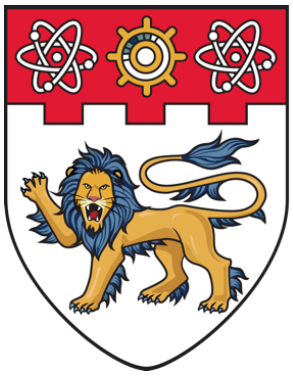

NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

CARBENE-CATALYZED DYNAMIC KINETIC RESOLUTION FOR ASYMMETRIC ACCESS TO PHTHALIDYL ESTERS AND BENZOFURANONE DERIVATIVES

MAJHI PANKAJ KUMAR

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2020

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MAJHI PANKAJ KUMAR

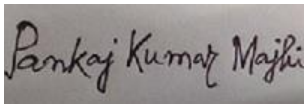
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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

2020

Statement of Originality

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



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Prof. Yonggui Robin Chi

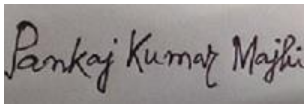
Authorship Attribution Statement

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

Chapter 2 is published as Liu, Y.; Majhi, P. K.; Song, R.; Mou, C.; Hao, L.; Chai, H.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed Dynamic Kinetic Resolution and Asymmetric Acylation of Hydroxyphthalides and Related Natural Products. *Angew. Chem. Int. Ed.* **2020,** *59*, 3859.

The contributions of the co-authors are as follows:

- Prof. Chi conceptualized the project and revised the manuscript drafts.
- I conducted most of the experiments and attended the manuscripts preparation.
- Dr. Liu designed parts of the study and wrote the manuscript drafts.
- R. Song conducted some experiments regarding substrate scope.
- Dr. Hao conducted the synthesis of catalysts.
- Prof. Chai, Prof. Jin and Dr. Mou contributed in discussion, mechanism study and manuscript revision.
- All authors contributed to discussions and manuscript preparation.



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Abstract

In this thesis, we have demonstrated two dynamic kinetic resolution strategies enabled by N-heterocyclic carbene. Firstly, asymmetric acylation of hydroxyphthalides through N-heterocyclic carbene catalyzed dynamic kinetic resolution approach has been achieved. In addition, enantioselective modification of hydroxyphthalides containing natural products has also been achieved utilizing this DKR process. Secondly, enantioselective synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-one derivatives bearing vicinal quaternary stereogenic centers, enabled by N-heterocyclic carbene catalyzed dynamic kinetic resolution process, has been developed. We anticipated that these methodologies can play a vital role in the synthesis of medicinally important molecules and natural products.

In chapter 1, a brief introduction of dynamic kinetic resolution approach and different modes of reactions enabled by NHC catalysis have been demonstrated. N-heterocyclic carbene-catalyzed kinetic resolution and dynamic kinetic resolution have also been introduced in this chapter.

In chapter 2, enantioselective acylation of hydroxyphthalides via NHC-catalyzed dynamic kinetic resolution approach has been discussed. Phthalidyl esters were achieved with high enantioselectivities and high yields (up to 99:1 e.r. and up to 96% yield). Moreover, asymmetric modification of natural products that contained hydroxyphthalide units, such as Corollosporine and Fimbricalyxlactone C, have also been demonstrated.

In chapter 3, asymmetric synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-one derivatives bearing vicinal quaternary stereogenic centers, enabled by N-heterocyclic carbene through dynamic kinetic resolution approach has been introduced. The reaction undergoes via intermolecular reversible aldol reaction followed by acylation between benzofuranyl carbonate and *N*-protected isatin derivatives in one pot. Chiral 3,3'-disubstituted benzofuran-2(*3H*)-one derivatives bearing vicinal quaternary stereogenic centers, have been achieved with excellent

yields (up to 98%), excellent enantioselectivities (up to 99:1 e.r.), and excellent diastereoselctivities (up to >20:1 dr).

Acknowledgements

I would like to express my sincere gratitude and respect to my supervisor, Professor Yonggui Robin Chi, for his continuous guidance and support during my entire PhD study and related research. His patience, inspiration, and immense knowledge helped me in my all-time research. The research attitude that I learned from Prof. Chi would be very useful for my future life.

I would like to thank my Thesis Advisory Committee (TAC) members, Prof. Shuzhou Li and Prof. Steve Zhou, for their valuable advice and guidance regarding my research projects.

I am also very thankful to all current and previous lab members for their assistance and advice throughout my PhD study. Especially, Dr. Hao Lin, Dr. Zhu Tingshun, Dr. Chen Xingkuan, Dr. Liu Yingguo, Dr. Yang Xing, Dr. Chen Qiao, Dr. Duan Xiaoyong, Dr. Zhou Leijin, Dr. Li Yongjia, Dr. Wang Fangxin, Dr. Wu Xingxing, Dr. Wang Yuhuang, Dr. Ren Shichao, Dr. Ke Jie, Dr. Zhou Shitian, Rakesh Maiti, Bivas Mondal, Wang Hongling, Liu Bin, Dr. Mou Chengli and Song Runjiang.

Moreover, I would like to thank the CBC instrument lab staff for their assistance with laboratory instruments usage such as NMR, LSMS, HRMS, XRD. I am thankful to Ms. Goh Ee Ling and Mr. Keith Leung for NMR machine usage. My sincere thanks to Dr. Rakesh Ganguly and Dr. Li Yongxin for X-ray analysis and Ms. Zhu Wenwei for mass spectroscopy analysis. My sincere to thanks to Ms. Ai Hua, Ms. Lim Yen Lin and Ms. Tan Si Min and other staff for their help with teaching labs instruments usage such as IR spectrometer and Polarimeter. I am also thankful to Ms. Lee yean chin and Ms. Koh Su Ping for their help in administrative matters such as qualifying examination, thesis submission and progress report related matters.

I would also like to thank Prof. Ramesh Ramapanicker and Prof. Y.D. Vankar from IIT Kanpur for their valuable suggestions and encouragement during my PhD study.

I am also thankful to my friends Mrinmoy das, Dr. Jit Sarkar, Deblin Jana, Md Shafiqur Rahman, Roshayed Ali Laskar for their help during my PhD study.

I gratefully acknowledge the NTU research scholarship from School of Physical and Mathematical Sciences (SPMS), Nanyang Technological University, which made my PhD work possible.

Last but not least, I would like to thank my family, particularly my parents and brother for their love and encouragement throughout my PhD study.

Table of Contents

Publications

1. Yingguo Liu, **Pankaj Kumar Majhi (equal contribution)**, Runjiang Song, Chengli Mou, Lin Hao, Huifang Chai, Zhichao Jin, and Yonggui Robin Chi. Carbene-Catalyzed Dynamic Kinetic Resolution and Asymmetric Acylation of Hydroxyphthalides and Related Natural Products. *Angew. Chem. Int. Ed.* **2020,** *59*, 3859.
2. Bin Liu, Runjiang Song, Jun Xu, **Pankaj Kumar Majhi**, Xing Yang, Song Yang, Zhichao Jin, and Yonggui Robin Chi. Access to Optically Enriched α-Aryloxycarboxylic Esters via Carbene-Catalyzed Dynamic Kinetic Resolution and Transesterification. *Org. Lett.* **2020,** *22*, 3335.
3. Qiao Chen, Tingshun Zhu, **Pankaj Kumar Majhi**, Chengli Mou, Huifang Chai, Jingjie Zhang, Shitian Zhuo, and Yonggui Robin Chi. Carbene-Catalyzed Enantioselective Oxidative Coupling of enals and di(hetero)arylmethanes. *Chem. Sci.* **2018**, *9*, 8711-8715.
4. **Pankaj Kumar Majhi**, Yingguo Liu, Ng Pei Rou, Jun Xu, Long Zhang, Hongmei Liu, Lin Hao, Bivas Mondal, Weiyi Tian, and Yonggui Robin Chi. Enantioselective Modification of Sulfonamides and Sulfonamide-Containing Drugs via Carbene Organic Catalysis (In preparation).
5. Xing Yang, **Pankaj Kumar Majhi (equal contribution)**, Huifang Chai, Bin Liu, Jun Sun, Ting Liu, Yonggui Liu, Liejin Zhou, Jun Xu, Jiawei Liu, Dongdong Wang, Yanli Zhao, Zhichao Jin, and Yonggui Robin Chi. Carbene-Catalyzed Enantioselective Aldol Reaction: Post-Aldol Stereochemistry Control and Formation of Quaternary Stereogenic Centers (Submitted)

Abbreviations

Ac	Acetyl
Ar	aryl
Boc	*tert*−butyloxycarbonyl
Bn	benzyl
Bu	butyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DKR	dynamic kinetic resolution
dr	diastereomeric ratio
e.r.	enantiomeric ratio
Equiv	equivalent
ESI	electrospray ionization
HRMS	High resolution mass spectrometry
HPLC	High-performance liquid chromatography
^{i}Pr	isopropyl
Mes	mesityl
NHC	N-heterocyclic carbene
TBS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
α	alpha

β	beta
γ	gamma
δ	delta
π	pi
σ	sigma
ω	Omega

Chapter 1

Introduction

1.1 Introduction on dynamic kinetic resolution (DKR)

Synthesis of enantiopure compounds for the medical and biological applications is one of the key parts of organic chemistry. New and more efficient strategies to obtain enantioenriched compounds have been developed continuously. Among the different strategies, kinetic resolution is one of the oldest methods in the field of asymmetric synthesis which has proved as a useful method for its simple operation.[1-2] In kinetic resolution (KR), one of the enantiomers in a racemic mixture converted to the corresponding product faster than another enantiomer in presence of chiral catalyst (**Figure 1.1**). Hence, one enantiomer completely leads to desired product and another isomer remains almost untouched. Therefore, the major drawback of the KR process is the theoretical yield of the reaction is maximum 50%. To overcome this drawback dynamic kinetic resolution (DKR) approach was devised. In dynamic kinetic resolution concept, *in situ* racemization was introduced in the reaction system. The fast-reacting enantiomer transforms to the desired product as well as racemization of another isomer occurs in a one-pot reaction. Hence, 100% theoretical yield could be achieved by DKR approach (**Figure 1.1**).[3-4]

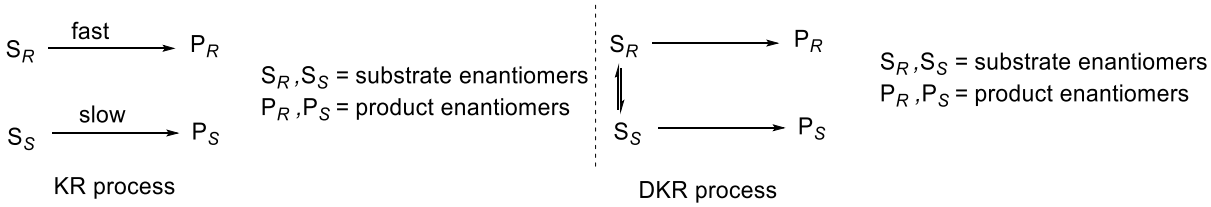


Figure 1.1 KR and DKR approach

Asymmetric catalysis made significant progress in the last decade. Various asymmetric transformations have been achieved with the application of natural product synthesis and drug synthesis. Metal catalysis also played a vital role in the DKR process at the end of the last century. However, in the last decade, organocatalytic DKR process has dominated. Kinetic resolution or dynamic kinetic resolution has been achieved with a variety of organocatalysis such as Brønsted base[5-6], Brønsted acid[7-8], phase transfer catalysis.[9] The advantages of using

organocatalysts in asymmetric transformation are, most of the organocatalysts are inexpensive, nontoxic, air stable and good tolerance to moisture.[10-12] N-heterocyclic carbenes (NHCs) organocatalysis have been studied broadly in the last decades.[13] A large class of asymmetric transformations has been achieved by NHC as organocatalysts. The reaction involving DKR and KR has also been studied in the field of NHC as a catalyst, however, compared to other catalysts N-heterocyclic carbene has been less studied to achieve the DKR or KR.[14-15]

1.2 Introduction to N-heterocyclic carbene (NHC)

NHCs have been extensively used as organocatalysts and ligands for metal-based catalysts due to their strong electron-donating property.[13, 16-17] Although the application of N-heterocyclic carbenes as organocatalysts was found in 1940s[18], the rapid development of this field appears in the last decade.[13] In 1960s, many works on NHC and its dimmers have been reported by Wanzlick and co-workers.[19-20] After that several types of NHCs have been developed such as imidazolium salt, thiazolium salt, and triazolium salt. The first stable carbene that contained bulky adamantyl groups on imidazolium nitrogen, was isolated by Arduengo in 1991 and it is a neutral two electron donor (**Figure 1.2**). This pioneering work established the pillar of future development of NHC-catalyzed reaction in organic synthesis.[21]

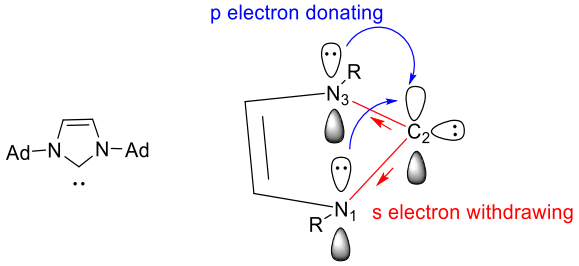
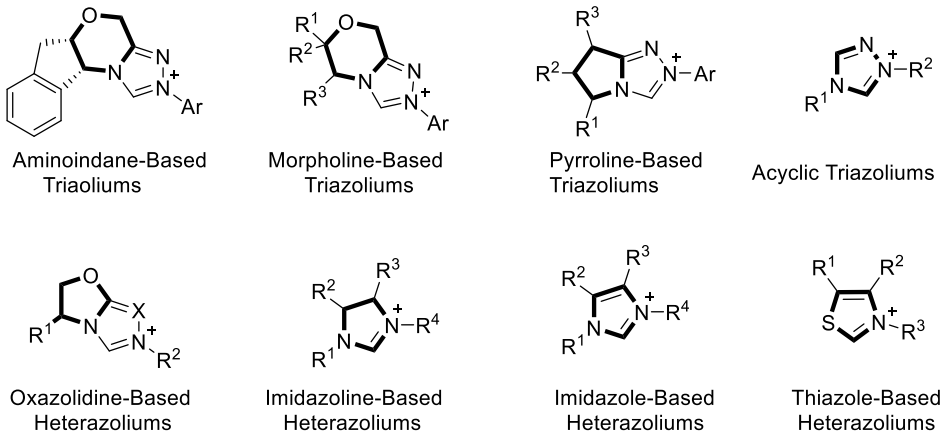


Figure 1.2 Ground state electronic structure of first stable NHC

1.2.1 Different class of NHC catalyst

A variety of NHC catalysts have been developed for the interest of various asymmetric transformations. At the early development of NHC catalysis, thiazolium salts were frequently used as an NHC catalyst precursor. After that, several triazolium and imidazolium-based NHCs

with different chiral moiety or different substituents have been discovered. There are 8 classes of NHC precursors have been categorized based on their different chemical structures such as (1) aminoindane-based triazoliums, (2) morpholine-based triazoliums (3) pyrroline-based triazoliums, (4) acyclic triazoliums, (5) oxazolidine-based heterazoliums, (6) imidazoline-based heterazoliums, (7) imidazole-based heterazoliums, (8) thiazole-based heterzoliums. (**Scheme 1.1**) [13]



Scheme 1.1 Different classes of NHC precursors

1.3 Different modes of reactions enabled by NHC Catalysis

Up to date, different modes of activation by NHC have been explored by NHC catalysis utilizing different types of aldehydic substrates, or esters substrates. The reaction modes are categorized into 6 types based on different reaction modes of activation enabled by NHC such as, (1) benzoin reaction, (2) Stetter reaction, (3) homoenolate formation enabled by NHC, (4) NHC-catalyzed reaction involving acylazolium, (5) NHC-catalyzed azolium enolate formation and saturated acyl azolium formation, (6) NHC-catalyzed MBH-type reaction.

1.3.1 NHC-catalyzed benzoin reactions

Most commonly used substrate aldehyde was utilized in the NHC-catalyzed C-C bond forming reaction. In 1943, Ukai group developed benzoin reaction using thiazolium salt as a catalyst. After this discovery in 1958, Breslow proposed the mechanism[22] of the reaction. *In situ* generated free carbene **1** attacked to aldehyde to form zwitter ion **2**, which underwent

proton transfer to afford Breslow intermediate **3**. Breslow intermediate reacted with another aldehyde to afford benzoin product with regeneration of NHC catalyst (**Figure 1.3**). The formation of "Breslow intermediate" is reversible in nature. Experimentally proved that, in presence of more reactive aldehyde, a rapid equilibrium exists between benzaldehyde-derived Breslow intermediate and more reactive aldehyde-derived Breslow intermediate. Cross-benzoin product was found as the major product (**Figure 1.3**).[13] This crossover experiment revealed that NHC-catalyzed benzoin reaction is reversible in nature. After the discovery of catalytic pathway, asymmetric version of benzoin reaction also has been developed by using chiral carbenes.

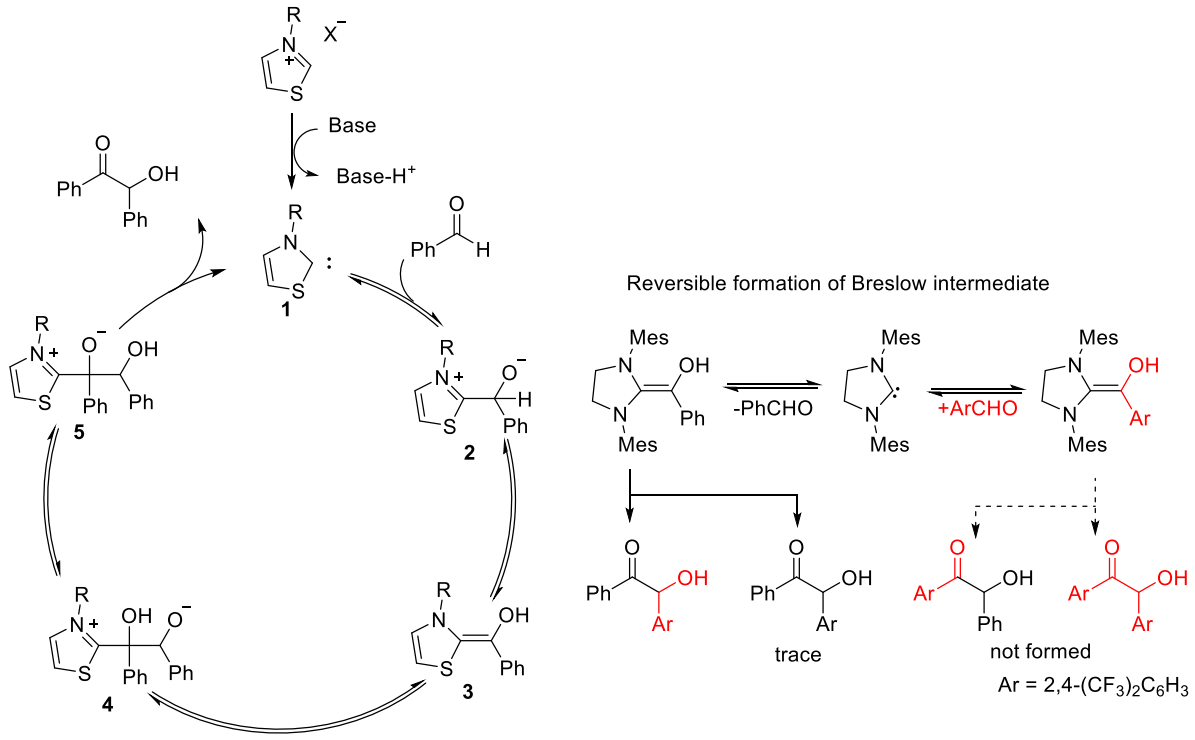
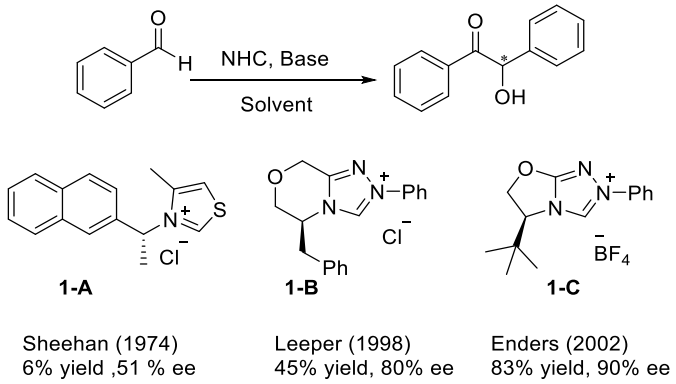


Figure 1.3 Mechanism of NHC-catalyzed benzoin reaction and reversible formation of Breslow intermediate

First asymmetric benzoin reaction was reported by Sheehan and co-workers in 1966, however, the benzoin product was formed with very low ee.[23] Later, the same group reported asymmetric benzoin reaction using chiral thiazolium salts as NHC precursor, the ee of the

product improved to 51% but yield of the reaction remained very low.[24] In 1998, Leeper and co-workers used morpholine-based triazolium catalyst as chiral catalyst in the asymmetric benzoin reaction and benzoin product was formed with moderate yields and moderate ee.[25]

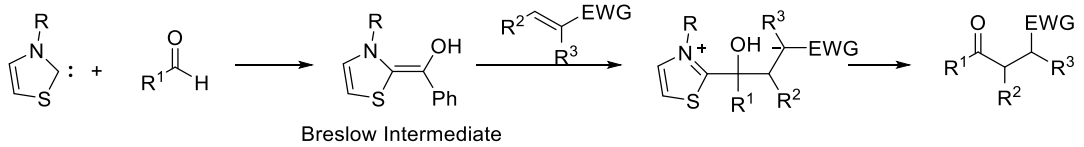


Scheme 1.2 NHC-catalyzed asymmetric benzoin reaction

Finally, in 2002 Enders group developed a highly enantioselective benzoin reaction using oxazolidine-based triazolium salt as NHC precatalyst (**Scheme 1.2**).[26]

1.3.2 NHC-catalyzed Stetter reactions

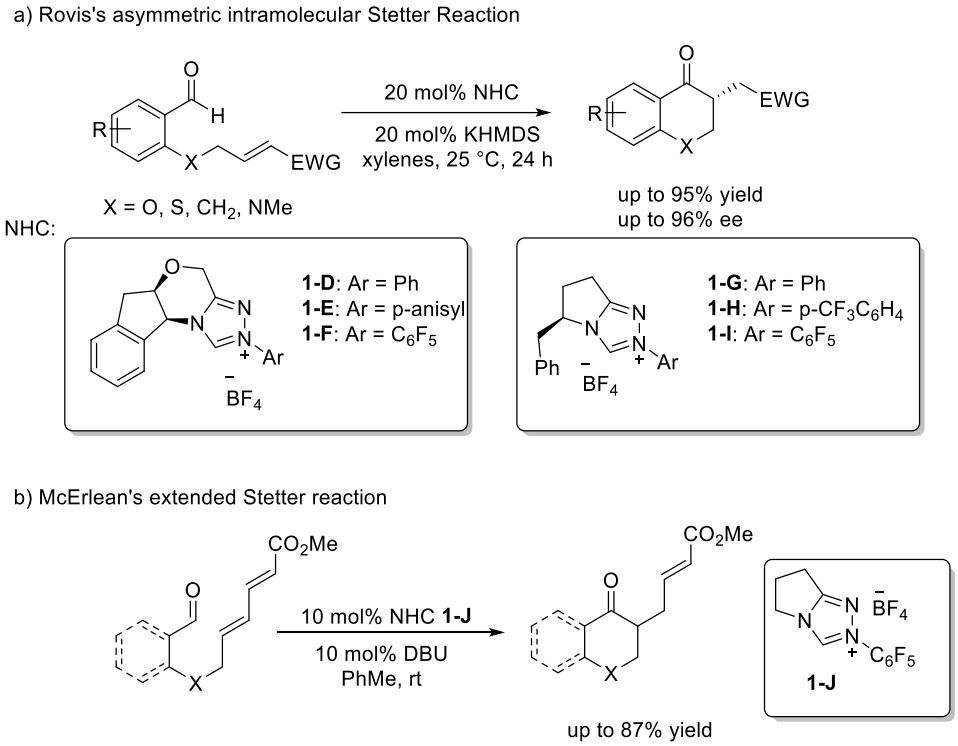
Instead of aldehydes as electrophiles *α,β*-unsaturated compounds were also utilized as electrophiles in NHC-catalyzed reaction by Stetter and co-workers,[27] these type of reaction are known as Stetter reaction (**Scheme 1.3**).



Scheme 1.3 Basic pathway of Stetter reaction

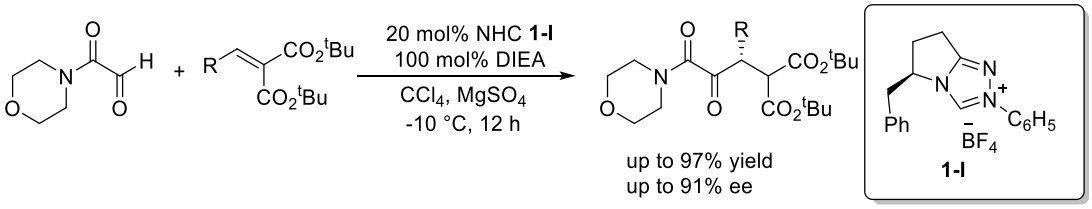
The first asymmetric version of Stetter reaction was developed by Enders and co-workers in intramolecular fashion using thiazolium salt as NHC precursor. However, yield and ee of the reaction were low.[28] After that, Rovis group successfully developed the variety of asymmetric Stetter reaction with the different heteroatom linkers such as oxygen, sulfur, nitrogen on the aldehydes substrate as well as the various Michael acceptor such as vinylphosphonates and phosphine oxides. Both aminoindane-based triazolium and pyrroline-

based triazolium NHC precursor were worked well in the reaction to afford corresponding product with high yield and high ee (**Scheme 1.4a**).[29-31] Further, Law and McErlean developed intramolecular Stetter reaction with 1,6-acceptor (**Scheme 1.4b**).[32]



Scheme 1.4 Selected examples of intramolecular Stetter reaction

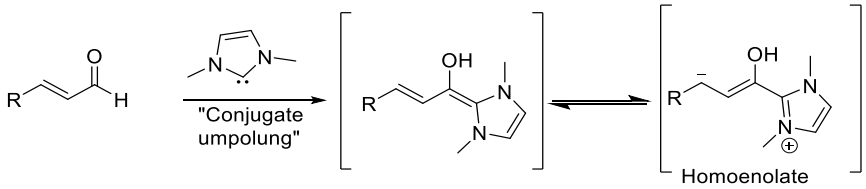
Intermolecular Stetter reaction has been played a vital role in the synthesis of many useful organic precursors. However, at the early stage, the major drawback of this reaction is benzoin condensation of donor aldehyde. In presence of β-substituted Michael acceptor, very low yield was observed.[33] However, in 2008, Rovis group has overcome the problem and developed a highly enantioselective intermolecular Stetter reaction using pyrroline-based triazolium chiral NHC precatalyst (**Scheme 1.5**).[34] Further, many groups developed intermolecular Stetter reaction using a variety of Michael acceptors such as chalcone, vinyl sulfones, 2-nitroglucals, vinylphosphonates.[13]



Scheme 1.5 Asymmetric intermolecular Stetter reaction

1.3.3 NHC-catalyzed homoenolate formation:

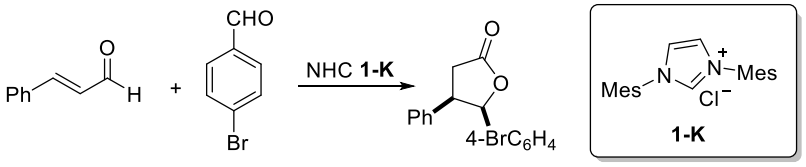
Not only the aldehydes but also *α,β*-unsaturated aldehydes also could be activated by NHC leading to the formation of *β*-carbanion. Nucleophilic addition of NHC to *α,β*-unsaturated aldehydes could afford extended Breslow intermediate. Due to the presence of extended conjugation in the system electron could transfer to *β*-carbon and furnish significant nucleophilicity at *β*-carbon. (**Scheme 1.6**)



Scheme 1.6 Generation of homoenolate

1.3.3.1 Oxygen-containing heterocycle synthesis via homoenolate pathway

In 2004, Glorius[35] and Bode[36] independently reported first lactone formation by using *α,β*-unsaturated aldehydes and aromatic aldehydes in presence of imidazolium NHC precursor. Two different reaction conditions were introduced.



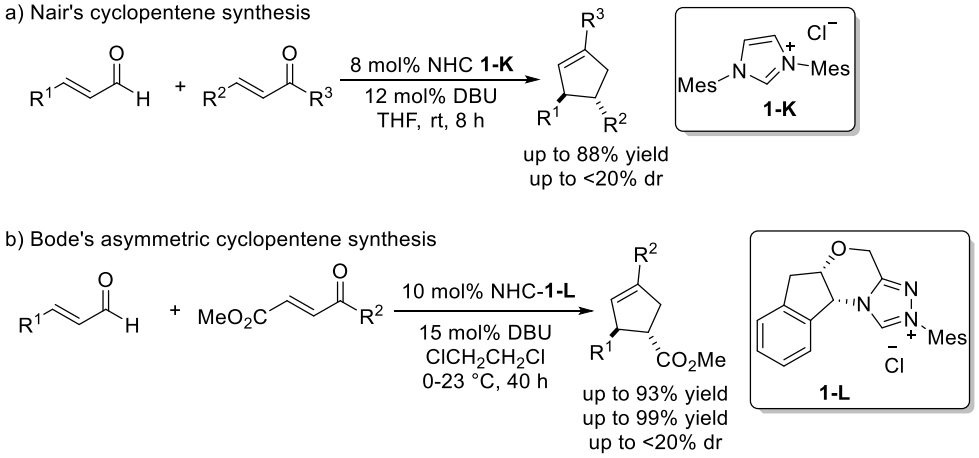
Bode's Condition	**Glorius's Condition**
enal(1 equiv), aldehyde (2 equiv)	enal (1 equiv.), aldehyde (1 equiv.)
8 mol% NHC	5 mol% NHC
7 mol% DBU,	10 mol% ^{t}BuOK
10:1,THF/ ^{t}BuOH	THF
rt, 15 h	rt, 16 h
79% yield, cis/trans: 4:1	49% yield, cis/trans: 4:1

Scheme 1.7 Homoenolate reaction with aldehydes

However, in both cases, γ-butyrolactone was afforded with the same diastereomeric ratio (**Scheme 1.7)**. After this pioneering work, a variety of electrophiles have been used to synthesize oxygen-containing heterocycle from simple enal in both achiral and chiral version. Besides aldehydes electrophile, Glorius's protocol also worked with ketone substrate to afford γ-butyrolactone with one quaternary center.[37] Further, glyoxalate,[38] 1,2-dicarbonyl[39] compounds have also been used as an electrophile to synthesize substituted γ-butyrolactone and spirocyclic-γ-lactones respectively.

1.3.3.2 Carbocycle synthesis via homoenolate pathway

Chalcone type of substrates was also used as an electrophile to access carbocycle. In 2006, Nair and co-workers reported a reaction between chalcone and homoenolate to afford 3-4-trans-disubstituted cyclopentenes (**Scheme 1.8a**).[40]



Scheme 1.8 Selected examples for carbocycle formation via homoenolate

Later, Bode and Co-workers disclosed asymmetric version of this reaction by utilizing aminoindane-based triazolium precatalyst. Corresponding cyclopentenes were formed with high enantio- and diastereo-selctivities (**Scheme 1.8b**).[41] The proposed mechanism for the cyclopentene formation is shown in **Figure 1.4**. Based on Nair's postulated mechanism, initially, enal was activated by NHC to afford homoenolate **7**, which underwent 1,4-addition reaction with chalcone substrate to form intermediate **8**. Subsequently, protonation of

intermediate **8** gave enolate intermediate **9,** which participated in intramolecular aldol reaction to furnish cyclopentane carbinolate intermediate **10**.

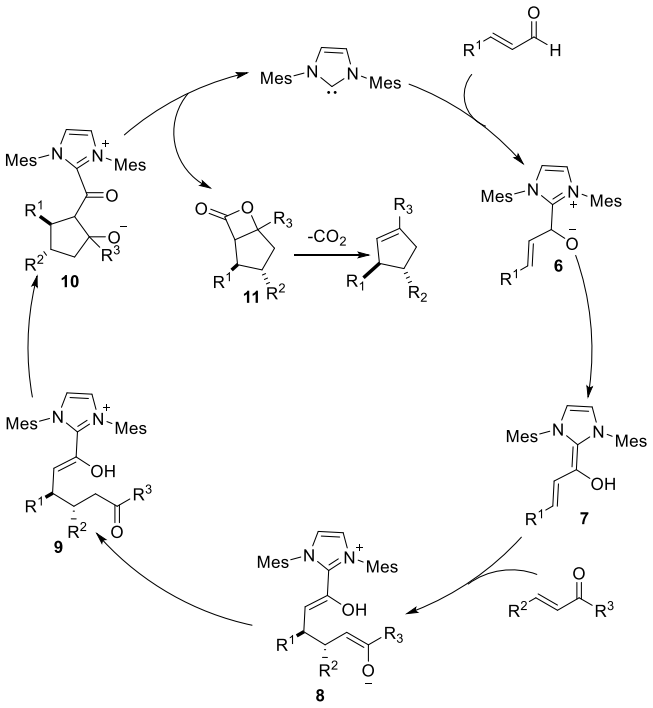
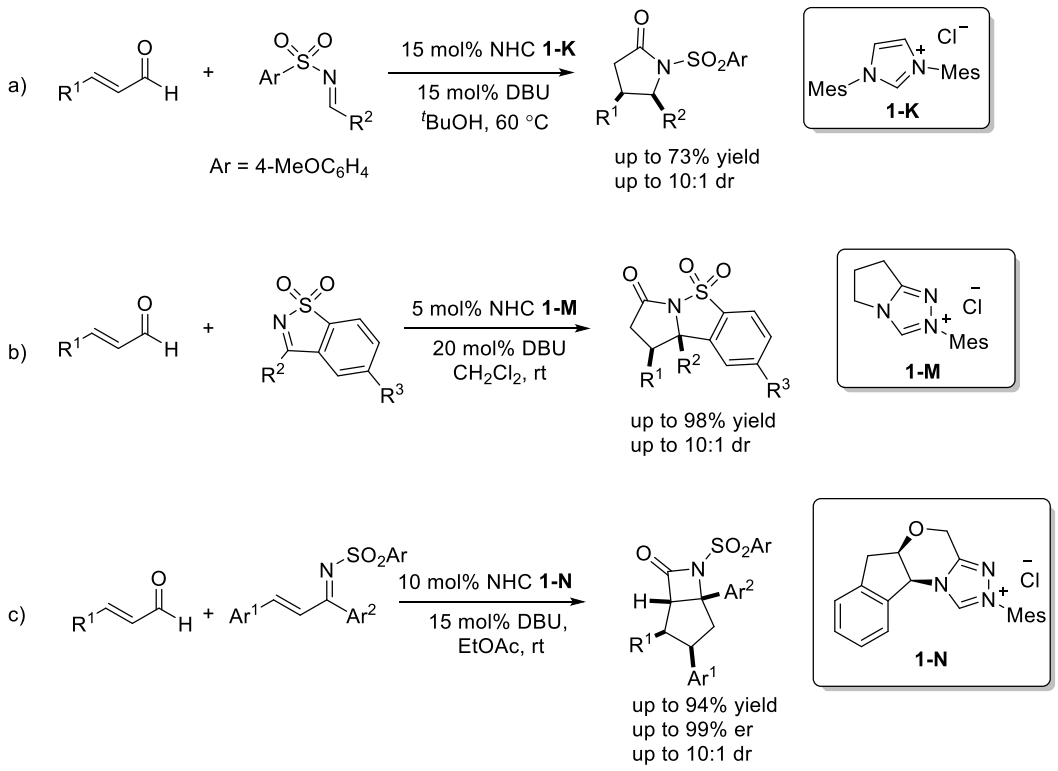


Figure 1.4 Mechanism of NHC-catalyzed carbocycle formation

Then carbenolate underwent lactonization reaction to form *β*-lactone **11** with regeneration of NHC catalyst for the next catalytic cycle. As the *β*-lactone **11** is unstable, it underwent decarboxylation to afford the cyclopentene.

1.3.3.3 Nitrogen-containing heterocycle synthesis via homoenolate pathway

Besides the synthesis of carbocycle, homoenolate has also been utilized to afford nitrogen-containing heterocycle. In 2005, Bode and co-workers first developed this reactivity using imine as electrophile.[42] Various aromatic enal and aryl imines were well tolerated in their reaction to afford *γ*-lactams with good yields and moderate diastereoselctivities (**Scheme 1.9a**) However, the reaction was limited to 4-methoxyphenyl sulfonyl imine because of carbene catalyst was deactivated by its addition to the imine moiety. The same group overcomes this issue utilizing cyclic sulfonyl ketimines as electrophile. Highly substituted *γ*-lactams



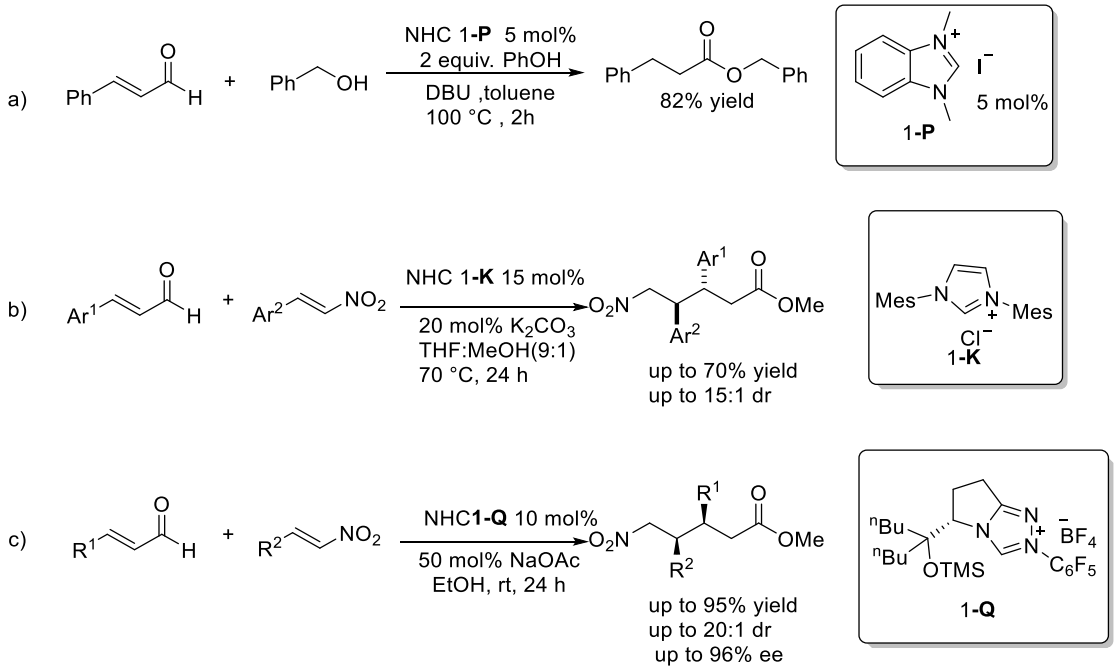
Scheme 1.9 Selected examples for nitrogen-containing heterocycle formation via homoenolate

were afforded with moderate yields and moderate diastereoselectivities (**Scheme 1.9b**).[43] Later, Bode group also reported asymmetric synthesis of bicyclic *β*-lactam utilizing *N*-sulfonyl ketimines as an electrophile. In presence of aminoindane-based triazolium catalyst, bicyclic *β*-lactams were afforded with excellent enantioselectivities and excellent yields (**Scheme 1.9c**).[44]

1.3.3.4 Non-annulative reaction via homoenolate pathway

Besides the annulative process, a variety of non-annulative reactions have been developed via homoenolate formation from enals. *α,β*-unsaturated aldehydes derived homoenolate could be trapped by external proton source. Scheidt group disclosed, in the presence of phenol, homoenolate could be protonated to form acylazolium followed by esterification with benzyl alcohol to form saturated ester (**Scheme 1.10a**).[45] In 2009, Nair group [46] reported 1,4-addition reaction between homoenolate and nitroalkenes to afford *δ*-nitro esters. The reaction underwent via 1,4-addition of homoenolate to nitroalkenes followed by esterification with alcohol

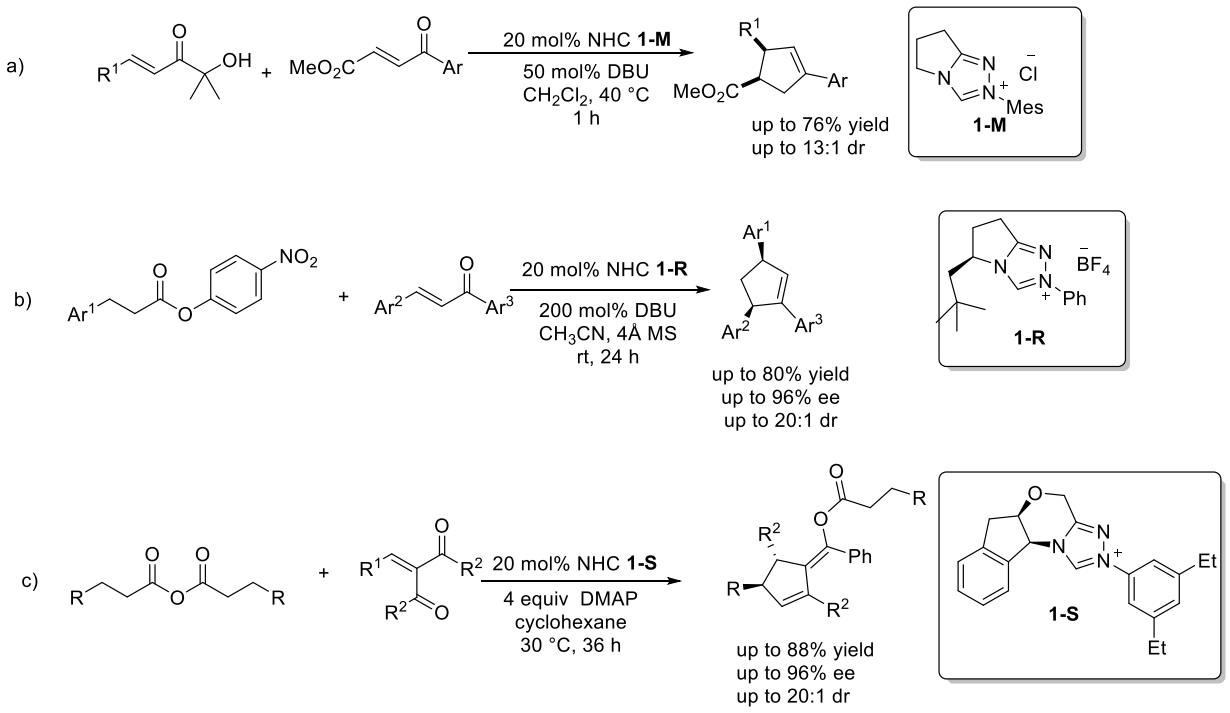
(**Scheme 1.10b**). Later, Rovis group disclosed asymmetric version of this reaction utilizing chiral triazolium catalyst. Corresponding esters were furnished with high yields, excellent diastereo- and enantio-selectivites (**Scheme 1.10c**).[47-48]



Scheme 1.10 Selected examples for non-annulative reaction formation via homoenolate

1.3.3.5 Alternative access to homoenolate

Homoenolate was also generated from other substrates instead of enals. In 2009, Bode and co-workers developed *α*-hydroxy enones could be an effective replacement of enal for N-heterocyclic carbene catalyzed homoenolate formation (**Scheme 1.11a**). However, increasing steric demands at the carbonyl center inhibit the use of bulky chiral NHC. In 2013, our group reported NHC catalyzed activation of saturated carboxylic ester to make nucleophilic *β*-carbon directly (**Scheme 1.11b**). Saturated esters that contained a good leaving group, such as 4-nitrophenol, were used for the formation of homoenolate equivalent. Chiral cyclopentene derivatives were obtained when enone was used as an electrophile. Further, trifluoro ketones and hydrazones electrophiles also worked well in the reaction.[49]



Scheme 1.11 Selected examples for alternative excess of homoenolate

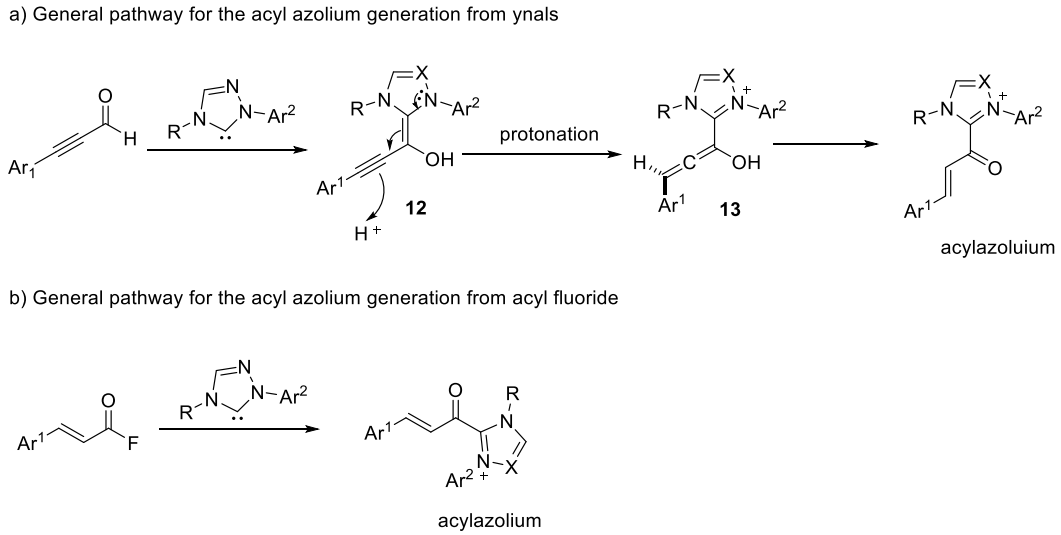
However, this method is limited to *β*-aryl substituted esters. This problem was solved by our group in 2014[50], anhydride substrate could also be activated by NHC to give homoenolate equivalent intermediate. In this case, both *β*-aryl and *β*-alkyl substituted anhydrides were worked in the reaction with enone substrate. Cyclopentene derivatives were obtained with high yields and high enantiomeric ratios (**Scheme 1.11c**).

1.3.4 NHC-catalyzed acylazolium formation

Besides umpolung chemistry, NHCs also act as a potential catalyst for some non-umpolung processes. Azolium enolate and acylazolium intermediate have played a vital role in this context. A variety of carbene-catalyzed reactions have been explored involving acylazolium intermediate in the last decade. NHC-bonded *α,β*-unsaturated acylazolium could be generated from *α*-oxidizable aldehyde such as bromo enals and ynals, enals, *α,β*-unsaturated esters or *α,β*-unsaturated acyl fluoride

1.3.4.1 Acylazolium generation from ynals and acyl fluoride

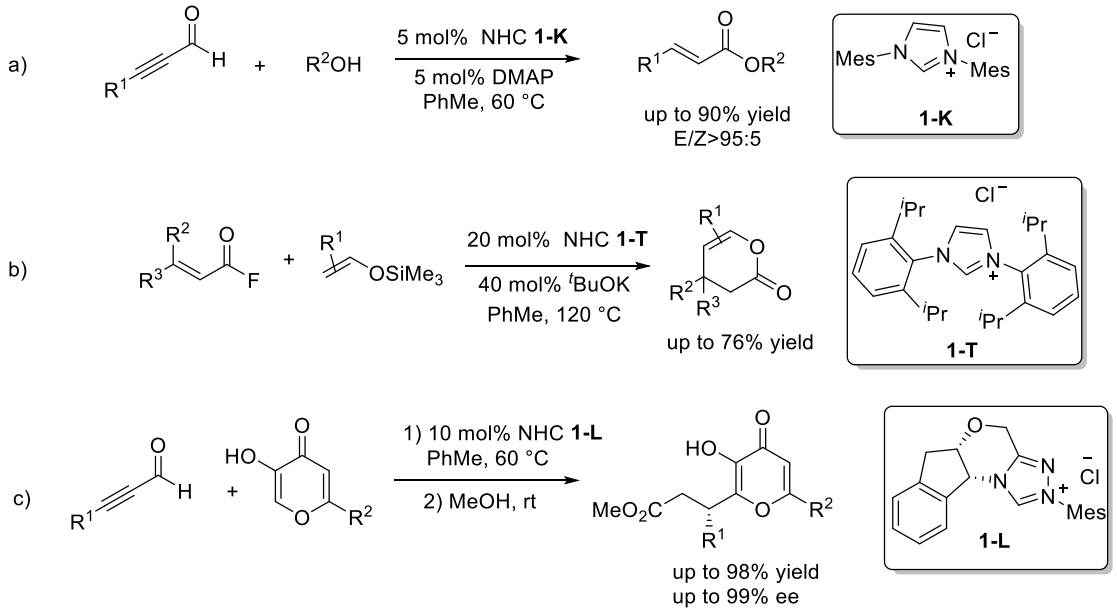
NHC-bonded *α,β*-unsaturated acylazolium could be generated from ynals and acyl fluoride. The formation of *α,β*-unsaturated acylazolium is shown in **Scheme 1.12**. Ynals could be activated by NHC to form intermediate **12** which underwent protonation and converted to acylazolium (**Scheme 12a**) Nucleophilic NHC addition to *α,β*-unsaturated acyl fluoride could afford acyl azolium (**Scheme 12b**).



Scheme 1.12 General pathway for the acyl azolium generation from ynals and acyl fluoride

There are two types of acyl azolium reactions have been developed in the field of NHC catalysis, one is esterification and another one is Michael addition reaction to the *α,β*-unsaturated acylazolium intermediates. In 2006, Zeitler[51] and co-workers reported NHC-bonded *α,β*-unsaturated acylazolium could be generated from ynals which could react with primary or secondary alcohol to afford *α,β*-unsaturated ester. Both aryl and aliphatic ynals were employed, however, in presence of secondary alcohols, ester products were formed with very low yields. (**Scheme 1.13a**) Lupton and co-workers also developed synthesis of dihydropyranones utilizing trimethylsilyl enol ethers, acyl fluorides (**Scheme 1.13b**).[52] This reaction also proceeded via 1,4-addition with *α,β*-unsaturated acylazolium intermediates. Later, Bode and co-workers.[53] reported enantioselective Claisen type rearrangement using aminoindane-based

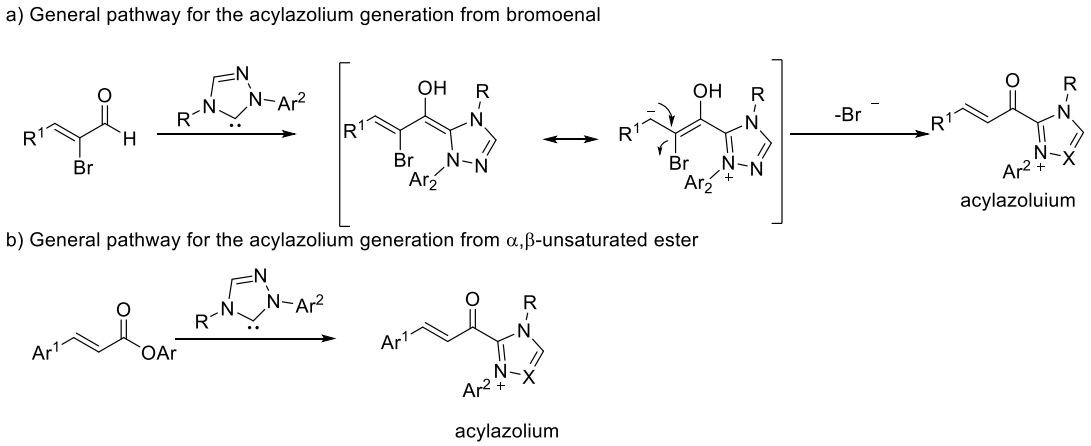
chiral triazolium catalyst-bonded acylazolium intermediate which was generated from ynals (**Scheme 1.13c**).



Scheme 1.13 Selected example of acylazolium intermediate involving reaction from ynals and acyl fluoride

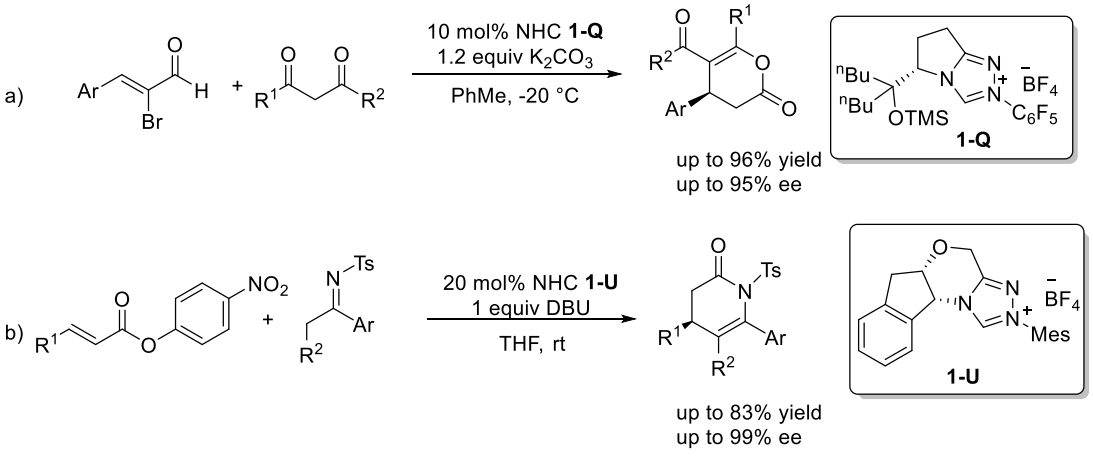
1.3.4.2 Acylazolium generation from bromoenals and *α,β*-unsaturated ester

Acylazolium could be generated from *α*-bromoenals. The general pathway is shown in **Scheme 1.14**. *α*-bromoenals could be activated by NHC. Then after bromide elimination acylazolium was generated (**Scheme 1.14a**). *α,β*-unsaturated ester also could be used for acylazolium generation . The *α,β*-unsaturated esters that contained electron-withdrawing aryl group, could be activated by nucleophilic NHC (**Scheme 1.14b**). Acylazolium could be generated from *α*-bromoenals, this chemistry was first introduced by Ye and co-workers.[54] NHC-catalyzed enantioselective Claisen type reaction was explored utilizing the acylazolium that generated from *α*-bromoenals and 1,3-dicarbonyl compounds as a nucleophilic partner. 3,4-dihydropyranones were obtained with excellent yields and excellent enantioselectivities (**Scheme 1.15a**)



Scheme 1.14 General pathway for the acylazolium generation from bromoenals and *α,β*-unsaturated ester

After that, many enantioselective reactions have been explored using *α*-bromoenals-derived acylazolium with a variety of nucleophilic partner. In 2013, our group developed activation of *α,β*-unsaturated esters by NHC catalyst.[55] Nucleophilic 1,2-addition of NHC to *α,β*-unsaturated ester, furnished *α,β*-unsaturated acylazolium intermediate, which reacted with. Ketone-derived imines. In presence of aminoindane-based chiral triazolium catalyst, various aryl imines were used as nucleophilic partner to afford dihydropyridinones ring with excellent yields and excellent ee values (**Scheme 1.15b**).



Scheme 1.15 Selected examples of acylazolium intermediate involving reaction from bromoenal and *α,β*-unsaturated ester

1.3.4.3 Acylazolium generation from oxidative methods

NHC-catalyzed oxidative transformation of aldehydic substrates is biomimetic. Oxidative decarboxylation of pyruvate, catalyzed by thiamine pyrophosphate (TPP), a cofactor of enzymes and a thiamine (vitamin B1). This oxidative reaction was promoted by pyruvate ferredoxins oxidoreductase and it is considered that SET pathway involved in this reaction.[56-57] After deprotonation of thiazolium, C2-H free thiamine pyrophosphate **14 (Figure 1.5)** was generated then it reacted with pyruvate to form intermediate **15**, which underwent decarboxylation to form Breslow intermediate **16**. Two consecutive single electron transfers from electron-rich Breslow intermediate **16**, furnished azolium intermediate **18**. During two consecutive SET processes, [Fe_4S_4] clusters were reduced. Finally, CoASH was transformed to CoASAc with regeneration of C2-H free thiamine pyrophosphate **14.**

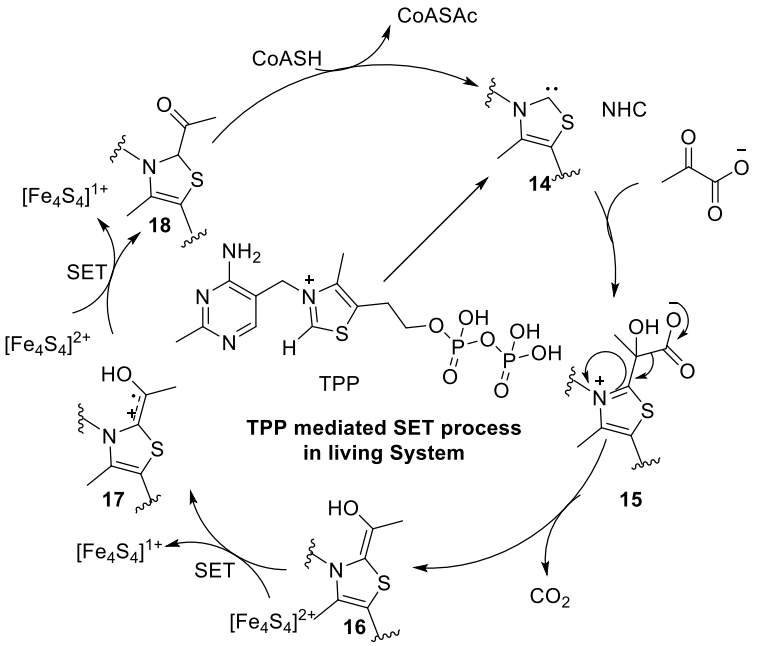
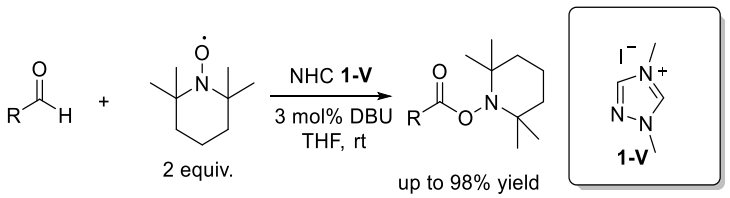


Figure 1.5 Thiamine pyrophosphate (TPP) catalyzed oxidative decarboxylation of pyruvate.

As TPP (precursor of thiazolium catalyst) involves in the natural process, this could be applied to the small molecule. In 2008, Studer and co-workers developed first biomimetic carbene-catalyzed oxidation of aldehydes in presence of TEMPO as an oxidant (**Scheme 1.16**).[58]



Scheme 1.16 TEMPO mediated oxidation of aldehyde

TEMPO acted as an oxidant similar to [Fe_4S_4] cluster in living system. The reaction was catalyzed by imidazolium NHC catalyst. The reaction pathway is shown in **Figure 1.6** which is similar to the pathway of oxidative decarboxylation of pyruvate in the living system. Two consecutive single electron transfers occurred from Breslow intermediate **20** to afford azolium intermediate **23**, which reacted with TEMPO anion to afford the corresponding ester product and NHC was regenerated for the next catalytic cycle.

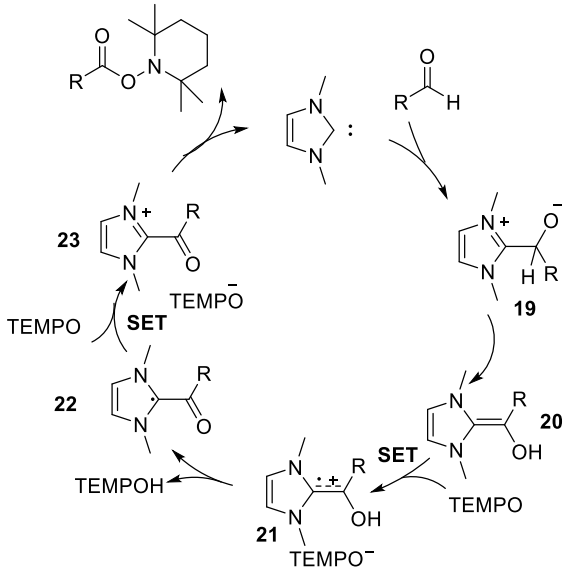
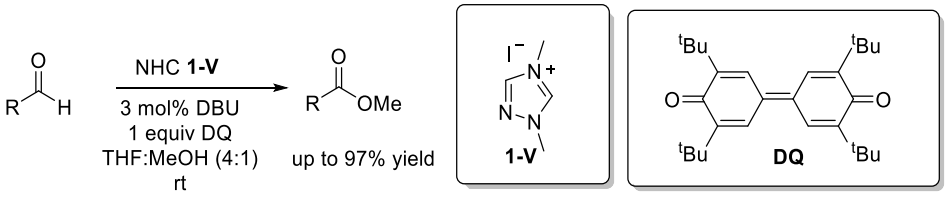


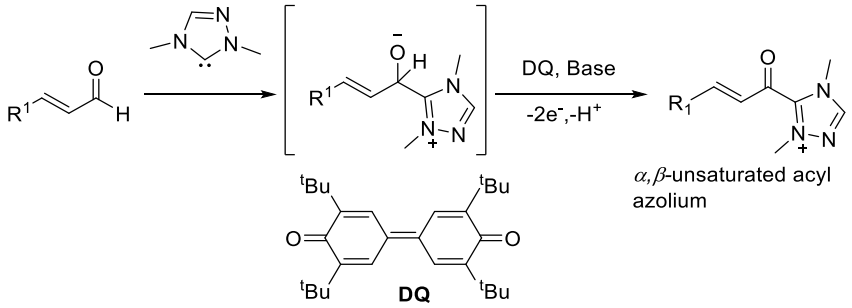
Figure 1.6 Mechanism of TEMPO mediated oxidation of aldehyde

DFT calculation on intermediate **21** suggested that it is a carbon-centered radical cation with partial double bond character. After this pioneering work, Studer and co-worker also developed NHC-catalyzed oxidation of aldehydes to access esters using 3,3',5,5'-tetra-tert-butyldiphenoquinone (DQ), which acted as two-electron oxidant, and it was recovered by air oxidation of the corresponding quinol derivatives (**Scheme 1.17**).[59] Hence, the use of DQ as an oxidant is more economically beneficial.



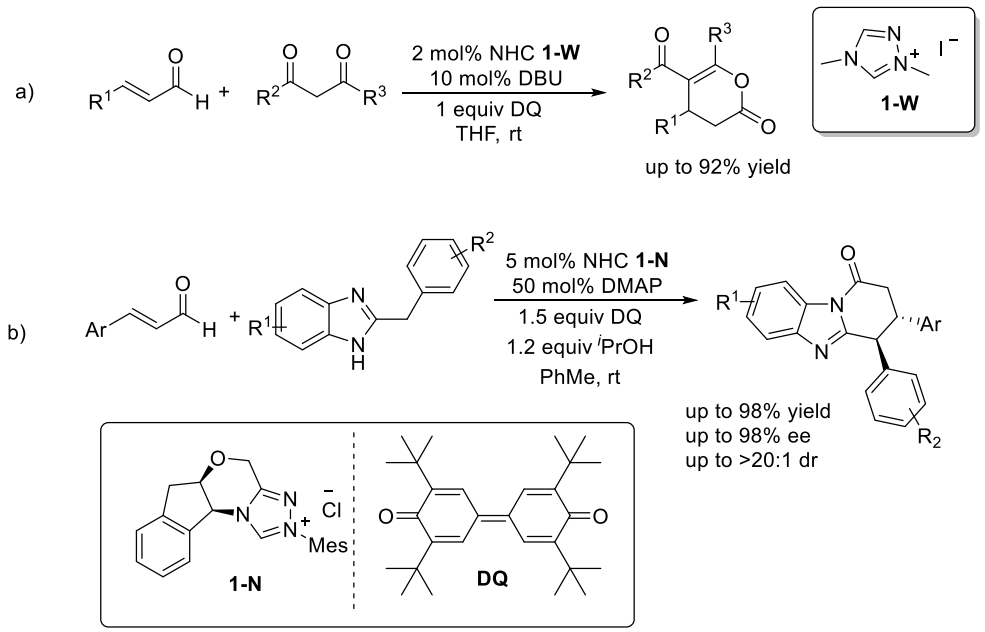
Scheme 1.17 DQ mediated esterification reaction

α,β-unsaturated acylazolium could be formed by oxidation of extended Breslow intermediate using external oxidant. In presence of DQ as an oxidant, the enal-derived NHC-bonded tetrahedral intermediate could be oxidized to *α,β*-unsaturated acyl azolium intermediate. (**Scheme 1.18**)



Scheme 1.18 Oxidative pathway of *α,β*-unsaturated acyl azolium formation

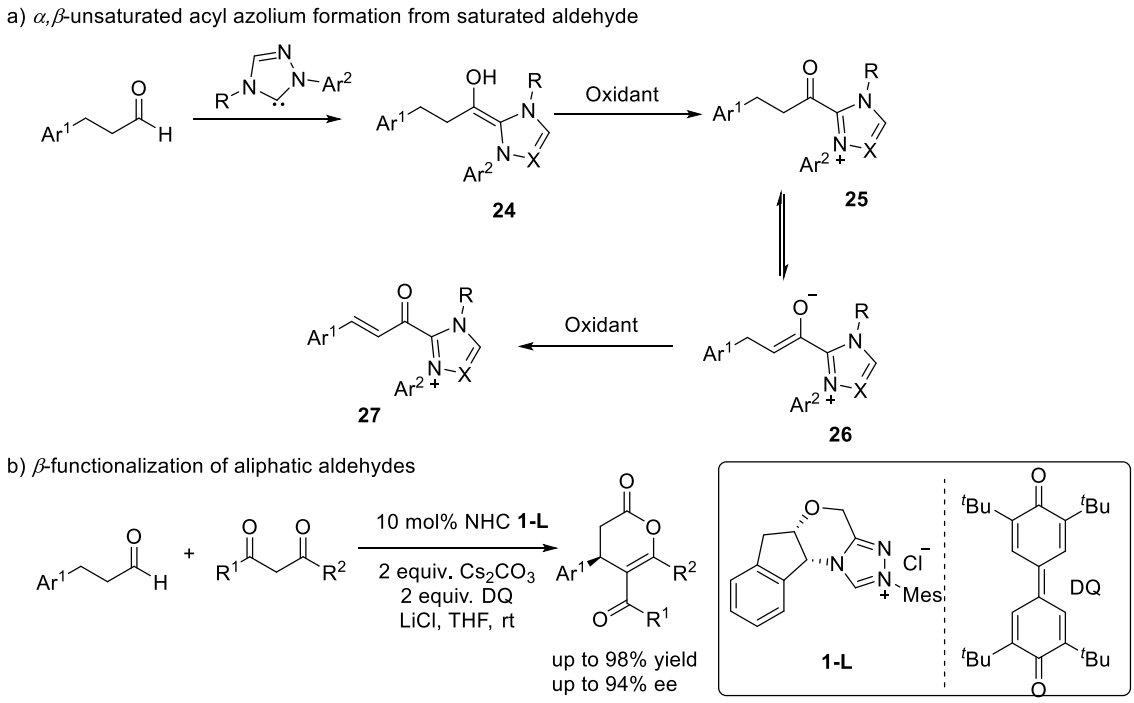
The first example was reported by Studer and co-worker[60], *α,β*-unsaturated acyl azolium was achieved from enal by using 3,3',5,5'-tetra-tert-butyldiphenoquinone (DQ) as an oxidant and then this intermediate was reacted with 1,3-dicarbonyl compounds to form 3,4-dihydropyranones (**Scheme 1.19a**). After this pioneering work, many research groups developed NHC-catalyzed annulation reactions via oxidative *α,β*-unsaturated acyl azolium formation. Most of the cases DQ has been utilized as an oxidant. Recently, our group developed oxidative coupling reaction of diaryl methane and enals. The reaction underwent via NHC-catalyzed redox activation of enal. Benzimidazole fused lactams were obtained with high yields, excellent diastereo- and enantioselectivities (**Scheme 1.19b**).[61]



Scheme 1.19 Selected examples of acylazolium intermediate formation via oxidative process

1.3.4.4 Acylazolium generation from saturated aldehydes

α,β-unsaturated acylazolium has also been achieved from saturated aldehydes, our group reported *β*-functionalization of saturated aldehydes. The pathway differs from the normal in the oxidation step. Initially, Breslow intermediate **24** was oxidized by external oxidant to from NHC-bound saturated acylazolium intermediate **25,** which underwent deprotonation of *α*-CH proton to afford azolium enolate intermediate **26** (**Scheme 1.20a**). Finally, the azolium enolate intermediate, was oxidized by another equivalent of oxidant and furnished *α,β*-unsaturated acyl azolium intermediate **27**. 1,3-dicarbonyl compounds were utilized as nucleophile to *β*-functionalization of saturated aldehydes. Dihydropyranones were obtained in presence of aminoindane-based triazolium catalyst with excellent yields and excellent enantioselectivities **(Scheme 1.20b)**.[62]



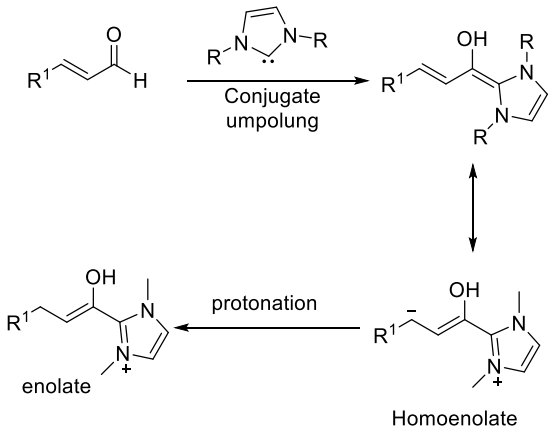
Scheme 1.20 Acylazolium formation from saturated aldehydes via oxidative process

1.3.5 NHC-catalyzed azolium enolate formation

A variety of carbene-catalyzed reactions have been explored involving azolium enolate intermediate in the last decade. NHC-bonded azolium enolate could be generated from enals, ketenes, *α*-chloroaldehydes and saturated esters.

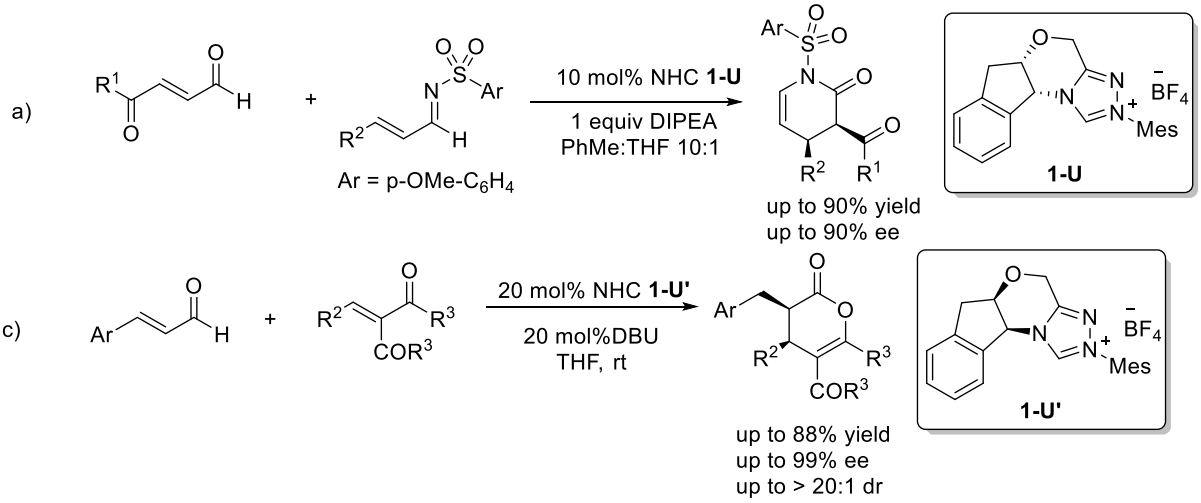
1.3.5.1 Azolium enolates generation from enals

As discussed previously, NHC could form homoenolate from enal substrates and *β*-functionalization of enals was achieved. Enolate intermediate also could be achieved from homoenolate after protonation at *β*-carbon of the enal substrates, this new reactivity of Breslow intermediate revealed a new reaction design. Intra- or intermolecular proton transfer at *β*-carbon of homoenolate gave azolium enolate, which could react with electrophiles to afford *α*-functionalized molecules (**Scheme 1.21**).



Scheme 1.21 Azolium enolate formation pathway from enal

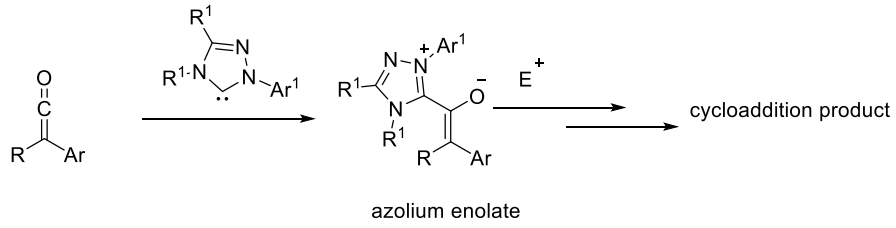
In 2006, Bode group first developed asymmetric [4+2] cycloaddition reaction using enal-derived azolium enolate.[63] Enal bearing with electron-withdrawing group reacted with *N*-protected *α,β*-unsaturated imines in presence of aminoindane-based chiral triazolium catalyst to afford dihydropyridinones with high yields and excellent enantioselectivities (**Scheme 1.22a**). In 2011, our group developed a reaction of azolium enolate with modified chalcone to afford lactone products with good yields, excellent diastereo- and enantio-selectivities (**Scheme 1.22b**).[64] After that, many research groups reported cycloaddition reaction with azolium enolate with a variety of electrophiles.



Scheme 1.22 Selected cycloaddition reaction of azolium enolate formation pathway

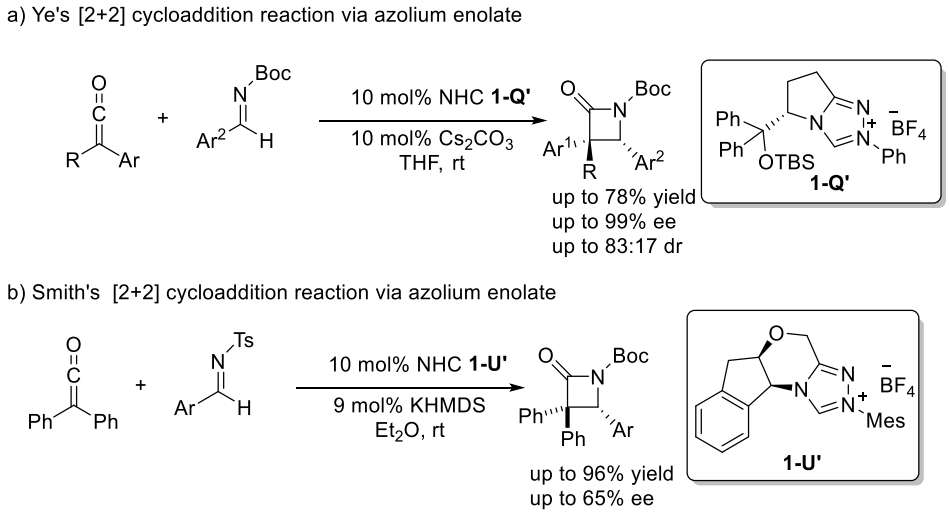
1.3.5.2 Azolium enolates generation from ketenes

Azolium enolates also could be generated from aryl(alkyl) disubstituted ketenes. Nucleophilic addition of NHC to ketene gave azolium enolate intermediate which could react with a variety of electrophiles to afford cycloaddition products (**Scheme 1.23**).



Scheme 1.23 Azolium enolate formation pathway from ketenes

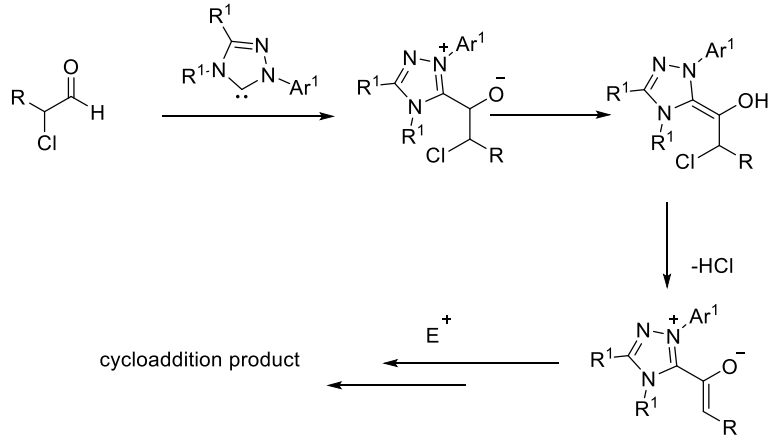
In 2008, Ye[65] and Smith[66] groups independently developed formal [2+2] cycloaddition reaction between ketene-derived azolium enolate and imines. Bulky chiral triazolam catalyst along with aryl(alkyl)-disubstituted ketenes and *N*-Boc protected imines were utilized in the reaction. *β*-Lactam was obtained with moderate yields and excellent enantioselectivities (**Scheme 1.24a**). Smith and co-workers used diphenyl substituted ketenes with *N*-sulfonyl imines in presence of aminoindane-based chiral triazolium catalyst. However, *β*-Lactam was obtained with low enantioselectivity (**Scheme 1.24b**).



Scheme 1.24 Selected examples of [2+2] cycloaddition reaction via ketene-derived azolium intermediate

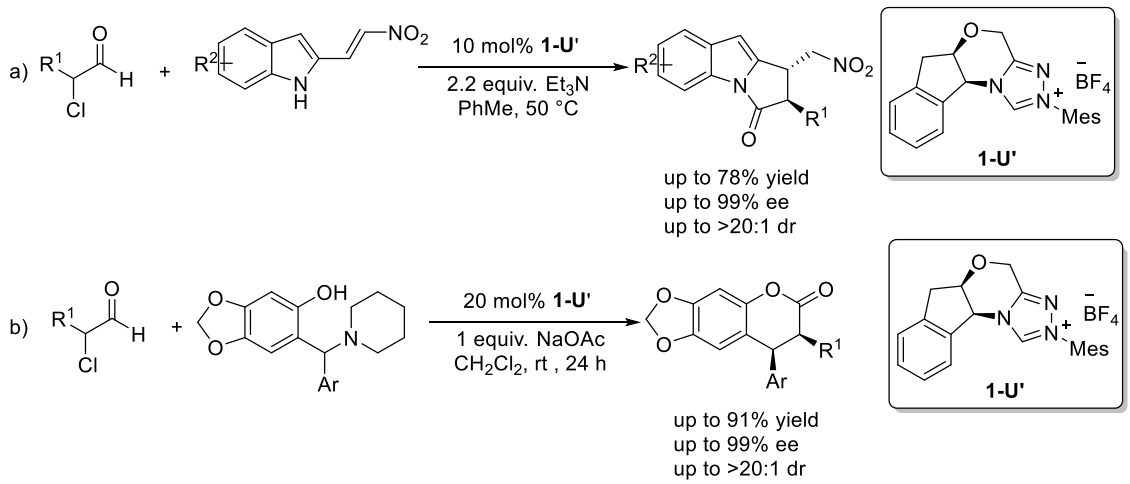
1.3.5.3 Azolium enolates generation from *α*-chloroaldehydes

NHC-catalyzed azolium enolate intermediate also could be achieved from saturated *α*-chloroaldehydes. Mechanistically, NHC addition to saturated *α*-chloroaldehydes gave chlorinated Breslow intermediate which could undergo hydrochloric acid elimination, leading to formation of azolium enolate intermediate (**Scheme 1.25**). Enders and co-worker reported [3+2] cycloaddition reaction of *α*-chloroaldehyde-derived azolium enolate and 2-nitrovinylindoles in presence of aminoindane-based chiral triazolium catalyst (**Scheme 1.26a**).[67] The corresponding tricyclic product was afforded with good yields and excellent enantio- and diastereoselctivities.



Scheme 1.25 Azolium enolate formation pathway from *α*-chloroaldehydes

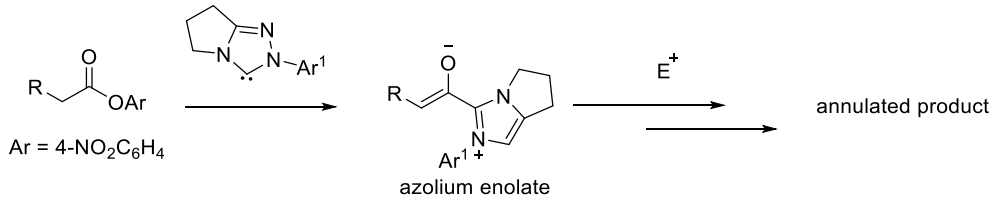
A variety of 2-nitrovinylindoles containing with electron-donating and electron-withdrawing groups worked well in their reaction. In 2017, our group reported a highly enantioselective method to access dihydrocoumarins.[68] NHC and acid cooperative catalysis was employed in this reaction. [4+2] cycloaddition reaction of *α*-chloroaldehyde-derived azolium enolate and *in situ* generated *ortho-quinone methide* (o-QM) intermediates. Dihydrocoumarin derivatives were obtained with good yields and excellent enantio- and diastereo-selctivities (**Scheme 1.26b**). This method was also utilized to synthesize many valuable pharmaceuticals.



Scheme 1.26 Selected examples cycloaddition reaction via α-chloroaldehydes-derived azolium intermediate

1.3.5.4 Azolium enolates generation from saturated esters

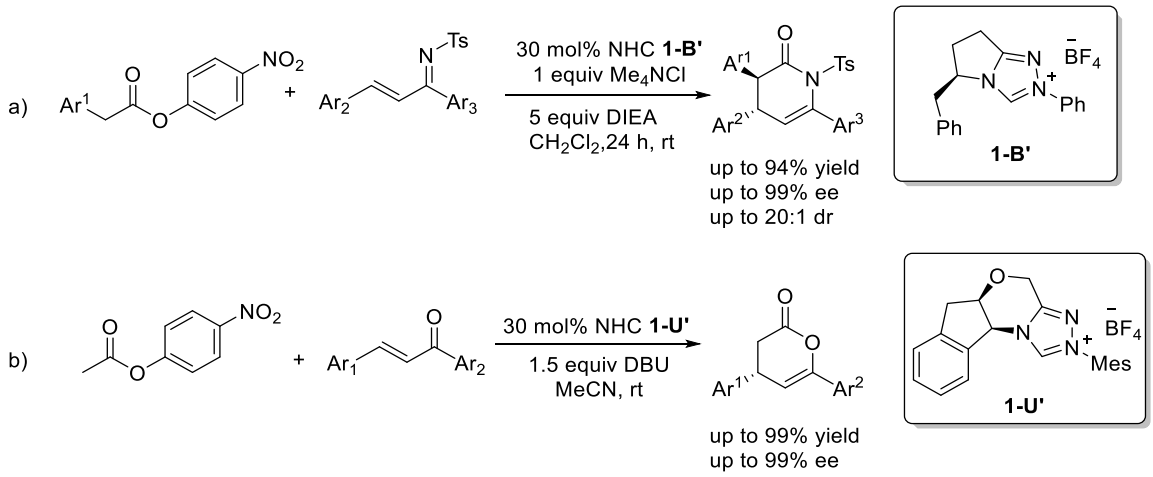
NHC-catalyzed azolium enolate intermediate also could be accessed saturated esters. In 2012, our group[69] developed saturated esters could be activated by NHC catalyst to afford azolium enolate intermediate after deprotonation of α-H. Ester-derived azolium enolate could react with electrophiles to furnish annulated products (**Scheme 1.27**).



Scheme 1.27 Azolium enolate formation from saturated esters

The esters are air stable substrates, this is the importance of using ester substrates in carbene catalysis over aldehydes and ketenes, which are unstable in air, leading to formation of oxidized products as side products. In 2012, our group first developed a reaction of α,β-unsaturated imines and saturated ester bearing with electron-withdrawing aryl group to afford chiral dihydropyridinones with high yields and good enantioselectivities (**Scheme 1.28a**).[69] The reaction underwent via formation of ester-derived azolium enolate intermediate Chiral pyrroline-based triazolium salt was used as a NHC precatalyst. In 2013,[70] our group also

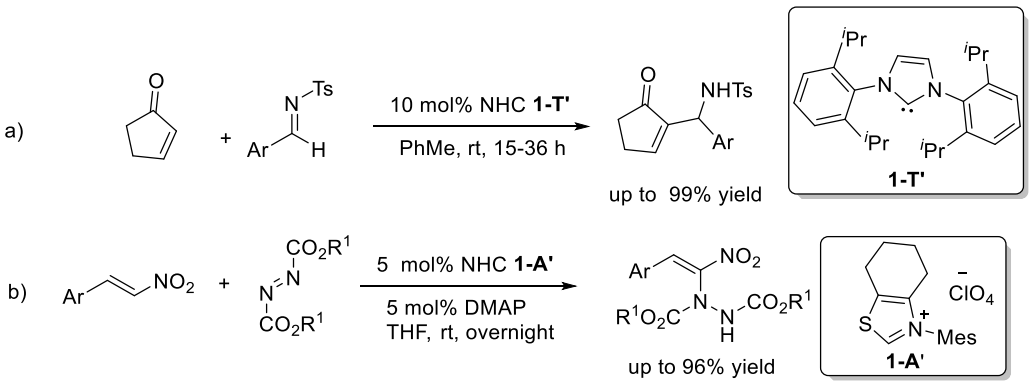
disclosed N-heterocyclic carbene-catalyzed enolate formation of acetic ester. Acetic ester bearing with 4-nitrophenol group was activated by NHC to form azolium enolate. Enolate underwent 1,4-addition reaction with chalcone substrates, leading to the formation of *δ*-lactones (**Scheme 1.28b**). *δ*-Lactams were also formed utilizing *α,β*-unsaturated imines substrates in presence of chiral pyrroline-based triazolium catalyst with high yields and high enantioselectivities.



Scheme 1.28 Selected examples of saturated ester-derived azolium enolate formation

1.3.6 NHC as catalyst for Morita-Baylis-Hillman reaction (MBH) type reaction

NHC-Catalyst also could act as a Lewis base catalyst. NHC-catalyzed Morita-Baylis-Hillman reaction (MBH) was developed by Ye group.[71] Cyclic enones and *N*-tosyl imine



Scheme 1.29 Selected examples of NHC-catalyzed MBH type reaction

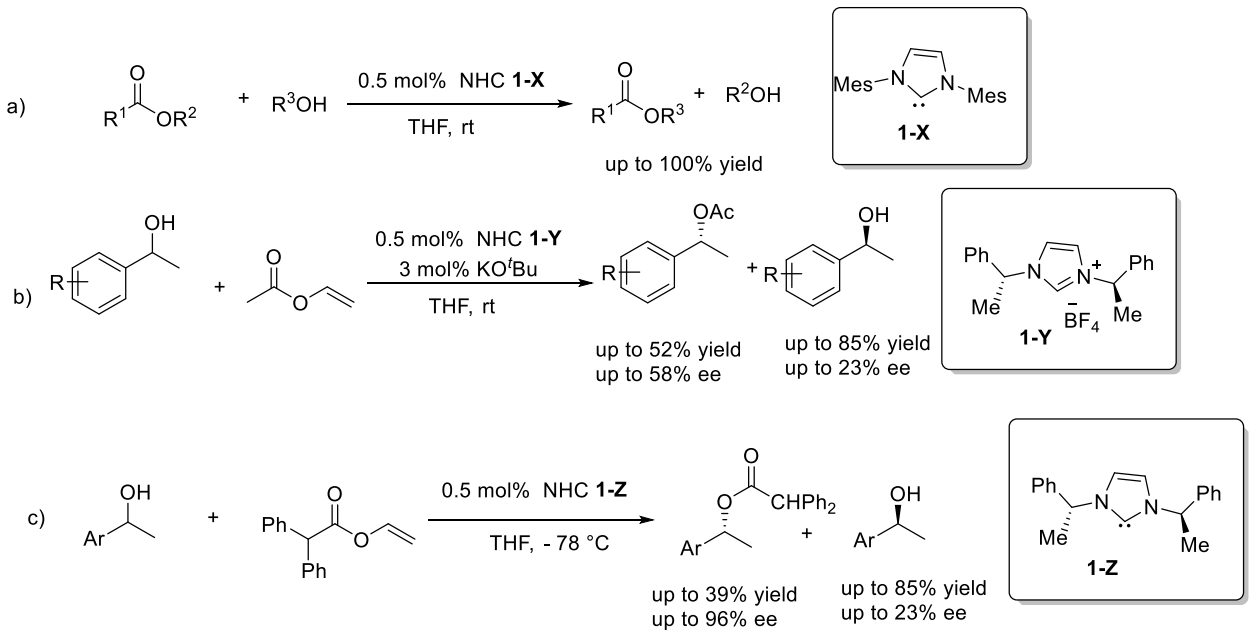
reacted in presence of NHC to afford coupling products with excellent yields (**Scheme 1.29a)**. Ye and co-workers also reported MBH reaction utilizing nitrostyrene and azodicarboxylates to furnish desired products with good yields utilizing thiazolium as NHC precatalyst (**Scheme 1.29b)**.[72]

1.4 NHC-catalyzed kinetic resolution

Different modes of reaction enabled by NHC catalysis have been discussed in the previous section. A large variety of asymmetric reactions have been achieved by chiral NHC catalysis. Kinetic resolution is one of the most effective strategies for the synthesis of enantiomerically pure functional molecules. Catalytic kinetic resolution has been extensively studied for the preparation of optically enriched functional molecules in the past few decades. N-heterocyclic carbenes have been played a vital role in this context. Many NHC-catalyzed reactions, such as esterification, benzoin, cycloaddition, ring expansion have been utilized for kinetic resolution. Over the past decade, many NHC-catalyzed kinetic resolutions have been well studied for the synthesis of a variety of optically enriched molecules.[15]

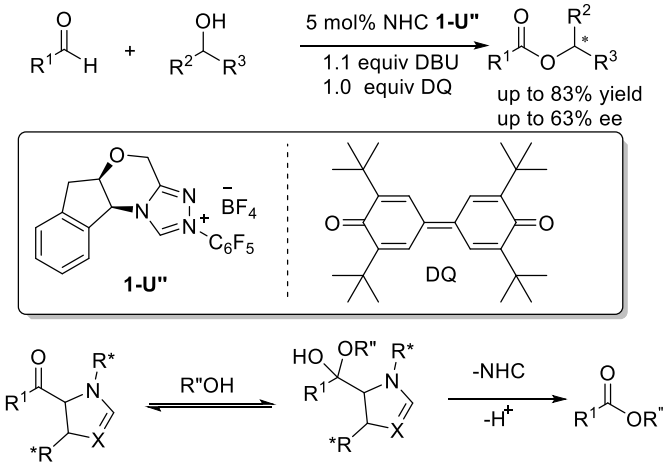
1.4.1 NHC-catalyzed kinetic resolution of alcohol

The first carbene catalyzed transesterification was introduced by Nolan[73] and Hedrick[74] independently(**Scheme 1-30a**) Initially, the proposed mechanism involved the formation of acyl azolium intermediate. However, later Movassaghi and Schmidt[75] showed that NHC acted as a base. Inspired by this work, Suzuki[76] reported the first carbene-catalyzed kinetic resolution of secondary alcohol in 2004 (**Scheme 1-30b)**. In presence of chiral imidazolium salt as precatalyst vinyl acetate was utilized as the acylating reagent. In 2005, Maruoka[77] developed highly enantioselective kinetic resolution of secondary alcohol by employing more steric vinyl diphenylacetate. Variety 1-phenylethanols with electron-donating and withdrawing functional groups were well-tolerated to give high s-factor (S = 30-80) and high ee values (**Scheme 1-30c)**.



Scheme 1.30 NHC-catalyzed transesterification and kinetic resolution of secondary alcohol

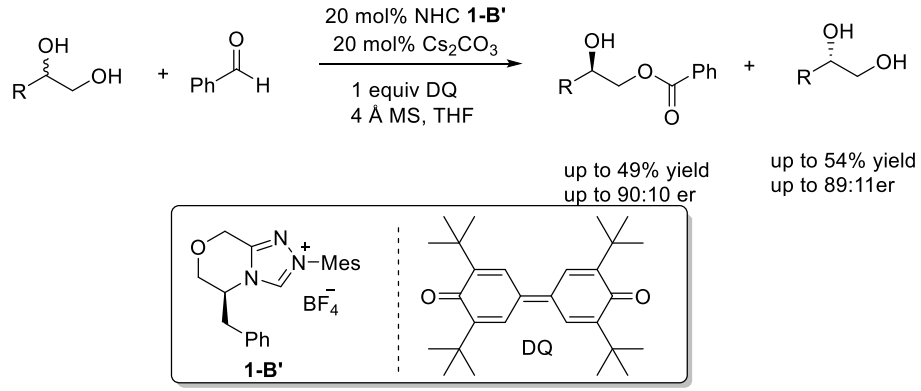
In 2011, Studer[78] demonstrated carbene-catalyzed kinetic resolution of alcohol via oxidative esterification (**Scheme 1.31**). pyridine-2-carbaldehyde was found as a suitable aldehyde with highest selectivity in the kinetic resolution of 1-(1-naphthyl) ethanol.



Scheme 1.31 NHC-catalyzed kinetic resolution of secondary alcohol via oxidative process

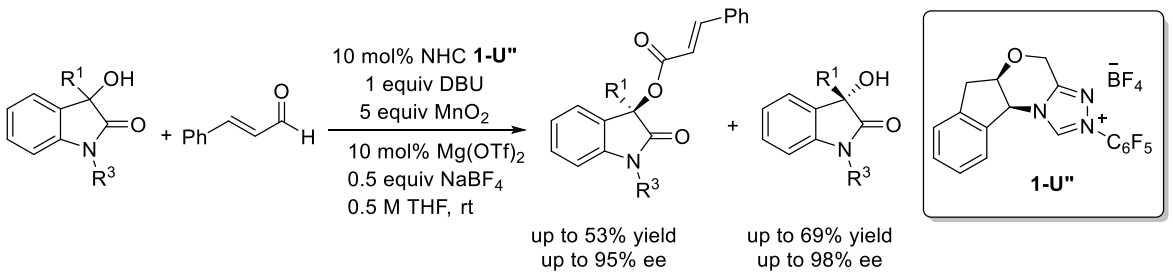
The author proposed 2-step process for the acylation reaction of secondary alcohol. In the first step, alcohol reacted with acylazolium in reversible manner, to provide a tetrahedral intermediate Subsequently, the ester product was afforded with regeneration of carbene catalyst for the next catalytic cycle (**Scheme 1.31**).

In 2018, our group developed kinetic resolution of diols via carbene-catalyzed site-selective oxidative esterification reaction (**Scheme 1.32).**[79] Primary alcohol selectively acylated and remaining diols remained in the enantiomeric pure form. Morpholine-based chiral triazolium NHC has been utilized in presence of DQ as an oxidant. Several substituents on the aromatic ring were well-tolerated to furnish the corresponding monoacylated diols and enantiopure diols with high enantioselectivities.



Scheme 1.32 Kinetic resolution of diols via site-selective oxidative esterification

In 2013, Zhao group[80] developed carbene-catalyzed kinetic resolution of tertiary alcohols by using oxidative esterification reaction (**Scheme 1.33**) In presence of aminoindane-based triazolium catalyst, 3-hydroxy-3-substituted oxindoles reacted with cinnamaldehyde under oxidative condition to furnish corresponding ester products with good ee values and good selectivities (S = 12-78). The use of $Mg(OTf)_2$ and $NaBF_4$ as additives enhanced the reaction rate and reaction selectivity in the catalytic system.



Scheme 1.33 NHC-catalyzed kinetic resolution of tertiary alcohol

The proposed mechanism is shown in **Figure 1.7**. First, cinnamaldehyde was activated NHC to form intermediate **28**, which underwent oxidation in presence of MnO_2 to afford acylazolium **29**. Subsequently tertiary alcohol attacked to acylazolium from back side of the chiral catalyst to furnish ester product and regenerate the NHC catalyst for the next catalytic cycle. Probably, Lewis acid activated the carbonyl group of the substrate in cooperative fashion. Interaction between styrenyl moiety of acylazolium **29** and aryl ring of the oxindole may have determined the conformation during the esterification reaction.

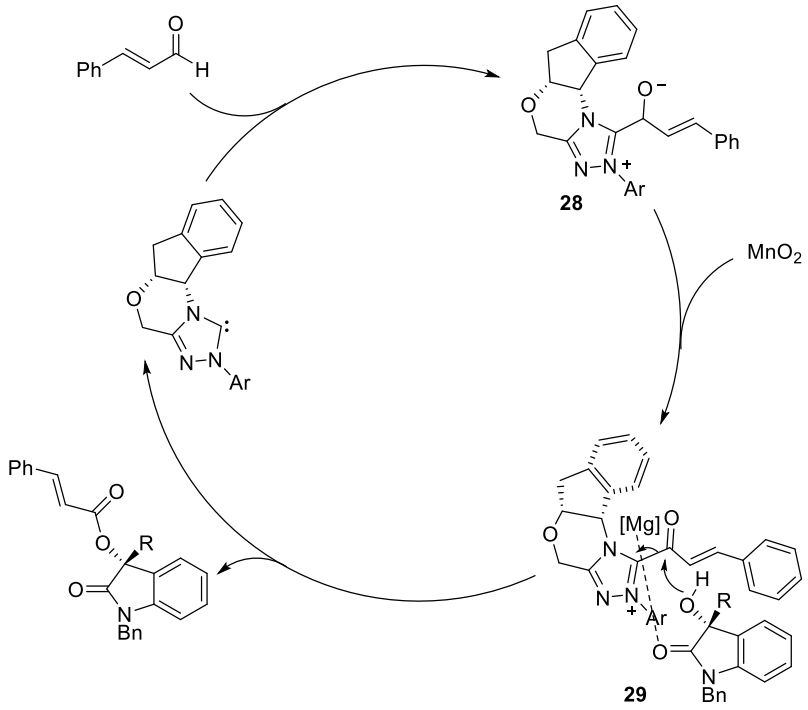
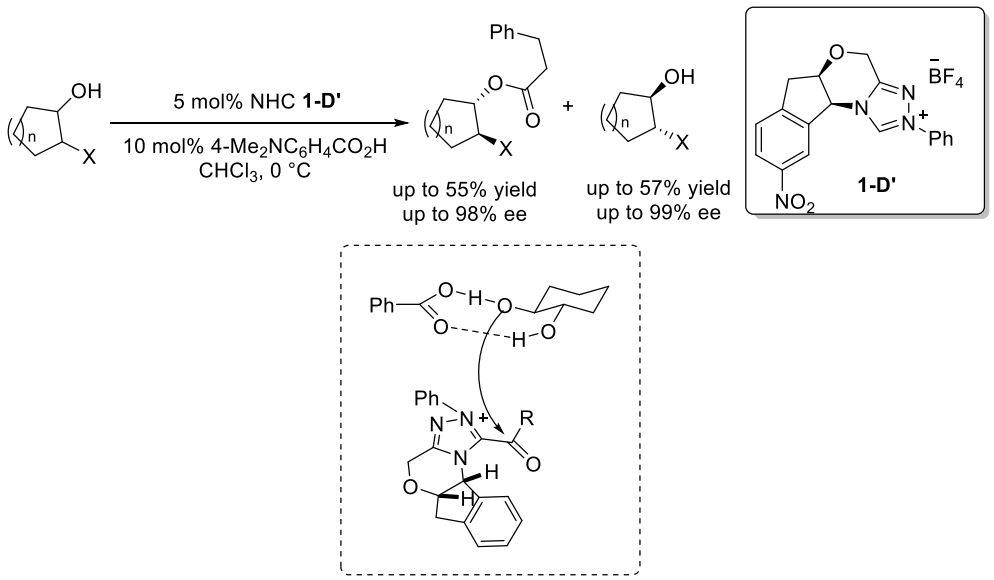


Figure 1.7 Mechanism of NHC-catalyzed kinetic resolution of tertiary alcohol

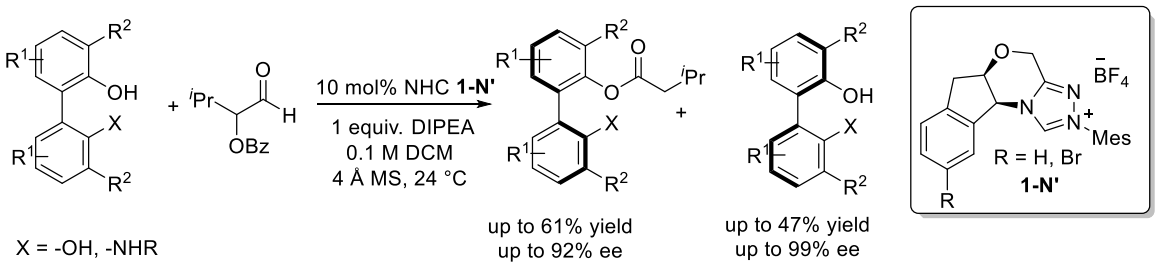
Yamada and co-workers[81] reported NHC-catalyzed kinetic resolution of diols and amino alcohol (**Scheme 1.34**). Alcohols that contained a vicinal hydrogen-bond-donor group have been utilized in their catalytic system. Introduction of carboxylate co-catalyst helped both the reaction rate and selectivity. In the presence of aminoindane-based triazolium catalyst, six-to eight-membered cycloalkanediols underwent asymmetric acylation reaction with α-bromo aldehyde to afford corresponding esters with excellent selectivities. (S = 149-218).



Scheme 1.34 NHC-catalyzed kinetic resolution of diols and amino alcohol

The reaction outcome has been described by their computational study. Carboxylate additive acted as a base to deprotonate the hydroxy group of the diol. The other hydroxy group stabilized the transition state via hydrogen bonding with the carboxylate (**Scheme 1.34)**.

In 2014, Zhao and co-workers[82] developed a highly efficient NHC-catalyzed kinetic resolution of 1,1'-biaryl-2,2'-diols and amino alcohol to afford axially chiral alcohol via acylation reaction (**Scheme 1.35**). Several aldehydes, such as substituted cinnamaldehydes, α-substituted aldehydes, were tested in their reaction. α-aryloxy aldehyde was found as the best aldehyde for the kinetic resolution of free BINOL. In the presence of aminoindane-based triazolium NHC, a variety of binaphthyl and biphenyl diols worked well in their reaction and furnished corresponding ester products with high selectivity (*S* = 22-116), BINOLS were

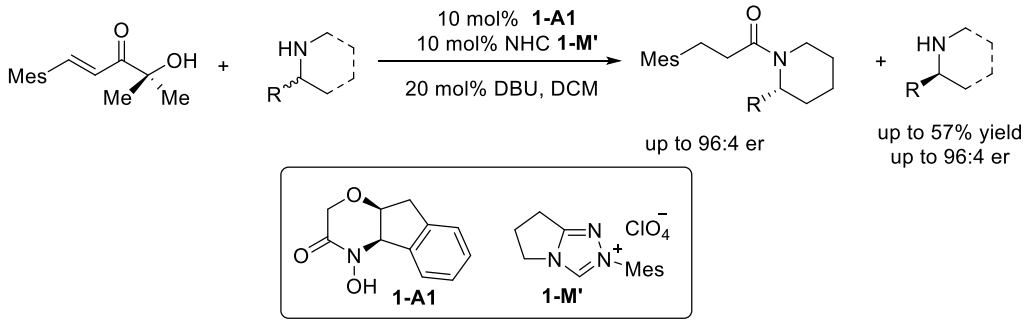


Scheme 1.35 NHC-catalyzed kinetic resolution of phenols

recovered with high enantioselectivity (>99%). Moreover, kinetic resolution of acyl- and -Boc protected NOBIN has also been achieved.

1.4.2 NHC-catalyzed kinetic resolution of amine and imine

In, 2011 Bode and co-workers explored kinetic resolution of cyclic amines via asymmetric amidation reaction with an achiral carbene catalyst and chiral hydroxamic acid as a co-catalyst (**Scheme 1.36**). [83]Mesityl-substituted α'-hydroxyenone was used as an acylating agent. Several 2-substituted piperidines, piperazines, morpholines, tetrahydroisoquinolines worked well in their reaction to give corresponding amide products with good selectivities (*S* = 8-74).



Scheme 1.36 NHC-catalyzed kinetic resolution of cyclic amine

A proposed mechanism is shown in **Figure 1.8**. The reaction proceeded via two catalytic cycles.

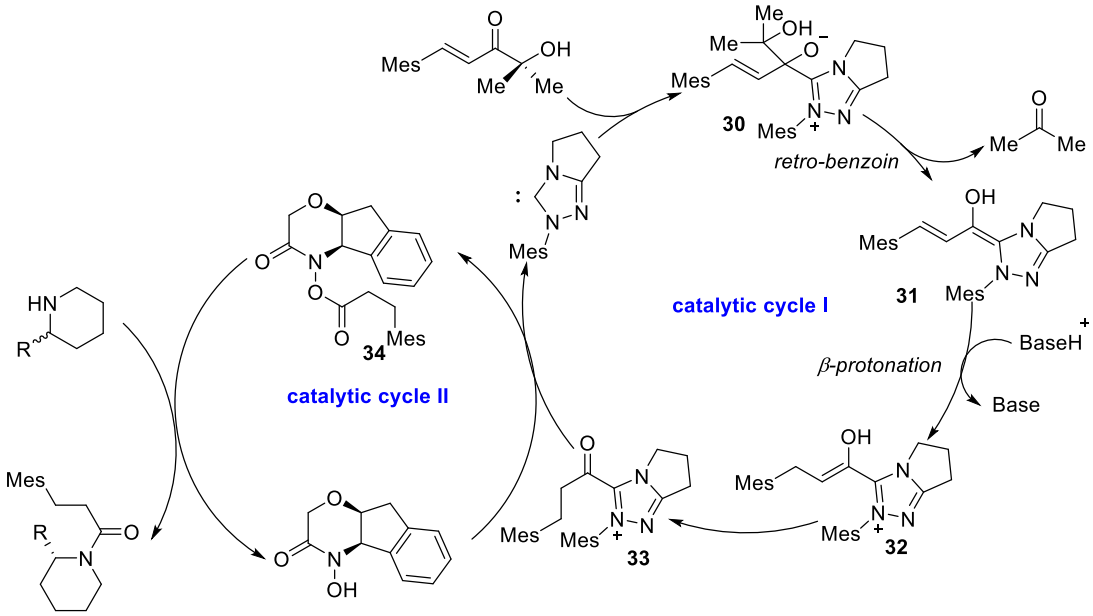
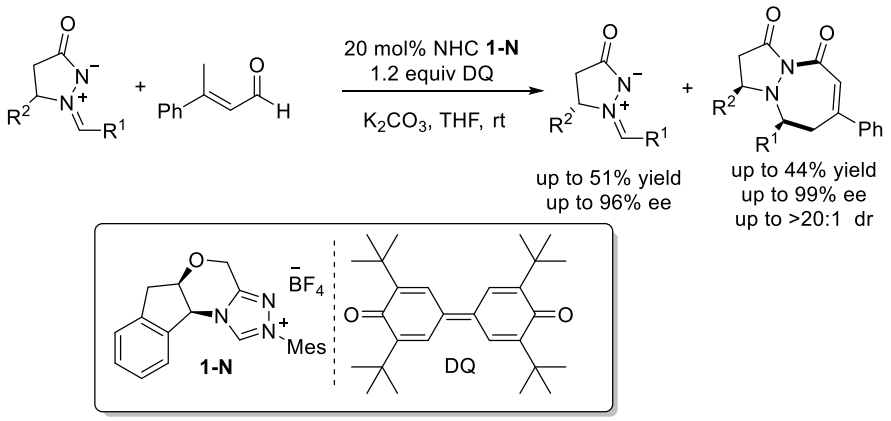


Figure 1.8 Mechanism of NHC-catalyzed kinetic resolution of cyclic amine

In the catalytic cycle I, acylazolium intermediate **33** was formed from Mesityl-substituted α'-hydroxyenone via retro-benzoin and *β*-protonation in the presence of racemic carbene catalyst. In catalytic cycle II, chiral co-catalyst reacted with the acylazolium **33** to give chiral intermediate **34** with regeneration of NHC, subsequently, amide product was obtained after asymmetric amidation with racemic amine.

In 2014, our group developed kinetic resolution of azomethine imines by using NHC-catalyzed [4+3] cycloaddition reaction (**Scheme 1.37**).[84] Azomethine imine reacted with the NHC-bound vinyl enolate to afford desired products with high selectivities (*S* = 60-339) and excellent ee values. Vinyl enolate was formed via carbene-catalyzed γ-carbon activation of an enal. A variety of azomethine imines were worked well in the reaction. It is worth to note that, in this reaction, the enantioselectivity of remote chiral centers was controlled by chiral NHC.



Scheme 1.37 NHC-catalyzed kinetic resolution of azomethine imines

The proposed mechanism is shown in **Figure 1.9**. First, enal reacted with NHC to furnish Breslow intermediate **35**. Oxidation gave azolium intermediate **36** and deprotonation of γ-carbon furnished vinyl enolate **37**. Vinyl enolate was utilized as 1,4-dipolarophile to react with azomethine imines to form the corresponding product with regeneration of NHC for the next catalytic cycle.

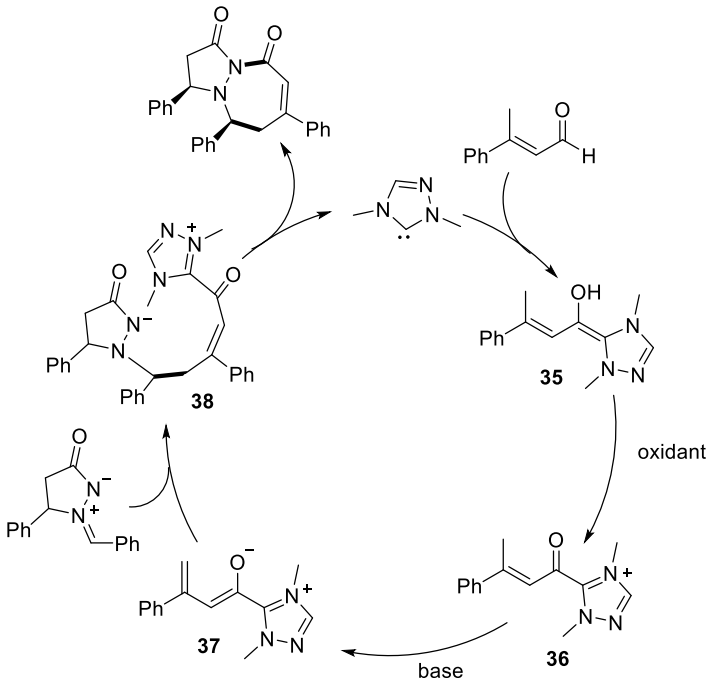
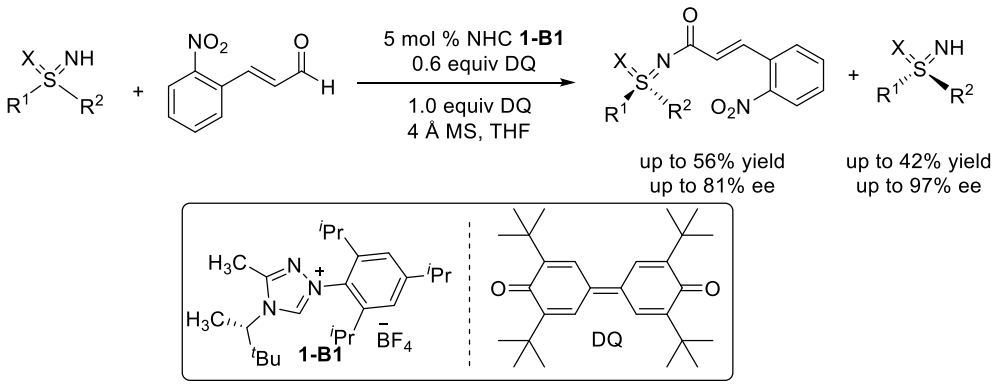


Figure 1.9 Mechanism of NHC-catalyzed kinetic resolution of azomethine imines

In 2016, Bolm group reported kinetic resolution of sulfoximines via NHC-catalyzed oxidative amidation reaction with enal (**Scheme 1.38**).[85] 2-nitrocinnamaldehyde was found as a suitable enal in their catalytic system. Variety of sulfoximines were well-tolerated in their reaction to afford the corresponding amide products with moderate to good enantioselectivities. The sulfoximines were recovered with good enantioselectivities.



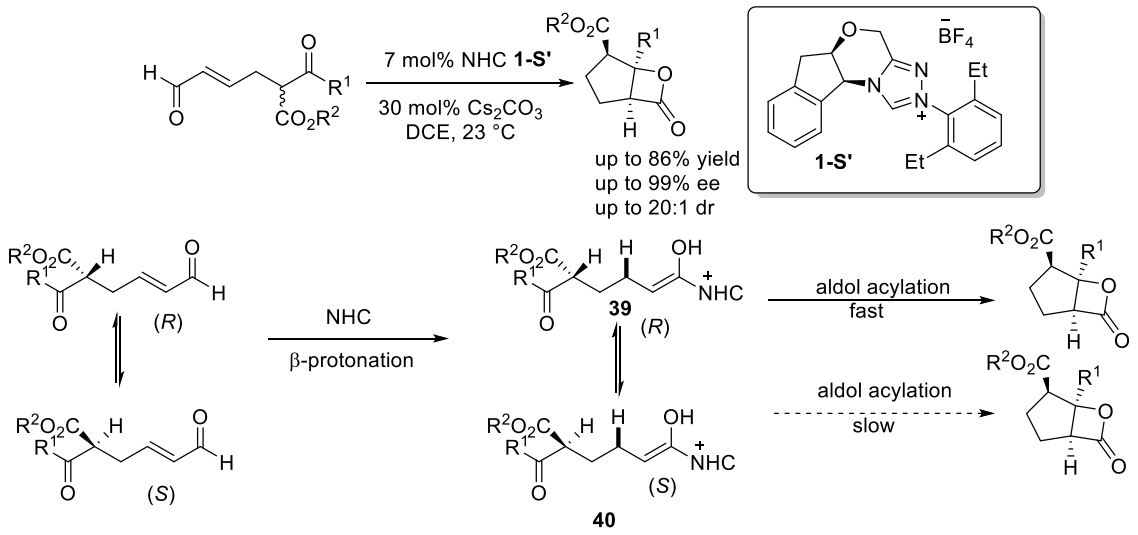
Scheme 1.38 NHC-catalyzed kinetic resolution of sulfoximines

1.5 NHC-Catalyzed dynamic kinetic resolution (DKR)

In the previous section, many carbene-catalyzed kinetic resolution strategies have been discussed. To obtain more efficient reaction with high yields and high enantioselectivities, DKR has been employed in recent years in the field of NHC catalysis.

1.5.1 NHC-catalyzed DKR of enal and ketoacid

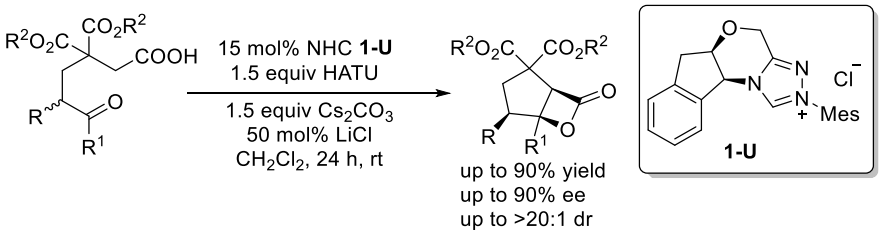
NHC-catalyzed dynamic kinetic resolution first reported by Scheidt[86] and co-workers utilizing enal substrate bearing a *β*-ketoester motif. The reaction proceeded via intramolecular enantioselective aldol reaction. Fused *β*-lactone products were obtained with good yields and excellent enantioselectivities. However, when highly electron-rich aryl ketone used as a substrate, decarboxylation occurred, leading to formation of cyclopentene moderate yields and moderate enantioselectivities (**Scheme 1.39**). Mechanistically, racemic enal was activated by NHC catalyst to form extended Breslow intermediate (**Scheme 1.39)**. Then, the homoenolate underwent *β*-protonation to afford enol intermediate **39** and **40**. Due to hydrogen bonding interaction between NHC and enol intermediate *re*-face attack was favored. Then, faster aldol addition in **39**, furnished the major product.



Scheme 1.39 NHC-catalyzed DKR of enal

In 2017, Biju and co-workers reported NHC-catalyzed enantioselective aldol lactonization of acyclic ketoacids via dynamic kinetic resolution.[87] In presence of chiral aminoindane-based

triazolium NHC and LiCl, cyclopentane-fused *β*-lactones were achieved with high diastereo- and enantio-selectivities (**Scheme 1.40**).



Scheme 1.40 NHC-catalyzed DKR of ketoacid

The proposed mechanism is shown in Figure **1.10**. Initially, acid was activated by coupling reagent HATU. Then, NHC addition to the activated acid furnished NHC-bonded intermediate **41** and **42**. In presence of base, enolate intermediates (**43** and **44**) were generated. As the reaction is base mediated **43** and **44** are in rapid equilibrium. Intermediate **43** underwent faster intramolecular aldol reaction followed by *β*-lactonization to afford cyclopentane-fused *β*-lactones **47**. Intermediate **44** is not favored due to presence of an interaction between (R) and the alkyl (R^1) groups. Therefore, product **48** formed as a minor diastereomer.

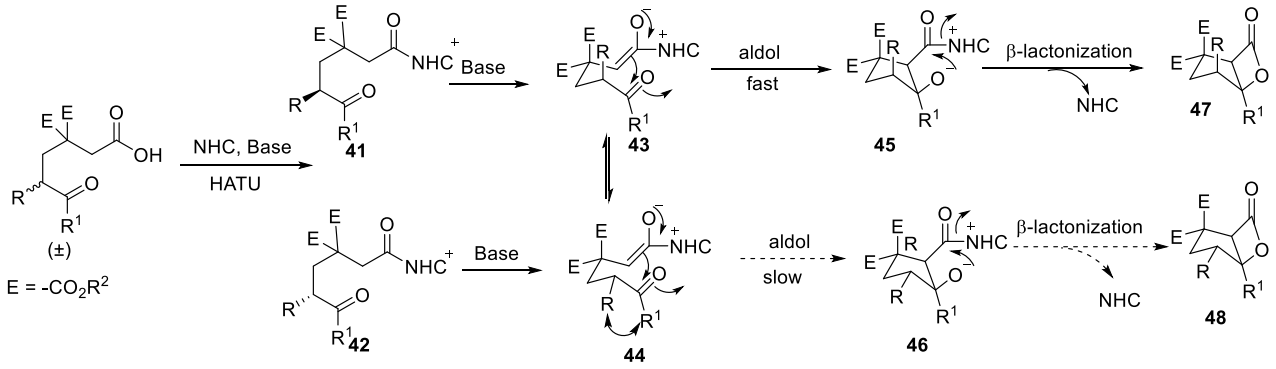
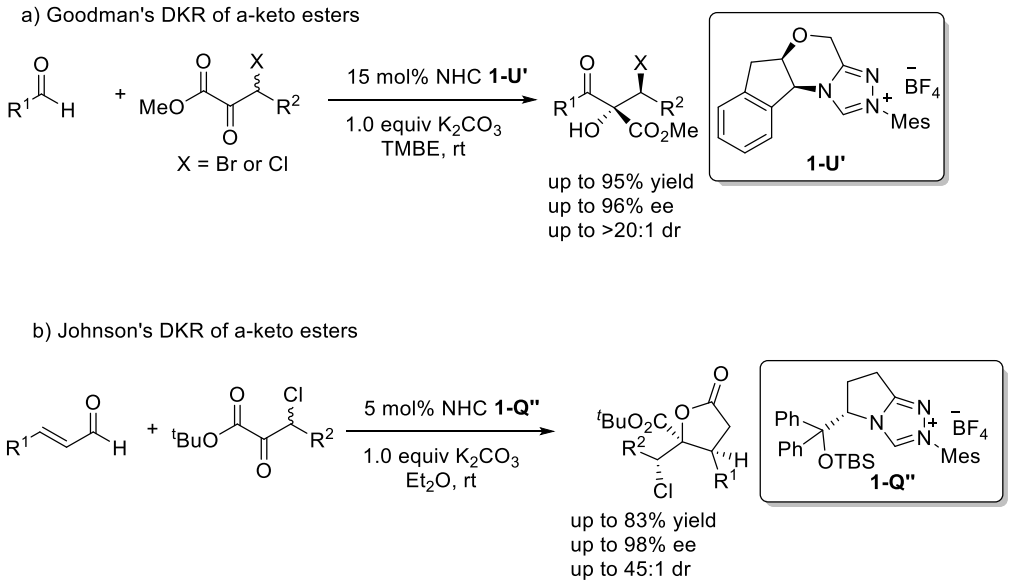


Figure 1.10 Mechanism of NHC-catalyzed DKR of ketoacid

1.5.2 NHC-catalyzed DKR of *α*-keto esters

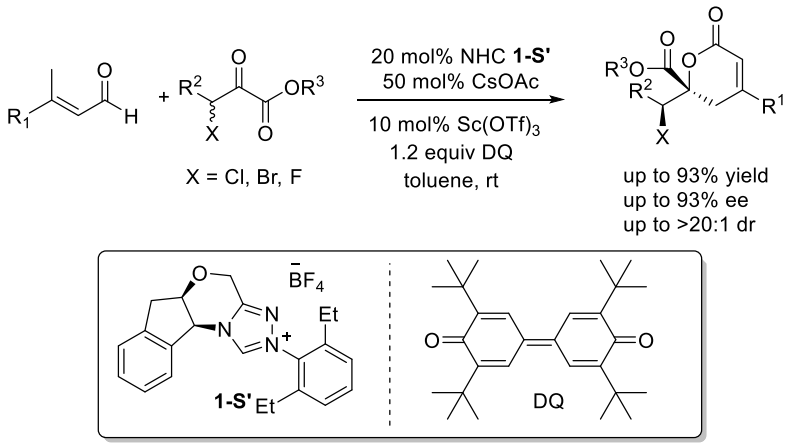
In 2014, Goodman[88] and co-workers reported an NHC-catalyzed dynamic kinetic resolution of *α*-keto esters. The DKR was achieved by asymmetric cross-benzoin reaction between *α*-keto esters and aldehydes in presence of aminoindane-based chiral triazolium catalyst. Variety of substituents on *α*-keto esters, such as arenes, alkanes, alkynes were well-

tolerated and cross-benzoin products were afforded with good yields and excellent enantioselectivities (**Scheme 1.41a**). Aldehydes bearing with both aromatic and heteroaromatic groups were also tolerated in the reaction. However, *ortho*-substituted different aromatic aldehydes did not react under the reaction condition due to the steric reason. In 2015, Johnson[89] group also disclosed dynamic kinetic resolution of α-keto esters. The reaction proceeded via [3+2] annulation reaction with enals in presence of chiral triazolium catalyst. γ-butyrolactone products were obtained in good enantioselectivities (**Scheme 1.41b**).



Scheme 1.41 NHC-catalyzed DKR of α-keto esters

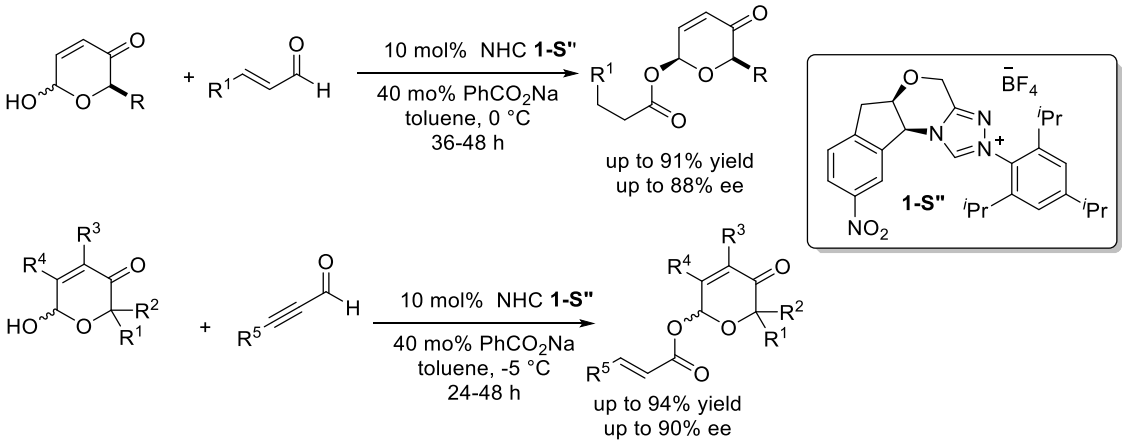
In the same year, Wang[90] and co-workers reported another dynamic kinetic resolution of α-keto esters. The DKR was achieved by asymmetric [4+2] cycloaddition reaction of β-substituted enals and α-keto esters in presence of aminoindane-based chiral triazolium catalyst. (**Scheme 1.42**). Mechanistically, γ-activation of enals under oxidative condition followed by cycloaddition of α-keto esters provided chiral δ-lactones in good yields good enantioselectivities. Scandium(III) trifluoromethanesulfonate was used as Lewis acid to facilitate the [4+2] cycloaddition reaction.



Scheme 1.42 NHC-catalyzed DKR of α-keto esters via [4+2] annulation

1.5.3 NHC-catalyzed DKR of alcohol

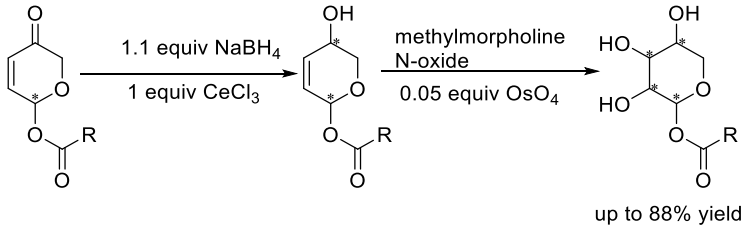
Dynamic kinetic resolution of alcohols also could be achieved by NHC catalyst. In 2016, wang and co-workers reported NHC-catalyzed DKR of pyranones.[91] The reaction proceeded via chiral NHC-catalyzed esterification under oxidative condition. Various enals and alkynals bearing with β-heteroaryl or aryl substituents were well-tolerated in presence of aminoindane-based chiral triazolium catalyst that contained nitro group at aminoindane moiety.



Scheme 1.43 NHC-catalyzed DKR of 6-hydroxypyranone derivatives

A variety of 2.2-disubstituted 6-hydroxy-3-pyranone substrates that contained different substituents at 2-, 4-, and 5-position were employed, and corresponding ester products were formed with good yields and good enantioselectivities (**Scheme 1.43**). Further, they employed

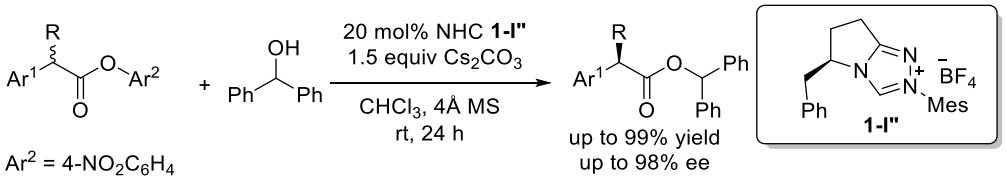
their methodology for the synthesis of sugar derivatives. Sugar derivatives were achieved by reduction and dihydroxylation of the chiral products (**Scheme 1.44**).



Scheme 1.44 Synthesis of sugar derivatives from 6-hydroxypyranone-derived chiral ester

1.5.4 NHC-catalyzed DKR of saturated ester

Saturated esters could be activated by NHC-catalyst, this methodology was employed by our group to achieve enantiopure *α*-substituted esters.[92] In presence of chiral triazolium catalyst, α-substituted esters bearing with 4-nitrophenyl group were activated and reacted with diphenyl alcohol. Enantiopure *α*-substituted esters were obtained with excellent enantioselectivities and yields (**Scheme 45**).



Scheme 1.45 NHC-catalyzed DKR of ester

A large variety of aryl esters that contained different substituents on aromatic rings were well-tolerated. Different alkyl substituents on the *α*-carbon of the esters were also worked well in the reaction. Notably, many naturally occurring esters, such as naproxen, ketoprofen, fenaprofen were synthesized by this protocol. A proposed reaction pathway is described in **Figure 1.11**. First, the chiral carbene catalyst reacted with racemic ester to afford two diastereomeric intermediates **49** and **50**. Intermediate **49** selectively reacted faster with the

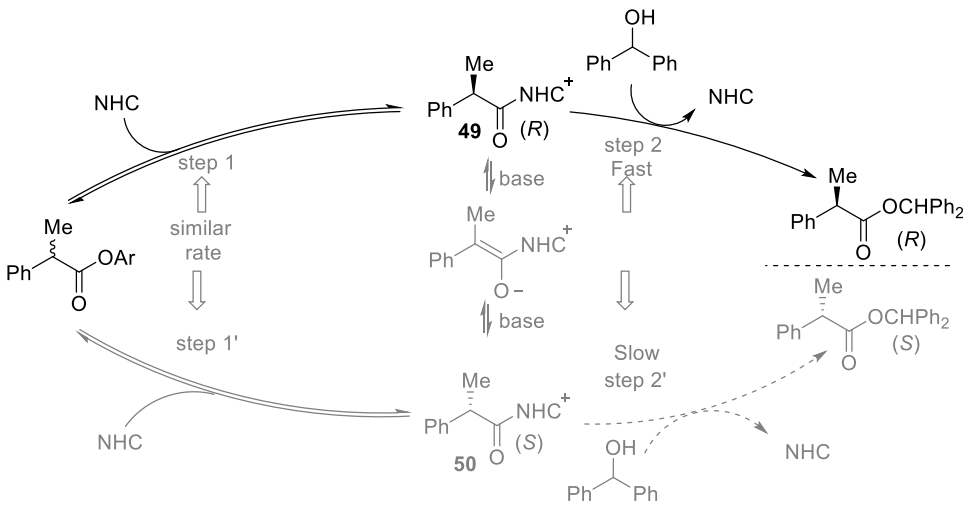


Figure 1.11 Mechanism of NHC-catalyzed DKR of ester

alcohol substrate to afford the corresponding ester product with high enantioselectivity.

1.6 Research design and summary of work

Development of new methodology to access functional molecules in enantioselective fashion is highly demanding in the field of organic synthesis. NHC catalysis has been played a vital role in this context for the last 20 years. Especially, development of new methodology with the application to synthesize medicinally important molecules is growing interest in the field of carbene catalysis. In this thesis, we introduced NHC-catalyzed dynamic kinetic resolution of hydroxyphthalides. Later, this strategy has been utilized for modification of natural products. In addition, NHC-catalyzed DKR and synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-one derivatives bearing vicinal quaternary stereogenic centers, has also been demonstrated. These two DKR approaches can also play a significant role to synthesize medicinally important chiral molecules as well as modification of chiral drugs.

In Chapter 2, dynamic kinetic resolution of hydroxyphthalide through NHC-catalyzed acylation reaction is demonstrated. Phthalidyl esters have been achieved with high enantioselectivities and high yields. Mechanistically, the *O*-acetylbenzoic (or formylbenzoic) forms hydroxyphthalides, which undergoes NHC-catalyzed asymmetric acylation reaction under oxidative condition. A wide range of aldehydes has been worked efficiently in this

strategy. Additionally, the synthesis and modifications of naturally occurring substances are discussed.

In chapter 3, asymmetric synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-ones bearing vicinal quaternary stereogenic centers, enabled by N-heterocyclic carbene through dynamic kinetic resolution approach is introduced. The reaction proceeds via intermolecular reversible aldol reaction followed by asymmetric acylation reaction in one-pot. Benzofuranyl carbonate reacts with several *N*-protected isatin derivatives to afford chiral 3,3'-disubstituted benzofuran-2(*3H*)-one derivatives bearing vicinal quaternary stereogenic centers in excellent yields, excellent diastereo- and enantio-selectivities.

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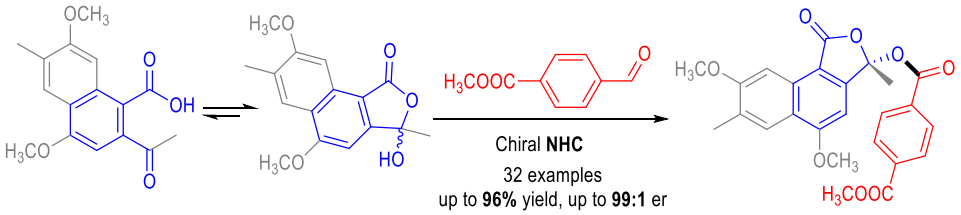
Chapter 2

Carbene-Catalyzed Dynamic Kinetic Resolution and Asymmetric Acylation of Hydroxyphthalides and Related Natural Products



2.1 Introduction

Phthalides are core structures of diverse natural products found in plants and fungal genera.[1] Many of these phthalide-containing molecules exhibit a broad spectrum of biological activities[2-7]with proven applications such as for the treatments of circulatory and heart diseases.[8-9] Hydroxyphthalides, with a hydroxyl group attached to the anomeric carbon to form a ketal/acetal moiety, are a subgroup of phthalides with wide natural occurrence and significant utilities (**Figure 2.1**)[10-11] For example, talosalate was marked to treat inflammation and pain.[12] Luteorosin was found in *chromodoris luteorosa* and exhibit ichthyotoxic activities.[13] Corollosporine is an antibacterial metabolite of marine fungus *corollospora maritima*.[14] Fimbricalyxlactone B & C were isolated from *Strophioblachia fimbricalyx* which is used as folk medicine to treat migraine, fever, and cancer.[11] Acylated hydroxyphthalides (such as talniflumate[15], talampicillin[16] and talmetacin[17]) have also been used as prodrugs of carboxylic acids.

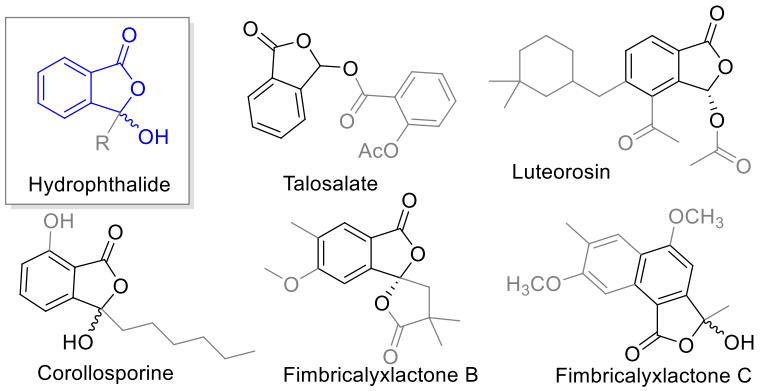


Figure 2.1 Examples of hydroxyphthalide-containing drugs and natural products

The acetal/ketal moiety in hydroxyphthalides and their derivatives contains a labile chiral center. Therefore, it remains difficult to prepare hydroxyphthalide-containing molecules in enantiomerically pure forms. Indeed, enantioselective access to acetals/ketals is a general challenge in organic synthesis.[18-23]List showed that with confined chiral phosphoric acids based on a C_2-symmetric imidodiphosphoric acid motif as organic catalysts,[24] an enantioselective

approach for spiroacetalization was developed in high yield and excellent e.r. value. In the area of N-heterocyclic carbene (NHC) organic catalysis, studies by Wang and co-workers showed 6-hydroxypyranones could be esterified asymmetrically with enals or alkynals through dynamic kinetic resolution pattern to form chiral acetal units (**Figure 2.2a**).[25-26]Tang and coworkers reported the dynamic kinetic diastereoselective acylation of lactols through chiral isothiourea catalytic reactions.[27-28] Our group recently disclosed a carbene-catalyzed enantioselective modification of carboxylic acids for asymmetric access to optically enriched acetal products (**Figure 2.2b**).[29]

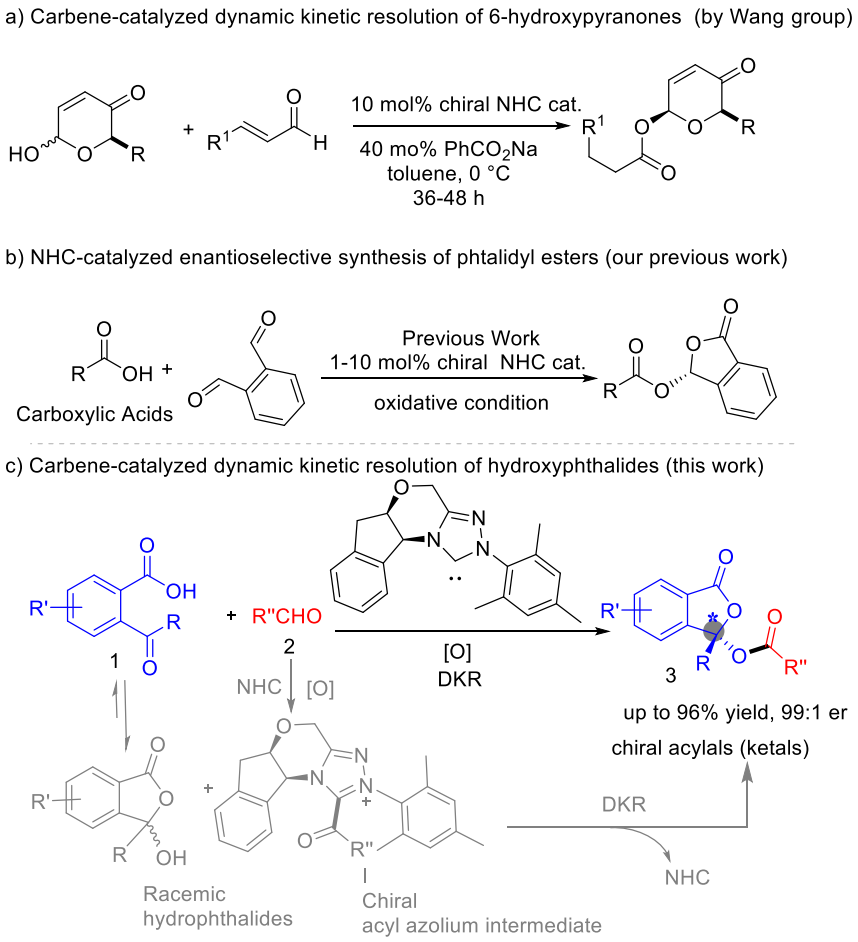


Figure 2.2 Enantioselective acylation via carbene-catalyzed dynamic kinetic resolution and DKR of hydroxyphthalides

Here we disclose a new approach for enantiomeric access to acylated hydroxyphthalides via a carbene-catalyzed dynamic kinetic resolution (DKR) process (**Figure 2.2c**). The *o*-acetylbenzoic (or formylbenzoic) acid substrate (**1**) undergoes an equilibrium with the corresponding racemic hydroxyphthalide (predominant in most solvents).[30] The aldehyde substrate (**2**) reacts with an NHC catalyst in the presence of an oxidant to form a chiral acyl azolium intermediate (**I**) [31-37]Similar acyl azolium intermediates can also be formed using enals as the aldehyde substrates without the need of oxidants. Selective acylation of hydroxyphthalide by acyl azolium intermediate **I** via a dynamic kinetic resolution process led to chiral acylal (**3**) with high e.r. values. This method works well for diverse substrates and allows for enantioselective access to commercially used pharmaceuticals such as talosalate with 1:99 e.r. value. Moreover, hydroxyphthalide-containing natural products such as corollosporine[14] and fimbricalyxlactone C[11] can be kinetically resolved and acylated in this method to form optically enriched ester products.

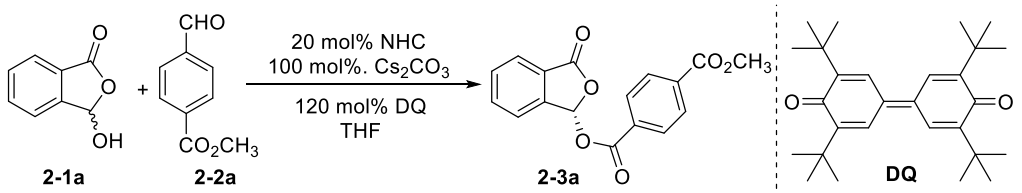
2.2 Results and discussions

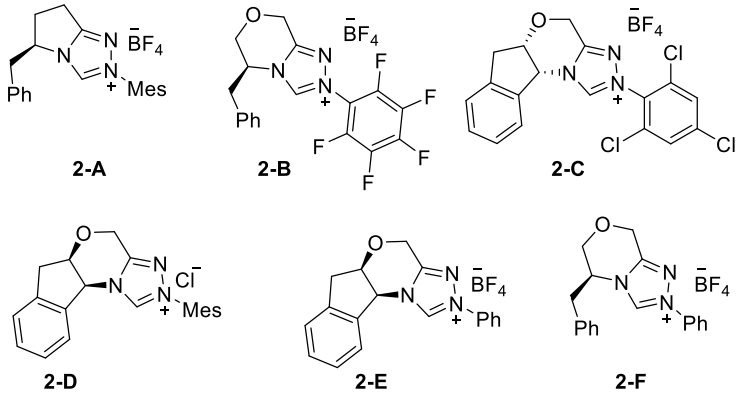
2.2.1 Reaction condition optimization

To optimize the reaction, *o*-carboxybenzaldehyde (**2-1a**) (in most of the solvent it appears as cyclic form) 4-formylbenzoate (**2-2a**) were used as the model substrates. First, several NHC precursors were tested in presence of Cs_2CO_3 as a base and THF as a solvent. The key results of catalyst screening are shown in Table 2.1. In the presence of triazolium precatalyst **2-A**[38], product **2-3a** was afforded in a moderate yield but a very low e.r. value (entry 1, 51% yield, 52:48). When NHC precursor **2-A** was replaced with chiral morpholine-derived NHC pre-catalyst **2-B**,[39] encouraging e.r. value was obtained but the yield was frustrating (Table 2.1 entry 2, 24% yield, 32:68). Replacing it with aminoindane-based NHC precatalyst **2-C**[40], **2-D**[41] led to the satisfactory yield and e.r. values (Table 2.1, entry 3, entry 4). Between them, the electron-rich precatalyst **2-D** could produce **2-3a** with the best yield and e.r. value (Table 2.1, entry 4).

Further, in presence of NHC precatalyst **2-E** and **2-F**, **2-3a** was formed in moderate yield and good e.r. value. Therefore, aminoinadane-based precatalyst **2-D** was selected as an optimal catalyst precursor for further optimization.

Table 2.1 Screening of NHC catalysts[a]

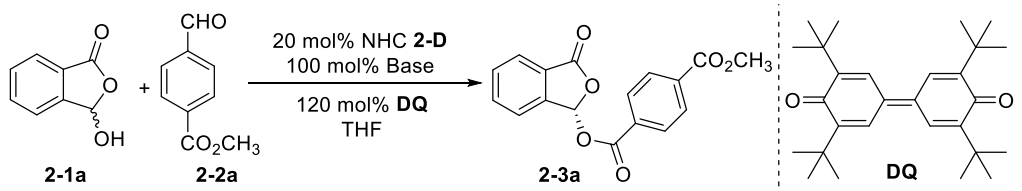




Entry	Catalyst	Yield	e.r.
1	2-A	48	52:48
2	2-B	24	32:68
3	2-C	59	6:94
4	**2-D**	**80**	**95:5**
5	2-E	67	94:6
6	2-F	69	87:13

Reaction condition: **2-1a** (0.12 mmol), **2-2a** (0.1 mmol), NHC pre-cat. (0.02 mmol), Base (0.1mmol), DQ (0.12 mmol) = 3,3',5,5'-tetra-tert-butyldiphenoquinone. solvent (2 mL). Yields were isolated yields after SiO_2 column chromatography. The e.r. was determined via chiral-phase HPLC analysis

Table 2.2 Screening of bases[a]



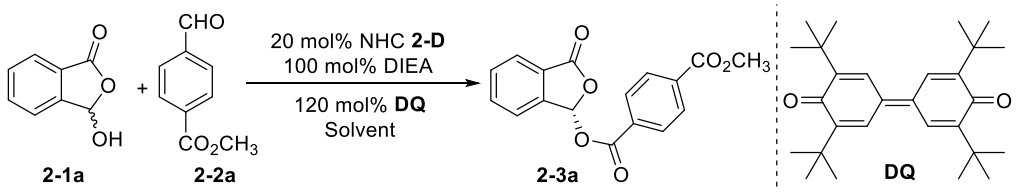
Entry	Base	Yield (%)	e.r.
1	K_2CO_3	81	96:4
2	NaOAc	66	97:3
3	Na_2CO_3	83	97:3
4	**DIEA**	**81**	**98:2**
5	DBU	71	97:3
6	DMAP	74	96:4
7	Et_3N	75	98:2

[a]Reaction condition: **2-1a** (0.12 mmol), **2-2a** (0.1 mmol), NHC pre-cat. (0.02 mmol), Base (0.1mmol), DQ (0.12 mmol) = 3,3',5,5'-tetra-tert-butyldiphenoquinone, solvent (2 mL). Yields were isolated yields after SiO_2 column chromatography. The e.r. was determined via chiral-phase HPLC analysis.

To obtain better yields and e.r value several bases were tested in the reaction in presence of **2-D** as NHC precursor and THF as the solvent. The key results from screening of bases are shown in the Table 2.2. In presence of in organic bases, such as Na_2CO_3, K_2CO_3, product **2-3a** was afforded in good yield and better e.r. value (Table 2.2, entry 3, entry 1). However, the yield was frustrating when NaOAc was used as a base (Table 2.2. entry 2). Further use of organic bases, such as DIEA, DBU, DMAP and Et_3N, a little influence on the e.r. value was observed.

Among the organic bases, DIEA could afford the product with best enantiomeric ratio (Table 2.2, entry 4). Hence, DIEA was selected as an optimal base for further optimization.

Table 2.3 Screening of solvents[a]



Entry	Solvent	Yield (%)	e.r.
1	CH_2Cl_2	67	97:3
2	**EtOAc**	**96**	**98:2**
3	CH_3CN	57	92:8
4	Acetone	74	98:2
5[b]	EtOAc	87	98:2
6[c]	EtOAc	76	99:1

[a]Reaction condition: **2-1a** (0.12 mmol.), **2-2a** (0.1 mmol), NHC pre-cat. (0.02 mmol), Base (0.1 mmol.), DQ (0.12 mmol) = 3,3',5,5'-tetra-tert-butyldiphenoquinone, Solvent (2 mL), Yields were determined by isolation. The e.r. was determined via chiral-phase HPLC analysis. [b]10 mol% **2-D** was used. [c]5 mol% **2-D** was used.

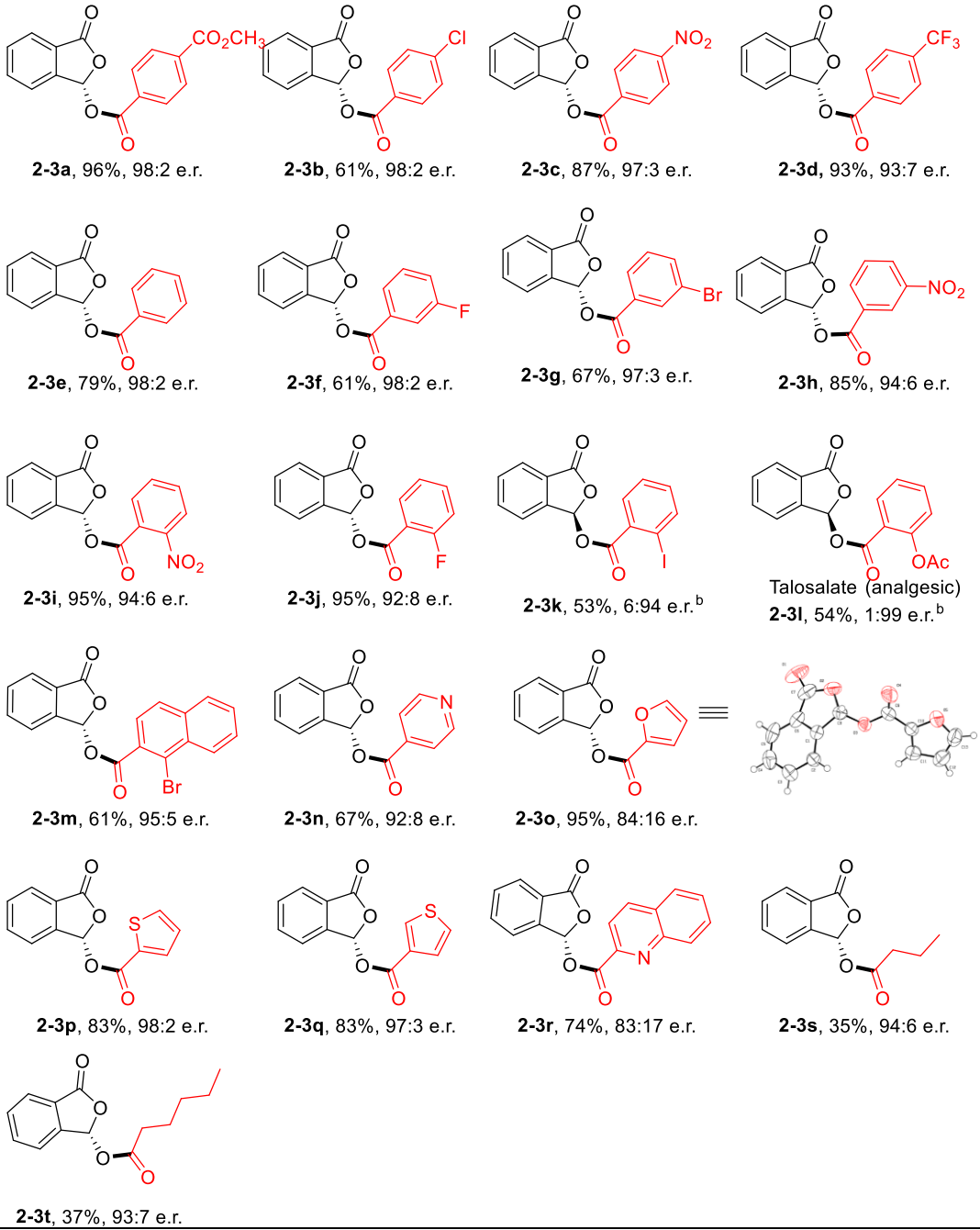
To improve the yields and e.r of the reaction many solvents were also examined in the reaction in presence of DIEA as a base and **2-D** as a NHC precatalyst. The solvent optimization is shown in Table 2.3. In presence of CH_2Cl_2 and CH_3CN as the solvent, the yields and e.r. of the reaction was low (Table 2.3, entry 1, entry 3). Further use of ethyl acetate as the solvent the yield of the reaction improved to 96% and e.r. of the reaction remained same (Table 2.3, Entry 4). After that, amount of catalyst loading was examined. Decreasing the catalyst loading

resulted in lower yields, although the e.r. of the product was not affected (Table 2.3 entries 5-6).

2.2.2 Substrate scope

With a few acceptable conditions in hand, the substrate scope was explored (**Table 2.4**) with both aryl aldehydes and aliphatic aldehydes as the formal acylating agents. Benzaldehyde derivatives containing various substituents [such as halogen, nitro (-NO_2), methylcarbonyl (-$COOCH_3$) and acetoxyl (-OAc) groups] were all-tolerated to give the desired products with excellent yields and e.r. values (**2-3a** to **2-3l**). In most of the cases, the substitution patterns on the benzene ring have little influence on the reaction enantioselectivities and yields (**3a**-**j**). When iodine or acetoxyl group were installed at the *ortho*-position of the benzene, relatively lower yields and e.r. values were obtained under the standard condition (with NHC precursor **2-D**, **2-3k**, 26% 93:7 e.r.; **2-3l**, 22%, 86:14 e.r.). When **2-D** was replaced by **2-C** as the NHC precatalyst, much-improved yields and e.r. values were obtained for **2-3k** (53%, 6:94 e.r.) and **2-3l** (54% yield, 1:99 e.r.). It's worth to note that talosalate (**2-3l**) is a drug marketed in the racemic form. With this method, talosalate could be prepared in essentially an optically pure form (1:99 e.r.). Replacing the phenyl unit of the aryl aldehyde substrate with a bromonaphthalene substituent was also tolerated (**2-3m**). A diverse set of heteroaryl aldehydes (such as those containing pyridine, furan, or thiofurans) also reacted effectively to afford the products (**2-3n** to **2-3q**) with good to excellent yields and excellent e.r. values. The absolute configuration of **2-3o** was confirmed via single crystal X-ray analysis. Using aliphatic aldehydes as the substrates, the high e.r. values of the products remained, while the reaction yields dropped significantly (**2-3s** to **2-3t**) under the standard and a few other conditions (see the section 2.4.6).

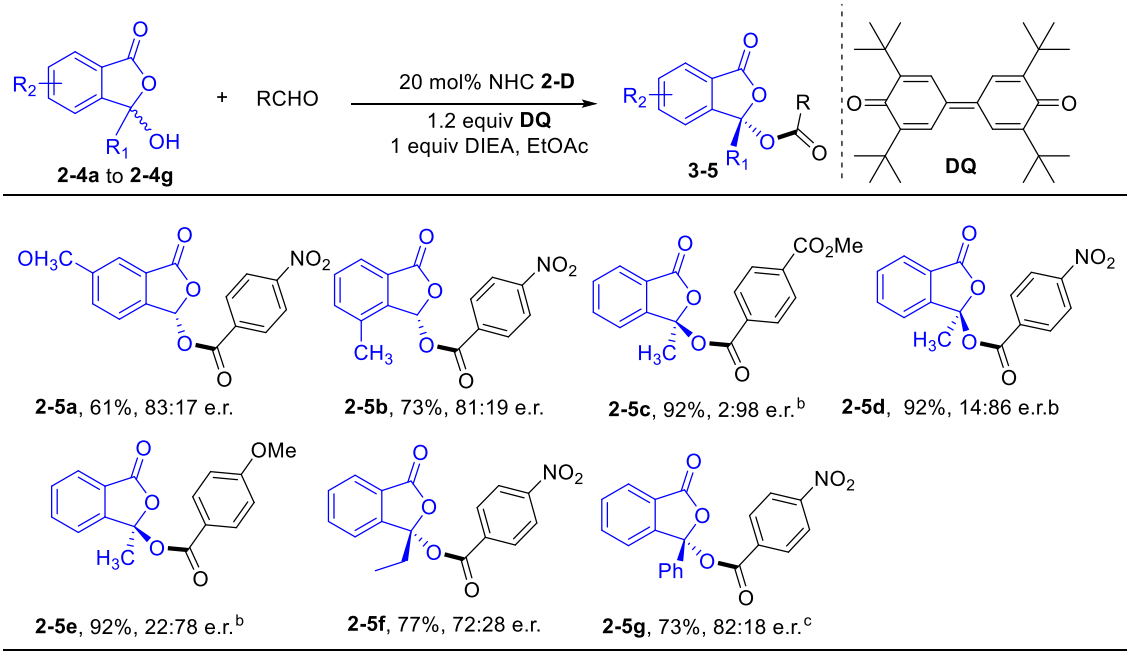
Table 2.4 Examples of the aldehyde substrates[a]



[a]Reaction condition: **2-1a** (0.12 mmol), RCHO (0.1 mmol.), NHC **2-D** (0.02 mmol), **DQ** (0.12 mmol), DIEA (0.1 mmol), EtOAc (2 mL), 12 h. [b]carried out using **2-C** as the NHC pre-catalyst.Yields were determined by isolation. The e.r. was determined via chiral-phase HPLC analysis.

The scope of the acetylbenzoic and formylbenzoic acid substrates were also examined. (**Table 2.5**). Placing substituents to the benzene ring of the formylbenzoic acid substrates led to a slight loss on product e.r. values under current conditions (**2-5a**, **2-5b**). Then it is worth to note that when the aldehyde moiety in the benzoic acid was replaced with a ketone group, this dynamic kinetic resolution process still worked effectively to deliver the acylated hydroxyphthalide products with excellent yields (**2-5c** to **2-5g**). The e.r. values of these products (**2-5c** to **2-5g**) varied from 28:72 to 2:98 depending on both the benzoic acid and the aryl aldehyde substrates. It appears the steric hindrance introduced by the ketone moiety has an influence on the selective acylation step of the reaction.

Table 2.5 Example of the acetylbenzoic and formylbenzoic acid substrates [a]

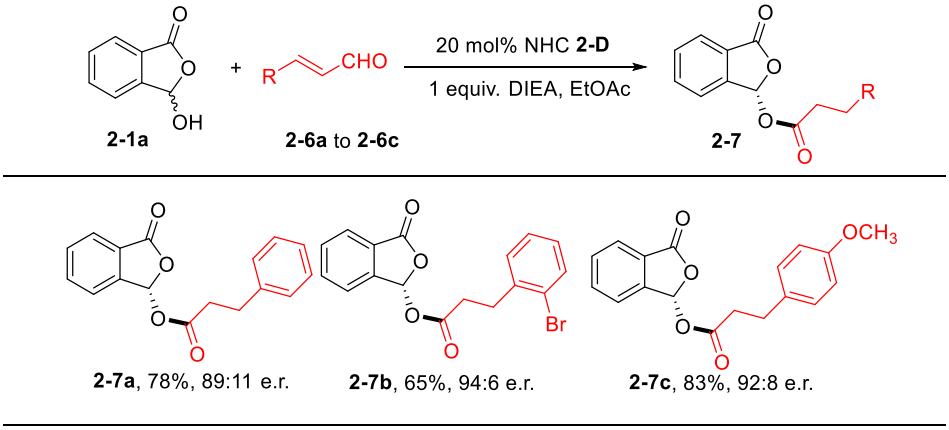


[a]Reaction condition: **2-4a** to **2-4g** (0.12 mmol), RCHO (0.1 mmol), **2-2a** or **2-2c** (0.12 mmol), NHC precursor **2-D** (0.02 mmol), **DQ** (0.12 mmol), DIEA (0.1 mmol), EtOAc (2 mL), 12 h. [b]carried out by NHC **2-C**. [c]carried out by NHC **2-E** Yields were determined by isolation.

The NHC catalyst-derived acyl azolium intermediate for the acylation reaction could also be prepared by using enals as the substrates[42] (**Table 2.6**). Without the need of external oxidants,

through an internal redox process enals can be converted to acyl azolium intermediate for efficient and enantioselective acylation reactions (**2-7a** to **2-7c**).

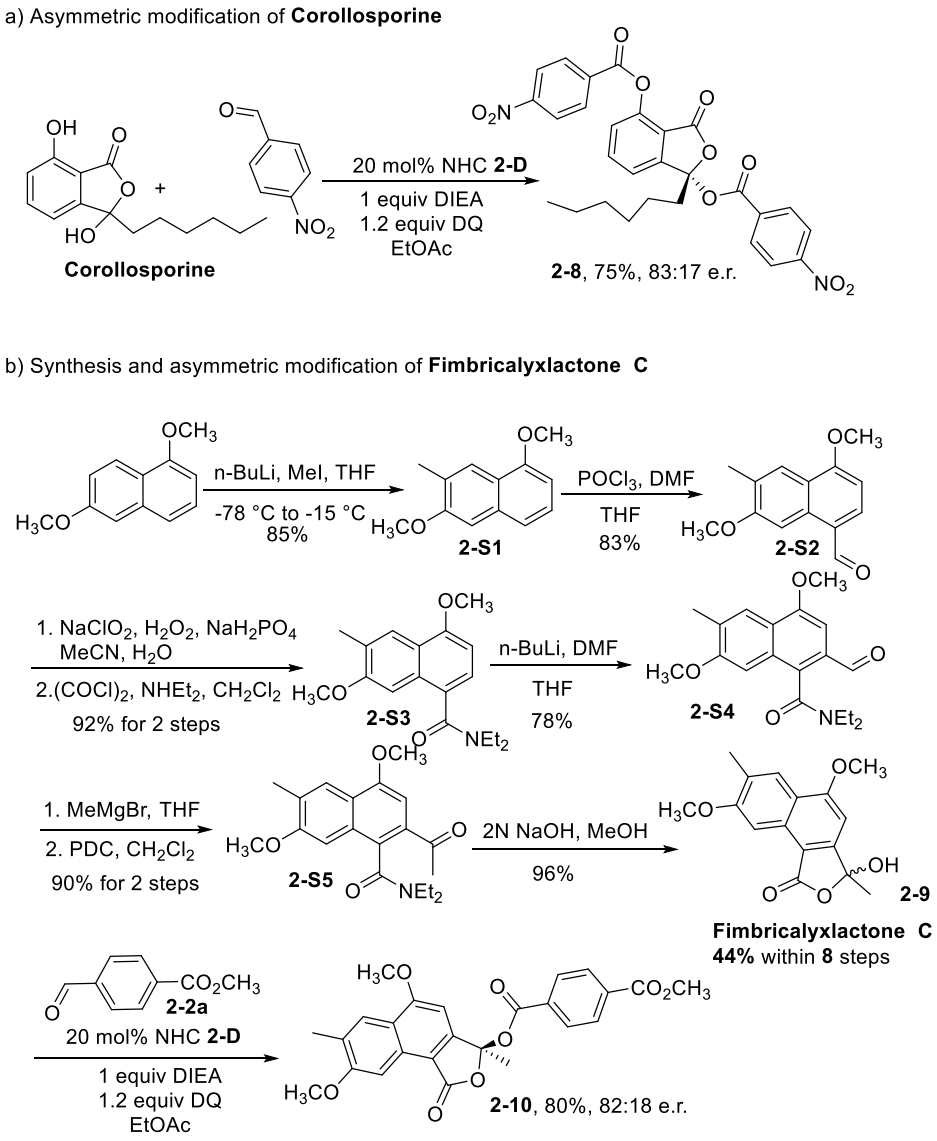
Table 2.6 Use of enals as acylation reagents without the need of external oxidants. [a]



[a]Reaction condition: **2-1a** (0.1 mmol.), **2-6a** to **2-6c** (0.15 mmol.), NHC **2-D** (0.02 mmol), DIEA (0.1 mmol), EtOAc (2 mL), 12 h. Yields were determined by isolation. The e.r. was determined via chiral-phase HPLC analysis.

2.2.3 Modification of natural products

At last, This DKR approach was applied for asymmetric acylation of two natural products (Corollosporine and Fimbricalyxlactone C) containing a hydroxyphthalide moiety (**Scheme 2.1)**. Corollosporine, prepared in one step using reported protocols[43](see the Section 2.4.2), could be asymmetrically acylated under the standard condition to form product **2-8** with 75% yield and 83:17 e.r. (**Scheme 2.1a**). A short route for total synthesis of fimbricalyxlactone C has been developed by starting from 1,6-dimethoxynaphthalene. The synthesis took 8 steps to afford fimbricalyxlactone C in 44% overall yield **(Scheme 2.1b).** Treatment of fimbricalyxlactone C under the standard catalytic reaction condition could afford acylated product **2-10** with 80% yield and 82:18 e.r. value.



Scheme 2.1 Modification of natural products

2.2.4 Proposed mechanism and transition state

A proposed mechanism is shown in **Figure 2.3**. Aldehyde substrate reacts with NHC catalyst to form a chiral Breslow intermediate **2-I**, which undergoes oxidation reaction in presence of DQ as an oxidant and form chiral acyl azolium intermediate **2-II**. Acyl azolium **2-II** selectively reacts with (*S*)-hydroxyphthalide by a dynamic kinetic resolution process to afford the tetrahedral intermediate **2-III**, which give phthalidyl ester **2-3e** with the regeneration of NHC catalyst. Phthalidyl ester products formed with (*S*)-absolute configuration. Based on this, a proposed transition state TS-(*S*) is shown in **Figure 2.4**. (*R*,*S*)-acyl azolium reacts with

(*S*)-hydroxyphthalide from the hydroxyphthalide racemization equilibrium to afford (*S*)-phthalidyl ester.

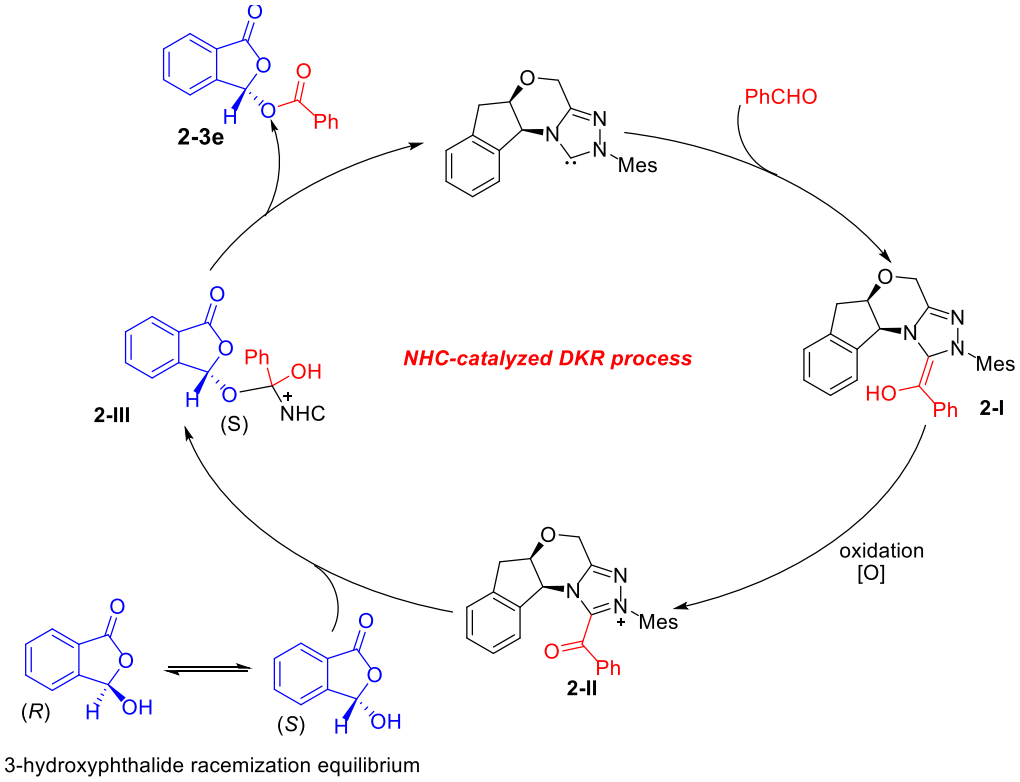


Figure 2.3 Proposed mechanism

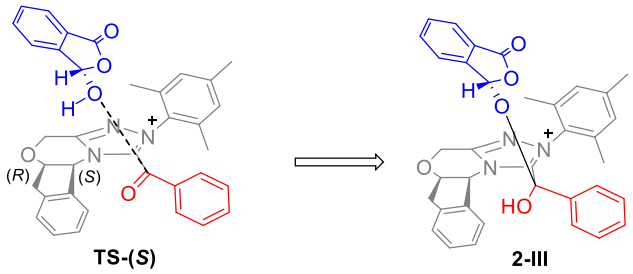


Figure 2.4 Proposed transition state

2.3 Conclusion

In summary, a carbene-catalyzed dynamic kinetic resolution and asymmetric acylation reaction of 3-hydroxyphthalide for quick access to optically enriched phthalidyl esters have been developed. The present study also offers a convenient approach for asymmetric

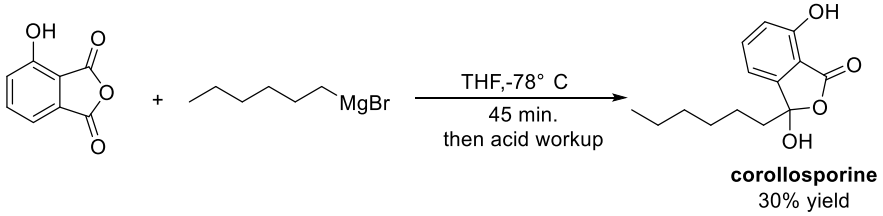
modification of natural products and other functional molecules bearing labile acetal moieties that are difficult to be fixed stereo-selectively. we also expect this method to find unique application for saccharide molecules containing many hydroxyl groups with minute reactivity differences.

2.4 Experimental section

2.4.1 General information

Commercially available materials purchased form TCI or Sigma Aldrich was used as received. All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. THF were distilled from sodium-benzophenone. Flash chromatography was performed using silica gel (200- 300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254nm and 365 nm). ^{1}H and ^{13}C NMR were recorded on Bruker BBFO 400 MHz NMR, Bruker AV400 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR = 7.26, ^{13}C NMR = 77.16). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (J) are reported in Hertz (Hz). High resolution Mass spectra (HRMS) were recorded by using Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of ee was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]^{rt}{}_{D}$ (c in g per 100 mL solvent). Melting points were determined via SRS OptiMelt MPA100.

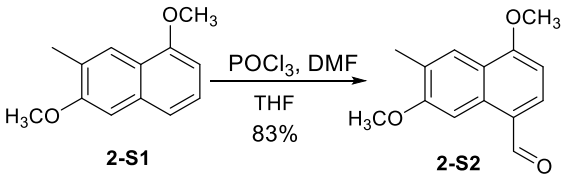
2.4.2 Synthesis of corollosporine



Corollosporine was synthesized by the minor modification of the reported method.[43] Under N_2 atmosphere 3-hydroxyphthalic anhydride (1.64 g, 10 mmol, 1 equiv.) was dissolved in 30 ml dry THF and cooled to -78 °C and allowed to stir for 30 minutes. Hexylmagnesium bromide solution (15 mmol, 15 mL ,1(M) in THF,1.5 equiv) was added dropwise to the cold hydroxyphthalic anhydride solution. The reaction mixture was allowed to stir for 15 minutes at -78 °C then the mixture was warmed to room temperature and quenched by 1 M HCl. Then the resulted solution was concentrated in *vacuo* and worked up with ethyl acetate and brine solution. The organic layer was dried with anhydrous sodium sulphate, and the solvent was removed in vacuo. The crude mixture was purified by column chromatography with chloroform-methanol (50:1-20:1) as eluent. Corollosporine was afforded as an off white solid in 30% yield (750 mg). The NMR is consistent with the reported NMR of corollosporine.[43]

2.4.3 Total synthesis of fimbricalyxlactone C

Synthesis of **2-S2**



Dissolve the compound **2-S1** (4.65 g) into the DMF (30 mL). The solution was placed into the ice bath under N_2 atmosphere, then $POCl_3$ (2.5 mL, 1.1 equiv.) was added. The resulting mixture was moved into the oil bath and heated to 100 ^oC. After 3 hours, H_2O (10 mL) was added into the reaction followed by neutralization to a pH value of 6. After extraction with CH_2Cl_2 (50 mL X 3) and washing with brine (30 mL X 3), The organic phase was dried over

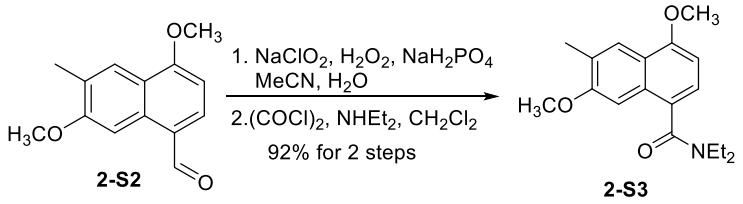
Na_2SO_4 and then evaporated to dryness. The resulting residue was applied onto the column chromatography with the hexane / ethyl acetate (3: 1) to afford the product **2-S2** in 83% yield as an off-white solid (4.40g, m.p. 79-80 ^oC).

IR ν_{max} (film, cm^{-1}):2962, 2848, 2721, 2102, 1670, 1630, 1573, 1462, 1246, 1051;

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.76 (s, 1H), 8.06 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.08 (s, 3H), 4.02 (s, 3H), 2.39 (d, J = 1.0 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 192.7, 160.6, 160.1, 140.2, 132.4, 128.5, 124.0, 123.3, 120.2, 102.7, 101.4, 55.9, 55.5, 17.0 ppm.

HRMS (ESI, m/z): calcd. for $C_{14}H_{15}O_3^+$ 231.1016$(M+H)^+$, found 231.1013.

Synthesis of **2-S3**



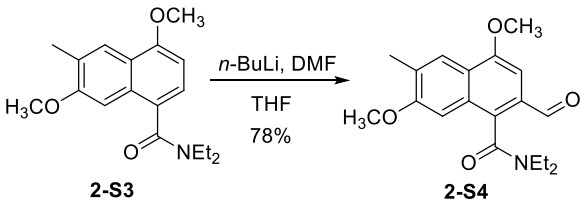
To the solution of product **2-S2** (4.20 g) in the CH_3CN/H_2O (15 mL, 2:1) was added $NaClO_2$ (80%, 5.14 g, 3 equiv.), NaH_2PO_3 (10g, 5.5 equiv.) and H_2O_2 (30% in water, 14.6 g). The reaction was stirred for 4 hours and diluted with water (50 mL). The solution was extracted with CH_2Cl_2 (100 ml X 3) and dried over Na_2SO_4. After the solvent was removed under vacuum and the residue was further dried by the oil pump. the dry residue was re-dissolved in CH_2Cl_2 and oxalyl chloride (1.44 ml, 1.1 equiv.) were added at 0 ^oC. one drop of DMF was added as catalyst. The resulting mixture was stirred at room temperature for 8 hours, diethyl amine (3.51 mL, 3 equiv.) was added. The mixture was stirred at room temperature for another 4 hours and then evaporated to dryness. The residue was applied into the column chromatography with hexane / ethyl acetate (2:1) to afford the product **2-S3** (92%) as a light yellow solid (5.07g, m.p. 195-196 ^oC).

IR ν_{max} (film, cm^{-1}): 2974, 1680, 1630, 1245, 1120;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.24 (d, J = 7.9 Hz, 1H), 6.98 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 3.98 (s, 3H), 3.88 (s, 3H), 3.85 (br, 1H), 3.44 (br, 1H)3.12 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 170.9, 157.8, 155.4, 130.9, 127.9, 126.2, 123.3, 123.2, 120.3, 101.4, 101.1, 55.4, 55.1, 43.0, 38.8, 16.9, 14.3, 13.0 ppm.

HRMS (ESI, m/z): calcd. for $C_{18}H_{24}NO_3^+$ 302.1751$(M+H)^+$, found 302.1751.

Synthesis of **2-S4**



2-S3 **2-S4**

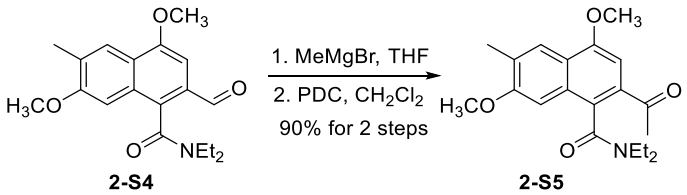
Dissolve the compound **2-S3** (3.9 g) into the dry THF (30 mL) under N_2, BuLi (20.7 mmol, 1.6 equiv.) was added dropwise at –78 ^{o}C. Then the solution was warmed up slowly to – 40 ^{o}C and stirred for 1.5 hours. Dry DMF (5 mL) was added. The resulting mixture was stirred for another 3 hours at room temperature followed by workup with H_2O (5 mL). After 0.5 hours, the reaction was diluted with ethyl acetate (70 mL), washed with sat. $NaHCO_3$ (30 mL X 3) and brine (30 mL X 3), dried over Na_2SO_4. The solvent was removed, and the resulting residue was applied onto chromatography with hexane/ethyl acetate (2:1) to give product **S4** in 78% yield as a beige solid (3.32 g, m.p.181-182 ^{o}C).

IR ν_{max} (film, cm^{-1}): 2974, 2360,1684, 1627, 1595, 1460, 1355, 1136;

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.06 (d, J = 1.2 Hz, 1H), 7.17 (s, 1H), 7.03 (s, 1H), 4.05 (s, 3H), 3.96 (dq, J = 13.6, 7.0 Hz, 1H), 3.90 (s, 3H), 3.58 (dq, J = 14.0, 7.1 Hz, 1H), 3.17 – 3.01 (m, J = 7.2 Hz, 2H), 2.40 (d, J = 1.0 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 190.6, 167.9, 158.4, 155.5, 133.1, 131.9, 130.5, 129.7, 123.7, 123.5, 102.3, 97.4, 55.7, 55.2, 43.2, 39.0, 17.2, 14.1, 12.8 ppm.

HRMS (ESI, m/z): calcd. for $C_{19}H_{24}NO_4^+$ 330.1700$(M+H)^+$, found 330.1698.

Synthesis of **2-S5**



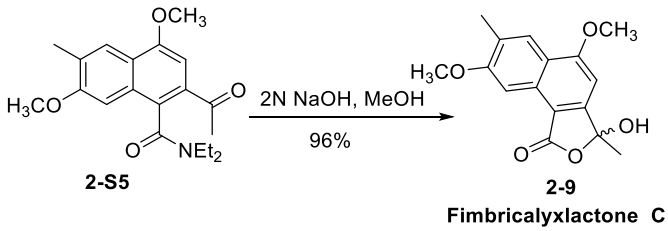
Compound **2-S4** (400 mg) was dissolved in the dry THF (15 mL) under N_2. The resulting solution was cooled down to –10 ^oC. MgMeBr (2 M, 1.3 mmol, 1.05 equiv.) was added dropwisely. After 4 hours, the reaction was quenched by NH_4Cl (sat. 3 mL). The resulting mixture was then diluted with H_2O (30 mL), extracted with ethyl acetate (30 mL X 3), washed with brine (15 mL X 3), dried over Na_2SO_4. The organic phase was evaporated to dryness and used in next step directly without further purification. The crude material was dissolved in CH_2Cl_2(20 mL). PDC (2.3 g, 6.0 mmol, 5 equiv.) was added portion wise. The reaction was stirred overnight and filtered through a pad of celite. The celite was washed with CH_2Cl_2 (20 mL X 2). The filtrate was collected and evaporated to dryness. The residue was applied into column chromatography with hexane / ethyl acetate (2:1) to afford the product **2-S5** (90%) as an off-withe solid (375 mg, m.p. 134-135 ^oC).

IR ν_{max} (film, cm^{-1}): 2059, 1629,1570, 1170, 1118, 1041;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.06 (s, 1H), 7.02 (s, 1H), 4.04 (s, 3H), 3.92 – 3.81 (m, 4H), 3.62 (dq, J = 14.0, 7.0 Hz, 1H), 3.04 (qd, J = 7.2, 3.9 Hz, 2H), 2.66 (s, 3H), 2.38 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 199.2, 170.3, 158.3, 155.0, 131.5, 130.6, 130.8, 127.7, 123.1, 122.3, 103.1, 100.9, 55.6, 55.2, 43.0, 38.7, 28.7, 17.1, 13.5, 12.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{20}H_{26}NO_4^+$ 344.1856$(M+H)^+$, found 344.1859.

synthesis of **fimbricalyxlactone C (2.9)**

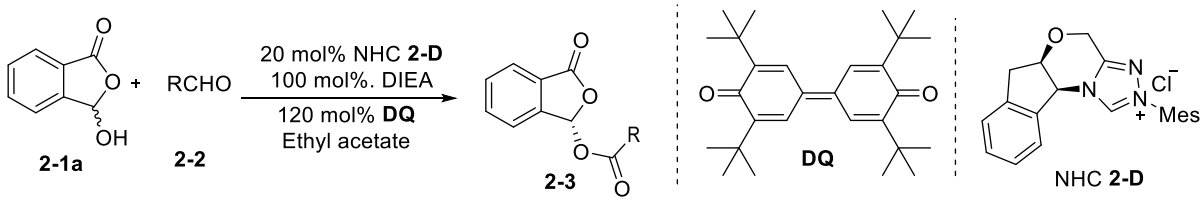


The resulting residue was dissolved in the mixture of 2 *N* NaOH/MeOH (1:2, 15 mL) and stirred for overnight. H_2O (30 mL) was added to precipitate the crude product fimbricalyxlactone C, which could be further purified by column chromatography with ethyl acetate to afford the pure fimbricalyxlactone C (96%) as a light-yellow semisolid. The ^{1}H NMR of fimbricalyxlactone C is consistent with the reported data. [44]

IR ν_{max} (film, cm^{-1}): 2924, 1732, 1583, 1462, 1238, 1146,1020;

^{1}H NMR (400 MHz, acetone-d_6) δ 8.16 (s, 1H), 8.06 (s, 1H), 7.04 (s, 1H), 4.15 (s, 3H), 4.00 (s, 3H), 2.38 (s, 3H), 1.86 (s, 3H) ppm.

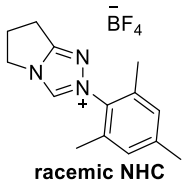
2.4.4 General procedure for synthesis of phthalidyl esters.



A dry 10 mL Schlenk tube with stir bar was charged with aldehyde (**2-2)** (0.10 mmol, 1.0 equiv.), NHC **F** (7.4 mg, 20 mol%), 2-carboxybenzaldehyde (**2-1a**) (0.12 mmol, 1.2 equiv.) and DQ (48.9 mg, 0.12 mmol, 1.2 equiv.). The tube was evacuated and refilled with nitrogen. Then *N*, *N*-Diisopropylethylamine (DIEA) (0.10 mmol, 1.0 equiv.) was added and the mixture was dissolved with dry ethyl acetate solvent (2.0 mL). Then the mixture was stirred at room temperature for 12 h when the substrate was consumed completely (monitored by TLC). The mixture was concentrated under vacuum and purified by column chromatography on silica gel

(hexane/ethyl acetate) to afford desired product **2-3**, which was confirmed by ^{1}H NMR, ^{13}C NMR spectra, and the enantiomeric excess was determined by chiral HPLC.

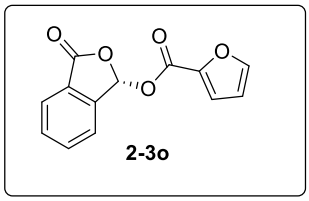
Note: Racemic products for chiral phase HPLC analysis were synthesized using the following racemic NHC



racemic NHC

2.4.5 Crystal Structure of determination of 2-3o

The product **3o** was recrystallize via vaporization of $CDCl_3$ solvent, colourless crystal was observed, and absolute configuration was determined by X-Ray structure analysis. (**Figure 2.3**) Supplementary information of the crystal is available under CCDC number 1914214, which could be accessible at free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk



2-3o

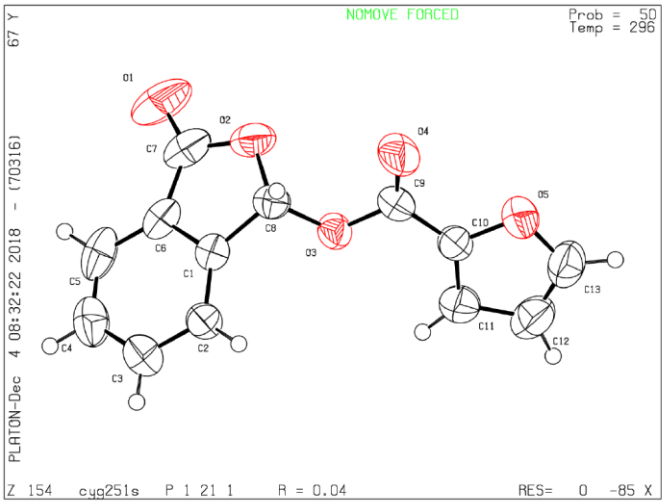
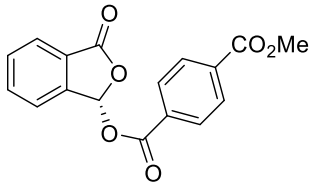


Figure 2.5 X-ray crystal structure of 2-3o

2.4.6 Characterization of products



2-3a

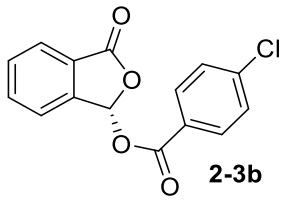
(S)-methyl (3-oxo-1,3-dihydroisobenzofuran-1-yl) terephthalate (2-3a):

29.9mg, white solid; m.p. 171-172.0 ºC **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (s, 4H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.73 – 7.67 (m, 3H), 3.95 (s, 3H).**^{13}C NMR** (101 MHz, CDCl3) δ 167.7, 166.0, 164.4, 144.2, 135.0, 134.9, 132.1, 131.5, 130.1, 129.7, 126.6, 125.9, 123.8, 93.4, 52.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{17}H_{12}O_6H^+$ 313.0707$(M+H)^+$, found 313.0709.

IR ν_{max} (film, cm^{-1}): 2951, 2922, 2850, 1784, 1742, 1726, 976, 752; **$[\alpha]^{21}_D$** = -59.4 (c = 1.05 in $CHCl_3$)

HPLC analysis: 98:2 e.r. (Chiralcel IB, 10:90 *i*-PrOH/Hexane, 0.6 mL/min), R_t (major) = 45.4 min, R_t (minor) = 20.9 min.



2-3b

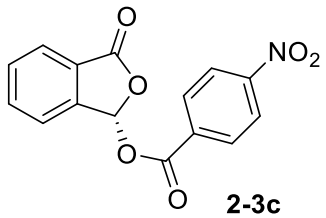
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-chlorobenzoate (2-3b):

17.6 mg, white solid; m.p. 146-147 ºC **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.96 (m, 3H), 7.78 (t, *J* = 7.4 Hz, 1H), 7.69 (dd, *J* = 11.3, 6.6 Hz, 3H), 7.44 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8, 164.3, 144.3, 140.7, 134.9, 131.5, 131.5, 131.4, 129.0, 129.0, 126.9, 126.6, 125.9, 123.7, 93.3 ppm.

HRMS (ESI, m/z): calcd. for $C_{15}H_9O_4ClH^+$ 289.0262$(M+H)^+$, found 289.0266.

IR ν_{max} (film, cm^{-1}): 2952, 2922, 2852, 1786, 1738, 1628, 1261, 754; **$[\alpha]^{21}_D$** = +69.8 (c = 0.42 in $CHCl_3$)

HPLC analysis: 98:2 e.r. (Chiralcel IA, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 16.2 min, R_t (minor) = 24.0 min.



2-3c

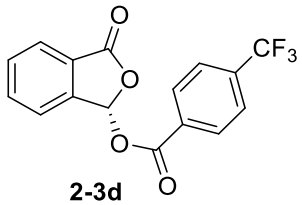
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-nitrobenzoate (2-3c):

26.0 mg, white solid; m.p. 182.7; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.4 Hz, 1H), 7.71 (dd, *J* = 14.3, 6.9 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 163.4, 151.1, 143.8, 135.1, 133.8, 131.7, 131.3, 126.5, 126.1, 123.8, 123.8, 93.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{15}H_9NO_6H^+$ 300.0503$(M+H)^+$, found 300.0501.

IR ν_{max} (film, cm^{-1}): 2957, 2922, 2853, 1780, 1749, 1527, 1346, 1260; **$[\alpha]^{21}$ D** = +74.5 (c = 0.62 in $CHCl_3$)

HPLC analysis: 97:3 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 37.5 min, R_t (minor) = 45.2 min.



2-3d

(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-(trifluoromethyl)benzoate (2-3d):

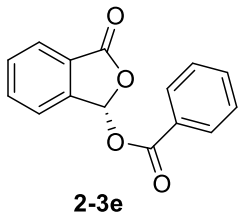
29.9 mg, white solid; m.p. 111-112 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.80 (td, *J* = 7.6, 1.1 Hz, 1H), 7.76-7.66 (m, 5H).**^{13}C NMR** (101 MHz,

$CDCl_3$) δ 167.7, 164.0, 144.1, 135.5(q, J = 32.7 Hz,), 135.0, 131.7, 131.5, 130.6, 130.6, 126.6, 125.7, 123.7(q, J = 3.7 Hz), 123.4 (q, J = 274.7 Hz), 93.5 ppm.

HRMS (ESI, m/z): calcd. for $C_{16}H_9F_3O_4H^+$ 323.0526$(M+H)^+$, found 323.0533.

IR ν_{max} (film, cm^{-1}):2958, 2922, 2852, 1773, 1741, 1628, 1323; **$[\alpha]^{21}_D$** = +49.3 (c = 1.1 in $CHCl_3$)

HPLC analysis: 93:7 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 13.9 min, R_t (minor) = 15.7 min.



2-3e

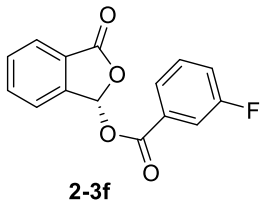
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl benzoate (2-3e):

20.0 mg, white solid; m.p. 127-128 ^oC **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 2H), 7.98 (d, J = 8.2 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.73 – 7.66 (m, 3H), 7.62 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 165.1, 144.5, 134.9, 134.1, 131.3, 130.2, 128.6, 128.4, 126.6, 125.9, 123.8, 93.3 ppm

HRMS (ESI, m/z): calcd. for $C_{15}H_{10}O_4H^+$ 255.0652$(M+H)^+$, found 255.0649.

IR ν_{max} (film, cm^{-1}):2958, 2922, 2853, 1782, 1740, 1636, 1263, 984; **$[\alpha]^{21}_D$** = +86.2 (c = 0.59 in $CHCl_3$)

HPLC analysis: 98:2 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 14.7 min, R_t (minor) = 18.2 min.



2-3f

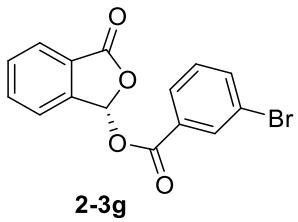
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 3-fluorobenzoate (2-3f):

15.5 mg, white solid; m.p.109-110^{o}C **^{1}H NMR** (400 MHz, CDCl3) δ 7.99 (d, J = 7.6 Hz, 1H), 7.88 – 7.84 (m, 1H), 7.79 (td, J = 7.5, 0.9 Hz, 1H), 7.75 – 7.68 (m, 3H), 7.67 (s, 1H), 7.45 (td, J = 8.0, 5.5 Hz, 1H), 7.35 – 7.29 (m, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.8, 162.6, 162.6, 162.4(d, J = 263.6 Hz), 144.3, 162.6 (d, J = 4.0 Hz), 134.9, 132.4, 131.4, 126.6, 125.8, 124.2(d, J = 4.0 Hz), 117.2(d, J = 21.9 Hz), 117(d, J = 9.0 Hz), 93.2 ppm.

HRMS (ESI, m/z): calcd. for $C_{15}H_9FO_4H^+$ 255.0558$(M+H)^+$, found 255.0552.

IR ν_{max} (film, cm^{-1}): 2922, 2852, 1778, 1591, 1444, 1267, 982; **$[\alpha]^{21}_D$** = +80.8 (c = 0.76 in $CHCl_3$)

HPLC analysis: 98:2 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 13.7 min, R_t (minor) = 18.7 min.



2-3g

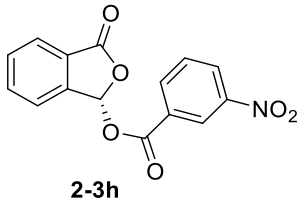
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 3-bromobenzoate (2-3g):

22.2 mg, white solid; m.p.118-119 ^{o}C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (t, J = 1.8 Hz, 1H), 8.00 (ddd, J = 7.5, 3.3, 2.0 Hz, 2H), 7.82 – 7.65 (m, 5H), 7.35 (t, J = 7.9 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7, 163.8, 144.2, 137.0, 135.0, 133.0, 131.5, 130.4, 130.2, 128.8, 126.6, 126.0, 123.8, 122.7, 93.4 ppm.

HRMS (ESI, m/z): calcd. for $C_{15}H_9BrO_4H^+$ 332.9757$(M+H)^+$, found 332.9763

IR ν_{max} (film, cm^{-1}): 2922, 2850, 1782, 1739, 1242, 974; **$[\alpha]^{21}_D$** = +65.1 (c = 0.58 in $CHCl_3$)

HPLC analysis: 97:3 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 15.3 min, R_t (minor) = 17.9 min.



2-3h

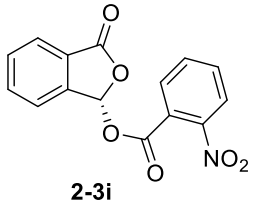
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 3-nitrobenzoate (2-3h):

25.4 mg, brown solid; m.p.153-154 ^{o}C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.87 – 8.85 (m, 1H), 8.48 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.41 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.81 (td, *J* = 7.5, 1.0 Hz, 1H), 7.75 – 7.67 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.6, 163.2, 148.4, 143.8, 135.7, 135.1, 131.7, 130.3, 130.0, 128.4, 126.5, 126.1, 125.1, 123.8, 93.6 ppm

HRMS (ESI, m/z): calcd. for $C_{15}H_9NO_6H^+$ 300.0503$(M+H)^+$, found 300.0519.

IR ν_{max} (film, cm^{-1}): 2924, 2852, 1790, 1746, 1531, 1352, 1251, 976; **$[\alpha]^{21}_D$** = +65.8 (c = 1.18 in $CHCl_3$)

HPLC analysis: 94:6 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 35.7 min, R_t (minor) = 42.7 min.



2-3i

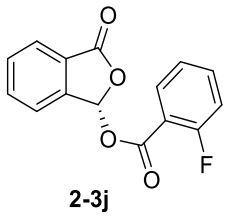
(R)-3-oxo-1,3-dihydroisobenzofuran-1-yl 2-nitrobenzoate (2-3i):

28.4 mg, light yellow semisolid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.82 – 7.65 (m, 7H), 7.62 (s, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.6, 164.3, 143.6, 135.1, 133.5, 132.4, 131.6, 130.1, 126.5, 126.2, 125.8, 124.2, 124.0, 124.0, 93.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{15}H_9NO_6H^+$ 300.0503$(M+H)^+$, found 300.0512.

IR ν_{max} (film, cm^{-1}): 2923, 2850, 1791, 1531, 1352, 1246, **$[\alpha]^{21}_D$** = +65.8 (c = 1.0 in $CHCl_3$)

HPLC analysis: 94:6 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 30.0 min, R_t (minor) = 33.0 min.



2-3j

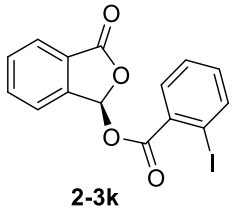
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 2-fluorobenzoate (2-3j):

24.1 mg, off white solid; m.p.127-128 ^oC **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.78 (t, *J* = 7.2 Hz, 1H), 7.68 (dd, *J* = 9.2, 5.6 Hz, 3H), 7.62 – 7.55 (m, 1H), 7.24 – 7.13 (m, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8, 162.6 (d, *J* = 4.0 Hz),162.4 (d, *J* = 263.6 Hz), 144.3, 135.7(d, *J* = 9.1 Hz), 134.9, 132.4, 131.4, 126.6, 125.8, 124.2 (d, *J* = 9.1 Hz), 123.8, 117.2(d, *J* = 21.2 Hz),117.0 (d, *J* = 9.1 Hz), 93.2 ppm.

HRMS (ESI, m/z): calcd. for $C_{15}H_9FO_4H^+$ 255.0558$(M+H)^+$, found 255.0562.

IR ν_{max} (film, cm^{-1}): 2956, 2922, 2852, 1784, 1749, 1612, 1489, 1250, 982; **$[\alpha]^{21}_D$** = +70.3 (c = 0.74 in $CHCl_3$)

HPLC analysis: 92:8 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 15.8 min, R_t (minor) = 17.8 min.



2-3k

(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 2-iodobenzoate (2-3k):

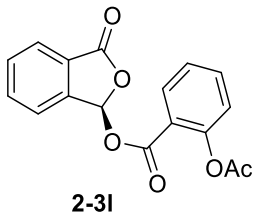
20.3 mg, white solid; m.p.157-158^oC **^{1}H NMR** (400 MHz, CDCl3) δ 8.05 (d, J = 7.9 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.81 – 7.66 (m, 4H), 7.41 (dd, *J* = 11.0,

4.2 Hz, 1H), 7.20 (td, *J* = 7.7, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.79, 164.6, 144.2, 141.8, 134.9, 133.7, 132.7, 131.8, 131.4, 128.1, 126.6, 125.9, 124.0, 94.8, 93.5 ppm.

HRMS (ESI, m/z): calcd. for $C_{15}H_9IO_4H^+$ 380.9618$(M+H)^+$, found 380.9619.

IR ν_{max} (film, cm^{-1}): 2922, 2852, 1778, 1751, 1579, 1236, 1082, 982; **$[\alpha]^{21}_D$** = -33.4 (c = 0.82 in $CHCl_3$)

HPLC analysis: 6:94 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 22.5 min, R_t (minor) = 17.1 min.



2-3l

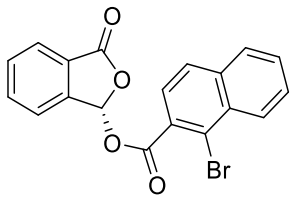
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 2-acetoxybenzoate (3l):

16.9 mg, yellow solid; m.p.134-135 ^oC **^{1}H NMR** (400 MHz, CDCl3) δ 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.1 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 2H), 7.64 – 7.59 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 2.22 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6, 167.8, 162.9, 151.2, 144.3, 135.1, 135.0, 132.2, 131.4, 126.5, 126.2, 125.9, 124.1, 123.9, 121.6, 93.2, 20.8 ppm.

HRMS (ESI, m/z): calcd. for $C_{17}H_{12}O_4H^+$ 313.0707$(M+H)^+$, found 313.0703

IR ν_{max} (film, cm^{-1}):2962, 2924, 2852, 1736, 1630, 1583, 1462, 1369, 1238; **$[\alpha]^{21}_D$** = -42.6 (c = 0.50 in $CHCl_3$)

HPLC analysis: 1:99 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major)= 22.5 min, R_t (minor) = 20.4 min.



2-3m

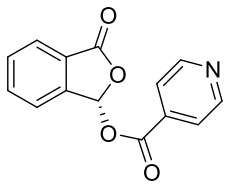
(R)-3-oxo-1,3-dihydroisobenzofuran-1-yl 1-bromo-2-naphthoate (2-3m):

23.3 mg, white solid; m.p.166-167°C **^{1}H NMR** (400 MHz, CDCl3) δ 8.48 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.78 (ddd, *J* = 19.6, 13.2, 5.0 Hz, 4H), 7.71 – 7.60 (m, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.8, 165.5, 144.2, 135.6, 135.0, 132.4, 131.4, 128.9, 128.8, 128.7, 128.4, 128.3, 128.0, 126.6, 125.9, 125.9, 124.0, 123.9, 93.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{19}H_{11}O_4H^+$ 382.9913$(M+H)^+$, found 382.9919.

IR ν_{max} (film, cm^{-1}): 2920, 2850, 1778, 1755, 1462, 1352, 1107; **$[\alpha]^{21}_D$** = +17.6 (c = 0.88 in $CHCl_3$)

HPLC analysis: 95:5 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 21.4 min, R_t (minor) = 25.9 min.



2-3n

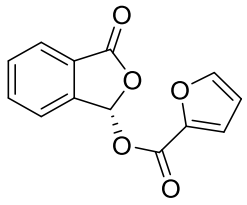
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl isonicotinate (2-3n):

17.1 mg, white solid; m.p.114-115°C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 – 8.80 (m, 2H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.86 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.70 (dd, *J* = 16.6, 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.6, 163.9, 150.9, 143.8, 135.7, 135.1, 131.6, 126.5, 126.0, 123.8, 123.0, 93.5 ppm.

HRMS (ESI, m/z): calcd. for $C_{14}H_9NO_4H^+$ 256.0604$(M+H)^+$, found 256.0613.

IR ν_{max} (film, cm^{-1}): 2292, 2852, 1788, 1743, 1406, 1271, 1105, 750; **$[\alpha]^{21}_D$** = +151.8 (c = 0.95 in $CHCl_3$)

HPLC analysis: 92:8 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 33.1 min, R_t (minor) = 39.3 min.



2-3o

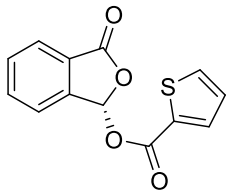
(R)-3-oxo-1,3-dihydroisobenzofuran-1-yl furan-2-carboxylate (2-3o):

23.2 mg, white solid; m.p.138-139 °C **^{1}H NMR** (400 MHz, CDCl3) δ 7.97 (d, J = 7.5 Hz, 1H), 7.77 (t, J = 7.1 Hz, 1H), 7.67 (dd, J = 14.0, 6.1 Hz, 4H), 7.28 (d, J = 3.5 Hz, 1H), 6.55 (dd, J = 3.5, 1.7 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7, 156.8, 147.7, 144.1, 143.0, 134.9, 131.4, 126.6, 125.9, 123.8, 120.4, 112.3, 92.9 ppm.

HRMS (ESI, m/z): calcd. for $C_{13}H_8O_5H^+$ 245.0444$(M+H)^+$, found 245.0451.

IR ν_{max} (film, cm^{-1}): 2927, 2854, 1782, 1741, 1480, 1294, 1280; **$[\alpha]^{21}_D$** = +55.6 (c = 0.48 in $CHCl_3$)

HPLC analysis: 84:16 e.r. (Chiralcel IB, 10:90 *i*PrOH/Hexane, 0.6 mL/min), R_t (major) = 18.6 min, R_t (minor) = 25.9 min.



2-3p

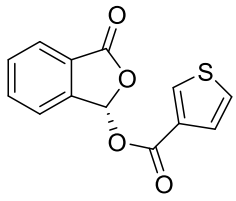
(R)-3-oxo-1,3-dihydroisobenzofuran-1-yl thiophene-2-carboxylate (2-3p):

21.6 mg, brown solid; m.p.151-152 °C **^{1}H NMR** (400 MHz, CDCl3) δ 7.97 (d, J = 7.5 Hz, 1H), 7.88 (dd, J = 3.8, 1.2 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.71 – 7.62 (m, 4H), 7.13 (dd, J = 4.9, 3.9 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.8, 160.6, 144.3, 135.2, 134.9, 134.3, 131.6, 131.4, 128.1, 126.6, 125.9, 123.8, 93.2 ppm.

HRMS (ESI, m/z): calcd. for $C_{13}H_8O_4SH^+$ 261.0216$(M+H)^+$, found 261.0219.

IR ν_{max} (film, cm^{-1}): 2927, 2856, 1782, 1741, 1470, 1294, 1176, 978; **$[\alpha]^{21}_D$** = +91.8 (c = 0.5 in $CHCl_3$)

HPLC analysis: 98:2 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 18.7 min, R_t (minor) = 26.6 min.



2-3q

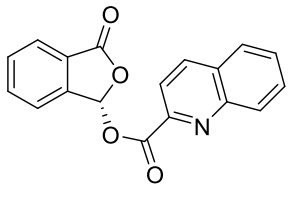
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl thiophene-3-carboxylate (2-3q):

21.5 mg, white solid; m.p.155-156 °C **^{1}H NMR** (400 MHz, CDCl3) δ 8.19 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.77 (td, *J* = 7.5, 1.0 Hz, 1H), 7.71 – 7.64 (m, 3H), 7.55 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.34 (dd, *J* = 5.1, 3.0 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.9, 160.9, 144.5, 134.9, 134.8, 131.6, 131.3, 128.0, 126.6, 126.6, 125.8, 123.7, 93.1 ppm.

HRMS (ESI, m/z): calcd. for $C_{13}H_8O_4SH^+$ 261.0216$(M+H)^+$, found 261.0222.

IR ν_{max} (film, cm^{-1}):2924, 2849, 2108, 1786, 1724, 1629, 1250, 972; **$[\alpha]^{21}_D$** = +19.9 (c = 0.23 in $CHCl_3$)

HPLC analysis: 97:3 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 18.9 min, R_t (minor) = 27.6 min.



2-3r

(R)-3-oxo-1,3-dihydroisobenzofuran-1-yl quinoline-2-carboxylate (2-3r):

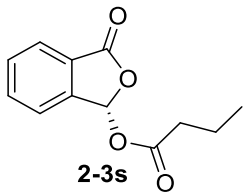
22.6 mg, brown solid; m.p.186-187 °C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 15.1, 8.6 Hz, 2H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.79 (m,

4H), 7.73 – 7.65 (m, 2H).**^{13}C NMR** (101 MHz, CDCl3) δ 167.8, 164.0, 147.8, 146.4, 144.2, 137.5, 135.0, 131.5, 130.9, 130.5, 129.6, 129.2, 127.6, 126.7, 125.9, 124.1, 121.3, 94.1 ppm.

HRMS (ESI, m/z): calcd. for $C_{18}H_{11}O_6H^+$ 306.0761$(M+H)^+$, found 313.0782.

IR ν_{max} (film, cm^{-1}): 2922, 2850, 2358, 1790, 1737, 1466, 1284, 979;**$[\alpha]^{21}_D$** = +24.6 (c = 0.5 in $CHCl_3$)

HPLC analysis: 83:17 e.r. (Chiralcel IA, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 47.6 min, R_t (minor) = 52.9 min.



2-3s

(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl butyrate (2-3s):

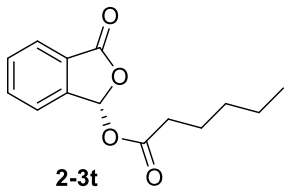
In presence of NHC **2-C**, 14 % 8:92 e.r.; NHC **2-E**, 11%, 89:11 e.r.

7.7 mg, light yellow oil;**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 1H), 7.75 (td, J = 7.5, 1.0 Hz, 1H), 7.75 (td, J = 7.5, 1.0 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.60 – 7.56 (m, 1H), 7.46 (s, 1H), 2.41 (t, J = 7.4 Hz, 2H), 1.71 (dt, J = 14.8, 7.4 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 172.1, 167.9, 144.5, 134.8, 131.2, 126.6, 125.8, 123.5, 92.6, 35.9, 18.1, 13.5 ppm.

HRMS (ESI, m/z): calcd. for $C_{12}H_{12}O_4H^+$ 221.0808$(M+H)^+$, found 221.0814.

IR ν_{max} (film, cm^{-1}): 2964, 1637, 1568, 1261, 1100; **$[\alpha]^{21}_D$** = +19.5 (c = 0.25 in $CHCl_3$)

HPLC analysis: 94:6 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 10.7 min, R_t (minor) = 12.1 min.



2-3t

(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl hexanoate (2-3t):

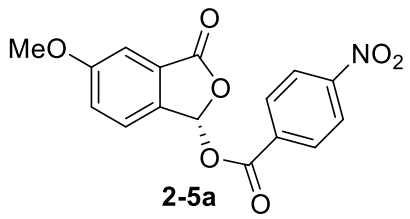
In presence of NHC **2-C**, 19 % 6:94 e.r.; NHC **2-E**, 13%, 87:13 e.r.

9.1 mg, colorless oil ;^{1}H NMR (400 MHz, CDCl3) δ 7.94 (d, J = 7.6 Hz, 1H), 7.75 (td, J = 7.5, 1.0 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.46 (s, 1H), 2.43 (t, J = 7.5 Hz, 2H), 1.69 (dq, J = 15.0, 7.4 Hz, 2H), 1.33 (dd, J = 7.3, 3.6 Hz, 4H), 0.94 – 0.86 (m, 3H).**^{13}C NMR** (101 MHz, CDCl3) δ 172.3, 167.9, 144.5, 134.8, 131.2, 126.6, 125.8, 123.5, 92.6, 34.0, 31.1, 24.2, 22.2, 13.8 ppm.

HRMS (ESI, m/z): calcd. for $C_{14}H_{16}O_4H^+$ 249.1121$(M+H)^+$, found 249.1130.

IR ν_{max} (film, cm^{-1}): 3018, 2358, 1522, 1423, 1261, 1215, 760; **$[\alpha]^{21}_D$** = +17.5 (c = 0.25 in $CHCl_3$)

HPLC analysis: 93:7 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 11.1 min, R_t (minor) = 12.5 min.



2-5a

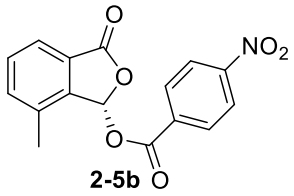
(S)-5-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-nitrobenzoate (2-5a):

20.0 mg, white solid; m.p.183-184 ^{o}C **^{1}H NMR** (400 MHz, CDCl3) δ 8.30 (d, J = 8.9 Hz, 2H), 8.23 (d, J = 8.9 Hz, 2H), 7.62 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 2.2 Hz, 1H), 7.31 (dd, J = 8.4, 2.3 Hz, 1H), 3.93 (s, 3H).**^{13}C NMR** (101 MHz, CDCl3) δ 167.6, 163.5, 162.6, 151.1, 136.0, 133.9, 131.3, 128.2, 124.7, 123.7, 123.4, 108.3, 93.7, 56.0 ppm

HRMS (ESI, m/z): calcd. for $C_{16}H_{11}NO_7H^+$ 330.0608$(M+H)^+$, found 330.0609.

IR ν_{max} (film, cm^{-1}):2961, 2924, 2850, 1780, 1742, 1628, 1261, 1094; **$[\alpha]^{21}_D$** = +32.4 (c = 0.43 in $CHCl_3$)

HPLC analysis: 83:17 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 41.2 min, R_t (minor) = 46.8 min.



2-5b

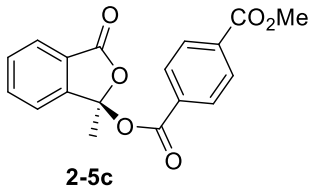
(S)-7-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-nitrobenzoate (2-5b):

22.8 mg, off white solid; m.p.209-210 ^{o}C;**^{1}H NMR** (400 MHz, CDCl3) δ 8.31 (d, J = 8.9 Hz, 2H), 8.26 – 8.23 (m, 2H), 7.83 (d, J = 7.3 Hz, 1H), 7.74 (s, 1H), 7.64 – 7.56 (m, 2H), 2.41 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.9, 163.2, 151.2, 141.9, 136.2, 134.5, 133.7, 131.8, 131.3, 126.5, 123.8, 123.6, 92.6, 17.3 ppm.

HRMS (ESI, m/z): calcd. for $C_{16}H_{11}NO_6H^+$ 314.0659$(M+H)^+$, found 314.0654.

IR ν_{max} (film, cm^{-1}): 2924, 2852, 1788, 1743, 1629, 1527, 1256, 976; **$[\alpha]^{21}_D$** = +106.5 (c = 0.32 in $CHCl_3$)

HPLC analysis: 81:19 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 33.7 min, R_t (minor) = 37.8 min.



2-5c

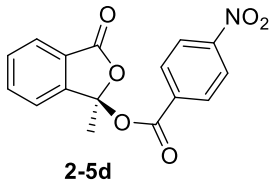
(R)-methyl (1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl) terephthalate (2-5c):

30.0 mg, white solid; m.p.194-195 ^{o}C **^{1}H NMR** (400 MHz, CDCl3) δ 8.10 – 8.06 (m, 2H), 8.04 – 8.00 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H), 7.75 – 7.60 (m, 3H), 3.94 (s, 3H), 2.14 (s, 3H).**^{13}C NMR** (101 MHz, CDCl3) δ 167.5, 166.1, 163.0, 147.6, 134.7, 134.5, 133.2, 130.8, 129.8, 129.6, 127.0, 125.6, 122.0, 105.9, 52.5, 25.1 ppm.

HRMS (ESI, m/z): calcd. for $C_{18}H_{14}O_6H^+$ 327.0863$(M+H)^+$, found 327.0862.

IR ν_{max} (film, cm^{-1}): 2954, 2920, 2850, 1784, 1730, 1716, 1282, 725; **$[\alpha]^{21}_D$** = +45.5 (c = 0.76 in $CHCl_3$)

HPLC analysis: 2:98 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 18.6 min, R_t (minor) = 15.3 min.



2-5d

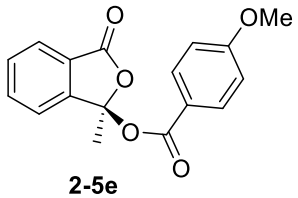
(R)-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-nitrobenzoate (2-5d):

28.8 mg, white solid; m.p.129-130 ºC **^{1}H NMR** (400 MHz, CDCl3) δ 8.27 (d, J = 8.9 Hz, 2H), 8.14 (d, *J* = 8.9 Hz, 2H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.68 – 7.63 (m, 2H), 2.16 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.3, 162.0, 150.9, 147.2, 134.9, 134.8, 131.0, 131.0, 126.9, 125.7, 123.6, 122.1, 106.1 ,25.0 ppm.

HRMS (ESI, m/z): calcd. for $C_{16}H_{11}NO_6H^+$ 314.0659$(M+H)^+$, found 314.060.

IR ν_{max} (film, cm^{-1}): 3055, 2986, 2304, 1789, 1743, 1531, 1265, 746; **$[\alpha]^{21}_D$** = +43.2 (c = 0.59 in $CHCl_3$)

HPLC analysis: 14:86 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 36.4 min, R_t (minor) = 26.1 min.



2-5e

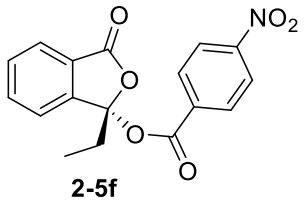
(R)-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-methoxybenzoate (2-5e):

27.4 mg, yellow solid; m.p.159-160 ºC **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 3H), 7.72 – 7.55 (m, 3H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 2.10 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8, 163.9, 163.5, 148.1, 134.6, 132.0, 130.5, 127.0, 125.5, 122.0, 121.8, 113.7, 105.5, 55.5, 25.3 ppm.

HRMS (ESI, m/z): calcd. for $C_{17}H_{14}O_6H^+$ 299.0914$(M+H)^+$, found 299.0916.

IR ν_{max} (film, cm^{-1}):2959, 2837, 1784, 1726, 1604, 1286, 1257, 1097; **$[\alpha]^{21}_D$** = +39.8 (c = 0.82 in $CHCl_3$)

HPLC analysis: 22:78 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 19.3 min, R_t (minor) = 16.3 min.



2-5f

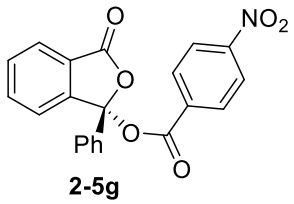
(S)-1-ethyl-3-oxo-1,3-dihydroisobenzofuran-1-yl 4-nitrobenzoate (2-5f):

25.2 mg, yellow solid; m.p.114-115 °C **^{1}H NMR** (400 MHz, CDCl3) δ 8.28 – 8.25 (m, 2H), 8.16 – 8.12 (m, 2H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.73 (td, *J* = 7.5, 1.0 Hz, 1H), 7.64 (dt, *J* = 15.1, 4.2 Hz, 2H), 2.60 (dq, *J* = 14.8, 7.4 Hz, 1H), 2.33 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.05 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.6, 161.9, 150.8, 146.2, 135.0, 134.7, 131.0, 130.9, 127.6, 125.7, 123.6, 122.0, 108.1, 31.1, 7.1 ppm.

HRMS (ESI, m/z): calcd. for $C_{17}H_{13}NO_6H^+$ 328.0816$(M+H)^+$, found 328.0819.

IR ν_{max} (film, cm^{-1}): 2930, 2855, 1786, 1734, 1636, 1528, 1267, 933; **$[\alpha]^{21}_D$** = -45.8 (c = 0.59 in $CHCl_3$)

HPLC analysis: 72:28 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 21.3 min, R_t (minor) = 32.2 min.



2-5g

(S)-3-oxo-1-phenyl-1,3-dihydroisobenzofuran-1-yl 4-nitrobenzoate(2-5g):

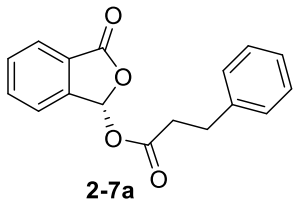
27.4 mg, off white solid; m.p.173-174 °C **^{1}H NMR** (400 MHz, CDCl3) δ 8.29 (d, J = 8.6 Hz, 2H), 8.19 (d, *J* = 8.6 Hz, 2H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.64 (dd, *J* = 12.9, 7.3 Hz, 4H), 7.47 (d, *J* = 4.0 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 167.5, 161.9, 151.0,

147.1, 136.5, 135.0, 134.8, 131.1, 130.0, 129.1, 129.1, 129.1 126.6, 125.9, 125.2, 125.2, 123.7, 123.2, 105.9 ppm.

HRMS (ESI, m/z): calcd. for $C_{21}H_{13}NO_6H^+$ 376.0816$(M+H)^+$, found 376.0820.

IR ν_{max} (film, cm^{-1}): 2927, 1786, 1627, 1527, 1263, 1230, 1091; **$[\alpha]^{21}_D$** = +1.12 (c = 0.8 in $CHCl_3$)

HPLC analysis: 82:18 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 30.6 min, R_t (minor) = 57.3 min.



2-7a

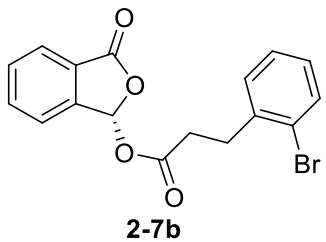
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 3-phenylpropanoate(2-7a):

22.0 mg, white solid; m.p.83-84 °C **^{1}H NMR** (400 MHz, CDCl3) δ 7.93 (d, *J* = 7.6 Hz, 1H), 7.72 (td, *J* = 7.5, 1.0 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.25 – 7.19 (m, 3H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.78 – 2.73 (m, 2H).**^{13}C NMR** (101 MHz, CDCl3) δ 171.4, 167.8, 144.3, 139.7, 134.8, 131.2, 128.6, 128.3, 128.3, 126.5, 125.8, 123.5, 92.7, 35.6, 30.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{17}H_{14}O_4H^+$ 283.0965$(M+H)^+$, found 283.0966.

IR ν_{max} (film, cm^{-1}):2960, 2922, 2852, 2360, 2343, 1784, 1627, 1261; **$[\alpha]^{21}_D$** = +35.5 (c = 0.45 in $CHCl_3$)

HPLC analysis: 89:11 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 18.0 min, R_t (minor) = 19.7 min.



2-7b

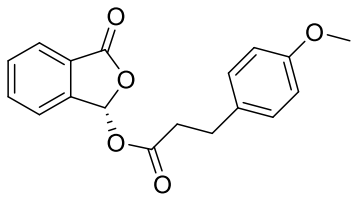
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 3-(2-bromophenyl)propanoate(2-7b):

23.4 mg, off white solid; m.p. 90-91 ^{o}C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.1, 1.0 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.75 (td, J = 7.5, 0.9 Hz, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.57 (ddd, J = 7.6, 4.3, 1.2 Hz, 2H), 7.45 – 7.39 (m, 3H), 3.29 (dd, J = 11.3, 4.2 Hz, 2H), 2.94 – 2.80 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 167.8, 149.1, 144.1, 134.9, 134.9, 133.5, 132.4, 131.3, 128.0, 126.4, 125.8, 125.1, 123.6, 92.7, 34.6, 28.2 ppm.

HRMS (ESI, m/z): calcd. for $C_{17}H_{13}BrO_4H^+$ 361.0070$(M+H)^+$, found 361.0069.

IR ν_{max} (film, cm^{-1}):2959, 2837, 1784, 1726, 1604, 1286, 1257, 1097; **$[\alpha]^{21}_D$** = +64.8 (c = 0.36 in $CHCl_3$)

HPLC analysis: 94:6 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 34.4 min, R_t (minor) = 42.2 min.



2-7c

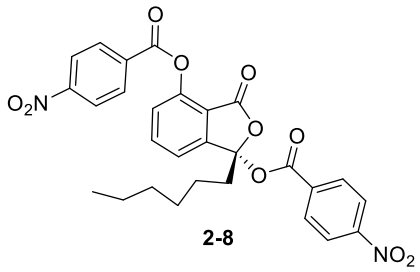
(S)-3-oxo-1,3-dihydroisobenzofuran-1-yl 3-(4-methoxyphenyl)propanoate(2-7c):

25.9 mg, off white solid; m.p.70-71 ^{o}C **^{1}H NMR** (400 MHz, CDCl3) δ 7.92 (d, J = 7.5 Hz, 1H), 7.72 (td, J = 7.5, 0.9 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.42 (s, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 2.94 (t, J = 7.6 Hz, 2H), 2.75 – 2.69 (m, 2H). **^{13}C NMR** (101 MHz, CDCl3) δ 171.5, 167.9, 158.3, 144.3, 134.8, 131.8, 131.2, 129.3, 129.2, 126.5, 125.8, 123.6, 114.0, 92.7, 55.3, 35.9, 29.7 ppm.

HRMS (ESI, m/z): calcd. for $C_{18}H_{16}O_4H^+$ 313.1071$(M+H)^+$, found 313.1077.

IR ν_{max} (film, cm^{-1}):2956, 2077, 1636, 1527, 1123; **$[\alpha]^{21}_D$** = +4.9 (c = 0.51 in $CHCl_3$)

HPLC analysis: 92:8 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 21.6 min, R_t (minor) = 27.2 min.



2-8

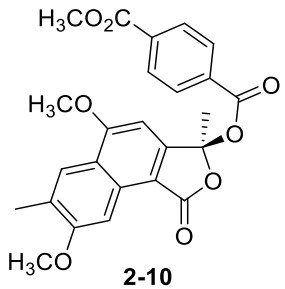
(S)-1-hexyl-3-oxo-1,3-dihydroisobenzofuran-1,4-diyl bis(4-nitrobenzoate) (2-8):

41.2 mg, White Solid; m.p.132-133 ^{o}C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.2 Hz, 2H), 8.23 (d, J = 8.2 Hz, 2H), 8.14 (d, J = 7.9 Hz, 2H), 8.02 – 7.93 (m, 3H), 7.74 (dd, J = 18.1, 10.8 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 2.53 (t, J = 12.6 Hz, 1H), 2.19 (t, J = 12.8 Hz, 1H), 1.28 (d, J = 25.1 Hz, 8H), 0.90 (dd, J = 20.1, 12.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 162.4, 161.6, 151.4, 150.8, 146.3, 144.6, 141.7, 137.4, 134.8, 133.1, 133.0, 131.2, 130.7, 130.5, 128.6, 124.1, 124.1, 123.6, 106.1, 37.1, 31.4, 28.8, 22.4, 22.3, 14.0 ppm.

HRMS (ESI, m/z): calcd. for $C_{28}H_{24}N_2O_{10}H^+$ 549.1504$(M+H)^+$, found 549.1506.

IR ν_{max} (film, cm^{-1}) 2959, 2926, 2854, 1791, 1749, 1627, 1527, 1263, 713; **$[\alpha]^{21}_D$** = +2.6 (c = 0.66 in $CHCl_3$)

HPLC analysis: 17:83 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 54.3 min, R_t (minor) = 34.2 min.



2-10

(S)-5,8-dimethoxy-3,7-dimethyl-1-oxo-1,3-dihydronaphtho[1,2-c]furan-3-yl methyl terephthalate (2-10):

36.0 mg, off white solid; m.p.137-138 ^{o}C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.07 (q, J = 8.5 Hz, 5H), 6.85 (s, 1H), 4.09 (s, 3H), 4.04 (s, 3H), 3.95 (s, 3H), 2.41 (s, 4H), 2.19 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 166.1, 163.0, 161.7, 160.1, 150.6, 134.4, 133.6,

130.4, 130.4, 129.8, 129.6, 124.0, 120.9, 111.9, 105.1, 101.1, 94.9, 56.1, 55.7, 52.5, 17.2, 14.1 ppm

HRMS (ESI, m/z): calcd. for $C_{25}H_{22}O_8H^+$ 451.1387$(M+H)^+$, found 451.1381.

IR ν_{max} (film, cm^{-1}): 2960, 2922, 2852, 2081, 1719, 1629, 1261, 1018; **$[\alpha]^{21}_D$** = +57.8 (c = 0.3 in $CHCl_3$)

HPLC analysis: 82:18 e.r. (Chiralcel IB, 10:90 iPrOH/Hexane, 0.6 mL/min), R_t (major) = 14.8 min, R_t (minor) = 16.9 min.

2.5 References

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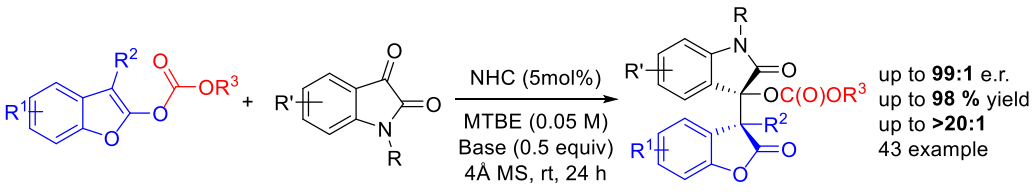
Chapter 3

Carbene-Catalyzed Dynamic Kinetic Resolution for Asymmetric Access to Benzofuranone Derivatives



♦Dynamic kinetic resolution ♦Excellent yields, diastereo- and enantio-selectivities

♦Access to vicinal quaternary stereocenters ♦New reaction pathway

3.1 Introduction

3,3'-disubstituted benzofuran-2(*3H*)-ones are the important class of molecules because of their significance in a wide range of biological activity.[1-3] Many bioactive natural products contain quaternary chiral centers at the 3-position benzofuran-2(*3H*)-ones moiety. For example *Usena longissimi* is an medicinal lichen which is widely used as a Chinese traditional folk medicine.[4] cadinane-type sesquiterpene was isolated from *Chloranthus henryi*, which has been used as a Chinese traditional medicines for the removal of toxic substance from body.[5] In addition, rosmadial is a herb spices belongs to Family Labiate, was isolated from rosemary leaves (*Rosmarinus officinalis* L.) [6] (**Figure 3.1**).

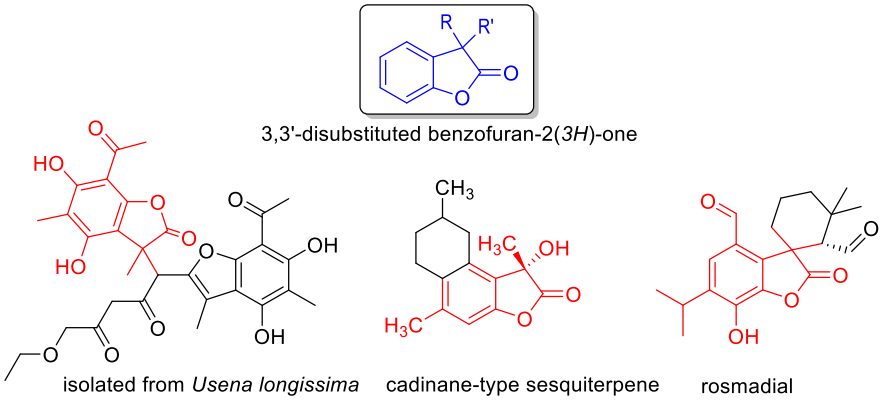
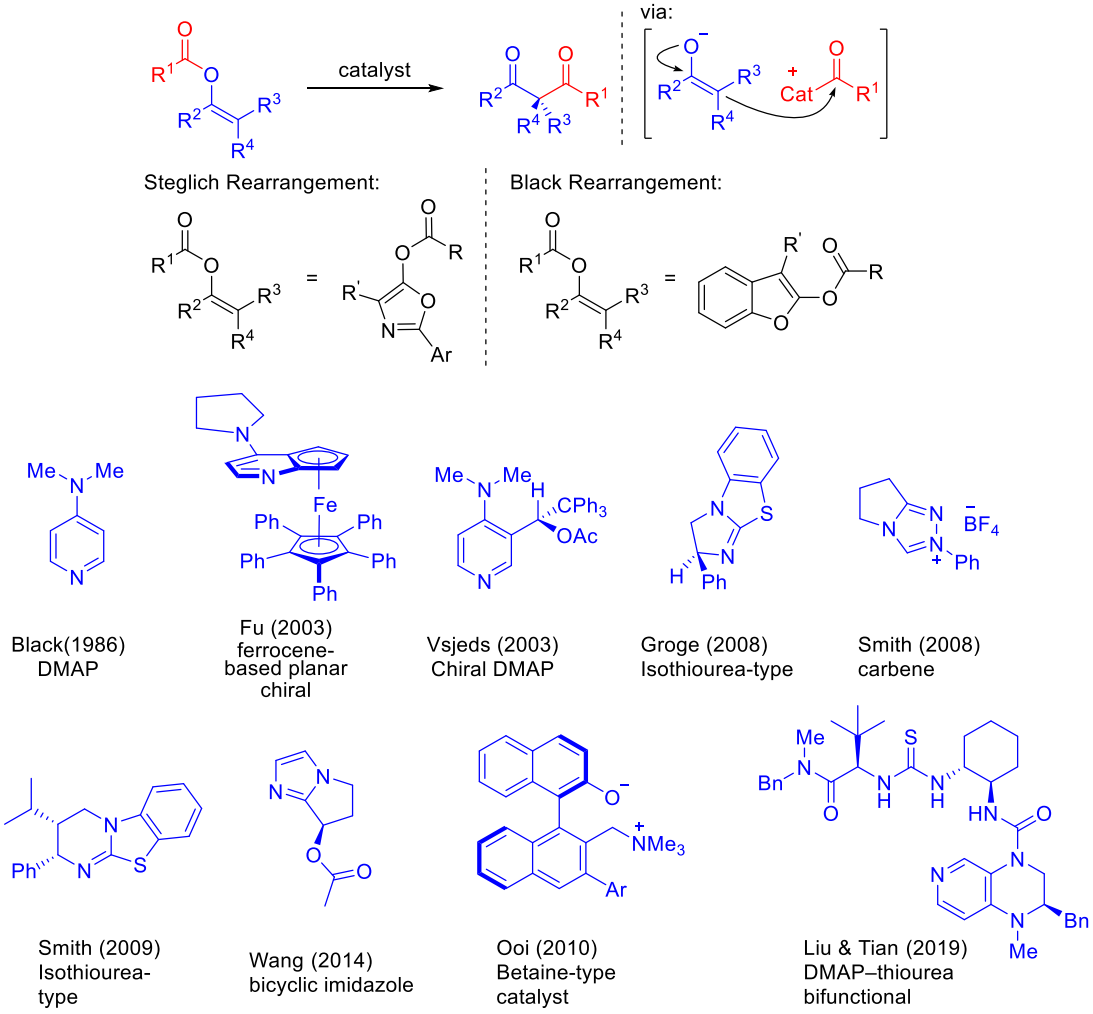


Figure 3.1 Natural products with 3,3'-disubstituted benzofuran-2(*3H*)-one structures

Therefore, development of new effective method for the synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-ones is important in the field of asymmetric synthesis. Acyl transfer reactions are one of the most effective processes to achieve 3,3'-disubstituted benzofuran-2(*3H*)-ones. Acyl transfer represents one of the common transformations in organic synthesis, which has been widely utilized in the synthesis of natural products and bioactive molecules.[7-8] Over the past few decades, many types of elegant and practical acyl transfer reaction have been developed by organic chemists.[9-12] Among that, the transformation of *O*-acylated azlactones to C-acylated products, also known as the Steglich rearrangement,[13] (**Scheme 3.1**) has drawn extremely tremendous attention due to its convenience to access *α,α*-disubstituted amino acid

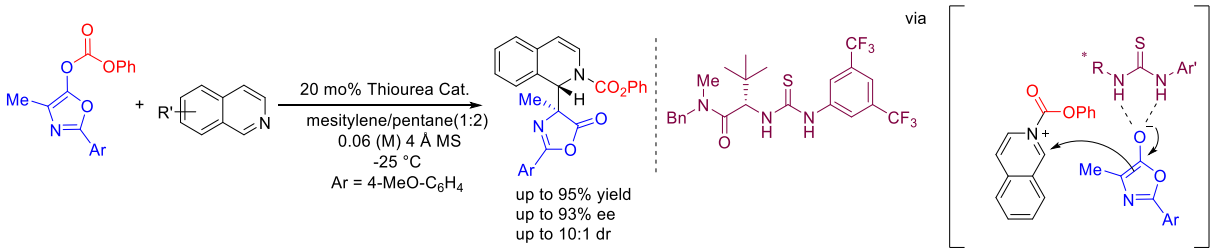
derivatives.[14-16] Various catalysts including 4-(dimethylamino)pyridine (DMAP) and its variants, isothioureas, imidazoles, phosphines, betaines, and carbenes have been successfully used to catalyze this process via ion pairs.[17-19] Besides, another similar rearrangement using *O*-acylated benzofurans as substrates has also been well studied since Black and co-workers reported the first example in 1986 [20] (**Scheme 3.1**).



Scheme 3.1 Catalytic Black and Steglich Rearrangement

In 2003, the first asymmetric variant of this reaction was developed by Fu[21] group utilizing ferrocene-based planar chiral PPY [PPY = 4-(pyrrolidino)pyridine] as catalyst. In the same year, Vsjeds[22] reported asymmetric black rearrangement reaction using chiral DMAP as catalyst. In 2008, Smith[23] group reported N-heterocyclic carbene (NHC) catalyzed Black rearrangement utilizing 3,3'-disubstituted benzofuran-2(*3H*)-one derivatives. However, the

asymmetric version has not been achieved. Further, In 2014, Wang group disclosed asymmetric Black rearrangement catalyzed by bicyclic imidazole.[24] Recently, Liu and Tian developed asymmetric black rearrangement utilizing chiral DMAP-thiourea bifunctional catalyst. Seidel and co-workers reported a thiourea/DMAP co-catalyzed enantioselective Steglich reaction.[25] They found that replacement of the co-catalyst DMAP with nucleophilic isoquinoline resulted in a different pathway, in which the enolate attacked the 1-position of isoquinoline ring rather than the acyl group (**Scheme 3.2**). Inspired by this work, we hypothesized that it is possible to introduce an external electrophile directly to capture the enolate and avoid the Steglich and Black rearrangement.



Scheme 3.2 Seidel's Steglich type rearrangement

N-heterocyclic carbene (NHC) organic catalysis has found impressive success in the activation of carbonyl compounds.[26-30] Many elegant works reported by Smith,[31-35] Lupton,[36-38] Gilmour,[39] Suzuki,[40] and Maruok [41] have demonstrated NHC could be used to activate the vinylic esters. Recently, we reported a carbene-catalyzed dynamic kinetic resolution (DKR) and asymmetric acylation of hydroxyphthalides. The reaction proceeded via an intramolecular semi-acetalization of 2-formylbenzoic acids and subsequent enantio-determining acylation (**Figure 3.2a**).[42] Here we disclose a carbene-catalyzed DKR of vinylic esters (*O*-acylated benzofurans) with active ketones. The key steps include activation of an *O*-acylated benzofuranone (**3-1**) by a NHC catalyst forms an ester enolate intermediate (**3-I**) and a catalyst-bound azolium carbonate intermediate (**3-II**). Subsequent aldol addition of **3-I** to isatin substrate (**3-2**) lead to aldol adduct **3-III**. This aldol addition step itself is substrate-controlled

and not influenced by the catalyst. This reversible aldol process is not selective with the formation of a racemic mixture of four possible stereo-isomers. The unprotected aldol adduct (protonated version of **3-III**) is unstable and thus achieving high conversion and clean reaction is unrealistic. Notably, in our approach, it does not matter much how the aldol process proceeds, as far as the process is reversible and a small amount of **3-III** can be formed. This is because our subsequent step of acylation is a dynamic kinetic resolution (DKR) process. This DKR uses the same chiral azolium carbonate intermediate (**3-II**, generated in the earlier step) for selective acylation with regeneration of the NHC catalyst. This DKR acylation step not only takes care of the diastereo- and enantio-selectivity issues but also drives the reaction toward complete formation of the protected aldol product 3,3'-disubstituted benzofuran-2(*3H*)-ones (**3-3 or 3-4**)

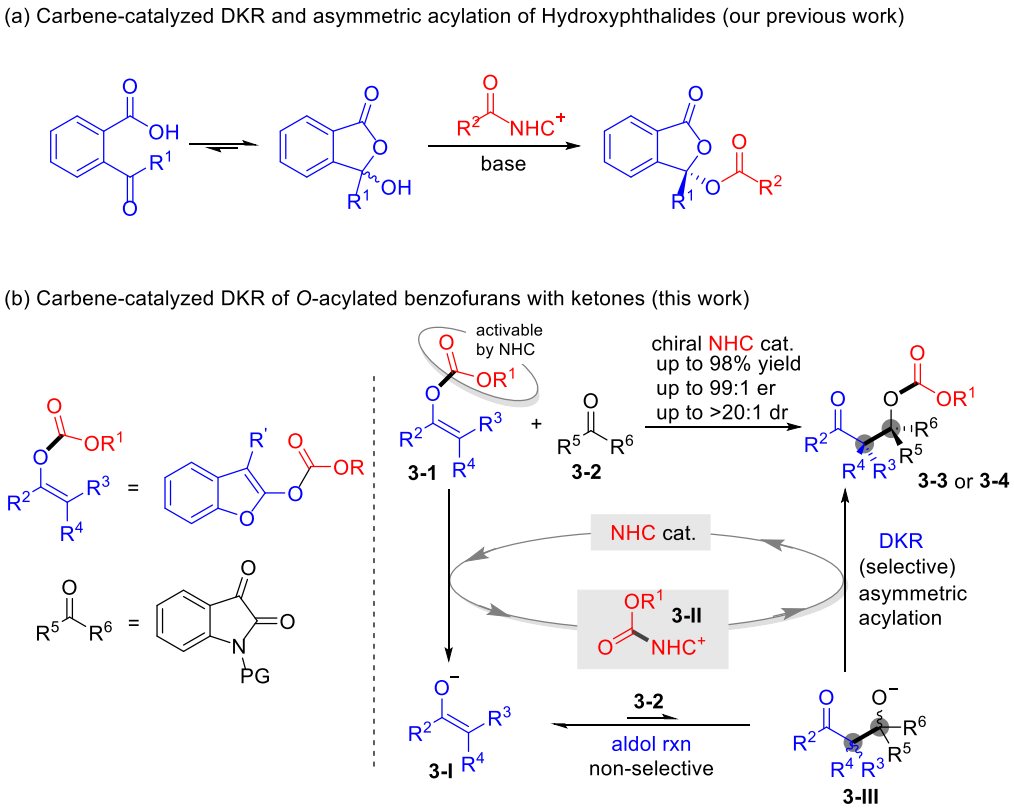


Figure 3.2 This DKR strategy

in excellent yields, diastereo- and enantio-selectivities (**Figure 3.2b**). Notably, this novel reaction pathway is different from the Steglich and Black rearrangements. Besides, the

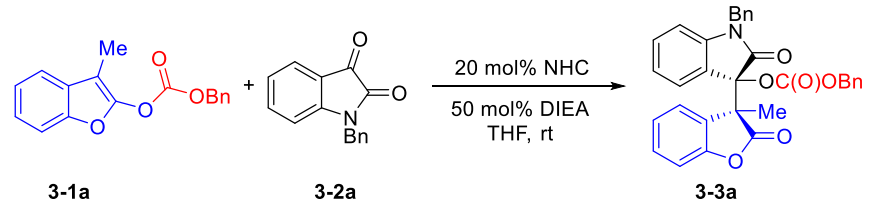
products obtained from our method contain vicinal quaternary stereocenters that are widely found in bioactive compounds.[43]

3.2 Result and discussion

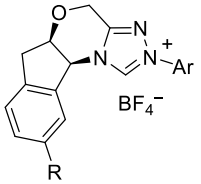
3.2.1 Reaction condition optimization

Benzofuranyl carbonates bearing a methyl group at 3-position of benzofuran moiety **3-1a** and *N*-benzyl protected isatin derivative **3-2a** were utilized as model substrates in the reaction. Key results are demonstrated in Table 3.1 after screening of several NHC precatalyst. The first reaction was performed in the presence of aminoindane-based triazolium catalyst **3-A** and DIEA as the base. 3,3'-disubstituted benzofuran-2(*3H*)-ones bearing vicinal quaternary stereocenters **3-3a** was obtained in low yield, moderate enantiomeric ratio, and moderate diastereomeric ratio (Table 3.1, entry 1, 30%, 80:20 e.r., 5:1 dr). The yield of the reaction was low due to the formation of black rearrangement product as a side product. The replacement of *N*-mesityl group to *N*-2,6-diethylphenyl group in the precatalyst, little improvement of e.r. value was achieved. However, yield of the reaction remained almost same (Table 3.1, entry 2, 28%, 83:17 e.r., 5:1 dr). Further use of precatalyst **3-C** good e.r. value was obtained however, yield and dr of the reaction remained almost same (Table 3.1, entry 3, 32%, 89:11 e.r., 5:1 dr). After that, many aminoindane-based NHC precursors such as **3-D**, **3-E**, **3-F** were employed, unfortunately, there is no such improvement in e.r., dr and yield was observed. Then the morpholine-based chiral triazolium precatalyst was used as precatalyst. Using precatalyst **3-G** that contained electron rich substituent on triazolium nitrogen, lead to the product with moderate yield and good e.r. (3.1, entry 7, 51%, 89:11 e.r., 5:1 dr). Further use of morpholine-based chiral triazolium precatalyst **3-H** bearing 2,4,6-trichlorophenyl group, little improvement of yields and similar er value (Table 3.1, entry 8, 52%, 89:11 e.r., 5:1 dr) was observed. Therefore, NHC-precatalyst **3-H** was selected for further optimization.

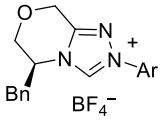
Table 3.1 Screening of NHC precatalyst



3-1a 3-2a 3-3a



3-A: Ar = Mes
3-B: Ar = 2,6-$Et_2C_6H_3$
3-C: Ar = 2,4,6-$Cl_3C_6H_2$
3-D: Ar = C_6F_5
3-E: Ar = 2, 6 CF_3
3-F: Ar = 2, 6 CF_3,R = Ph



3-G: Ar = Mes
3-H: Ar = 2,4,6-$Cl_3C_6H_2$

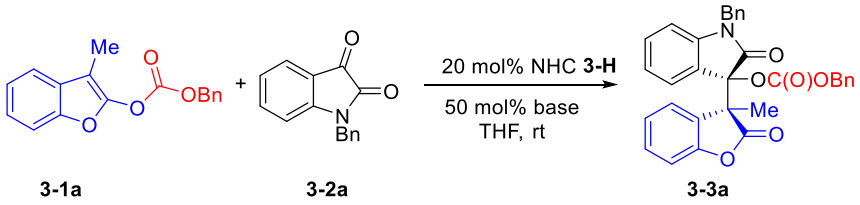
Entry	NHC	t/h	Yield (%)[b]	dr[c]	e.r.[d]
1	**3-A**	24	30	5:1	80:20
2	**3-B**	24	28	5:1	83:17
3	**3-C**	6	32	5:1	89:11
4	**3-D**	6	32	4:1	60:40
5	**3-E**	2	30	5:1	79:21
6	**3-F**	2	32	5:1	81:19
7	**3-G**	2	51	5:1	89:11
8	**3-H**	**2**	**52**	**5:1**	**89:11**

[a]Reaction conditions**: 3-1a** (0.05 mmol), **3-2a** (0.05 mmol), THF (0.5 mL), DIEA (0.5 equiv); [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; [c]Determined by ^{1}H NMR analysis of the crude product; [d]Determined by chiral HPLC.

After screening several NHC precatalysts, to improve the yield and e.r. value, we move to find a suitable base for the reaction. The key results from the screening of bases are introduced in Table 3.2. In presence of morpholine-base triazolium catalyst **3-H**, several bases, both organic and inorganic bases were tested. Among organic bases, in presence of DABCO the corresponding product was afforded with moderate yield and good e.r. value. (Table 3.2, entry

3, 55%, 89:11 e.r., 5:1 dr). Further, the use of inorganic bases, such as K_2CO_3, Cs_2CO_3, NaOAc, and K_3PO_4, the yield of the reaction decreased, and e.r. of the reaction remained similar.

Table 3.2 Screening of base



3-1a 3-2a 3-3a

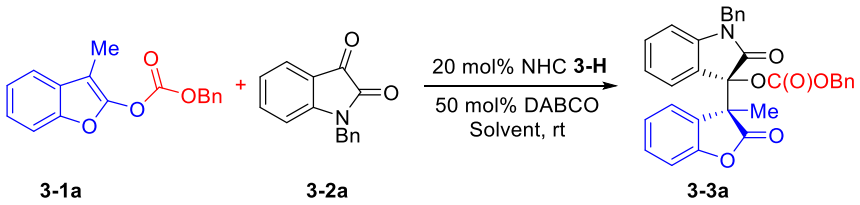
Entry	Base	t/h	Yield(%)[b]	dr[c]	e.r.[d]
1	DIEA	6	52	5:1	89:11
2	DBU	3	35	5:1	84:16
3	**DABCO**	**2**	**55**	**5:1**	**89:11**
4	Et_3N	3	28	4:1	89:11
5	K_2CO_3	2	45	5:1	83:17
6	Cs_2CO_3	2	46	5:1	81:19
7	NaOAc	3	16	5:1	89:11
8	K_3PO_4	2	28	5:1	86:14

[a]Reaction conditions**: 3-1a** (0.05 mmol), **3-2a** (0.05 mmol), THF (0.5 mL), DIEA (0.5 equiv); [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; [c]Determined by ^{1}H NMR analysis of the crude product; [d]Determined by chiral HPLC.

Therefore, we found DABCO as an optimal base for the reaction with moderate yield and good enantiomeric ratio. To improve yield, e.r. and dr of the reaction various solvents were tested in presence of DABCO as base and NHC **3-H** as NHC precatalyst. The key results from further optimization are discussed in the Table 3.3. Several solvents such as dichloromethane, toluene, diethylether were utilized in the reaction. However, the yield of the desired product decreased

a little and e.r. value also slightly decreased. In the presence of acetonitrile as the solvent, the e.r. of the reaction reduced highly (Table 3.3, entry 6, 46%, 72:28, e.r., 5:1 dr). Notably, the e.r. of the reaction slightly increases when methyl tert-butyl ether (MTBE) was used as solvent (Table 3.3, entry 5, 55%, 90:10, e.r., 5:1 dr).

Table 3.3 Screening of solvent



3-1a 3-2a 3-3a

Entry	Solvent	t/h	Yield (%)[b]	dr[c]	e.r.[d]
1	CH_2Cl_2	2	42	5:1	85:15
2	toluene	2	47	5:1	88:12
3	Et_2O	3	48	5:1	86:14
4	EtOAc	2	46	5:1	84:16
5	MTBE	2	55	5:1	90:10
6	MeCN	2	46	5:1	72:28
7[e]	MTBE	24	38	5:1	67:33
8[f]	**MTBE**	**2**	**73**	**5:1**	**90:10**

[a]Reaction conditions**: 3-1a** (0.05 mmol), **3-2a** (0.05 mmol), Solvent (0.5 mL), DABCO (0.5 equiv); [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; [c]Determined by ^{1}H NMR analysis of the crude product; [d]Determined by chiral HPLC, [e]50 mol% LiCl was used; [f]**3-1a** (0.06 mmol), **3-2a** (0.05 mmol), precatalyst **3-G** (20 mol%), 50 mg 4Ä molecular sieve.

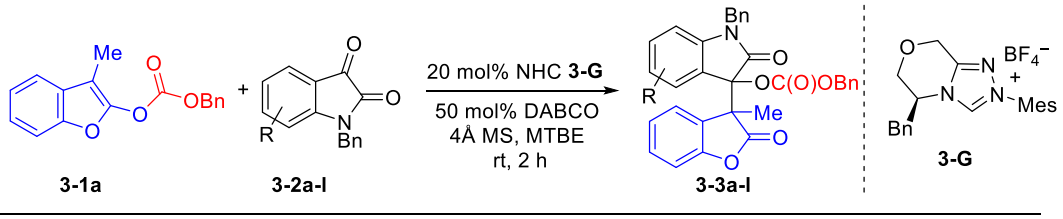
Further, lithium chloride was used as additive. However, e.r. value decreased dramatically (Table 3.3, entry 7, 38%, 67:33 e.r., 5:1 dr). This is due to the lithium cation, that can coordinate with several carbonyl functionality presents in the starting materials. Further, 1.2 equivalents

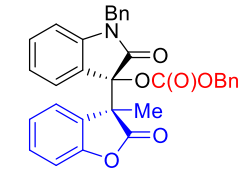
of benzofuranyl carbonate **3-1a** were used along with 4Ä molecular sieve and NHC precatalyst **3-G**, leading to formation of desired product in good yield, good enantiomeric ratio, and moderate diastereoselctivity. (Table 3.3, entry 8, 73%, 90:10 e.r., 5:1 dr).

3.2.2 Substrate scope of *N*-benzyl protected isatins

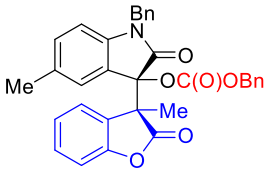
After getting suitable condition in hands, the scope of the reaction was explored. A Variety of *N*-benzyl protected isatin derivatives with different substituents were tolerated in the optimized condition.

Table 3.4 Substrate scope[a,b,c,d]

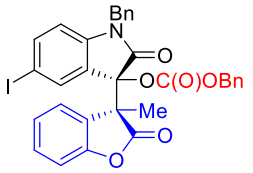




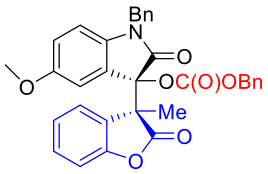
3-3a, 75%, 5:1 dr, 90:10 er



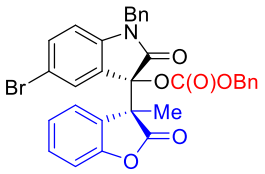
3-3b, 58%, 5:1 dr, 90:10 er



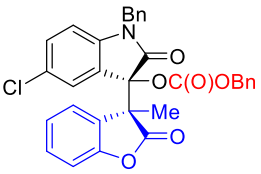
3-3c, 87% , 5:1 dr, 76:24 er



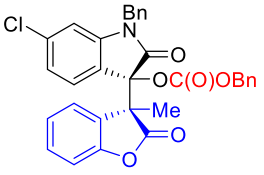
3-3d, 87%, 5:1 dr, 90:10 er



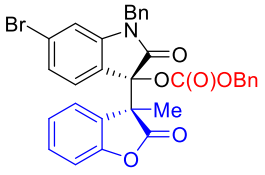
3-3e, 75%, 4:1 dr, 83:17 er



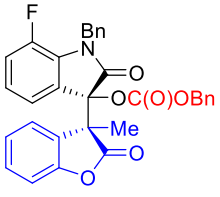
3-3f, 73%, 5:1 dr, 67:33 er



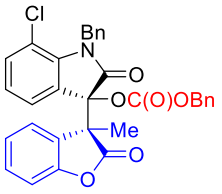
3-3g, 87%, 5:1 dr, 85;15 er



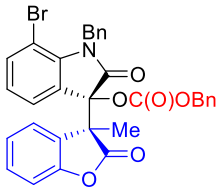
3-3h, 75%, 5:1 dr, 83:17 er



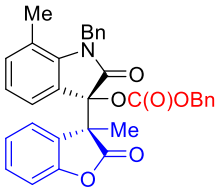
3-3i, 72%, 7:1 dr, 97:3 er



3-3j, 68%, 4:1 dr, 72:28 er



3-3k, 68%, 4:1 dr, 88:12 er



3-3l, 78%, 4:1 dr, 87:13 er

[a]Reaction conditions: **3-1a** (0.12 mmol), **3-2a** (0.1 mmol), MTBE (1 mL), DABCO (0.5 equiv), 50 mg 4Å MS; [b]Yields are isolated yield; [c]er was determined by chiral HPLC; [d]dr was determined by ^{1}H NMR analysis of the crude product.

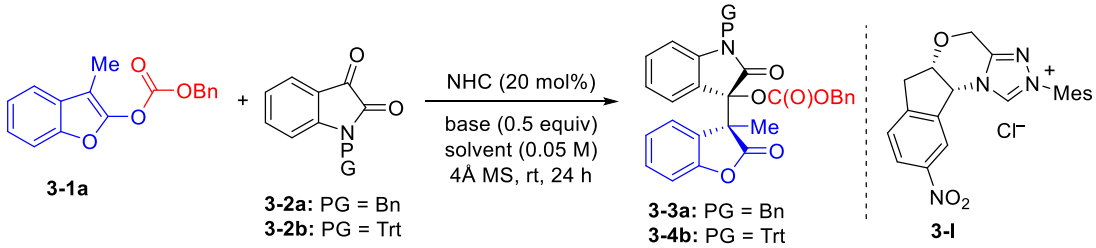
Substituents on 5-position of the isatin derivatives, such as alkyl, halogens, methoxy were worked in the reaction with good to high yields and moderate to good e.r. values. Notably, in presence of 5-iodo substituted isatin derivative, excellent yield of the corresponding product was observed. However, enantiomeric ratio of the product was low (Table 3.4, **3-3c**). Substituents on the 6-position of isatin derivatives were also tolerated. 6-chloro and 6-bromoisatin derivatives reacted with benzofuranyl ester **3-1a** to afford corresponding products with high yields, moderate e.r. and dr values. Isatins that contained halogens and methyl group on the 7-position, were also worked in the optimized condition to furnish corresponding 3,3'-disubstituted benzofuran-2(*3H*)-one derivatives with good yields, moderate e.r. and dr values (Table 3.4, **3-3i** to **3-3l**). It's worth to note that product **3-3i** bearing with fluorine at 7-position of the isatin moiety, was formed in better e.r. (97:3 e.r) and moderate yield. After achieving several substrates bearing with different substituents on the isatin moiety, it showed substitution pattern on the isatin ring in most of the substrates have little influence on yields, enantioselectivities, and diastereoselctivities.

3.2.3 Optimization of Reaction with 3-I as NHC precatalyst

Further, we optimized the reaction using **3-I** as a NHC precatalyst. We then found that when precatalyst **3-I** was used, the product **3-3a** was generated in good yield, diastereo- and enantio-selectivity in THF as the solvent with DIEA as the base in the presence of 4Å MS (Table 3.5, entry 1) Subsequently, the assessment of bases revealed that the weak organic base DIEA was the best (Table 3.5, entries 2-4). During the screening of solvents (Table 3.5, entries 5-6), we found that the MTBE could almost completely suppress the Black rearrangement and **3-3a** was formed in excellent yield and good diastereo- and enantio-selectivity (Table 3.5, entry

6). To our delight, when trityl-protected isatin **3-2b** was used, the product **3-4b** was obtained in excellent yield, diastereo- and enantio-selectivity (>20:1 dr and 98:2 er, Table 3.5, entry 7). Notably, Decreasing the amount of catalyst loading to 5 mol% could also give almost the same results (Table 3.5, entry 8).

Table 3.5 Optimization of reaction using 3-I NHC precatalyst[a]



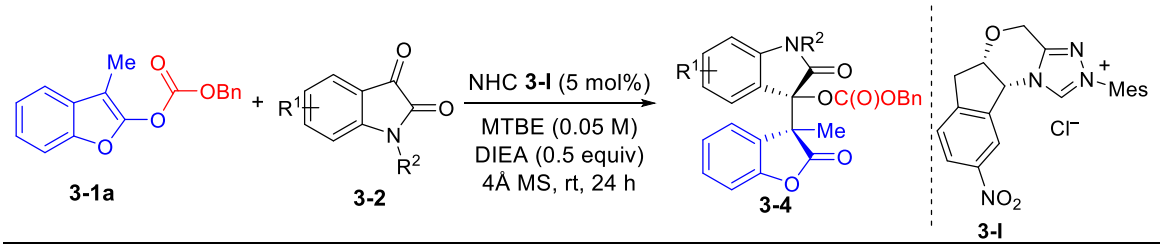
Entry	NHC	Base	Solvent	Yield(%)[b]	dr[c]	er[d]
1	3-D	DIEA	THF	81	9:1	92:8
2	3-D	Cs_2CO_3	THF	65	9:1	88:12
3	3-D	K_2CO_3	THF	68	8:1	89:11
4	3-D	DBU	THF	66	9:1	88:12
5	3-D	DIEA	CH_2Cl_2	70	9:1	90:10
6	3-D	DIEA	MTBE	90	12:1	92:8
7[e]	3-D	DIEA	MTBE	95	>20:1	98:2
8[e,f]	**3-D**	**DIEA**	**MTBE**	**94 (92)**	**>20:1**	**98:2**

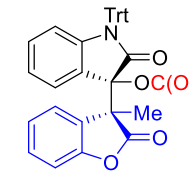
[a]Reaction conditions: 3-1a (0.1 mmol), 3-2a (0.15 mmol), base (0.5 equiv), NHC (20 mol%), and 4Å MS (100 mg) in solvent (2.0 mL) at rt. [b]The yields were determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal standard as the internal standard. The data in parenthesis is isolated yield. [c]The dr were determined by ^{1}H NMR analysis of crude product. [d] Enantiomeric ratio was determined via chiral HPLC [e]Substrate 3-2b was used. [f]5 mol% of catalyst loading.

3.2.4 Substrate scope with *N*-protected isatins

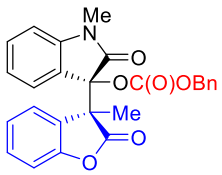
With the optimal reaction conditions in hand, we set out to explore the generality of this protocol. First, the scope of isatins **3-2** was examined (Table 3.6). Replacing the protecting group of isatin with methyl group, the product **3-4c** was obtained in lower stereoselectivity.

Table 3.6 Scope of isatins[a]

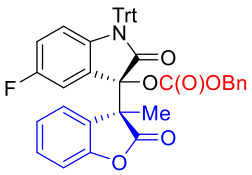




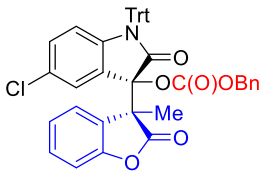
3-4b, 92%
98:2 er, > 20:1 dr



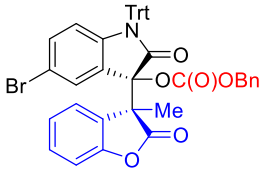
3-4c,[b] 86%
93:7 er, 10:1 dr



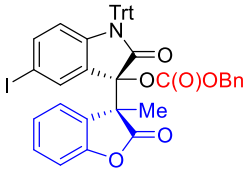
3-4d, 90%
98:2 er, > 20:1 dr



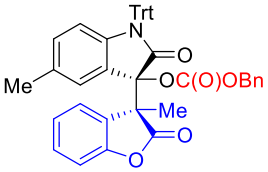
3-4e, 87%
98:2 er, 15:1 dr



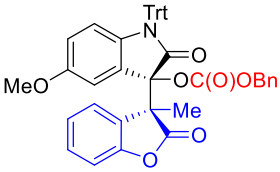
3-4f, 89%
97:3 er, 15:1 dr



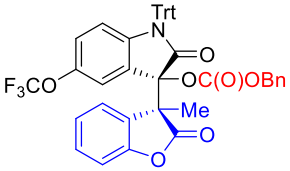
3-4g, 88%
98:2 er, 15:1 dr



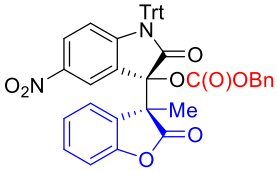
3-4h, 90%
98:2 er, 15:1 dr



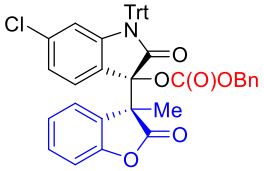
3-4i, 92%
98:2 er, > 20:1 dr



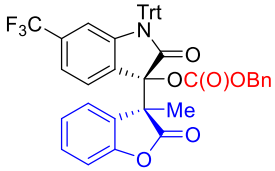
3-4j, 92%
98:2 er, 15:1 dr



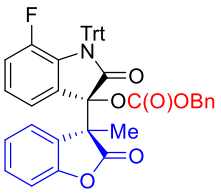
3-4k, 90%
96:4 er, 15:1 dr



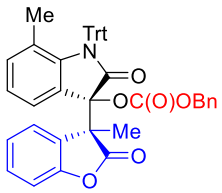
3-4l, 90%
97:3 er, > 20:1 dr



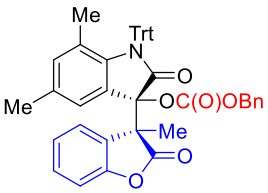
3-4m,[b] 87%
97:3 er, 15:1 dr



3-4n, 90%
98:2 er, > 20:1 dr



3-4o, 90%
97:3 er, > 20:1 dr



3-4p, 82%
97:3 er, > 20:1 dr

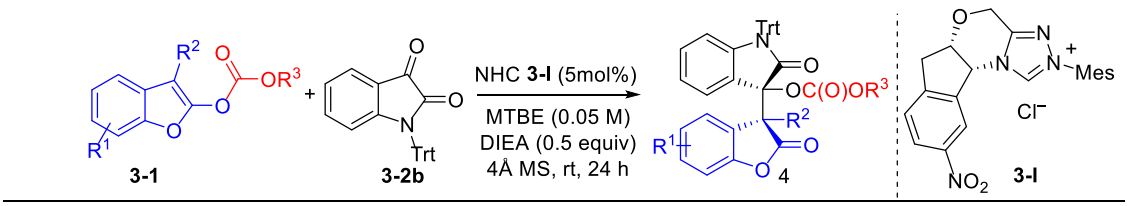
[a] Reaction conditions: 1a (0.1 mmol), 2 (0.15 mmol), DIEA (0.5 equiv), and NHC (5 mol%) in MTBE (2.0 mL) at rt for 24 h. [b]Reaction was performed at rt for 48 h.

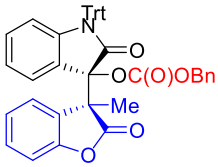
Both electron-donating and electron-withdrawing substituents were all-tolerated at the 5-position of trityl-protected isatin (**3-4d** to **3-4k**). Introducing chloride atom or trifluoromethyl group at the 6-position of isatin, both products **3-4l** and **3-4m** were accessed in high yields with excellent diastereo- and enantio-selectivities. Isatin with fluoride atom and methyl group at 7-position furnished the corresponding products **3-4n** and **3-4o** in similar results. Besides, 5,7-dimethyl substituted isatin gave the desired product **3-4p** in 82% yield with 97:3 er and >20:1 dr value. Notably, the Black rearrangement could be completely suppressed in all the above reaction systems.

3.2.5 Substrate scope with *O*-acylated benzofurans

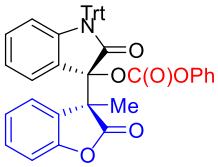
Next, we turned our attention to examine the scope of *O*-acylated benzofurans **3-1** with isatin **3-2b** as the model substrate. The results are summarized in Table 3.6. The protecting group (R^3) of compound **3-1** was first investigated. The incorporation of benzyl group gave the desired product **3-4q** with similar result to **3-4b**. Replacing the protecting group with ethyl group, the product **3-4r** was produced in excellent diastereo- and enantio-selectivity, albeit with 45% isolated yield (82% brsm). Substrates bearing different alkyl substituents at the 3-position gave the corresponding products **3-4s** to **3-4u** in good yields with high er and dr values. Various substituents were all tolerated at the 5-position, regardless of their steric hindrance (**3-4v** to **3-4z**). Installing a methyl or methoxy group at the 6-position, both products **3-4aa** and **3-4ab** were isolated in good results. When 7-isopropyl substituted O-acylated benzofurans was employed, the desired product **3-4ac** was generated in 95% yield with 96:4 er and >20:1 dr. Substrates possessing naphthyl groups were found to provide extremely good results as well (**3-4ad** and **3-4ae**). However, benzofuran with phenyl group at 3-position and oxindole-derived vinylic carbonate gave trace amount of desired products (**3-4af** and **3-4ag**).

Table 3.6 Scope of O-acylated benzofurans [a]

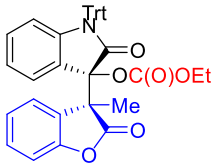




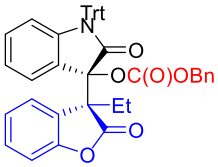
3-4b, 92%
98:2 er, > 20:1 dr



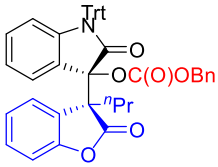
3-4q, 89%
98:2 er, > 20:1 dr



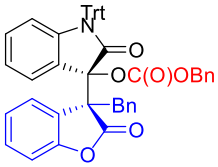
3-4r,[b] 45% (84% brsm)
98:2 er, 15:1 dr



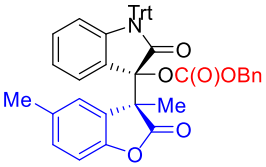
3-4s, 95%
98:2 er, > 20:1 dr



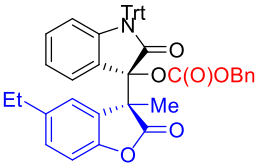
3-4t, 93%
97:3 er, > 20:1 dr



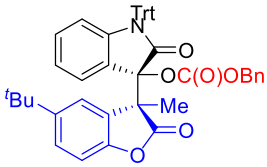
3-4u,[c] 75%
99:1 er, > 20:1 dr



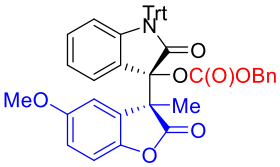
3-4v, 95%
98:2 er, > 20:1 dr



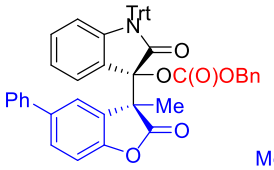
3-4w, 98%
97:3 er, > 20:1 dr



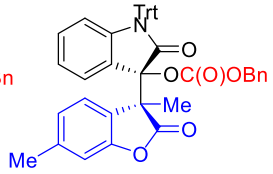
3-4x, 95%
97:3 er, > 20:1 dr



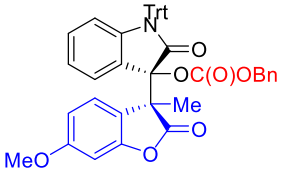
3-4y, 90%
98:2 er, > 20:1 dr



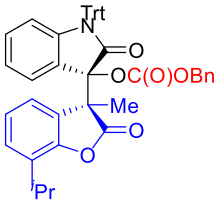
3-4z, 97%
98:2 er, > 20:1 dr



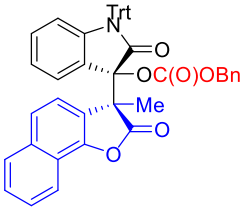
3-4aa, 96%
98:2 er, > 20:1 dr



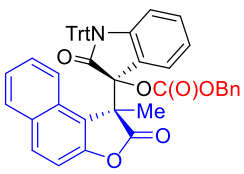
3-4ab, 91%
96:4 er, > 20:1 dr



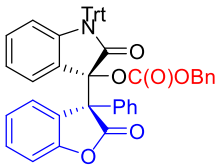
3-4ac, 95%
96:4 er, > 20:1 dr



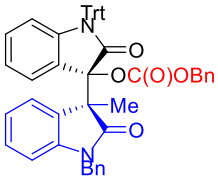
3-4ad, 97%
98:2 er, > 20:1 dr



3-4ae, 94%
99:1 er, > 20:1 dr



3-4af, trace

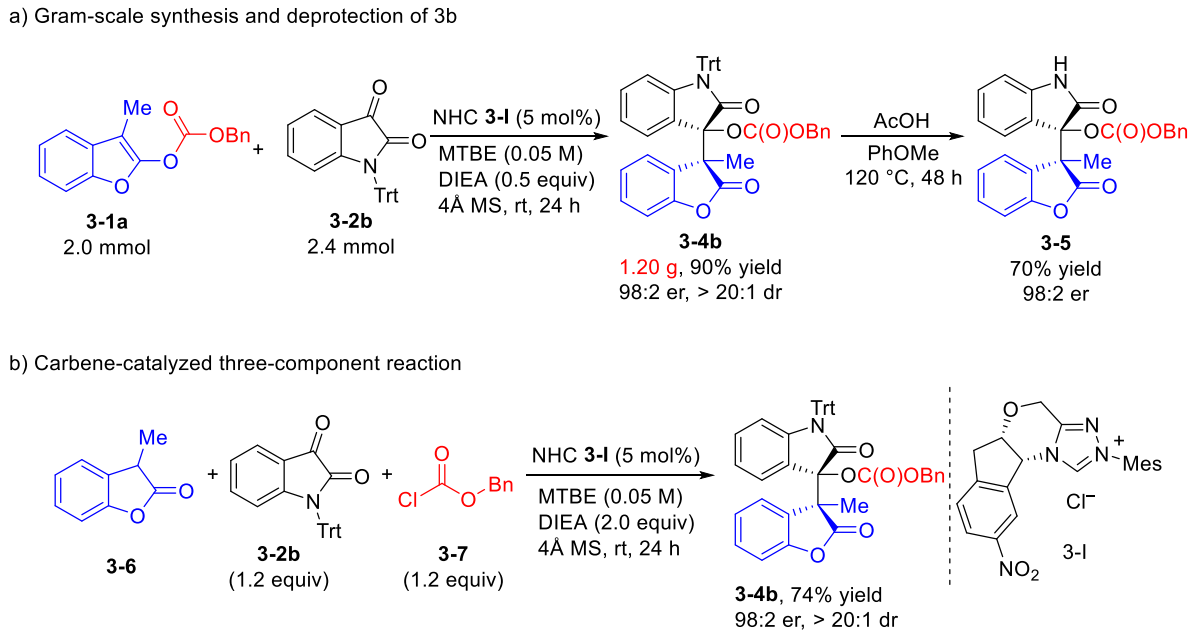


3-4ag, trace

[a]Reaction conditions: 1 (0.1 mmol), 2b (0.15 mmol), DIEA (0.5 equiv), and NHC (5 mol%) in MTBE (2.0 mL) at rt for 24 h. [b]Reaction was performed at rt for 48 h. [c]Reaction was performed at rt for 36 h.

3.2.6 Practical utilities of our new strategy

To evaluate the practicality of this carbene-catalyzed DKR process, a scale-up reaction was carried out. Treatment of **3-1a** (2.0 mmol) and **3-2b** (2.4 mmol) under the previous optimal conditions, 1.20 g of chiral product **3-4b** was isolated with similar results to the small-scale case. The trityl protecting group on **3-4b** could be effectively removed by acetic acid to form compound **3-5** in satisfactory yield with complete retention of enantiomeric purity (**Scheme 3.3a**). Besides, we found that the carbene catalyst **3-I** could also promote the three-component enantioselective reaction of 3-methylbenzofuran-2(*3H*)-one **3-6**, isatin **3-2b** and benzyl chloroformate **3-7**, which provided the product **3-4b** in 74% yield with 98:2 er and >20:1 dr value. (**Scheme 3.3b**).

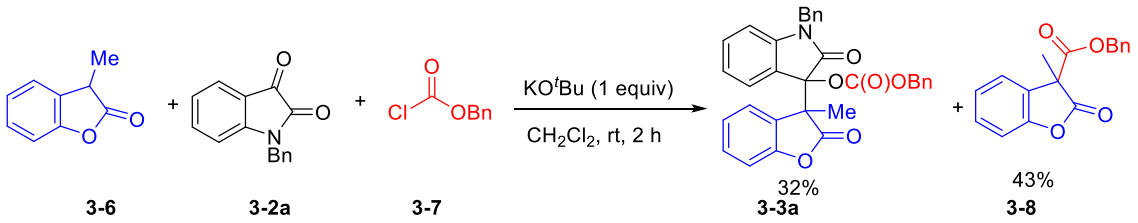


Scheme 3.3 Practical utilities of our new strategy

3.2.7 Mechanism study

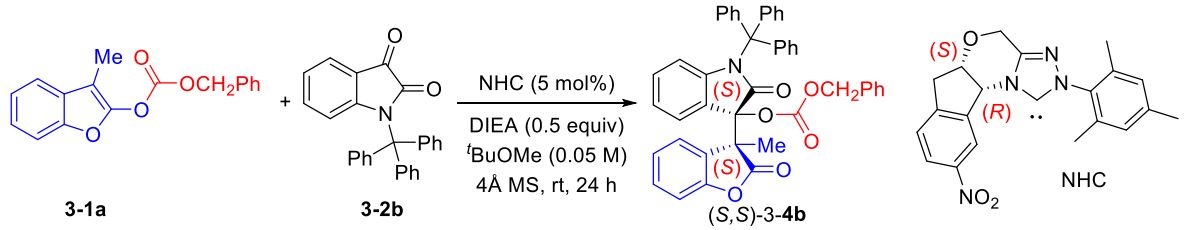
To study the mechanism, a control experiment was performed. Without NHC catalyst 3-component reaction was tested. 3-methylbenzofuran-2(*3H*)-one **3-6** reacted with isatin derivative **3-2a** in presence of benzyl chloroformate **3-7** to afford the desired product **3-3a** along with black rearrangement product **3-8** (**Scheme 3.4**). Therefore, from this experiment, it

is concluded that intermolecular aldol reaction occurred between benzofuranone derivative and isatin to form the corresponding alcohol, that reacts with benzyl chloroformate to furnish the desired product **3-3a**. In addition, the enolate that generated from benzofuranone derivative **3-6** reacts with benzyl chloroformate to afford the black rearrangement product **3-8**.

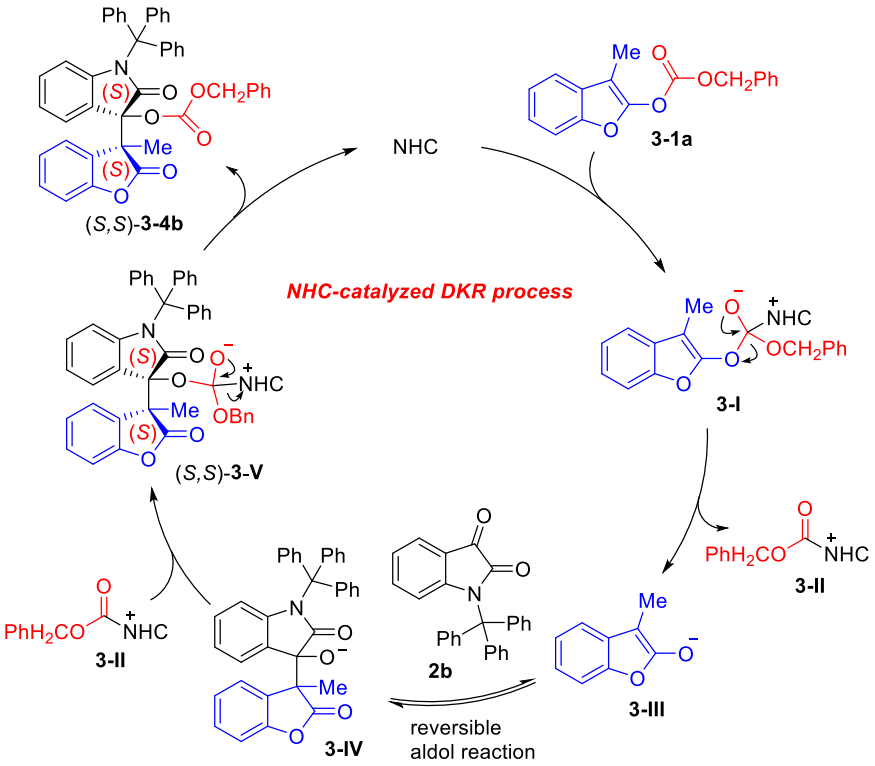


Scheme 3.3 Control experiment

Based on the control experiment, we have demonstrated the plausible mechanism of the reaction (**Figure 3.3)**. Initially, in the presence of base free NHC was generated then addition



proposed reaction mechanism:



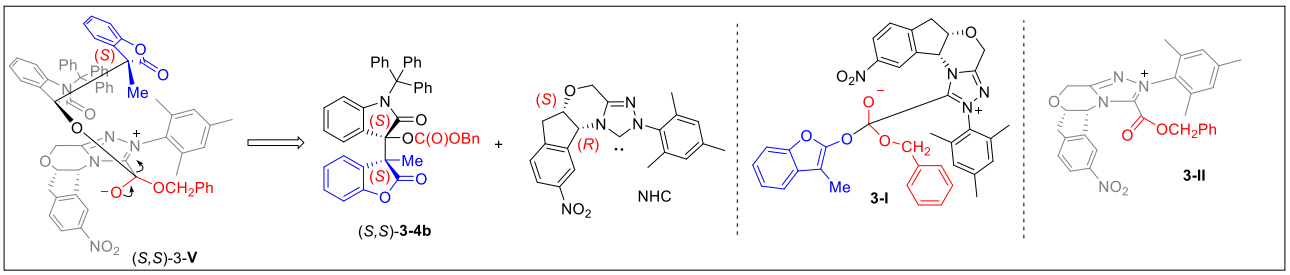


Figure 3.3 Proposed mechanism

of NHC to benzofuranyl carbonate **3-1a,** leading to formation of NHC-bound tetrahedral intermediate **3-I** which undergoes elimination reaction to furnish azolium carbonate intermediate **3-II** and enolate intermediate **3-III**. Enolate intermediate **3-III** undergoes reversible aldol reaction with isatin derivative, leading to formation of corresponding aldol ion **3-IV** in the racemic form, which reacts with chiral NHC-bound azolium carbonate **3-II** to furnish intermediate (*S*,*S*)-**3-V** which leads to corresponding carbonate (*S*,*S*)-**3-4b** in enantiopure form with the regeneration of NHC catalyst. The product was formed with (*S*,*S*) absolute configuration, based on this, a proposed transition state was shown in **Figure 3.4**.

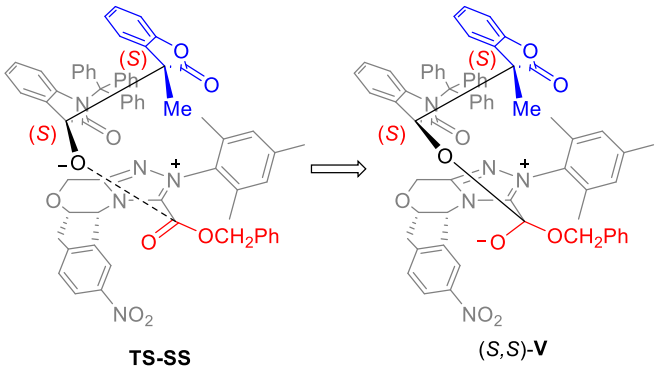


Figure 3.4 Proposed transition state

3.3 Conclusion

In summary, we have developed a NHC-catalyzed dynamic kinetic resolution and asymmetric acylation of benzofuranyl carbonate with isatins for the construction of 3,3'-disubstituted benzofuran-2(*3H*)-ones derivatives with vicinal quaternary stereocenters. The NHC catalysts play dual roles in our reactions, one is to activate the benzofuranyl carbonate for aldol reaction with isatin, another is to promote the post-aldol dynamic kinetic resolution

and acylation. Besides, this process represents a novel stereoselective carbon-carbon bond-forming reaction, which is different from traditional Steglich and Black rearrangements. Our study also expands the utility of vinylic esters in asymmetric catalysis and synthesis.

3.4 Experimental section

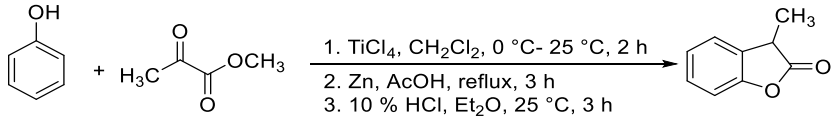
3.4.1 General information

Please refer to Chapter 2, Section 2.4.1

3.4.2 Synthesis of benzofuranyl carbonate:

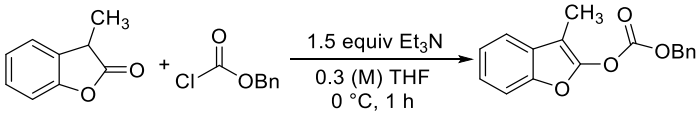
Benzofuranyl carbonate derivative was synthesized by reported procedure via 2-steps.

Step 1: Synthesis of 3-Methylbenzofuran-2(3*H*)-one[44]



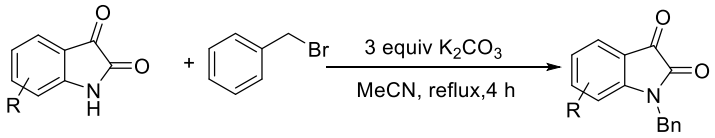
TiCl4 (30 mmol) was added dropwise to a solution of phenol (25 mmol) in DCM (50 mL) at 25 °C in 250 ml round-bottom flask. Then the reaction mixture was cooled to 0 °C and methyl pyruvate (30 mmol) was added slowly and allowed to stir at room temperature for 2 h. Then AcOH (15 mL) and Zn (25 mmol) was then added and the resulting mixture was heated for 3 h at 60 °C. The reaction mixture was filtrated and dried under vacuum. To the resulting residue 10% HCl (15 mL) and Et_2O (15 mL) was added and allowed to stir at room temperature for 3 h. After completing the reaction, the reaction mixture was extracted with EtOAc (25 mL × 3). The whole organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was allowed to dry under vacuum. The resulting residue was then purified by column chromatography, 5:1 hexane/ethyl acetate as eluent to furnish the 3-Methylbenzofuran-2(3*H*)-one as colorless liquid in 32% yield.

Step 2: Synthesis of benzyl (3-methylbenzofuran-2-yl) carbonate[45]



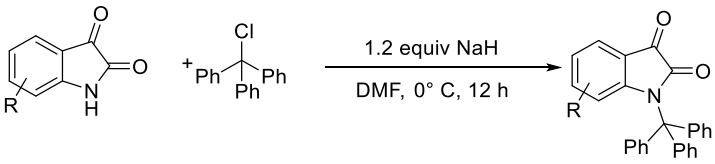
In a 100 ml round-bottom flask, 3-Methylbenzofuran-2(3*H*)-one (10 mmol) and THF was added. Then Et_3N (15 mmol) was added to the solution and allowed to cool at 0 °C. Benzyl chloroformate (15 mmol) was added to the reaction mixture dropwise and allowed to stir the mixture for 1 h at 0 °C. After completing the reaction, reaction mixture was diluted with Et_2O and was quenched by 0.1 M HCl. The organic layer was extracted with Et_2O (20 mL × 3). Combined organic phases were dried over anhydrous Na_2SO_4 and filtered. Et_2O was removed under vacuum and residue was purified by SiO_2 column chromatography utilizing 20:1 hexane/ Et_2O as eluent to give benzyl (3-methylbenzofuran-2-yl) carbonate as white solid in 85% yield.

3.4.3 General Procedure: Synthesis of *N*-benzyl protected isatin derivatives[46]



Isatin derivative (10 mmol) and K_2CO_3 was placed in a 100 ml round-bottom flask. Then acetonitrile (50 ml) was added to the mixture. Benzyl bromide (12 mmol) was then added to the reaction mixture and was allowed to reflux for 4 h. After completion of the reaction, the mixture was allowed to cool to room temperature and remove the acetonitrile under vacuum. Resulting residue was extracted with EtOAc (25 mL × 3) and dried over anhydrous Na_2SO_4. Ethyl acetate was removed by vacuum and resulting residue was purified by SiO_2 column chromatography utilizing 2:1 hexane/ethyl acetate as eluent to afford the corresponding N-benzyl protected isatin derivatives in 85-99% yields.

3.4.4 General Procedure: Synthesis of *N*-trityl protected isatin derivatives[47]

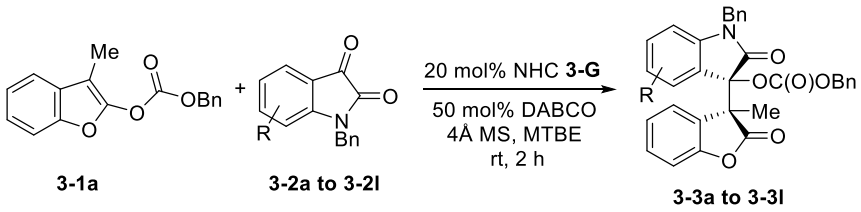


Isatin derivative (1.0 equiv.) was placed in a dry round-bottom flask. Then in N,N-dimethylformamide was added and solution was cooled to 0 °C. Sodium hydride (60%

dispersion in mineral oil, 1.2 equiv.) was added and allowed to stir 15 minutes at 0 °C. Then triphenylmethyl chloride (1.2 equiv.) was added slowly, and the resulting brown solution was allowed to stir at 0 °C for 12 h. Ice-cooled water was added to the reaction mixture, and a precipitate formed. The precipitate was filtered, washed with water and hexane. The resulting solid was dried and dissolved in DCM purified by SiO_2 column chromatography utilizing 1:1:0.1 hexane/ethyl acetate/DCM as eluent to afford the corresponding N-Trityl protected isatin derivatives in 80-95% yields.

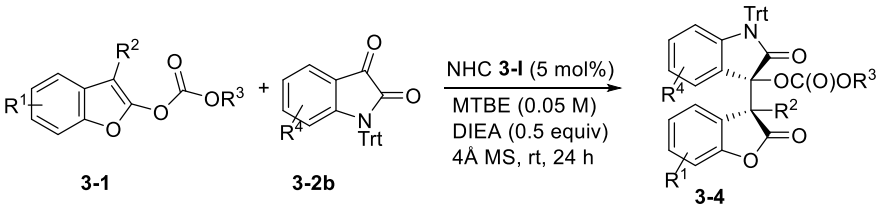
3.4.5 General Procedure: Asymmetric Synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-ones

Synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-ones with catalyst 3-G:



NHC **3-G** (8.4 mg, 20 mol%), isatin derivatives (0.1 mmol, 1 equiv), benzyl (3-methylbenzofuran-2-yl) carbonate **3-1a** (33.8 mg, 0.12 mmol, 1.2 equiv) and 50 mg 4Ä MS was added in a dry 10 mL Schlenk tube with stir bar. Then DABCO (5.6 mg, 0.05mmol) was added to the reaction mixture. The tube was evacuated and refilled with nitrogen. After that dry MTBE (1 mL) was added. The resulting mixture was allowed to stir for 2 h at room temperature. The completion of the reaction monitored by TLC. After completion of the reaction, reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel with DCM/Hexane/EtOAc (25:25:1) as eluent to afford the corresponding 3,3'-disubstituted benzofuran-2(*3H*)-ones (**3-3a** to **3-3l**). Two diastereomers were separated by same eluent. The product was confirmed by ^{1}H NMR, ^{13}C NMR spectra. The enantiomeric ratio(e.r.) of major diastereomer was determined by chiral HPLC and diastereomeric ratio(dr) was determined by ^{1}H NMR analysis of crude product.

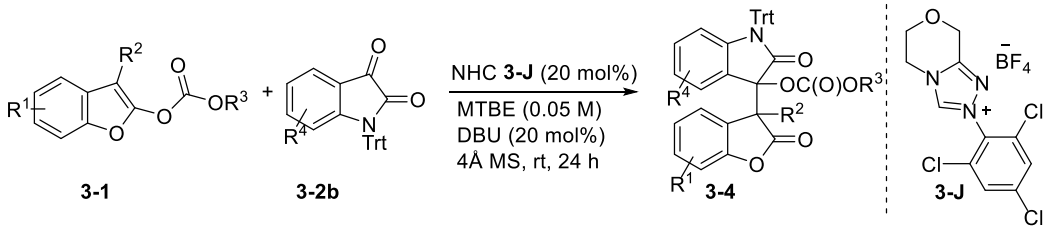
General procedure: Synthesis of 3,3'-disubstituted benzofuran-2(*3H*)-ones with catalyst 3-I:



To a dried 4 mL test tube with a stir bar was added the carbene catalyst (5 mol %), benzofuranyl carbonate (0.1 mmol), isatins (1.5 or 1.2 equiv), anhydrous MTBE (2.0 mL) and DIEA (9 uL, 0.5 equiv). The reaction mixture was stirred at rt for the time indicated in the table, then directly subjected to the preparative thin layer chromatography (Hexane/DCM/EA = 40:20:1 or Hexane/EA = 3:1).

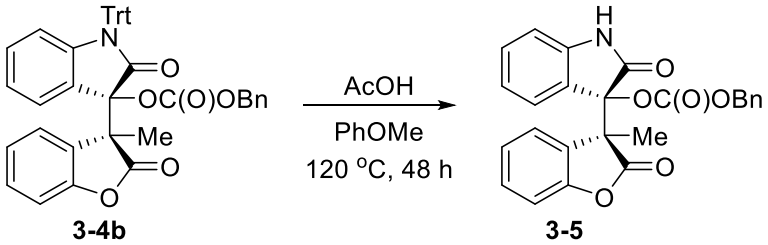
Synthesis of racemic compounds:

All the racemic compounds were synthesized using **3-J** as a NHC precatalyst in the presence of DBU as a base and MTBE as a solvent (**Scheme 3.4**).



Scheme 3.4 Synthesis of racemic compounds

3.4.6 General procedure: Synthetic transformation



To a dried 10 mL test tube with a stir bar was added compound **3a** (0.1 mmol, 67.2 mg), AcOH (2.0 mL) and PhOMe (0.5 mL). The reaction mixture was stirred at 120 °C for 48 h. Then yellow solution was concentrated and directly subjected to the preparative thin layer

chromatography (Hexane/EA = 3:1) to give the desired product **7** (70% yield, 98:2 er) as a slightly yellow oil.

3.4.7 Crystal Structure determination of 3-4e

The product **3-4e** was recrystallize via vaporization of MTBE solvent, colourless crystal was observed, and absolute configuration was determined by X-Ray structure analysis. (**Figure 3.5**) Supplementary information of the crystal is available under CCDC number1989499, which could be accessible at free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk

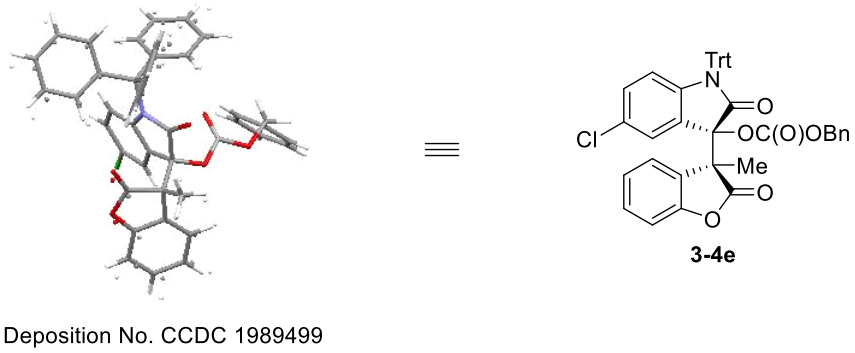
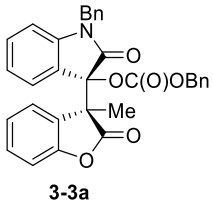


Figure 3.5 X-ray crystal structure of 3-4e

3.4.8 Characteristization of products



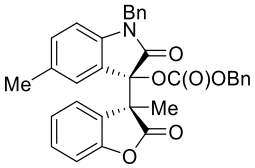
benzyl ((S)-1-benzyl-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3a):

white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dt, J = 4.5, 3.6 Hz, 4H), 7.34 – 7.27 (m, 5H), 7.24 (m, 4H), 7.15 (t, J = 7.2 Hz, 2H), 7.01 (d, J = 8.0 Hz, 1H), 6.72 (t, J = 7.5 Hz, 1H), 6.55 (d, J = 7.8 Hz, 1H), 5.13 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 4.88 (s, 2H), 1.94 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3, 171.1, 153.1, 152.2, 144.1, 135.2, 134.4, 131.1,

129.9, 128.7, 128.7, 128.6, 128.4, 127.4, 127.2, 125.6, 124.4, 123.7, 123.2, 122.3, 110.8, 109.9, 81.0, 70.5, 44.6, 17.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{32}H_{25}NO_6H^+$ 520.1755$(M+H)^+$, found 520.1750.

HPLC analysis: 90:10 e.r. (Chiralcel IA, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 19.4 min, R_t (minor) = 24.9 min.



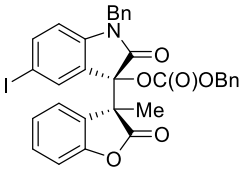
3-3b

benzyl ((S)-1-benzyl-5-methyl-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3b):

white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.34 – 7.26 (m, 5H), 7.23 (d, *J* = 2.7 Hz, 4H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.85 (d, *J* = 6.4 Hz, 2H), 2.02 (s, 3H), 1.94 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3, 171.0, 153.2, 152.2, 141.7, 135.3, 134.5, 131.8, 131.4, 129.8, 128.7, 128.6, 128.6, 128.4, 127.4, 127.2, 125.7, 124.6, 124.3, 123.2, 110.6, 109.6, 81.3, 70.4, 44.6, 20.8, 17.4 ppm.

HRMS (ESI, m/z): calcd. for $C_{33}H_{27}NO_6H^+$ 534.1911$(M+H)^+$, found 534.1912.

HPLC analysis: 90:10 e.r. (Chiralcel IB, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 12.7 min, R_t (minor) = 12.2 min.



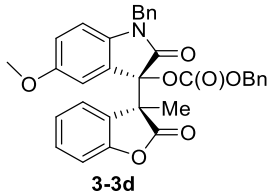
3-3c

benzyl ((S)-1-benzyl-5-iodo-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3c):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 5H), 7.38 (t, J = 5.8 Hz, 2H), 7.36 – 7.30 (m, 3H), 7.30 – 7.19 (m, 5H), 7.06 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 8.3 Hz, 1H), 5.16 (d, J = 12.0 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 4.94 (d, J = 16.0 Hz, 1H), 4.81 (d, J = 16.0 Hz, 1H), 1.93 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 170.4, 153.1, 152.1, 143.6, 139.7, 134.7, 134.2, 132.5, 130.2, 128.8, 128.7, 128.6, 128.4, 127.6, 127.2, 125.6, 124.6, 111.8, 110.8, 84.5, 80.6, 70.7, 44.6, 16.9.

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}INO_6H^+$ 646.0721$(M+H)^+$, found 646.0727.

HPLC analysis: 76:24 e.r. (Chiralcel IA, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 17.4 min, R_t (minor) = 15.4 min.



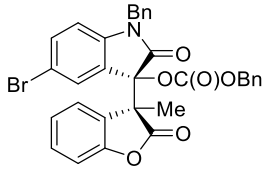
3-3d

benzyl ((S)-1-benzyl-5-methoxy-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3d):

white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (ddd, J = 9.9, 3.9, 2.0 Hz, 4H), 7.34 – 7.27 (m, 5H), 7.24 (m, 4H), 7.18 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.67 (dd, J = 8.6, 2.6 Hz, 1H), 6.44 (d, J = 8.6 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 4.92 – 4.80 (m, 2H), 3.43 (s, 3H), 1.95 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3, 170.8, 155.3, 153.2, 152.1, 152.1, 137.4, 135.3, 134.5, 129.9, 128.7, 128.7, 128.6, 128.4, 128.2, 127.4, 127.3, 125.7, 124.4, 124.2, 116.1, 110.8, 110.4, 81.1, 70.5, 55.4, 44.7, 17.4 ppm

HRMS (ESI, m/z): calcd. for $C_{33}H_{27}NO_7H^+$ 550.1860$(M+H)^+$, found 550.1866.

HPLC analysis: 90:10 e.r. (Chiralcel IB, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 13.8 min, R_t (minor) = 13.3 min.



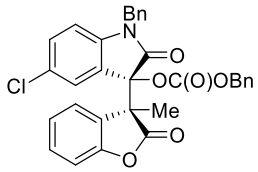
3-3e

benzyl ((S)-1-benzyl-5-bromo-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3e):

off white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 5H), 7.36 – 7.30 (m, 4H), 7.30 – 7.26 (m, 4H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 4.94 (d, *J* = 16.0 Hz, 1H), 4.83 (d, *J* = 16.0 Hz, 1H), 1.94 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 170.5, 153.2, 152.0, 143.0, 134.6, 134.2, 133.7, 130.3, 128.8, 128.8, 128.7, 128.4, 127.7, 127.6, 127.2, 126.9, 125.6, 125.1, 124.6, 114.9, 111.3, 110.9, 80.7, 70.7, 44.7, 17.1 ppm.

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}BrNO_6H^+$ 598.0866$(M+H)^+$, found 598.0863.

HPLC analysis: 83:17 e.r. (Chiralcel IA, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 16.1 min, R_t (minor) = 14.7 min.



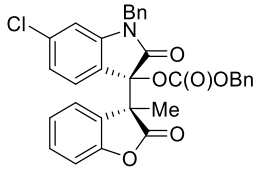
3-3f

benzyl ((S)-1-benzyl-5-chloro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3f):

white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 5H), 7.35 – 7.31 (m, 4H), 7.30 – 7.26 (m, 4H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 4.93 (d, *J* = 16.0 Hz, 1H), 4.84 (d, *J* = 16.0 Hz, 1H), 1.94 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1, 170.6, 153.1, 152.4, 142.6, 142.2, 134.8, 134.6, 134.3, 130.9, 130.3, 128.8, 128.8, 128.7, 128.4, 127.7, 127.6, 127.2, 125.6, 124.6, 124.2, 110.9, 110.8, 80.7, 70.7, 44.7, 17.2 ppm

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}ClNO_6H^+$ 554.1365$(M+H)^+$, found 554.1370.

HPLC analysis: 33:67 e.r. (Chiralcel IA, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 15.8 min, R_t (minor) = 14.7 min.



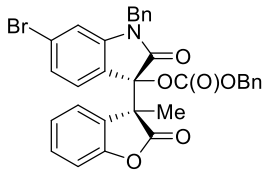
3-3g

benzyl ((S)-1-benzyl-6-chloro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3g):

white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 5H), 7.34 – 7.31 (m, 4H), 7.29 (dd, *J* = 7.7, 5.0 Hz, 4H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 1.8 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 16.5 Hz, 1H), 4.84 (d, *J* = 16.5 Hz, 1H), 1.93 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2, 171.0, 153.1, 152.1, 145.4, 137.2, 134.6, 134.3, 130.1, 128.8, 128.7, 128.5, 128.0, 127.7, 127.2, 125.7, 124.6, 124.5, 122.3, 121.7, 110.9, 110.5, 80.5, 70.7, 44.8, 17.4 ppm.

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}ClNO_6H^+$ 554.1365$(M+H)^+$, found 554.1371.

HPLC analysis: 85:15 e.r. (Chiralcel IA, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 15.9 min, R_t (minor) = 13.3 min.



3-3h

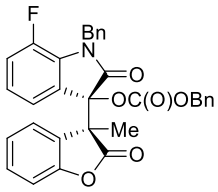
benzyl (1-benzyl-6-bromo-3-(3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate(3-3h):

white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 5H), 7.33 (dd, *J* = 5.2, 2.1 Hz, 4H), 7.31 – 7.26 (m, 4H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 1.6 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.93 – 4.81 (m,

2H), 1.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 170.4, 153.1, 152.0, 143.0, 134.5, 134.2, 133.6, 130.2, 128.7, 128.7, 128.6, 128.3, 127.6, 127.5, 127.1, 126.9, 125.6, 125.1, 124.2, 114.8, 111.2, 110.8, 80.6, 70.6, 44.6, 17.0 ppm.

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}BrNO_6H^+$ 598.0866$(M+H)^+$, found 598.0861.

HPLC analysis: 83:17 e.r. (Chiralcel IA, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 14.7 min, R_t (minor) = 12.8 min.



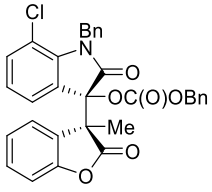
3-3i

benzyl ((S)-1-benzyl-7-fluoro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3i):

pale yellow solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 5H), 7.31 (dd, J = 5.6, 3.7 Hz, 4H), 7.27 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 10.1 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 11.0, 8.7 Hz, 1H), 6.71 – 6.64 (m, 1H), 5.13 (d, J = 12.0 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 5.02 (d, J = 12.0 Hz, 1H), 4.92 (d, J = 15.6 Hz, 1H), 1.91 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.1, 170.8, 153.0, 152.1, 148.2, 146.2, 136.4, 134.3, 130.8, 130.1, 128.8, 128.6, 128.4, 128.3, 127.3, 127.3, 126.2, 125.5, 124.5, 123.0, 122.9, 119.6, 119.4, 110.8, 80.8, 70.6, 46.0, 46.0, 17.5 ppm.

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}FNO_6H^+$ 538.1660$(M+H)^+$, found 538.1663.

HPLC analysis: 97:3 e.r. (Chiralcel IA, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 16.4 min, R_t (minor) = 14.8 min.



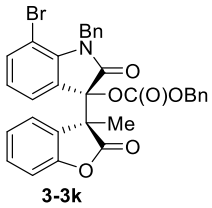
3-3j

benzyl ((S)-1-benzyl-7-chloro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3j):

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 5H), 7.34 – 7.27 (m, 5H), 7.25 – 7.20 (m, 4H), 7.17 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.66 (t, *J* = 7.8 Hz, 1H), 5.30 (d, *J* = 16.6 Hz, 1H), 5.21 (d, *J* = 16.6 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 1.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1, 171.8, 153.1, 152.1, 140.4, 137.41, 134.3, 133.7, 130.2, 128.8, 128.7, 128.4, 128.3, 127.8, 126.8, 126.4, 126.3, 125.6, 124.5, 123.0, 122.1, 116.0, 110.9, 80.3, 70.7, 45.9, 17.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}ClNO_6H^+$ 554.1365$(M+H)^+$, found 554.1362.

HPLC analysis: 28:72 e.r. (Chiralcel IB, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 11.9 min, R_t (minor) = 11.4 min.



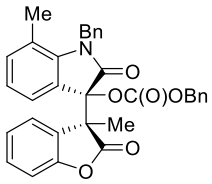
3-3k

benzyl ((S)-1-benzyl-7-bromo-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3k):

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 5H), 7.34 – 7.27 (m, 5H), 7.24 (m, 4H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.60 (t, *J* = 7.8 Hz, 1H), 5.29 (s, 2H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.06 (d, *J* = 12.0 Hz, 1H), 1.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1, 172.0, 153.1, 152.1, 141.9, 137.4, 137.1, 134.3, 130.2, 128.8, 128.7, 128.4, 128.3, 127.7, 126.7, 126.6, 126.3, 125.7, 124.5, 123.3, 122.6, 110.9, 102.9, 80.2, 70.7, 45.7, 17.6 ppm.

HRMS (ESI, m/z): calcd. for $C_{32}H_{24}BrNO_6H^+$ 598.0866$(M+H)^+$, found 598.0863.

HPLC analysis: 88:12 e.r. (Chiralcel IB, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 12.4 min, R_t (minor) = 11.7 min.



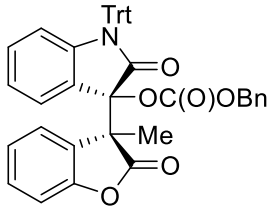
3-3l

benzyl ((S)-1-benzyl-7-methyl-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-3l):

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 5H), 7.34 – 7.31 (m, 3H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.20 (dt, *J* = 15.2, 7.3 Hz, 4H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.65 (t, *J* = 7.5 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 5.01 (d, *J* = 17.1 Hz, 2H), 2.13 (s, 3H), 1.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.4, 172.3, 153.2, 152.2, 142.3, 137.6, 135.1, 134.5, 129.9, 128.7, 128.6, 128.4, 128.2, 126.9, 125.9, 125.7, 124.3, 124.2, 122.2, 121.5, 120.4, 110.7, 80.6, 70.4, 46.1, 18.7, 17.7 ppm.

HRMS (ESI, m/z): calcd. for $C_{33}H_{27}NO_6H^+$ 534.1911$(M+H)^+$, found 534.1918.

HPLC analysis: 87:13 e.r. (Chiralcel IB, 20:80 *i*-PrOH/Hexane, 0.5 mL/min), R_t (major) = 13.5 min, R_t (minor) = 12.1 min



3-4b

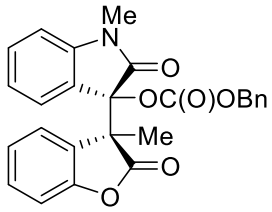
Benzyl ((S)-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4b): yellow solid, 61.7 mg, 92% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.12 (m, 23H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.9 Hz, 1H), 6.59 (t, *J* = 6.7 Hz, 1H), 6.42 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 1.87 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.2, 153.2, 151.7, 144.5, 141.7, 134.8, 130.0, 129.6, 129.4, 128.6, 128.2, 128.0, 127.4, 127.3, 126.7, 126.4, 124.6, 124.3, 122.7, 121.9, 116.1, 110.6, 80.6, 75.7, 69.9, 53.4, 18.2;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 672.2381, found: 672.2381;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 14.1 min, t_{major} = 16.2 min), $[\alpha]_D^{25}$ = –23.12 (c = 1.0, $CHCl_3$).



3-4c

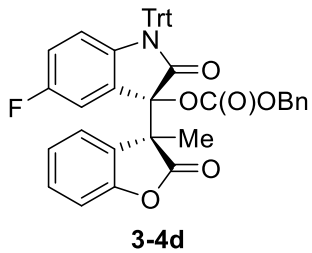
Benzyl ((S)-1-methyl-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxoindolin-3-yl) carbonate (3-4c): slightly yellow oil, 38.1 mg, 86% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 5.2 Hz, 1H), 7.40 – 7.32 (m, 4H), 7.32 – 7.26 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.07 (d, *J* = 6.6 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 5.01 (d, *J* = 12.0 Hz, 1H), 3.18 (s, 3H), 1.90 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 170.8, 153.1, 152.2, 144.7, 134.4, 131.3, 129.9, 128.8, 128.6, 128.4 (2C), 125.7, 124.4, 123.5, 123.3, 122.1, 110.7, 108.6, 81.0, 70.5, 53.3, 26.4, 17.2;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 444.1442, found: 444.1440;

HPLC analysis: 93:7 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 15.9 min, t_{minor} = 21.7 min), $[\alpha]_D^{25}$ = +78.06 (c = 1.0, $CHCl_3$).



3-4d

Benzyl ((S)-5-fluoro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4d): white solid, 62.0 mg, 90% yield

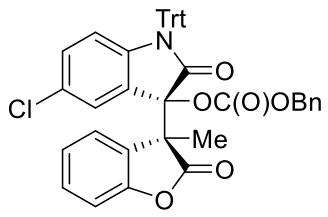
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.13 (m, 23H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.59 (td, *J* = 8.9, 2.8 Hz, 1H), 6.36 (dd, *J* = 9.0, 4.2 Hz, 1H), 5.68 (s, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 1.87 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 172.0, 157.9 (d, *J* = 243.9 Hz), 153.2, 151.7, 141.4, 140.3, 134.6, 130.4, 129.6, 128.7, 128.6, 128.3, 127.9, 127.5, 126.9, 126.4, 125.9 (d, *J* = 7.9 Hz), 124.8, 116.9 (d, *J* = 7.5 Hz), 115.9 (d, *J* = 22.9 Hz), 110.9, 110.7 (d, *J* = 25.7 Hz), 80.4, 76.0, 70.2, 53.5, 18.1;

^{19}F NMR (377 MHz, $CDCl_3$) δ -120.0 (1F);

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 690.2286, found: 690.2288;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 10.7 min, t_{major} = 11.6 min), $[\alpha]_D^{25}$ = –16.76 (c = 1.0, $CHCl_3$).



3-4e

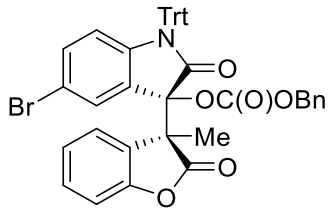
Benzyl ((S)-5-chloro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4e): white solid, 61.4 mg, 87% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.04 (m, 24H), 6.86 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.35 (d, *J* = 8.8 Hz, 1H), 5.87 (s, 1H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 1.87 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 171.8, 153.2, 151.6, 143.0, 141.3, 134.5, 130.3, 129.5, 129.4, 128.7, 128.6, 128.3, 127.8, 127.5 (2C), 126.9, 126.3, 126.0, 124.8, 123.1, 117.0, 110.8, 80.2, 76.0, 70.1, 53.4, 17.9;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 706.1991, found: 706.1993;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 10.4 min, t_{major} = 11.2 min), $[\alpha]_D^{25}$ = –28.60 (c = 1.0, $CHCl_3$).



3-4f

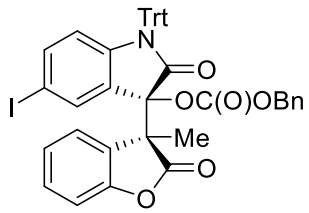
Benzyl ((S)-5-bromo-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4f): white solid, 66.8 mg, 89% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.06 (m, 24H), 7.01 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.30 (d, *J* = 8.7 Hz, 1H), 5.99 (s, 1H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 1.86 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 171.7, 153.2, 151.7, 143.5, 141.3, 134.5, 132.2, 130.3, 129.5, 128.7, 128.6 (2C), 128.3, 127.8, 127.5, 126.9, 126.3, 126.0, 124.8, 117.5, 114.9, 110.8, 80.2, 76.0, 70.2, 53.5, 17.8;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 750.1486, found: 750.1489;

HPLC analysis: 97:3 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 10.3 min, t_{major} = 11.1 min), $[\alpha]_D^{25}$ = –46.98 (c = 1.0, $CHCl_3$).



3-4g

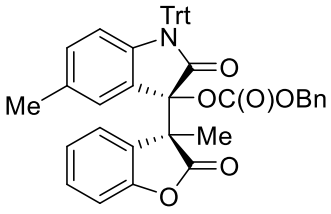
Benzyl ((S)-5-iodo-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4g): yellow solid, 70.2 mg, 88% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 6.96 (m, 25H), 6.17 – 6.12 (m, 2H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 1.86 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 171.5, 153.3, 151.7, 144.3, 141.3, 138.1, 134.6, 134.1, 131.7, 130.3, 129.5, 128.7, 128.6, 128.3, 127.5, 126.9, 126.5, 126.3, 124.8, 117.9, 110.7, 85.0, 80.2, 76.0, 70.2, 53.5, 17.7;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 798.1347, found: 798.1344;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 10.5 min, t_{major} = 11.2 min), $[\alpha]_D^{25}$ = –31.28 (c = 1.0, $CHCl_3$).



3-4h

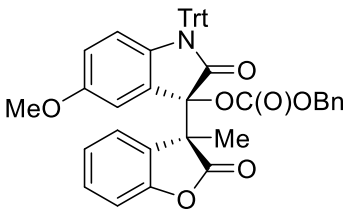
Benzyl ((S)-5-methyl-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4h): white solid, 61.7 mg, 90% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 6.94 (m, 24H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.29 (d, *J* = 8.3 Hz, 1H), 5.78 (s, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.71 (d, *J* = 12.1 Hz, 1H), 1.91 (s, 3H), 1.87 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.2, 153.3, 151.7, 141.9, 141.8, 134.8, 131.4, 130.0, 129.6, 128.6, 128.4, 128.3, 128.0, 127.9, 127.4, 126.7, 126.5, 124.6, 124.3, 123.7, 115.8, 110.5, 80.8, 75.7, 70.0, 53.5, 20.7, 18.1;

HRMS (ESI, m/z): calcd. for $[M+Na]^+$: 708.2357, found: 708.2357;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 14.8 min, t_{major} = 18.2 min), $[\alpha]_D^{25}$ = –57.82 (c = 1.0, $CHCl_3$).



3-4i

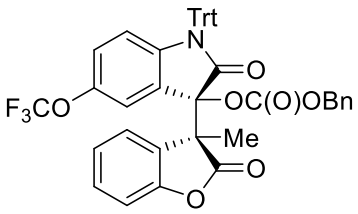
Benzyl ((S)-5-methoxy-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4i): yellow solid, 64.6 mg, 92% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 6.98 (m, 24H), 6.43 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.32 (d, *J* = 8.9 Hz, 1H), 5.54 (s, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.71 (d, *J* = 12.1 Hz, 1H), 3.33 (s, 3H), 1.88 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.0, 154.6, 153.3, 151.7, 141.8, 137.4, 134.8, 130.0, 129.6, 128.6 (2C), 128.4, 128.3, 127.4, 126.7, 126.5, 125.4, 124.6, 116.8, 114.7, 110.7, 109.0, 80.7, 75.7, 70.0, 55.0, 53.6, 18.1;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 702.2486, found: 702.2488;

HPLC analysis: 98:2 er, (CHIRALCEL IA column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 10.1 min, t_{major} = 10.8 min), $[\alpha]_D^{25}$ = –34.12 (c = 1.0, $CHCl_3$).



3-4j

Benzyl ((S)-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-5-(trifluoromethoxy)-1-tritylindolin-3-yl) carbonate (3-4j): yellow solid, 69.5 mg, 92% yield

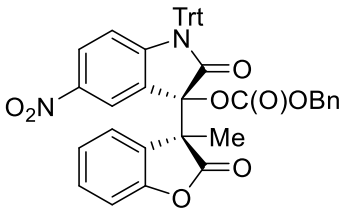
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 6.96 (m, 24H), 6.74 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.42 (d, *J* = 8.9 Hz, 1H), 5.76 (s, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 1.87 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.0, 153.1, 151.7, 143.6, 142.9, 141.3, 134.6, 130.4, 129.6, 128.7, 128.6, 128.3, 127.7, 127.6, 126.9, 126.3, 125.8, 124.9, 122.2, 120.2 (q, *J* = 258.6 Hz), 116.7, 116.0, 110.9, 80.1, 76.2, 70.2, 53.6, 17.9;

^{19}F NMR (377 MHz, $CDCl_3$) δ -58.1 (3F);

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 756.2204, found: 756.2205;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 8.9 min, t_{major} = 9.5 min), $[\alpha]_D^{25}$ = –11.54 (c = 1.0, $CHCl_3$).



3-4k

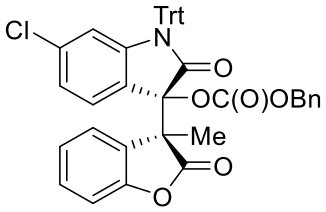
Benzyl ((S)-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-5-nitro-2-oxo-1-tritylindolin-3-yl) carbonate (3-4k): yellow solid, 64.5 mg, 90% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.70 – 7.14 (m, 23H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 6.55 (d, *J* = 9.1 Hz, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 1.89 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.3, 153.0, 151.8, 150.3, 142.3, 140.9, 134.3, 130.8, 129.5, 129.3, 128.9, 128.7, 128.4, 127.7, 127.2, 126.4, 125.7, 125.3, 125.2, 118.4, 115.7, 111.0, 79.6, 77.3, 70.5, 53.7, 17.7;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 717.2231, found: 717.2234;

HPLC analysis: 96:4 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 13.2 min, t_{minor} = 14.3 min), $[\alpha]_D^{25}$ = –44.28 (c = 1.0, $CHCl_3$).



3-4l

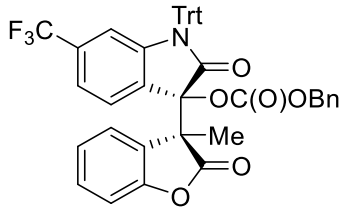
Benzyl ((S)-6-chloro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4l): yellow solid, 63.6 mg, 90% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 6.99 (m, 24H), 6.54 (d, *J* = 7.7 Hz, 1H), 6.39 (d, *J* = 1.7 Hz, 1H), 5.86 (s, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 1.85 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.0, 153.2, 151.8, 150.3, 145.7, 141.3, 135.4, 134.6, 130.3, 129.5, 128.7, 128.6, 128.3, 127.6, 127.0, 126.4, 124.7, 123.4, 122.8, 122.0, 116.7, 110.8, 80.1, 76.2, 70.1, 53.6, 18.1;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 706.1991, found: 706.1992;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 12.6 min, t_{minor} = 13.6 min), $[\alpha]_D^{25}$ = –28.60 (c = 1.0, $CHCl_3$).



3-4m

Benzyl ((S)-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-6-(trifluoromethyl)-1-tritylindolin-3-yl) carbonate (3m): white solid, 64.3 mg, 87% yield

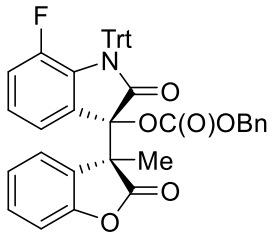
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 6.99 (m, 24H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.62 (s, 1H), 6.03 (s, 1H), 4.94 (d, *J* = 12.1 Hz, 1H), 4.72 (d, *J* = 12.1 Hz, 1H), 1.88 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 172.0, 153.2, 151.7, 145.2, 141.1, 134.5, 134.6, 131.3 (q, *J* = 32.5 Hz), 130.4, 129.6, 129.4, 128.7, 128.6, 128.3, 127.6, 127.0, 126.9, 126.4, 126.2 (q, *J* = 271.2 Hz), 122.7, 118.7 (q, *J* = 4.0 Hz), 113.0 (q, *J* = 4.0 Hz), 110.9, 80.1, 76.4, 70.3, 53.6, 18.2;

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.2 (3F);

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 740.2254, found: 740.2256;

HPLC analysis: 97:3 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 13.0 min, t_{minor} = 14.6 min), $[\alpha]_D^{25}$ = –46.56 (c = 1.0, $CHCl_3$).



3-4n

Benzyl ((S)-7-fluoro-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4n): white solid, 62.0 mg, 90% yield

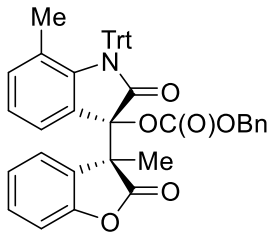
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 6.89 (m, 24H), 6.77 – 6.56 (m, 2H), 5.95 (s, 1H), 5.03 (d, *J* = 12.1 Hz, 1H), 4.86 (d, *J* = 12.1 Hz, 1H), 1.84 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 172.0, 153.3, 151.8, 146.5 (d, *J* = 251.3 Hz), 134.6, 131.8 (d, *J* = 8.8 Hz), 130.3, 129.4, 129.3 (2C), 128.7, 128.6, 128.4, 128.0, 127.2, 126.6, 126.5, 124.7, 123.7 (d, *J* = 7.3 Hz), 120.4 (d, *J* = 24.3 Hz), 119.0, 110.8, 80.3, 76.6, 70.2, 53.5, 18.5;

^{19}F NMR (377 MHz, $CDCl_3$) δ -109.5 (1F);

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 690.2286, found: 690.2285;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 14.3 min, t_{minor} = 15.5 min), $[\alpha]_D^{25}$ = –4.46 (c = 1.0, $CHCl_3$).



3-4o

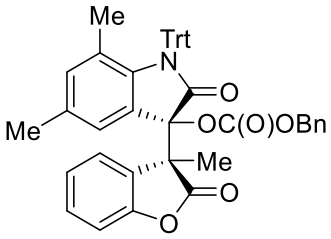
Benzyl ((S)-7-methyl-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4o): yellow solid, 61.7 mg, 90% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 6.92 (m, 24H), 6.80 (d, *J* = 6.9 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.16 (s, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 5.00 (d, *J* = 12.1 Hz, 1H), 1.74 (s, 3H), 1.27 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 172.9, 153.3, 151.9, 146.9, 144.9, 136.6, 134.7, 130.1, 130.0, 128.6, 128.3, 128.2, 127.9 (2C), 127.2, 126.7, 125.0, 124.4, 124.0, 122.6, 121.0, 110.6, 80.0, 76.5, 70.1, 53.5, 23.2, 18.7;

HRMS (ESI, m/z): calcd. for $[M+Na]^+$: 708.2357, found: 708.2355;

HPLC analysis: 97:3 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 14.2 min, t_{minor} = 15.2 min), $[\alpha]_D^{25}$ = +7.94 (c = 1.0, $CHCl_3$).



3-4p

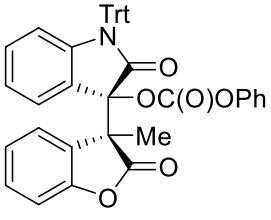
Benzyl ((S)-5,7-dimethyl-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4p): yellow solid, 57.3 mg, 82% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 6.97 (m, 25H), 6.60 (s, 1H), 5.89 (s, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 5.00 (d, *J* = 12.1 Hz, 1H), 1.95 (s, 3H), 1.75 (s, 3H), 1.23 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 172.9, 153.4, 152.0, 146.9, 142.3, 137.1, 134.8, 131.9, 130.1, 129.8, 128.5, 128.3, 127.9 (2C), 127.2, 126.8, 126.7, 125.0, 124.4, 123.5, 122.0, 110.5, 80.1, 76.4, 70.1, 53.5, 23.1, 20.3, 18.6;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 700.2694, found: 700.2691;

HPLC analysis: 97:3 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 13.7 min, t_{minor} = 14.5 min), $[\alpha]_D^{25}$ = –5.52 (c = 1.0, $CHCl_3$).



3-4q

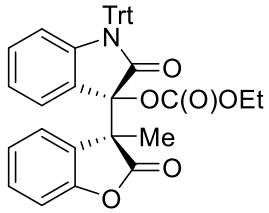
(S)-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl phenyl carbonate (3-4q): yellow solid, 58.5 mg, 89% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 6.96 (m, 24H), 6.87 (dd, *J* = 11.6, 4.3 Hz, 1H), 6.60 (t, *J* = 7.1 Hz, 1H), 6.40 (d, *J* = 8.2 Hz, 1H), 6.09 (s, 1H), 1.90 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 172.2, 153.3, 150.9, 149.6, 146.9, 146.9, 144.6, 141.6, 130.2, 129.5, 129.3, 127.9, 127.4, 126.7, 126.3, 126.0, 124.6, 124.0, 122.1, 120.9, 116.3, 110.8, 82.0, 81.3, 75.9, 18.3;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 658.2224, found: 658.2222;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{major} = 14.4 min, t_{minor} = 16.0 min), $[\alpha]_D^{25}$ = –4.40 (c = 1.0, $CHCl_3$).



3-4r

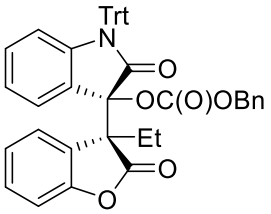
Ethyl ((S)-3-((S)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3r): slightly yellow oil, 27.4 mg, 45% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 6.98 (m, 24H), 6.89 (dd, *J* = 11.6, 4.3 Hz, 1H), 6.60 (t, *J* = 7.2 Hz, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 6.08 (s, 1H), 3.97 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.82 (dq, *J* = 10.6, 7.1 Hz, 1H), 1.88 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.4, 153.3, 151.7, 146.9, 144.5, 141.7, 130.0, 129.6, 129.3, 127.9, 127.3, 126.7, 126.3, 124.5, 122.7, 121.9, 116.2, 110.7, 80.4, 75.8, 64.5, 29.7, 18.3, 14.0;

HRMS (ESI, m/z): calcd. for $[M+Na]^+$: 632.2044, found: 632.2042;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 11.4 min, t_{major} = 12.2 min), $[\alpha]_D^{25}$ = –18.96 (c = 1.0, $CHCl_3$).



3-4s

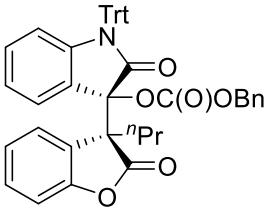
benzyl ((S)-3-((S)-3-ethyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4s): white solid, 67.2 mg, 98% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.05 (m, 25H), 6.90 (t, J = 7.8 Hz, 1H), 6.59 (s, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.95 (d, J = 12.2 Hz, 1H), 4.73 (d, J = 12.1 Hz, 1H), 2.67 (dq, J = 14.4, 7.2 Hz, 1H), 2.44 (dq, J = 14.7, 7.4 Hz, 1H), 0.63 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 172.3, 154.1, 151.6, 146.8, 144.4, 141.6, 134.7, 130.0, 129.5, 129.3, 128.5, 128.2, 127.9, 127.4, 127.2, 126.7, 125.6, 124.5, 124.5, 122.8, 121.9, 116.1, 110.5, 81.24, 75.7, 69.8, 59.4, 23.9, 14.1, 8.9 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 686.2537, found: 686.2536;

HPLC analysis: 2:98 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 9.3 min, t_{major} = 10.1 min), $[\alpha]_D^{25}$ = -10.22 (c = 1 in $CHCl_3$).



3-4t

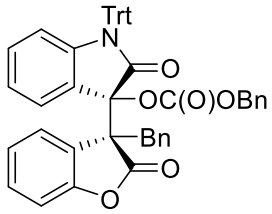
benzyl ((S)-2-oxo-3-((S)-2-oxo-3-propyl-2,3-dihydrobenzofuran-3-yl)-1-tritylindolin-3-yl) carbonate (3-4t): white solid, 66.4 mg, 93% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.12 (m, 24H), 7.07 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.59 (s, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.94 (d, J = 12.1 Hz, 1H), 4.71 (d, J = 12.1 Hz, 1H), 2.58 (d, J = 18.4 Hz, 1H), 2.39 (t, J = 11.4 Hz, 1H), 0.83 (d, J = 3.5 Hz, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 172.3, 154.0, 151.7, 146.9, 144.5, 141.7, 134.8, 130.0, 129.5, 129.3, 128.5, 128.2, 127.9, 127.4, 127.2, 126.7, 126.1, 124.6, 124.5, 122.8, 121.9, 116.1, 110.5, 81.2, 75.8, 69.9, 58.6, 32.7, 18.1, 14.0 ppm.

HRMS (ESI, m/z): calcd. for $[M+Na]^+$: 722.2513, found: 722.2518;

HPLC analysis: 97:3 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 11.09 min, t_{major} = 10.09 min), $[\alpha]_D^{25}$ = -11.28 (c = 1.0, $CHCl_3$).



3-4u

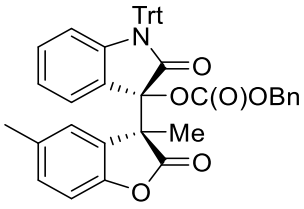
benzyl ((S)-3-((S)-3-benzyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4u): white solid, 56.1 mg, 75% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.15 (m, 24H), 7.08 – 6.99 (m, 3H), 6.93 – 6.84 (m, 3H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.53 (s, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.98 (d, *J* = 12.1 Hz, 1H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.06 (d, *J* = 13.5 Hz, 1H), 3.62 (d, *J* = 13.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 172.3, 153.7, 151.6, 144.5, 141.7, 134.7, 134.5, 130.4, 130.1, 129.6, 129.4, 128.6, 128.6, 128.3, 128.0, 127.4, 127.2, 126.9, 126.8, 125.6, 124.4, 124.2, 122.9, 122.0, 116.1, 110.4, 81.1, 75.8, 70.0, 60.4, 36.4 ppm

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 748.2694, found: 748.2697;

HPLC analysis: 99:1 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 13.1 min, t_{major} = 16.0 min), $[\alpha]_D^{25}$ = 28.57 (c = 0.45, $CHCl_3$).



3-4v

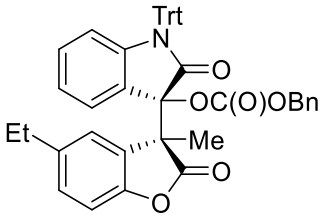
benzyl ((S)-3-((S)-3,5-dimethyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4v): white solid, 65.4 mg, 95% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.30 (m, 9H), 7.19 (ddd, *J* = 21.1, 9.2, 5.1 Hz, 14H), 6.99 – 6.88 (m, 2H), 6.63 (s, 1H), 6.42 (d, *J* = 8.2 Hz, 1H), 4.95 (d, *J* = 12.2 Hz, 1H), 4.74 (d, *J* = 12.2 Hz, 1H), 2.37 (s, 3H), 1.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 172.3, 151.7, 151.1, 144.4, 141.6, 134.8, 134.19, 130.5, 129.5, 129.3, 128.5, 128.5, 128.1, 127.9, 127.4, 127.2, 126.7, 124.4, 122.9, 121.9, 116.1, 110.3, 80.7, 75.7, 69.8, 53.4, 21.3, 18.4 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 686.2537, found: 686.2540;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 14.0 min, t_{major} = 12.8 min), $[\alpha]_D^{25}$ = 11.46 (c = 1.0, $CHCl_3$).



3-4w

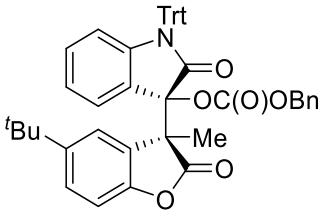
benzyl ((S)-3-((S)-5-ethyl-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4w): white solid, 68.6 mg, 98% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.13 (m, 23H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.8 Hz, 1H), 6.61 (s, 1H), 6.42 (d, *J* = 8.2 Hz, 1H), 4.94 (d, *J* = 12.2 Hz, 1H), 4.76 (d, *J* = 12.2 Hz, 1H), 2.74 – 2.59 (m, 2H), 1.86 (s, 3H), 1.20 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 172.3, 151.7, 151.3, 146.9, 144.5, 141.7, 140.7, 134.8, 129.5, 129.3, 129.3, 128.5, 128.4, 128.1, 127.9, 127.4, 127.2, 126.7, 125.5, 124.4, 122.8, 121.9, 116.1, 110.3, 80.7, 75.7, 69.8, 53.5, 28.6, 18.3, 15.7 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 700.2694, found: 700.2696;

HPLC analysis: 97:3 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 12.8 min, t_{major} = 12.0 min), $[\alpha]_D^{25}$ = 22.5 (c = 1 in $CHCl_3$).



3-4x

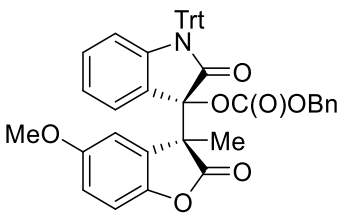
benzyl ((S)-3-((S)-5-(tert-butyl)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4x): white solid, 69.1 mg, 95% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.13 (m, 23H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.57 (s, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 4.91 (d, *J* = 12.2 Hz, 1H), 4.81 (d, *J* = 12.2 Hz, 1H), 1.87 (s, 3H), 1.29 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 172.2, 151.6, 151.0, 147.8, 144.4, 141.7, 134.9, 129.5, 129.3, 128.4, 128.4, 127.9, 127.4, 126.7, 126.5, 124.3, 123.6, 122.5, 121.9, 116.1, 109.7, 80.5, 75.7, 69.6, 53.8, 34.7, 31.5, 18.1 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 728.3007, found: 728.3005;

HPLC analysis: 3:97 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 9.8 min, t_{major} = 10.8 min), $[\alpha]_D^{25}$ = 38.48 (c = 1 in $CHCl_3$).



3-4y

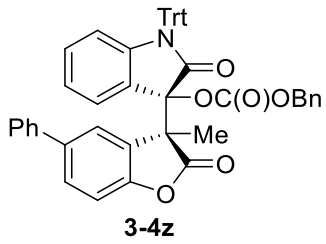
benzyl ((S)-3-((S)-5-methoxy-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4y): white solid, 63.1 mg, 90% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.10 (m, 22H), 7.01 (d, J = 8.8 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.66 (s, 1H), 6.43 (d, J = 8.2 Hz, 1H), 4.95 (d, J = 12.2 Hz, 1H), 4.76 (d, J = 12.2 Hz, 1H), 3.74 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 172.2, 156.7, 151.6, 147.1, 144.6, 141.6, 134.8, 129.5, 129.4, 128.5, 128.5, 128.1, 127.4, 126.7, 124.3, 122.9, 122.0, 116.2, 115.6, 111.2, 80.7, 75.7, 69.9, 55.8, 53.8, 18.4;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 702.2486, found: 702.2484;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 17.6 min, t_{major} = 15.9 min), $[\alpha]_D^{25}$ = 10.9 (c = 1.0, $CHCl_3$).



3-4z

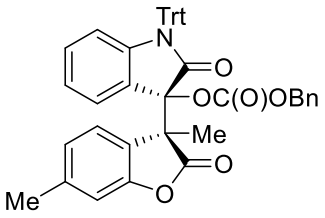
benzyl ((S)-3-((S)-3-methyl-2-oxo-5-phenyl-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4z): white solid, 72.5 mg, 97% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 8.4, 2.0 Hz, 1H), 7.58 – 7.10 (m, 28H), 6.98 (s, 1H), 6.70 (s, 1H), 6.45 (d, J = 8.2 Hz, 1H), 4.94 (d, J = 12.2 Hz, 1H), 4.80 (d, J = 12.2 Hz, 1H), 1.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 172.2, 152.7, 151.6, 146.9, 144.6, 141.6, 139.9, 137.7, 134.8, 128.9, 128.8, 128.5, 128.4, 128.1, 127.9, 127.5, 127.4, 126.9, 126.7, 124.7, 124.4, 123.0, 122.1, 116.2, 80.7, 75.7, 69.9, 53.1, 18.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 748.2694, found: 748.2699;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 17.0 min, t_{major} = 15.4 min), $[\alpha]_D^{25}$ = 36.76 (c = 1, $CHCl_3$).



3-4aa

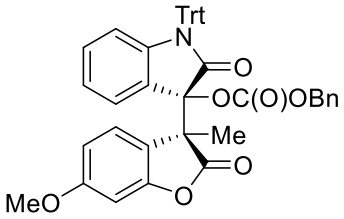
benzyl ((S)-3-((S)-3,6-dimethyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4aa): white solid, 68.4 mg, 96% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 22H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.93 – 6.86 (m, 1H), 6.61 (s, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 6.12 (s, 1H), 4.94 (d, *J* = 12.1 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 2.40 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 172.3, 153.3, 151.7, 146.9, 144.5, 141.7, 140.6, 134.8, 129.6, 129.3, 128.5, 128.2, 127.9, 127.4, 127.3, 126.7, 126.0, 125.3, 124.5, 122.8, 121.9, 116.1, 111.2, 80.8, 75.7, 69.9, 53.3, 21.8, 18.4 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 686.2537, found: 686.2541;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 14.1 min, t_{major} = 12.6 min), $[\alpha]_D^{25}$ = -8.34 (c = 1.0, $CHCl_3$).



3-4ab

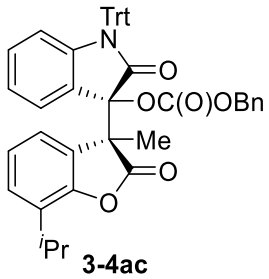
benzyl ((S)-3-((S)-6-methoxy-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3ab): light yellow solid, 63.8 mg, 91% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.12 (m, 22H), 6.91 (t, J = 7.8 Hz, 1H), 6.68 (dd, J = 37.0, 4.8 Hz, 3H), 6.42 (d, J = 8.2 Hz, 1H), 4.95 (d, J = 12.1 Hz, 1H), 4.73 (d, J = 12.1 Hz, 1H), 3.82 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 172.3, 161.3, 154.2, 151.7, 144.5, 141.7, 134.8, 129.5, 129.3, 128.5, 128.2, 127.4, 126.7, 124.5, 122.8, 122.0, 119.8, 116.1, 110.2, 97.2, 80.9, 75.7, 69.9, 55.7, 53.2, 18.5 ppm;

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 702.2486, found: 702.2485;

HPLC analysis: 96:4 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 16.8 min, t_{major} = 14.9 min), $[\alpha]_D^{25}$ = –0.94 (c = 1.0, $CHCl_3$).



3-4ac

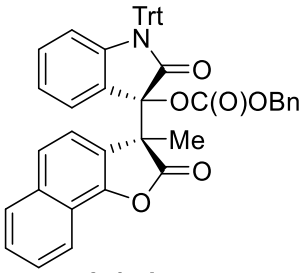
benzyl ((S)-3-((S)-7-isopropyl-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4ac): white solid, 67.8 mg, 95% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.13 (m, 24H), 6.88 (t, J = 7.8 Hz, 1H), 6.53 (s, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.94 (d, J = 12.1 Hz, 1H), 4.71 (d, J = 12.1 Hz, 1H), 3.12 (dt, J = 13.6, 6.8 Hz, 1H), 1.87 (s, 3H), 1.24 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 172.2, 151.7, 150.7, 144.3, 141.7, 134.8, 131.6, 129.6, 129.2, 128.5, 128.5, 128.2, 127.8, 127.4, 127.1, 126.7, 124.6, 124.4, 123.7, 122.6, 121.8, 116.0, 80.6, 75.8, 69.8, 53.8, 28.0, 22.6, 22.0, 17.8 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 714.2850, found: 714.2853;

HPLC analysis: 96:4 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 10.6 min, t_{major} = 9.7 min), $[\alpha]_D^{25}$ = -22.26 (c = 1 in $CHCl_3$).



3-4ad

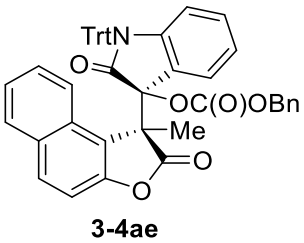
Benzyl ((S)-3-((S)-3-methyl-2-oxo-2,3-dihydronaphtho[1,2-b]furan-3-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4ad): white solid, 70.0 mg, 97% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 4.4 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.70 – 7.43 (m, 8H), 7.37 – 7.11 (m, 17H), 6.89 (d, J = 7.4 Hz, 1H), 6.54 (s, 1H), 6.43 (d, J = 8.2 Hz, 1H), 4.97 (d, J = 12.2 Hz, 1H), 4.77 (d, J = 12.2 Hz, 1H), 1.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 172.3, 151.8, 149.1, 146.9, 144.5, 141.6, 134.8, 134.5, 129.5, 129.4, 128.5, 128.5, 128.2, 127.9, 127.9, 127.4, 127.3, 126.9, 126.7, 124.5, 124.3, 122.9, 122.2, 122.0, 121.6, 119.6, 116.2, 81.0, 75.7, 69.9, 54.2, 18.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 722.2537, found:722.2537;

HPLC analysis: 98:2 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 19.9 min, t_{major} = 14.7 min), $[\alpha]_D^{25}$ = -42.92 (c = 1, $CHCl_3$).



3-4ae

Benzyl ((S)-3-((S)-1-methyl-2-oxo-1,2-dihydronaphtho[2,1-b]furan-1-yl)-2-oxo-1-tritylindolin-3-yl) carbonate (3-4ae): white solid, 68.3 mg, 94% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J = 11.4, 9.0 Hz, 2H), 7.63 – 6.95 (m, 25H), 6.90 (t, J = 7.8 Hz, 1H), 6.60 (s, 1H), 6.36 (d, J = 8.2 Hz, 1H), 4.93 (d, J = 12.4 Hz, 1H), 4.74 (d, J = 12.4 Hz, 1H), 2.17 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 172.6, 151.6, 151.5, 144.6, 141.5, 134.9, 132.0, 131.6, 130.5, 129.5, 129.4, 128.4, 128.3, 127.9, 127.7, 127.4, 127.3, 126.7, 124.8, 124.4, 123.2, 121.9, 119.9, 116.3, 111.3, 81.7, 75.8, 69.6, 56.1, 17.2 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 722.2537, found: 722.2538;

HPLC analysis: 99:1 er, (CHIRALCEL ID column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 15.1 min, t_{major} = 13.2 min), $[\alpha]_D^{25}$ = -2.73 (c = 1.5, $CHCl_3$).

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