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Activation of Aldehydes via Oxidative N-Heterocyclic Carbene Catalysis

MO JUNMING

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Activation of Aldehydes via Oxidative N-Heterocyclic Carbene Catalysis

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TABLE OF CONTENT

LIST OF ABBREVIATIONS

^{1}H NMR	proton nuclear magnetic resonance
^{13}C NMR	carbon-13 nuclear magnetic resonance
Ar	Aryl
Bu	Butyl
Cat.	Catalyst
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIEA	Ethyldiisopropylamine
DMAP	4-dimethylamiopryidine
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
Et	Ethyl
HRMS	high resolution mass spectrometry
Me	Methyl
Mes	mesitylene
NHC	N-heterocyclic carbene
Ph	phenyl
R	arbitrary substituent
rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl
J	coupling constant(s)
m/z	mass per charge ratio

Min	minute(s)
mg	milligram(s)
mmol	millimole
mol%	mole percent
ppm	parts per million
Equiv	equivalent(s)

LIST OF PUBLICATION

1. Direct *β*-Activation of Saturated Aldehydes to Formal Michael Acceptors through Oxidative NHC Catalysis

   Junming Mo, Liang Shen, Yonggui Robin Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8588-8591.

2. Direct *α*-Functionalization of Simple Aldehydes via Oxidative N-Heterocyclic Carbene Catalysis

   Junming Mo, Ruojie Yang, Xingkuan Chen, Bhoopendra Tiwari, Yonggui Robin Chi, *Org. Lett.* **2013**, *15*, 50-53.

3. Highly Enantioselective Addition of Enals to Isatin-Derived Ketimines Catalyzed by N-Heterocyclic Carbenes: Synthesis of Spirocyclic γ-Lactams

   Hui Lv, Bhoopendra Tiwari, **Junming Mo**, Chong Xing, Yonggui Robin Chi, *Org. Lett.* **2012**, *14*, 5412-5415.

4. Oxidative *γ*-Addition of Enals to Trifluoromethyl Ketones: Enantioselectivity Control via Lewis Acid/N-Heterocyclic Carbene Cooperative Catalysis

   Junming Mo, Xingkuan Chen, Yonggui Robin, *J. Am. Chem. Soc.* **2012**, *134*, 8810-8813.

5. Formal Diels–Alder Reactions of Chalcones and Formylcyclopropanes Catalyzed by Chiral N-Heterocyclic Carbenes

   Hui Lv, **Junming Mo**, Xinqiang Fang, Yonggui Robin Chi, *Org. Lett.* **2011**, *13*, 5366-5369.

Abstract

My Ph.D research mainly focuses on developing new reactions and synthetic methods via oxidative N-Heterocyclic Carbene catalysis. This thesis contains four major parts:

Chapter 1 gives a brief introduction to history and present development of NHC catalysis, and shows the challenges in NHC catalysis need to be overcome.

Chapter 2 discloses the first example of enolate equivalents generated from cleavage of C-C bond promoted by NHC catalysts. The innovative cyclolization of enolate equivalents with chalcones is investigated.

Chapter 3 describes the oxidative NHC-catalyzed direct β-activation of simple saturated aldehydes. The oxidation of enolate intermediate in NHC catalysis is realized at the first time.

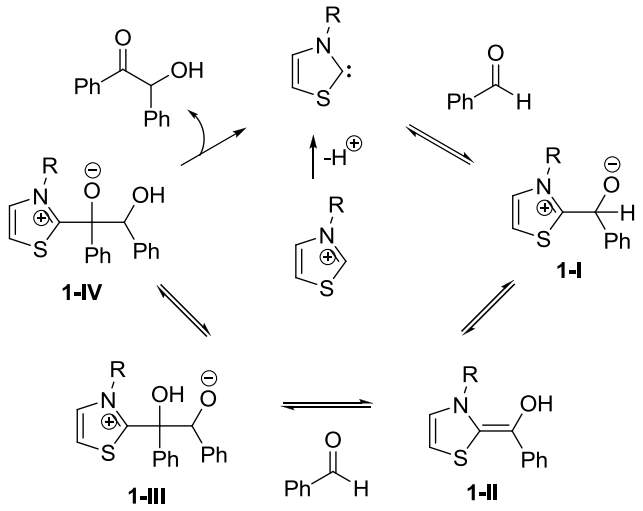
Chapter 4 introduces the γ-activation of β-methyl cinnamaldehyde mediated by NHC. Vinyl enolate intermediate generated from deprotonation of α,β-unsaturated acyl azolium reacts with activated ketone to offer δ-lactone. Challenging enantioselective control is realized by Lewis acid/NHC co-operative catalysis.

Chapter 1

Introduction

1.1 N-Heterocyclic carbene (NHC) catalysis

Wöhler and Liebig discovered the coupling of benzaldehyde to benzoin catalyzed by cyanide in 1832.[1] In 1943, Ugai and coworkers realized this benzoin condensation with thiazolium salts as catalysts.[2] Fifteen years later, Breslow proposed a carbene (thiazolin-2-ylidene) catalytic model mechanism for the thiazolium salt-catalyzed benzoin condensation (Scheme 1.1).[3] In Breslow's mechanism, the thiazolium salt is deprotonated to form a carbene, the actual catalytic species. Nucleophilic addition of the carbene to benzaldehyde gives an adduct **1-I**. This adduct undergoes deprotonation/protonation to generate Breslow intermediate **1-II**, which is the most important key intermediate in NHC catalysis. Breslow intermediate reacts with another benzaldehyde molecule, and eventually gives the benzoin product. From then on, many different types of NHC-catalyzed reaction have been developed, and the advantages of NHC catalysis are revealed gradually.[4]



Scheme 1.1 Mechanism of NHC-catalyzed benzoin reaction

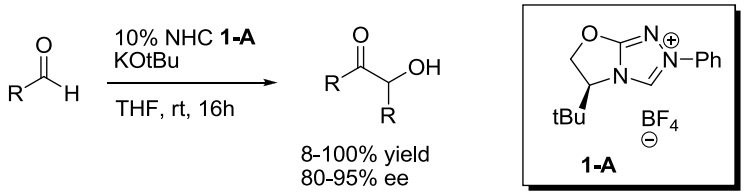
Until now, NHCs usually are used to activate carbonyl compounds, which are among the most commonly used substrates in organic synthesis. According to the activation sites, NHC catalysis could be categorized into four groups: (1) carbonyl carbon activation; (2) α-carbon activation; (3) β-carbon activation; and (4) γ-carbon activation.

1.2 NHC-catalyzed carbonyl carbon activation

NHC-catalyzed carbonyl carbon activation is well-developed research field in NHC catalysis. It contains benzoin condensation, Stetter reaction and transesterification reaction.

1.2.1 NHC-catalyzed benzoin condensation

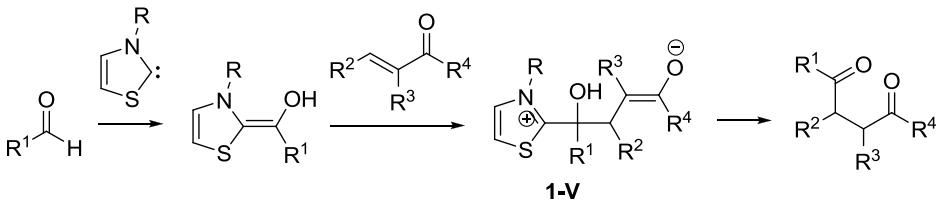
As a powerful strategy for C-C bond formation, benzoin condensation is widely used in organic synthesis. Benzoin condensation was discovered by Wöhler and Liebig in 1832.[1] In 1966, the first enantioselective version of benzoin condensation was reported by Sheehan and Hunneman.[5] However, Sheehan and Hunneman's protocol with a chiral thiazolium NHC as a catalyst only gave very low enantiomeric excess of the benzoin product (~22% ee). After this early study many attempts of achieving highly yield and enantiomeric excess were reported. In 2002, Enders reported a highly enantioselective aromatic benzoin condensation (Scheme 1.2). A new triazolium NHC **1-A**, derived from (*S*)-*tert*-leucine, was applied to produce excellent ee value.[6]



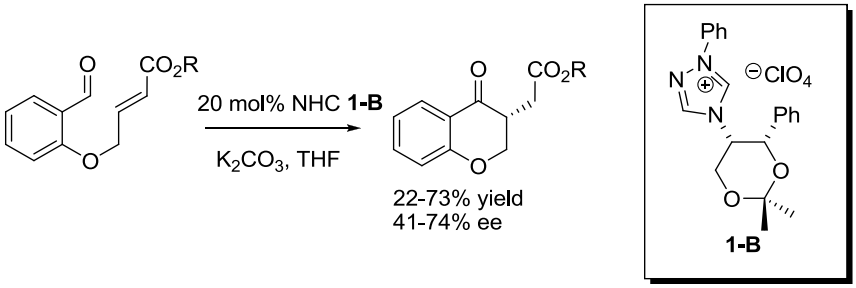
Scheme 1.2 highly enantioselective aromatic benzoin condensation

1.2.2 NHC-catalyzed Stetter reaction

Stetter reaction is NHC-catalyzed nucleophilic acylation to Michael acceptors.[7] It is a powerful strategy to access 1,4-dicarbonyl compounds and related derivatives. The mechanism is shown below (Scheme 1.3). Similar to benzoin condensation, nucleophilic addition of Breslow intermediate to a Michael acceptor gives an dduct **1-V**. This adduct undergoes deprotonation/protonation to generate Stetter product. The first racemic Stetter reaction catalyzed by thiazolium NHC was reported in 1976.[8] Several years later, Enders group did the first attempt of Stetter reaction with a chiral thiazolium NHC as a catalyst. However, only 4% yield of the product with an enantiomeric excess of 39% was obtained. In 1996, Enders group found that a modified triazolium NHC shows good catalytic activity and enantioselectivity in intramolecular Stetter reaction (Scheme 1.4).[9] Inspired by Enders' work, several new types of triazolium NHC were successfully applied in enantioselective intermolecular Stetter reaction in the last decade.[10]



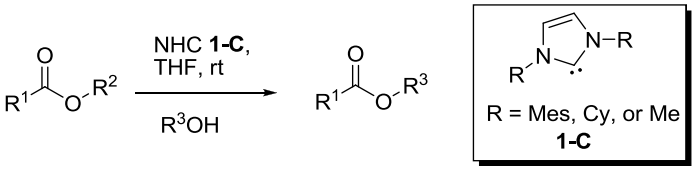
Scheme 1.3 Mechanism of Stetter reaction



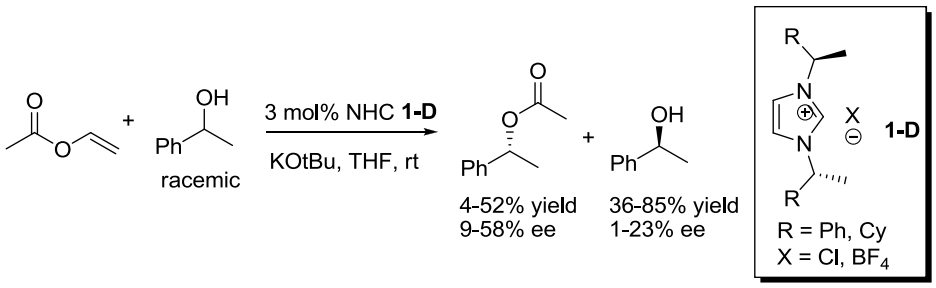
Scheme 1.4 Asymmetric intramolecular Stetter reaction

1.2.3 NHC-catalyzed transesterification reaction

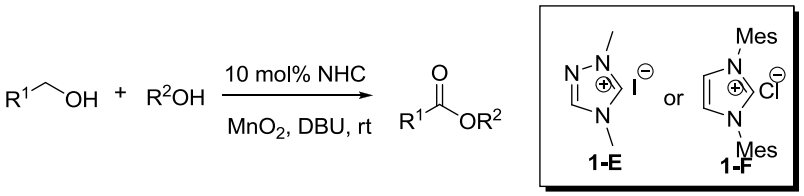
The first NHC-catalyzed transesterification was reported in 2002 by Nolan and Hedrick independently (Scheme 1.5).[11] After that, different types of transesterification and corresponding applications were investigated by many groups. In 2004, Suzuki reported the first carbene-catalyzed kinetic resolution of secondary alcohols (Scheme 1.6).[12] By employing a chiral imidazolium NHC catalyst, low to good ee values of the products could be obtained. In 2007, Scheidt reported the first oxidative NHC-catalyzed transesterification (Scheme 1.7).[13] In this conversion, an allylic alcohol is oxidized to an aldehyde first, and then Breslow intermediate is oxidized to an acyl azolium intermediate. The acyl azolium intermediate reacts with an alcohol to give the ester product.



Scheme 1.5 NHC promoted transesterification by Nolan and Hedrick



Scheme 1.6 NHC promoted kinetic resolution by Suzuki



Scheme 1.7 NHC promoted oxidative transesterification by Scheidt

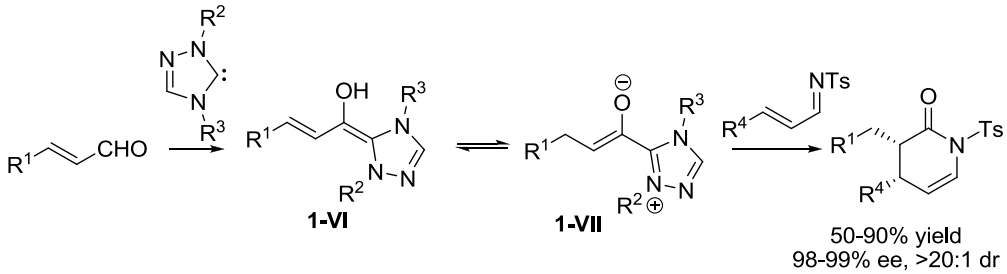
1.3 NHC-catalyzed *α*-carbon activation

Until now, all of NHC-catalyzed *α*-carbon activation reactions of carbonyl compounds go through an enolate intermediate to react with substrates. The Enolate intermediate is usually derived from five major types of carbonyl compound: (1) *α,β*-unsaturated aldehydes; (2) *α*-substituted aldehydes; (3) ketenes; (4) esters; and (5) saturated aldehydes.

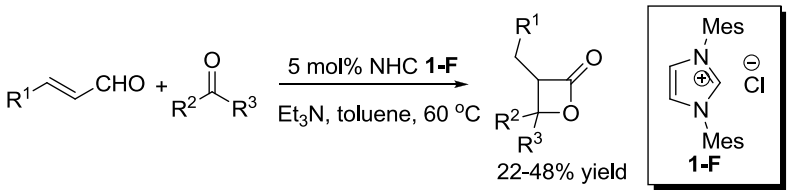
1.3.1 NHC-catalyzed *α*-carbon activation of *α,β*-unsaturated aldehydes

In 2006, almost simultaneously Glorius and Bode reported NHC-catalyzed *α*-functionalization of enals (Scheme 1.8 & 1.9).[14] Formal Diels-Alder reaction between enals and *α,β*-unsaturated imines produced lactam products with good yield and highly enantioselectivity. The key step of the reaction mechanism is proton transfer or deprotonation/protonation between the hydroxyl group and the

β-carbon. After that, several examples of enolate reactions of enals with different substrates were disclosed by various groups.[15]



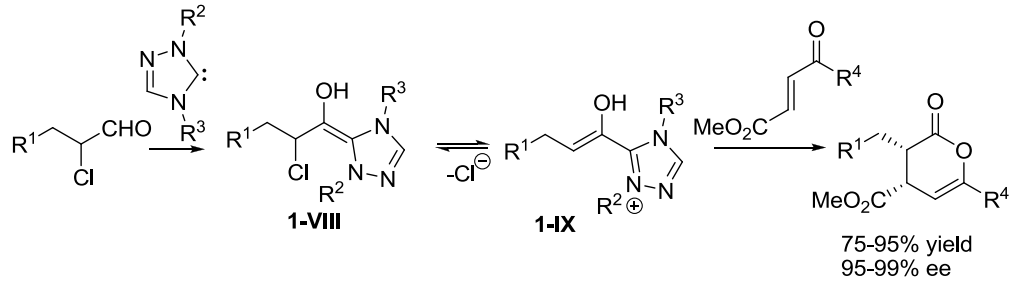
Scheme 1.8 Enolate intermediates from enals by Bode



Scheme 1.9 Enolate intermediates from enals by Glorius

1.3.2 NHC-catalyzed *α*-carbon activation of *α*-substituted aldehydes

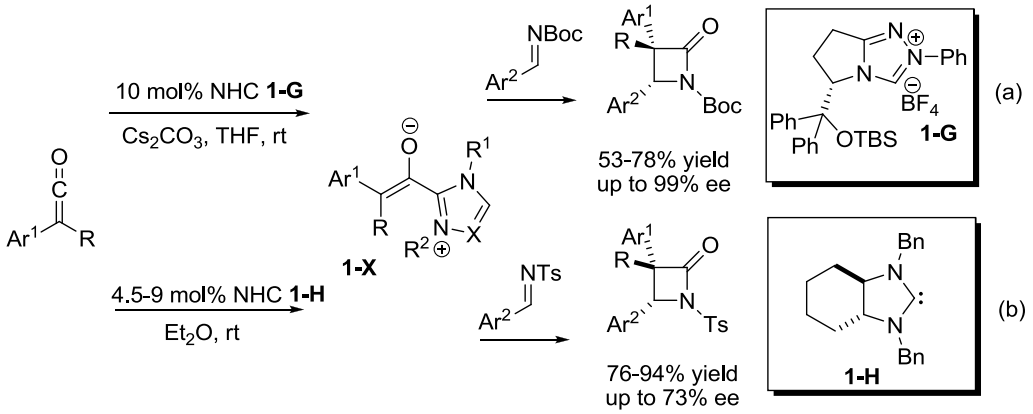
In 2006, Bode group reported NHC-catalyzed Diels-Alder reaction using *α*-chloro aldehydes as enolate precursors. The reaction mechanism is illustrated in Scheme 1.10.[16] After forming Breslow intermediate **1-VIII**, chloride ion leaves through self-redox process. Other *α*-prefunctionalized aldehyde derivatives, such as *α*-aryloxy acetaldehydes[17] and *α*-aroyloxy aldehydes,[18] were also reported as enolate precursors.



Scheme 1.10 Enolate intermediates from *α*-chloro aldehydes by Bode

1.3.3 NHC-catalyzed *α*-carbon activation of ketenes

An enolate intermediate derived from ketene under NHC catalysis was disclosed by Ye (a, Scheme 1.11) and Smith (b, Scheme 1.11) independently in 2008.[19] Their works show that triazolium NHCs are efficient catalysts for Staudinger reaction of ketenes with N-substituted imines. In the reaction, nucleophilic addition of NHC with ketene forms enolate intermediate directly.

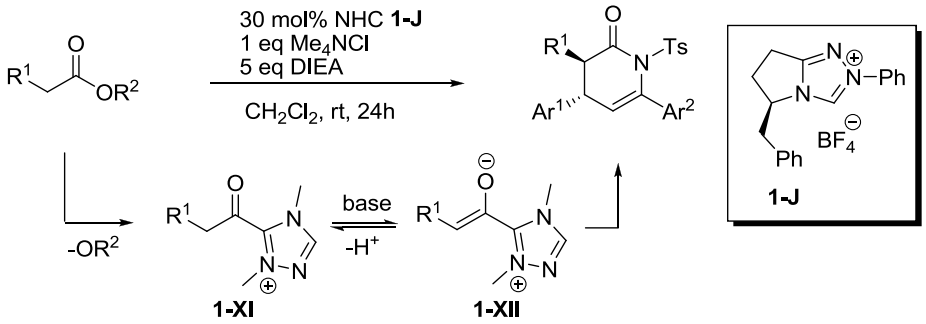


Scheme 1.11 Enolate intermediates from ketenes by Ye and Smith

1.3.4 NHC-catalyzed *α*-carbon activation of esters

The first example of NHC-catalyzed enantioselective activation of carboxylic

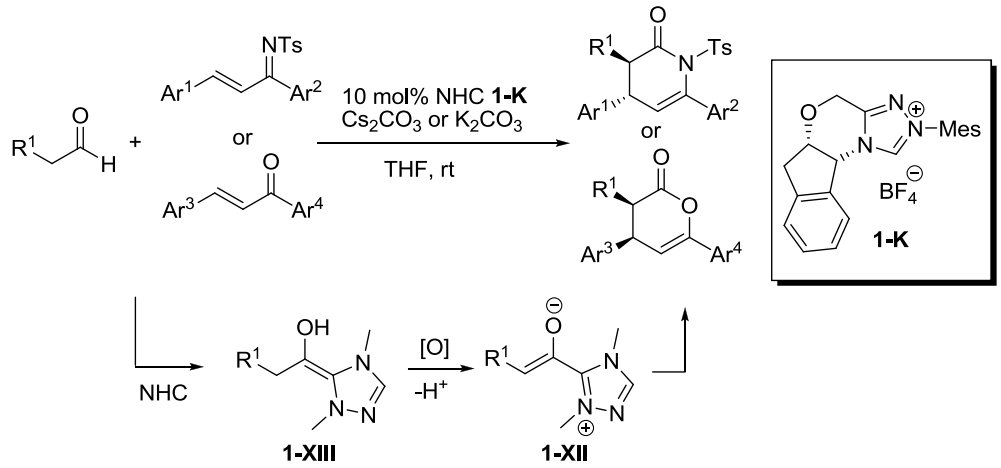
acid esters as enolate equivalents was reported by our group in 2012.[20] Compared to other enolate precursors mentioned above, esters are more stable and readily available. The proposed mechanism is illustrated in Scheme 1.12. NHC catalyst reacts with a stable ester bearing a good leaving group to form acyl azolium intermediate **1-XI**. Through deprotonation step, the acyl azolium intermediate **1-XI** transforms to the key enolate intermediate **1-XII**, which can react with electrophiles.



Scheme 1.12 NHC-catalyzed generating enolate intermediates from stable esters

1.3.5 NHC-catalyzed *α*-carbon activation of saturated aldehydes

In recent years, Rovis and our groups independently developed direct *α*-functionalization of simple saturated aldehydes under NHC-catalyzed oxidation.[21] The key enolate intermediate **1-XII** is generated by oxidation of Breslow intermediate **1-XIII** followed by *α*-deprotonation. Both aliphatic and aromatic substituted aldehydes could be used as effective substrates in this transformation (Scheme 1.13).



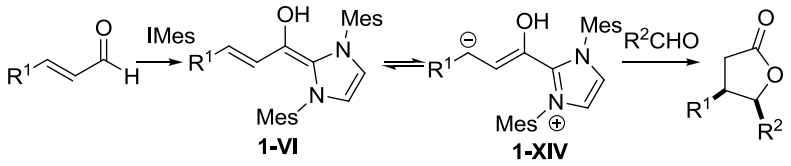
Scheme 1.13 NHC-catalyzed *α*-carbon activation of saturated aldehydes by Rovis and our group

1.4 NHC-catalyzed *β*-carbon activation

NHC-catalyzed *β*-carbon activation of carbonyl compounds contains two major types of reaction: (1) homoenolate type reaction (carbonyl compounds as nucleophile); and (2) formal Michael type reaction (carbonyl compounds as electrophile).

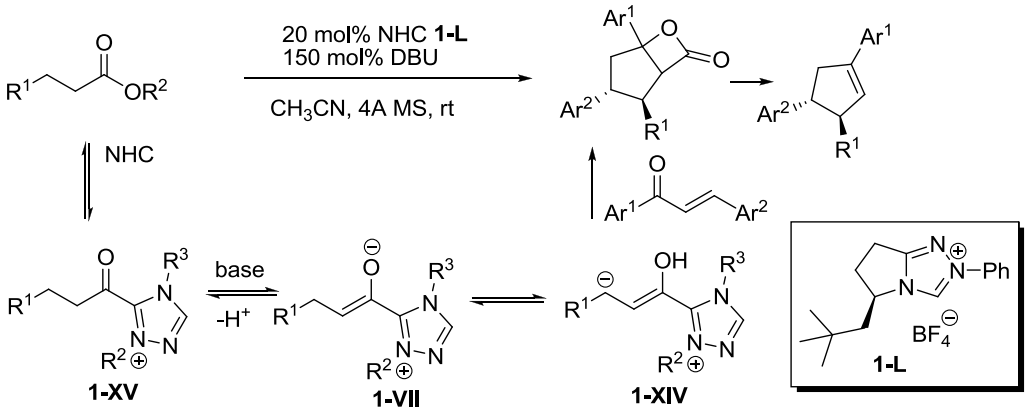
1.4.1 NHC-catalyzed generation of homoenolate

NHC-catalyzed generation of homoenolate from *α,β*-unsaturated aldehydes was disclosed by Bode and Glorius independently in 2004 (Scheme 1.14).[22] An enal reacts with an NHC catalysts to form Breslow intermediate **1-VI**, which is then transformed into an NHC-bounded homoenolate equivalent **1-XIV**. The nucleophilic carbanion generated under mild and convenient reaction conditions can react with electrophilic aldehydes. Later, various types of electrophile for homoenolate reaction were investigated by many research groups.[23]



Scheme 1.14 NHC-catalyzed homoenolate reaction by Glorius and Bode

Last year, our group reported an innovative generation of homoenolate from saturated carboxylic acid esters under NHC catalysis (Scheme 1.15).[24] Nucleophilic attack of the NHC catalyst on the carboxylic ester gives an acyl azolium adduct **1-XV**, which can afford an enolate intermediate **1-VII** through deprotonation. The enolate intermediate **1-VII** is transformed to a homoenolate **1-XIV** via *β*-deprotonation, which represents the key step of the transformation.

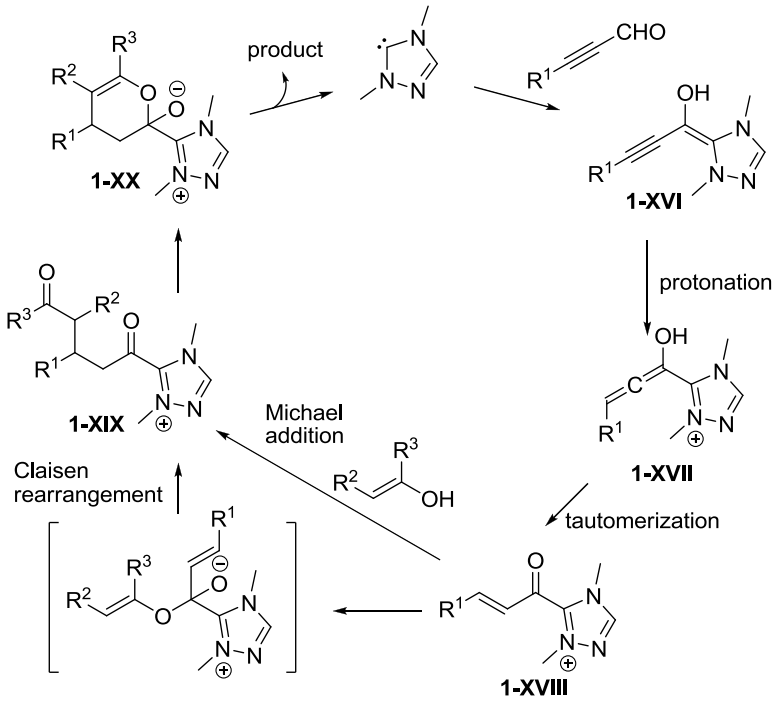


Scheme 1.15 NHC-catalyzed homoenolate generated from saturated esters

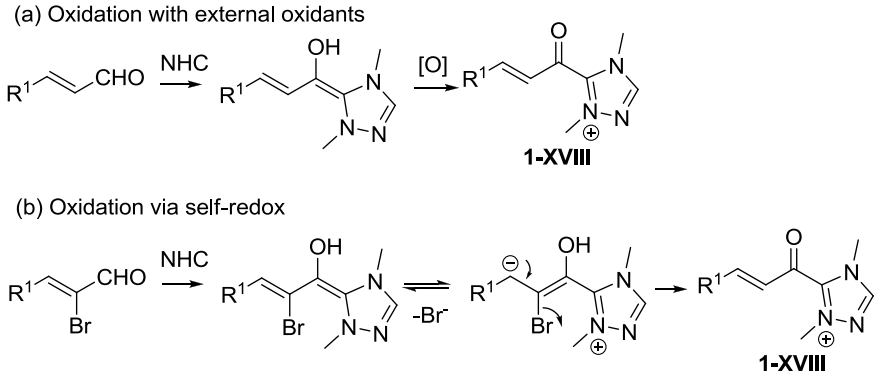
1.4.2 NHC-catalyzed generation of formal Michael acceptors

In 2010, Bode reported the first *α,β*-unsaturated acyl azolium derived from

alkynyl aldehydes as formal Michael acceptors under NHC catalysis.[25] Breslow intermediate **1-XVI** affords an *α,β*-unsaturated acyl azolium **1-XVIII** via *β*-protonation and sequential tautomerization (Scheme 1.16). In the same year, generation of formal Michael acceptors from *α,β*-unsaturated aldehydes under oxidative NHC catalysis was disclosed by Studer (a, Scheme 1.17).[26a] Oxidation of Breslow intermediate gives the same *α,β*-unsaturated acyl azolium intermediate **1-XVIII**. The active intermediate **1-XVIII** can react with a nucleophile to form C-C bond at *β*-position.[26] Furthermore, *α*-bromo enals could also be used as acyl azolium precursors (b, Scheme 1.17).[26g] There are two possible mechanisms for the formation of C-C bond. Studer proposed that the new C-C bond at the *β*-position is formed by direct Michael addition. However, in Bode's paper, a mechanism involving Claisen rearrangement is preferred.



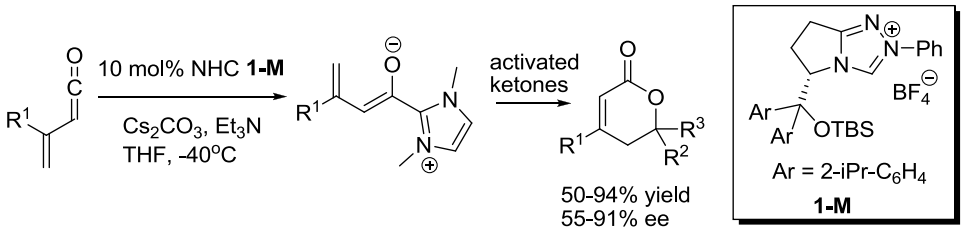
Scheme 1.16 NHC-catalyzed alkynyl aldehydes as formal Michael acceptors



Scheme 1.17 Acyl azolium intermediates generated from enals

1.5 NHC-catalyzed *γ*-carbon activation

Recently, Ye group developed NHC-catalyzed enantioselective *γ*-activation of *α,β*-unsaturated ketenes.[27] Dienolate equivalents, obtained directly by nucleophilic addition of NHC with ketene, can react with electrophiles (isatins and trifluoromethyl ketones) to form formal Diels-Alder products. Enantioselective control at such a remote position is still challenging.



Scheme 1.18 NHC-catalyzed *γ*-activation of vinyl ketenes

1.6 Future challenges

In the last two decades, many successful and efficient organic synthetic methods under NHC catalysis were developed as mentioned above. However, several challenges still remain. First, compared to C-H bond activation, examples of C-C bond activation under NHC catalysis are still limited. Also, simple non-functionalized aliphatic aldehydes, as an important class of basic building blocks in organic synthesis, are still underdeveloped except for benzoin and Stetter reaction. Furthermore, remote control of enantioselectivity still needs to be investigated.

1.7 References

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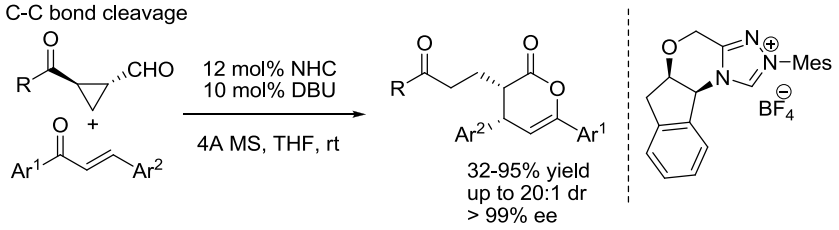
Chapter 2

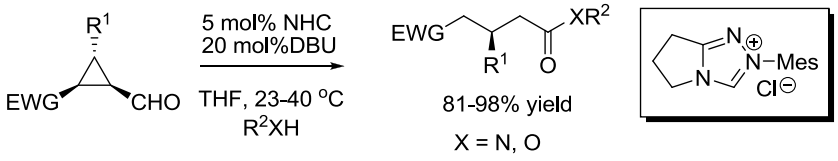
NHC-catalyzed Self-redox α-activation of Formylcyclopropanes



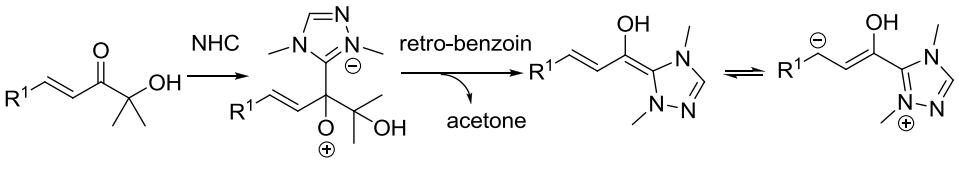
2.1 Introduction

2.1.1 NHC-catalyzed C-C bond activation

Carbon-carbon bond cleavage catalyzed by NHCs was reported by Bode firstly in 2006 (Scheme 2.1).[1a] NHC-bounded activated carboxylate esters generated by NHC-mediated self-redox ring-opening of formylcyclopropanes were trapped by alcohols or amines to afford corresponding carboxylic esters or amides. Since this report, this ring-opening strategy has been applied to heterocycle synthesis through intra- or intermolecular trapping of NHC-bounded ester intermediates by several groups.[1] In 2009, Bode disclosed C-C bond cleavage of *α'*-hydroxyenones through NHC-catalyzed retro-benzoin condensation (Scheme 2.2).[2] The homoenolate intermediates were trapped by activated enones to form cyclopentenes, and *α,β*-unsaturated acyl azolium intermediates could be trapped by amine to give corresponding amides. Until now, there has been no report on trapping enolate intermediates generated by NHC-catalyzed self-redox activation of C-C bond.



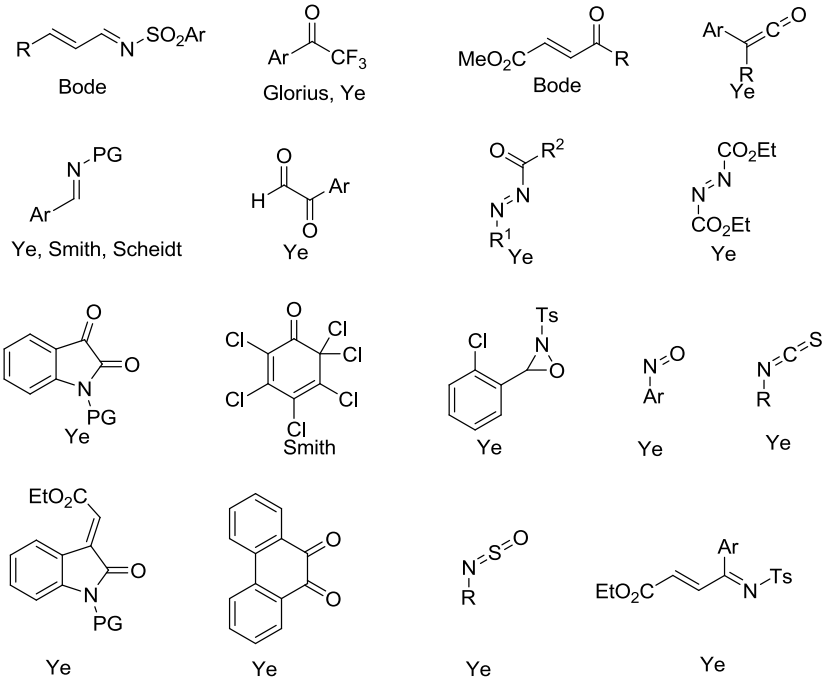
Scheme 2.1 Ring-opening under NHC catalysis



Scheme 2.2 C-C bond cleavage via NHC-catalyzed retro-benzoin condensation

2.1.2 NHC-catalyzed generation of enolates

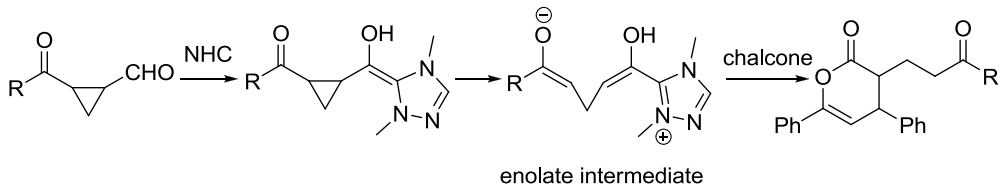
Carbon-carbon bond formation via reaction of activated enolate equivalents with electrophiles under asymmetric organocatalysis is a powerful strategy for α-functionalization of carbonyl compounds. Ketenes have been widely used as enolate precursors catalyzed by cinchona alkaloids,[3] chiral DMAP derivatives,[4] and chiral NHCs.[5] Because of relative unstability of ketene, development of other approaches to enolate equivalents is desired. In the last decade, the use of α,β-unsaturated aldehydes[6] and α-heteroatom substituted aldehydes[7] as enolate precursors has been successfully achieved under NHC catalysis. These NHC-bounded nucleophilic enolates intermediates can react with activated electrophiles, such as trifluoromethyl ketones, α,β-unsaturated N-sulfonylimines, and ketoenones et al., to form various products (Scheme 2.3). However, the reaction of NHC-bounded nucleophilic enolates with simple chalcones, relatively inert electrophiles, is underdeveloped.



Scheme 2.3 Common electrophiles for enolates reaction

2.1.3 Our proposal

As mentioned in the earlier section, trapping of an enolate intermediates, which is generated by NHC-catalyzed self-redox activation of a C-C bond, is still challenging. Compared to the retro-benzoin reaction of *α'*-hydroxyenones that generate an enolate intermediate indirectly via deprotonation/protonation of an *α,β*-unsaturated acyl azolium intermediate, NHC-mediated ring-opening of a formylcyclopropane can afford an enolate intermediate directly. Therefore, we plan to investigate ring-opening of formylcyclopropanes as enolate precursors in the presence of NHC catalysts. The reaction of this new type of enolate equivalent with chalcone is also studied (Scheme 2.4).



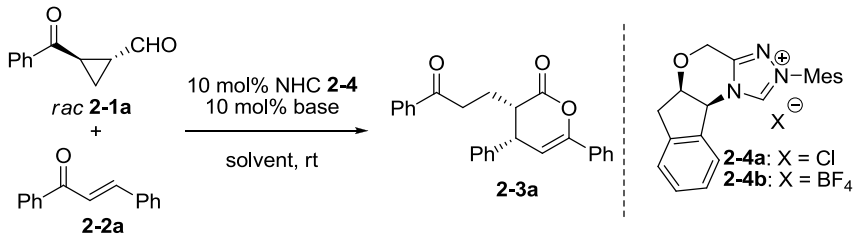
Scheme 2.4 Enolate intermediate from ring-opening of formylcyclopropanes: project hypothesis

2.2 Results and discussion

The results of optimization of conditions for the model reaction between formylcyclopropane **2-1a** and chalcone **2-2a** are summarized in Table 2.1. We initially carried out this reaction using 10% triazolium NHC **2-4a** as the precatalyst and 30% DBU as a base in 1 mL THF (Table 2.1, entry 1). Fortunately, a

hetero-Diels-Alder product **2-3a** was obtained with 68% yield but poor dr (Table 2.1, entry 1). Encouraged by the proof of principle, we started optimization of the reaction conditions. Reduction of the amount of DBU base from 30% to 10% led to a high dr without loss of the yield. This result indicated that low dr was mainly caused by the base (DBU)-induced post-reaction epimerization of **2-3a** at the α-carbon next to the ester group. A carboxylic acid generated in the course of trapping pathway was detected as a side product. To suppress the side reaction, a slight excess amount of formylcyclopropane **2-1a** (1.2 to 1.5 equiv) was used, which eventually led to higher yields. Further screenings of solvents revealed that the use of THF as the solvent gave the best results in terms of both yield and stereoselectivities (Table 2.1, entries 3-4). After obtaining the optimal solvent, we next examined the effect of different bases (Table 2.1, entries 5-8). The reaction with DBU as the base provided the best yield and good dr. Weaker bases such as NMM and DAMP afforded products with high dr but low yields. The use of 4A MS, which could suppress the side reaction, led to a notable drop of dr (Table 2.1, entry 10). Finally, screening of NHC precursors shared, compared to the NHC precursor (**2-4a**) with Cl^-, the NHC precursor with counter anion BF_4^- (**2-4b**) could consistently afford the product with high yield and dr (Table 2.1, entry 11-12). The counter anion effect had been discussed before.[8]

Table 2.1 Optimization of cyclolization of aldehyde **2-1a** with chalcone **2-2a**



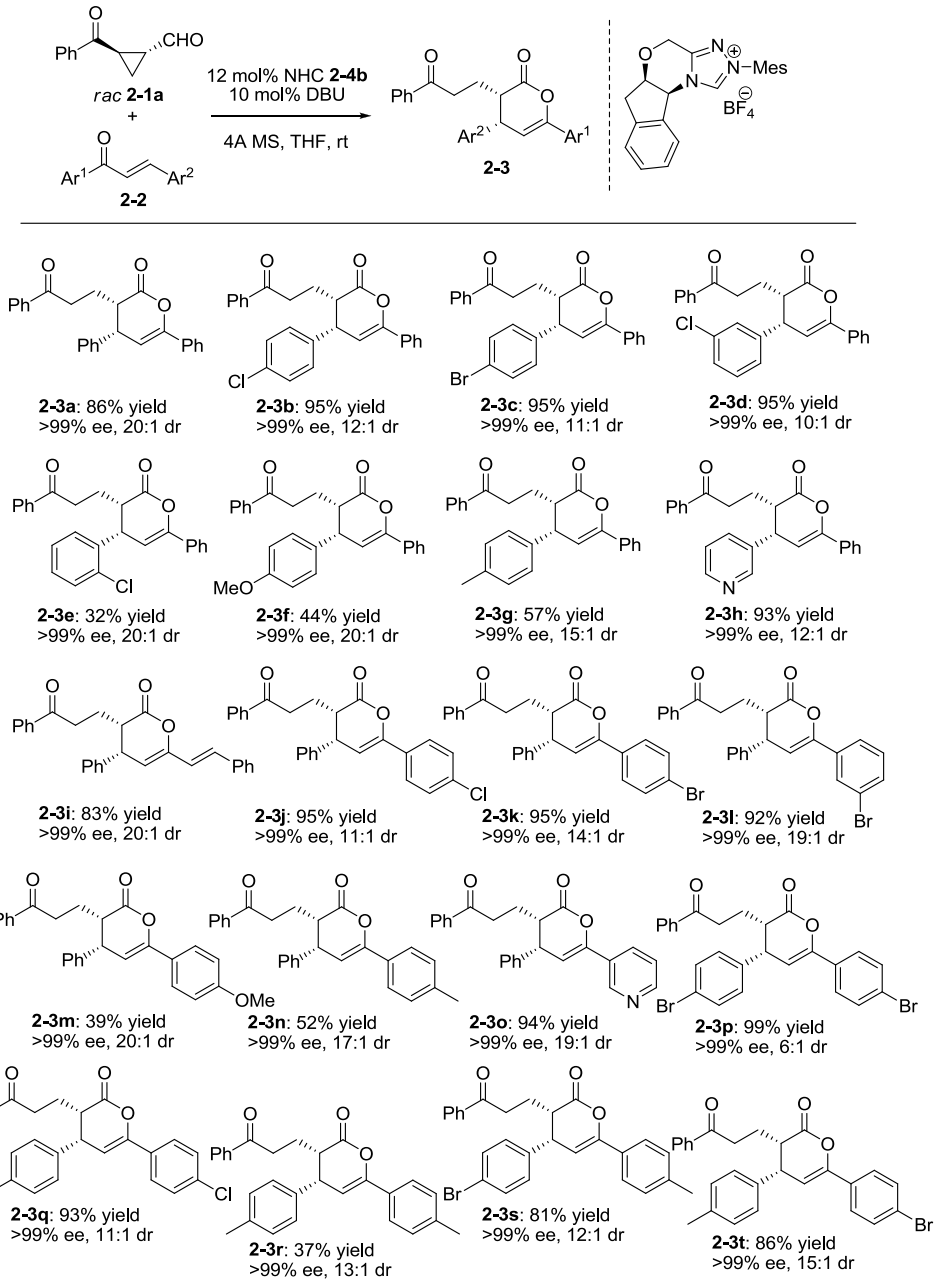
Entry[a]	NHC	condition	Yield (%)[b]	dr[c]	ee (%)[d]
1	**2-4a**	DBU (30 mol%), THF	68	2:3	>99
2	**2-4a**	DBU, THF	68	14:1	>99
3	**2-4a**	DBU, toluene	39	12:1	>99
4	**2-4a**	DBU, DCM	52	4:1	>99
5	**2-4a**	KO^{t}Bu, THF	50	16:1	>99
6	**2-4a**	Cs_2CO_3, THF	28	12:1	>99
7	**2-4a**	NMM, THF	12	>20:1	>99
8	**2-4a**	DMAP, THF	20	>20:1	>99
9[e]	**2-4a**	DBU, THF	83	13:1	>99
10[e]	**2-4a**	DBU, THF, 4A MS	93	4:1	>99
11[e]	**2-4b** (12 mol%)	DBU, THF, 4A MS	81	>20:1	>99
12[f]	**2-4b** (12 mol%)	DBU, THF, 4A MS	86	>20:1	>99

[a] General condition: 0.24 mmol **2-1a**, 0.2 mmol **2-2a**, 10 mol% NHC **2-4**, 10 mol% base, 1 mL solvent, 2-3 h. [b] Isolated yield based on **2-2a**. [c] Determined via crude ^{1}H NMR analysis. [d] Determined via chiral-phase HPLC analysis. [e] 0.3 mmol **2-1a**. [f] 0.3 mmol **2-1a** was added in two portions.

With the optimized conditions (Table 2.1, entry 12) in hand, the scope of substituted chalcone substrates **2-2** was explored using the formylcyclopropane **2-1a** (Chart 2.1). In all cases the desired products were obtained with excellent enantioselectivity and good to excellent diastereoselectivity. The yield of the lactone product was singnificantly influenced by the electronic property of substitutent on chalcone. Good to excellent yields were achieved when electron-withdrawing substituents were installed on Ar^1 and/or Ar^2 groups (e.g., Chart 2.1, **2-3b** to **2-3d**, **2-3j** to **2-3l**, and **2-3p** to **2-3q**). Chalcones with electron-donating groups led to lower but acceptable yields (e.g., Chart 2.1, **2-3e** to

2-3g, **2-3m** and **2-3n**). Electronic properties of chalcones also affected the reaction rate. Generally, the reaction with electron-deficient chalcones completed in 5 hours; electron-rich chalcones led to slightly longer reaction times (10~24 hours). Chalcones with heteroaryl groups (Chart 2.1, **2-3h** and **2-3o**) or cinnamyl group (Chart 2.1, **2-3i**) were all tolerated.

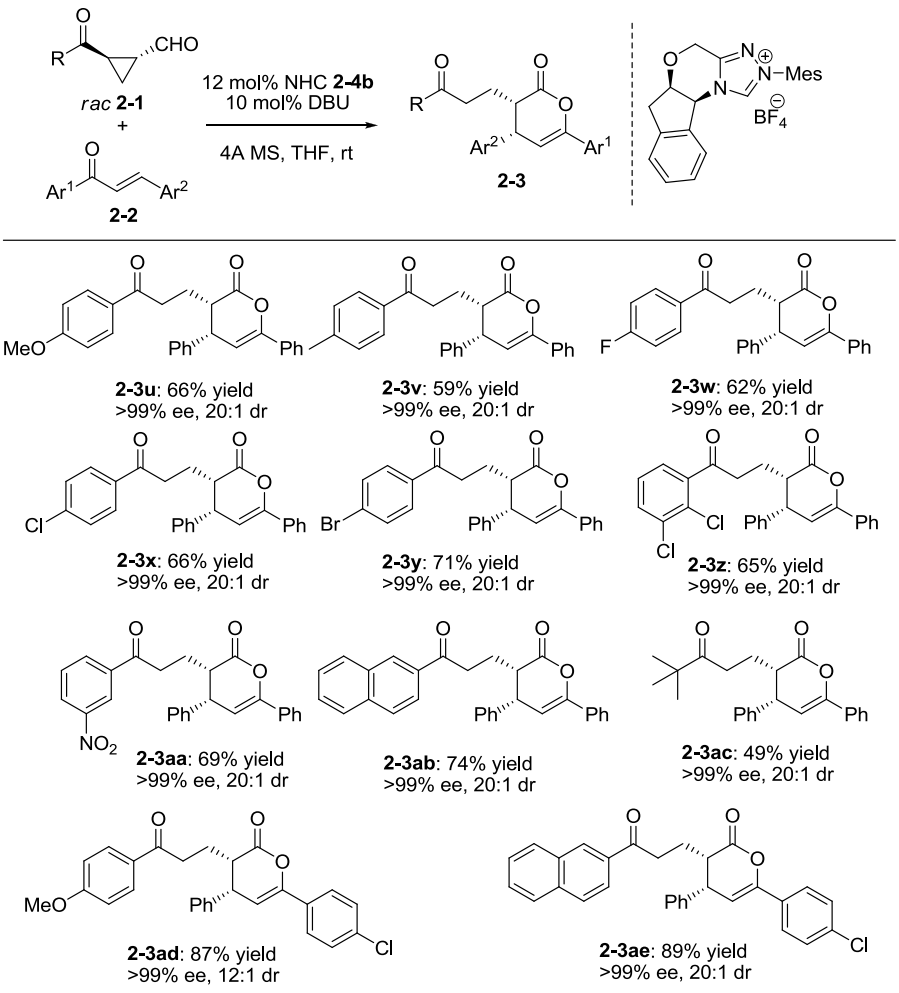
Chart 2.1 Scope of cyclization of aldehyde **2-1a** with chalcones **2-2**[a]



[a] Conditions as entry 12 in Table 2.1; reaction time: 3-24h.

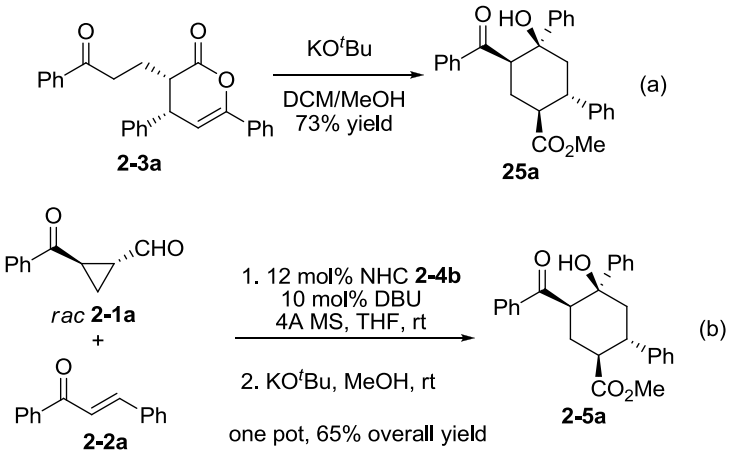
The scope of formylcyclopropanes **2-1** was also examined (Chart 2.2). The reaction yield and stereoselectivities are less sensitive to the electronic property of the aryl groups (R) of the formylcyclopropane. All of electron-withdrawing and electron-donating substituents installed on the R group led to good to excellent yields and stereoselectivities. A formylcyclopropane with bulky alkyl group (^{t}Bu) also reacted smoothly with a slightly lower yield.

Chart 2.2 Scope of aldehyde **2-1**[a]



[a] Conditions as entry 12 in Table 2.1; reaction time: 3-24h.

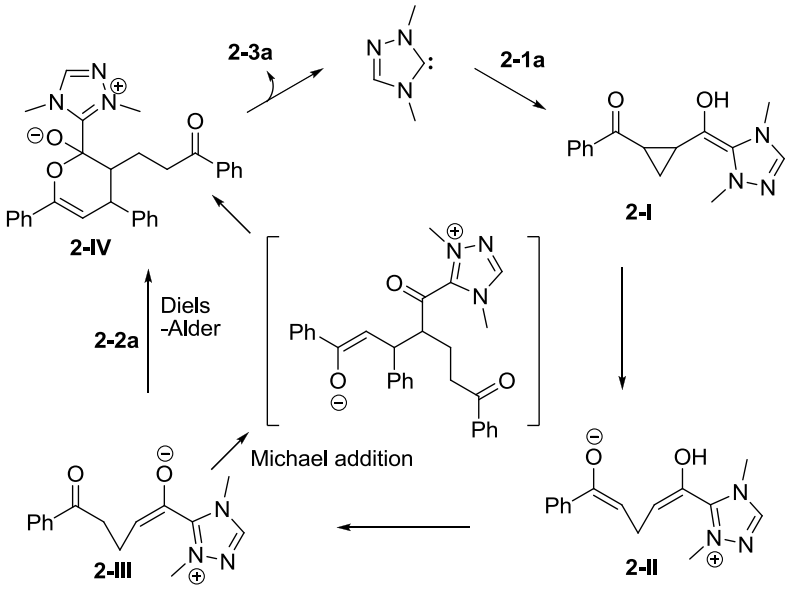
Further chemical transformation of the lactone product was also tested. The lactone product **2-3a** provided highly functionalized cyclohexane **2-5a** as a single stereoisomer in 73% isolated yield via domino transesterification/ regio- (> 9:1 regioselectivity) and stereoselective aldol reaction (a, Scheme 2.5). Additional two new chiral centers were formed with nearly complete stereo-controls in one step. A combination of the NHC catalyzed hetero-Diels-Alder reaction with transesterification and aldol reaction in one pot operation could afford the product **2-5a** in 65% overall isolated yield under unoptimized conditions (b, Scheme 2.5). In this way, the functionalized cyclohexane product **2-5a** was obtained as a formal [3+3] annulation product in a single operation with good yield and excellent stereoselectivity.



Scheme 2.5 Chemical transformation of lactone product **2-3a**

The proposed reaction mechanism is shown in Scheme 2.6. Breslow

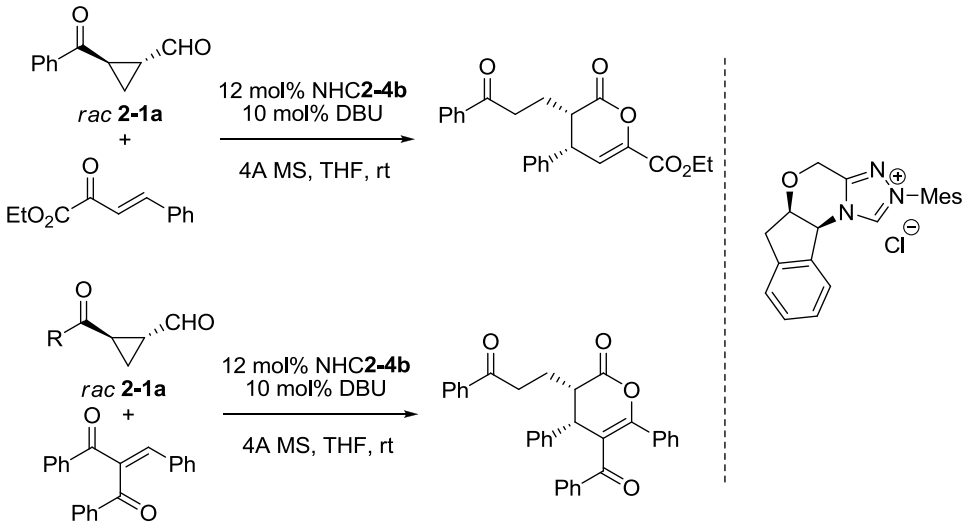
intermediate **2-I** is formed by nucleophilic addition of the NHC catalyst and aldehyde **2-1a**. The self-redox ring opening process is followed by protonation and subsequent enal-ketone tautomerization to give an enolate **2-III** as a key intermediate. Then the enolate **2-III** reacts with chalcone **2-2a** via Diels-Alder reaction to give an intermediate **2-IV** that eventually leads to the product **2-3a**. Note that, a stepwise pathway via Michael addition followed by transesterification cannot be ruled out.



Scheme 2.6 Plausible reaction pathway

Electron-deficient enones as substrates

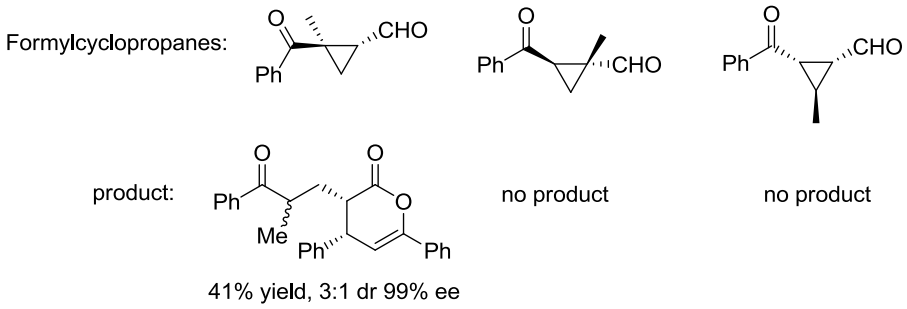
Although our purpose is to develop Diels-Alder reaction of formylclopropanes and simple chalcones, several commonly used electron-deficient enones were also investigated. We found that these electron-deficient enones are good substrates for the Diels-Alder reactions as well.



Scheme 2.7 Electron-deficient enones as substrates

Mutisubstituted formylcyclopropane as substrates.

The below formylcyclopropanes were also investigated. However, they gave the desired products in a low yield or not at all.



2.3 Conclusions

In summary, we have developed NHC-catalyzed self-redox α-activation of formylcyclopropanes to produce novel enolate intermediates. Cycloaddition of the enolate intermediates with chalcones as relatively inert oxodienes is achieved. Functionalized δ-lactone products can be obtained in good to excellent yields and

stereoselectivities. The lactone product can be transformed into a highly functionalized cyclohexane under simple conditions, which demonstratesthe synthetic utility of this methodology.

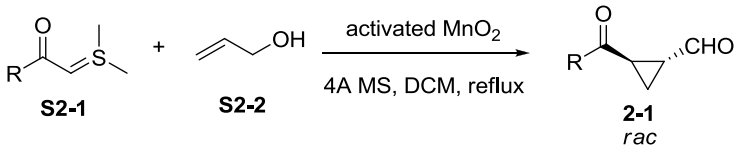
2.4 Experimental section

2.4.1 Materials and Instrumentation

Commercially available materials purchased from Alfa Aesar or Aldrich was used as received. Proton nuclear magnetic resonance (1H NMR) spectra were recorded on a Bruke AV300 (300 MHz) or Bruke AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruke AV300 (300 MHz) (75 MHz) or Bruke AV400 (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-tof Premier mass spectrometer. The determination of *e.e.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1

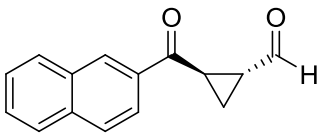
cm path length on a Jasco P1030 digital polarimeter and are reported as follows: $[\alpha]^{rt}{}_{D}$ (c in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp or potassium permanganate stain.

2.4.2 General Procedures for the Synthesis of formylcyclopropranes[9]

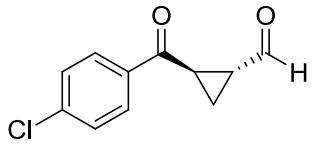


To the solution of allylic alcohol **S2-2** (5.0 mmol) in DCM (25 mL) was added 4A MS (1.0 g), **S2-1** (6.0 mmol) and activated manganese dioxide (4.35 g, 50.0 mmol). The reaction was refluxed for 2 h before cooled to room temperature. The crude mixture was filtered through celite and the residue washed with DCM (100 mL), affording a pale yellow solution. After removal of the solvent in vacuum, the brown oil residue was purified by flash column chromatography (hexanes/EtOAc = 19 / 1 – 5 / 1) to give the desired product **2-1**.

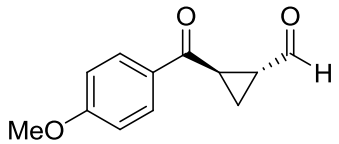
2.4.3 Characterization of Formylcyclopropranes



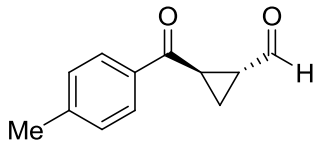
2-(2-naphthoyl)cyclopropanecarbaldehyde: Colorless solid, 73% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69-1.88 (m, 2 H), 2.71-2.76 (m, 1 H), 3.44-3.50 (m, 1 H), 7.57-7.63 (m, 2 H), 7.87-7.93 (m, 2 H), 7.97-8.05 (m, 2 H), 8.55 (s, 1 H), 9.61 (d, 1 H, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 26.2, 32.8, 123.7, 127.0, 127.8, 128.7, 128.8, 129.6, 130.2, 132.4, 134.1, 135.7, 195.9, 198.9; HRMS (ESI) calcd for $C_{15}H_{12}O_2$ $(M+H)^+$: 225.0916 Found: 225.0913.



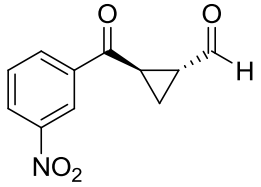
2-(4-chlorobenzoyl)cyclopropanecarbaldehyde: Light yellow oil, 57% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64-1.82 (m, 2 H), 2.65-2.70 (m, 1 H), 3.22-3.28 (m, 1 H), 7.47 (d, 2 H, *J* = 8.4 Hz), 7.94 (d, 2 H, *J* = 8.7 Hz), 9.57 (d, 1 H, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 25.9, 32.8, 129.1, 129.6, 135.1, 140.1, 195.0, 198.5; HRMS (ESI) calcd for $C_{11}H_9O_2ClNa$ $(M+Na)^+$: 231.0189 Found: 231.0195.



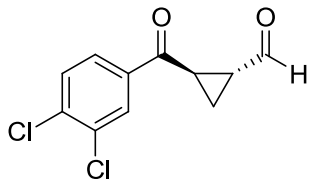
2-(4-methoxybenzoyl)cyclopropanecarbaldehyde: Light yellow oil, 79% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61-1.79 (m, 2 H), 2.60-2.65 (m, 1 H), 3.22-3.29 (m, 1 H), 3.88 (s, 3 H), 6.96 (dd, 2 H, J_1 = 1.8 Hz, J_2 = 8.7 Hz), 7.99 (dd, 2 H, J_1 = 1.8 Hz, J_2 = 8.7 Hz), 9.52 (d, 1 H, *J* = 3.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 25.6, 32.6, 55.5, 113.9, 129.8, 130.5, 163.9, 194.3, 198.9; HRMS (ESI) calcd for $C_{12}H_{13}O_3$ $(M+H)^+$: 205.0865 Found: 205.0869.



2-(4-methylbenzoyl)cyclopropanecarbaldehyde: Light yellow oil, 50% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62-1.79 (m, 2 H), 2.43 (s, 3 H), 2.61-2.66 (m, 1 H), 3.25-3.31 (m, 1 H), 7.28 (d, 2 H, *J* = 8.1 Hz), 7.90 (d, 2 H, *J* = 8.4 Hz), 9.52 (d, 1 H, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 21.6, 25.8, 32.7, 128.3, 129.4, 134.3, 144.5, 195.6, 198.8; HRMS (ESI) calcd for $C_{12}H_{13}O_2$ $(M+H)^+$: 189.0916 Found: 189.0917.

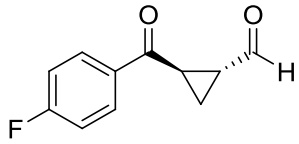


2-(3-nitrobenzoyl)cyclopropanecarbaldehyde: Light yellow oil, 12% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74-1.88 (m, 2 H), 2.73-2.78 (m, 1 H), 3.31-3.37 (m, 1 H), 7.74 (t, 1 H, *J* = 8.1 Hz), 8.34 (d, 1 H, *J* = 7.8 Hz), 8.46 (dd, 1 H, J_1 = 1.2 Hz, J_2 = 8.1 Hz), 8.83 (s, 1 H), 9.60 (d, 1 H, *J* = 3.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3, 26.0, 33.1, 123.1, 127.7, 130.0, 133.7, 138.0, 148.5, 194.3, 198.1; HRMS (ESI) calcd for $C_{11}H_{10}NO_4$ $(M+H)^+$: 220.0610 Found: 220.0618.

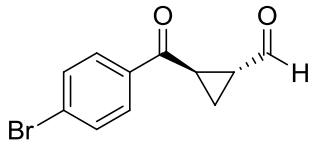


2-(3,4-dichlorobenzoyl)cyclopropanecarbaldehyde: Light yellow oil, 38% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68-1.81 (m, 2 H), 2.68-2.72 (m, 1 H), 3.19-3.24 (m, 1 H), 7.58 (d, 1 H, *J* = 8.4 Hz), 7.83 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 8.07 (d,

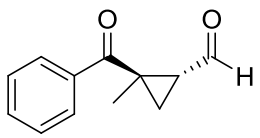
1 H, *J* = 2.0 Hz), 9.59 (d, 1 H, *J* = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 26.0, 32.9, 127.2, 130.2, 130.9, 133.5, 136.3, 138.3, 194.1, 198.3; HRMS (ESI) calcd for $C_{11}H_8O_2Cl_2Na$ $(M+Na)^+$: 264.9799 Found: 264.9790.



2-(4-fluorobenzoyl)cyclopropanecarbaldehyde: Light yellow oil, 66% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64-1.82 (m, 2 H), 2.64-2.69 (m, 1 H), 3.23-3.29 (m, 1 H), 7.14-7.19 (m, 2 H), 8.02-8.06 (m, 2 H), 9.56 (d, 1 H, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 25.8, 32.7, 115.7, 115.9, 130.8, 130.9, 133.2, 133.2, 164.3, 167.7, 194.5, 198.5, HRMS (ESI) calcd for $C_{11}H_9O_2FNa$ $(M+Na)^+$: 215.0484 Found: 215.0482.



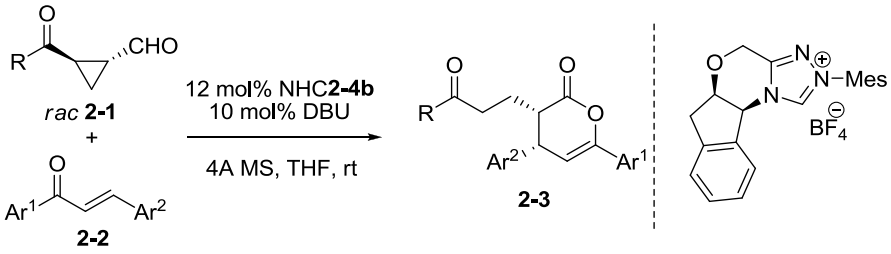
2-(bromobenzoyl)cyclopropanecarbaldehyde: Light yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68-1.70 (m, 1 H), 1.77-1.81 (m, 1 H), 2.65-2.70 (m, 1 H), 3.22-3.27 (m, 1 H), 7.64 (d, 2 H, *J* = 8.8 Hz), 7.87 (d, 2 H, *J* = 8.84 Hz), 9.57 (d, 1 H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 25.9, 32.8, 128.9, 129.7, 132.1, 135.5, 195.2, 198.5, HRMS (ESI) calcd for $C_{11}H_9O_2FNa$ $(M+H)^+$: 252.9864 Found: 252.9875.



2-benzoyl-2-methylcyclopropanecarbaldehyde: Light yellow oil, 48% yield; ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 3 H), 1.67-1.70 (m, 1 H), 1.78-1.81 (m, 1 H), 2.56-2.61 (m, 1 H), 7.46-7.57 (m, 3 H), 7.83-7.86 (m, 2 H), 9.56 (d, 1 H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 20.2, 32.7, 36.4, 128.6, 128.8, 132.8, 135.5, 199.3, 199.5; HRMS (ESI) calcd for $C_{12}H_{13}O_2$ $(M+H)^+$: 189.0916 Found: 189.0913.

2.4.4 NHC-catalyzed Diels-Alder reactions of chalcones and formylcyclopropanes.



General Procedure

All substituted chalcones were synthesized according to literatures[10].

Method A:

This method was used for chalcones with electron withdrawing group.

A dry Schlenk tube with stir bar was charged with formylcyclopropane (0.3 mmol), chalcones (0.2 mmol), triazolium salt (10.0 mg, 0.024 mmol) and 4A molecular sieves (100 mg). The Schlenk tube was closed with a septum, evacuated, and refilled with nitrogen. Then newly distilled solvent THF (1.0 mL) and DBU (3 μL, 0.02mmol) were added to the mixture. Then mixture was stirred at room

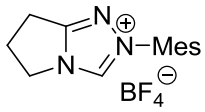
temperature until chalcone was consumed completely (monitored by TLC). The mixture was concentrated by rotary distillation and purified by column chromatography on silica gel (5:1 hexanes/EtOAc) to afford desired product.

Method B:

This method was used for chalcones with electron donating group.

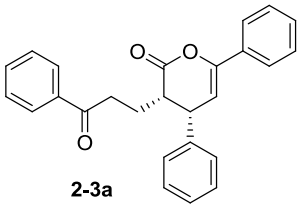
A dry Schlenk tube with stir bar was charged with formylcyclopropane (0.2 mmol), chalcones (0.2 mmol), triazolium salt (10.0 mg, 0.024 mmol) and 4A molecular sieves (100 mg). The Schlenk tube was closed with a septum, evacuated, and refilled with nitrogen. Then newly distilled THF (1.0 mL) and DBU (3 μL, 0.02mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 1h, then another portion of formylcyclopropane (0.1 mmol) was added and continue stirring at room temperature until formylcyclopropane was consumed completely (some chalcone remains monitored by TLC). Finally the reaction mixture was concentrated by rotary distillation and then purified via column chromatography on silica gel (5:1 hexanes/EtOAc) to afford the desired product.

Racemic samples for the standard of chiral HPLC spectra were prepared via the use of **S2-3** as the catalyst. In most cases, this catalyst was slightly less efficient in terms of chemical yield than the chiral triazolium salts used in this manuscript.



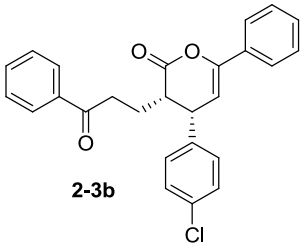
S2-3

2.4.5 Characterization of Products



2-3a

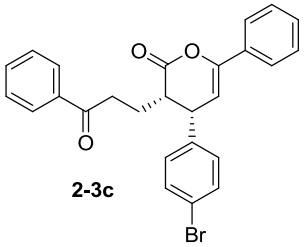
(3*S*,4*S*)-3-(3-oxo-3-phenylpropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3a): The title compound was prepared according to Method B for 6 h. Colorless solid, 86% yield; $[\alpha]_D^{23}$ = +124.2 (30 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84-1.88 (m, 2 H), 3.14-3.24 (m, 3 H), 3.91 (t, 1 H, *J* = 6.8 Hz), 6.08 (d, 1 H, *J* = 6.4 Hz), 7.21 (d, 2 H, *J* = 8.0 Hz), 7.26-7.46 (m, 8 H), 7.55 (t, 1 H, *J* = 7.2 Hz), 7.66 (dd, 2 H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.93 (d, 2 H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 36.3, 42.8, 43.4, 104.8, 124.7, 127.8, 128.0, 128.2, 128.5, 128.6, 129.0, 129.2, 132.1, 133.2, 136.7, 137.8, 150.2, 170.6, 199.7; HRMS (ESI) calcd for $C_{26}H_{23}O_3$ $(M+H)^+$: 383.1647 Found: 383.1634; >99% ee (3*S*, 4*S*)-isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1ml/min), t_r(3*S*, 4*S*) = 34.3 min, t_r(3*R*, 4*R*) = 28.9 min.



2-3b

(3*S*,4*S*)-4-(4-chlorophenyl)-3-(3-oxo-3-phenylpropyl)-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3b): The title compound was prepared according to Method A for

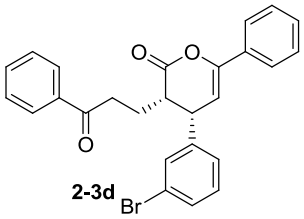
6 h. Colorless solid, 95% yield; $[\alpha]_D^{23}$ = +157.1 (25 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81-1.87 (m, 2 H), 3.13-3.25 (m, 3 H), 3.88 (t, 1 H, *J* = 6.6 Hz), 6.04 (d, 1 H, *J* = 6.6 Hz), 7.13 (d, 2 H, *J* = 8.4 Hz), 7.29 (d, 2 H, *J* = 8.4 Hz), 7.36-7.47 (m, 5 H), 7.53-7.58 (m, 1 H), 7.64-7.67 (m, 2 H), 7.93 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 36.2, 42.2, 43.2, 104.3, 124.7, 128.0, 128.5, 128.6, 129.1, 129.3, 129.5, 131.9, 133.2, 133.7, 136.3, 136.6, 150.5, 170.2, 199.6; HRMS (ESI) calcd for $C_{26}H_{21}O_3NaCl$ $(M+Na)^+$: 439.1077 Found: 439.1082; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1ml/min), t_r(3*S*, 4*S*) = 28.9 min, t_r(3*R*, 4*R*) = 22.1 min.



2-3c

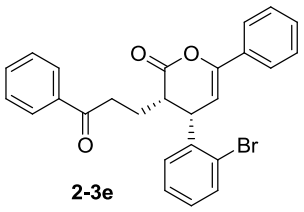
(3*S*,4*S*)-4-(4-bromophenyl)-3-(3-oxo-3-phenylpropyl)-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3c): The title compound was prepared according to Method A for 6 h. Colorless solid, 95% yield; $[\alpha]_D^{23}$ = +130.8 (35 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.79-1.86 (m, 2 H), 3.11-3.24 (m, 3 H), 3.87 (t, 1 H, *J* = 6.6 Hz), 6.03 (d, 1 H, *J* = 6.6 Hz), 7.07 (d, 2 H, *J* = 8.4 Hz), 7.36-7.46 (m, 7 H), 7.52-7.57 (m, 1 H), 7.63-7.67 (m, 2 H), 7.93 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 36.2, 42.3, 43.1, 104.2, 121.7, 124.7, 128.0, 128.5, 128.6, 129.3, 129.8, 131.9, 132.1, 133.2, 136.6, 136.8, 150.5, 170.2, 199.6; HRMS (ESI) calcd for $C_{26}H_{21}O_3BrNa$ $(M+Na)^+$: 483.0572 Found: 483.0548; >99% ee (3*S*, 4*S*)-isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1 ml/min), t_r(3*S*, 4*S*) =

30.0 min, t_r(3*R*, 4*R*) = 23.6 min.



2-3d

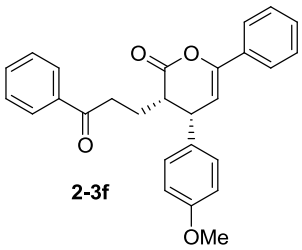
(3*S*,4*S*)-4-(3-bromophenyl)-3-(3-oxo-3-phenylpropyl)-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (3d): The title compound was prepared according to Method A for 3 h. Colorless solid, 95% yield; $[\alpha]_D^{22}$ = +104.4 (60 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84-1.88 (m, 2 H), 3.16-3.25 (m, 3 H), 3.87 (t, 1 H, *J* = 6.8 Hz), 6.03 (d, 1 H, *J* = 6.4 Hz), 7.13-7.21 (m, 2 H), 7.34-7.46 (m, 7 H), 7.53-7.55 (m, 1 H), 7.65-7.67 (m, 2 H), 7.94 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 36.2, 42.5, 43.1, 104.0, 123.0, 124.7, 126.7, 128.0, 128.5, 128.6, 129.3, 130.6, 131.0, 131.3, 131.8, 133.2, 136.6, 140.2, 150.6, 170.1, 199.6; HRMS (ESI) calcd for $C_{26}H_{22}O_3$ $(M+H)^+$: 461.0752 Found: 461.0771; >99% ee (3*S*, 4*S*)-isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 43.1 min, t_r(3*R*, 4*R*) = 38.3 min.



2-3e

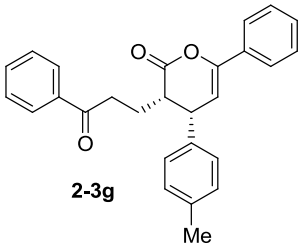
(3*S*,4*S*)-4-(2-bromophenyl)-3-(3-oxo-3-phenylpropyl)-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3e): The title compound was prepared according to Method B for 24 h. Colorless solid, 32% yield; $[\alpha]_D^{23}$ = +110.1 (15 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95-2.01 (m, 2 H), 3.17-3.28 (m, 3 H), 4.64 (t, 1 H, *J*

= 6.3 Hz), 6.03 (d, 1 H, *J* = 6.3 Hz), 7.10-7.16 (m, 1 H), 7.23-7.29 (m, 2 H), 7.36-7.46 (m, 5 H), 7.52-7.67 (m, 4 H), 7.93 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 36.1, 40.5, 42.4, 103.7, 124.6, 124.7, 128.0, 128.4, 128.5, 128.6, 128.9, 129.2, 129.3, 132.0, 133.1, 133.3, 136.6, 137.8, 150.3, 170.4, 199.4; HRMS (ESI) calcd for $C_{26}H_{21}O_3NaBr$ $(M+Na)^+$: 483.0572 Found: 483.0595; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 98:2 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 70.9 min, t_r(3*R*, 4*R*) = 58.2 min.



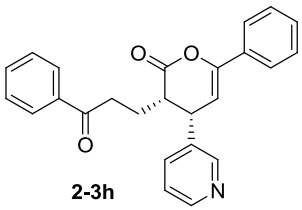
2-3f

(3*S*,4*S*)-4-(4-methoxyphenyl)-3-(3-oxo-3-phenylpropyl)-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3f): The title compound was prepared according to Method B for 48 h. Colorless solid, 44% yield; $[\alpha]_D^{23}$ = +102.5 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85-1.87 (m, 2 H), 3.09-3.24 (m, 3 H), 3.77 (s, 3 H), 3.85 (t, 1 H, *J* = 6.8 Hz), 6.07 (d, 1 H, *J* = 6.8 Hz), 6.84 (d, 2 H, *J* = 8.8 Hz), 7.12 (d, 2 H, *J* = 8.8 Hz), 7.36-7.46 (m, 5 H), 7.53-7.55 (m, 1 H), 7.66 (d, 2 H, *J* = 8.4 Hz), 7.94 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 36.3, 42.0, 43.6, 55.3, 105.1, 114.4, 124.6, 128.0, 128.5, 128.6, 129.1, 129.2, 129.6, 132.1, 133.2, 136.7, 149.9, 159.2, 170.7, 199.8; HRMS (ESI) calcd for $C_{27}H_{25}O_4$ $(M+H)^+$: 413.1753 Found: 413.1749; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 78.5 min, t_r(3*R*, 4*R*) = 48.2 min.



2-3g

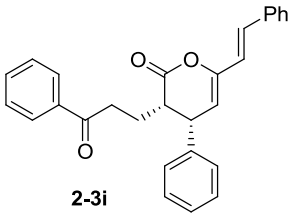
(3*S*,4*S*)-3-(3-oxo-3-phenylpropyl)-6-phenyl-4-p-tolyl-3,4-dihydro-2*H*-pyran-2-one (2-3g): The title compound was prepared according to Method B for 24 h. Colorless solid, 57% yield; $[\alpha]_D^{23}$ = +56.6 (30 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85-1.87 (m, 2 H), 2.31 (s, 3 H), 3.11-3.22 (m, 3 H), 3.85 (t, 1 H, *J* = 6.8 Hz), 6.06 (d, 1 H, *J* = 6.8 Hz), 7.07-7.13 (m, 3 H), 7.36-7.45 (m, 6 H), 7.52-7.54 (m, 1 H), 7.65 (d, 2 H, *J* = 8.4 Hz), 7.93 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 22.3, 36.3, 42.3, 43.4, 105.0, 124.6, 128.0, 128.5, 128.6, 129.1, 129.7, 130.1, 132.1, 133.1, 134.6, 136.6, 137.5, 150.0, 170.6, 199.7; HRMS (ESI) calcd for $C_{27}H_{25}O_3$ $(M+H)^+$: 397.1804 Found: 397.1799; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1 ml/min), t_r(3*S*, 4*S*) = 30.4 min, t_r(3*R*, 4*R*) = 39.2 min.



2-3h

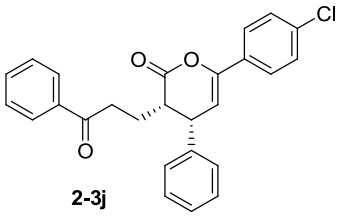
(3*S*,4*S*)-3-(3-oxo-3-phenylpropyl)-6-phenyl-4-(pyridin-3-yl)-3,4-dihydro-2*H*-pyran-2-one (2-3h): The title compound was prepared according to Method A for 3 h. Colorless solid, 93% yield; $[\alpha]_D^{23}$ = +76.0 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83-1.88 (m, 2 H), 3.22-3.27 (m, 3 H), 3.95 (t, 1 H, *J* = 6.9 Hz), 6.05 (d, 1 H, *J* = 6.6 Hz), 7.26-7.28 (m, 1 H), 7.38-7.47 (m, 5 H), 7.50-7.56 (m, 2 H),

7.64-7.67 (m, 2 H), 7.93 (d, 2 H, *J* = 6.9 Hz), 8.51-8.55 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 36.1, 40.2, 43.0, 103.7, 124.0, 124.8, 128.0, 128.6, 128.7, 129.5, 131.7, 133.3, 133.6, 135.4, 136.6, 149.3, 149.8, 151.0, 170.0, 199.5; HRMS (ESI) calcd for $C_{25}H_{22}NO_3$ $(M+H)^+$: 384.1600 Found: 384.1591; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 80:20 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 72.1 min, t_r(3*R*, 4*R*) = 56.9 min.



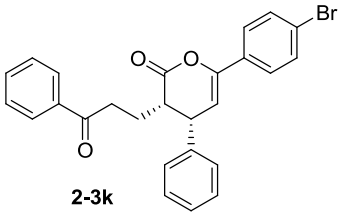
2-3i

(3*S*,4*S*)-3-(3-oxo-3-phenylpropyl)-4-phenyl-6-styryl-3,4-dihydro-2*H*-pyran-2-one (2-3i): The title compound was prepared according to Method A for 12 h. Colorless solid, 83% yield; $[\alpha]_D^{22}$ = +214.1 (25 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80-1.87 (m, 2 H), 3.10-3.21 (m, 3 H), 3.84 (t, 1 H, *J* = 6.9 Hz), 5.61 (d, 1 H, *J* = 6.6 Hz), 6.52 (d, 1 H, *J* = 15.9 Hz), 7.09 (d, 1 H, *J* = 15.9 Hz), 7.17 (dd, 2 H, J_1 = 1.8 Hz, J_2 = 7.8 Hz), 7.25-7.36 (m, 5 H), 7.41-7.45 (m, 4 H), 7.51-7.54 (m, 1 H), 7.92 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 36.2, 42.9, 43.4, 109.3, 119.8, 126.8, 127.8, 128.0, 128.1, 128.3, 128.6, 128.7, 129.0, 130.1, 133.1, 136.1, 136.6, 137.8, 149.5, 170.3, 199.6; HRMS (ESI) calcd for $C_{28}H_{25}O_3$ $(M+H)^+$: 409.1804 Found: 409.1817; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 85:15 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 68.0 min, t_r(3*R*, 4*R*) = 86.1 min.



2-3j

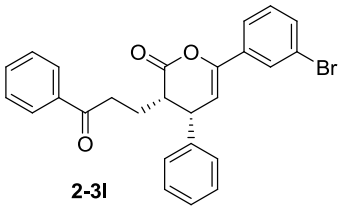
(3*S*,4*S*)-6-(4-chlorophenyl)-3-(3-oxo-3-phenylpropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3j): The title compound was prepared according to Method A for 6 h. Colorless solid, 95% yield; $[\alpha]_D^{23}$ = +125.8 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84-1.87 (m, 2 H), 3.14-3.23 (m, 3 H), 3.90 (t, 1 H, *J* = 6.8 Hz), 6.06 (d, 1 H, *J* = 6.4 Hz), 7.19 (d, 2 H, *J* = 6.8 Hz), 7.29-7.37 (m, 5 H), 7.44 (t, 2 H, *J* = 8.0 Hz), 7.54-7.60 (m, 3 H), 7.93 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 36.2, 42.8, 43.2, 105.3, 126.0, 127.9, 128.0, 128.2, 128.6, 128.8, 129.1, 130.6, 133.2, 135.1, 136.7, 137.6, 149.2, 170.2, 199.8; HRMS (ESI) calcd for $C_{26}H_{22}O_3Cl$ $(M+H)^+$: 417.1257 Found: 417.1245; >99% ee (3*S*, 4*S*)-isomer as determined by HPLC (OD-H, 95:5 hexanes/i-PrOH, 1 ml/min), t_r(3*S*, 4*S*) = 45.9 min, t_r(3*R*, 4*R*) = 39.3 min.



2-3k

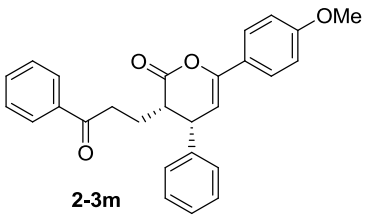
(3*S*,4*S*)-6-(4-bromophenyl)-3-(3-oxo-3-phenylpropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3k): The title compound was prepared according to Method A for 6 h. Colorless solid, 96% yield; $[\alpha]_D^{23}$ = +128.1 (60 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82-1.89 (m, 2 H), 3.13-3.23 (m, 3 H), 3.90 (t, 1 H, *J* = 6.8 Hz), 6.08 (d, 1 H, *J* = 6.8 Hz), 7.19 (d, 2 H, *J* = 6.8 Hz), 7.27-7.35 (m, 3 H), 7.44 (t,

2 H, *J* = 8.0 Hz), 7.52-7.56 (m, 5 H), 7.93 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 36.2, 42.8, 43.2, 105.4, 123.3, 126.2, 127.9, 128.0, 128.1, 128.6, 129.1, 131.1, 131.7, 133.2, 136.7, 137.6, 149.3, 170.3, 199.7; HRMS (ESI) calcd for $C_{26}H_{22}O_3Br$ $(M+H)^+$: 461.0752 Found: 461.0773; 99% ee (3*S*, 4*S*)-isomer as determined by HPLC (OD-H, 95:5 hexanes/i-PrOH, 1 ml/min), t_r(3*S*, 4*S*) = 50.6 min, t_r(3*R*, 4*R*) = 42.1 min.



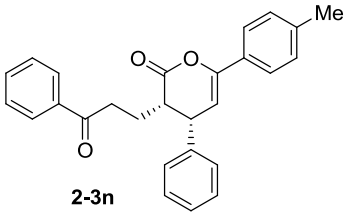
2-3l

(3*S*,4*S*)-6-(3-bromophenyl)-3-(3-oxo-3-phenylpropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3l): The title compound was prepared according to Method A for 3 h. Colorless solid, 92% yield; $[\alpha]_D^{23}$ = +121.4 (60 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84-1.88 (m, 2 H), 3.14-3.22 (m, 3 H), 3.90 (t, 1 H, *J* = 6.8 Hz), 6.09 (d, 1 H, *J* = 6.4 Hz), 7.19 (d, 2 H, *J* = 8.0 Hz), 7.24-7.32 (m, 4 H), 7.42-7.48 (m, 3 H), 7.53-7.57 (m, 2 H), 7.81 (t, 1 H, *J* = 2.0 Hz), 7.94 (d, 2 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 36.1, 42.7, 43.2, 106.0, 122.8, 123.2, 127.7, 127.9, 128.0, 128.1, 128.6, 129.0, 130.0, 132.0, 133.2, 134.1, 136.6, 137.4, 148.7, 170.1, 199.6; HRMS (ESI) calcd for $C_{26}H_{21}O_3BrNa$ $(M+Na)^+$: 483.0572 Found: 483.0588; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 35.6 min, t_r(3*R*, 4*R*) = 32.1 min.



2-3m

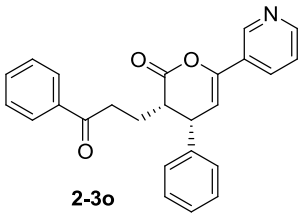
(3*S*,4*S*)-6-(4-methoxyphenyl)-3-(3-oxo-3-phenylpropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3m): The title compound was prepared according to Method B for 48 h. Colorless solid, 39% yield; $[\alpha]_D^{23}$ = +55.1 (13 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83-1.87 (m, 2 H), 3.13-3.23 (m, 3 H), 3.83 (s, 3 H), 3.87 (t, 1 H, J = 6.8 Hz), 5.94 (d, 1 H, J = 6.4 Hz), 6.90 (d, 2 H, J = 9.2 Hz), 7.20 (d, 2 H, J = 8.4 Hz), 7.25-7.33 (m, 3 H), 7.44 (t, 2 H, J = 7.6 Hz), 7.53-7.60 (m, 3 H), 7.93 (d, 2 H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 36.3, 42.8, 43.4, 55.3, 103.0, 113.9, 124.7, 126.1, 127.7, 128.0, 128.2, 128.6, 129.0, 133.2, 136.7, 138.1, 150.0, 160.3, 170.7, 199.8; HRMS (ES+) calcd for C27H25O4 $(M+H)^+$: 413.1753 Found: 413.1751; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 101.6 min, t_r(3*R*, 4*R*) = 62.6 min.



2-3n

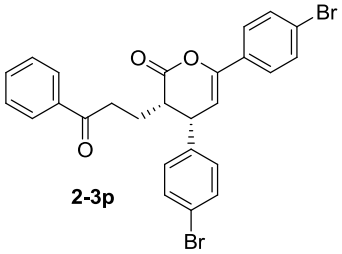
(3*S*,4*S*)-3-(3-oxo-3-phenylpropyl)-4-phenyl-6-p-tolyl-3,4-dihydro-2*H*-pyran-2-one (2-3n): The title compound was prepared according to Method B for 24 h. Colorless solid, 52% yield; $[\alpha]_D^{23}$ = +32.4 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83-1.87 (m, 2 H), 2.36 (s, 3 H), 3.12-3.23 (m, 3 H), 3.88 (t, 1 H, *J* = 6.8 Hz), 6.01 (d, 1 H, *J* = 6.4 Hz), 7.18-7.21 (m, 4 H), 7.25-7.31 (m, 3 H), 7.43 (t,

2 H, *J* = 7.6 Hz), 7.52-7.56 (m, 3 H), 7.93 (d, 2 H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 22.3, 36.3, 42.7, 43.4, 103.9, 124.6, 127.7, 128.0, 128.2, 128.6, 128.9, 129.2, 129.3, 133.2, 136.6, 137.9, 139.2, 150.2, 170.7, 199.7; HRMS (ESI) calcd for $C_{27}H_{25}O_3$ $(M+H)^+$: 397.1804 Found: 397.1789; >99% ee (3*S*, 4*S*)-isomer as determined by HPLC (OD-H, 95:5 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 79.1 min, t_r(3*R*, 4*R*) = 54.5 min.



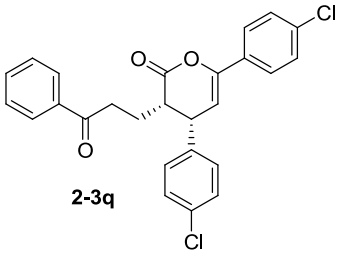
2-3o

(3*S*,4*S*)-3-(3-oxo-3-phenylpropyl)-4-phenyl-6-(pyridin-3-yl)-3,4-dihydro-2*H*-pyran-2-one (2-3o): The title compound was prepared according to Method A for 3 h. Colorless solid, 94% yield; $[\alpha]_D^{23}$ = +123.3 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83-1.91 (m, 2 H), 3.19-3.24 (m, 3 H), 3.94 (t, 1 H, *J* = 6.9 Hz), 6.15 (d, 1 H, *J* = 6.6 Hz), 7.19-7.22 (m, 2 H), 7.26-7.35 (m, 4 H), 7.44 (t, 2 H, *J* = 7.8 Hz), 7.53-7.55 (m, 1 H), 7.92-7.97 (m, 3 H), 7.59 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 4.8 Hz), 8.90 (d, 1 H, *J* = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 36.1, 42.8, 43.2, 106.5, 123.3, 128.0, 128.1, 128.2, 128.6, 129.1, 132.1, 133.2, 136.6, 137.3, 146.1, 147.9, 149.9, 170.0, 199.6; HRMS (ESI) calcd for $C_{25}H_{22}NO_3$ $(M+H)^+$: 384.1600 Found: 384.1599; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 80:20 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 124.3 min, t_r(3*R*, 4*R*) = 34.5 min.



2-3p

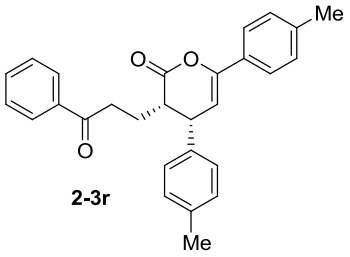
(3*S*,4*S*)-4,6-bis(4-bromophenyl)-3-(3-oxo-3-phenylpropyl)-3,4-dihydro-2*H*-pyran-2-one (2-3p): The title compound was prepared according to Method A for 6 h. Colorless solid, 99% yield; $[\alpha]_D^{22}$ = +161.4 (13 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.85 (m, 2 H), 3.14-3.24 (m, 3 H), 3.87 (t, 1 H, *J* = 6.8 Hz), 6.04 (d, 1 H, *J* = 6.4 Hz), 7.06 (d, 2 H, *J* = 8.4 Hz), 7.43-7.56 (m, 9 H), 7.93 (d, 2 H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 36.1, 42.3, 43.0, 104.7, 121.9, 123.5, 126.2, 128.0, 128.7, 129.8, 130.8, 131.8, 132.2, 133.3, 136.6, 149.6, 170.0, 199.6; HRMS (ESI) calcd for $C_{26}H_{21}O_3Br_2$ $(M+H)^+$: 538.9857 Found: 538.9857; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1 ml/min), t_r(3*S*, 4*S*) = 29.8 min, t_r(3*R*, 4*R*) = 25.3 min.



2-3q

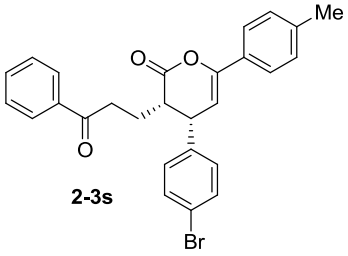
(3*S*,4*S*)-4,6-bis(4-chlorophenyl)-3-(3-oxo-3-phenylpropyl)-3,4-dihydro-2*H*-pyran-2-one (2-3q): The title compound was prepared according to Method A for 6 h. Colorless solid, 93% yield; $[\alpha]_D^{21}$ = +67.5 (30 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81-1.86 (m, 2 H), 3.13-3.24 (m, 3 H), 3.88 (t, 1 H, *J* = 6.9 Hz), 6.02 (d, 1 H, *J* = 6.6 Hz), 7.12 (d, 2 H, *J* = 8.4 Hz), 7.26-7.60 (m, 9 H), 7.92 (d, 2 H, *J* =

8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 36.1, 42.2, 43.1, 104.7, 126.0, 128.0, 128.6, 128.8, 129.2, 129.5, 130.4, 133.3, 133.8, 135.3, 136.1, 136.6, 149.6, 170.0, 199.6; HRMS (ESI) calcd for $C_{27}H_{21}O_3Cl_2$ $(M+H)^+$: 463.0868 Found: 463.0882; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 98:2 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 56.7 min, t_r(3*R*, 4*R*) = 46.2 min.

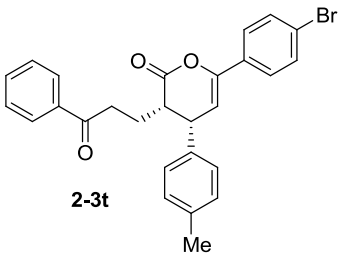


2-3r

(3*S*,4*S*)-3-(3-oxo-3-phenylpropyl)-4,6-dip-tolyl-3,4-dihydro-2*H*-pyran-2-one (2-3r): The title compound was prepared according to Method B for 24 h. Colorless solid, 37% yield; $[\alpha]_D^{23}$ = +49.0 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (q, 2 H, *J* = 6.9 Hz), 2.31 (s, 3 H), 2.36 (s, 3 H), 3.10-3.22 (m, 3 H), 3.84 (t, 1 H, *J* = 6.9 Hz), 6.00 (d, 1 H, *J* = 6.6 Hz), 7.09-7.20 (m, 6 H), 7.43 (t, 2 H, *J* = 7.8 Hz), 7.52-7.56 (m, 3 H), 7.93 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 21.2, 22.3, 36.3, 42.4, 43.5, 104.1, 124.6, 128.0, 128.6, 129.2, 129.4, 129.6, 133.1, 134.8, 136.7, 137.5, 139.1, 150.1, 170.7, 199.7; HRMS (ESI) calcd for $C_{28}H_{27}O_3$ $(M+H)^+$: 411.1960 Found: 411.1967; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 95:5 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 61.0 min, t_r(3*R*, 4*R*) = 44.1 min.

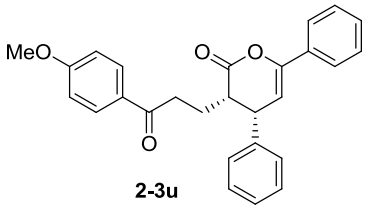


(3*S*,4*S*)-4-(4-bromophenyl)-3-(3-oxo-3-phenylpropyl)-6-p-tolyl-3,4-dihydro-2*H*-pyran-2-one (2-3s): The title compound was prepared according to Method A for 2 h. Colorless solid, 81% yield; $[\alpha]_D$ ^{22} = +30.9 (15 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.87 (m, 2 H), 2.37 (s, 3 H), 3.12-3.24 (m, 3 H), 3.86 (t, 1 H, *J* = 6.8 Hz), 5.98 (d, 1 H, *J* = 6.8 Hz), 7.08 (d, 2 H, *J* = 8.4 Hz), 7.20 (d, 2 H, *J* = 8.0 Hz), 7.43-7.47 (m, 4 H), 7.54 (dd, 1 H, J_1 = 1.6 Hz, J_2 = 7.2 Hz), 7.93 (dd, 1 H, J_1 = 1.6 Hz, J_2 = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 22.3, 36.2, 42.3, 43.2, 103.3, 121.7, 124.6, 128.0, 128.6, 129.1, 129.3, 129.9, 132.1, 133.2, 136.6, 137.0, 139.4, 150.6, 170.4, 199.6; HRMS (ESI) calcd for $C_{27}H_{23}O_3NaBr$ $(M+Na)^+$: 497.0728 Found: 497.0710; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 97:3 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 110.9 min, t_r(3*R*, 4*R*) = 95.8 min.



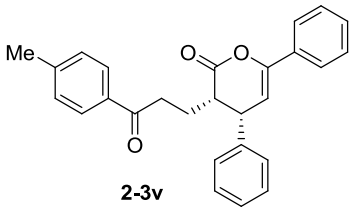
(3*S*,4*S*)-6-(4-bromophenyl)-3-(3-oxo-3-phenylpropyl)-4-p-tolyl-3,4-dihydro-2*H*-pyran-2-one (2-3t): The title compound was prepared according to Method A for 5 h. Colorless solid, 86% yield; $[\alpha]_D$ ^{22} = +45.4 (20 mg/ml, CH_2Cl_2); ^{1}H NMR

($CDCl_3$, 400 MHz) δ 1.84-1.86 (m, 2 H), 2.31 (s, 3 H), 3.11-3.22 (m, 3 H), 3.85 (t, 1 H, *J* = 6.8 Hz), 6.06 (d, 1 H, *J* = 6.4 Hz), 7.06-7.13 (m, 4 H), 7.42-7.55 (m, 7 H), 7.93 (dd, 1 H, J_1 = 1.2 Hz, J_2 = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 22.2, 36.2, 42.4, 43.2, 105.5, 123.2, 126.2, 127.9, 128.0, 128.6, 129.7, 131.1, 131.7, 133.2, 134.4, 136.6, 137.6, 149.1, 170.4, 199.7; HRMS (ESI) calcd for $C_{27}H_{23}O_3NaBr$ $(M+Na)^+$: 497.0728 Found: 497.0710; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 40.5 min, t_r(3*R*, 4*R*) = 35.1 min.



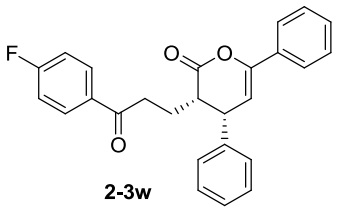
2-3u

(3*S*,4*S*)-3-(3-(4-methoxyphenyl)-3-oxopropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3u): The title compound was prepared according to Method A for 24 h. Colorless solid, 66% yield; $[\alpha]_D^{23}$ = +175.4 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82-1.87 (m, 2 H), 3.12-3.17 (m, 3 H), 3.85 (s, 3 H), 3.89 (t, 1 H, *J* = 6.8 Hz), 6.07 (d, 1 H, *J* = 6.4 Hz), 6.91 (dd, 2 H, J_1 = 2.0 Hz, J_2 = 7.2 Hz), 7.19-7.38 (m, 8 H), 7.65-7.67 (m, 2 H), 7.92 (dd, 2 H, J_1 = 2.0 Hz, J_2 = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 35.9, 42.8, 43.4, 55.4, 104.9, 113.7, 124.7, 127.8, 128.2, 128.5, 129.0, 129.1, 129.8, 130.3, 132.1, 137.8, 150.1, 163.5, 170.6, 198.3; HRMS (ESI) calcd for $C_{27}H_{24}O_3Na$ $(M+Na)^+$: 419.1623 Found: 419.1619; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 91.1 min, t_r(3*R*, 4*R*) = 81.0 min.



2-3v

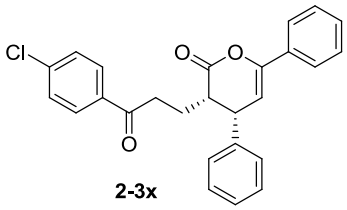
(3*S*,4*S*)-3-(3-oxo-3-p-tolylpropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3v): The title compound was prepared according to Method A for 24 h. Colorless solid, 59% yield; $[\alpha]_D^{23}$ = +49.0 (10 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83-1.87 (m, 2 H), 2.39 (s, 3 H), 3.16-3.20 (m, 3 H), 3.90 (t, 1 H, *J* = 6.9 Hz), 6.07 (d, 1 H, *J* = 6.3 Hz), 7.19-7.39 (m, 10 H), 7.66 (dd, 2 H, J_1 = 2.1 Hz, J_2 = 7.8 Hz), 7.83 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 22.4, 36.1, 42.8, 43.4, 104.8, 124.7, 128.1, 128.2, 128.5, 129.0, 129.1, 129.3, 132.1, 134.2, 137.8, 144.0, 150.2, 162.3, 170.6, 199.4; HRMS (ESI) calcd for $C_{27}H_{25}O_3$ $(M+H)^+$: 397.1804 Found: 397.1800; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (ADH, 96:4 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 74.7 min, t_r(3*R*, 4*R*) = 87.3 min.



2-3w

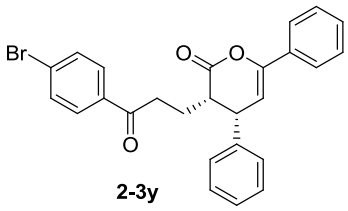
(3*S*,4*S*)-3-(3-(4-fluorophenyl)-3-oxopropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3w): The title compound was prepared according to Method A for 3 h. Colorless solid, 63% yield; $[\alpha]_D^{22}$ = +161.6 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82-1.87 (m, 2 H), 3.15-3.18 (m, 3 H), 3.89 (t, 1 H, *J* = 6.9 Hz), 6.08 (d, 1 H, *J* = 6.6 Hz), 7.10 (t, 2 H, *J* = 8.7 Hz), 7.20 (dd, 2 H, J_1 = 1.8 Hz, J_2 = 8.1

Hz), 7.26-7.39 (m, 6 H), 7.66 (dd, 2 H, J_1 = 2.1 Hz, J_2 = 7.8 Hz), 7.93-7.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4, 36.3, 42.9, 43.4, 104.8, 115.6, 115.8, 124.7, 127.8, 128.2, 128.5, 129.0, 129.2, 130.6, 130.7, 132.1, 133.1, 137.8, 150.2, 170.5, 198.1; HRMS (ESI) calcd for $C_{26}H_{21}O_3NaF$ $(M+Na)^+$: 423.1372 Found: 423.1390; 99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 63.2 min, t_r(3*R*, 4*R*) = 36.6 min.



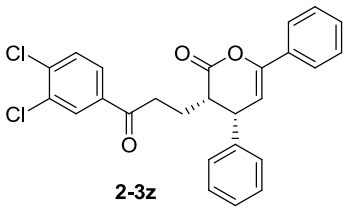
2-3x

(3*S*,4*S*)-3-(3-(4-chlorophenyl)-3-oxopropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3x): The title compound was prepared according to Method A for 24 h. Colorless solid, 66% yield; $[\alpha]_D^{23}$ = +107.0 (35 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81-1.86 (m, 2 H), 3.09-3.19 (m, 3 H), 3.88 (t, 1 H, *J* = 6.9 Hz), 6.07 (d, 1 H, *J* = 6.3 Hz), 6.91 (d, 2 H, *J* = 8.1 Hz), 7.25-7.32 (m, 3 H), 7.35-7.41 (m, 5 H), 7.66 (d, 2 H, *J* = 7.8 Hz), 7.86 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 36.3, 42.8, 43.3, 104.7, 124.7, 128.1, 128.5, 128.9, 129.0, 129.2, 129.4, 132.0, 134.9, 137.7, 139.6, 150.2, 170.5, 198.5; HRMS (ESI) calcd for $C_{26}H_{22}O_3Cl$ $(M+H)^+$: 417.1257 Found: 417.1245; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1 ml/min), t_r(3*S*, 4*S*) = 29.6 min, t_r(3*R*, 4*R*) = 31.8 min.



2-3y

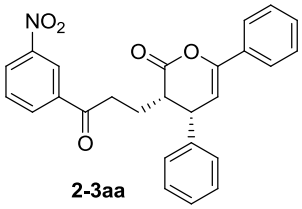
(3*S*,4*S*)-3-(3-(4-bromophenyl)-3-oxopropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3y): The title compound was prepared according to Method A for 3 h. Colorless solid, 71% yield; $[\alpha]_D^{22}$ = +111.2 (40 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.89 (m, 2 H), 3.12-3.20 (m, 3 H), 3.89 (t, 1 H, *J* = 6.8 Hz), 6.08 (d, 1 H, *J* = 6.4 Hz), 7.20 (dd, 2 H, J_1 = 1.6 Hz, J_2 = 8.4 Hz), 7.26-7.39 (m, 6 H), 7.58 (d, 2 H, *J* = 8.8 Hz), 7.67 (dd, 2 H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.79 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 36.3, 42.9, 43.3, 104.8, 124.7, 127.9, 128.2, 128.4, 128.6, 129.0, 129.2, 129.6, 131.9, 132.1, 135.3, 137.7, 150.2, 170.5, 198.7; HRMS (ESI) calcd for $C_{26}H_{22}O_3Br$ $(M+H)^+$: 461.0752 Found: 461.0750; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1ml/min), t_r(3*S*, 4*S*) = 23.9 min, t_r(3*R*, 4*R*) = 26.3 min.



2-3z

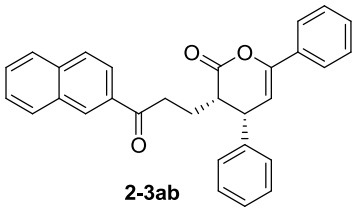
(3*S*,4*S*)-3-(3-(3,4-dichlorophenyl)-3-oxopropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3z): The title compound was prepared according to Method A for 3 h. Colorless solid, 65% yield; $[\alpha]_D^{21}$ = +148.7 (35 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81-1.86 (m, 2 H), 3.12-3.16 (m, 3 H), 3.88 (t, 1 H, *J* = 6.6 Hz), 6.08 (d, 1 H, *J* = 6.6 Hz), 7.19 (dd, 2 H, J_1 = 1.8 Hz, J_2 = 8.1 Hz), 7.26-7.39

(m, 6 H), 7.51 (d, 1 H, J = 8.4 Hz), 7.65-7.68 (m, 2 H), 7.19 (dd, 1 H, J_1 = 2.1 Hz, J_2 = 8.4 Hz), 8.00 (d, 1 H, J = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 36.4, 42.9, 43.3, 104.7, 124.7, 127.1, 127.9, 128.1, 128.5, 129.0, 129.2, 130.0, 130.7, 132.0, 133.3, 136.2, 137.6, 137.8, 150.2, 170.4, 197.4; HRMS (ESI) calcd for $C_{26}H_{21}O_3Cl_2$ $(M+H)^+$: 451.0868 Found: 451.0880; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 112.8 min, t_r(3*R*, 4*R*) = 56.9 min.



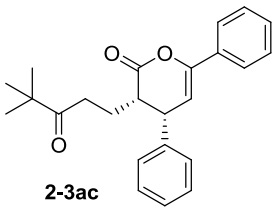
2-3aa

(3*S*,4*S*)-3-(3-(3-nitrophenyl)-3-oxopropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran -2-one (2-3aa): The title compound was prepared according to Method A for 3 h. Colorless solid, 69% yield; $[\alpha]_D^{21}$ = +162.0 (35 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88-1.94 (m, 2 H), 3.13-3.29 (m, 3 H), 3.91 (t, 1 H, J = 6.9 Hz), 6.10 (d, 1 H, J = 6.6 Hz), 7.20-7.40 (m, 8 H), 7.65-7.69 (m,3 H), 8.24-8.27 (m, 1 H), 8.38-8.42 (m, 1 H), 8.74 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 36.7, 42.9, 43.3, 104.7, 122.9, 124.7, 127.4, 127.9, 128.1, 128.6, 129.1, 129.2, 129.9, 132.0, 133.5, 137.6, 137.9, 150.3, 162.3, 170.4, 197.4; HRMS (ESI) calcd for $C_{26}H_{22}NO_5$ $(M+H)^+$: 428.1498 Found: 428.1519; 99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 143.3 min, t_r(3*R*, 4*R*) = 157.4 min.



2-3ab

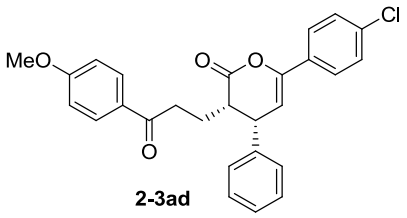
(3*S*,4*S*)-3-(3-(naphthalen-2-yl)-3-oxopropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3ab): The title compound was prepared according to Method A for 24 h. Colorless solid, 74% yield; $[\alpha]_D^{23}$ = +196.7 (15 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90-1.94 (m, 2 H), 3.17-3.22 (m, 1 H), 3.33-3.37 (m, 2 H), 3.93 (t, 1 H, *J* = 6.8 Hz), 6.09 (d, 1 H, *J* = 6.4 Hz), 7.22-7.39 (m, 8 H), 7.54-7.60 (m, 2 H), 7.66 (d, 1 H, *J* = 8.4 Hz), 7.85-7.88 (m, 2 H), 7.95 (d, 1 H, *J* = 8.0 Hz), 8.00 (dd, 1 H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 8.46 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 36.4, 42.8, 43.4, 104.8, 123.7, 124.7, 126.8, 127.7, 127.8, 128.2, 128.4, 128.5, 128.5, 129.0, 129.2, 129.6, 129.9, 132.1, 132.5, 134.0, 135.6, 137.8, 150.2, 170.6, 199.7; HRMS (ESI) calcd for $C_{30}H_{25}O_3$ $(M+H)^+$: 433.1804 Found: 433.1812; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 97:3 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 91.9 min, t_r(3*R*, 4*R*) = 83.8 min.



2-3ac

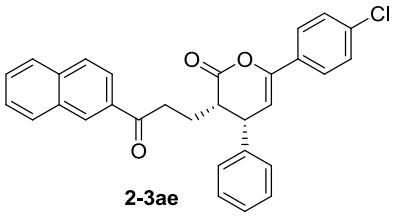
(3*S*,4*S*)-3-(4,4-dimethyl-3-oxopentyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (2-3ac): The title compound was prepared according to Method A for 24 h. Colorless solid, 49% yield; $[\alpha]_D^{23}$ = +69.5 (20 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (s, 9 H), 1.62-1.68 (m, 2 H), 2.72 (t, 2 H, *J* = 6.3 Hz), 2.99-3.04

(m, 1 H), 3.84 (t, 1 H, *J* = 6.9 Hz), 6.05 (d, 1 H, *J* = 6.6 Hz), 7.17 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 7.5 Hz), 7.26-7.39 (m, 6 H), 7.67 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 26.4, 34.2, 42.9, 43.2, 44.0, 104.8, 124.6, 127.7, 128.1, 128.5, 128.9, 129.1, 132.1, 137.8, 150.1, 170.5, 215.9; HRMS (ESI) calcd for $C_{24}H_{27}O_3$ $(M+H)^+$: 363.1960 Found: 363.1958; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (IC, 95:5 hexanes/i-PrOH, 1 ml/min), t_r(3*S*, 4*S*) = 20.7 min, t_r(3*R*, 4*R*) = 14.9 min.



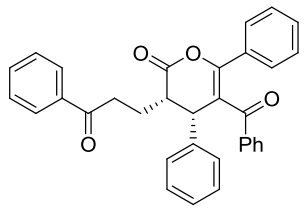
2-3ad

(3*S*,4*S*)-6-(4-chlorophenyl)-3-(3-(4-methoxyphenyl)-3-oxopropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3ad): The title compound was prepared according to Method A for 2 h. Colorless solid, 86% yield; $[\alpha]_D^{23}$ = +159.1 (50 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82-1.85 (m, 2 H), 3.13-3.16 (m, 3 H), 3.85 (s, 3 H), 3.89 (t, 1 H, *J* = 6.8 Hz), 6.05 (d, 1 H, *J* = 6.4 Hz), 6.91 (d, 2 H, *J* = 8.8 Hz), 7.19 (d, 2 H, *J* = 8.0 Hz), 7.26-7.36 (m, 5 H), 7.58 (d, 2 H, *J* = 8.8 Hz), 7.91 (d, 2 H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 35.8, 42.7, 43.2, 55.4, 105.3, 113.7, 125.9, 127.8, 128.1, 128.7, 129.0, 129.7, 130.3, 130.6, 135.0, 137.6, 149.2, 163.5, 170.3, 198.2; HRMS (ESI) calcd for $C_{27}H_{24}O_4Cl$ $(M+H)^+$: 447.1363 Found: 447.1347; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 67.2 min, t_r(3*R*, 4*R*) = 76.8 min.



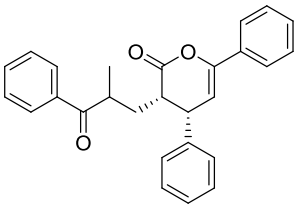
2-3ae

(3*S*,4*S*)-6-(4-chlorophenyl)-3-(3-(naphthalen-2-yl)-3-oxopropyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (2-3ae): The title compound was prepared according to Method A for 2 h. Colorless solid, 74% yield; $[\alpha]_D^{23}$ = +140.9 (40 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89-1.94 (m, 2 H), 3.17-3.21 (m, 1 H), 3.34(t, 2 H, *J* = 6.8 Hz), 3.92 (t, 1 H, *J* = 6.8 Hz), 6.06 (d, 1 H, *J* = 6.4 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.28-7.36 (m, 5 H), 7.54-7.60 (m, 4 H), 7.84-7.88 (m, 2 H), 7.94 (d, 1 H, *J* = 8.0 Hz), 7.99 (dd, 1 H, J_1 = 1.6 Hz, J_2 = 8.4 Hz), 8.45 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 36.2, 42.8, 43.3, 105.3, 123.6, 125.9, 126.8, 127.7, 127.9, 128.1, 128.4, 128.5, 128.7, 129.1, 129.6, 129.8, 130.6, 132.5, 133.9, 135.0, 135.6, 137.6, 149.2, 170.3, 199.6; HRMS (ESI) calcd for $C_{30}H_{23}O_3NaCl$ $(M+Na)^+$: 489.1233 Found: 489.1245; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 67.5 min, t_r(3*R*, 4*R*) = 55.1 min.



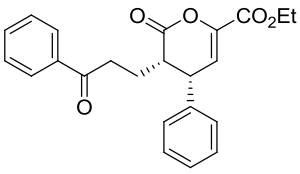
(3*S*,4*S*)-5-benzoyl-3-(3-oxo-3-phenylpropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one: The title compound was prepared according to Method A for 6 h. Colorless solid, 89% yield; $[\alpha]_D^{23}$ = +131.7 (60 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92-1.97 (m, 2 H), 3.21-3.37 (m, 3 H), 4.53 (d, 1 H, *J* = 7.2 Hz),

7.00-7.46 (m, 17 H), 7.52-7.54 (m, 1 H), 7.93 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 35.9, 42.6, 45.5, 119.9, 127.8, 127.9, 128.0, 128.6, 129.0, 129.1, 129.2, 130.2, 131.8, 132.4, 133.1, 136.5, 136.6, 137.1, 154.3, 169.7, 195.6, 199.3; HRMS (ESI) calcd for $C_{33}H_{27}O_4$ $(M+H)^+$: 477.1909 Found: 487.1915; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (ADH, 90:10 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 74.0 min, t_r(3*R*, 4*R*) = 56.2 min.



(3*S*,4*S*)-3-(2-methyl-3-oxo-3-phenylpropyl)-4,6-diphenyl-3,4-dihydro-2*H*-pyra

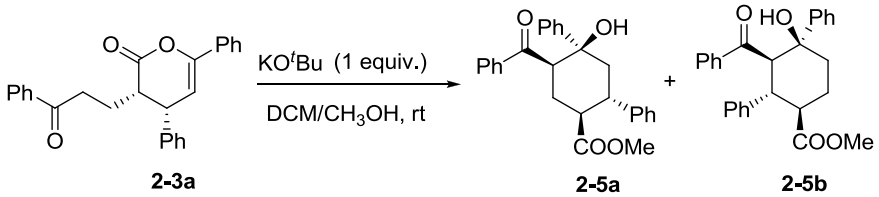
n-2-one: The title compound was prepared according to Method B for 6 h. Colorless solid, 41% yield; $[\alpha]_D^{22}$ = +191.1 (12 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, 3 H, *J* = 6.8 Hz), 1.39-1.46 (m, 1 H), 2.06-2.13 (m, 1 H), 3.14-3.19 (m, 1 H), 3.72-3.79 (m, 2 H), 6.04 (d, 1 H, *J* = 6.4 Hz), 6.14 (d, 2 H, *J* = 8.4 Hz), 7.24-7.31 (m, 2 H), 7.38-7.40 (m, 3 H), 7.46 (t, 2 H, *J* = 7.2 Hz), 7.54-7.56 (m, 1 H), 7.67 (dd, 2 H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 8.04 (d, 2 H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 30.9, 37.8, 41.5, 42.6, 104.7, 124.7, 127.8, 128.0, 128.5, 128.6, 128.7, 129.1, 129.2, 132.1, 133.2, 135.9, 137.7, 150.3, 170.5, 203.6; HRMS (ESI) calcd for $C_{27}H_{24}O_3Na$ $(M+Na)^+$: 419.1623 Found: 419.1607; >99% ee (3*S*, 4*S*)- isomer as determined by HPLC (OD-H, 95:5 hexanes/i-PrOH, 0.75 ml/min), t_r(3*S*, 4*S*) = 48.2 min, t_r(3*R*, 4*R*) = 24.0 min.



(3S,4S)-ethyl2-oxo-3-(3-oxo-3-phenylpropyl)-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate: The title compound was prepared according to Method B for 24 h. Colorless solid, 40% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3 H, *J* = 7.2 Hz), 1.80-1.85 (m, 2 H), 3.05-3.09 (m, 1 H), 3.18 (t, 2 H, *J* = 6.6 Hz), 3.90 (t, 1 H, *J* = 6.9 Hz), 4.32 (q, 2 H, *J* = 7.2 Hz), 6.72 (d, 1 H, *J* = 6.6 Hz), 7.13-7.16 (m, 2 H), 7.31-7.34 (m, 3 H), 7.44 (t, 2 H, *J* = 7.8 Hz), 7.53-7.56 (m, 1 H), 7.91 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.0, 36.0, 42.5, 42.7, 61.9, 118.1, 128.0, 128.1, 128.3, 128.6, 129.2, 133.3, 135.9, 136.6, 142.3, 160.6, 169.0, 199.5.

2.4.6 Chemical Transformation of 2-3a

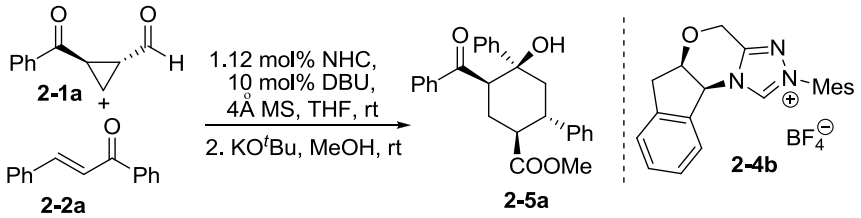
Method A:



To the solution of **2-3a** (90mg, 0.23mmol) in 2 mL 1:1 DCM/MeOH, was added KO^{t}Bu (26.4mg, 0.23mmol)，and was stirred for 48h at rt. The reaction mixture was concentrated by rotary distillation. The resulting residue was purified via column chromatography on silica gel (hexane/dichloromethane/ethyl acetate, 10:1:1) to afford the desired product **2-5a (**71.2 mg, 73% yield)

Note: Under the basic condition, compound **2-3a** was transformed to **2-5a** and **2-5b** completely in half an hour with around 1:1 regioselectivity. It appears the aldol reaction for the conversation of **2-3a** (through its methyl ester) to **2-5b** is reversible. Thus compound **2-5b** was consumed and end up as the more stable regio-isomer **2-5a** at extended reaction time; and after 48 hours, the ratio of **2-5a** to **2-5b** could be enhanced to 9:1.

Method B (one-pot operation combing NHC catalysis and aldol reaction):



A dry Schlenk tube with stir bar was charged with formylcyclopropane (52.3mg, 0.3 mmol), chalcone (41.6mg, 0.02), triazolium salt (10.0 mg, 0.024 mmol), DBU (3 μL, 0.02mmol), 4 A molecular sieves (100 mg). The Schlenk tube was closed with a septum, evacuated, and refilled with nitrogen. Then newly distilled solvent THF (1.0 mL) and DBU (3 μL, 0.02mmol) were added to the solution by injection. Reaction mixture was stirred at room temperature for 4h, then MeOH (1 ml) and KO^{t}Bu (22.4 mg, 0.2 mmol) were added to reaction mixture, and stirred for another 48h. The solvent was removed via rotary distillation and the crude residue was purified through column chromatography on silica gel (hexane/dichloromethane/ethyl acetate, 10:1:1) to afford desired product

2-5a (54.1 mg, 65% yield)

(1*S*,2*S*,4*S*,5*S*)-methyl

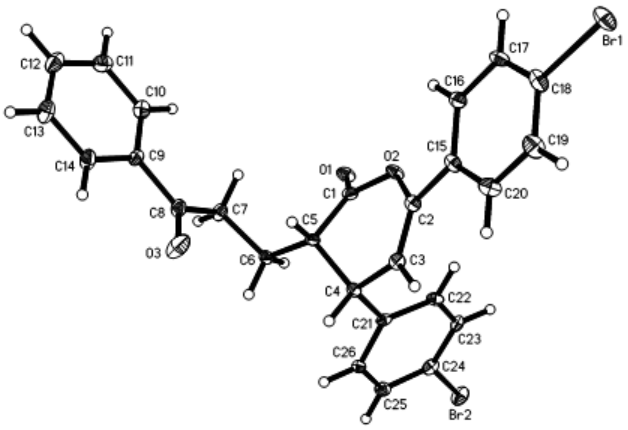
5-benzoyl-4-hydroxy-2,4-diphenylcyclohexanecarboxylate (2-5a): Colorless solid; $[\alpha]_D^{23}$ = +115.6 (10 mg/ml, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94-1.97 (m, 1 H), 2.13 (dd, 1 H, J_1 = 4.0 Hz, J_2 = 14.4 Hz), 2.25 (dt, 1 H, J_1 = 3.6 Hz, J_2 = 13.2 Hz), 2.54 (q, 1 H, J = 12.8 Hz), 3.00 (td, 1 H, J_1 = 3.6 Hz, J_2 = 12.0 Hz), 3.49 (s, 3 H), 3.71 (td, 1 H, J_1 = 3.6 Hz, J_2 = 12.8 Hz), 4.25 (dd, 1 H, J_1 = 3.6 Hz, J_2 = 12.8 Hz), 5.28 (d, 1 H, J = 2.8 Hz), 7.13-7.31 (m, 8 H), 7.46-7.53 (m, 4 H), 7.61 (t, 1 H, J = 7.6 Hz), 7.90 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.0, 41.6, 48.1, 49.2, 49.4, 51.6, 74.7, 124.5, 126.7, 126.9, 127.4, 128.2, 128.4, 128.5, 128.9, 134.0, 135.9, 142.9, 146.9, 174.1, 205.2; HRMS (ESI) calcd for $C_{27}H_{24}O_3Na$ $(M+H)^+$: 415.1909 Found: 415.1900.

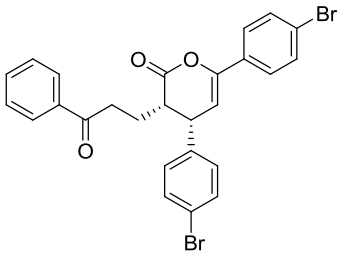
2.4.7 Determination of the absolute configurations of δ-lactones

The absolute configuration of δ-lactones **2-3p** was determined by X-ray to be (*3S, 4S*) (Figure 1).

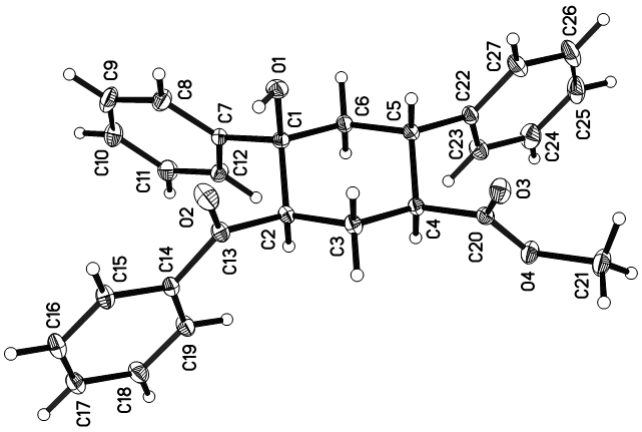
(1) X-ray Structure of **2-3p**

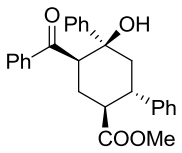
A colorless solution of **2-3p** (99% ee) in hexane/ethyl acetate (5:1) was prepared. A colorless crystal suitable for X-ray structural analysis was obtained through slow evaporation of solvents at room temperature.





(2) X-ray Structure of **2-5a**





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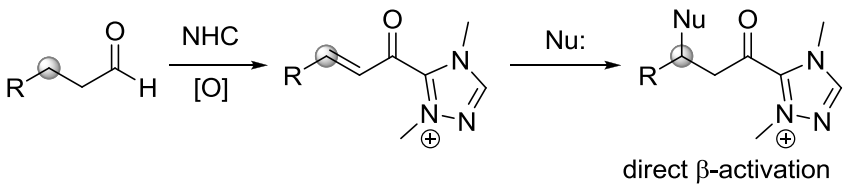
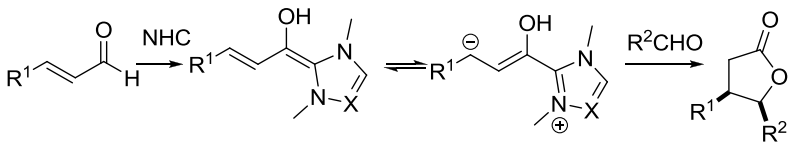
Chapter 3

Oxidative NHC-Catalyzed Direct β-Activation of Saturated Aldehydes as Formal Michael Acceptors

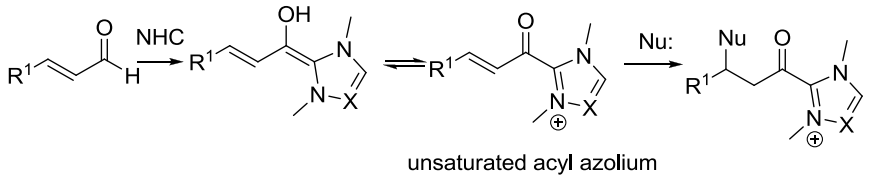


3.1 Introduction

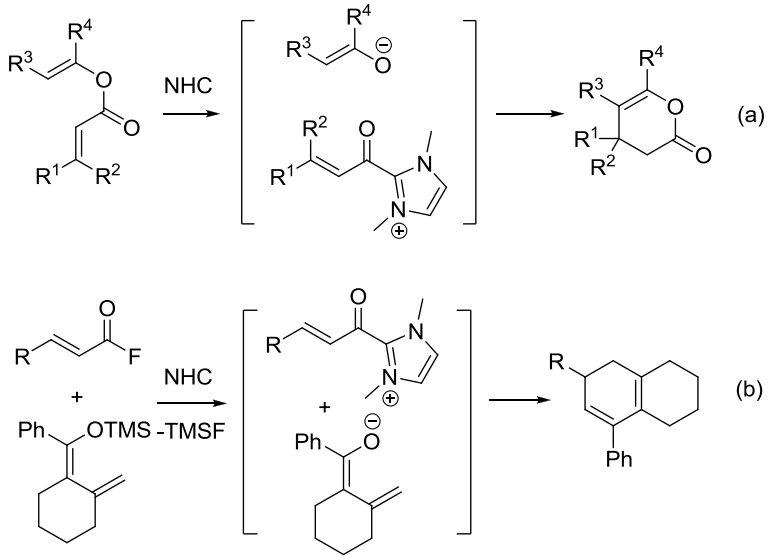
Activation of simple carbonyl compounds, such as saturated esters and aldehydes, is powerful strategy for constructing complex organic molecules. Reactions occurring at the carbonyl carbon atom or the α-carbon atom of carbonyl compounds have been well-studied. In organocatalysis, enamine[1] or SOMO[2] catalysis has been successfully applied to functionalization of the α-carbon atom of aldehydes. Recently, our group reported NHC catalyzed α-functionalization of saturated esters.[3] In the same year, Rovis[4a] and our group[4b] independently developed α- functionalization of saturated aldehydes via oxidative NHC catalysis. To realize β-functionalization of carbonyl compounds, reactions usually start with α,β-unsaturated compounds as substrates. In NHC catalysis, β-activation of an α,β-unsaturated aldehyde could be achieved via a homoenolate pathway, developed by Bode and Glorius (Scheme 3.1).[5] Michael addition to α,β-unsaturated acyl azolium, genereated from ynals[6] or oxidation of enals,[7] was also a successful approach to β-functionalization in NHC catalysis (Scheme 3.2). Besides, Lupton reported pioneering works on a new strategy for the generation of α,β-unsaturated acyl-imidazoliums, which were generated from enol ester[8a] (a, Scheme 3.3) and acyl fluorides[8b] (b, Scheme 3.3) under NHC catalysis for functionalizations of the β-sp^2 carbon atoms.



Scheme 3.1 β-functionalization via homoenolate intermediates



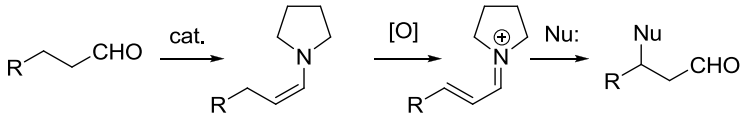
Scheme 3.2 β- functionalization via α,β-unsaturated acyl azolium as Michael acceptors



Scheme 3.3 β- functionalization of α,β-unsaturated enol esters (a) and acyl fluorides (b) by Lupton

Compared to those successful catalytic approaches to functionalization of α-sp^3 carbon atoms [3][4] and/or β-sp^2 carbon atoms[5][6][7][8] of carbonyl compounds, activation of the relatively inert β-sp^3 carbon of simple saturated carbonyl compounds is underdeveloped. It is worth noting that the β-position of saturated amides or esters could be activated under transition metal catalysis.[9] In organocatalysis, β-carbon functionalization of saturated aldehydes by oxidation of enamines was disclosed by Wang, Hayashi, and Enders (Scheme 3.4).[10] Enamine

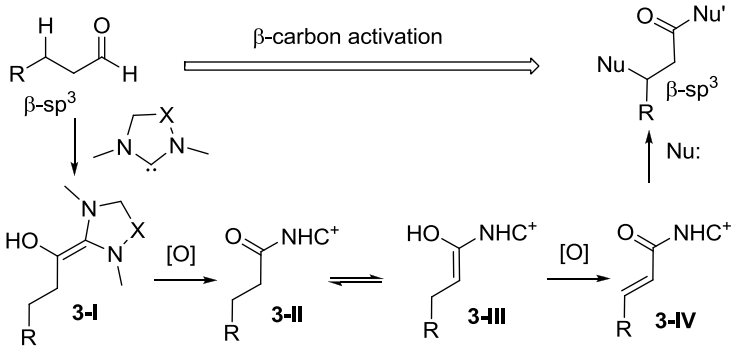
intermediates are oxidized to the corresponding *α,β*-unsaturated iminium ions, which can react with nucleophiles. Although this elegant progress is impressive, organocatalytic direct activation of *β*-C(sp^3) of simple saturated carbonyl compounds is still underdeveloped. The development of new strategies for this research field is desired.



Scheme 3.4 *β*-activation of saturated aldehyde via oxidation of enamines

Our proposal

In this work, we try to develop oxidative NHC-catalyzed direct *β*-activation of simple saturated aldehydes. The project hypothesis is shown in Scheme 3.5. Oxidation of Breslow intermediates to NHC-bounded ester intermediates (**3-I** to **3-II**) had been investigated before by several research groups. The NHC-bounded ester intermediate is transformed into a nenolate equivalent (**3-II** to **3-III**) via deprotonation of the *α*-CH of the intermediate **3-II**. This process was disclosed in the previous work on NHC-catalyzed ester activation[3] by our group and in the recent studies on *α*-functionalization of simple aldehydes via oxidative NHC-catalysis by Rovis[4a] and our group[4b]. To generate the key *α,β*-unsaturated acyl azolium intermediate, further oxidation of the enolate intermediate is realized. The key intermediate (**3-IV**) could react with nucleophiles to give desired *β*-activation products.



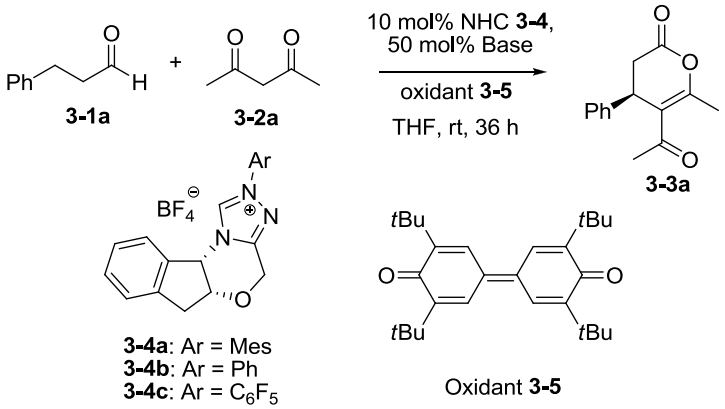
Scheme 3.5 Project hypothesis: *β*-activation of saturated aldehyde

3.2 Results and discussions

We took the reaction between 3-phenyl propionaldehyde (**3-1a**, 1.0 equiv) and acetylacetone (**3-2a**, 1.0 equiv) as a model reaction. With a chiral triazolium NHC (**3-4a**, 0.1 equiv) as a precatalyst and a quinone **3-5** as an oxidant (Table 3.1, entry 1), the desired lactone product **3-3a** was obtained in a low yield (33% yield) and enantioselectivity (76:24 er) through activation of the *β*-CH of the aldehyde (Table 3.1, entry 1). Encouraged by this proof of concept, we started optimization of the reaction conditions. Hydrolysis of the acyl azolium intermediate produced unsaturated and saturated acids as by-products, leading to a low yield of the desired product. Therefore, an excess amount of aldehyde (2.5 equivalents) brought an impressive improvement of the yield (88% yield; Table 3.1, entry 2). NHCs **3-4b** and **3-4c** were less effective in term of both yield and enantioselectivity (Table 3.1, entry 3-4). Screening of bases suggested that an inorganic base give higher yield, and Cs_2CO_3 was still the best among others (Table 3.1, entry 5-8). Next the solvent effect was also examined. Toluene as

solvent could provide higher enantioselectivity (91:9 er; Table 3.1, entry 9), but moderate yield of product (54%). Then our attention turned to improvement of enantioselectivity by using Lewis acids or other additives in THF or toluene. Improvement of enantioselectivity of NHC catalysis by Lewis acids has benn previous observed by Scheidt, You, Zhao, and our group.[11] In this work, we found that LiCl could enhance er for reactions in both tetrahydrofuran and toluene (entries 12, 13 and 18). Molecular sieves as additive gave a slight improvement of er value in tetrahydrofuran but a remarkable drop of er in toluene (entries 16, 17). Finally, a combination of LiCl and 4A MS as additivse in THF could lead to the best result (92% yield, 95:5 er; entry 18).

Table 3.1 Optimized condition[a]



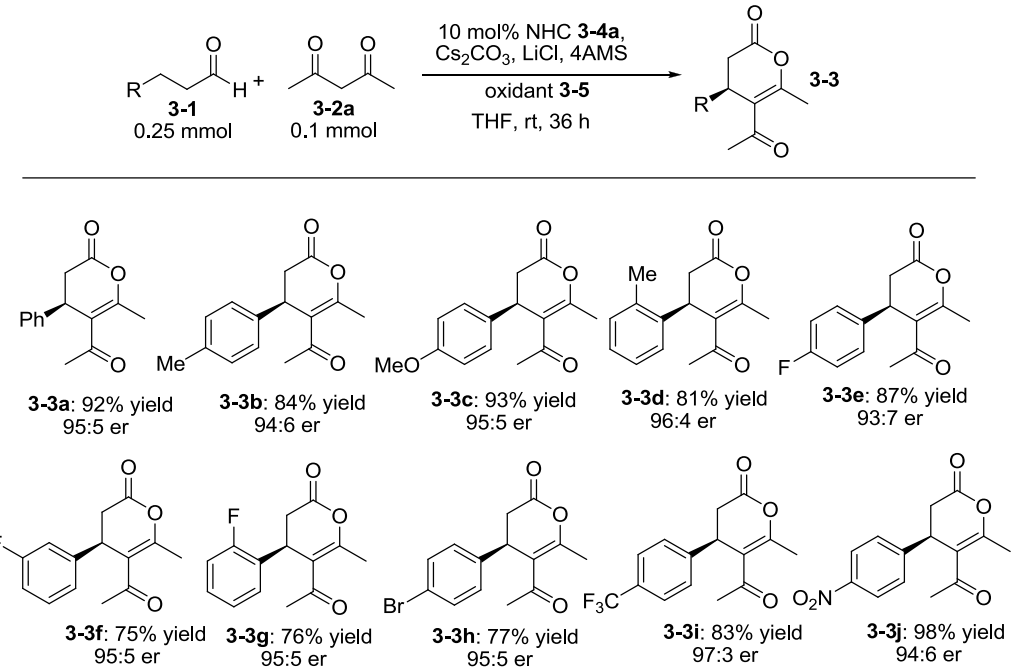
Entry	NHC	Base	Solvent	Lewis acids	Yield (%)[c]	er[d]
1[b]	**3-4a**	Cs_2CO_3	THF	-	33	76:24
2	**3-4a**	Cs_2CO_3	THF	-	88	76:24
3	**3-4b**	Cs_2CO_3	THF	-	62	62:28
4	**3-4c**	Cs_2CO_3	THF	-	<5	-
5	**3-4a**	DBU	THF	-	63	65:35
6	**3-4a**	DIEA	THF	-	<5	-
7	**3-4a**	KAcO	THF	-	84	76:24
8	**3-4a**	K_2CO_3	THF	-	76	78:22
9	**3-4a**	Cs_2CO_3	toluene	-	54	91:9

10	**3-4a**	Cs_2CO_3	CH_3CN	-	<5	-
11	**3-4a**	Cs_2CO_3	CH_2Cl_2	-	50	67:33
12	**3-4a**	Cs_2CO_3	THF	LiCl[e]	92	89:11
13	**3-4a**	Cs_2CO_3	toluene	LiCl[e]	41	94:6
14	**3-4a**	Cs_2CO_3	THF	$Sc(OTf)_3$[e]	77	71:29
15	**3-4a**	Cs_2CO_3	THF	$Mg(OTf)_2$[e]	58	72:28
16	**3-4a**	Cs_2CO_3	THF	4A MS[f]	81	85:15
17	**3-4a**	Cs_2CO_3	toluene	4A MS[f]	51	80:20
18	**3-4a**	Cs_2CO_3	THF	LiCl[e] + 4A MS[f]	92	95:5

[a] Standard conditions: **3-1a** (0.25 mmol), **3-2a** (0.1 mmol), **3-4** (0.01 mmol), **3-5** (0.4 mmol), solvent (1 mL), 36 h. [b] **3-1a** (0.1 mmol), **3-2a** (0.1 mmol), **3-4** (0.01 mmol), **3-5** (0.2 mmol), solvent (1 mL), 36 h. [c] Isolated yield based on **3-2a**. [d] Enantiomeric ratio of **3-3a** was determined via Chiral HPLC. [e] 0.1 mmol Lewis acids. [f] 20 mg 4A MS powder.

With the optimized conditions in hand, we screened the substrate scope of aldehydes. When the aryl groups were installed at the *β*-position of aldehydes, all the reactions provided desired products in good yields and er values. The yield and enantioselectivity of the reaction were less sensitive to electronic properties of substituent on the *β*-aryl groups. However, aldehydes with alkyl group in the *β*-position or with *β*,*β*-disubstituents did not give the desired *δ*-lactones under the standard reaction conditions. In these cases only the corresponding saturated carboxylic acids were detected as products generated by trapping of the acyl azolium intermediates by residual water. Note that the *β*-activation of *β*-alkyl-aldehydes was also challenging in the related enamine-catalyzed oxidative strategy.

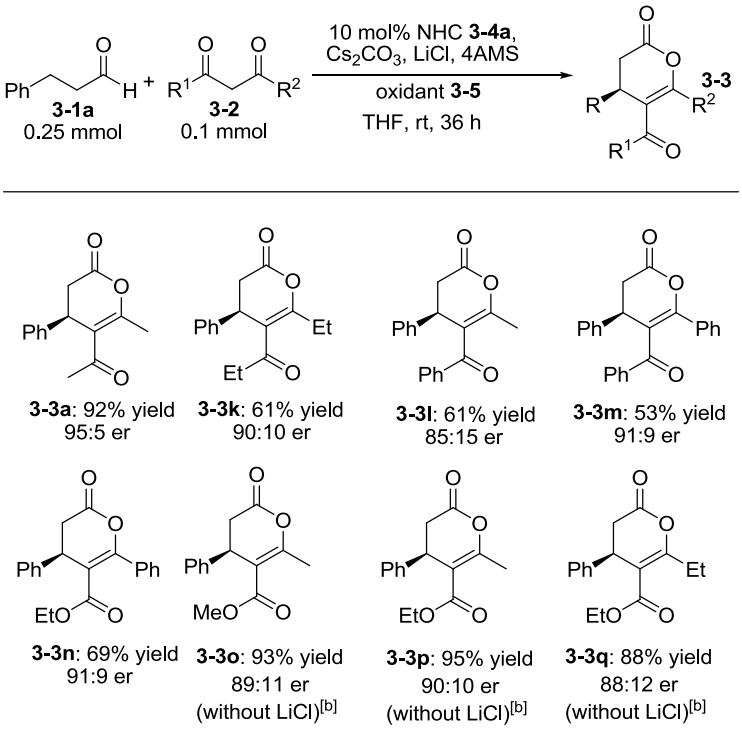
Chart 3.1 Scope of saturated aldehyde **3-1**[a]



[a] Reaction conditions as entry 18, in Table 3.1.

The substrate scope of 1,3-dicarbonyl compounds was also explored. Both alkyl and aryl-substituted 1,3-diketones could be tolerated (**3-3k** to **3-3m**). When the standard reaction conditions were applied to *β*-keto esters (**3-3o** to **3-3q**), no desired Michael addition product was generated, and conversion of the aldehyde substrate was very low. Interestingly, we found that the desired product could be generated in good yields and enantioselectivity in the absence of LiCl. The reason why LiCl inhibits the desired transformation in the cases of ketoesters (**3-3o** to **3-3q**) is unclear.

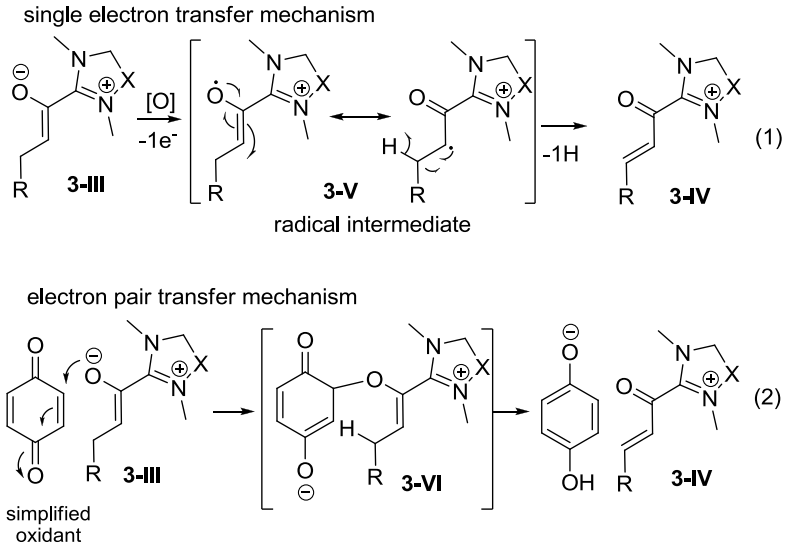
Chart 3.2 Scope of 1,3-dicarbonyl compounds **3-2**[a]



[a] Reaction conditions as entry 18, in Table 3.1. [b] Reaction was performed without LiCl.

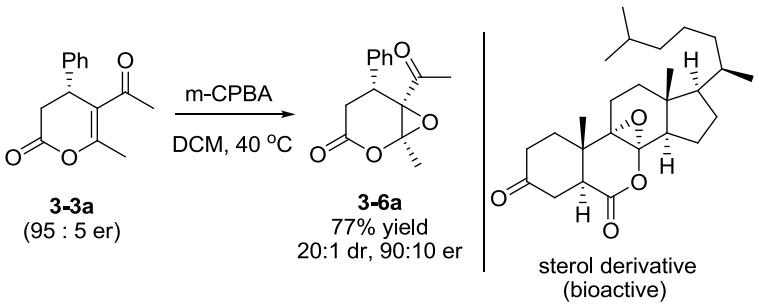
Two proposed pathways for the oxidative transformation of a NHC-bounded enolate equivalent to the acyl azolium intermediate are summarized in Scheme 3.6. The first mechanism would produce a radical intermediate via single electron transfer (Scheme 3.6, eq 1).[12] Our effort to trap the radical intermediate by using TEMPO (a common scavenger) failed. The reaction proceeded smoothly in the presence of TEMPO (1.0 equiv, relative to **3-2a**) to afford *δ*-lactone **3-3a** in a good yield (68%; compared to 88% yield obtained in entry 2, Table 3.1; the enantioselectivity was not affected). This result indicated that the oxidative process might not go through the radical intermediates **3-V**, and single electron transfer mechanism was unlikely the dominating one. The second pathway via electron pair transfer seems to be probable (Scheme 3.6, eq 2).[13] When the R group is an alkyl group, the enolate intermediate (**3-III**) could not be oxidized to the *α,β*-unsaturated

acyl azolium intermediate (**3-IV**). The relatively weak acidity of the *β*-CH of the alkyl-intermediate **3-VI** may be major hinderance for the sequential oxidation.



Scheme 3.6 Plausible oxidative pathways of enolate intermediate

The enol *δ*-lactone product could be transformed into a compound with a useful *δ*-lactone epoxide skeleton under simple reaction conditions. For example, *δ*-lactone **3-3a** reacted with *m*-CPBA to afford an enantioenriched *δ*-lactone epoxide **3-6a** in good yield and excellent diastereoselectivity, which features the core structure of a bioactive sterol derivative.



Scheme 3.7 Chemical transformation of *δ*-lactone **3-3a**

3.3 Conclusions

In conclusion, we have achieved a direct β-C (sp^3) functionalization of simple saturated aldehydes via oxidative NHC catalysis. Oxidation of NHC-bounded enolate equivalents to α,β-unsaturated acyl azolium intermediates is realized for the first time. Enol δ-lactones are formed via formal Michael addition of the α,β-unsaturated acyl azolium and 1,3-dicarbonyl compounds in good yields and enantioslectivities.

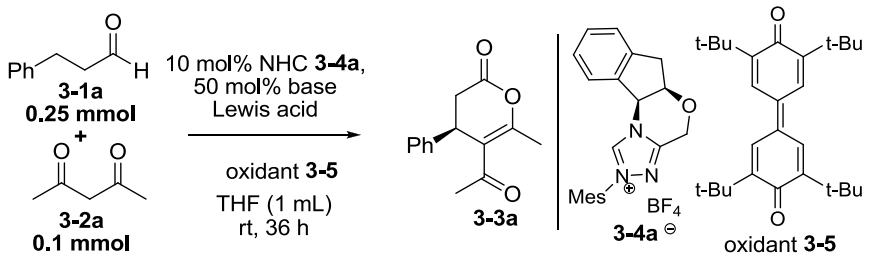
3.4 Experimental section

3.4.1 General information

Commercially available materials purchased from Alfa Aesar or Aldrich was used as received. Anhydrous tetrahydrofuran and toluene were distilled from benzophenone and sodium. Dichloromethane and acetonitrile were distilled over CaH_2. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100

MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. The determination of er was performed via chiral phase HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 1 mL cell with a 1 cm path length on a Jasco P1030 digital polarimeter and are reported as follows: $[\alpha]_D^T$ (concentration (g/100 ml), solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

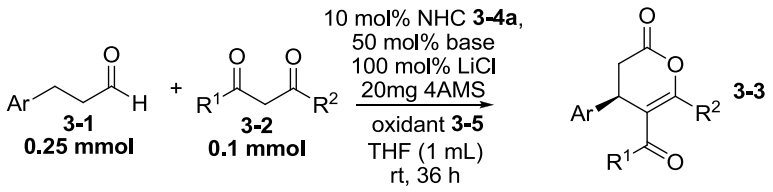
3.4.2 LiCl and 4A MS[a]



Entry	Base	LiCl (mol%)	4A MS (mg)	Yield (%)[b]	er[c]
1	Cs_2CO_3	-	-	88	76:24
2	Cs_2CO_3	10	-	92	83:17
3	Cs_2CO_3	50	-	91	88:12
4	Cs_2CO_3	100	-	92	89:11
5	Cs_2CO_3	150	-	-	-
6	Cs_2CO_3	100	10	89	92:8
7	Cs_2CO_3	100	20	92	95:5
8	Cs_2CO_3	100	50	88	95:5
9	Cs_2CO_3	100	100	79	95:5

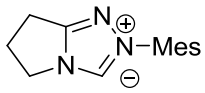
[a] Standard conditions: 0.25 mmol **3-1a**, 0.1 mmol **3-2a**, 0.4 mmol **3-5**. [b] Isolated yield based on **3-2a**. [c] Enantiomeric ratio of **3-3a** was determined via Chiral HPLC.

3.4.3 General procedure for the catalytic reactions

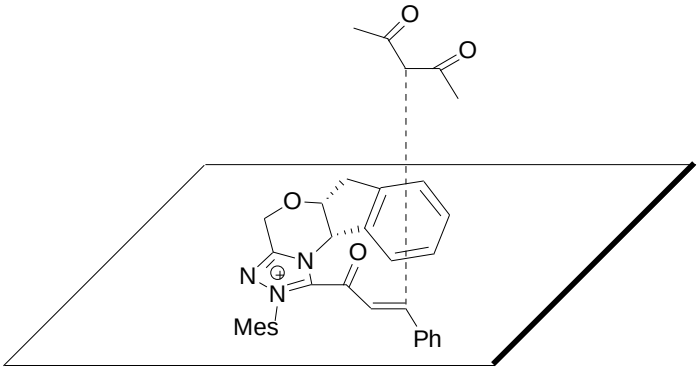


To a dry Schlenk tube with a magnetic stir bar, was added aldehyde **3-1** (0.25 mmol), 1,3-dicarbonyl compounds **3-2** (0.1 mmol), triazolium salt **3-4a** (0.01 mmol), oxidant **3-5** (0.4 mmol), LiCl (0.1mmol), 4A MS powder (20 mg) and Cs_2CO_3 (0.05 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled tetrahydrofuran (1mL) was added to the tube and then the mixture was stirred at room temperature till 1,3-dicarbonyl compounds was completely consumed (monitored by TLC). The solvent was removed by rotary distillation. The resulting residue was purified through column chromatography on silica gel (3:1 hexanes/EtOAc) to provide the desired product **3-3**.

Note: Racemic samples for chiral phase HPLC analysis were prepared using **3-4d** as the NHC pre-catalyst without the presence of Lewis acid co-catalyst and 4AMS. Absolute configuration of the products were estimated *via* optical rotation comparisons [e.g., **3-3a:**$[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -111.0; literature value:$[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -114.3] with literature.[14] The stereochemical model of the enantioselectivity-determining is shown below (Scheme 3.8).

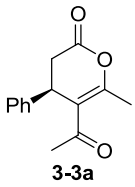


3-4d BF_4



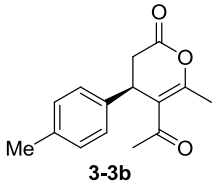
Scheme 3.8 Stereochemical model of the enantioselectivity-determining

3.4.4 Characterization of Products



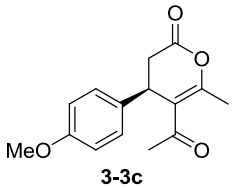
3-3a

(*R*)-5-acetyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (3-3a): Colorless solid, yield: 21.2 mg (92%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -111.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.12 (s, 3 H), 2.43 (s, 3 H), 2.83 (dd, *J* = 2.4, 15.6 Hz, 1 H), 2.97 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.15 (d, *J* = 6.0 Hz, 1 H), 7.15 (d, *J* = 6.9 Hz, 2 H), 7.26-7.36 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 29.8, 37.2, 38.9, 117.3, 126.7, 127.9, 129.4, 139.7, 160.3, 165.6, 197.9; HRMS (ESI) calcd for $C_{14}H_{15}O_3$ $(M+H)^+$: 231.1021 Found: 231.1013; 95:5 er determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_r(R)$ = 21.6 min, $t_r(S)$ = 16.5 min.



3-3b

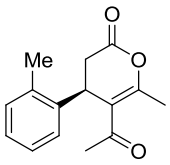
(*R*)-5-acetyl-6-methyl-4-p-tolyl-3,4-dihydro-2*H*-pyran-2-one (3-3b): Colorless solid, yield: 20.5 mg (84%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -120.1; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.12 (s, 3 H), 2.32 (s, 3 H), 2.42 (s, 3 H), 2.79 (dd, *J* = 2.4, 15.6 Hz, 1 H), 2.95 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.10 (d, *J* = 6.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 21.0, 29.7, 37.3, 38.5, 117.4, 126.5, 130.1, 136.6, 137.7, 160.1, 165.7, 198.0; HRMS (ESI) calcd for $C_{15}H_{17}O_3$ $(M+H)^+$: 245.1178 Found: 245.1192; 94:6 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), $t_r(R)$ = 29.0 min, $t_r(S)$ = 22.1 min.



3-3c

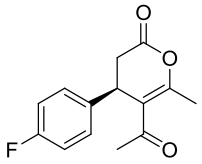
(*R*)-5-acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (3-3c): Colorless solid, yield: 24.2 mg (89%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -122.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.12 (s, 3 H), 2.42 (s, 3 H), 2.79 (dd, *J* = 2.4, 15.6 Hz, 1 H), 2.94 (dd, *J* = 7.2, 15.6 Hz, 1 H), 3.78 (s, 3 H), 4.09 (d, *J* = 5.6 Hz, 1 H), 7.03 (dd, *J* = 2.0, 6.8 Hz, 2 H), 7.13 (dd, *J* = 2.0, 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 29.7, 37.4, 38.1, 55.3, 114.8, 117.5, 127.8, 131.5, 159.2, 160.0, 165.8, 198.1; HRMS (ESI) calcd for $C_{15}H_{17}O_4$ $(M+H)^+$: 261.1127 Found: 261.1135; 95:5 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), $t_r(R)$ =

48.4 min, $t_r(S)$ = 40.8 min.



3-3d

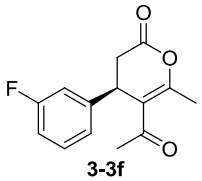
(*R*)-5-acetyl-6-methyl-4-o-tolyl-3,4-dihydro-2*H*-pyran-2-one (3-3d): Colorless solid, yield: 19.7 mg (81%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -101.5; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05 (s, 3 H), 2.41 (s, 3 H), 2.45 (s, 3 H), 2.72 (dd, *J* = 2.8, 15.6 Hz, 1 H), 2.94 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.35 (d, *J* = 6.4 Hz, 1 H), 6.97 (d, *J* = 8.8 Hz, 1 H), 7.15-7.22 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 19.2, 29.3, 35.0, 35.5, 117.3, 125.5, 127.2, 127.9, 131.4, 134.7, 137.2, 160.5, 165.6, 197.9; HRMS (ESI) calcd for $C_{15}H_{17}O_3$ $(M+H)^+$: 245.1178 Found: 245.1189; 96:4 er determined by HPLC (OD-H, 98:2 hexanes/*i*-PrOH, 0.75ml/min), $t_r(R)$ = 33.0 min, $t_r(S)$ = 37.3 min.



3-3e

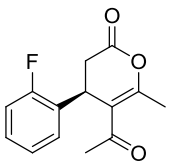
(*R*)-5-acetyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (3-3e): Colorless solid, yield: 21.7 mg (87%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -109.3; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.14 (s, 3 H), 2.43 (s, 3 H), 2.81 (dd, *J* = 2.4, 15.6 Hz, 1 H), 2.96 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.16 (d, *J* = 6.4 Hz, 1 H), 7.03 (t, *J* = 8.0 Hz, 2 H), 7.11-7.14 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 29.8, 37.2, 38.1, 116.4 (d, *J* = 22 Hz), 117.4, 128.3 (d, *J* = 8 Hz), 135.4 (d, *J* = 3 Hz), 160.4, 162.5 (d, *J* = 251

Hz), 165.4, 197.6; HRMS (ESI) calcd for $C_{14}H_{14}O_3F$ $(M+H)^+$: 249.0927 Found: 249.0935; 93:7 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), t_r(*R*) = 39.9 min, t_r(*S*) = 28.3 min.



3-3f

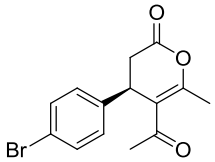
(*R*)-5-acetyl-4-(3-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (3-3f): Colorless solid, yield: 18.6 mg (75%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -128.7; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.16 (s, 3 H), 2.44 (s, 3 H), 2.84 (dd, *J* = 2.8, 15.6 Hz, 1 H), 2.98 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.17 (d, *J* = 6.4 Hz, 1 H), 6.85 (d, *J* = 9.6 Hz, 1 H), 6.94-7.01 (m, 2 H), 7.31 (q, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 29.9, 36.9, 38.4, 113.8 (d, *J* = 19 Hz), 115.0 (d, *J* = 21 Hz), 117.0, 122.3 (d, *J* = 3 Hz), 131.1 (d, *J* = 8 Hz), 142.3 (d, *J* = 7 Hz), 160.8, 163.3 (d, *J* = 246 Hz), 165.2, 197.4; HRMS (ESI) calcd for $C_{14}H_{14}O_3F$ $(M+H)^+$: 249.0927 Found: 249.0938; 95:5 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), t_r(*R*) = 48.2 min, t_r(*S*) = 31.5 min.



3-3g

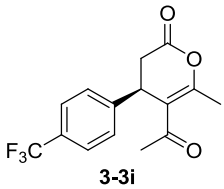
(*S*)-5-acetyl-4-(2-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (3-3g): Colorless solid, yield: 18.9 mg (76%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -141.5; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (s, 3 H), 2.45 (s, 3 H), 2.88 (dd, *J* = 2.4, 15.6 Hz, 1 H),

2.97 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.51 (d, *J* = 5.6 Hz, 1 H), 7.00-7.05 (m, 1 H), 7.08-7.13 (m, 2 H), 7.26-7.30 (m, 1 H),; ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 29.4, 31.8 (d, *J* = 3 Hz), 35.5, 115.7, 116.1 (d, *J* = 21 Hz), 124.9 (d, *J* = 3 Hz), 126.2 (d, *J* = 14 Hz), 127.6 (d, *J* = 3 Hz), 129.8 (d, *J* = 8 Hz), 160.2 (d, *J* = 245 Hz), 161.3, 165.4, 197.4; HRMS (ESI) calcd for $C_{14}H_{14}O_3F$ $(M+H)^+$: 249.0927 Found: 249.0932; 95:5 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), t_r(*S*) = 22.8 min, t_r(*R*) = 19.5 min.



3-3h

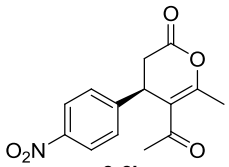
(*R*)-5-acetyl-4-(4-bromophenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (3-3h): Colorless solid, yield: 23.6 mg (77%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -111.5; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3 H), 2.43 (s, 3 H), 2.80 (dd, *J* = 2.4, 15.6 Hz, 1 H), 2.96 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.14 (d, *J* = 6.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 29.9, 36.9, 38.2, 117.1, 121.9, 128.4, 132.6, 138.8, 160.6, 165.2, 197.4; HRMS (ESI) calcd for $C_{14}H_{14}O_3Br$ $(M+H)^+$: 309.0126 Found: 309.0114; 95:5 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), t_r(*R*) = 52.3 min, t_r(*S*) = 37.1 min.



3-3i

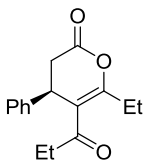
(*R*)-5-acetyl-6-methyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyran-2-o

ne (3-3i): Colorless solid, yield: 24.6 mg (83%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -88.2; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3 H), 2.46 (s, 3 H), 2.84 (dd, *J* = 2.4, 15.6 Hz, 1 H), 3.00 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.26 (d, *J* = 6.8 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.60 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 30.0, 36.7, 38.5, 117.1, 123.8 (q, *J* = 257 Hz), 126.4 (q, *J* = 3 Hz), 127.2, 130.4 (q, *J* = 33 Hz), 144.0, 160.9, 165.1, 197.1; HRMS (ESI) calcd for $C_{15}H_{14}O_3F_3$ $(M+H)^+$: 299.0895 Found: 299.0899; 97:3 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), $t_r(R)$ = 52.8 min, $t_r(S)$ = 34.3 min.



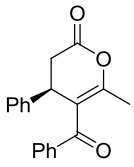
3-3j

(*R*)-5-acetyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydro-2*H*-pyran-2-one (3-3j): Colorless solid, yield: 27.0 mg (98%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -102.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3 H), 2.48 (s, 3 H), 2.85 (dd, *J* = 2.4, 15.6 Hz, 1 H), 3.02 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.34 (d, *J* = 6.8 Hz, 1 H), 7.34 (dd, *J* = 1.6, 6.8 Hz, 2 H), 8.21 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 30.3, 36.3, 38.3, 117.1, 124.6, 127.8, 147.3, 147.6, 161.3, 164.7, 196.6; HRMS (ESI) calcd for $C_{14}H_{14}O_5N$ $(M+H)^+$: 276.0872 Found: 276.0879; 94:6 er determined by HPLC (OD-H, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_r(R)$ = 41.2 min, $t_r(S)$ = 28.8 min.



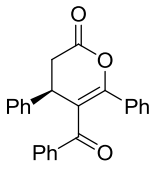
3-3k

(*R*)-6-ethyl-4-phenyl-5-propionyl-3,4-dihydro-2*H*-pyran-2-one (3-3k): Colorless solid, yield: 15.7 mg (61%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -58.6; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.6 Hz, 3 H), 2.15 (dq, *J* = 17.8, 7.2 Hz, 1 H), 2.42 (dq, *J* = 17.8, 7.2 Hz, 1 H), 2.72-2.84 (m, 3 H), 2.95 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.11 (dd, *J* = 2.8, 7.2 Hz, 1 H), 7.14 (d, *J* = 7.2 Hz, 2 H), 7.26-7.36 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.84, 11.9, 25.3, 34.6, 37.3, 38.6, 116.4, 126.6, 127.9, 129.4, 139.7, 163.7, 165.9, 201.1; HRMS (ESI) calcd for $C_{16}H_{19}O_3$ $(M+H)^+$: 259.1334 Found: 259.1325; 90:10 er determined by HPLC (OD-H, 99:1 hexanes/*i*-PrOH, 0.75ml/min), $t_r(R)$ = 39.6 min, $t_r(S)$ = 23.1 min.



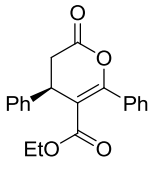
3-3l

(*R*)-5-benzoyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (3-3l): Colorless solid, yield: 17.8 mg (61%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -25.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.82 (d, *J* = 0.8 Hz, 3 H), 2.93 (dd, *J* = 2.4, 15.6 Hz, 1 H), 3.07 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.33 (dd, *J* = 3.2, 7.2 Hz, 1 H), 7.13-7.15 (m, 2 H), 7.21-7.28 (m, 3 H), 7.38-7.41 (m, 2 H), 7.50-7.52 (m, 1 H), 7.62-7.64 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 36.2, 39.4, 117.7, 126.8, 127.6, 128.7, 128.8, 129.2, 133.1, 138.4, 139.9, 154.8, 166.5, 195.8; HRMS (ESI) calcd for $C_{19}H_{17}O_3$ $(M+H)^+$: 293.1187 Found: 193.1186; 85:15 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), $t_r(R)$ = 27.9 min, $t_r(S)$ = 21.8 min.



3-3m

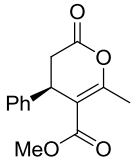
(*R*)-5-benzoyl-4,6-diphenyl-3,4-dihydro-2*H*-pyran-2-one (3-3m): Colorless solid, yield: 18.6 mg (53%); $[\alpha]_D^{20}$ (c 2.0, $CHCl_3$): -8.4; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.06 (dd, *J* = 2.4, 15.6 Hz, 1 H), 3.21 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.56 (dd, *J* = 3.2, 7.2 Hz, 1 H), 7.06-7.17 (m, 5 H), 7.21-7.29 (m, 6 H), 7.36-7.38 (m, 2 H), 7.48-7.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.9, 40.4, 118.3, 126.8, 127.8, 127.9, 128.0, 129.0, 129.2, 129.2, 130.3, 131.9, 132.6, 137.1, 139.7, 154.8, 166.7, 195.9; HRMS (ESI) calcd for $C_{24}H_{19}O_3$ $(M+H)^+$: 355.1334 Found: 355.1326; 91:9 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), t_r(*R*) = 25.6 min, t_r(*S*) = 32.2 min.



3-3n

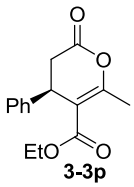
(*R*)-ethyl 2-oxo-4,6-diphenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (3-3n): Colorless solid, yield: 22.2 mg (69%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -6.7; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 2.94 (dd, *J* = 2.4, 15.6 Hz, 1 H), 3.10 (dd, *J* = 7.2, 15.6 Hz, 1 H), 3.89-3.97 (m, 2 H), 4.41 (dd, *J* = 2.4, 7.6 Hz, 1 H), 7.24-7.29 (m, 3 H), 7.32-7.34 (m, 2 H), 7.41-7.45 (m, 3 H), 7.50-7.53 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 36.3, 38.8, 61.0, 111.7, 126.7, 127.7, 128.0, 128.6, 129.2, 130.1, 133.1, 139.9, 158.5, 166.0, 166.4; HRMS (ESI) calcd for

$C_{20}H_{19}O_4$ $(M+H)^+$: 323.1283 Found: 323.1292; 91:9 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), t_r(*R*) = 21.0 min, t_r(*S*) = 17.2 min.



3-3o

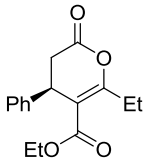
(*R*)-methyl 6-methyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (3-3o): Colorless solid, yield: 22.8 mg (93%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -133.5; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (d, *J* = 1.0 Hz, 3 H), 2.83 (dd, *J* = 2.4, 15.6 Hz, 1 H), 2.94 (dd, *J* = 7.2, 15.6 Hz, 1 H), 3.68 (s, 3 H), 4.26 (d, *J* = 6.0 Hz, 1 H), 7.13 (d, *J* = 6.9 Hz, 2 H), 7.24-7.32 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 36.5, 37.7, 51.9, 109.7, 126.6, 127.6, 129.1, 140.4, 161.8, 166.1, 166.5; HRMS (ESI) calcd for $C_{14}H_{15}O_4$ $(M+H)^+$: 247.0970 Found: 247.0962; 89:11 er determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.7ml/min), t_r(*R*) = 32.0 min, t_r(*S*) = 13.2 min.



3-3p

(*R*)-ethyl 6-methyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (3-3p): Colorless solid, yield: 24.7 mg (95%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -141.0; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 2.48 (d, *J* = 1.0 Hz, 3 H), 2.84 (dd, *J* = 2.4, 15.6 Hz, 1 H), 2.93 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.25 (d, *J* = 7.2 Hz, 1 H), 7.14 (d, *J* = 6.9 Hz, 2 H), 7.24-7.30 (m, 3 H); ^{13}C NMR

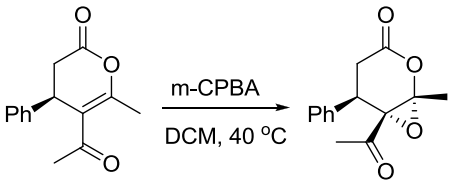
(100 MHz, $CDCl_3$): δ 14.0, 18.9, 36.4, 37.8, 60.9, 110.0, 126.6, 127.5, 129.0, 140.6, 161.3, 165.9, 166.1; HRMS (ESI) calcd for $C_{15}H_{17}O_4$ $(M+H)^+$: 261.1127 Found: 261.1120; 90:10 er determined by HPLC (OD-H, 97:3 hexanes/*i*-PrOH, 0.75ml/min), $t_r(R)$ = 25.9 min, $t_r(S)$ = 12.3 min.



3-3q

(*R*)-ethyl 6-ethyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (3-3q): Colorless solid, yield: 24.1 mg (88%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -101.7; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 2.79-2.84 (m, 2 H), 2.88-2.96 (m, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.25 (dd, *J* = 2.4, 7.6 Hz, 1 H), 7.12-7.14 (m, 2 H), 7.20-7.32 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 14.0, 25.5, 36.4, 37.8, 60.8, 109.3, 126.6, 127.5, 129.0, 140.6, 165.8, 165.9, 166.3; HRMS (ESI) calcd for $C_{16}H_{19}O_4$ $(M+H)^+$: 275.1283 Found: 275.1278; 88:12 er determined by HPLC (IA, 99:1 hexanes/*i*-PrOH, 0.5ml/min), $t_r(R)$ = 19.8 min, $t_r(S)$ = 18.7 min.

3.4.5 Chemical transformation of *δ*-lactone



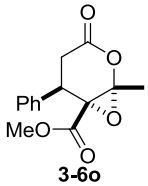
3-3a

3-6a: 77% yield
>20:1 dr, 90:10 er

To solution of **3-3a** (23.1 mg, 0.1 mmol) in DCM (1.0 mL) at room temperature was added *m*-CPBA (55%, 63.0 mg, 0.2 mmol). After 16 h of stirring at 40^{o}C, the solution was quenched with an aqueous KOH solution (10 wt%, 10 mL). The aqueous phase was extracted twice with DCM. Organic phases were combined, dried over Na_2SO_4 and filtered. Filtrate was concentrated by rotary distillation. The solid residue was purified via SiO_2 flash chromatography (c-Hexane/AcOEt 3:1) to afford **3-6a** (18.9 mg, 77%) as colorless oil.

(1*R*,5*R*,6*R*)-6-acetyl-1-methyl-5-phenyl-2,7-dioxabicyclo[4.1.0]heptan-3-one

(3-6a): Colorless oil, yield: 18.9 mg (77%); $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$): -91.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (s, 3 H), 2.08 (s, 3 H), 2.59 (dd, *J* = 1.6, 16.4 Hz, 1 H), 3.09 (dd, *J* = 7.2, 16.4 Hz, 1 H), 3.82 (d, *J* = 6.4 Hz, 1 H), 7.19-7.21 (m, 2 H), 7.26-7.36 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 27.8, 36.0, 39.8, 68.1, 86.5, 127.3, 128.5, 129.6, 137.5, 165.9, 200.9; HRMS (ESI) calcd for $C_{14}H_{15}O_4$ $(M+H)^+$: 247.0970 Found: 247.0978; 90:10 er determined by HPLC (OD-H, 92:8 hexanes/*i*-PrOH, 0.7ml/min), t_r(*1R,5R,6R*) = 20.4 min, t_r(*1S,5S,6S*) = 18.5 min.



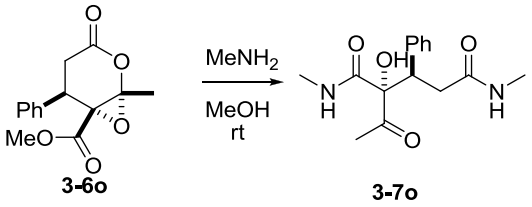
3-6o

(This product was prepared from rac-**3-3o** using the above method)

Methyl 1-methyl-3-oxo-5-phenyl-2,7-dioxabicyclo[4.1.0]heptane-6-carboxylate

(3-6o): Colorless oil, yield: 21.4 mg (81%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (s, 3 H), 2.58 (dd, *J* = 1.6, 16.4 Hz, 1 H), 3.06 (dd, *J* = 7.2, 16.4 Hz, 1 H), 3.62 (s, 3 H), 3.99 (dd, *J* = 1.6, 7.2 Hz, 1 H), 7.18-7.20 (m, 2 H), 7.31-7.38 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 36.0, 39.6, 52.8, 63.1, 86.5, 127.0, 128.1, 129.3, 138.0, 165.9, 166.3; HRMS (ESI) calcd for $C_{14}H_{15}O_5$ $(M+H)^+$: 263.0919 Found: 263.0917.

Synthesis of amide 3-7o:



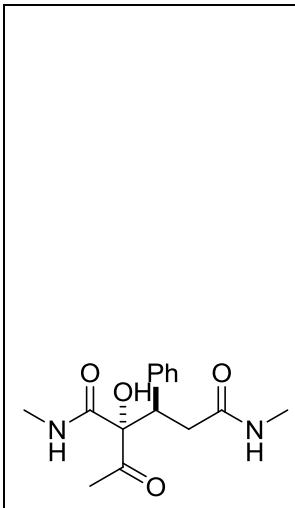
To a stirred solution of **3-6o** (26.2 mg, 0.1 mmol) in methanol (0.5 mL) at room temperature was added $MeNH_2$/MeOH solution (1 mL, 1 mol/L, 1 mmol). After 12 h of stirring at rt, the solution was concentrated by rotary distillation. The crude residue was purified via SiO_2 flash chromatography (Hexane/EtOAc, 1:2) to afford **6o** (26.3 mg, 90%) as a colorless solid.

2-Acetyl-2-hydroxy-*N*1,*N*5-dimethyl-3-phenylpentanediamide (3-7o): Colorless solid, yield: 26.3 mg (90%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3 H), 2.51-2.57 (m, 2 H), 2.59 (d, *J* = 5.2 Hz, 3 H), 2.87 (d, *J* = 5.2 Hz, 3 H), 4.17 (dd, *J* = 4.4, 10.0 Hz, 1 H), 5.15 (s, 1 H), 5.25 (br, 1 H), 7.16-7.26 (m, 3 H), 7.31-7.33 (m,

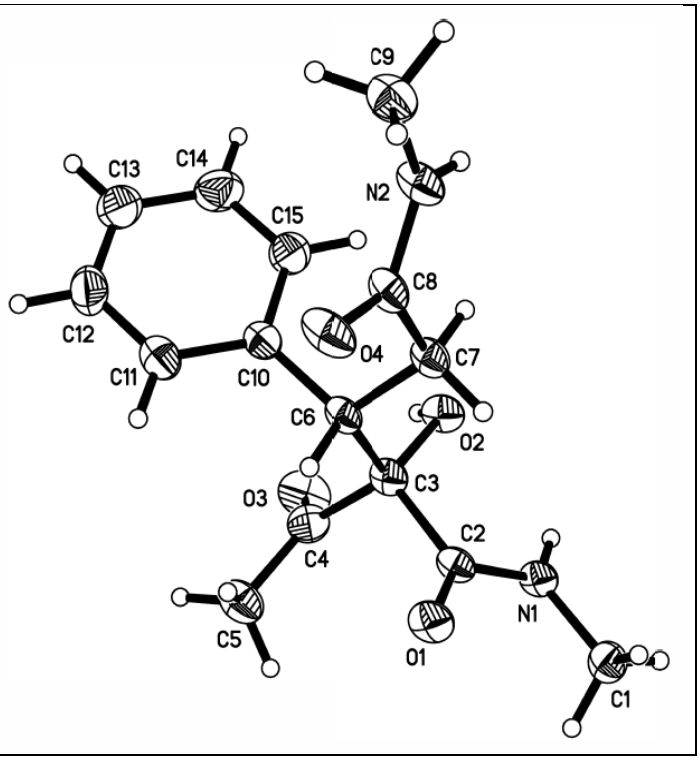
2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 26.2, 26.7, 38.3, 47.9, 87.4, 127.7, 128.4, 128.9, 137.6, 169.2, 171.0, 207.7; HRMS (ESI) calcd for $C_{15}H_{21}N_2O_4$ $(M+H)^+$: 293.1501 Found: 293.1496.

3.4.6 The determination of relative configuration of 3-6

The relative configuration of the product **3-6** was determined by X-ray crystallographic analysis of its racemic amide derivative (**3-7o**). Good quality crystal of **3-7o** (colorless needle crystal) was obtained by vaporization of a acetone/hexane solution of compound **3-7o**. CCDC 938524 contains the supplementary crystallographic data. The data can be approached on the website of www.ccdc.cam.ac.uk/data request/cif.



3-7o



3.5 References

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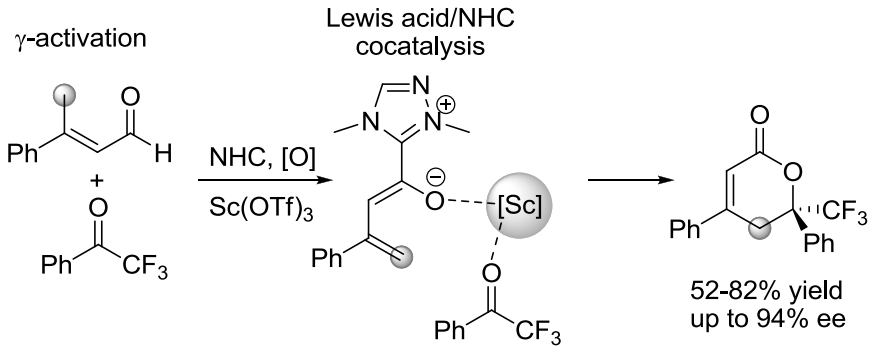
Chapter 4

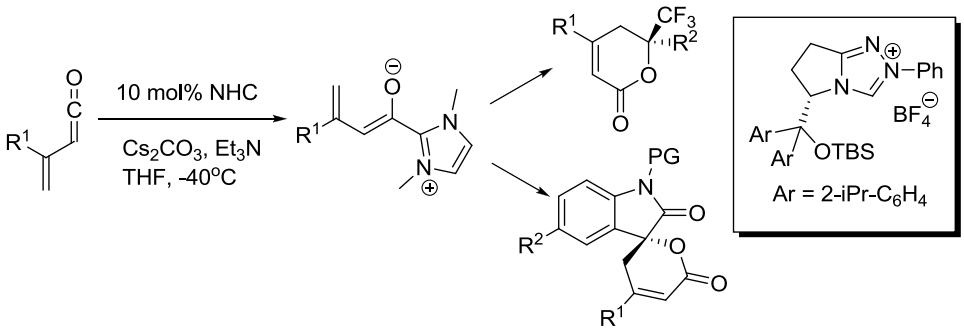
Oxidative NHC-Catalyzed γ-Activation of Enals: Enantioselectivity Control via Lewis Acid/NHC Cooperative Catalysis



4.1 Introduction

4.1.1 NHC-catalyzed *γ*-activation of carbonyl compounds

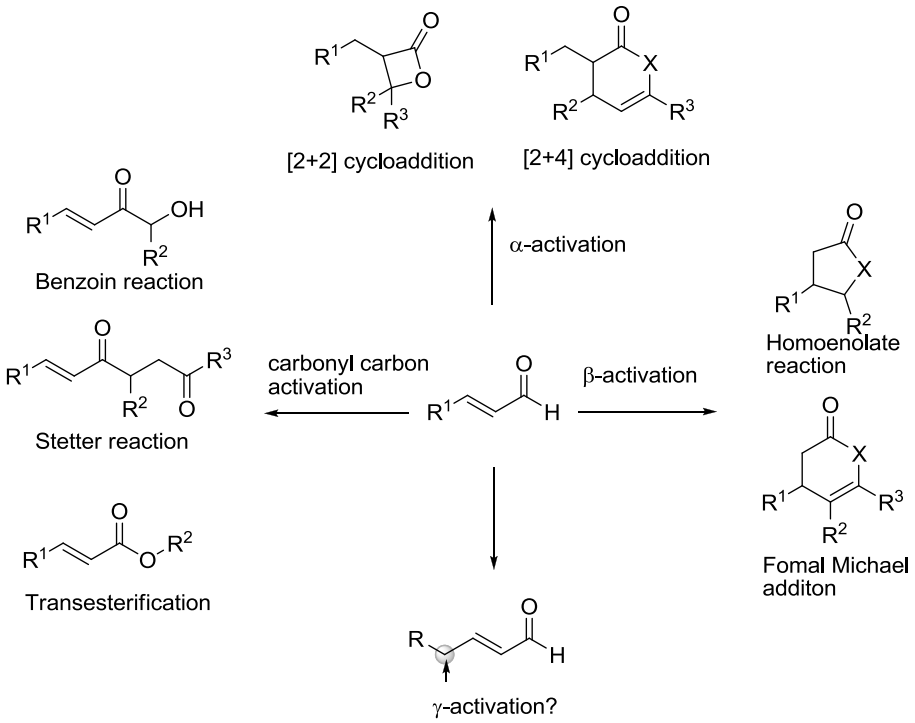
Activation of a C-H bond which is remote form a functional group is significant and challenging. In NHC catalysis, many successful approaches to activation of carbonyl compounds on the carbonyl carbon, the *α*-activation and *β*-activation have been developed (see chapter I). On other hand, *γ*-activation of carbonyl compounds has been rarely investigated. In 2011, Ye group firstly reported enantioselective *γ*-activation of *α,β*-unsaturated ketenes mediated by an NHC-based nucleophilic catalyst (Scheme 4.1).[1]



Scheme 4.1 Vinyl enolate intermediate from ketene for annulation

Activation of *α,β*-unsaturated aldehydes, which are considered basic building blocks in organic synthesis, has been widely investigated in the last decade. In NHC catalysis, nucleophilic addition of the carbene to enals under different reaction conditions can provide acyl anion equivalent (carbonyl carbon activation),[2] NHC-bounded enolate intermediate (*α*-C activation),[3] NHC-bounded homoenolate intermediate (*β*-C activation)[4] and *α,β*-unsaturated acyl azolium (*β*-C activation)[5] for enantioselective reactions. Compared with

these successful approaches to activate carbonyl carbon, α-carbon and β-carbon, strategy for γ-activation of enals is underdeveloped.

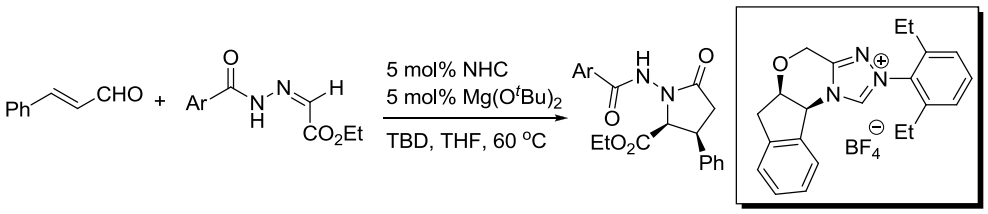


Scheme 4.2 Common activation modes for enals

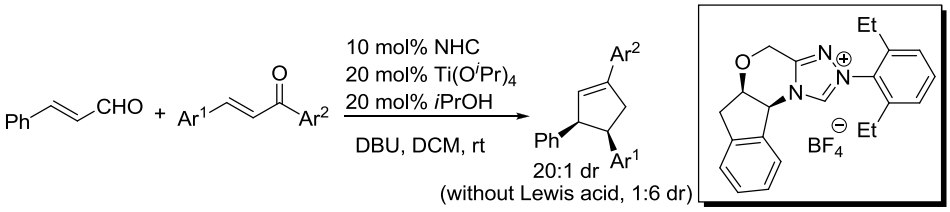
4.1.2 Lewis acid/NHC cooperative catalysis

One apparent difficulty in NHC-catalyzed γ-functionalization of enals is the control of enantioselectivity, because of a relatively long distance between the γ-carbon of enals and chiral element of the NHC catalyst. Besides modification of NHC catalysts, Lewis acid/NHC cooperative catalysis is another effective strategy for the improvement of enantioselectivity. Scheidt and coworkers disclosed an elegant concept of Lewis acid/NHC cooperative catalysis in 2010 (Scheme 4.3).[6a] They founded that a Lewis acid [$Mg(O^tBu)_2$] could promote formation of γ-lactams

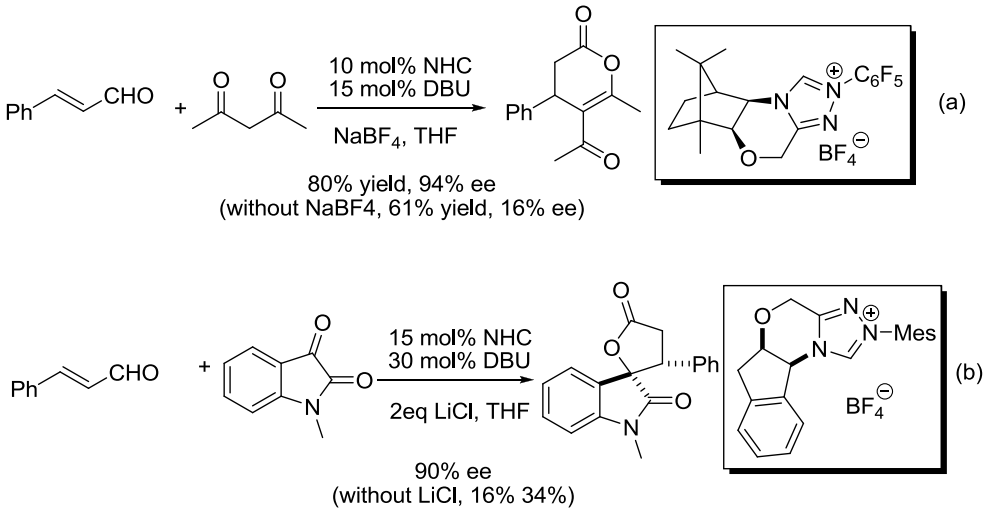
in NHC-catalyzed cycloaddition of enal homoenolates with hydrazones. Later, they realized diastereoselectivity switching by employing $Ti(O^iPr)_4$ as a Lewis acid in NHC-catalyzed substituted cyclopentene formation (Scheme 4.4).[6b] In 2011, You group found that $NaBF_4$ as an additive could lead to high enantioselectivity in NHC-catalyzed redox-type Michael reaction (a, Scheme 4.5).[6c] Next year, LiCl was also employed as a mild Lewis acid in NHC-catalyzed reaction of enal homoenolates with isatines to induce a large ee improvement (b, Scheme 4.5).[6d]



Scheme 4.3 NHC/Lewis acid co-catlysis for homoenolate reaction



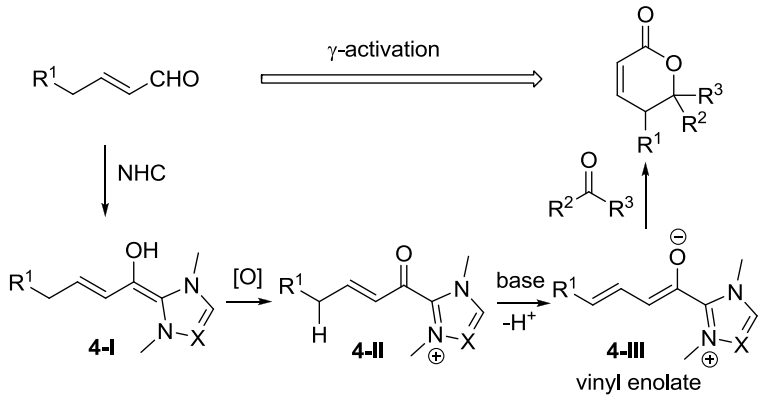
Scheme 4.4 NHC/Lewis acid co-catlysis for dr switching



Scheme 4.5 NHC/Lewis acid co-catlysis for improvement of ee

4.1.3 Our proposal

Here we try to realize *γ*-activation of an enal to form a vinyl enolate intermediate **4-III** under oxidative NHC catalysis (Scheme 4.6). Trapping the vinyl enolate intermediate with an activated ketone, such as trifluoromethyl ketone, is explored to give a *δ*-lactone via cycloaddition. Challenging enantioselective control may be achieved by Lewis acid/NHC cooperative catalysis.

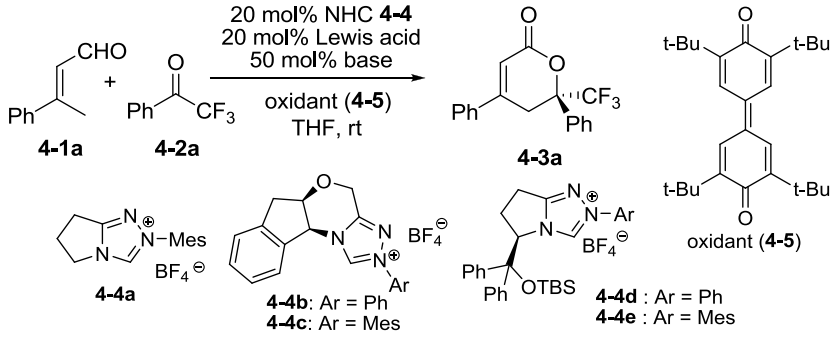


Scheme 4.6 Project hypothesis: *γ*-activation of enals

4.2 Results and discussions

We started our research by treating crotonaldehyde with trifluoroacetophenone (**4-2a**) in the presence of triazolium salt **4-4a** as a precatalyst, quinone **4-5** as an oxidant, Cs_2CO_3 as a base and THF as a solvent. No any proposed δ-lactone product from γ-activation was observed because of a competing typical NHC-mediated homoenolate reaction. To suppress this side reaction, an aldehyde **4-1a** bearing an additional phenyl group at the β-position was examined under the same reaction conditions. Fortunately, the desired δ-lactone product **4-3a** from γ-activation of the enal was obtained in 70% yield (Table 4.1, entry 1). Encouraged by this result, we attempted to get enantioselective product by employing chiral NHCs which have been widely used in various types of NHC-catalyzed reaction before. The NHC catalyst **4-4b** and **4-4c** derived from aminoindanol could offer the desired δ-lactone product in good yields but only 21-29% ee (Table 4.1, entry 2-3). The relatively bulky NHCs **4-4d** and **4-4e**, which were employed in γ-activation of ketenes, gave almost no product. Screening of bases (Table 4.2) and solvents (Table 4.3) did not provide any improvement of the ee value.

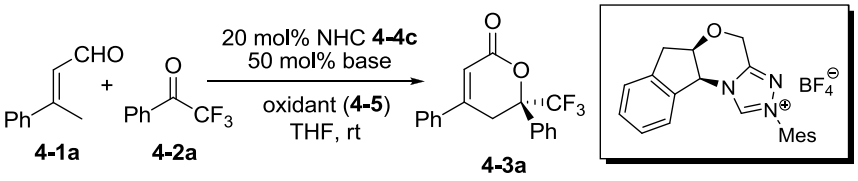
Table 4.1. Summary of optimized condition [a]



Entry	Pre-catalyst	Lewis acid	base	yield (%)[b]	ee (%)[c]
1	**4-4a**	-	Cs_2CO_3	70	-
2	**4-4b**	-	Cs_2CO_3	50	21
3	**4-4c**	-	Cs_2CO_3	63	29
4	**4-4d**	-	Cs_2CO_3	-	-
5	**4-4e**	-	Cs_2CO_3	<5	-
6	**4-4b**	-	K_2CO_3	59	13
7	**4-4c**	-	K_2CO_3	67	16
8	**4-4b**	$Sc(OTf)_3$	Cs_2CO_3	52	64
9	**4-4c**	$Sc(OTf)_3$	Cs_2CO_3	64	73
10	**4-4c**	$Mg(OTf)_2$	Cs_2CO_3	59	60
11	**4-4c**	$Mg(OTf)_2$	K_2CO_3	55	55
12	**4-4c**	$Sc(OTf)_3$/ $Mg(OTf)_2$	K_2CO_3	72	88
13[d]	**4-4c**	$Sc(OTf)_3$	K_2CO_3	69	91
14[e]	**4-4c**	$Sc(OTf)_3$	K_2CO_3	84	91
15[d][e]	**4-4c**	$Sc(OTf)_3$/ $Mg(OTf)_2$	K_2CO_3	81	94

[a] 0.15 mmol **4-1a** and 0.15 mmol **4-2a** were reacted in 1.5 mL THF with 0.15 mmol oxidant **4-5** for 12-24h. [b] Isolated yield. [c] Enantiomeric excess of **4-3a**, determined via chiral-phase HPLC analysis. [d] 0.015 mmol $Sc(OTf)_3$ and 0.015 mmol $Mg(OTf)_2$. [e] 0.18 mmol of **4-1a** at 0 ℃; under these conditions without Lewis acid, the product was obtained in 19% ee.

Table 4.2. Screening of bases[a]

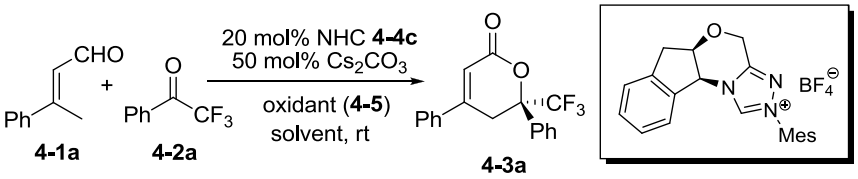


Entry	Pre-catalyst	base	Conv. (%)[b]	ee (%)[c]
1	**4-4c**	LiOH	-	-

2	**4-4c**	Li_2CO_3	-	-
3	**4-4c**	KOAc	99	16
4	**4-4c**	K_2CO_3	99	16
5	**4-4c**	Cs_2CO_3	99	29
6	**4-4c**	DMAP	99	-
7	**4-4c**	Et_3N	99	24
8	**4-4c**	DBU	-	-

[a] 0.15 mmol **4-1a** and 0.15 mmol **4-2a** were reacted in 1.5 mL THF with 0.15 mmol oxidant **4-5** for 12-24h. [b] Determined by ^{1}H NMR of the unpurified reaction. [c] Enantiomeric excess of **4-3a**, determined via chiral-phase HPLC analysis.

Table 4.3. Screening of solvents[a]



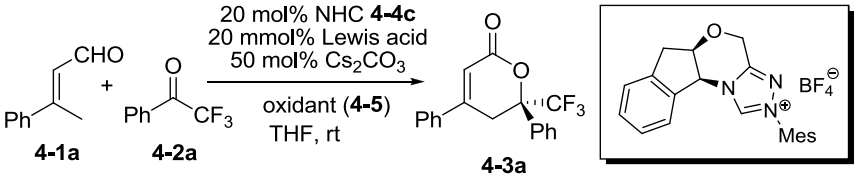
Entry	Pre-catalyst	slovent	Conv. (%)[b]	ee (%)[c]
1	**4-4c**	THF	99	29
2	**4-4c**	toluene	99	25
3	**4-4c**	CH_2Cl_2	-	-
4	**4-4c**	CH_3CN	99	13
5	**4-4c**	Hexane	-	-
6	**4-4c**	Et_2O	99	20

[a] 0.15 mmol **4-1a** and 0.15 mmol **4-2a** were reacted in 1.5 mL THF with 0.15 mmol oxidant **4-5** for 12-24h. [b] Determined by ^{1}H NMR of the unpurified reaction. [c] Enantiomeric excess of **4-3a**, determined via chiral-phase HPLC analysis.

Taking into account difficulty of developing new NHC catalysts, we introduced additional catalysts to interact with either or both of the reaction partners. Several chiral hydrogen bond donating catalysts, including thioureas, tartaric acids, and BINOL derivatives were examined. However, all of these

co-catalysts gave no improvement in the ee value. Then our attention was turned to the use of Lewis acids as co-catalysts. After screening several metal salts (Table 4.4), good enantioselectivity (73% and 60%) was obtained in the presence of $Sc(OTf)_3$ or $Mg(OTf)_2$ with **4-4c** as the NHC pre-catalyst and Cs_2CO_3 as the base (Table 4.1, entry 9 and 10). Combination of NHC **4-4b** with Lewis acids gave a similar ee enhancement (Table 4.1, entry 8). Among several solvents, THF gave the best result. Further optimization showed that K_2CO_3 was superior to Cs_2CO_3 in the presence of NHC **4-4c** as the pre-catalyst (88% ee; Table 4.1, entry 12). Lower temperature had a positive effect on the enantioselectivity. The reaction carried out at 0°C over a long time in the presence of NHC **4-4c** and $Sc(OTf)_3$ afforded the *δ*-lactone product with 91% ee. Further decrease of the reaction temperature to -10°C led to no desired product. Interestingly, a combination of the two effective Lewis acids [$Mg(OTf)_2$ and $Sc(OTf)_3$, 10 mol% each] brought a slight (~3%) but consistent additional ee enhancement. The exact mechanism at this point is unclear. At last, the best result (81% yield, 94% ee; Table 4.1, entry 15) was obtained in the presence of NHC **4-4c**, $Sc(OTf)_3$, $Mg(OTf)_2$ and K_2CO_3 at 0 °C.

Table 4.4. Screening of Lewis acids[a]

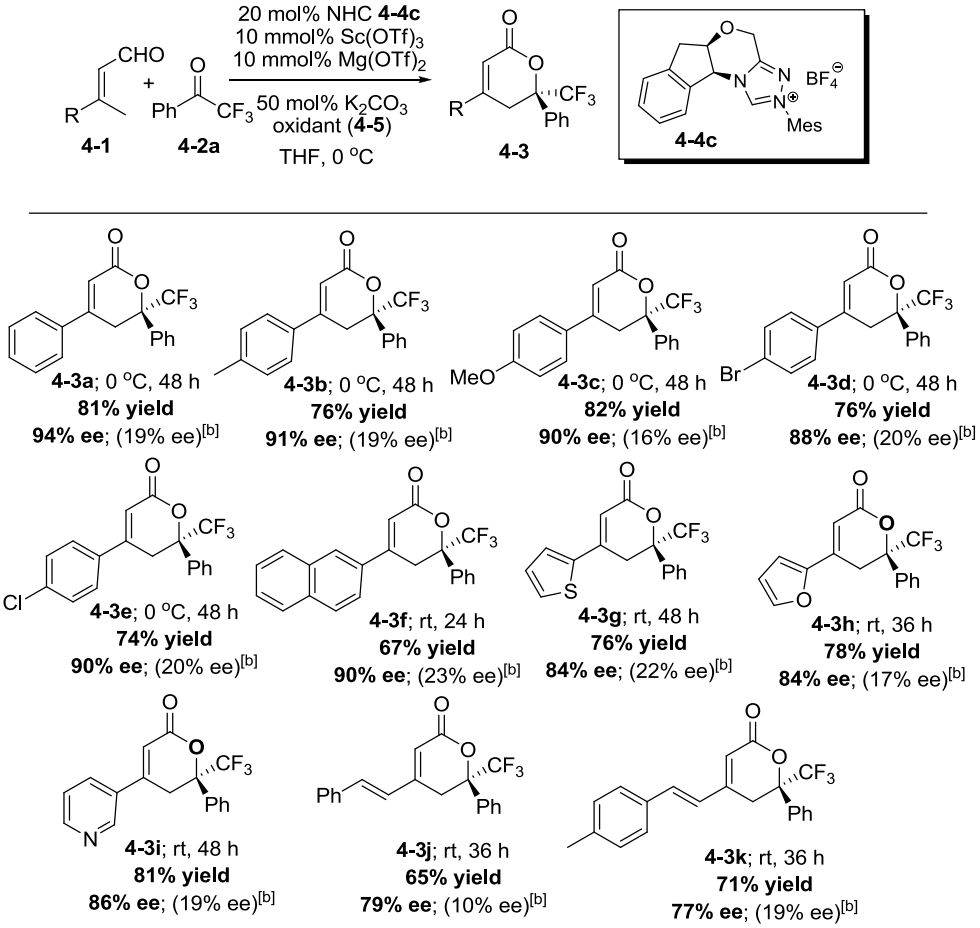


Entry	Pre-catalyst	Lewis acid	Conv. (%)[b]	ee (%)[c]
1	**4-4c**	LiCl	-	-

2	**4-4c**	$MgSO_4$	99	24
3	**4-4c**	$Mg(OTf)_2$	99	60
4	**4-4c**	$Mg(Ot\text{-}Bu)_2$	99	21
5	**4-4c**	MgF_2	99	15
6	**4-4c**	$Ti(OMe)_4$	99	17
7	**4-4c**	$InCl_3$	-	-
8	**4-4c**	$In(OTf)_3$	-	-
9	**4-4c**	$Yb(OTf)_3$	-	-
10	**4-4c**	$Sc(OTf)_3$	99	73
11	**4-4c**	$Zn(OTf)_2$	-	-
12	**4-4c**	$NaBF_4$	99	21

[a] 0.15 mmol **4-1a** and 0.15 mmol **4-2a** were reacted in 1.5 mL THF with 0.15 mmol oxidant **4-5** for 12-24h. [b] Determined by ^{1}H NMR of the unpurified reaction. [c] Enantiomeric excess of **4-3a**, determined via chiral-phase HPLC analysis.

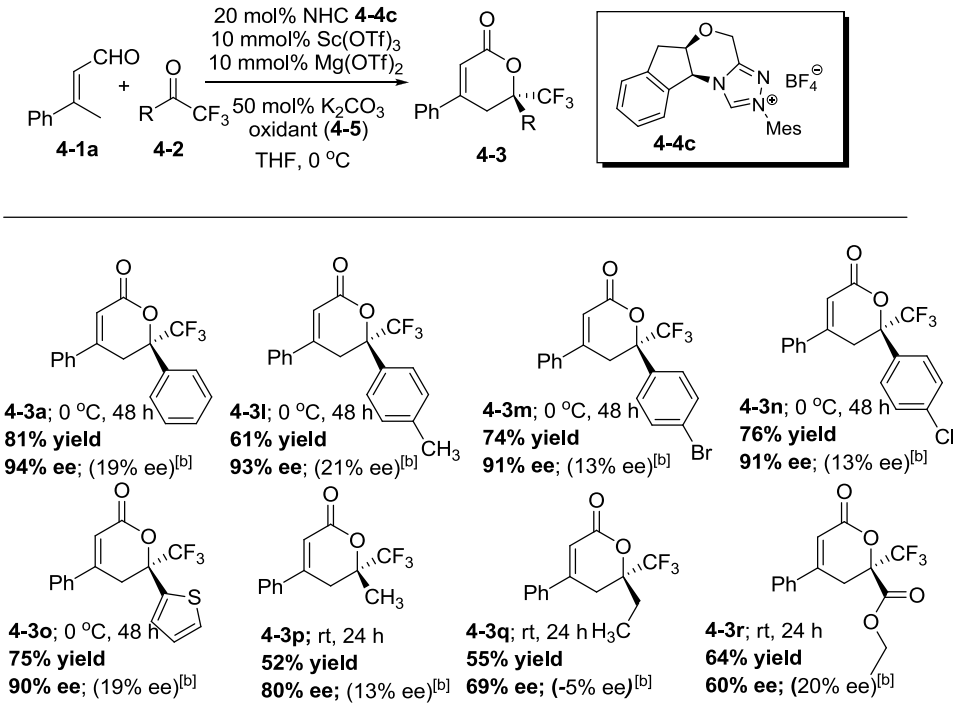
Chart 4.1. Scope of *β*-methyl enals[a]



[a] Reaction condition as Table 4.1, entry 15. [b] Ee for the reaction performed without Lewis acid.

With the optimized reaction conditions in hand, the substrate scope of *α,β*-unsaturated aldehydes was explored for the reaction with trifluoroacetophenone (Chart 4.1). For every example ee values of products generated under the standard conditions and that from the reaction without the Lewis acid are included, in order to demonstrate the generality of Lewis acid effects. All enals with electron-donating substituents and electron-withdrawing substituents on the *β*-aryl moiety gave good yields and ee values. Naphthyl (**4-3f**) and heteroaryl groups (**4-3g** to **4-3i**) at the *β*-position were also tolerated. Installing styryl groups at the *β*-carbon of the enal offered products with slightly lower of ee (**4-3j** and **4-3k**). The use of *β,β*-dialkyl enals led to low conversion to the desired *δ*-lactone products.

Chart 4.2. Scope of trifluoromethyl ketones[a]

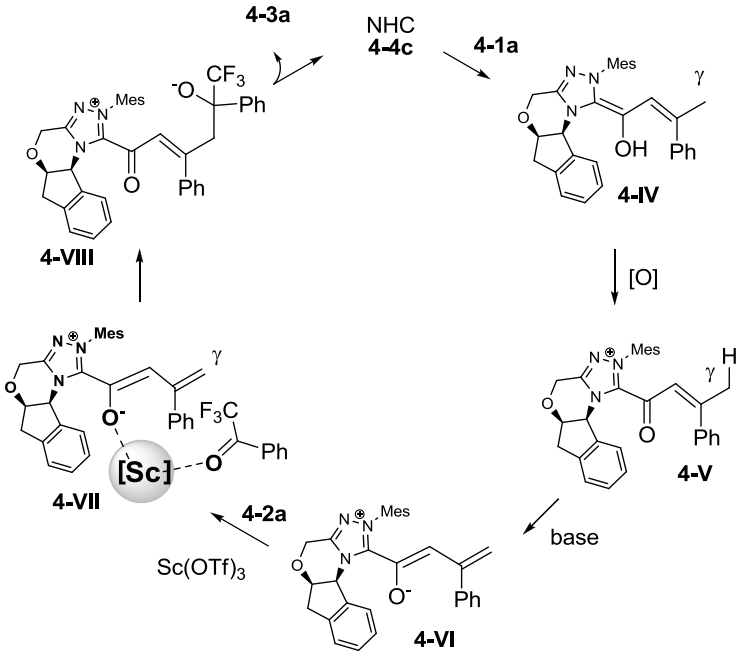


[a] Reaction condition as Table 4.1, entry 15. [b] Ee for the reaction performed without Lewis acid.

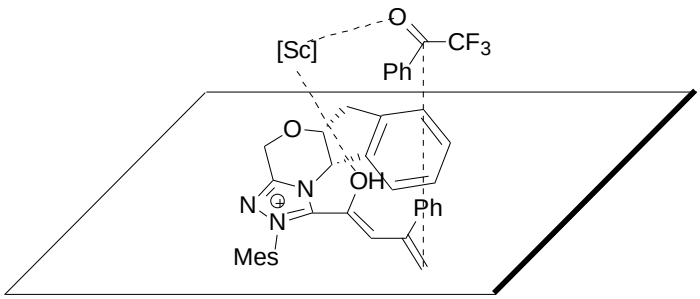
The scope of trifluoromethyl ketones was also investigated (Chart 4.2). Enantioselectivities were less sensitive to electronic properties of substituents on aryl and hetero-aryl trifluoroacetones. All aryl and hetero-aryl trifluoroacetones examined afforded moderate to good yields with good ee. Very encouragingly, alkyl substituted trifluoroacetones (**4-3p** and **4-3q**) and trifluoroketo ester (**4-3r**) also participated in the reaction, albeit with decreased yields and ees.

A plausible pathway is summarized in Scheme 4.7. Oxidation of Breslow intermediate (**4-IV**) generates an acyl azolium intermediate (**4-V**), and eventually gives vinyl enolate intermediate (**4-VI**) via sequential γ-deprotonation. Nucleophilic addition of the vinyl enolate intermediate (**4-VI**) to trifluoromethyl ketone **4-2a** gives an adduct (**4-VIII**), and then affords the final product via

transesterification. The Sc(III) Lewis acid may coordinate to the enolate oxygen and the carbonyl oxygen to bring the ketone electrophile into the close proximity of the chiral NHC catalyst, as shown by **4-VII**. The possible stereochemical model of enantioselectivity-determining is shown as Scheme 4.8.



Scheme 4.7 Possible reaction pathway



Scheme 4.8 Possible stereochemical model of enantioselectivity-determining

4.3 Conclusions

In summary, we have realized the first oxidative NHC catalyzed γ-activation

of *α,β*-unsaturated aldehydes to generate vinyl enolate intermediates for cyclization with trifluoromethyl ketones. The remote enantioselectivity control was realized by employing Lewis acid/NHC cooperative catalysis. Exploration of exact mechanism of the cooperative catalytic activation, which remains unknown, is underway in our group.

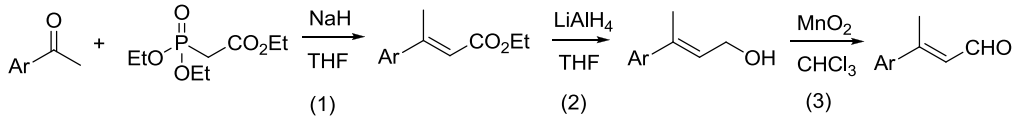
4.4 Experimental section

4.4.1 General information

Commercially available materials purchased from Alfa Aesar or Aldrich was used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV300 (300 MHz) or Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV300 (75 MHz) or Bruker AV400 (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. The determination of *ee* was performed *via* chiral phase HPLC analysis using Shimadzu LC-20AD HPLC workstation.

Optical rotations were measured using a 1 mL cell with a 1 cm path length on a Jasco P1030 digital polarimeter and are reported as follows: $[\alpha]^{25}_{D}$. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

4.4.2 General pathway for the preparation of enals [7]



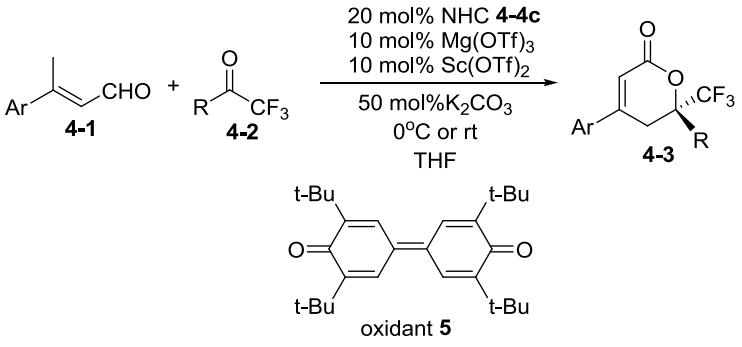
Step 1: To a 100 mL round bottom flask containing NaH (20 mmol, 60% mineral dispersion) and anhydrous THF (40 mL) at 0 ^{o}C, was added triethyl phosphonoacetate (21.5 mmol) dropwise via an addition funnel. The flask was naturally warmed to room temperature, followed by a dropwise addition of a acetophenone solution (13 mmol, in 20 mL anhydrous THF). After stirred for 12 hours, the solution was poured into a separating funnel containing water. The organic phase was collected, and the aqueous phase was extracted with Et_2O (50 mL*2). Organic phases were combined, dried over Na_2SO_4 and filtered. Filtrate was concentrated by rotary distillation. The crude residue was purified by flash chromatography (hexanes/EtOAc: 95/5) to afford the corresponding *α,β*-unsaturated ester as a light yellow oil.

Step 2: To a 100 mL round bottom flask containing the unsaturated ester (20 mmol) obtained above and anhydrous THF (40 mL), was carefully added $LiAlH_4$

(25 mmol) in a few portions at 0 ^{o}C. The flask was gradually warmed to rt and stirred for overnight. The flask was cooled to 0 ^{o}C and quenched with 1 M aqueous HCl. The organic phase was collected, and the aqueous phase was extracted twice with CH_2Cl_2 (50 mL*2). The organic phase was dried over Na_2SO_4, and concentrated by rotary distillation. The yellow residue was subjected to flash chromatography (hexanes/EtOAc: 50/50) to provide the corresponding allylic alcohol as a light yellow oil.

Step 3: To a 100 mL round bottom flask containing the allylic alcohol (20 mmol) obtained above, was added activated MnO_2 (100 mmol) and anhydrous $CHCl_3$ (40 mL) at rt. The flask was then stirred at 60 ^{o}C. After complete consumption of the allylic alcohol (as indicated by TLC analysis), the mixture was passed through a pad of celite. The filtrate was concentrated by rotary distillation. The yellow residue was subjected to flash chromatography (hexanes/EtOAc: 95/5) to afford the corresponding *β,β*-disubstituted enal as a light yellow oil.

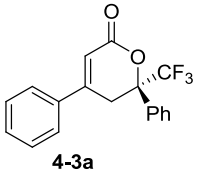
4.4.3 General procedure for the catalytic oxidative γ-addition of enals to ketones



To a dry Schlenk tube with a magnetic stir bar, was added unsaturated aldehyde **4-1** (0.18 mmol), trifluoromethyl ketones **4-2** (0.15 mmol), triazolium salt **4-4c** (0.03 mmol), Mg $(OTf)_2$ (0.015 mmol), $Sc(OTf)_3$ (0.015 mmol) and K_2CO_3 (0.075 mmol). The Schlenk tube was closed with a septum, evacuated, and refilled with nitrogen. The reaction mixture was cooled to 0 ^oC (or at rt, as specified in Charts 4.1-4.2) and freshly distilled THF (1.5 mL) was injected. The reaction mixture was stirred at the same temperature till trifluoromethyl ketone was completely consumed (monitored by TLC). The solution was then concentrated by rotary distillation. The residue was purified through column chromatography on silica gel (10:1 hexanes/EtOAc) to give desired product **3**.

Note: Racemic samples for the chiral phase HPLC analysis were prepared using NHC **4-4a** as the NHC pre-catalyst without the presence of Lewis acid co-catalyst. Absolute configuration of the products were estimated *via* optical rotation comparisons [e.g., **4-3a:**$[\alpha]_D^{20}$ = -80.3 ° (10 mg/ml, $CHCl_3$); literature value:$[\alpha]_D^{25}$ = -73.2 °(10 mg/ml, $CHCl_3$)] with literature.[1]

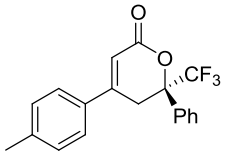
4.4.4 Characterization of Products



4-3a

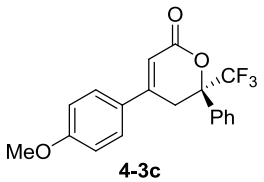
(*R*)-4,6-diphenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3a): Colorless solid, yield: 38.6 mg (81%); $[\alpha]_D^{20}$ = -80.3 (10 mg/ml, $CHCl_3$); ^1H NMR

($CDCl_3$, 300 MHz) δ 3.52 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.4 Hz), 3.63 (d, 1 H, J = 17.4 Hz), 6.25 (d, 1 H, J = 2.4 Hz), 7.38-7.56 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 82.5 (q, J = 30 Hz), 114.9, 123.7 (q, J = 282 Hz), 126.0, 126.5, 128.8, 129.2, 129.7, 131.2, 133.7, 135.5, 151.9, 161.8; HRMS (ESI) calcd for $C_{18}H_{14}O_2F_3$ $(M+H)^+$: 319.0946 Found: 319.0952; 94% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75ml/min), t_r(*R*) = 22.1 min, t_r(*S*) = 50.4 min.



4-3b

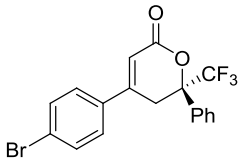
(*R*)-6-phenyl-4-*p*-tolyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3b): Colorless solid, yield: 37.6 mg (76%); $[\alpha]_D^{20}$ = -124.5 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3 H), 3.49 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.4 Hz), 3.61 (d, 1 H, J = 17.4 Hz), 6.22 (d, 1 H, J = 2.4 Hz), 7.25 (d, 2 H, J = 8.4 Hz), 7.37-7.41 (m, 5 H), 7.53-7.55 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 29.4, 82.5 (q, J = 30 Hz), 113.8, 123.7 (q, J = 282 Hz), 125.9, 126.5, 128.8, 129.7, 129.9, 132.5, 133.8, 141.9, 151.8, 162.0; HRMS (ESI) calcd for $C_{19}H_{16}O_2F_3$ $(M+H)^+$: 333.1102 Found: 333.1118; 91% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75ml/min), t_r(*R*) = 18.3 min, t_r(*S*) = 27.8 min.



4-3c

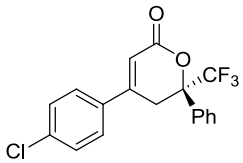
(*R*)-4-(4-methoxyphenyl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-

2-one (4-3c): Colorless solid, yield: 42.8 mg (82%); $[\alpha]_D^{20}$ = -145.5 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.47 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.4 Hz), 3.61 (d, 1 H, J = 17.4 Hz), 3.85 (s, 3 H), 6.17 (d, 1 H, J = 2.4 Hz), 6.95 (d, 2 H, J = 8.8 Hz), 7.34-7.38 (m, 3 H), 7.47-7.54 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3, 55.5, 82.4 (q, J = 30 Hz), 112.5, 114.6, 123.7 (q, J = 282 Hz), 126.5, 127.5, 127.7, 128.8, 129.6, 133.8, 151.2, 162.1; HRMS (ESI) calcd for $C_{19}H_{16}O_3F_3$ $(M+H)^+$: 349.1052 Found: 349.1062; 90% *ee* (*R*)- isomer as determined by HPLC (OD-H, 80:20 hexanes/*i*-PrOH, 0.75ml/min), t_r(*R*) = 60.1 min, t_r(*S*) = 69.5 min.



4-3d

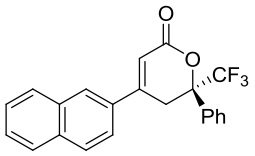
(*R*)-4-(4-bromophenyl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3d): Colorless solid, yield: 45.2 mg (76%); $[\alpha]_D^{20}$ = -134.7 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.47-3.60 (m, 2 H), 6.24 (d, 1 H, J = 2.8 Hz), 7.34-7.40 (m, 5 H), 7.50-7.60 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 82.5 (q, J = 30 Hz), 115.3, 123.7 (q, J = 282 Hz), 125.8, 126.4, 127.4, 128.9, 129.8, 132.5, 133.5, 134.3, 150.6, 161.5; HRMS (ESI) calcd for $C_{18}H_{13}O_2F_3Br$ $(M+H)^+$: 397.0051 Found: 397.0053; 88% *ee* (*R*)- isomer as determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 29.1 min, t_r(*S*) = 38.2 min.



4-3e

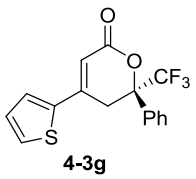
(*R*)-4-(4-chlorophenyl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-

one (4-3e): Colorless solid, yield: 39.1 mg (74%); $[\alpha]_D^{20}$ = -108.4 (15 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.48-3.59 (m, 2 H), 6.23 (d, 1 H, *J* = 2.8 Hz), 7.39-7.43 (m, 7 H), 7.51-7.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 82.5 (q, *J* = 30 Hz), 115.3, 123.7 (q, *J* = 282 Hz), 126.4, 127.3, 128.9, 129.5, 129.8, 133.5, 133.9, 137.5, 150.6, 161.5; HRMS (ESI) calcd for $C_{18}H_{13}O_2F_3Cl$ $(M+H)^+$: 353.0056 Found: 353.0057; 90% *ee* (*R*)- isomer as determined by HPLC (OD-H, 95:5 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 24.6 min, t_r(*S*) = 32.7 min.



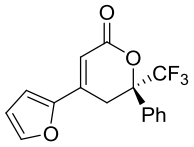
4-3f

(*R*)-4-(naphthalen-2-yl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3f): Colorless solid, yield: 36.9 mg (67%); $[\alpha]_D^{20}$ = -187 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.63 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.2 Hz), 3.77 (d, 1 H, *J* = 17.2 Hz), 6.39 (d, 1 H, *J* = 2.4 Hz), 7.37-7.39 (m, 3 H), 7.53-7.58 (m, 5 H), 7.84-7.91 (m, 3 H), 7.99 (d, 1 H, *J* = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 82.5 (q, *J* = 30 Hz), 115.0, 122.5, 123.7 (q, *J* = 282 Hz), 126.4, 126.6, 127.2, 127.8, 128.0, 128.7, 128.8, 129.1, 129.7, 132.6, 132.9, 133.7, 134.4, 151.5, 161.8; HRMS (ESI) calcd for $C_{22}H_{16}O_2F_3$ $(M+H)^+$: 369.1102 Found: 369.1112; 90% *ee* (*R*)- isomer as determined by HPLC (IA, 98:2 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 37.2 min, t_r(*S*) = 30.8 min.



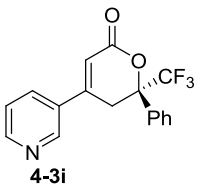
4-3g

(*R*)-6-phenyl-4-(thiophen-2-yl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3g): Colorless solid, yield: 37.1 mg (76%); $[\alpha]_D^{20}$ = -147 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.50 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.2 Hz), 3.62 (d, 1 H, J = 17.2 Hz), 6.17 (d, 1 H, J = 2.0 Hz), 7.14 (dd, 1 H, J_1 = 4.0 Hz, J_2 = 5.2 Hz), 7.38-7.56 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 82.3 (q, J = 30 Hz), 111.8, 123.7 (q, J = 282 Hz), 126.4, 128.3, 128.7, 128.8, 129.8, 130.3, 133.5, 139.6, 145.0, 161.8; HRMS (ESI) calcd for $C_{16}H_{12}O_2F_3S$ $(M+H)^+$: 325.0510 Found: 325.0523; 84% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 13.0 min, t_r(*S*) = 21.6 min.



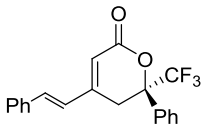
4-3h

(*R*)-4-(furan-2-yl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3h): Colorless solid, yield: 36.4 mg (78%); $[\alpha]_D^{20}$ = -113.3 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.39 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.2 Hz), 3.52 (d, 1 H, J = 17.2 Hz), 6.22 (d, 1 H, J = 2.0 Hz), 6.55 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 3.6 Hz), 6.87 (d, 1 H, J = 3.6 Hz), 7.38-7.40 (m, 3 H), 7.53-7.56 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 82.3 (q, J = 30 Hz), 110.3, 112.7, 113.9, 123.7 (q, J = 282 Hz), 126.5, 128.8, 129.8, 133.5, 139.7, 146.3, 149.7, 161.8; HRMS (ESI) calcd for $C_{16}H_{12}O_3F_3$ $(M+H)^+$: 309.0739 Found: 309.0725; 84% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 10.4 min, t_r(*S*) = 13.8 min.



4-3i

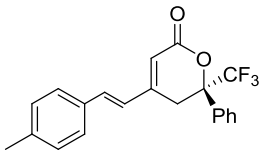
(*R*)-6-phenyl-4-(pyridin-3-yl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (3i): Colorless solid, yield: 38.2 mg (81%); $[\alpha]_D^{20}$ = -96.4 (20 mg/ml, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.53 -3.64 (m, 2 H), 6.30 (d, 1 H, *J* = 2.0 Hz), 7.39-7.43 (m, 4 H), 7.53-7.56 (m, 2 H), 7.77-7.80 (m, 1 H), 8.70-8.77 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 82.5 (q, *J* = 30 Hz), 116.5, 123.7 (q, *J* = 282 Hz), 123.8, 126.4, 128.9, 129.9, 131.3, 133.3, 133.4, 147.1, 149.0, 151.9, 161.0; HRMS (ESI) calcd for $C_{17}H_{13}NO_2F_3$ $(M+H)^+$: 320.0898 Found: 320.0886; 86% *ee* (*R*)-isomer as determined by HPLC (OD-H, 80:20 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 35.1 min, t_r(*S*) = 76.1 min.



4-3j

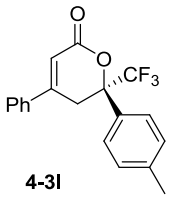
(*R*,E)-6-phenyl-4-styryl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3j): Colorless solid, yield: 33.0 mg (65%); $[\alpha]_D^{20}$ = -100.4 (20 mg/ml, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.29 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 17.2 Hz), 3.53 (d, 1 H, *J* = 17.2 Hz), 5.90 (d, 1 H, *J* = 2.4 Hz), 6.81 (d, 1 H, *J* = 16.4 Hz), 7.10 (d, 1 H, *J* = 16.4 Hz), 7.37-7.42 (m, 6 H), 7.51-7.55 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.0, 82.3 (q, *J* = 30 Hz), 117.2, 123.7 (q, *J* = 282 Hz), 126.1, 126.5, 127.6, 128.8, 129.0, 129.7, 129.9, 133.7, 135.0, 136.9, 149.5, 162.0; HRMS (ESI) calcd for $C_{20}H_{16}O_2F_3$ $(M+H)^+$: 345.1102 Found: 345.1109; 79% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 26.8

min, $t_r(S)$ = 17.8 min.



4-3k

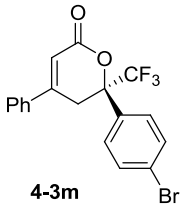
(*R*,E)-4-(4-methylstyryl)-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3k): Colorless solid, yield: 39.0 mg (71%); $[\alpha]_D^{20}$ = -114.0 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3 H), 3.27 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 17.2 Hz), 3.52 (d, 1 H, J = 17.2 Hz), 5.87 (d, 1 H, J = 2.0 Hz), 6.77 (d, 1 H, J = 16.4 Hz), 7.08 (d, 1 H, J = 16.4 Hz), 7.20 (d, 2 H, J = 8.0 Hz), 7.38-7.42 (m, 5 H), 7.52-7.54 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 27.0, 82.3 (q, J = 30 Hz), 116.6, 123.7 (q, J = 282 Hz), 125.1, 126.5, 127.6, 128.2, 128.8, 129.7, 129.8, 132.3, 133.8, 136.9, 140.4, 149.7, 162.2; HRMS (ESI) calcd for $C_{21}H_{18}O_2F_3$ $(M+H)^+$: 359.1259 Found: 359.1263; 77% *ee* (*R*)- isomer as determined by HPLC (OD-H, 97:3 hexanes/*i*-PrOH, 0.75 ml/min), $t_r(R)$ = 33.1 min, $t_r(S)$ = 23.8 min.



4-3l

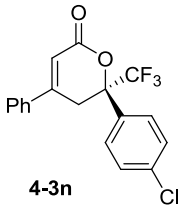
(*R*)-4-phenyl-6-p-tolyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3l): Colorless solid, yield: 30.6 mg (61%); $[\alpha]_D^{20}$ = -112.2 (10 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3 H), 3.48 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.4 Hz), 3.60 (d, 1 H, J = 17.4 Hz), 6.24 (d, 1 H, J = 2.1 Hz), 7.18 (d, 2 H, J = 8.1 Hz), 7.40-7.51 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 29.6, 82.5 (q, J = 30 Hz), 115.0, 123.7 (q, J = 282 Hz), 126.0, 126.5, 129.2, 129.6, 130.7, 131.2, 135.6, 139.9,

152.0, 161.9; HRMS (ESI) calcd for $C_{19}H_{16}O_2F_3$ $(M+H)^+$: 333.1102 Found: 333.1116; 93% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 18.5 min, t_r(*S*) = 40.2 min.



4-3m

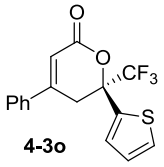
(*R*)-6-(4-bromophenyl)-4-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3m): Colorless solid, yield: 44.7 mg (74%); $[\alpha]_D^{20}$ = -102.8 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.54 (s, 2 H), 6.26 (s, 1 H), 7.39-7.54 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 82.3 (q, *J* = 30 Hz), 114.9, 124.4, 126.0, 128.3, 129.3, 131.4, 132.1, 132.9, 135.3, 151.9, 161.4; HRMS (ESI) calcd for $C_{18}H_{13}O_2F_3Br$ $(M+H)^+$: 397.0051 Found: 397.0072; 91% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 30.8 min, t_r(*S*) = 76.9 min.



4-3n

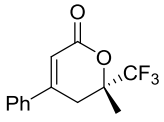
(*R*)-6-(4-chlorophenyl)-4-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3n): Colorless solid, yield: 40.7 mg (76%); $[\alpha]_D^{20}$ = -106.4 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.55 (s, 2 H), 6.26 (s, 1 H), 7.35-7.49 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 82.5 (q, *J* = 30 Hz), 114.9, 123.7 (q, *J* = 282 Hz), 126.0, 128.0, 128.9, 129.2, 129.3, 131.4, 132.4, 135.3, 136.1, 151.9, 161.1; HRMS (ESI) calcd for $C_{18}H_{13}O_2F_3Cl$ $(M+H)^+$: 353.0556 Found: 353.0573;

91% *ee* (*R*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*R*) = 28.7 min, t_r(*S*) = 71.9 min.



4-3o

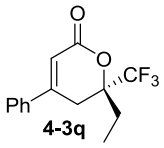
(*S*)-4-phenyl-6-(thiophen-2-yl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (3o): Colorless solid, yield: 35.8 mg (75%); $[\alpha]_D^{20}$ = -116.9 (20 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.51 (s, 2 H), 6.29 (d, 1 H, *J* = 1.5 Hz), 7.01 (dd, 1 H, J_1 = 3.9 Hz, J_2 = 5.1 Hz), 7.25 (d, 1 H, *J* = 2.7 Hz), 7.35 (dd, 1 H, J_1 = 1.2 Hz, J_2 = 5.1 Hz), 7.46-7.55 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2, 82.4 (q, *J* = 30 Hz), 114.7, 123.7 (q, *J* = 282 Hz), 126.2, 127.4, 127.5, 128.5, 129.2, 131.3, 135.4, 136.8, 151.9, 161.2; HRMS (ESI) calcd for $C_{16}H_{12}O_2F_3S$ $(M+H)^+$: 325.0510 Found: 325.0510; 90% *ee* (*S*)- isomer as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.75 ml/min), t_r(*S*) = 24.2 min, t_r(*R*) = 51.0 min.



4-3p

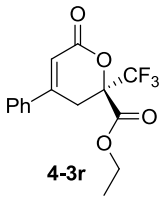
(*S*)-6-methyl-4-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3p): Colorless solid, yield: 19.4 mg (52%); $[\alpha]_D^{20}$ = -46.5 (10 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3 H), 2.88 (d, 1 H, *J* = 18.0 Hz), 3.23 (dd, 1 H, J_1 = 2.1 Hz, J_2 = 18.0 Hz), 6.41 (t, 1 H, *J* = 1.2 Hz), 7.47-7.56 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 30.4, 79.5 (q, *J* = 30 Hz), 113.7, 123.7 (q, *J* = 282 Hz), 126.0, 129.2, 131.2, 135.5, 151.6, 161.6; HRMS (ESI) calcd for $C_{13}H_{12}O_2F_3$ $(M+H)^+$: 257.0789 Found: 267.0801; 80% *ee* (*S*)- isomer as determined by HPLC

(OD-H, 97:3 hexanes/*i*-PrOH, 0.75 ml/min), $t_r(S)$ = 76.6 min, $t_r(R)$ = 69.6 min.



4-3q

(*S*)-6-ethyl-4-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (4-3q): Colorless solid, yield: 23.0 mg (55%); $[\alpha]_D^{20}$ = -21.6 (10 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, 3 H, *J* = 8.0 Hz), 1.96-2.14 (m, 2 H), 2.97 (d, 1 H, *J* = 18.4 Hz), 3.13 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 18.4 Hz), 6.39 (t, 1 H, *J* = 1.6 Hz), 7.47-7.56 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.6, 27.4, 27.8, 81.6 (q, *J* = 30 Hz), 113.7, 124.7 (q, *J* = 282 Hz), 126.0, 129.2, 131.1, 135.5, 151.5, 161.9; HRMS (ESI) calcd for $C_{14}H_{14}O_2F_3$ $(M+H)^+$: 271.0946 Found: 271.0958; 69% *ee* (*S*)-isomer as determined by HPLC (OD-H, 97:3 hexanes/*i*-PrOH, 0.75 ml/min), $t_r(S)$ = 44.3 min, $t_r(R)$ = 39.8 min.



4-3r

(*R*)-ethyl

6-oxo-4-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran-2-carboxylate

(4-3r): Colorless solid, yield: 29.6 mg (64%); $[\alpha]_D^{20}$ = -99.2 (10 mg/ml, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3 H, *J* = 7.2 Hz), 3.19 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 17.4 Hz), 3.62 (d, 1 H, *J* = 17.4 Hz), 4.31 (q, 2 H, *J* = 7.2 Hz), 6.39 (d, 1 H, *J* = 2.4 Hz), 7.47-7.55 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 28.6, 64.0, 81.8 (q, *J* = 30 Hz), 114.5, 121.5 (q, *J* = 282 Hz), 126.3, 129.2, 131.5, 134.8, 151.7, 160.6, 165.1; HRMS (ESI) calcd for $C_{15}H_{14}O_4F_3$ $(M+H)^+$: 315.0844 Found:

315.0854; 60% *ee* (*R*)- isomer as determined by HPLC (OD-H, 97:3 hexanes/*i*-PrOH, 0.75 ml/min), $t_r(R)$ = 54.1 min, $t_r(S)$ = 51.2 min.

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