.73, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 6H), 7.28-7.19 (m, 10H), 6.78 (dd, $J = 8.8, 1.6$ Hz, 1H), 6.28 (d, $J = 9.2$ Hz, 1H), 4.13 (dd, $J = 14.4, 6.8$ Hz, 2H), 3.91 (s, 1H), 2.95 (d, $J = 1.6$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 169.7, 144.6 (d, $J = 1.0$ Hz), 141.8, 141.5, 131.0, 129.2, 127.8, 127.1, 121.7, 121.3, 119.2, 116.9 (d, $J = 6.0$ Hz), 74.8, 73.3, 61.3, 42.1, 14.0;

HRMS (ESI) $[M+H]^+$ calcd. for $C_{32}H_{27}F_3NO_5$, 561.1841 found, 561.1851; HPLC analysis: 95:5 er (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 12.0 min, R_t (minor) = 20.4 min.

(R)-ethyl 2-(3-hydroxy-5-iodo-2-oxo-1-tritylindolin-3-yl)acetate (4-2j): 63% yield;

$[\alpha]_D^{23} = -65$ (c 3.23, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, $J = 1.6$ Hz, 1H), 7.44-7.42 (m, 6H), 7.27-7.18 (m, 10H), 6.06 (d, $J = 8.4$ Hz, 1H), 4.15 (dd, $J = 14.0, 6.8$ Hz, 2H), 3.84 (s, 1H), 2.94 (dd, $J = 22.0, 15.6$ Hz, 2H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 169.7, 143.2, 141.5, 137.4, 132.2, 131.8, 129.2, 127.8, 127.1,

118.2, 85.8, 74.7, 73.1, 61.3, 42.1, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{31}H_{27}INO_4$, 604.0985 found, 604.0993; HPLC analysis: 96:4 er (Chiralcel OJ-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 12.8 min, R_t (minor) = 20.6 min.

(R)-ethyl 2-(3-hydroxy-5-nitro-2-oxo-1-tritylindolin-3-yl)acetate (4-2k): 45% yield; $[\alpha]_D^{23} = -52$ (c 1.83, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, $J = 2.4$ Hz, 1H), 7.86 (dd, $J = 9.2, 2.4$ Hz, 1H), 7.45-7.43 (m, 6H), 7.30-7.23 (m, 9H), 6.42 (d, $J = 9.2$ Hz, 1H), 4.18-4.11 (m, 2H), 3.85 (s, 1H), 3.05 (d, $J = 0.8$ Hz, 2H), 1.21 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 169.5, 149.4, 143.1, 141.1, 130.4, 129.2, 128.0, 127.4, 119.1, 115.9, 75.3, 72.7, 61.5, 41.8, 14.1; HRMS (ESI) $[M+H]^+$ calcd. for $C_{31}H_{27}N_2O_6$, 523.1869 found, 523.1892; HPLC analysis: 96.5:3.5 er (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 17.5 min, R_t (minor) = 31.5 min.

(R)-ethyl 2-(7-fluoro-3-hydroxy-2-oxo-1-tritylindolin-3-yl)acetate (4-2l): 62% yield; $[\alpha]_D^{23} = -16$ (c 2.78, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 6H), 7.26-7.17 (m, 10H), 7.00-6.96 (m, 1H), 6.76-6.70 (m, 1H), 4.15-4.06 (m, 2H), 3.90 (s, 1H), 3.01 (dd, $J = 24.8, 15.2$ Hz, 2H), 1.14 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 169.6, 148.1, 145.6, 143.4 (d, $J = 3.0$ Hz), 132.1 (d, $J = 3.0$ Hz), 130.3 (d, $J = 8.0$ Hz), 128.9 (d, $J = 2.0$ Hz), 127.5, 126.8, 124.6 (d, $J = 7.0$ Hz), 119.6 (d, $J = 4.0$ Hz), 119.2 (d, $J = 23.0$ Hz), 75.1, 73.3 (d, $J = 2.0$ Hz), 61.2, 42.3, 14.0; HRMS (ESI) $[M+H]^+$

calcd. for $C_{31}H_{27}FNO_4$, 496.1924 found, 496.1939; HPLC analysis: 92:8 er (Chiralcel OD-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 13.7 min, R_t (minor) = 18.6 min.

(R)-ethyl 2-(1-benzyl-3-hydroxy-7-methyl-2-oxoindolin-3-yl)acetate (4-2m): 60% yield; $[\alpha]_D^{23} = +18$ (c 2.25, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (m, 6H), 6.98-6.97 (m, 2H), 5.16 (dd, $J = 24.8, 17.2$ Hz, 2H), 4.49 (s, 1H), 4.18-4.12 (m, 2H), 3.04 (d, $J = 15.6$ Hz, 1H), 2.94 (d, $J = 15.6$ Hz, 1H), 2.24 (s, 3H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 170.4, 140.7, 137.2, 134.0, 130.1, 128.9, 127.3, 125.7, 123.4, 121.8, 120.4, 72.8, 61.2, 45.2, 41.5, 18.7, 14.0; HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{22}NO_4$, 340.1549 found, 340.1546; HPLC analysis: 83:17 er (Chiralcel OJ-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 26.5 min, R_t (minor) = 62.1 min.

(R)-ethyl 2-(1-benzyl-7-chloro-3-hydroxy-2-oxoindolin-3-yl)acetate (4-2n): 52% yield; $[\alpha]_D^{23} = +18$ (c 1.58, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.19 (m, 7H), 7.00 (t, $J = 8.0$ Hz, 1H), 5.32 (s, 2H), 4.53 (br, 1H), 4.18-4.12 (m, 2H), 3.00 (d, $J = 15.6$ Hz, 1H), 2.93 (d, $J = 15.6$ Hz, 1H), 1.20 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 170.1, 138.8, 137.1, 132.6, 132.2, 128.6, 127.3, 126.5, 124.2, 122.5, 116.0, 72.9, 61.4, 45.0, 41.4, 14.0; HRMS (ESI) $[M+H]^+$ calcd. for $C_{19}H_{19}ClNO_4$, 360.1003 found, 360.1008; HPLC analysis: 77:23 er (Chiralcel OJ-H, 10:90 *i*PrOH/Hexane, 0.5 mL/min), R_t (major) = 30.5 min, R_t (minor) = 55.6 min.

(R)-ethyl 2-(1-benzyl-7-bromo-3-hydroxy-2-oxoindolin-3-yl)acetate (4-2o): 50% yield;

$[\alpha]_D^{23} = +13$ (c 1.63, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.36 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.23 (m, 3H), 6.94 (t, $J = 7.2$ Hz, 1H), 5.38 (s, 2H), 4.51 (br, 1H), 4.18-4.12 (m, 2H), 3.00 (d, $J = 15.6$ Hz, 1H), 2.92 (d, $J = 16.0$ Hz, 1H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.3, 170.1, 140.3, 137.0, 136.0, 132.6, 128.6, 127.2, 126.4, 124.6, 123.1, 103.0, 72.8, 61.4, 44.6, 41.4, 14.0; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{19}\text{BrNO}_4$, 406.0477 found, 406.0483; HPLC analysis: 75:25 er (Chiralcel OJ-H, 10:90 i PrOH/Hexane, 0.5 mL/min), R_t (major) = 31.4 min, R_t (minor) = 62.8 min.

4.5 References

(1) General review of asymmetric aldol reactions: (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, **2004**; (b) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131-173.

(2) Reviews of direct catalytic asymmetric aldol reactions: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187-2210; (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595-1601; (c) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580-591; (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.

(3) For a selection of early examples of direct catalytic asymmetric aldol reactions, see: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1871-1873; (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168-4178; (c) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396; (d) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003-12004; (e) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 4459-4461.

(4) Direct catalytic asymmetric aldol (-type) reactions using alkyl nitriles as aldol donors: (a) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757-3760.

(5) (a) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706-8707; (b) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704-8705; (c) Iwata, M.; Yazaki, R.; Suzuki, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 18244-18245; (d) Weidner, K.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 6150-6154.

(6) (a) α -isocyanoacetates: Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406; (b) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852-2853.

(7) β,γ -Unsaturated ester: (a) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 10842-10843. 5H-oxazol-4-ones: (b) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286-6287. α -Sulfanyl lactones: (c) Takechi, S.; Yasuda, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4218-4222.

(8) For recent NHC reviews, see: (a) Grossman, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314-325; (b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522; (c) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11686-11698; (d) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906-4917.

(9) NHC catalyzed transesterification reactions of esters: (a) Connor, E. F.; Nyce, G. W.; Myers, M.; Mock, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914-915; (b) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583-3586; (c) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587-3590; (d) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770-2771; (e) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347-1349; (f) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453-2456; (g) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176-14177.

(10) Our previous work on ester activation: (a) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154-2157; (b) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956-4959; (c) Cheng, J.; Huang, Z.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8592-8596; (d) Hao, L.; Chuen, C. W.; Ganguly, R.; Chi, Y. R. *Synlett* **2013**, 1197-1200. (e) Chen, S.; Hao, L.; Zhang, Y.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5822-5825; (f) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835-839; (g) Xu, J.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5028-5031.

(11) For natural products derivatized from isatins, see: (a) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783-2784; (b) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523-5528; (c) Kamano, Y.; Kotake, A.; Hashima, H.; Hayakawa, I.; Hiraide, H.; Zhang, H.-P.; Kizu, H.; Komiyama, K.; Hayashi, M.; Pettit, G. R. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1147-1153; (d) Hayashi, M.; Kim, Y.-P.; Takamatsu, S.; Enomoto, A.; Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Ojmura, S. J. *Antibiot.* **1996**, *49*, 1091-1095; (e) Takamatsu, S.; Kim, Y.-P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Ojmura, S. J. *Antibiot.* **1997**, *50*, 1069-1072; (f) Hayashi, M.; Rho, M.-C.; Enomoto, A.; Fukami, A.; Kim, Y.-P.; Kikuchi, Y.; Sunazuka, T.; Hirose, T.; Komiyama, K.; Ojmura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14728-14739; (g) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199-3202.

(12) Selected examples of asymmetric aldol reactions of isatins with aldehydes and ketones: (a) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2009**, *15*, 6790-6793; (b) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854-3857; (c) Guang, J.; Guo, Q.; Zhao, J. C. *Org. Lett.* **2012**, *14*, 3174-3177; (d) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W. Tan, D.; Huang, K.-W.; Jiang, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 6666-6670.

(13) The stereochemistry of product **4-2b** was determined by literature, see: 12c.

APPENDIX

N-Heterocyclic Carbenes Catalyzed Enolate Formation from α,β -Unsaturated Aldehydes¹

5.1 Introduction

N-Heterocyclic carbenes catalyzed selective generation of enolate from α,β -unsaturated aldehyde has emerged as powerful synthetic strategy in asymmetric organocatalysis.¹ Diels-Alder reactions of α,β -unsaturated aldehydes with enones and ketimines have attracted much attention for the biological utility of lactone and lactam products, as reported by the groups of Bode,² Nair,³ and ourselves⁴. It is observed that only the substrates with two electrowithdrawing groups, such as carboxylic ester with aldehyde or ketone groups, are effective in these elegantly established reactions (Scheme 5.1). The

Scheme 5.1 Substrates for NHC catalyzed homoenolate and enolate reactions

¹ The initial enolate reaction of aldehyde with enone was discovered by Fu Zhenqian. The optimization of reactions with aldehydes and enones was finished by Fu Zhenqian and Chen Shaojin cooperately. The examination of substrate scope of aldehydes and enones was finished by Fu Zhenqian. The optimization of reactions with aldehydes and nitrostyrene or isatin was done by Chen Shaojin.

only exception is Nair's work, which employed β -unsubstituted vinylketones in the [4+2] annulation with α,β -unsaturated aldehydes, but only racemic reactions were reported.³ In 2006, Glorius and co-workers disclosed that activated ketones could also be suitable for the enolate involved cycloaddition, providing γ -lactones in low yield with poor diastereoselectivity.⁵ Besides these specific substrates, the enolate additions of enals to other types of electrophiles are rarely reported.

Detailed investigation of electronic feature of the Breslow intermediate revealed that the control of these two competing reaction pathway could be realized by several methods, including decreasing the reactivity of electrophiles or increasing the steric bulkiness of the substrates, as realized by Nair³ and our group⁴. Herein, we want to generate the enolate intermediate by a reaction condition control approach *via* simple addition of acid into reaction mixture (scheme 5.2).⁶ This strategy could be the optimal choice, as it could get rid of the limitation of substrates scope, providing an opportunity for the reactions with other common electrophiles. Besides these advantages, several challenges existed in this approach. The enolate intermediate is easily protonated by acids, leading to less reactive acyl azolium⁷ and carbenes could also be deactivated under acidic conditions.

Scheme 5.2 Chemoselectivity between homoenolate and enolate

5.2 Results and Discussion

Table 5.1 Effect of bases in model reaction.^a

Entry	Condition	Conv. [%] ^b	5-3a : 5-4a ^c
1	DBU	85	<1:99
2	DBU, HOAc	81	1:13
3	Cs ₂ CO ₃ , HOAc	>95	1:5.6
4	K ₂ CO ₃ , HOAc	44	1:1.2
5	K₃PO₄, HOAc	51	1.3:1
6	KOAc, HOAc	35	1.2:1
7	NaOAc, HOAc	n.r.	n.d.
8	DABCO, HOAc	16	1.2:1
9	Et ₃ N, HOAc	n.r.	n.d.
10	NMM, HOAc	n.r.	n.d.

^a Reaction condition: **5-1a** (0.25 mmol), **5-2a** (0.50 mmol), base (0.50 mmol) (and acid 0.125 mmol), Cat. (12 mol%), 4Å MS, and THF (1.0 mL). ^b Conversion based on **5-1a**, determined *via* ¹H NMR analysis of the crude reaction mixture. n.r.=no reaction. ^c Determined *via* ¹H NMR analysis of the crude reaction mixture. n.d.=not determined.

At the outset, we evaluated the cycloaddition reaction of chalcone **5-1a** and enal **5-2a** to examining the efficiency of our proposed approach (Table 5.1). When acetic acid was used with DBU, the obtained product is mainly from the homoenolate pathway, which is similar to the reaction condition without acid additive (Entry 2).⁸ Then, we investigated

the effect of bases in this reaction. In the presence of caesium carbonate and acetic acid, a small amount of enolate product was observed, which encouraged us to screen other weak inorganic bases (Entry 3). Using potassium carbonate instead of caesium carbonate leads to enolate product almost the same amount as homoenolate product (Entry 4). However, only moderate conversion could be achieved. Further screening revealed that potassium phosphate is a better choice, giving a higher conversion and good ratio of enolate to homoenolate product (Entry 5). With potassium acetate as base, lower conversion was observed (Entry 6). When a much weak base was used, such as sodium acetate, neither of those products was obtained (Entry 7). In the presence of weak organic base, such as DABCO, triethyl amine and *N*-methyl morpholine, much poor reactivity was observed compared to the cases of inorganic bases (Entries 8-10). With K_3PO_4 as base, other acids

Table 5.2 Screen of catalysts for model reaction^a

Entry	Cat.	Conv. [%] ^b	5-3a:5-4a ^c
1	Cat.2	n.r.	n.d.
2	Cat.3	20	1:2.8
3	Cat.4	18	1:2.4
4	Cat.5	>95	9.0:1
5	Cat.6	>95	5.6:1(99) ^d

^a Reaction condition: **5-1a** (0.25 mmol), **5-2a** (0.50 mmol), K₃PO₄ (0.50 mmol) (and acid 0.125 mmol), Cat. (12 mol %), 4Å MS, and THF (1.0 mL). ^b Conversion based on **5-1a**, determined *via* ¹H NMR analysis of the crude reaction mixture. n.r.= no reaction. ^c Determined *via* ¹H NMR analysis of the crude reaction mixture. n.d.=not determined. ^d No. in the parenthesis indicates the *ee* of **5-3a**.

have also been tested. Strong acids, such as HCl, could only provide little or trace of product, while weak acids, such as benzoic acid, could provide low yield of the desired lactone product, and did not show any advantage compared to acetic acid on chemoselectivity. Although the initial chemoselective ratio is not good, it is delighting that enolate product could be generated using acetic acid as proton source.

Table 5.3 Screening of weak bases under chiral catalyst.^a

Entry	Condition	Conv. [%] ^b	5-3a:5-4a ^c	<i>dr</i> ^c
1	Et ₃ N	78	1.6:1	8:1
2	Et ₃ N, HOAc	73	6:1	20:1
3	DIEA	63	2.5:1	8:1
4	DIEA, HOAc	52	7.8:1	20:1
5	DMAP	54	2.1:1	9:1
6	DMAP, HOAc	23	12:1	14:1
7 ^d	KOAc, HOAc	75	10:1	20:1
8 ^{d,e}	KOAc, HOAc	>95(86) ^f	10:1 ^g	20:1(99) ^h

^a Reaction condition: **5-1a** (0.25 mmol), **5-2a** (0.50 mmol), base (0.50 mmol) (and acid 0.125 mmol), cat. (12 mol%), 4Å MS, and THF (1.0 mL). ^b Conversion based on **5-1a**, determined *via* ¹H NMR analysis of the crude reaction mixture. ^c Determined *via* ¹H

NMR analysis of the crude reaction mixture. ^d 20 mol% of cat. was used. ^e 0.62 mmol of KOAc, 0.062 mmol of HOAc, THF (0.5 mL). ^f No. in the parenthesis indicates the isolated yield of **5-3a** (single diastereomer). ^g the ratio of **5-3a:5-4a** is 4.4:1 under optimized conditions without acid. ^h *ee* [%] of **5-3a**, determined *via* chiral phase HPLC analysis; absolute configuration of the major diastereomer was assigned based on X-ray structure of **5-3c**.

With potassium phosphate as the ideal base, we continued to investigate the effect of various NHC catalysts (Table 5.2). While *iso*-propyl substituted imidazolium salt was proved to be not effective for this reaction (Entry 1), triazolium salts with methyl or phenyl group could provide homoenolate product as the major product in low conversion (Entry 2 and 3). When a methyl substituted triazolium salt was employed, most of the products were generated from enolate intermediate in high conversion (Entry 4). Based on this result, we further tested the chiral aminoalcohol derived catalyst, and enolate product was also formed as the major product with high conversion (Entry 5).

As the asymmetric enolate reaction was applicable, more weak bases were investigated under the standard condition (Table 5.3). Using weak organic bases, such as DIEA and triethylamine, the enolate product could be generated in preference to homoenolate product with good conversion, which is quite different from the previous cases under racemic catalysts (Entry 2 and 4). With a weaker base like DMAP, the chemoselectivity increased dramatically, but the conversion turned to be unacceptable (Entry 6). When potassium acetate was employed, enolate product prevailed in high conversion with only trace amount of homoenolate product formed (Entry 7). Control experiments show that the ratio of enolate to homoenolate product significantly decreased without acetic acid (Entry 1, 3, 5 and 8^g). Further optimization on the ratio of base and acid revealed that 2.5 equiv. of potassium acetate with 0.25 equiv. of acetic acid could give the best result, furnishing lactones in good yield with high diastereo- and enantioselectivity.

The optimized reaction condition proved to be effective for various aromatic or aliphatic enals (Table 5.4). Electron donating or withdrawing substituents at *ortho* or *para* position of phenyl ring were tolerated (Entries 1-5). Enals with *ortho* substitution shows much higher chemoselectivity toward enolate products than those with *para* substitution. This

Table 5.4 Scope of the enals **5-2**.^a

Entry	R	Yield [%] ^b	<i>dr</i> ^c	<i>ee</i> [%] ^d	5-3:5-4 ^c
1	4-MeOC ₆ H ₄ (5-2a)	86 (5-3a)	20:1	99	10:1
2	2-MeOC ₆ H ₄ (5-2b)	89 (5-3b)	20:1	99	26:1
3 ^e	4-BrC ₆ H ₄ (5-2c)	73 (5-3c)	20:1	99	6:1
4 ^e	2-BrC ₆ H ₄ (5-2d)	83 (5-3d)	20:1	99	21:1
5	4-Me ₂ NC ₆ H ₄ (5-2e)	81 (5-3e)	20:1	99	5:1
6 ^e	2-naphthyl (5-2f)	84 (5-3f)	19:1	99	9:1
7 ^e	Ph (5-2h)	88 (5-3h)	20:1	99	10:1
8 ^e	2-furyl (5-2g)	69 (5-3g)	20:1	99	n.d. ^f
9 ^e	<i>n</i> -C ₅ H ₁₁ (5-2i)	79 (5-3i)	20:1	99	9:1
10 ^e	<i>n</i> -C ₃ H ₇ (5-2j)	77 (5-3j)	9:1	99	10:1

^a Reaction condition: **5-1a** (0.25 mmol), **5-2** (0.50 mmol), cat. (0.05 mmol), AcOH (0.062 mmol), base (0.62 mmol), 4Å MS, THF (0.5 mL). ^b Isolated yield of **5-3** (mostly single diastereomer) based on **5-1a**. ^c Determined *via* ¹H NMR analysis of the unpurified reaction mixtures. ^d Enantiomeric excess of **5-3** (major diastereomer), determined *via* chiral-phase HPLC analysis. ^e 0.75 mmol of **5-2** and THF (0.25 mL) was used. ^f n.d. = not determined.

Table 5.5 Scope of the chalcones **5-1**.^a

Entry	Ar	Ar'	Yield [%] ^b	<i>dr</i> ^c (<i>ee</i> [%]) ^d	5-3 : 5-4 ^c
1	PMP	Ph	79 (5-3k)	16:1(99)	12:1
2	4-MeC ₆ H ₄	Ph	82 (5-3l)	20:1(99)	18:1
3 ^e	2-MeC ₆ H ₄	Ph	50 (5-3m)	20:1(99)	17:1
4 ^f	4-ClC ₆ H ₄	Ph	66 (5-3n)	20:1(99)	6:1
5	Ph	PMP	70 (5-3o)	11:1(99)	10:1
6	Ph	4-MeC ₆ H ₄	73 (5-3p)	20:1(99)	10:1
7 ^f	Ph	4-ClC ₆ H ₄	75 (5-3q)	19:1(99)	8:1
8	Ph	2-furyl	60 (5-3r)	8:1(99)	11:1
9	4-BrC ₆ H ₄	4-MeC ₆ H ₄	70 (5-3s)	16:1(99)	5:1

^a Reactions were performed under similar conditions as in Table 5.4. PMP = 4-MeOC₆H₄

^b Isolated yield of **5-3** (mostly single diastereomer). ^c Determined *via* ¹H NMR analysis of unpurified reaction mixtures. ^d Enantiomeric excess of **5-3** (major diastereomer),

determined *via* chiral-phase HPLC analysis.^e 40 h.^f 0.37 mmol of AcOH and 0.50 mmol of KOAc was used.

could be attributed to the steric hindrance of the *ortho* groups, which made the homoenolate intermediate difficult to react with enones. Simple cinnamaldehyde and its 2-naphthyl substituted analogue were well converted under the standard condition (Entries 6 and 7). Heterocyclic substrates with 2-furyl group could also be tolerated (Entry 8). Besides aromatic enals, aliphatic ones were also effective substrates (Entry 9 and 10). It is noteworthy that all the lactones were obtained in good yield with excellent diastereo- and enantioselectivity.⁹

Next, we continued to probe the substrate scope of chalcones using 4-methoxy phenyl substituted enal (Table 5.5). Various electron donating or withdrawing groups on phenyl rings were investigated, providing lactones in moderate to good yield with high diastereo- and enantioselectivity. With *ortho*-substituent on phenyl group, the lactone was obtained in lower yield even under longer reaction time compared to the one with *para*-substituent (Entries 2 and 3). Typically, chalcones with electron-donating substituents, such as methyl and methoxy group (Entries 1-3, 5 and 6), gave higher ratio of enolate to homoenolate product than those with electron-withdrawing groups (Entries 4, 7 and 9). With the later substrates, more acetic acid should be added to achieve a better chemoselectivity, and diastereoselectivity of products was also improved.

Based on these experiments, we proposed a mechanism for this chemoselective reaction (Scheme 5.3). The Breslow intermediate, generated from addition of free carbene to enal, could be protonated under weak basic condition to give enolate intermediate. Following Diels-Alder reaction with enones provided a six-membered adduct, which could be transformed to the lactone product by releasing free carbene catalyst. If strong base was employed, electrophilic chalcone could react with homoenolate intermediate at the β

position. Following intramolecular aldol reaction could provide a cyclopentane fused lactone, which was further converted to cyclopentene through decarboxylation.

Scheme 5.3 Proposed mechanism

Having identified chalcones as suitable substrates in this enolate chemistry, we further examined several other electrophiles. As shown in table 5.6, benzyl group protected isatin was converted to five membered lactone using potassium phosphates as base in THF. The desired spiro- β -lactone from enolate pathway was not observed under this condition. Further screening of reaction condition disclosed that only the product derived from homoenolate could be obtained. Instead of the chemocontrol between homoenolate and enolate, the control of the formation of diastereomers was realized, with increased diastereoselectivity under weak basic conditions (Entries 3-5). If much weaker base was employed, the isatin and enal could not convert to any product (Entries 6-8). As NaOAc is a weaker base compared to KOAc and its solubility in THF is poor, the reaction using

NaOAc combined with HOAc (Entry 6) gave much poor result compared to the reaction using KOAc/HOAc (Entry 4).

Table 5.6 Reaction condition screening of enolate reactions with isatin.^a

Entry	Condition	Conv. [%] ^b	5-6a : 5-6b ^c	<i>dr</i> ^c
1	DBU	>95	5-6a	1:2.6
2	K ₃ PO ₄	>95	5-6a	1:4.4
3	K ₃ PO ₄ , HOAc	>95	5-6a	1:5.8
4	KOAc, HOAc	>95	5-6a	1:6.7
5 ^d	KOAc, HOAc	>95	5-6a	1:7
6	NaOAc, HOAc	n.r.	n.d.	n.d.
7	NMM, HOAc	n.r.	n.d.	n.d.
8	4-NO ₂ PhO ₂ Na, HOAc	n.r.	n.d.	n.d.

^a Reactions condition: **5-5a** (0.25 mmol), **5-2a** (0.50 mmol), cat. (0.05 mmol), AcOH (0.25 mmol), base (0.50 mmol), THF (0.5 mL). ^b Conversion based on **5-5a**, determined via ¹H NMR analysis of unpurified reaction mixtures. n.r.=no reaction. ^c Determined via ¹H NMR analysis of unpurified reaction mixtures. n.d.=not determined. ^d 2 equiv. of AcOH was used.

Next, we investigated β-nitrostyrene with methanol in anticipation of enolate addition of enal as shown in table 5.7. In initial attempt, nitrostyrene underwent homoenolate addition with enal **5-2a**, providing 4-nitroester **5-8a** other than the desired 3-nitroester **5-8b**, with

opposite diastereoselectivity observed using triazolium salt Cat. **5** compared to the previous report (Entries 1 and 2).¹⁰ Lower temperature was found amenable to the yield of this reaction, and decreased diastereoselectivity was observed (Entry 3). Further screening revealed that weaker base lead to higher diastereoselectivity, which is similar to the case of isatin (Entries 4-6). Screening of solvents revealed that toluene was the best choice, affording the product in good yield with high diastereoselectivity (Entry 8).

Table 5.7 Reaction condition screening of enolate reaction with β -nitrostyrene^a

Entry	Cat.	Condition	yield [%] ^b	5-8a : 5-8b ^c	<i>dr</i> ^c
1 ^d	Cat. 1	KOAc, HOAc	<10	5-8a	0.5:1
2 ^d	Cat. 5	KOAc, HOAc	50	5-8a	6.3:1
3 ^e	Cat. 5	KOAc, HOAc	70	5-8a	4:1
4	Cat. 5	KOAc	70	5-8a	4.5:1
5	Cat. 5	Cs ₂ CO ₃	54	5-8a	3.44:1
6	Cat. 5	DBU	50	5-8a	2.8:1
7 ^f	Cat. 5	KOAc	65	5-8a	3.5:1
8 ^g	Cat. 5	KOAc	75	5-8a	7.5:1
9 ^g	Cat. 5	KHCO ₃	73	5-8a	7.2:1

^a Reactions condition: **5-7a** (0.25 mmol), **5-2a** (0.50 mmol), cat. (0.0375 mmol), base (0.50 mmol), THF: MeOH=9:1 (1.0 mL). ^b Isolated yield of **5-8a**. ^c Determined *via* ¹H NMR analysis of unpurified reaction mixtures. ^d Reaction run at 70°C with 0.125 mmol of acetic acid. ^e 0.125 mmol of acetic acid added. ^f DCM was used instead of THF. ^g Toluene was used instead of THF.

5.3 Conclusion

In summary, we were delighted to observe that the chemselectivity of enolate to homoenolate reaction could be successfully controlled by a simple acetic acid additive. Various enals and chalcones could be converted to δ -lactones in good yield with excellent control of diastereo- and enantioselectivity. It is observed that the enolate/homoenolate selectivity was sensitive to the bulkness as well as electric feature of substituents on the enals and enone substrates. At this stage, efforts on other electrophiles, such as isatins and nitrostyrenes, could lead to stereo-control of product generated from homoenolate intermediate. The enolate additions of enals to these substrates catalyzed by *N*-heterocyclic carbene are still not successful.

5.4 Experimental Section

General Information

Commercially available materials were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker AV400 (400 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AV400 (400 MHz) (100 MHz) spectrometers. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *ee* was performed by chiral phase HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 0.5 mL cell with a 10 mm path length on a PerkinElmer Model 341 digital polarimeter and are reported as follows: $[\alpha]_{\text{D}}^{\text{rt}}$ (*c* in mmol per mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

General procedure for the synthesis of **5-3**:

A dry 10 mL Schlenk tube equipped with a stir magnetic bar was successively charged with chalcone **5-1a** (52 mg, 0.25 mmol), enal **5-2a** (81 mg, 0.5 mmol), NHC pre-catalyst **Cat. 6** (18.4 mg, 0.05 mmol), KOAc (61.4 mg, 0.625 mmol) and 4Å MS (100 mg). The tube was closed with a septum, evacuated, and refilled with nitrogen. To this mixture was added freshly distilled THF (0.5 mL), followed by AcOH (7.2 μL , 0.0625 mmol). The

reaction mixture was stirred at RT for 24 h. After complete consumption of **5-1a**, as indicated by TLC and crude ^1H NMR analysis, the solvent was removed under reduced pressure. The resulting residue was purified *via* column chromatography on silica gel with hexanes/ethyl acetate (10:1) as eluent to afford product **5-3a** as a white solid in 86% yield (79.6 mg), 20:1 dr and 99% *ee*.

Similar procedure was used in the reactions with isatins **5-6** and β -nitrostyrenes **5-8**. The spectra of obtained product **5-7** and **5-8** were in correspondence to those in literature.¹¹

Note: The corresponding racemic products for chiral HPLC method development were prepared using the above method in presence of Cat. **5**. In most cases, this catalyst gave products with lower dr than the use of chiral NHC Cat. **6**.

Stereochemistry determination *via* X-ray crystallographic analysis:

Good quality crystal of **5-3c** (colorless flaky crystal) was obtained by vaporization of a hexane/ethyl acetate solution of compound **5-3c**. CCDC 870337 contains the supplementary crystallographic data.

Characterization Data

(3*S*,4*S*)-3-(4-Methoxybenzyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3a):

White solid, 80 mg; $[\alpha]_D^{23}$ (c 1.13, CH_2Cl_2) = +252; ^1H NMR (400 MHz, CDCl_3) δ = 2.38 (dd, J = 14.8, 9.2 Hz, 1H), 3.21 (dd, J = 14.4, 5.2 Hz, 1H), 3.33 (ddd, J = 9.2, 7.2, 5.2 Hz, 1H), 3.66 (t, J = 6.8 Hz, 1H), 3.79 (s, 3H), 6.02 (d, J = 6.8 Hz, 1H), 6.84–6.87 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.09–7.11 (m, 2H), 7.25–7.40 (m, 6H), 7.64–7.66 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 170.3, 158.3, 150.0, 137.9, 132.2, 130.6, 130.0, 129.2, 129.0, 128.6, 128.5, 127.8, 124.7, 114.0, 105.2, 55.3, 45.8, 40.8, 31.5; HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{O}_3(\text{M}+\text{H})^+$: 371.1647, Found: 371.1640; >99% *ee* (3*S*, 4*S*)- isomer as

determined by HPLC (Chiralcel OD, 99.9:0.1 hexanes/i-PrOH, 0.7 mL/min), t_r (major) = 169.3 min, t_r (minor) = 147.3 min.

(3*S*,4*S*)-3-(2-Methoxybenzyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3b):

White solid, 82 mg; $[\alpha]_D^{23}$ (c 1.72, CH_2Cl_2) = +234; ^1H NMR (400 MHz, CDCl_3) δ = 2.50 (dd, J = 14.4, 8.4 Hz, 1H), 3.19 (dd, J = 14.4, 5.6 Hz, 1H), 3.55–3.57 (m, 1H), 3.65 (t, J = 6.8 Hz, 1H), 3.80 (s, 3H), 6.03 (d, J = 6.8 Hz, 1H), 6.84–6.88 (m, 2H), 6.98 (dd, J = 7.2, 1.6 Hz, 1H), 7.14–7.16 (m, 2H), 7.20–7.39 (m, 7H), 7.64–7.67 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 170.7, 157.7, 149.8, 138.4, 132.4, 131.7, 129.1, 128.9, 128.5, 128.5, 127.9, 127.7, 126.8, 124.6, 120.3, 110.1, 105.4, 55.2, 43.4, 41.3, 28.4; HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{O}_3(\text{M}+\text{H})^+$: 371.1647, Found: 371.1649; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel IA, 99.9:0.1 hexanes/i-PrOH, 0.7 mL/min), t_r (major) = 83.0 min, t_r (minor) = 77.3 min.

(3*S*,4*S*)-3-(4-Bromobenzyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3c):

White solid, 76 mg; $[\alpha]_D^{23}$ (*c* 1.96, CH₂Cl₂) = +237; ¹H NMR (400 MHz, CDCl₃) δ = 2.42 (dd, *J* = 14.8, 9.2 Hz, 1H), 3.18 (dd, *J* = 14.8, 5.6 Hz, 1H), 3.34 (ddd, *J* = 8.8, 6.8, 5.6 Hz, 1H), 3.65 (t, *J* = 6.8 Hz, 1H), 6.03 (d, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.07–7.10 (m, 2H), 7.29–7.44 (m, 8H), 7.64–7.66 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 169.9, 150.0, 137.7, 137.6, 132.0, 131.6, 130.8, 129.3, 129.1, 128.6, 128.4, 128.0, 124.7, 120.4, 105.0, 45.5, 41.0, 32.0; HRMS(ESI) calcd for C₂₄H₂₀O₂Br(M+H)⁺: 419.0647, Found: 419.0642; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OJ-H, 92:8 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 98.0 min, *t_r* (minor) = 79.0 min.

(3*S*,4*S*)-3-(2-Bromobenzyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3d):

White solid, 86 mg; $[\alpha]_D^{23}$ (*c* 0.78, CH₂Cl₂) = +204; ¹H NMR (400 MHz, CDCl₃) δ = 2.74 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.08 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.48–3.53 (m, 1H), 3.82 (t, *J* = 6.8 Hz, 1H), 6.06 (d, *J* = 6.8 Hz, 1H), 7.07–7.11 (m, 1H), 7.20–7.24 (m, 4H), 7.31–7.39 (m, 6H), 7.53 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.64–7.66 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.0, 150.0, 138.4, 138.0, 132.8, 132.4, 132.1, 129.2, 129.1, 128.6, 128.4, 127.9, 127.3, 124.7, 104.9, 44.0, 42.1, 33.8; HRMS(ESI) calcd for C₂₄H₂₀O₂Br(M+H)⁺: 419.0647, Found: 419.0645; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OD, 99.9:0.1 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 45.7 min, *t_r* (minor) = 58.3 min.

(3*S*,4*S*)-3-(4-(Dimethylamino)benzyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3e):

yellow oil, 77 mg; $[\alpha]_D^{23}$ (*c* 1.2, CH₂Cl₂) = +193; ¹H NMR (400 MHz, CDCl₃) δ = 2.33 (dd, *J* = 14.8, 9.6 Hz, 1H), 2.93 (s, 6H), 3.20 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.31 (ddd, *J* = 9.6, 6.8, 4.8 Hz, 1H), 3.67 (t, *J* = 6.8 Hz, 1H), 6.02 (d, *J* = 6.8 Hz, 1H), 6.70 (dd, *J* = 6.8, 2.0 Hz, 2H), 6.99 (d, *J* = 2.0 Hz, 2H), 7.10–7.13 (m, 2H), 7.24–7.39 (m, 6H), 7.64–7.66 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.5, 149.9, 149.4, 138.0, 132.3, 129.7, 129.1, 128.9, 128.6, 127.7, 126.3, 124.7, 112.9, 105.5, 46.0, 40.8, 40.6, 31.2; HRMS(ESI) calcd for C₂₆H₂₆NO₂(M+H)⁺: 384.1964, Found: 384.1967; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OJ-H, 95:5 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 353.3 min, *t_r* (minor) = 294.0 min.

(3*S*,4*S*)-3-(Naphthalen-2-ylmethyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3f):

White solid, 82 mg; $[\alpha]_D^{23}$ (*c* 1.64, CH₂Cl₂) = +252; ¹H NMR (400 MHz, CDCl₃) δ = 2.61 (dd, *J* = 14.4, 9.2 Hz, 1H), 3.44–3.52 (m, 2H), 3.66 (t, *J* = 6.8 Hz, 1H), 6.02 (d, *J* =

6.8 Hz, 1H), 7.09–7.11 (m, 2H), 7.25–7.40 (m, 7H), 7.45–7.49 (m, 2H), 7.53 (s, 1H), 7.65–7.67 (m, 2H), 7.76–7.84 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ = 170.2, 150.0, 137.8, 136.0, 133.5, 132.3, 123.2, 129.2, 129.0, 128.6, 128.5, 128.3, 127.9, 127.7, 127.6, 127.5, 127.2, 126.2, 125.6, 124.7, 105.2, 45.6, 40.8, 32.5; HRMS(ESI) calcd for $\text{C}_{28}\text{H}_{23}\text{O}_2(\text{M}+\text{H})^+$: 391.1698, Found: 391.1699; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OJ-H, 92:8 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 241.2 min, t_r (minor) = 150.1 min.

(3*S*,4*S*)-3-(Furan-2-ylmethyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3g):

Yellow oil, 56 mg; $[\alpha]_D^{23}$ (*c* 0.95, CH_2Cl_2) = +263; ^1H NMR (400 MHz, CDCl_3) δ = 2.48 (dd, J = 16.0, 9.6 Hz, 1H), 3.23 (dd, J = 16.0, 4.8 Hz, 1H), 3.46–3.50 (m, 1H), 3.76 (t, J = 6.8 Hz, 1H), 6.04 (d, J = 3.2 Hz, 1H), 6.07 (d, J = 6.8 Hz, 1H), 6.33 (dd, J = 2.8, 1.6 Hz, 1H), 7.13–7.15 (m, 2H), 7.27–7.42 (m, 7H), 7.66–7.68 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 170.0, 152.5, 150.3, 141.5, 137.4, 132.1, 129.2, 129.0, 128.6, 128.5, 127.9, 124.7, 110.4, 107.1, 105.0, 43.3, 40.8, 25.2; HRMS(ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{O}_3(\text{M}+\text{H})^+$: 331.1334, Found: 331.1337; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OD, 99.5:0.5 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 38.8 min, t_r (minor) = 34.6 min.

(3*S*,4*S*)-3-Benzyl-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3h):

White solid, 75 mg; $[\alpha]_D^{23}$ (*c* 1.5, CH₂Cl₂) = +238; ¹H NMR (400 MHz, CDCl₃) δ = 2.44 (dd, *J* = 14.8, 9.6 Hz, 1H), 3.29 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.39 (ddd, *J* = 9.2, 7.2, 5.2 Hz, 1H), 3.66 (t, *J* = 6.8 Hz, 1H), 6.03 (d, *J* = 6.8 Hz, 1H), 7.09–7.14 (m, 4H), 7.24–7.40 (m, 9H), 7.64–7.67 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.2, 150.0, 138.7, 137.8, 132.2, 129.2, 129.0, 128.9, 128.6, 128.5, 127.8, 126.6, 124.7, 105.2, 45.7, 40.8, 32.3; HRMS(ESI) calcd for C₂₄H₂₁O₂(M+H)⁺: 341.1542, Found: 341.1539; >99% *ee* (3*S*, 4*S*)-isomer as determined by HPLC (Chiralcel OD, 99.9: 0.1 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 69.7 min, *t_r* (minor) = 87.9 min.

(3*S*,4*S*)-3-Hexyl-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3i):

White solid, 69 mg; $[\alpha]_D^{23}$ (*c* 1.61, CH₂Cl₂) = +206; ¹H NMR (400 MHz, CDCl₃) δ = 0.86 (t, *J* = 6.8 Hz, 3H), 1.18–1.29 (m, 9H), 1.38–1.73 (m, 1H), 2.93 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.82 (t, *J* = 6.8 Hz, 1H), 6.07 (d, *J* = 6.8 Hz, 1H), 7.16–7.18 (m, 2H), 7.26–7.41 (m, 6H), 7.66–7.69 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.6, 150.2, 138.1, 132.3, 129.1, 128.9, 128.6, 128.2, 127.7, 124.7, 104.8, 44.3, 41.5, 31.6, 29.1, 27.3, 26.5, 22.6, 14.1; HRMS(ESI) calcd for C₂₃H₂₇O₂(M+H)⁺: 335.2011, Found: 335.2010; >99% *ee* (3*S*,

4*S*)- isomer as determined by HPLC (Chiralcel OD, 99.9:0.1 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 36.7 min, t_r (minor) = 67.4 min.

(3*S*,4*S*)-3-Butyl-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (5-3j):

White solid, 59 mg; $[\alpha]_D^{23}$ (c 2.07, CH₂Cl₂) = +225; ¹H NMR (400 MHz, CDCl₃) δ = 0.87 (t, J = 7.2 Hz, 3H), 1.25–1.44 (m, 5H), 1.71–1.74 (m, 1H), 2.93 (dd, J = 14.0, 6.8 Hz, 1H), 3.83 (t, J = 6.8 Hz, 1H), 6.07 (d, J = 6.8 Hz, 1H), 7.16–7.18 (m, 2H), 7.27–7.42 (m, 6H), 7.67–7.69 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.6, 150.2, 132.3, 129.1, 128.9, 128.5, 128.2, 127.7, 124.7, 104.8, 44.3, 41.5, 29.5, 26.2, 22.5, 13.9; HRMS(ESI) calcd for C₂₁H₂₃O₂(M+H)⁺: 307.1698, Found: 307.1702; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OD, 99.9:0.1 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 35.6 min, t_r (minor) = 56.7 min.

(3*S*,4*S*)-3-(4-Methoxybenzyl)-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (5-3k):

Yellow oil, 78 mg; $[\alpha]_D^{23}$ (*c* 2.25, CH₂Cl₂) = +225; ¹H NMR (400 MHz, CDCl₃) δ = 2.39 (dd, *J* = 14.8, 9.2 Hz, 1H), 3.21 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.30 (ddd, *J* = 9.2, 6.8, 5.2 Hz, 1H), 3.61 (t, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 6.01 (d, *J* = 6.8 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 4H), 6.99–7.06 (m, 4H), 7.34–7.40 (m, 3H), 7.64–7.66 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.4, 159.2, 158.2, 149.8, 132.3, 130.6, 130.0, 129.7, 129.5, 129.1, 128.5, 124.6, 114.3, 113.9, 105.6, 55.3, 46.0, 39.9, 31.4; HRMS(ESI) calcd for C₂₆H₂₅O₄(M+H)⁺: 401.1753, Found: 401.1755; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel IA, 99.5:0.5 hexanes/*i*-PrOH, 0.7 mL/min), *t*_r(major) = 176.7 min, *t*_r(minor) = 321.1 min.

(3*S*,4*S*)-3-(4-Methoxybenzyl)-6-phenyl-4-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (5-3l):

White solid, 80 mg; $[\alpha]_D^{23}$ (*c* 1.51, CH₂Cl₂) = +247; ¹H NMR (400 MHz, CDCl₃) δ = 2.34 (s, 3H), 2.39 (dd, *J* = 14.8, 9.2 Hz, 1H), 3.20 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.30 (ddd, *J* = 9.2, 7.2, 5.2 Hz, 1H), 3.62 (t, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 6.01 (d, *J* = 6.8 Hz, 1H), 6.83–6.87 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.34–7.40 (m, 3H), 7.63–7.66 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.4, 158.2, 149.8, 137.5, 134.7, 132.2, 130.7, 130.0, 129.6, 129.1, 128.5, 128.3, 124.6, 113.9, 105.5, 55.3, 45.9, 40.3, 31.4, 21.1; HRMS(ESI) calcd for C₂₆H₂₅O₃(M+H)⁺: 385.1804, Found: 385.1801; >99% (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OD-H, 99:1 hexanes/*i*-PrOH, 0.7 mL/min), *t*_r(major) = 47.2 min, *t*_r(minor) = 63.8 min.

(3*S*,4*S*)-3-(4-Methoxybenzyl)-6-phenyl-4-(*o*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (5-3m):

White solid, 47 mg; $[\alpha]_D^{23}$ (*c* 1.22, CH₂Cl₂) = +223; ¹H NMR (400 MHz, CDCl₃) δ = 2.05 (s, 3H), 2.53 (dd, *J* = 13.2, 8.0 Hz, 1H), 3.26–3.36 (m, 2H), 3.78 (s, 3H), 3.93 (t, *J* = 6.8 Hz, 1H), 5.92 (d, *J* = 6.8 Hz, 1H), 6.77–6.80 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.11–7.20 (m, 4H), 7.32–7.38 (m, 3H), 7.60–7.63 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.9, 158.3, 149.4, 137.0, 135.9, 132.4, 130.8, 130.4, 129.8, 129.0, 128.5, 127.3, 127.1, 124.6, 114.0, 104.3, 55.3, 44.6, 35.7, 31.5, 19.6; HRMS(ESI) calcd for C₂₆H₂₅O₃(M+H)⁺: 385.1804, Found: 385.1805; 99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel IA, 98:2 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 53.4 min, *t_r* (minor) = 35.0 min.

(3*S*,4*S*)-4-(4-Chlorophenyl)-3-(4-methoxybenzyl)-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (5-3n):

White solid, 67 mg; $[\alpha]_D^{23}$ (c 1.25, CH₂Cl₂) = +267; ¹H NMR (400 MHz, CDCl₃) δ = 2.35 (dd, J = 14.8, 9.6 Hz, 1H), 3.23 (dd, J = 14.8, 5.2 Hz, 1H), 3.34 (ddd, J = 9.6, 6.8, 5.2 Hz, 1H), 3.64 (t, J = 6.8 Hz, 1H), 3.81 (s, 3H), 5.99 (d, J = 6.8 Hz, 1H), 6.84–6.87 (m, 2H), 7.00–7.04 (m, 4H), 7.27–7.30 (m, 2H), 7.36–7.40 (m, 3H), 7.64–7.66 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.0, 158.3, 150.3, 136.4, 133.7, 132.0, 130.2, 129.9, 129.8, 129.3, 129.1, 128.6, 124.7, 114.0, 104.7, 55.3, 45.5, 40.0, 31.4; HRMS(ESI) calcd for C₂₅H₂₂O₃Cl(M+H)⁺: 405.1257, Found: 405.1262; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OD, 99:1 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 59.6 min, t_r (minor) = 81.5 min.

(3*S*,4*S*)-3-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (5-3o):

White solid, 70 mg; $[\alpha]_D^{23}$ (c 0.51, CH₂Cl₂) = +204; ¹H NMR (400 MHz, CDCl₃) δ = 2.37 (dd, J = 14.8, 9.2 Hz, 1H), 3.19 (dd, J = 14.8, 5.2 Hz, 1H), 3.31 (ddd, J = 9.2, 6.8, 5.2 Hz, 1H), 3.63 (t, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 5.88 (d, J = 6.8 Hz, 1H), 6.83–6.90 (m, 4H), 7.02–7.10 (m, 4H), 7.25–7.33 (m, 3H), 7.58 (dd, J = 6.8, 2.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.5, 160.4, 158.2, 149.8, 138.2, 130.6, 130.0, 129.4, 128.9, 128.5, 127.7, 126.1, 124.8, 114.3, 113.9, 103.4, 55.4, 55.3, 45.9, 40.7, 31.5; HRMS(ESI) calcd for C₂₆H₂₅O₄(M+H)⁺: 401.1753, Found: 401.1758; >99% *ee* (3*S*, 4*S*)-

isomer as determined by HPLC (Chiralcel OD, 99.5:0.5 hexanes/i-PrOH, 0.7 mL/min), t_r (major) = 117.1 min, t_r (minor) = 188.5 min.

(3*S*,4*S*)-3-(4-Methoxybenzyl)-4-phenyl-6-(p-tolyl)-3,4-dihydro-2*H*-pyran-2-one (5-3p):

White solid, 70 mg; $[\alpha]_D^{23}$ (c 1.14, CH_2Cl_2) = +211; ^1H NMR (400 MHz, CDCl_3) δ = 2.34–2.40 (m, 4H), 3.20 (dd, J = 14.8, 5.2 Hz, 1H), 3.32 (ddd, J = 9.2, 6.8, 5.2 Hz, 1H), 3.64 (t, J = 6.8 Hz, 1H), 3.79 (s, 3H), 5.97 (d, J = 6.8 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.09 (dd, J = 8.0, 1.6 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.28–7.34 (m, 3H), 7.54 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 170.4, 158.3, 150.1, 139.2, 138.1, 130.6, 130.0, 129.4, 129.2, 128.9, 128.5, 127.8, 124.6, 113.9, 104.3, 55.3, 45.9, 40.7, 31.5, 21.3; HRMS(ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{O}_3(\text{M}+\text{H})^+$: 385.1804, Found: 385.1805; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel IA, 98:2 hexanes/i-PrOH, 0.7 mL/min), t_r (major) = 114.2 min, t_r (minor) = 68.5 min.

(3*S*,4*S*)-6-(4-Chlorophenyl)-3-(4-methoxybenzyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (5-3q):

White solid, 76 mg (75% yield); $[\alpha]_{\text{D}}^{23}$ (*c* 1.45, CH₂Cl₂) = +212; ¹H NMR (400 MHz, CDCl₃) δ = 2.38 (dd, *J* = 14.8, 9.2 Hz, 1H), 3.20 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.32 (ddd, *J* = 9.6, 7.2, 5.2 Hz, 1H), 3.66 (t, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 6.01 (d, *J* = 6.8 Hz, 1H), 6.85 (dd, *J* = 11.2, 2.8 Hz, 2H), 7.02–7.09 (m, 4H), 7.27–7.36 (m, 5H), 7.56–7.59 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.0, 158.3, 149.1, 137.7, 135.1, 130.7, 130.4, 130.0, 129.0, 128.8, 128.4, 127.9, 126.0, 114.0, 105.7, 55.3, 45.8, 40.8, 31.4; HRMS(ESI) calcd for C₂₅H₂₂O₃Cl(M+H)⁺: 405.1257, Found: 405.1253; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel IA, 99:1 hexanes/*i*-PrOH, 0.7 mL/min), *t_r* (major) = 168.6 min, *t_r* (minor) = 76.2 min.

(3*S*,4*S*)-6-(Furan-2-yl)-3-(4-methoxybenzyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (5-3r):

White solid, 53 mg; $[\alpha]_{\text{D}}^{23}$ (*c* 1.10, CH₂Cl₂) = +179; ¹H NMR (400 MHz, CDCl₃) δ = 2.37 (dd, *J* = 14.8, 9.2 Hz, 1H), 3.19 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.33 (ddd, *J* = 9.2, 6.8,

5.2 Hz, 1H), 3.63 (t, $J = 6.8$ Hz, 1H), 3.81 (s, 3H), 5.88 (d, $J = 6.8$ Hz, 1H), 6.83–6.85 (m, 2H), 7.01–7.04 (m, 3H), 7.09 (dd, $J = 8.0, 1.6$ Hz, 2H), 7.27–7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 169.8, 158.3, 145.9, 137.8, 135.8, 130.4, 130.0, 129.0, 128.4, 127.9, 127.6, 125.8, 124.8, 114.0, 104.3, 55.3, 45.9, 40.8, 31.5$; HRMS(ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{O}_4(\text{M}+\text{H})^+$: 361.1440, Found: 361.1429; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel OD, 99.5:0.5 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 82.1 min, t_r (minor) = 98.5 min.

(3*S*,4*S*)-4-(4-Bromophenyl)-3-(4-methoxybenzyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (5-3s):

White solid, 81 mg; $[\alpha]_{\text{D}}^{23}$ (c 1.85, CH_2Cl_2) = +219; ^1H NMR (400 MHz, CDCl_3) $\delta = 2.31\text{--}2.39$ (m, 4H), 3.22 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.33 (ddd, $J = 9.2, 6.8, 5.2$ Hz, 1H), 3.61 (t, $J = 6.8$ Hz, 1H), 3.81 (s, 3H), 5.93 (d, $J = 6.8$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.95 (dd, $J = 6.8, 1.6$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.44 (dd, $J = 6.8, 1.6$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 170.0, 158.4, 150.4, 139.4, 137.1, 132.0, 130.2, 130.1, 129.9, 129.3, 129.2, 124.6, 121.7, 114.0, 103.7, 55.3, 45.5, 40.1, 31.4, 21.3$; HRMS(ESI) calcd for $\text{C}_{26}\text{H}_{24}\text{O}_3\text{Br}(\text{M}+\text{H})^+$: 463.0909, Found: 463.0910; >99% *ee* (3*S*, 4*S*)- isomer as determined by HPLC (Chiralcel IA, 95:5 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 67.7 min, t_r (minor) = 37.2 min.

5.5 References

- (1) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis*, **2012**, *44*, 2295-2309.
- (2) (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420; (b) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A* **2010**, *107*, 20661-20665.
- (3) Nair, V.; Paul, R. R.; Lakshmi, K. C. S.; Menon, R. S.; Jose, A.; Sinu, C. R. *Tetrahedron Lett.* **2011**, *52*, 5992-5994.
- (4) Fang, X. Q.; Chen, X. K.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708-4711.
- (5) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418-2439.
- (6) For the use of weak acidic condition in NHC catalysis, see: (a) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628-13630; (b) Enders, D.; Grossmann, A.; Huang, H.; Raabe, G. *Eur. J. Org. Chem.* **2011**, 4298-4301; (c) Jacobsen, C. B.; Jensen, K. L.; Udmark, J.; Jorgensen, K. A. *Org. Lett.* **2011**, *13*, 4790-4793; (d) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835-1838; (e) DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 2391- 2394.
- (7) For protonation of the enal β -carbons leading to acyl azolium intermediate for self-redox formations of esters/amides/acids, see: (a) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873-3876; (b) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905-908; (c) Zeitler, K. *Org. Lett.* **2006**, *8*, 637-640; (d) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798-13799; (e) Maki, B. E.; Patterson, E. V.; Cramer, C. J.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 3942-3945.
- (8) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736-8737.
- (9) CCDC 870337 contains the supplementary crystallographic data for **5-3c**.

(10) Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E. *Org. Lett.* **2009**, *11*, 5570-5573.

(11) For reaction with isatins, see: Sun, L.; Shen, L.; Ye, S. *Chem. Commun.* **2011**, *47*, 10136-10138. For reactions with β -nitrostyrenes, see: Maji, B.; Ji, L.; Wang, S.; Vedachalam, S.; Ganguly, R.; Liu, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 8276-8280.