Organocatalytic Enantioselective Synthesis of Functionalized Cyclopentenes, beta-Lactones and Spirocyclohexenols

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In

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BY

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November 2017

Dedicated to

My Beloved Parents

and

Teachers

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Organocatalytic Enantioselective Synthesis of Functionalized Cyclopentenes, beta-Lactones and Spirocyclohexenols"** submitted by **Mr. Santigopal Mondal** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Organocatalytic Enantioselective Synthesis of Functionalized Cyclopentenes, beta-Lactones and Spirocyclohexenols''** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. A. T. Biju**, Senior Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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Santigopal Mondal

List of Abbreviations

Ac	:	Acetyl
ACN	:	Acetonitrile
Ar	:	Aryl
BHT	:	2,6-Di-tert-butyl-4-methylphenol
bs	:	Broad singlet
Bn	:	Benzyl
t-Bu	:	Tertiary Butyl
Cat.	:	Catalytic
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
DBU	:	1 8-Diazabicyclo 5.4.0 undec-7-ene
DCE	:	1,2-Dichloroethane
DCM	:	Dichloromethane
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	:	Density functional theory
Dipp	:	2,6-Diisopropylphenyl
DIPEA	:	N,N-Diisopropylethylamine
DMAP	:	4-Dimethylaminopyridine
DME	:	1,2-Dimethoxyethane
DMP	:	Dess-Martin Periodinane
dr	:	Diastereomer
E^+	:	Electrophile
ee	:	Enantiomeric excess
ent	:	Enantiomer
er	:	Enantiomeric ratio
Et	:	Ethyl
Et_3N	:	Triethyl amine
g	:	gram(s)
h	:	hour(s)
HPLC	:	High Performance Liquid Chromatography

HRMS	:	High-resolution mass spectrometry
Hz	:	Hertz
IMes.HCl	:	1,3-Dimesitylimidazoliumchloride
IR	:	Infra red
J	:	Coupling constant in NMR
M	:	Multiplet
Me	:	Methyl
Mes	:	Mesityl
min	:	Minute(s)
mL	:	Milliliter(s)
mmol	:	Millimole(s)
NHC	:	N-Heterocyclic Carbene
NMR	:	Nuclear magnetic resonance
Nu^-	:	Nucleophile
ORTEP	:	Oak Ridge Thermal Ellipsoid Plot
Ph	:	Phenyl
i-Pr	:	Isopropyl
q	:	Quartet
rt	:	Room temperature
s	:	Singlet
t	:	Triplet
TEMPO	:	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	:	Tetrahydofuran
TLC	:	Thin layer chromatography
TMEDA	:	Tetramethylethylenediamine
TMS	:	Trimethylsilyl
TBS	:	Tertiarybutylsilyl
p-Tol	:	*para*-Tolyl
PivCl	:	Pivaloyl Chloride

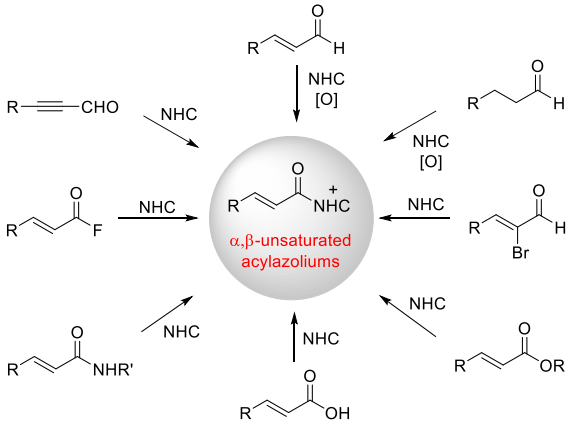
Synopsis

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	Mr. Santigopal Mondal
Degree Enrolment No. & Date	Ph. D in Chemical Sciences (10CC13A26010); August 2013
Title of the Thesis	**Organocatalytic Enantioselective Synthesis of Functionalized Cyclopentenes, beta-Lactones and Spirocyclohexenols**
Research Supervisor	Dr. A. T. Biju (CSIR-NCL, Pune)

The proposed thesis is divided into five chapters. The first chapter deals with a brief introduction to N-heterocyclic carbene (NHC)-organocatalysis and its various modes of reactivity. The second chapter describes NHC-catalyzed enantioselective synthesis of functionalized cyclopentenes proceeding via α,β-unsaturated acylazolium intermediates. An enantioselective synthesis of functionalized β-lactones by NHC-catalyzed aldol-lactonization of linear ketoacids has been demonstrated in the third chapter. The fourth chapter is focused on the aldol-lactonization of ketoacids via dynamic kinetic resolution strategy. A substrate controlled β-lactone ring-opening has been shown for the synthesis of highly substituted succinimide derivatives. The focal theme of the fifth chapter is the asymmetric synthesis of pyrazolone fused-spirocyclohexenols using proline-based secondary amine catalyst. The details are presented below.

Chapter 1: Introduction to NHC-organocatalysis

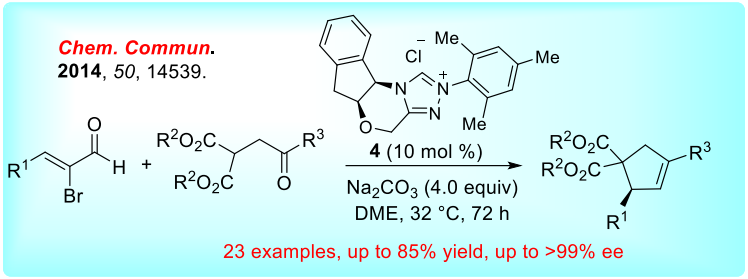
N-heterocyclic carbene (NHC)-based organocatalysis has emerged as one of the efficient and powerful synthetic tool for the rapid construction of complex molecules from simple starting materials, mostly in asymmetric manner.[1] Apart from the NHC-catalyzed umpolung strategies (acyl anion or homoenolate), NHCs are also used as catalysts in non-umpolung transformations. One of the important modes of reactivity is the α,β–unsaturated acylazoliums. In most of the cases, this versatile intermediate acts as a bis-electrophile allowing the addition of various bis-nucleophile in a 1,4-fashion followed by a 1,2-pathway to form wide variety of carbocycles and heterocycles. The α,β-unsaturated acylazoliums can be generated from a wide range of α,β-unsaturated carbonyl compounds, which are not compatible with other covalent organocatalysis (Scheme 1).



Scheme 1. Methods for the generation of α,β-unsaturated acylazoliums

Chapter 2: N-Heterocyclic Carbene-Catalyzed Enantioselective Synthesis of Functionalized Cyclopentenes via α,β-Unsaturated Acyl Azoliums

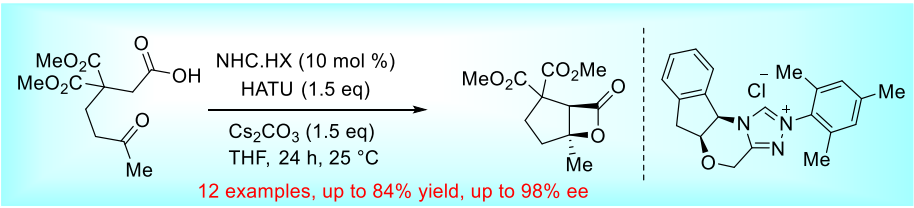
A NHC-catalyzed highly enantioselective cascade reaction for the synthesis of functionalized cyclopentenes by the reaction of modified enals with malonic ester derivatives bearing a γ-aroyl group has been demonstrated in this chapter (Scheme 2).[2] The NHC generated from the chiral aminoindanol-derived triazolium salt using Na_2CO_3 as the base was key for the high reactivity and selectivity. The highly selective organocascade reaction proceeds via the generation of the chiral α,β-unsaturated acyl azolium intermediates from 2-bromoenals and takes place through a Michael-intramolecular aldol-β-lactonization-decarboxylation sequence to afford the corresponding cyclopentenes in good yield and excellent enantioselectivity. Further, this methodology was extended to malonic ester derivatives bearing a γ-acyl group, which leads to form cyclopantane fused β-lactones in moderate yields and excellent diastereoselectivity and enantioselectivity.



Scheme 2. Enantioselective synthesis of functionalized cyclopentenes

Chapter 3: Enantioselective Synthesis of Functionalized β-Lactones by NHC-Catalyzed Aldol Lactonization of Ketoacids

Although NHC-catalyzed reactions of aldehydes are well-known, the use of carboxylic acids in NHC-catalysis has received only limited attention. In this chapter, an acid activation strategy in NHC-organocatalysis has been disclosed for the enantioselective synthesis of cyclopentane fused β-lactones (Scheme 3).[3] The generation of chiral azolium-bound enolate intermediate from readily available ketoacids in the presence of peptide coupling reagent HATU is the key to the success of this reaction. The highly enantioselective reaction proceeds through intramolecular aldol- lactonization sequence to afford the desired β-lactone product in high yields and excellent enantioselectivity.

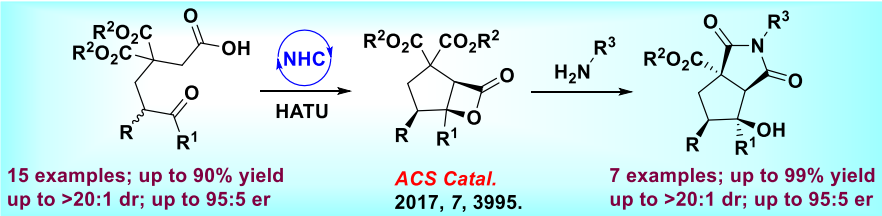


Scheme 3. Enantioselective NHC-catalyzed aldol lactonization of ketoacids

Chapter 4: N-Heterocyclic Carbene-Catalyzed Aldol-Lactonization of Ketoacids via Dynamic Kinetic Resolution

A dynamic kinetic resolution approach has been applied for the NHC-catalyzed aldol lactonization of racemic acyclic ketoacids for the enantioselective synthesis of cyclopentane-fused β-lactones (Scheme 4).[4] The generation of chiral carbene in the

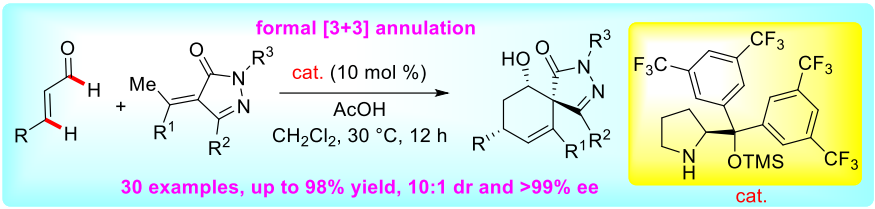
reaction mixture in presence of Lewis acid additive LiCl is the key factor for the success of this reaction. This bis cyclization reaction takes place through the generation of chiral azolium-bound enolate intermediate formed in the presence of HATU, and a subsequent intramolecular aldol-β-lactonization reaction to form the desired product. The reaction allowed the diastereoselective and enantioselective synthesis of cyclopentane-fused β-lactones having three contiguous stereocenters. Also the reaction products are shown to undergo substrate-controlled β-lactone opening in presence of primary amines to afford succinimide derivatives in good yields and good stereoselectivity.



Scheme 4. NHC-catalyzed Aldol lactonization of ketoacids via dynamic kinetic resolution

Chapter 5: Organocatalytic Enantioselective Vinylogous Michael-Aldol Cascade for the Synthesis of Spirocyclic Compounds

Organocatalytic vinylogous Michael reactions are well documented but the organocascade reaction involving vinylogous Michael addition has received scant attention. In this chapter, a secondary amine-catalyzed cascade reaction of α,β-unsaturated aldehydes with α-arylidene pyrazolinones for the enantioselective synthesis of pyrazolone-fused spirocyclohexenols has been presented (Scheme 5).[5] The generation of α,β-unsaturated iminium from enals and tandem dienolate/enolate formation from pyrazolinones are the key for the success of this reaction. This formal [3+3] organocascade reaction proceeds through a vinylogous Michael-aldol sequence to furnish the desire product in good yields and selectivities.



Scheme 5. Enantioselective vinylogous Michael-aldol cascade for the synthesis of spirocyclic compounds

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TABLE OF CONTENTS

Chapter 1: N-Heterocyclic Carbene-Organocatalysis via the Non-Umpolung Mode of Reactivity

Title		Page No.
1.1.	Introduction	2
1.2.	Important Intermediates in NHC-Catalysis	2
1.3.	NHC-Catalyzed Reaction via Acyl Azolium Intermediate	3
1.4.	NHC-Catalyzed Reaction via α,β-unsaturated Acyl Azolium Intermediate	4
	1.4.1. Generation of α,β-Unsaturated Acyl azoliums from Enals under Oxidative Conditions	6
	1.4.2. Generation of α,β-Unsaturated Acyl azoliums from Saturated Aldehyde under Oxidative Conditions	8
	1.4.3. Generation of α,β-Unsaturated Acyl azoliums from 2-Bromoenals	8
	1.4.4. Generation of α,β-Unsaturated Acyl azoliums from Ynals	10
	1.4.5. Generation of α,β-Unsaturated Acyl azoliums from Esters	12
	1.4.6. Generation of α,β-Unsaturated Acyl azoliums from Acid Fluorides	13
	1.4.7. Generation of α,β-Unsaturated Acyl azoliums from Acids	14
	1.4.8. Generation of α,β-Unsaturated Acyl azoliums from Amides	15
	1.4.9. Generation of α,β-Unsaturated Acyl azoliums from Thioesters	15
1.5.	NHC-Catalyzed Reaction via Enolate Intermediate	15
1.6.	NHC-Catalyzed Reaction via Dienolate Intermediate	17
1.7.	Conclusion and Focal Theme of the Present Work	19
1.8.	References	20

Chapter 2: N-Heterocyclic Carbene-Catalyzed Enantioselective Synthesis of Functionalized Cyclopentenes via α,β-Unsaturated Acyl Azoliums

	Title	Page No.
2.1.	Introduction	24
	2.1.1 NHC-Catalyzed Synthesis of Cyclopentenes	24

2.1.2. Enantioselective Synthesis of Cyclopentane-fused β-Lactone via α,β-Unsaturated Acylammonium Intermediate 29
2.2. Statement of the Problem 30
2.3. Results and Discussion 31
2.3.1. Optimization Studies 31
2.3.2. Spectral Data of **35a** 32
2.3.3 Enantioselective Synthesis of Functionalized Cyclopentenes from Malonic Ester Derivatives 34
2.3.4. Enantioselective Synthesis of Functionalized Cyclopentenes from 2-Bromoenals 35
2.3.5. Reaction Mechanism 36
2.3.6. Synthetic Transformations of Functionalized Cyclopentenes 37
2.3.7. Enantioselective Synthesis of Cyclopentane-Fused β-Lactones 38
2.3.8. Synthesis of Spiroglutarimide Derivatives 39
2.4. Conclusion 40
2.5. Experimental Details 40
2.5.1. General Information 40
2.5.2. General Procedure for the Optimization of Reaction Conditions 41
2.5.3. General Procedure for the Enantioselective Synthesis of Functionalized Cyclopentenes 42
2.5.4. X-ray Data of **35c** and **45t** 42
2.5.5 Synthesis and Characterization of Functionalized Cyclopentenes 44
2.5.6. Diastereoselective Hydrogenation of **35a** 60
2.5.7. Decarboxylation of **35a** 61
2.5.8. Synthesis and Characterization of Cyclopentane-Fused β-Lactones 61
2.5.9. Synthesis and characterization of Spiroglutarimide derivative 63
2.6 References 64

Chapter 3: Enantioselective Synthesis of Functionalized β-Lactones by NHC-Catalyzed Aldol Lactonization of Ketoacids

	Title	Page No.
3.1.	Introduction	67
	3.1.1 Synthesis of β-Lactone via Azolium Enolate Intermediate	68
	3.1.2. Synthesis of β-Lactone via Homoenolate Intermediates	70
	3.1.3. Synthesis of β-Lactones via α,β-Unsaturated Acyl Azolium Intermediates	71
3.2.	Statement of the Problem	74
3.3.	Results and Discussion	74
	3.3.1. Optimization Studies	74
	3.3.2 Spectral Data of **42a**	76
	3.3.3. NHC-Catalyzed Aldol Lactonization of Ketoacids: Substrate Scope	77
	3.3.4. Proposed Mechanism	79
	3.3.5. Synthetic Transformations of Cyclopentane-fused β-Lactones	80
3.4.	Conclusion	80
3.5.	Experimental Details	81
	3.5.1. General Information	81
	3.5.2. General Procedure for the Preparation of Ketoacids	81
	3.5.3. General Procedure for the Optimization of Reaction Conditions	82
	3.5.4. General Procedure for the Enantioselective Synthesis of Cyclopentane-fused β-Lactones	82
	3.5.5. X-ray Data of **42l**	83
	3.5.6. Synthesis and Characterization of Functionalized Cyclopentane fused β-Lactones	84
3.6.	References	94

Chapter 4: N-Heterocyclic Carbene-Catalyzed Aldol-Lactonization of Ketoacids via Dynamic Kinetic Resolution

	Title	Page No.
4.1.	Introduction	98
	4.1.1. NHC-Catalyzed Kinetic Resolutions	98
	4.1.2. NHC-Catalyzed Dynamic Kinetic Resolution	102
4.2.	Statement of the Problem	105
4.3.	Results and Discussion	105
	4.3.1. Optimization Studies	105
	4.3.2. Spectral Data of **41a**	107
	4.3.3. Aldol Lactonization of Ketoacids: Substrate Scope	108
	4.3.4. Kinetic Study of the Aldol Lactonization Reaction	109
	4.3.5. Reaction Mechanism	111
	4.3.6. NHC-Catalyzed Parallel Kinetic Resolution of Ketoacid	112
	4.3.7. Functionalization of cyclopentane-fused β-lactone	112
4.4.	Conclusion	114
4.5.	Experimental Details	114
	4.5.1. General Information	114
	4.5.2. General Procedure for the Optimization of Reaction Conditions	115
	4.5.3. General Procedure for the Enantioselective Synthesis of Cyclopentane-fused β-Lactones	115
	4.5.4. Procedure for Parallel Kinetic Resolution for Synthesis of Cyclopentane-fused β-Lactone	116
	4.5.5. General Procedure for the Synthesis of Functionalized Succinimide Derivatives	116
	4.5.6. X-Ray Data of **48g**	117
	4.5.7. Kinetics Study	118
	4.5.8. Synthesis and Characterization of Ketoacids	120
	4.5.9. Synthesis and Characterization of Functionalized Cyclopentane	

fused β-Lactones 121
4.5.10. Synthesis and Characterization of Functionalized Succinimide Derivatives 131
4.6. References 137

Chapter 5: Organocatalytic Enantioselective Vinylogous Michael-Aldol Cascade for the Synthesis of Spirocyclic Compounds

Title **Page No.**
5.1. Introduction 141
5.1.1. Organocatalytic Enantioselective Michael-Aldol Cascade 141
5.1.2. Organocatalytic Enantioselective Vinylogous Michael Reaction 143
5.1.3. Organocatalytic Enantioselective Vinylogous Michael Involving Cascade Reaction 146
5.2. Statement of the Problem 148
5.3. Results and Discussion 148
5.3.1. Optimization Studies 148
5.3.2. Spectral Data of **49a** 150
5.3.3. Enantioselective Synthesis of Spirocyclohexenols from α,β-Unsaturated Enals 151
5.3.4. Enantioselective Synthesis of Spirocyclohexenols from α-arylidene pyrazolinone 153
5.3.5. Enantioselective Gram Scale Synthesis of Pyrazolone-fused Spirocyclohexenols 155
5.3.6. Robustness Screen of the Spiroannulation Reaction 155
5.3.7. Reaction Mechanism 156
5.4. Conclusion 157
5.5. Experimental Details 158
5.5.1. General Information 158
5.5.2. General Procedure for the Optimization of Reaction Conditions 158
5.5.3. General Procedure for the Enantioselective Synthesis of Pyrazolone-fused Spirocyclohexenols 159

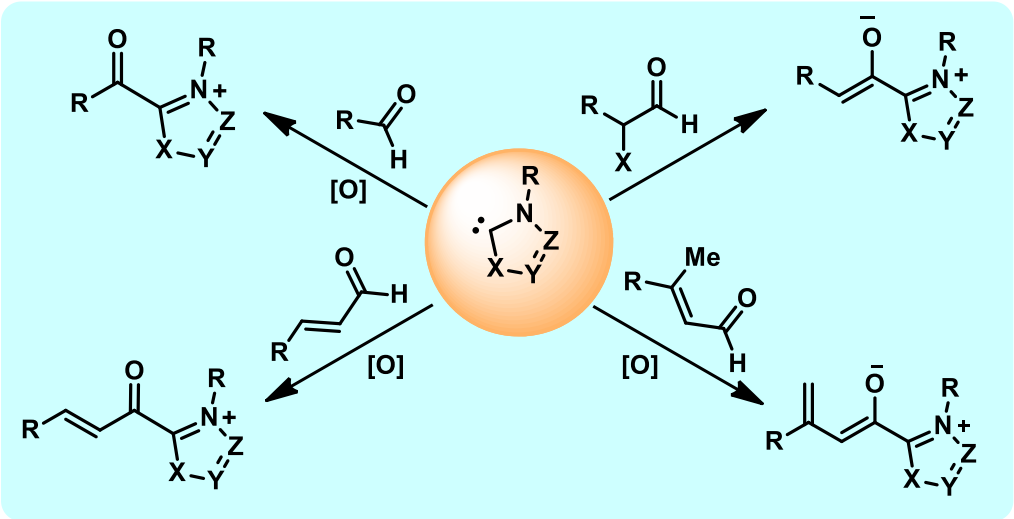
5.5.4. Procedure for the Gram Scale Synthesis of Pyrazolone-fused Spirocyclohexenols 159
5.5.5. General Procedure for the Additive Reactions 160
5.5.6. X-Ray Data of **49g** 160
5.5.7. Synthesis and Characterization of Spirocyclohexenols 161
5.6. References 186

List of Publications 191

Chapter 1

N-Heterocyclic Carbene-Organocatalysis via the Non-Umpolung Mode of Reactivity

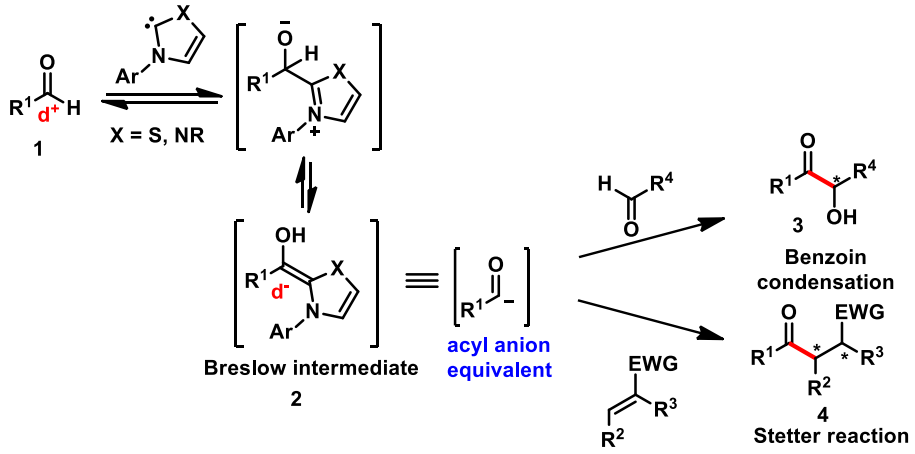
N-heterocyclic carbene have received much attention in the field of transition metal-catalysis as a ligand. But in the last two decades, synthetic chemists have recognized NHCs as an attractive alternative to metal-catalysis for the construction of carbon-carbon and carbon-heteroatom bonds in terms of toxicity and price. A dramatic progress has been achieved in the NHC-organocatalyzed polarity reversal reactions (umpolung) like benzoin condensation and Stetter reaction. Also, NHC-catalyzed non-umpolung mode of reactivity has grown simultaneously. In this chapter, the non-umpolung mode of reactivity of NHCs has been highlighted.



1.1. Introduction

Ever since the seminal independent reports by the Bertrand[1] and Arduengo[2] groups on the isolation of free carbenes, N-heterocyclic carbene (NHC)-based organocatalysis has emerged as one of the efficient and sophisticated synthetic tool for the rapid construction of medicinally and biologically important molecules from simple starting materials.[3] Initially, the NHC-catalyzed reversal of polarity (umpolung) of carbonyl was the major field of study. It is assumed that the addition NHC to an aldehyde **1** followed by intra or intermolecular proton transfer affords an enaminol intermediate **2**, referred to as the Breslow intermediate,[4] in which the originally electrophilic carbonyl carbon atom of the aldehyde has gained nucleophilic character. The reaction of the Breslow intermediate with a second molecule of aldehyde provides an α-hydroxy ketone product **3**, known as benzoin condensation[5] and it affords 1,4-bifunctionalized compound **4** upon reaction with a Michael acceptor, known as Stetter reaction[6] (Scheme 1.1).

Scheme 1.1: Umpolung of Aldehydes



1.2. Important Intermediates in NHC-Catalysis

Apart from these two historic reactions, various other modes of reactivity are known in NHC organocatalysis. When the aldehyde molecule contains an additional conjugation, it can generate extended Breslow intermediate known as homoenolate intermediate. Also, NHC can generate allenoate intermediate upon treatment with ynals. In the presence of external oxidant, the Breslow intermediate can oxidized to acyl azolium intermediate. If the acyl azoliums contain an α-hydrogen, it can form azolium enolates. Moreover, enals under oxidative NHC-catalysis can produce α,β-unsaturated acyl azolium and dienolate intermediates. In this chapter, the NHC-catalyzed reaction proceeding via non-umpolung mode has been described.

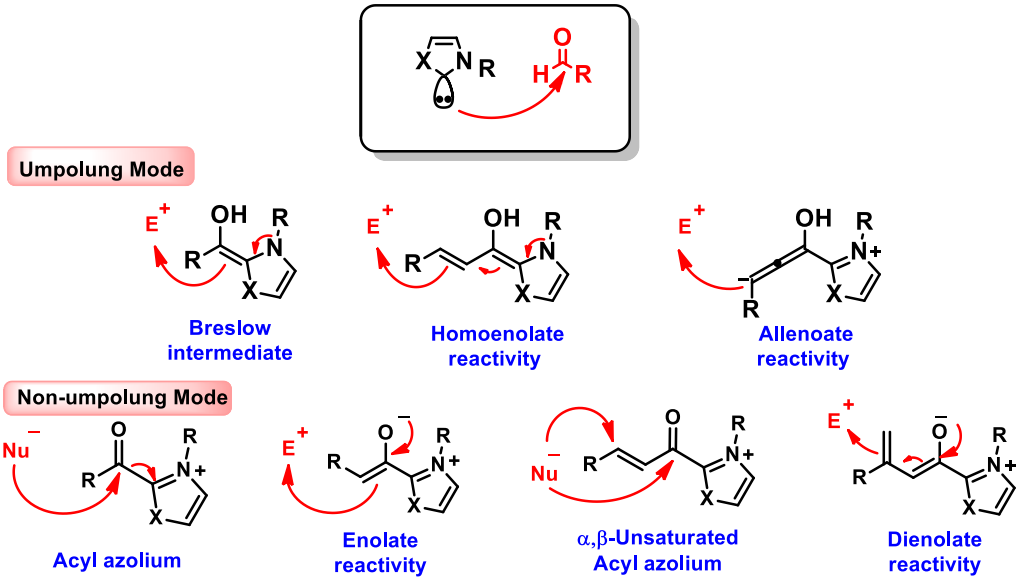
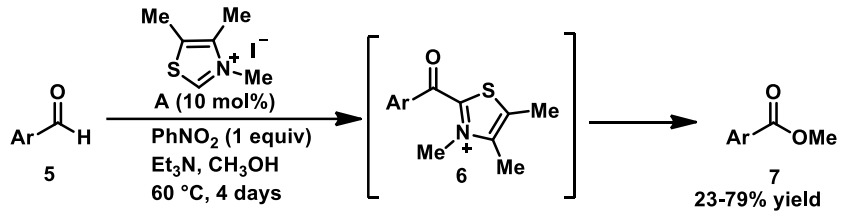


Figure 1.1: Important Intermediates in NHC-Organocatalysis

1.3. NHC-Catalyzed Reaction via Acyl Azolium Intermediate

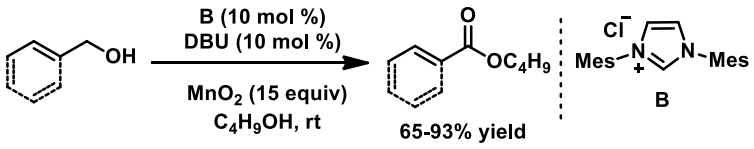
In 1977, Castells and co-workers demonstrated the first example of NHC-catalyzed non-umpolung reactivity.[7] The conversion of aromatic aldehyde **5** to the corresponding ester **7**, in presence of nitrobenzene as an organic oxidant and thiazolium salt precatalyst **A**, proceeds via acyl azolium intermediate **6** (Scheme 1.2). Interestingly, for 4-nitrobenzaldehyde, no external oxidant was required for oxidation to 4-nitrobenzoic acid.

Scheme 1.2: NHC-Catalyzed Oxidative Conversion of Aldehyde to ester.



In 2007, Scheidt and co-workers employed, for the first time, NHC-catalysis for the tandem oxidation of allylic or benzylic alcohols using MnO_2 as a mild oxidant (Scheme 1.3).[8] A variety of benzylic, allylic and propargylic alcohols were efficiently oxidized to corresponding esters in good to excellent yields (65-93%) using the NHC generated from the imidazolium salt **B** using DBU as the base. The method was also applicable for the synthesis of saturated esters. Moreover, the nucleophilic acylation of catalytically generated α,β-

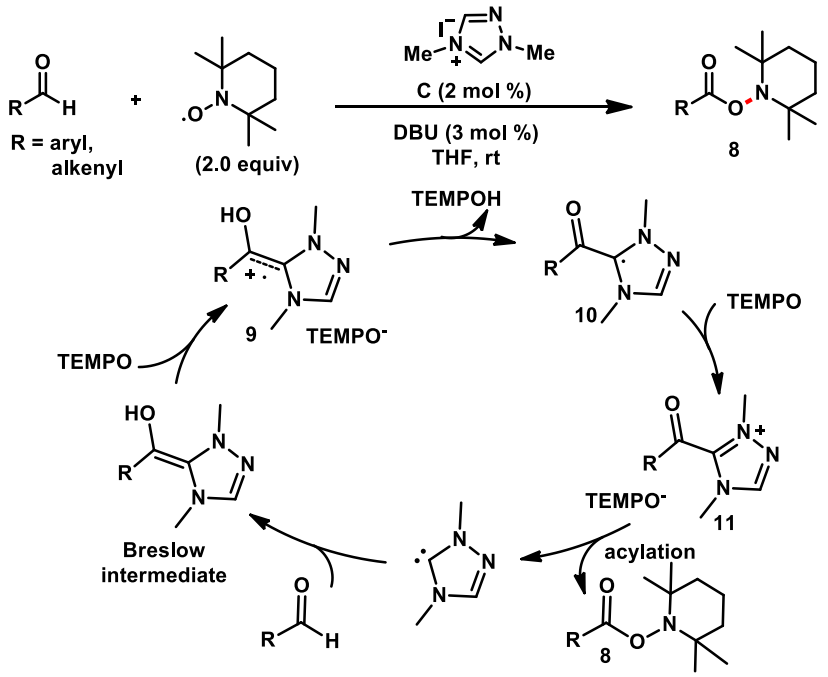
Scheme 1.3: NHC-Catalyzed Oxidative Esterification Reaction



unsaturated acyl azolium has been demonstrated for the desymmetrization of *meso*-diols using NHC generated from the chiral triazolium salt, and the desymmetrized product was formed in up to 80% ee.

Subsequently, Studer and co-workers disclosed the biomimetic oxidation of Breslow intermediates with the aid of the organic single-electron transfer (SET) oxidant 2,2,6,6-tertramethyl piperidine *N*-oxyl radical (TEMPO). Both electron-donating and -withdrawing benzaldehydes as well as enals and aliphatic aldehydes furnished the ester product **8** in good to excellent yield (Scheme 1.4).[9] Mechanistically, the reaction proceeds via a single electron transfer from Breslow intermediate to TEMPO to generate radical cation **9** and TEMPO$^-$. An abstraction of proton from **9** by TEMPO- leads to radical **10**. Another SET from **10** by TEMPO provides acyl azolium intermediate **11** and a subsequent interception by TEMPO$^-$ furnished the desired ester product **8**. The TEMPO esters can easily be hydrolysed to recover the TEMPO after oxidation, which makes this procedure economically viable.

Scheme 1.4. Biomimetic Oxidation of Aldehydes using TEMPO



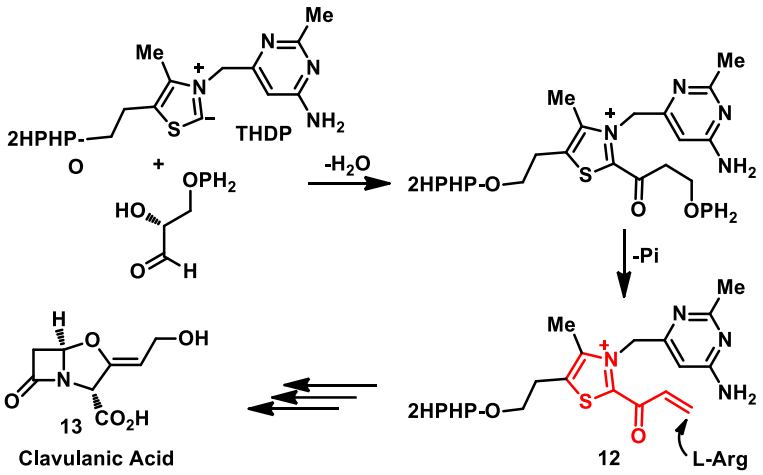
Moreover, NHC-catalyzed acylation of alcohols and amines proceeding via acyl azolium intermediate leading to the kinetic resolution of the product have been discussed in details in chapter 4, section 4.1.1, page 98.

1.4. NHC-Catalyzed Reaction via α,β-unsaturated Acyl Azolium Intermediate

Similar to the NHC-catalyzed umpolung of aldehydes, the chemistry of α,β-unsaturated acyl azoliums also have the biological origin. The α,β-unsaturated acyl azoliums

are found to be the key intermediates in the biosynthesis of clavulanic acid **13**. In 2007, Merski and Townsend successfully demonstrated that the conjugate addition of L-arginine to a thiamine diphosphate (ThDP, vitamin B1)-derived α,β-unsaturated acyl azolium ion **12** is the key step in the biosynthesis of clavulanic acid **13**, a potent β-lactamase inhibitor (Scheme 1.5).[10]

Scheme 1.5: Biosynthesis of Clavulanic Acid



The α,β-unsaturated acyl azoliums can be generated from a wide range of α,β-unsaturated carbonyl compounds, and in many cases, these precursors are not compatible with other modes of organocatalysis. The important methods for the generation of α,β-unsaturated acyl azoliums include (i) treatment of enals and α,β-unsaturated aldehydes with NHCs followed by stoichiometric oxidation of the generated Breslow intermediate, (ii) reaction of ynals with NHCs in the absence of external oxidants, (iii) the reaction of NHCs with α,β-unsaturated esters or acyl fluorides, (iv) the reaction of 2-bromoenals with NHCs

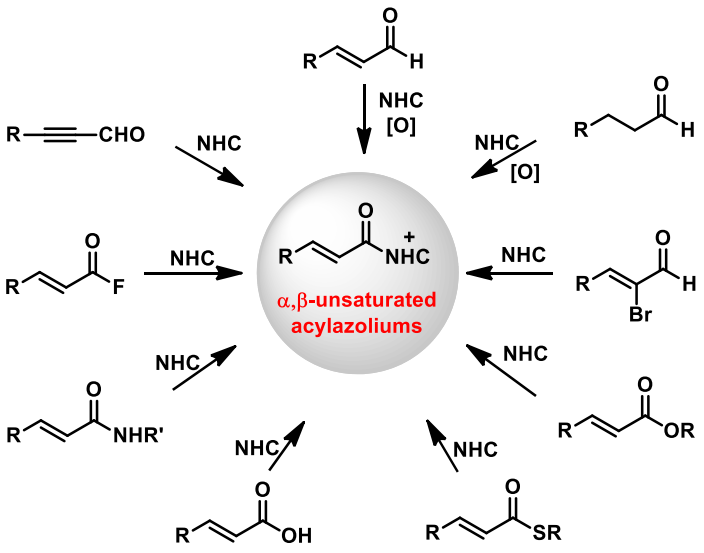


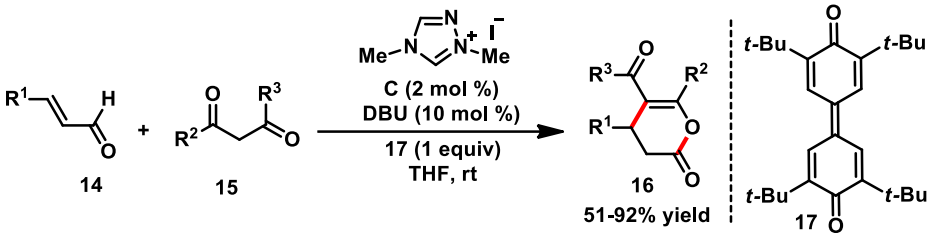
Figure 1.2: Methods for the Generation of α,β-Unsaturated Acylazoliums.

and more recently (v) the reaction of NHCs with α,β-unsaturated acids, amides and thioesters (Figure 1.2).

1.4.1. Generation of α,β-Unsaturated Acyl azoliums from Enals under Oxidative Conditions

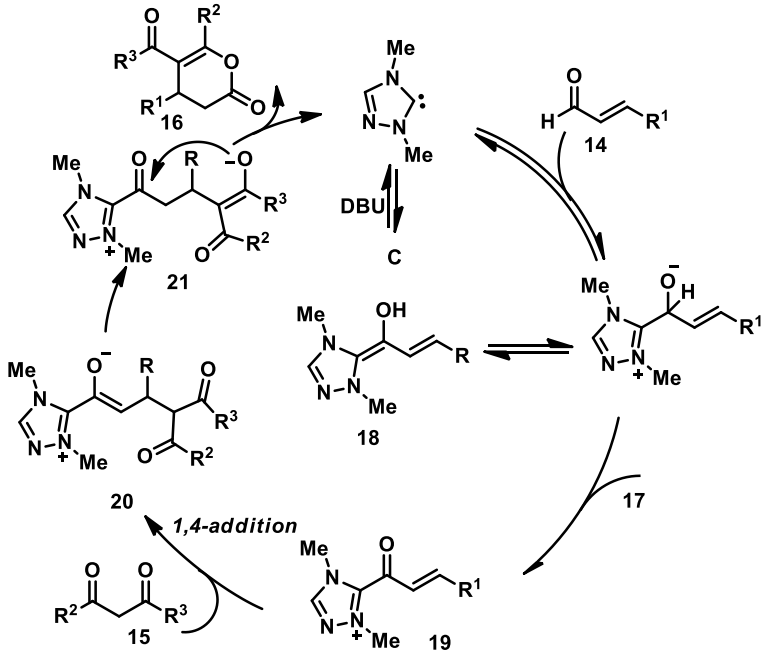
In 2010, De Sarkar and Studer disclosed an elegant conjugate addition of soft carbon nucleophiles such as 1,3-dicarbonyl compounds **15** to catalytically generated α,β-unsaturated acyl azoliums generated from enals under NHC-catalysis in the presence of the bisquinone oxidant **17** (Scheme 1.6).[11] The reaction afforded functionalized dihydropyranones **16** in good to excellent yields using NHC generated from the triazolium salt **C** (51-92%). A wide variety of α,β-unsaturated aldehydes are well tolerated under the optimized reaction conditions and nucleophiles like β-diketones and β-keto esters underwent smooth annulation reaction to afford the desired products.

Scheme 1.6: Synthesis of Dihydropyranones under Oxidative NHC-Catalysis



The authors proposed the probable pathway of the reaction by the two electron oxidation and deprotonation of the in situ generated Breslow intermediate **18** to generate α,β-

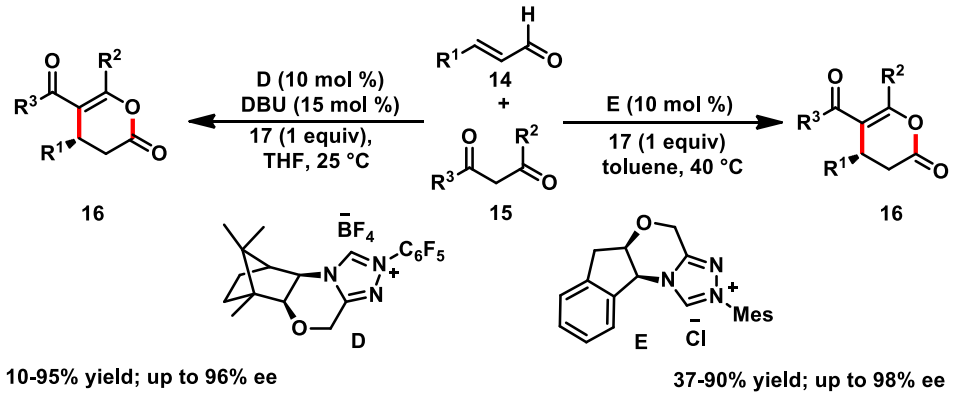
Scheme 1.7: Proposed Mechanism of the NHC-Catalyzed Dihydropyranone Synthesis



unsaturated acylazolium intermediate **19** (Scheme1.7)**.** 1,4-addition of 1,3-bisnucleophilic **15** to **19** affords **20**. Proton transfer followed by cyclization leads to dihydropyranone **16**. Moreover they have performed experimental and theoretical investigations on the mode of addition of nucleophiles to the α,β-unsaturated acyl azolium ions and found that 1,4-addition is more preferable than 1,2-addition.[12]

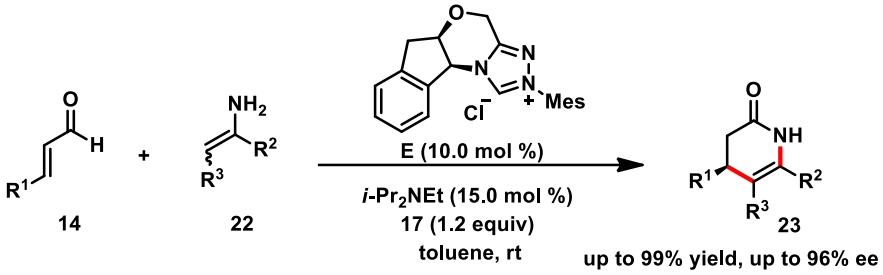
Subsequently, the You[13] and Xiao[14] groups independently reported the enantioselective annulation reactions of enals with 1,3-dicarbonyl compounds under oxidative conditions using oxidant **17** (Scheme 1.8). You and co-workers employed *D*-camphor derived triazolium precatalyst **D**, DBU as the base and $NaBF_4$ as an additive to furnish dihydropyranones **16** in moderate to good yields (10-95%) and high ee values (up to 96%). Simultaneously, Xiao and co-workers used NHC generated from the aminoindanol derived chiral triazolium salt **E** to obtain the annulated products **16** in good yields with excellent selectivity (up to 98% ee) under base-free condition from enal in the presence of oxidant **17**. Notably, the reaction of oxidatively generated α,β-unsaturated acyl azolium with various 1,3-bisnucleophile for the synthesis of dihydropyranones were demonstrated by the research group of Xu,[15] Du,[16] Biju,[17] and You.[18]

Scheme 1.8: Enantioselective Synthesis of Dihydropyranones



Generation of α,β-unsaturated acyl azolium intermediate under oxidative condition is not only limited for the synthesis of dihydropyranones, but in 2011, Bode and co-workers reported the annulation of enals **14** or their α′-hydroxyenones surrogates with unprotected vinylogous amides **22** via NHC-catalyzed aza-Claisen rearrangement (scheme 1.9).[19] Using chiral triazoliun salt **E** and oxidant **17** a variety of enals (aliphatic and aromatic) and unprotected enamines containing electron withdrawing group react smoothly to afforded 3,4-dihydropyridinones **23** in good yields (60-99%) and high enantioselectivity (up to 96% ee). Later, the same research group[20] as well as Du[21] and Zhong[22] groups reported the synthesis of dihydropyridinones using other1,3-bisnucleophiles.

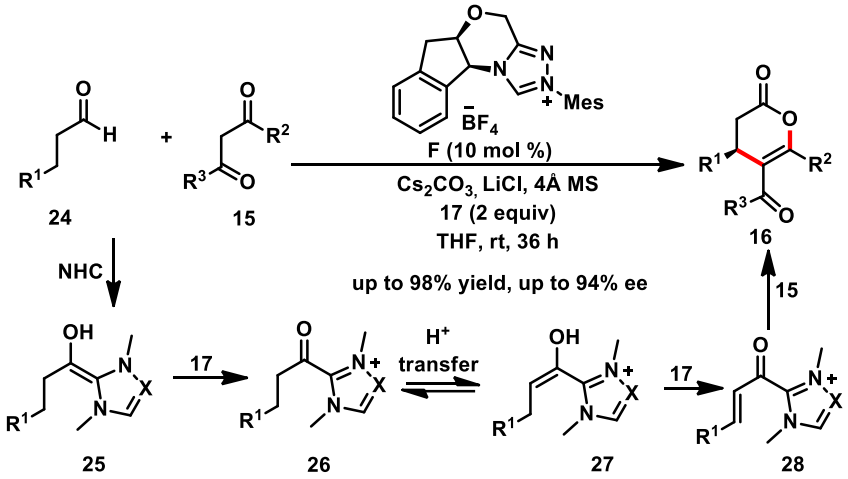
Scheme 1.9: NHC-Catalyzed Enantioselective Synthesis of Dihydropyridinones.



1.4.2. Generation of α,β-Unsaturated Acyl azoliums from Saturated Aldehyde under Oxidative Conditions

In 2013, Chi and co-workers developed a unique method for the direct functionalization of typically inert β-C(sp^3)-H bond of saturated aldehyde **24** through oxidative NHC catalysis for the enantioselective synthesis of dihydropyranones **16** (Scheme 1.10).[23] This double oxidation process differs from the traditional oxidation of the homoenolate to α,β-unsaturated acylazoliums. The reaction proceeds via the generation of Breslow intermediate **25** from aldehyde **24** and NHC generated from the triazolium salt **F**, which is oxidized to the NHC-bound acyl azolium ion **26**. A subsequent proton transfer generates the azolium enolate **27**, which on oxidation using excess bisquinone **17** forms the α,β-unsaturated acyl azolium intermediates **28**. Interception of **28** with 1,3-dicarbonyl compounds resulted in the formation of dihydropyranones **16** in good yields (53-98%) with good ee values (up to 94%).

Scheme 1.10: Direct Functionalization of β-C-H Bond of Saturated Aldehydes

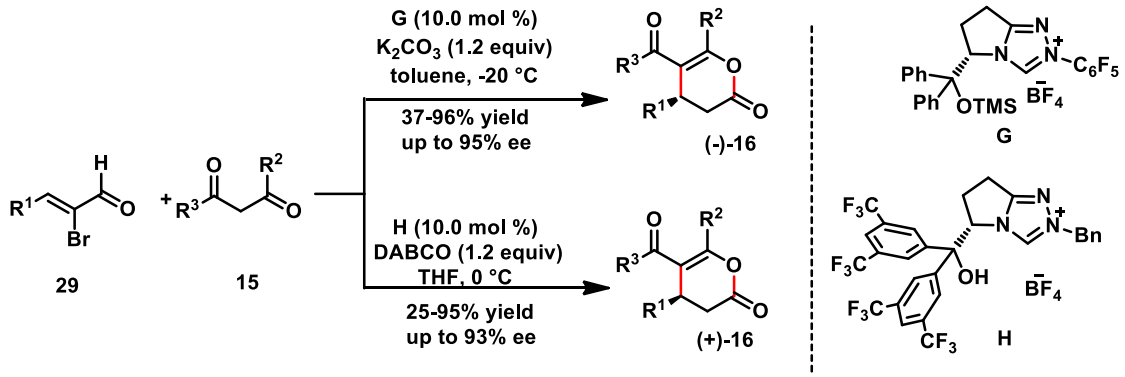


1.4.3. Generation of α,β-Unsaturated Acyl azoliums from 2-Bromoenals

Instead of starting with enals under oxidative conditions, the α,β-unsaturated acyl azoliums can also be generated starting with an oxidized enals. In 2011, Ye and co-workers introduced 2-bromoenals **29** as a bench stable precursor for the generation of chiral α,β-

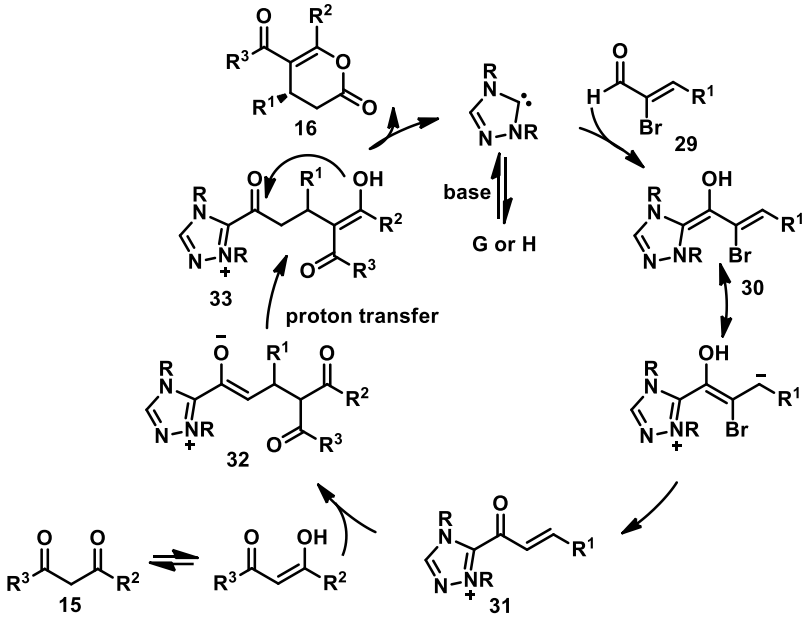
unsaturated acyl azoliums. A highly enantioselective [3+3] annulation reaction of this intermediate with 1,3-dicarbonyl compounds **15** afforded the dihydropyranones **16** in high yield (37-96%) and high enantioselectivity (up to 95%) (Scheme 1.11).[24] A variety of electronically different α-bromo-β-aryl enals as well as aliphatic bromoenals and several 1,3-dicarbonyl compounds were well tolerated under the optimized reaction conditions. Interestingly, both enantiomers of dihydropyranones **16** can be synthesized depending upon the proper choice of catalyst and base. The reaction performed using NHC generated from triazolium salt **G** with a protected –OH moiety afforded the **(-)-16** enantiomer whereas the employing NHC generated from triazolium salt **H** having a free -OH group afforded the **(+)-16** enantiomer. A hydrogen bonding interaction between 1,3-dicarbonyl compound and free -OH group of the catalyst in the transition state illustrated the high stereoselectivity in the reaction. Independent work by Yao and co-workers also demonstrated the synthesis of racemic dihydropyranones by the reaction of 2-bromoenals with 1,3-dicarbonyl compounds in the presence of NHC generated from IMes.HCl.[25] Additionally, the synthesis of various dihydropyranones and dihydropyridinones proceeding through the generation of α,β-unsaturated acyl azolium intermediate from 2-bromoenal was uncovered by Biju,[26] Enders[27] and Ye.[28]

Scheme 1.11: NHC-Catalyzed Annulation of 2-Bromoenals with 1,3-Dicarbonyls



Mechanistically, the reaction is initiated by the addition of free carbene to the 2-bromoenal **29** generating the Breslow intermediate **30**, which undergoes debromination to generate the key α,β-unsaturated acyl azolium intermediate **31** (Scheme 1.12). Nucleophilic addition of **15** to intermediate **31** generates the NHC-bound enolate **32**, which undergoes proton transfer to form **33** and a subsequent intramolecular acylation resulted in the formation of the dihydropyranones.

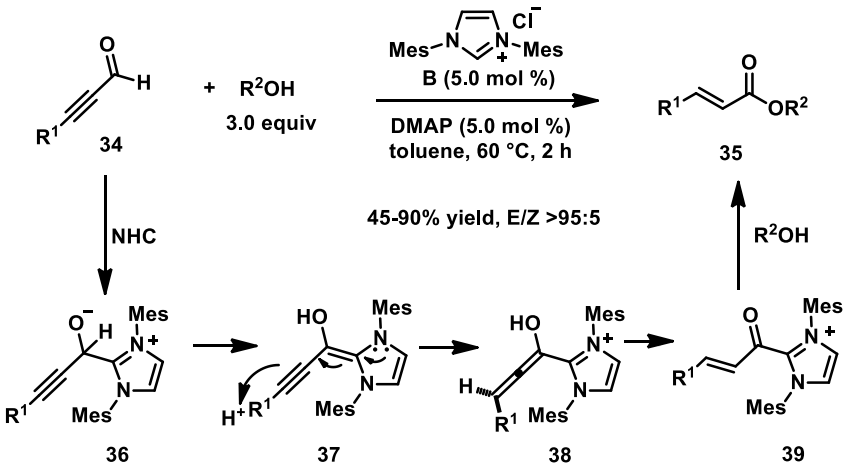
Scheme 1.12: Proposed Mechanism of Dyhydropyaranone Formation from 2-Bromoenals



1.4.4. Generation of α,β-Unsaturated Acyl azoliums from Ynals

In 2006, Zeitler uncovered the potential use of propargylic aldehydes **34** as precursor for the NHC-catalyzed generation of α,β-unsaturated acyl azoliums **39**, and reported an atom-economic redox esterification to provide α,β-unsaturated esters **35** (Scheme 1.13).[29] Under optimized reaction conditions, various aryl and aliphatic ynals as well as a range of primary alcohols were well tolerated to furnish desired unsaturated esters in good yields (45-90%) with good selectivity. The use of sterically demanding carbene generated from the imidazolium salt **B** was mandatory for the stereoselectivity of this esterification reaction. The reaction proceeds via the generation of tetrahedral intermediate **36** by the 1,2-addition of NHC generated from **B** to ynal **34**. This can then generate the unsaturated Breslow intermediate **37** by proton transfer, followed by β-protonation results in the formation of the

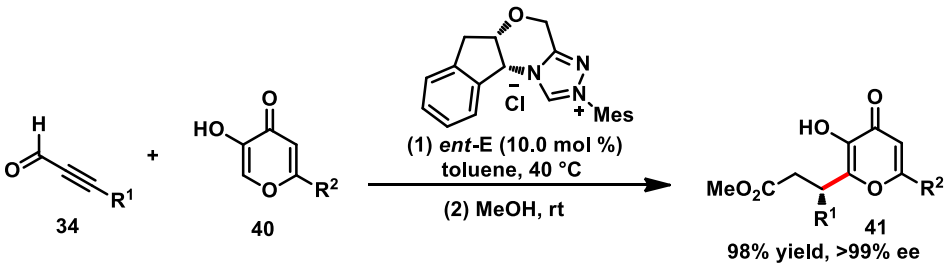
Scheme 1.13: Redox-Esterification of Ynals via α,β-Unsaturated Acyl Azolium



allenol intermediate **38**. The allenol **38** can undergo rapid tautomerization to afford α,β-unsaturated acylazolium **39**. Interception of **39** with alcohols provide the corresponding unsaturated esters **35**.

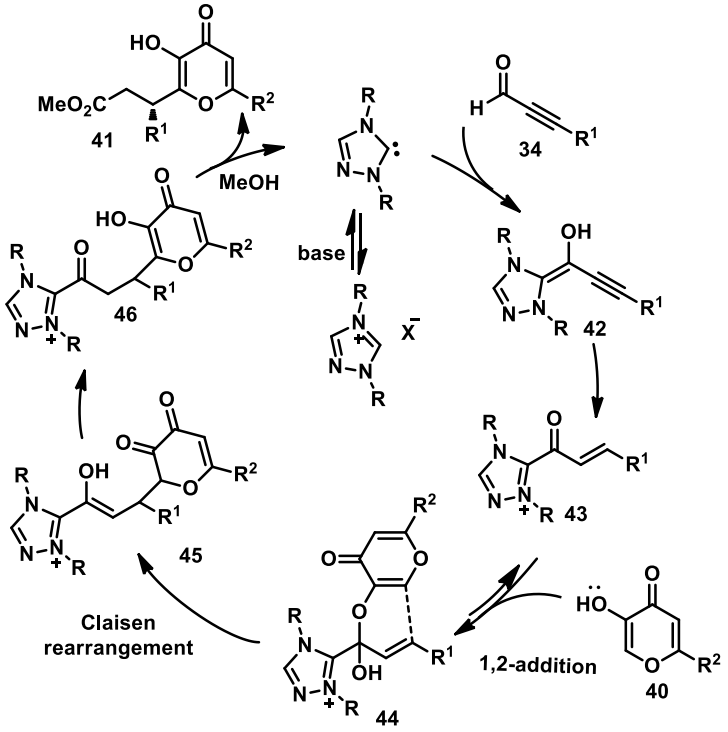
Efficient coupling of ynals with enolic *C*-nucleophiles such as kojic acids **40** proceeding via the enantioselective Claisen rearrangement was disclosed by Bode and co-workers (Scheme 1.14).[30] The expected dihydropyranone product was unstable under the reaction conditions, and in presence of methanol, the ring-opened product **41** was formed in good yield (78-98%) and excellent enantioselectivity (upto >99%). Employing the NHC generated from the chiral triazolium salt ***ent*-E**, various aliphatic and aromatic ynals as well as substituted kojic acids are well tolerated. In addition to kojic acid, pyruvic esters and β-naphthol afforded the corresponding functionalized dihydropyranone under the present conditions. Notably, this annulation was found to proceed in the absence of added base and the counterion of the azolium salt acts as a mild base for the generation of free carbenes.

Scheme 1.14: Annulation of Ynals with Kojic Acid via Claisen Rearrangement



Based on detailed kinetic studies, the mechanism of the NHC-catalyzed reaction of ynals with kojic acids is proposed (Scheme 1.15). The reaction proceeds via the addition of NHC to the ynals generating the Breslow intermediate **42**, which is converted into the key α,β-unsaturated acylazolium intermediate **43**. The 1,2-addition of kojic acid to the intermediate **43** generates the hemiketal intermediate **44**, which undergoes a Claisen rearrangement to give the enol intermediate **45**. Rapid proton transfer to the intermediate **45** followed by the methanolysis afforded the observed product **41**. Moreover, DFT computational studies from Schoenebeck and co-workers suggested a two-step mechanism beginning with 1,2 addition followed by [3,3] sigmatropic rearrangement as a key carbon-carbon bond-forming step[31] which is more favoured than 1,4-addition step proposed by Studer group.[12] Subsequently, Xiao and co-workers disclosed an efficient and atom economic NHC-catalyzed annulation reaction of ynals with 1,3-diketones or 1,3-keto esters for the synthesis of dihydropyranones.[32]

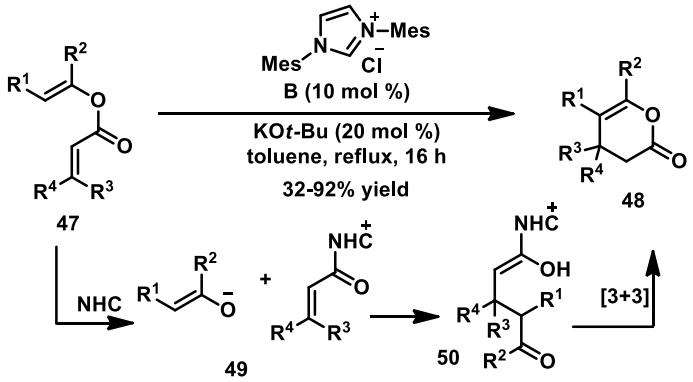
Scheme 1.15: Proposed Mechanism of the Ynal Annulation with Kojic Acids



1.4.5. Generation of α,β-Unsaturated Acyl azoliums from Esters

In 2009, Lupton and co-workers reported the conjugated addition reaction involving α,β-unsaturated acyl azolium intermediate. NHC-catalyzed fragmentation of α,β-unsaturated enol esters **47** followed by the recombination of corresponding acyl azolium/enolate ion pair **49** to furnish 2,3-dihydropyranones **48** (scheme 1.16).[33] A variety of enol esters including the β,β-disubstituted ones underwent smooth annulation reaction to afford the dihydropyranones in good yields (up to 92%). Later, the same research group demonstrated α,β-unsaturated dienyl ester as a precursor for α,β-unsaturated acyl azolium intermediate.[34]

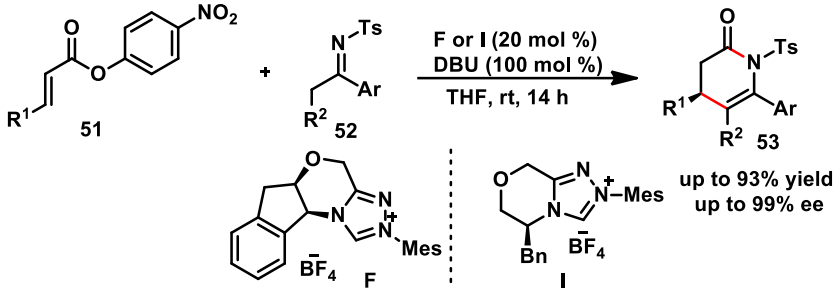
Scheme 1.16: NHC-Catalyzed Annulation of α,β-Unsaturated Enol Esters



NHC-catalyzed LUMO activation of α,β-unsaturated esters **51** and subsequent formal [3+3] annulation reaction with imines **52** for the enantioselective synthesis of

dihydropyridinones **53** was developed by Chi and co-workers (Scheme 1.17).[35] A range of substitution in aryl ring of α,β-unsaturated ester as well as differently substituted arylimines are well tolerated under the optimized reaction conditions to afford the product in good to excellent yield (45-93%) and excellent enantioselectivity (up to 99%). The 4-nitro phenyl moiety on the ester was crucial for the reactivity. Notably, using proper chiral NHC precursor, sterically demanding α,β-disubstituted ester and β,β-disubstituted esters were tolerated well under the present conditions.

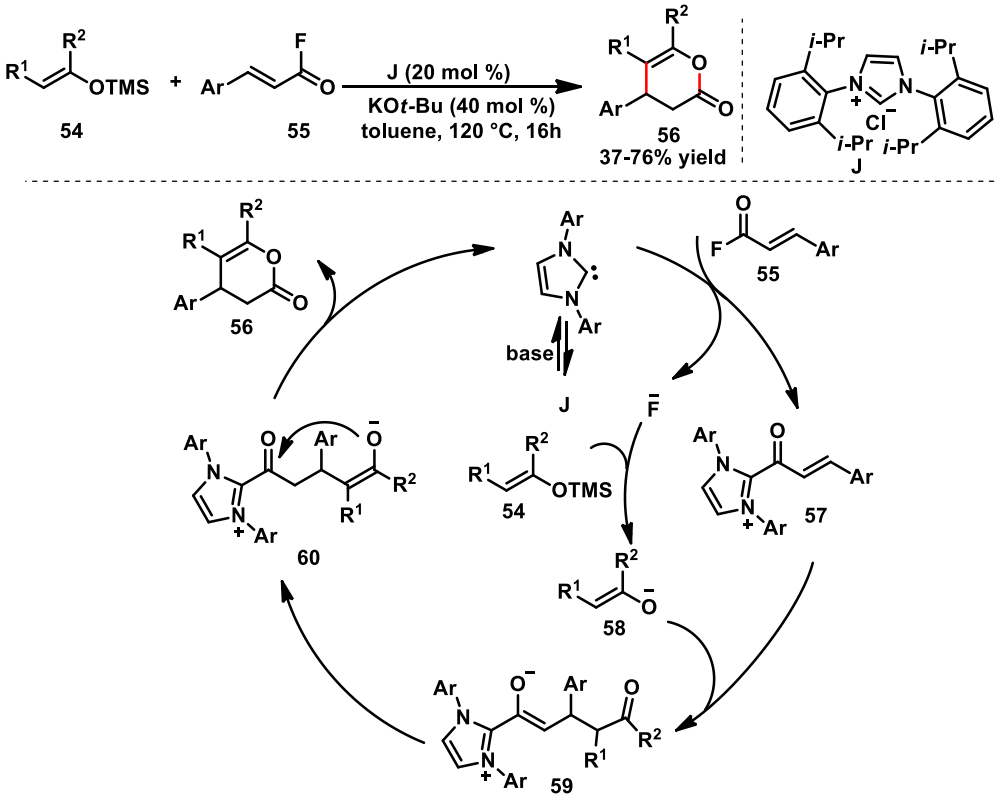
Scheme 1.17: Enantioselective [3+3] Annulation of α,β-Unsaturated Ester and Imines.



1.4.6. Generation of α,β-Unsaturated Acyl azoliums from Acid Fluorides

In 2009, Lupton and co-workers demonstrated the NHC catalyzed [3+3] annulation reaction of TMS enol ethers **54** with α,β-unsaturated acid fluoride **55** leading to the synthesis of dihydropyranones **56** in 37-76% yield (Scheme 1.18).[36] The addition of NHC to the α,β-

Scheme 1.18: Synthesis of Dihydropyranones from Unsaturated Acyl Fluorides.

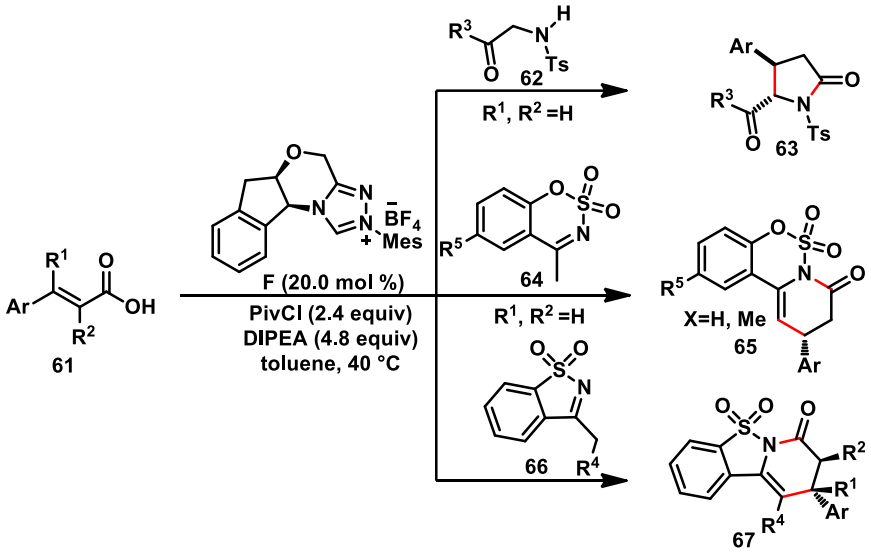


unsaturated fluoride generates the α,β-unsaturated acyl azolium **57** and at the same time the generated fluoride deprotects the enol ether to form the naked enolate **58**. The addition of enolate **58** to the azolium **57** generates the enolate **59**, which on proton transfer gives the azolium **60** and a subsequent acylation affords the dihydropyranone derivatives **56**.

1.4.7. Generation of α,β-Unsaturated Acyl azoliums from Acids

In 2014, Ye and co-workers demonstrated the activation of α,β-unsaturated carboxylic acids **61** using NHC organocatalysis. Using chiral triazolium precatalyst **F**, the generation of chiral α,β-unsaturated acyl azolium intermediate via the formation of mixed anhydride with pivaloyl chloride was possible and their subsequent interception with various 1,2 or 1,3-bis nucleophile afforded five or six-membered heterocycle product (Scheme 1.19).[37] Employing α-amino ketones **62** as 1,2-bisnucleophiles, the reaction furnished the γ-butyrolactams **63** in good yields (52-73%), moderate diastereoselectivity (up to 12:1 dr) and high ee value (up to 98% ee). Furthermore, sulfamate-derived cyclic imines **64** as 1,3-bisnucleophiles afforded the corresponding dihydropyridinones **65** in good yields (57-86%) and excellent

Scheme 1.19: NHC-Catalyzed Annulation of α,β-Unsaturated Carboxylic Acids

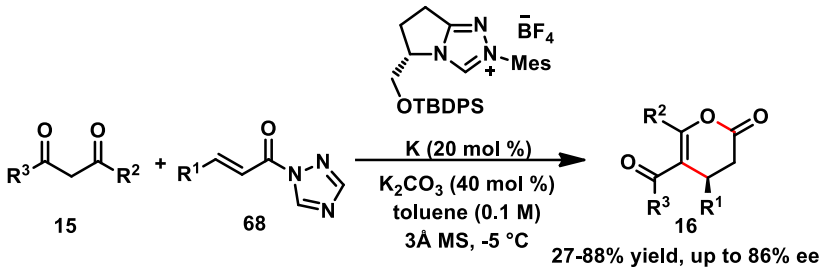


enantioselectivity (up to 99%) under the same optimized conditions. Moreover, the sultam-derived cyclic imines **66** were also successfully employed as potential substrates for the [3+3] cyclocondensation with α,β-unsaturated acids, to provide the desired tricyclic sultams **67** in good yields (52-90%) and with high enantioselectivity (up to 98% ee). Remarkably, β,β-disubstituted and α,β-disubstituted acids also reacted to furnish the products with quaternary carbon centres.

1.4.8. Generation of α,β-Unsaturated Acyl azoliums from Amides

In addition to the acid activation mentioned before, α,β-unsaturated amides can also be used as a stable precursor for α,β-unsaturated acyl azolium intermediates. In 2015, Enders and co-workers disclosed the activation of α,β-unsaturated *N*-acyltriazoles **68** for the generation of α,β-unsaturated acylazolium intermediates (Scheme 1.20).[38] This allows enantioselective synthesis of dihydropyranones **16** through [3+3] cycloaddition with 1,3-dicarbonyl compounds **15**. Under optimized conditions the corresponding products were formed in good yields (27-88%) with high enantioselectivities (up to 99% ee).

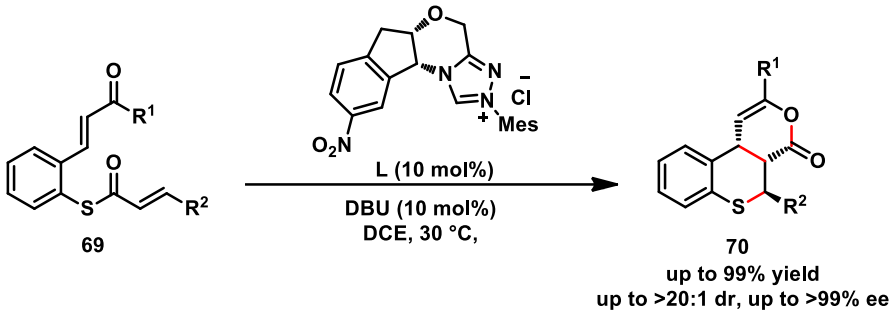
Scheme 1.20: Enantioselective NHC-Catalyzed Annulation of α,β-Unsaturated Amides.



1.4.9. Generation of α,β-Unsaturated Acyl azoliums from Thioesters

Very recently, Xu and co-workers showed the generation of α,β-unsaturated acyl azolium intermediate from α,β-unsaturated thioester **69** (Scheme 1.21).[39] In presence of carbene generated from chiral triazolium salt **L**, the highly efficient organocascade reaction proceeds through sulpha-Michael/Michael/lactonization sequence to form highly substituted thiochroman derivative **70** in excellent yield and stereoselectivity.

Scheme 1.21: Generation of α,β-Unsaturated Acyl azoliums from Thioesters

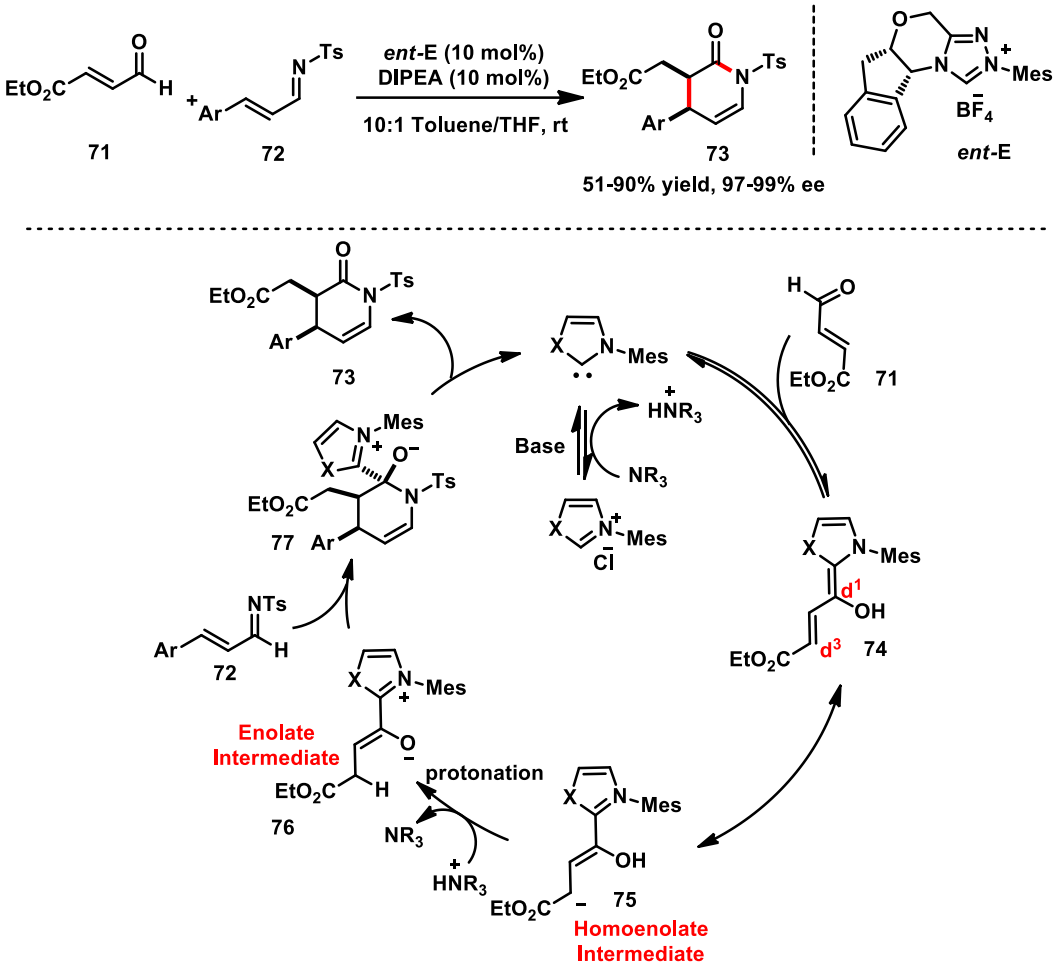


1.5. NHC-Catalyzed Reaction via Enolate Intermediate

NHC-catalyzed generation of azolium bound enolate intermediate and their reaction with various electrophiles are one of the important modes of non-umpolung reactivity. Also it can undergo various cycloaddition reactions. In 2006, Bode and co-workers reported the enantioselective synthesis of dihydropyridinone derivatives **73** by NHC-catalyzed formal hetero Diels-Alder reaction of enals **71** with α,β-unsaturated imines **72** (Scheme 1.22).[40] The

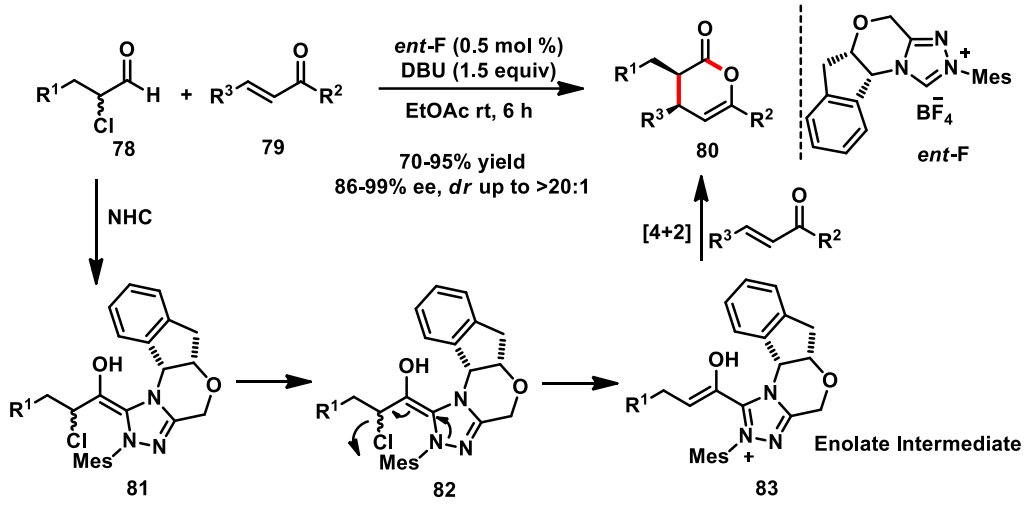
mechanism involves the generation of homoenolate intermediate **75** by the initial attack NHC to enal **71**. The key to success of these reactions is the use of catalytic amount of mild organic base. If the conjugate acid of the catalytic base, generated by deprotonation of the azolium salt, is acidic enough to protonate the conjugated Breslow intermediate at the β-position, the formation of enolate equivalent **76** occurs. A [4+2] cycloaddition between **72** and the enolate **76** generates the alkoxide **77**, which releases free NHC to furnish **73**.

Scheme 1.22: NHC-Catalyzed Generation of Enolate Intermediate



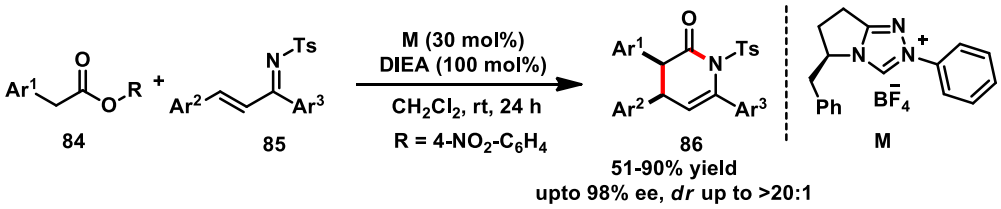
Subsequently, the same group reported the generation of enolate intermediate **83** from α-chloro aldehydes **78** for highly enantioselective inverse-electron demand Diels-Alder reactions with enones **79** to give enantioenriched dihydropyranone product **80** (Scheme 1.23).[41] Aromatic and aliphatic α-chloro aldehydes when treated with enones furnished the desired dihydropyranones products **80** under mild reaction conditions. The reaction proceeds with low catalyst loading of NHC precursor ***ent*-F** and provides the dihydropyranones **80** in good yield and excellent diastereo- and enantioselectivity.

Scheme 1.23: Diels-Alder Reaction of α-Chloro Aldehydes with Enones



In 2012, Chi and co-workers developed an elegant method for the generation of azolium enolate intermediate from stable carboxylate ester **84** (Scheme 1.24).[42] The catalytically generated arylacetic ester enolates from **84** using carbene generated from triazolium salt **M** undergo enantioselective inverse electron demand hetero Diels-Alder reactions with α,β-unsaturated imines **85** to form the desired dihydropyridinone derivatives **86** with good yield and moderate to good enantioselectivity. Moreover, the generation of azolium enolate intermediate from carboxylic acid or cyclopropane aldehyde was developed by the research group of Scheidt [43] and Chi.[44] The general description of the NHC-catalyzed formation of enolate intermediate from ketenes has been described in chapter 3, section 3.1.1, page 68.

Scheme 1.24: NHC-Catalyzed Generation of Enolate Intermediate form Carboxylate Esters

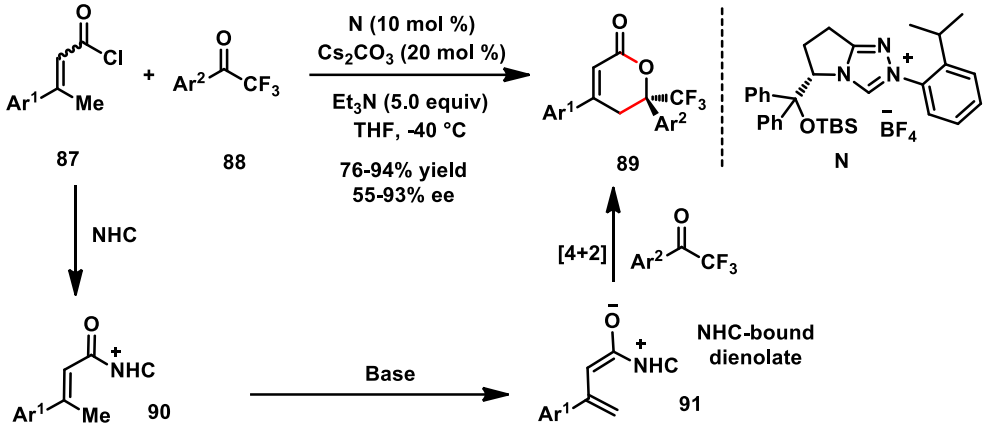


1.6. NHC-Catalyzed Reaction via Dienolate Intermediate

A recent development in NHC-organocatalysis is the NHC-bound dienolates, which play a vital role in the construction of six-membered heterocycles and carbocycles via [4+2] cycloaddition reactions through the activation of a remote C(sp3)-H bond. In 2011, Ye and co-workers developed the catalytically generated NHC-bound dienolates **91** from unsaturated acylchlorides **87** (Scheme 1.25).[45] Interception of these intermediates with trifluoromethyl ketones **88** afforded the enantioselective synthesis of trifluoromethyl substituted δ-lactones **89** in good yields with high enantioselectivity. Best results were obtained with NHC

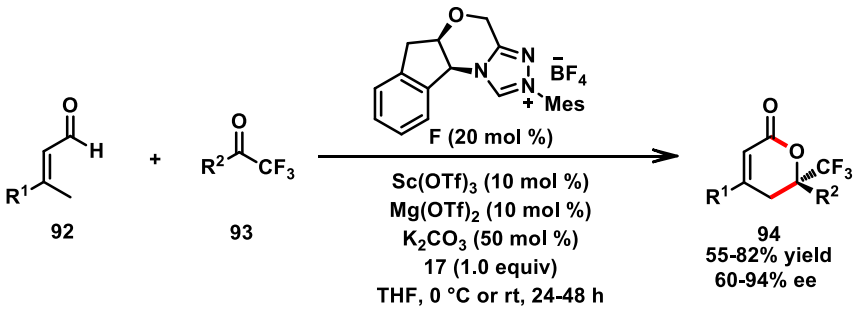
generated from **N** and catalytic amounts of Cs_2CO_3 in excess Et_3N. The reactions are found to be quite general with other activated ketones such as isatins for the enantioselective synthesis of spirocyclic oxindole-δ-lactones.

Scheme 1.25: Generation of NHC-bound Vinylenolates from Unsaturated Acylchlorides



Subsequently, Chi and co-workers developed the oxidative NHC-catalyzed [4+2] cycloaddition of β,β-disubstituted enals with trifluoromethyl ketones **93** for the remote γ-functionalization of enals (Scheme 1.26).[46] The reaction proceeds via the key NHC- bound dienolate intermediates generated under oxidative NHC-catalysis. The use of NHC in combination with the Lewis acid cocatalyst was essential for the high reactivity and selectivity resulting in the formation of unsaturated δ-lactones in moderate to good yields (55-82%) with high enantioselectivity (up to 94% ee).

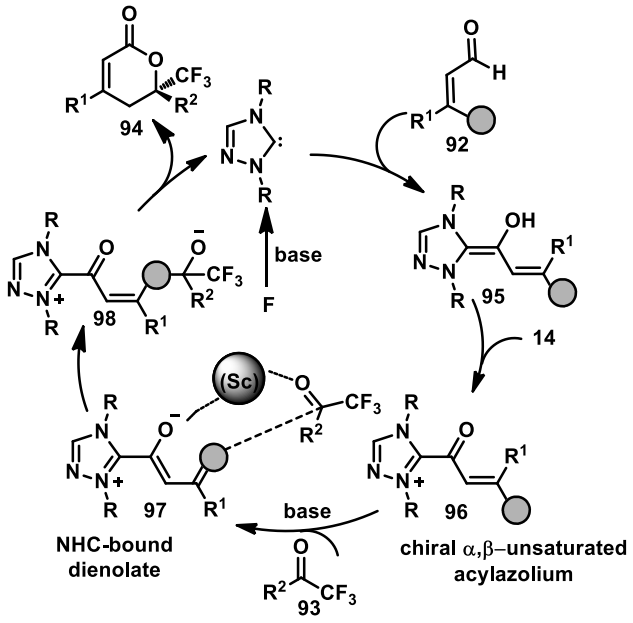
Scheme 1.26: NHC-catalyzed synthesis of δ-lactones via dienolate intermediates.



The mechanism of this transformation involves the initial 1,2-addition of free carbene to α,β-unsaturated aldehyde followed by proton transfer to generate the extended Breslow intermediate **95**. Oxidation of **95** with oxidant **17** forms the α,β-unsaturated acyl azolium intermediate **96**. The γ-deprotonation of **96** forms the key NHC-bound dienolate intermediate **97**. Nucleophilic addition of dienolate **97** to the trifluoromethyl ketone forms the azolium intermediate **98**, which on intramolecular acylation leads to the product dihydropyranone **94** and regeneration of the NHC catalyst (Scheme 1.27). The Lewis acid coordinates with the

NHC-bound dienolate as well as the ketone thus assisting the stereocontrol at the remote γ-carbon of enal. Additionally, the annulation reaction of NHC-bound dienolate, generated from other precursors was developed by the research group of Chi[47], Yao[48] and Zhong.[49]

Scheme 1.27: Proposed Mechanism of the Reaction



1.7. Conclusion and Focal Theme of the Present Work

As discussed in the above sections, the NHC-catalyzed non-umpolung reactivity is one of the fast growing field for the enantioselective construction of cyclic and acyclic molecules. The focal theme of this thesis is to utilize the chiral α,β-unsaturated acyl azolium and azolium bound enolate intermediates in various organocascade processes. If successful, this can result in the enantioselective construction of various carbocycles and heterocycles.

NHC-catalyzed enantioselective synthesis of functionalized cyclopentenes and cyclopentane-fused β-lactones by the reaction of α-bromoenals with α-substituted malonate has been described in the second chapter. The NHC-catalyzed generation of α,β-unsaturated acyl azolium ion and their reaction with malonate ester derivatives affords the expected cyclopentene products. Depending on the substitution at the γ position of malonate (alkyl or aryl), functionalized lactones and cyclopentenes are formed.

Moreover, the compatibility of carboxylic acid substrate with carbenes is one of the most challenging tasks in NHC-organocatalysis. In view of this, we treated linear ketoacid substrates under NHC-catalyzed condition in presence of peptide coupling agent. The detailed study of the NHC-catalyzed aldol lactonization of ketoacids for the enantioselective synthesis of cyclopentane-fused β-lactones has been discussed in chapter 3 of the thesis.

Recently, kinetic resolution or dynamic kinetic resolution is considered as an efficient and alternative approach for asymmetric synthesis. In the fourth chapter, the aldol lactonization of ketoacids has been presented which proceeds via dynamic kinetic resolution. Additionally, a synthetic utility of the β-lactone products for the synthesis of succinimides has been demonstrated.

In the context of our recent success in employing α-arylidine pyrazolinone for the tandem generation of dienolate/enolate in oxidative NHC-catalysis for the synthesis of spirocyclohexadienone,[50] we envisioned the use of this strategy in secondary amine catalysis. The detailed investigation on the enantioselective synthesis of spirocyclohexenols by the reaction of enals with α-arylidine pyrazolinones in presence of secondary amine catalyst is presented in the last chapter of the thesis.

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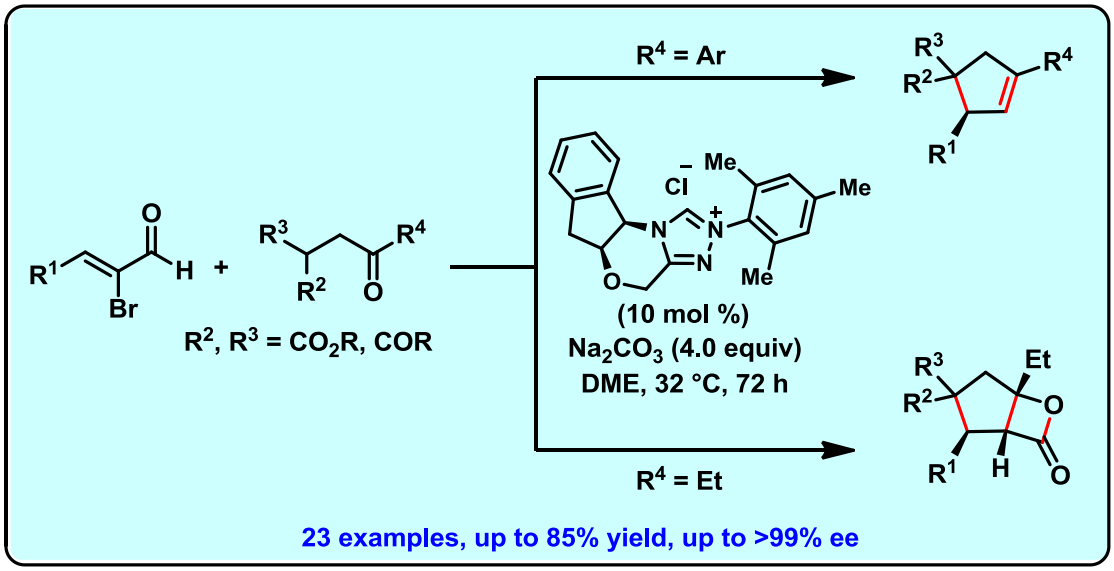
Chapter 2

N-Heterocyclic Carbene-Catalyzed Enantioselective Synthesis of Functionalized Cyclopentenes via α,β-Unsaturated Acyl Azoliums

A highly enantioselective NHC-organocatalyzed synthesis of functionalized cyclopentenes proceeding via α,β-unsaturated acyl azolium intermediates is described in this chapter. The organocascade reaction of modified enals with malonic ester derivatives containing a γ-benzoyl group furnished cyclopentenes in good yields and excellent ee values. Additionally, an enantio and diastereoselective synthesis of cyclopentane-fused β-lactone is demonstrated with malonic ester derivatives containing a γ-acyl group.



Chem. Commun. **2014**, *50*, 14539-14542.

2.1. Introduction

N-heterocyclic carbene organocatalysis has contributed tremendously in the field of asymmetric catalysis from the last decade. It is used as an important synthetic tool for the construction of biologically significant molecules. Functionalized cyclopentenes are one of the essential core structures found in various natural product and biologically relevant molecules. For example, the natural product laurokamurene A is a rearranged aromatic sesquiterpene isolated from the Chinese marine organism *Laurencia*,[1] and sequosempervirin A is a spirocyclic cyclopentene natural product found in the branches and leaves of *Sequoia sempervirens* (Figure 2.1).[2] Furthermore, vibralactone is a cyclopentene-fused β-lactone type metabolite, which is a pancreatic lipase inhibitor.[3] Apart from this, a wide variety of cyclopentenes are employed as an intermediate in the total synthesis of various natural and unnatural products.[4] Due to the wide application of chiral cyclopentenes, development of enantioselective and flexible synthetic routes to these molecules is highly desirable.

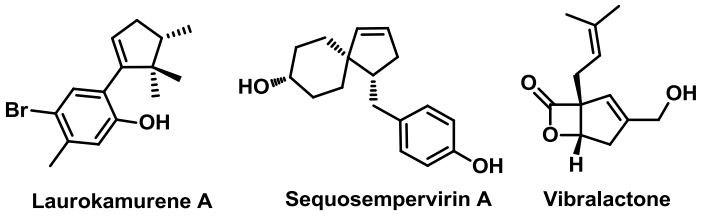


Figure 2.1: Selected Biologically Active Cyclopentene Natural Products

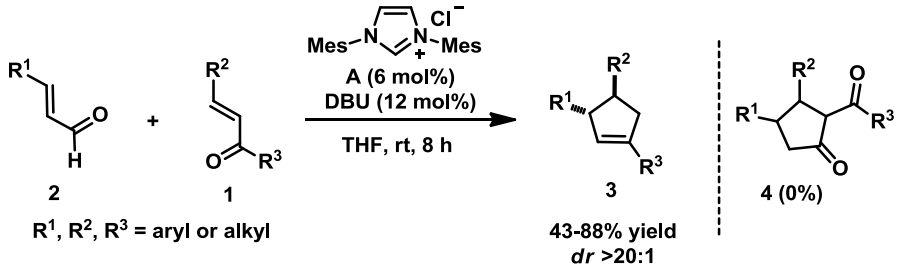
2.1.1. NHC-Catalyzed Synthesis of Cyclopentenes

2.1.1.1. Synthesis of Cyclopentenes via Homoenolate Intermediate

In 2004, the research group of Bode and Glorius independently developed the generation of NHC-bound homoenolate intermediate for the first time, and subsequent reaction with aromatic aldehyde for the synthesis of γ-butyrolactones. [5] In 2006, Nair and co-worker introduced α,β-unsaturated ketones **1** as an electrophilic coupling partner for NHC-bound homoenolate intermediate generated from α,β-unsaturated enals **2**. The reaction resulted in the formation of cyclopentenes **3** instead of the expected cyclopentanones **4** (Scheme 2.1).[6] This observation has led to the development of a new

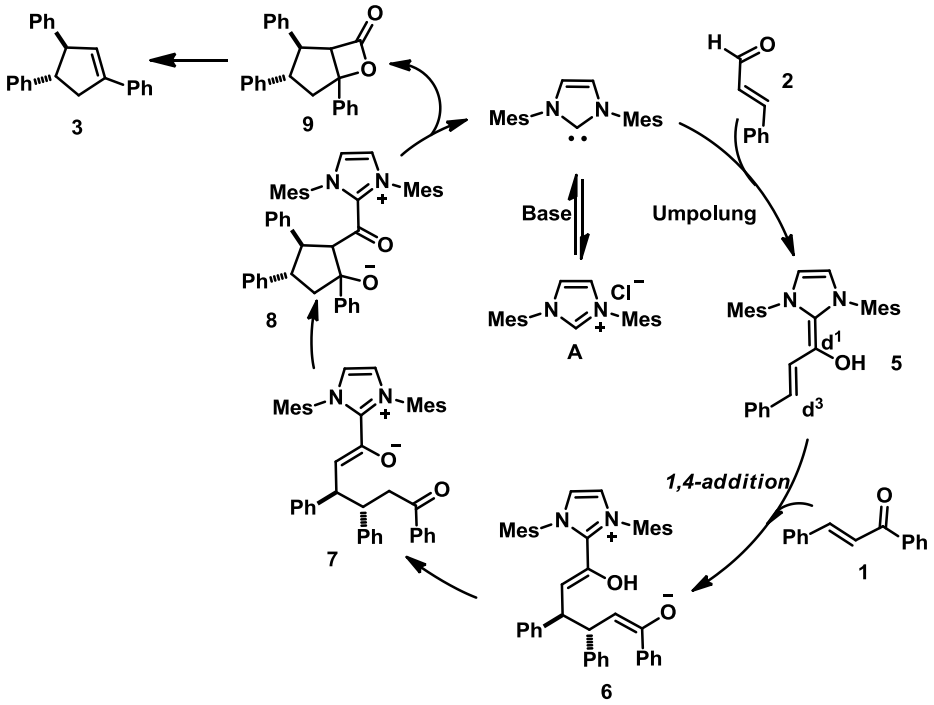
NHC-catalyzed homoenolate annulation method. Interestingly, the reaction afforded a single diastereomer with *trans* selectivity.

Scheme 2.1: NHC-Catalyzed Annulation of Enals and Chalcones



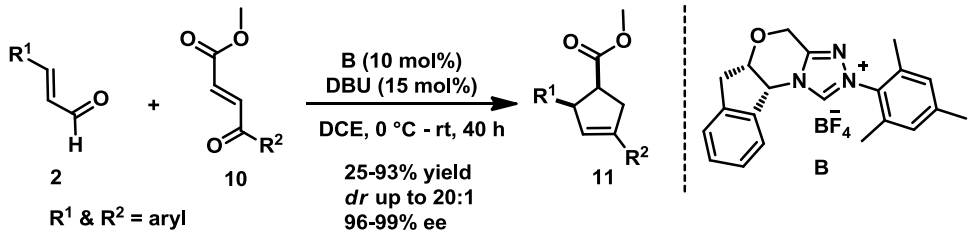
A plausible mechanism is described in Scheme 2.2. The 1,2-addition of NHC to *trans*-cinnamaldehyde **2** gives rise to the extended Breslow intermediate **5**, which undergoes the 1,4-addition to the chalcone **1** to produce the enolate **6**. Tautomerization of **6** leads to the ketone **7**, which then undergoes an intramolecular aldol reaction followed by β-lactonization generates **9**. A spontaneous decarboxylation from β-lactone **9** to form the 3,4-*trans*-disubstituted-1-aryl cyclopentene **3**. Notably, the loss of CO_2 from β-lactone **9** was supported by IR studies. As the reaction progresses in the forward direction, the IR peak of β-lactone carbonyl functionality disappeared.

Scheme 2.2: Proposed Mechanism for Cyclopentene Formation



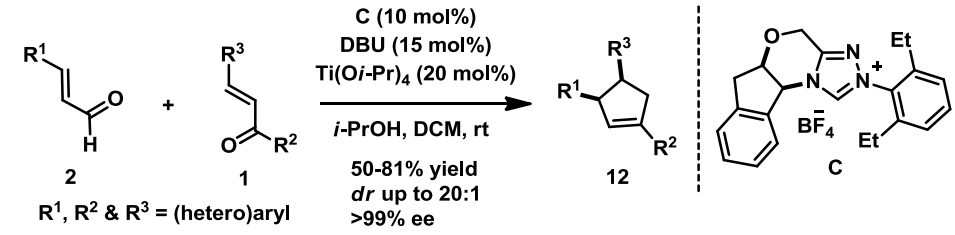
One year later, Bode and co-workers established the enantioselective synthesis of cyclopentenes **11** from enals and 4-oxoenoates **10** in presence of the NHC generated from the chiral aminoindanol derived triazolium precatalyst **B** (Scheme 2.3).[7] The reaction afforded the desired product **11** with high enantio- and diastereoselectivity. Interestingly, this method provides the chiral cyclopentenes in *cis*-isomer, in contrast to the Nair's protocol, which delivered the *trans*-isomer. According to their mechanistic and stereochemical study, the reaction proceeds via an intermolecular cross-benzoin condensation followed by a NHC-promoted oxy-Cope rearrangement.

Scheme 2.3: NHC-Catalyzed Annulation of Enals with 4-Oxoenoates



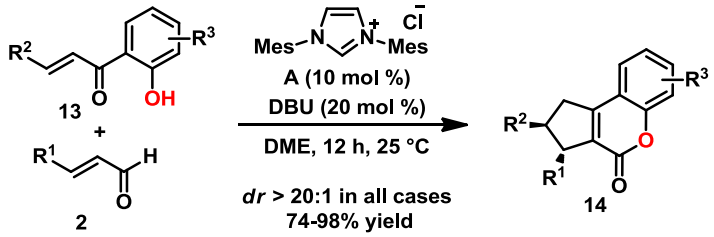
In 2010, Scheidt and co-workers reported a highly enantioselective synthesis of *cis*-cyclopentenes **12** using NHC-Lewis acid cooperative catalysis (Scheme 2.4).[8] The addition of homoenolate, generated from enal **2** in the presence of chiral NHC derived from precatalyst **C** and titanium isopropoxide as a Lewis acid additive to chalcone **1** resulted the formation of the product **12** with moderate to good yields and with excellent enantioselectivity.

Scheme 2.4: Lewis Acid/NHC-Catalyzed Enantioselective Annulation of Enals and Chalcones



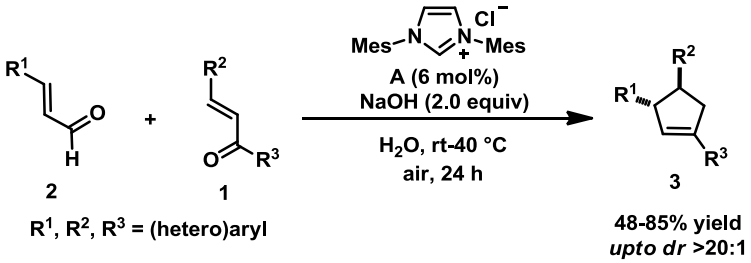
A highly diastereoselective annulation of homoenolate with 2'-hydroxy chalcone **13** for the synthesis of cyclopentane-fused coumarin **14** was demonstrated by our group (Scheme 2.5).[9] Mechanistically, the reaction prefer δ-lactonization unlike the case of usual β-lactonization and a subsequent dehydration to form the desire product in excellent yield and diastereoselectivity.

Scheme 2.5: NHC-Catalyzed Cascade Cyclopentane-Fused Coumarin Synthesis



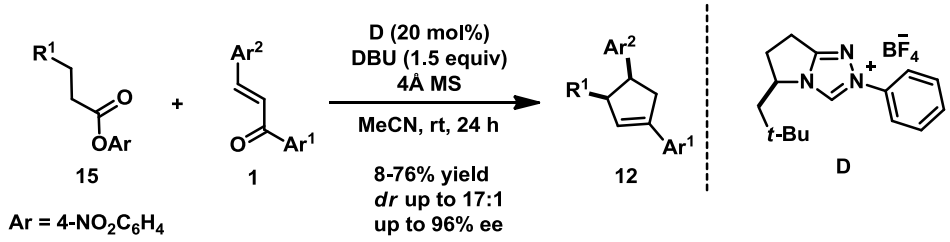
Recently, Chi and co-workers showed the tolerance of this cyclopentanulation reactions by performing in aqueous medium (Scheme 2.6).[10] The generation of homoenolate from enal **2** in water under basic condition, followed by their reaction with chalcone **1** furnished the cyclopentene derivatives **3** in good yield and diasteresselectivity.

Scheme 2.6: NHC-Catalyzed Annulation of Enals and Chalcones under Aqueous Medium



In 2013, the same research group introduced saturated ester **15** as an alternative precursor for homoenolate intermediate. The activation of unactive β-carbon in presence of NHC catalyst for the generation of homoenolate intermediate and the subsequent reaction with chalcone **1** afforded the formation of chiral cyclopentene derivatives **12** in moderate to good yield and stereoselectivity (Scheme 2.7).[11]

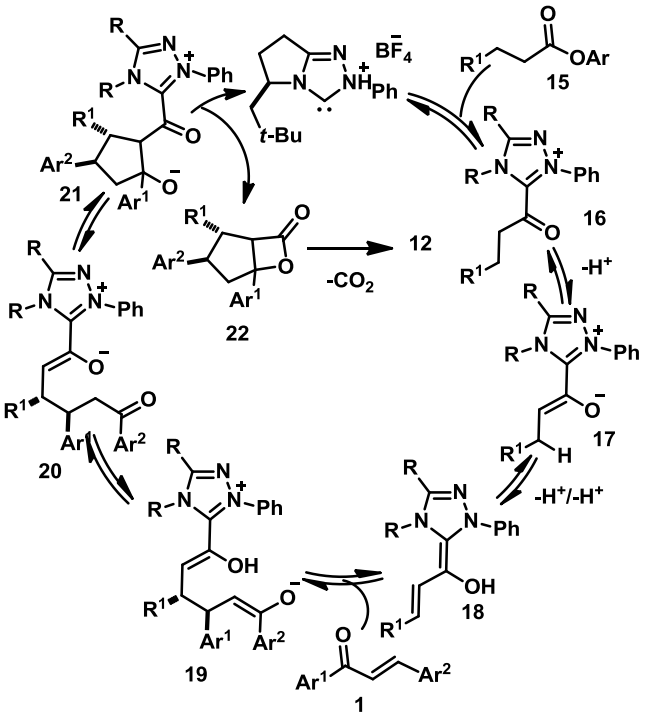
Scheme 2.7: Generation of Homoenolate from Saturated Ester



Mechanistically the reaction proceeds via the generation of acyl azolium species **16** by the initial attack of NHC to the ester **15** (Scheme 2.8). Enolization of acyl azolium followed by β-proton transfer to enolate oxygen generates the homoenolate intermediate **18**

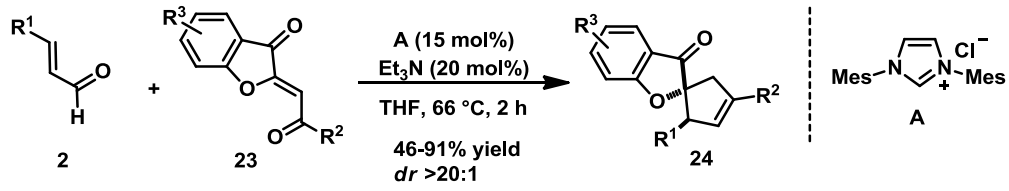
via the NHC-enolate **17**. The addition of intermediate **18** with chalcone furnished the functionalized cyclopentenes **12** proceeds via Nair's pathway via the intermediate **19-22**.

Scheme 2.8: Proposed Mechanism for β-Functionalization of Saturated Ester

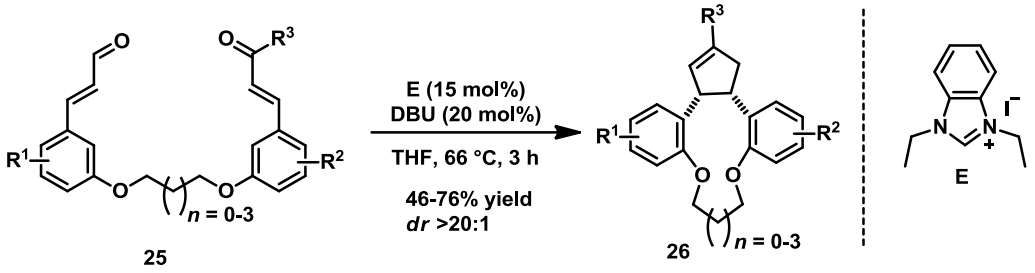


Recently, Nair and co-workers demonstrated the homoenolate annulation of enal **2** with 2-aroylidene benzofuran-ones **23** (Scheme 2.9).[12] The reaction afforded highly diastereoselective cyclopentene-fused spirobenzofuran-3-ones **24** with moderate to excellent yields. The mechanism is similar to the enal-chalcone annulation, while the first nucleophilic homoenolate addition happened with the endocyclic double bond. Simultaneously, the same group employed tethered enal-chalcone substrates **25** in the cyclopentannulation reaction to form the cyclopentene-fused macrocyclic ethers **26** (Scheme 2.10).[13] This process allowed the synthesis of 10-13 membered heterocycles with moderate to good yields and with excellent diastereoselectivity.

Scheme 2.9: NHC-Catalyzed Annulation of Enals with Aurone Derivatives



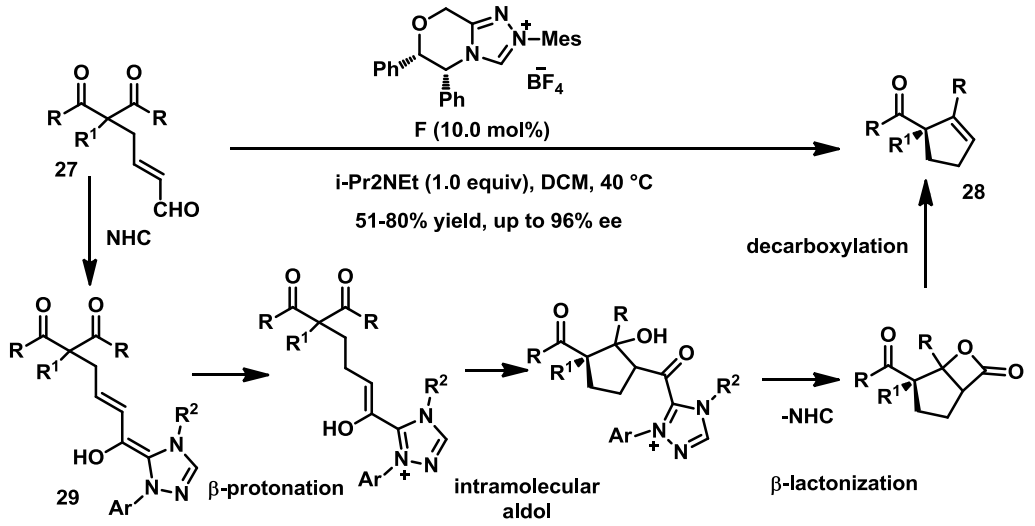
Scheme 2.10: NHC-Catalyzed Macrocycle Synthesis



2.1.1.2. Synthesis of Cyclopentenes via Enolate Intermediate

An enantioselective synthesis of cyclopentenes proceeding via NHC-catalyzed desymmetrization strategy was uncovered by Scheidt and co-workers.[14] In presence the carbene generated from precatalyst **F** and *i*-Pr_2NEt as base, β-protonation of the initially generated homoenolate intermediate **29** takes place, and the subsequent reaction proceeds through intramolecular aldol, β-lactonization and decarboxylation sequence (Scheme 2.11). Additionally, they have demonstrated two examples, in which β-lactone can be isolated without decarboxylation.

Scheme 2.11: Enantioselective Synthesis of Cyclopentene by Desymmetrization Strategy

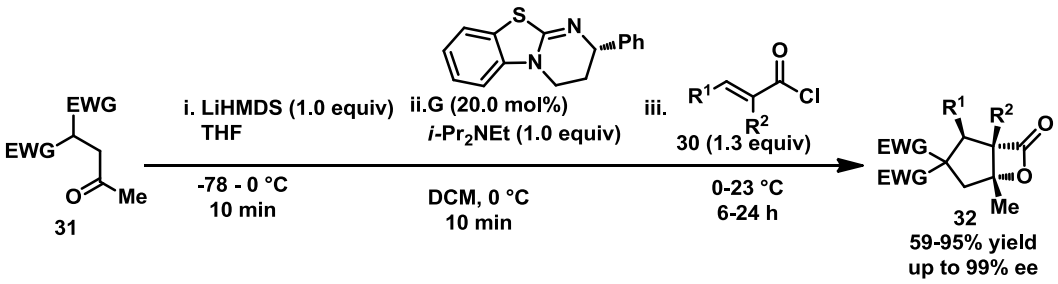


2.1.2. Enantioselective Synthesis of Cyclopentane-fused β-Lactone via α,β-Unsaturated Acyl ammonium Intermediate

In 2013, the research group of Romo developed an elegant method for the enantioselective synthesis of cyclopentane-fused β-lactone **32** by the isothioures catalyzed cascade reaction of α,β-unsaturated acyl chloride **30** with malonic ester containing a β-

oxyalkyl group **31** (Scheme 2.12).[15] The highly efficient organocascade reaction proceeds in the presence of isothiourea catalysist **G** through Michael-aldol-lactonization sequence, leading to the desired product in good yield, excellent enantio- and diastereoselectivity.

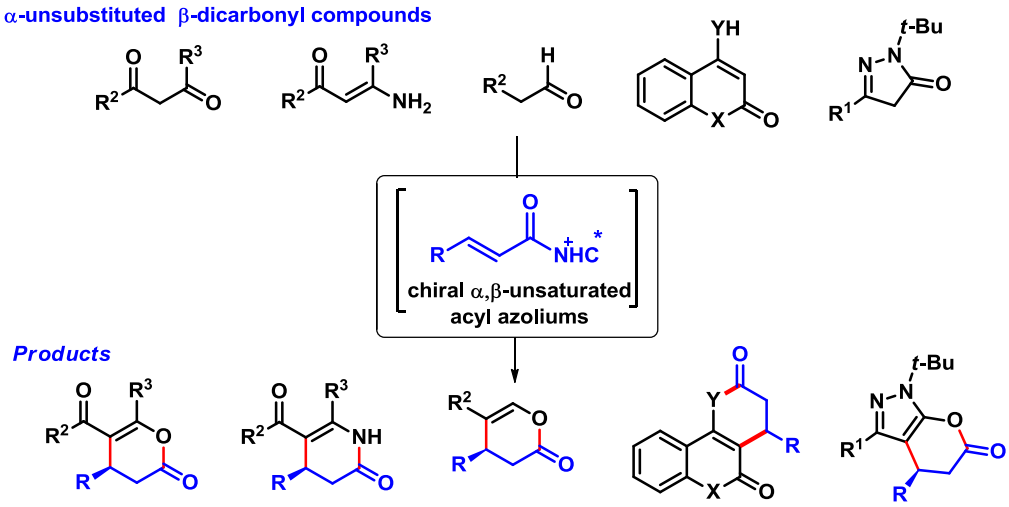
Scheme 2.12: Enantioselective Synthesis of Cyclopentane-Fused β-Lactone Using Isothiourea Catalyst



2.2. Statement of the Problem

As discussed in the introduction section, most of the NHC-catalyzed cyclopentene forming reactions proceed through homoenolate intermediate, also known as conjugated umpolung pathway. But we envisaged the synthesis of cyclopentenes via a non-umpolung strategy, which can engage α,β-unsaturated acyl azolium as key intermediate. Recently, our group has demonstrated the reaction of α,β-unsaturated acyl azolium with α-unsubstituted β-dicarbonyl compounds for the enantioselective synthesis of dihydropyranone and dihydropyridinone (Scheme 2.13).[16]

Scheme 2.13: Reaction of α,β-Unsaturated Acyl Azoliums with α-Unsubstituted β-Dicarbonyl Compounds



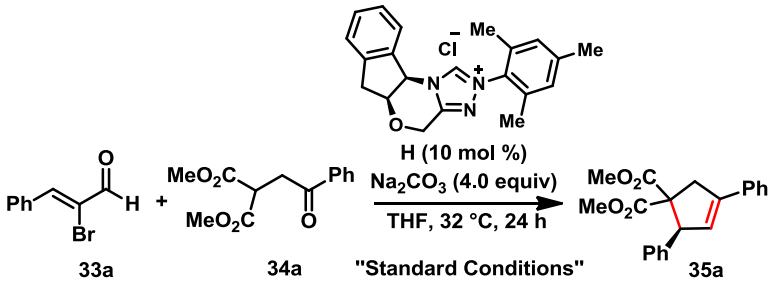
In this context, we envisioned the reaction of α-substituted β-diester with α,β-unsaturated acyl azoliums. The study on NHC-catalyzed reaction between 2-bromocinnamaldehyde and malonic ester derivatives containing a γ-benzoyl group, resulting in the formation of chiral cyclopentenes is presented in the following sections.

2.3. Results and Discussion

2.3.1. Optimization Studies

The present study was initiated by the treatment of α-bromocinnamaldehyde **33a** with the malonate **34a** in the presence of the triazolium salt **H**[17] and excess of Na_2CO_3 in THF resulting in the formation of the trisubstituted cyclopentene derivative **35a** in 52% yield and an excellent enantiomeric excess of 99% (Table 2.1, entry 1). Under this reaction conditions, the cyclopentane-fused β-lactone derivative was not observed.[15] The yield of the product **35a** was increased to 65% (maintaining the 99% ee) upon increasing the

Table 2.1. Optimization of the Reaction Conditions[a]



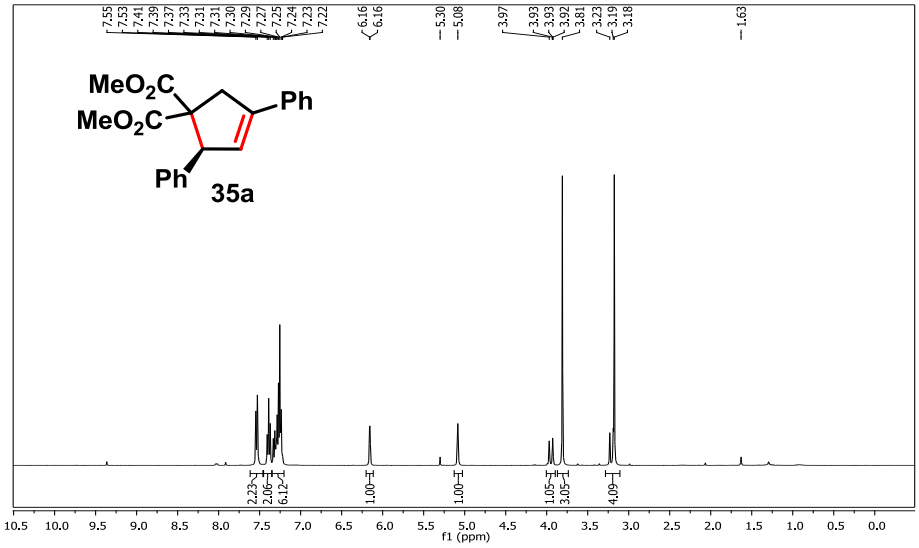
entry	variation of the standard conditions[a]	yield **35a** (%)[b]	ee **35a** (%)[c]
1	none	52	99
2	reaction time 60 h instead of 24 h	65	99
3	reaction run at 60 °C instead of 32 °C	<5	n.d.
4	Cs_2CO_3 instead of Na_2CO_3	48	91
5	KO*t*-Bu instead of Na_2CO_3	<5	n.d.
6	DBU instead of Na_2CO_3	<5	n.d.
7	DABCO instead of Na_2CO_3	30	93
8	Et_3N instead of Na_2CO_3	10	86
9	1,4-dioxane instead of THF	<5	n.d.
10	toluene instead of THF	10	99
11	DME instead of THF	54	99
12	**DME instead of THF, run for 72 h**	**75**	**99**

[a] Standard conditions: **33a** (0.38 mmol), **34a** (0.25 mmol), **B** (10 mol %), Na_2CO_3 (4.0 equiv), THF (3.0 mL), 32 °C and 24 h. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis on a chiral column.

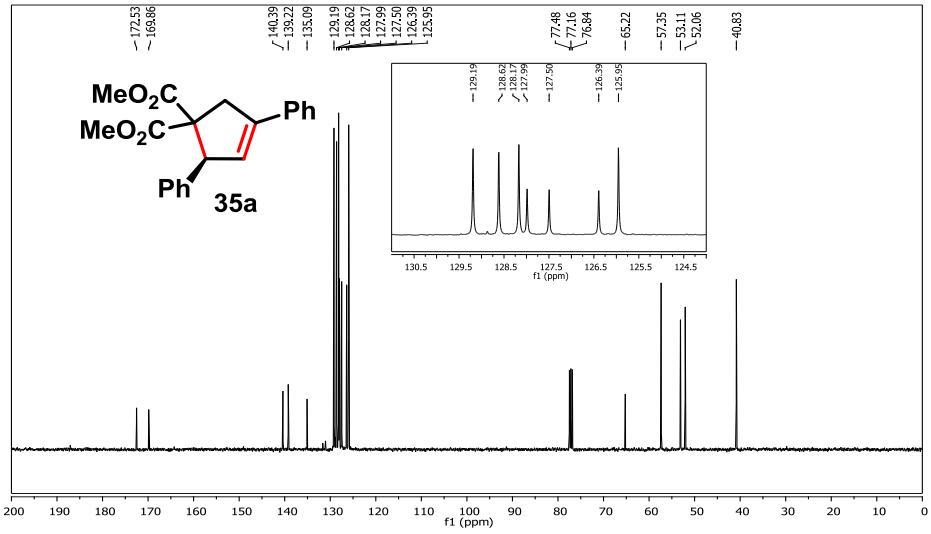
reaction time to 60 h, whereas the reaction afforded only traces of **35a** when carried out at 60 °C (entries 2,3). Screening of different bases furnished the product in reduced yield and selectivity (entries 4-8). Among the various solvents screened, 1,4-dioxane and toluene returned inferior results (entry 9,10). Interestingly, when the reaction was carried out in DME, the functionalized cyclopentene **35a** was formed in an improved yield of 54% maintaining the 99% ee (entry 11). Further studies using DME as solvent showed that **35a** was formed in an improved yield of 75% maintaining the excellent ee value of 99% upon increasing the reaction time to 72 h (entry 12).

2.3.2. Spectral Data of 35a

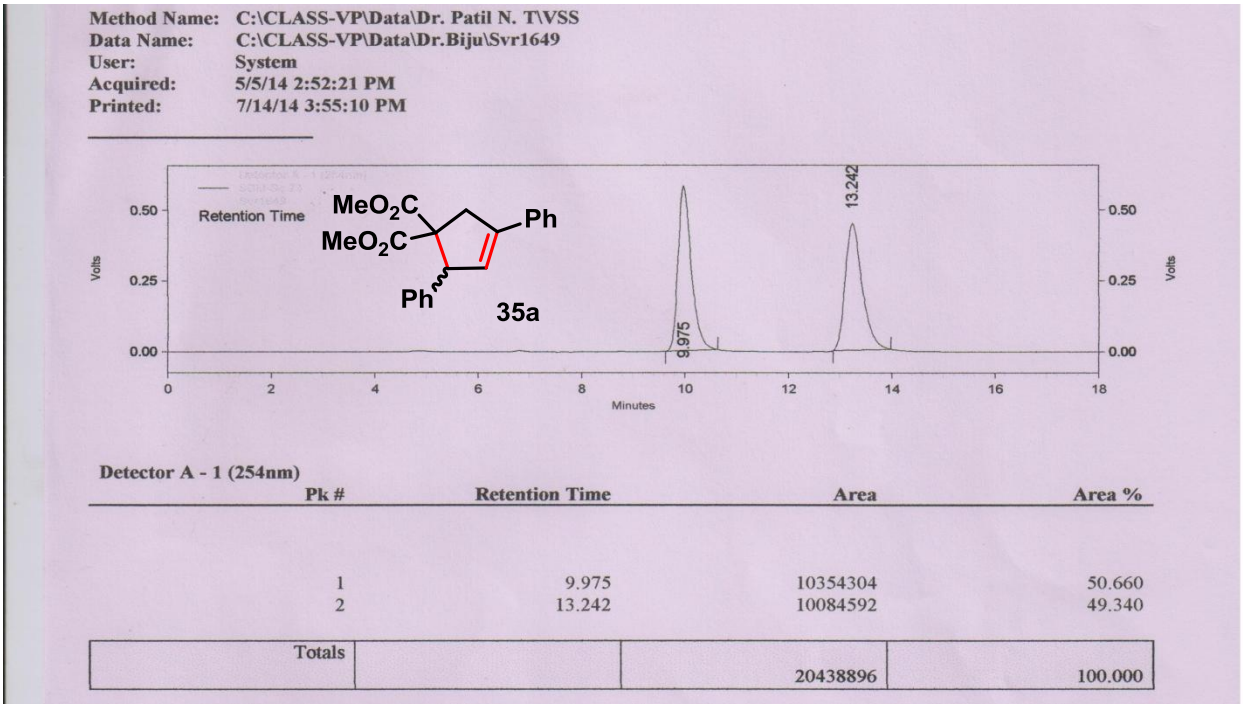
^{1}H NMR Spectrum of 35a ($CDCl_3$)



^{13}C NMR Spectrum of 35a ($CDCl_3$)



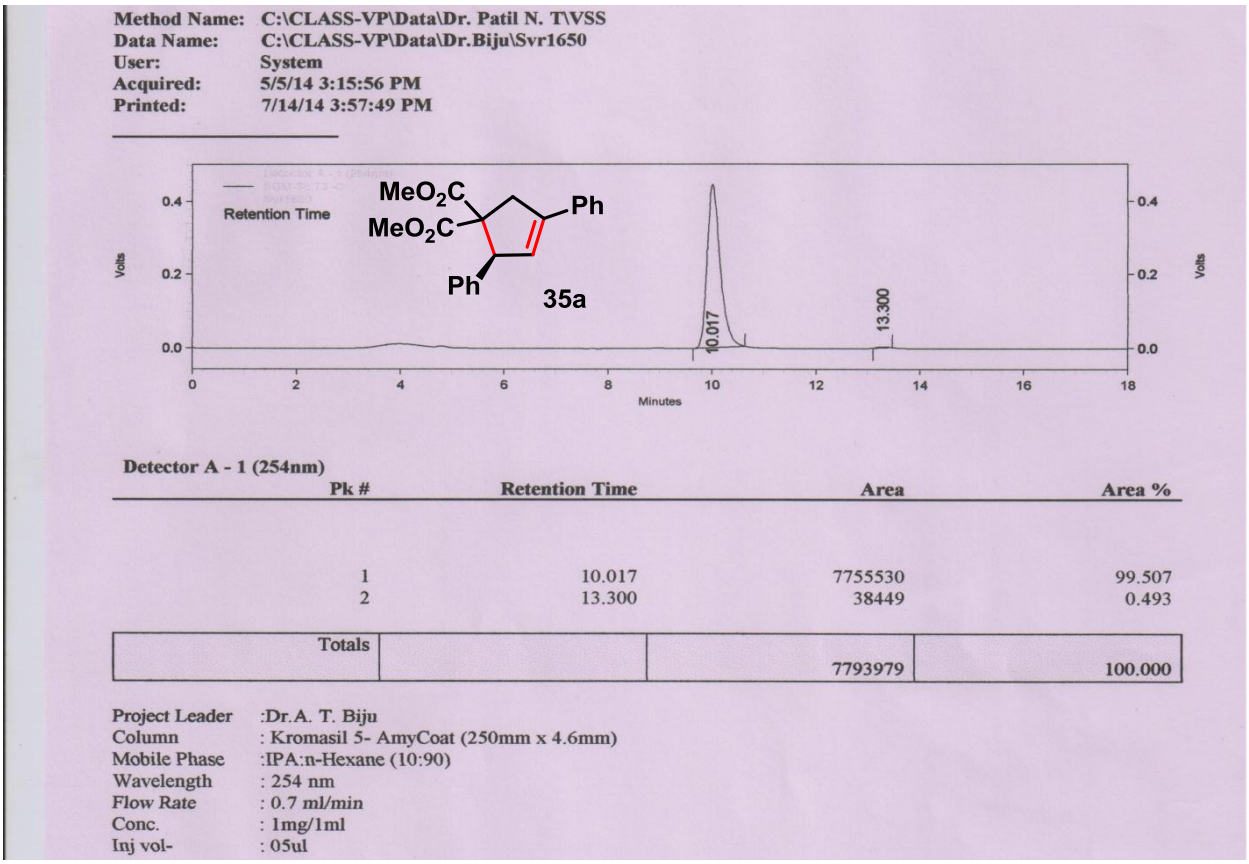
HPLC Chromatogram of Racemic- 35a



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	9.975	10354304	50.660
2	13.242	10084592	49.340
Totals		20438896	100.000

HPLC Chromatogram of Enantiomerically Pure-35a



Detector A - 1 (254nm)

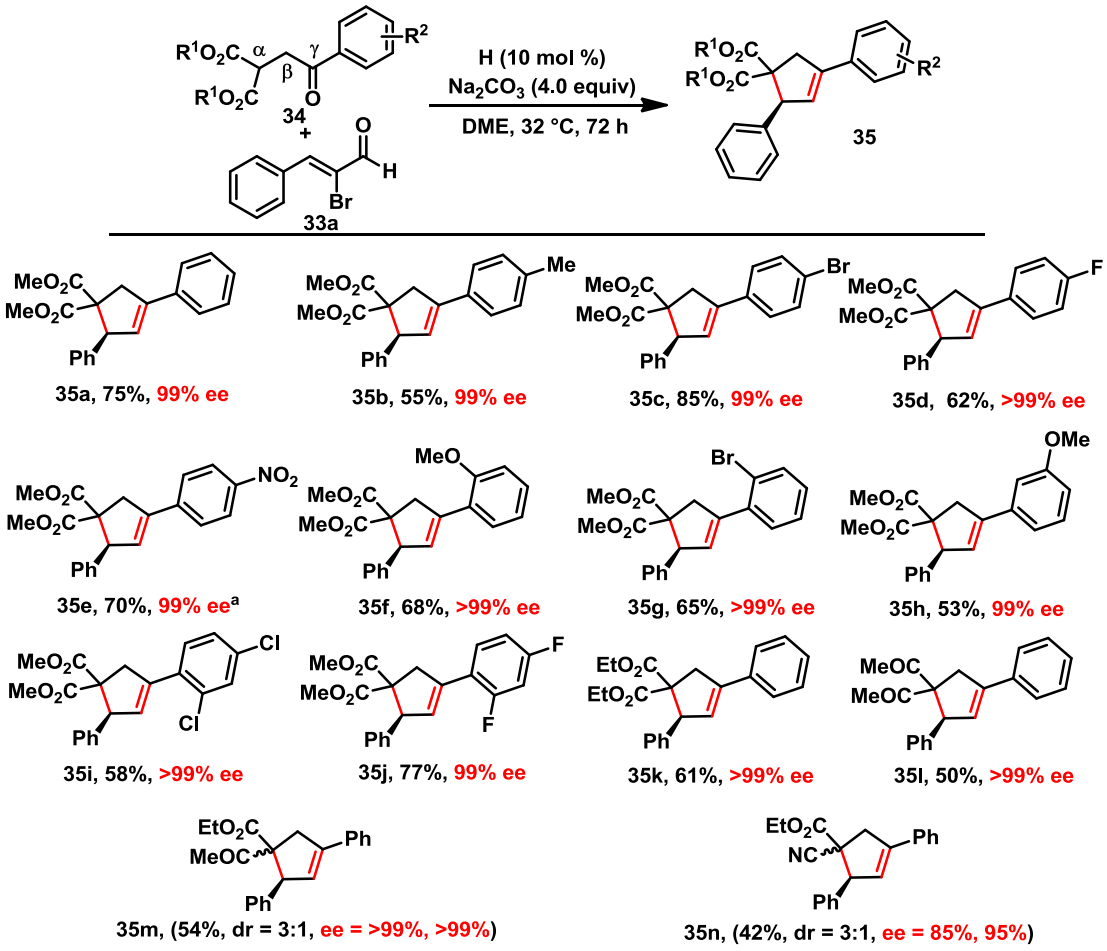
Pk #	Retention Time	Area	Area %
1	10.017	7755530	99.507
2	13.300	38449	0.493
Totals		7793979	100.000

Project Leader :Dr.A. T. Biju
Column : Kromasil 5- AmyCoat (250mm x 4.6mm)
Mobile Phase :IPA:n-Hexane (10:90)
Wavelength : 254 nm
Flow Rate : 0.7 ml/min
Conc. : 1mg/1ml
Inj vol- : 05ul

2.3.3. Enantioselective Synthesis of Functionalized Cyclopentenes from Malonic Ester Derivatives

After getting the optimized condition in hand, first we investigated the tolerance of this organocascade reaction with various malonic ester derivatives with electron donating and electron withdrawing groups at the 4-position of the benzene ring of γ-benzoyl moiety. All the cases the corresponding chiral cyclopentene derivatives are isolated in moderate to good yields and excellent enantioselectivity of 99% (**35a-35e**). The structure and

Scheme 2.14: Variation of the Malonic Ester Derivatives.



General reaction conditions: **33a** (0.75 mmol), **34** (0.50 mmol), **H** (10 mol%), Na_2CO_3 (4.0 equiv.), DME (6.0 mL) at 32 °C for 72 h. Given are isolated yields and the ee values were determined by HPLC analysis on a chiral column. [a] The reaction mixture stirred for 120 h.

stereochemistry of **35c** was determined by single-crystal X-ray analysis (figure 2.2).[18] Moreover, the malonic ester derivatives with substitution at the 2 and 3-position of γ-

benzoyl group underwent smooth cyclopentannulation reaction furnished the desired product in good yields and excellent ee values (**35f-35h**). In addition, disubstitution on the benzene ring of **34** also afforded the chiral cyclopentene derivative in moderate to good yield and high ee values (**35i-35j**). Furthermore, we varied the alkoxy part on the malonic ester **34**, and the acetyl acetone-derived triketone can also be used as a nucleophile for addition to α,β-unsaturated acyl azoliums thus demonstrating the versatile nature of this annulation reaction (**35k-35l**). Additionally, we also studied the scope of the reaction using differently substituted nucleophilic component, derived from ethyl acetoacetate and ethyl cyanoacetate. Both the cases, the reactions afforded the desire product in a separable mixture of diastereomers in the ratio of 3:1, moderate yield and good to excellent enantioselectivity (**35m-35n**).

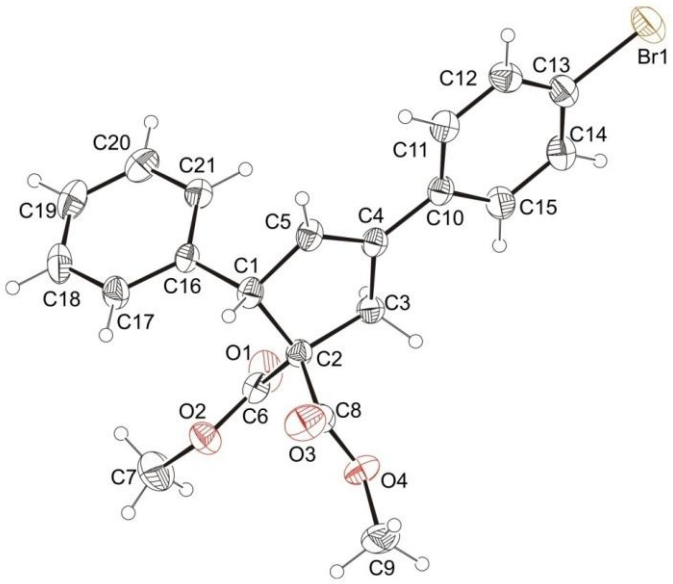


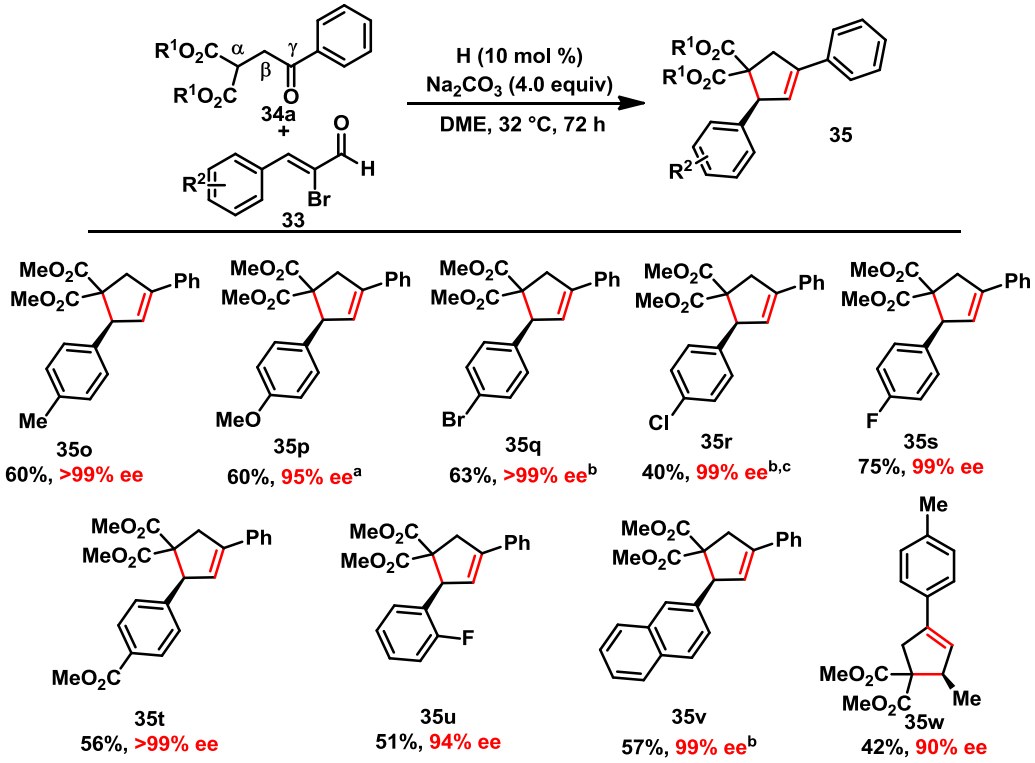
Figure 2.2: ORTEP of **35c** Showing Atom Numbering Scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

2.3.4. Enantioselective Synthesis of Functionalized Cyclopentenes from 2-Bromoenals

Next, we evaluated the feasibility of this reaction with 2-bromoenal derivatives. A number of 2-bromo enals with electron rich and electron poor substituents at the 4-position of benzene ring underwent smooth annulation reaction affording the desired products in

moderate to good yields and excellent ee values of 99% in all cases (**35o-35t**). Moreover, substitution at the ortho position of the β-aryl ring as well as the 2-naphthyl substitution at the β-position is worked well and the corresponding cyclopentenes are formed in moderate yields and high ee values further expanding the scope of this reaction (**35u-35v**). It is noteworthy that the present method is not limited to aromatic 2-bromoenals. Interestingly, bromoenal derived from crotonaldehyde can also be used as the aldehyde coupling partner furnishing **35w** in 42% yield and 90% ee.

Scheme 2.15: Variation of the 2-Bromoenal Derivatives.



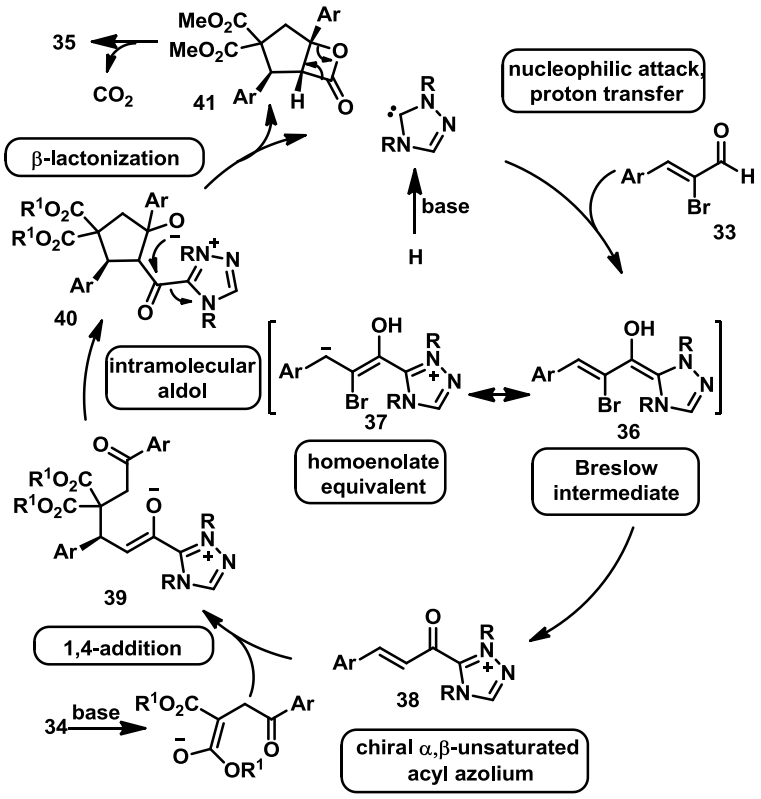
General reaction conditions: **33** (0.75 mmol), **34a** (0.50 mmol), **H** (10 mol %), Na_2CO_3 (4.0 equiv.), DME (6.0 mL) at 32 °C for 72 h. Given are isolated yields and the ee values were determined by HPLC analysis on a chiral column. [a] The reaction was carried out in THF using Cs_2CO_3 (4.0 equiv) as base. [b] The reaction was run on 0.25 mmol scale. [c] The reaction was performed in THF.

2.3.5. Reaction Mechanism

A plausible mechanism for this NHC-catalyzed cyclopentannulation reaction is shown in Scheme 2.16. The chiral NHC generated from **H** under basic condition undergo nucleophilic attack on 2-bromoenal **33** followed by a proton transfer generates the nucleophilic Breslow intermediate **36**.[19] This Breslow intermediate **36** can also represented as a zwitterionic homoenolate equivalent **37**. The intermediate **36** undergoes quick

debromination to generate key chiral α,β-unsaturated acyl azolium intermediate **38**. Nucleophilic addition of enolate generated from **34** onto β-position of intermediate **38** from below the plane containing the triazolium moiety results in the formation of the NHC-bound enolate intermediate **39**, which can undergo a highly selective intramolecular aldol reaction leading to the cyclopentane intermediate **40**. β-Lactonization of intermediate **40** followed by the release of free carbene affords the cyclopentane-fused β-lactone **41**. Rapid decarboxylation of **41** results in the formation of the desired product **35**. The formation of the styrenic double bond in **35** may be the driving force for the rapid decarboxylation of **41**.

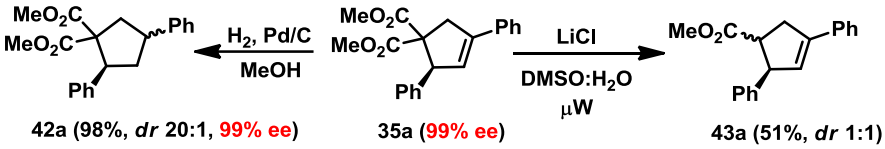
Scheme 2.16: Proposed Mechanism of the Reaction



2.3.6. Synthetic Transformations of Functionalized Cyclopentenes

A diastereoselective hydrogenation reaction of functionalized cyclopentene **35a** in presence of palladium on activated charcoal catalyst and hydrogen gas furnished the trisubstituted cyclopentane derivative **42a** in 98% yield and 99% ee (Scheme 2.17). Moreover, a Krapcho decarboxylation of **35a** using LiCl under microwave conditions afforded the monoester **43a** in 51% yield and in 1:1 diastereomeric ratio.

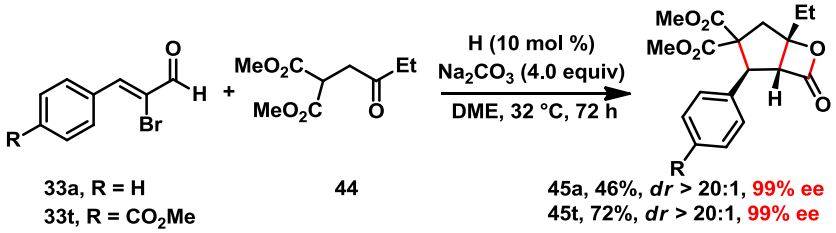
Scheme 2.17: Synthetic Transformations



2.3.7. Enantioselective Synthesis of Cyclopentane-Fused β-Lactones

Interestingly, upon treatment of 2-bromoenals with malonate derivatives possessing a γ-acyl group **44** under the optimized reaction conditions, the reaction resulted in the

Scheme 2.18: Synthesis of Cyclopentane-fused β–Lactones



highly diastereoselective and enantioselective synthesis of cyclopentane-fused β-lactones **45** (Scheme 2.18). Thus, the parent 2-bromoenal **33a** upon reaction with **44** furnished the β-lactone **45a** in 46% yield, >20:1 dr, and 99% ee.[20] Similarly, the substituted 2-bromoenal **33t** afforded the corresponding β-lactone **45t** in 72% yield, >20:1 dr, and 99% ee. The

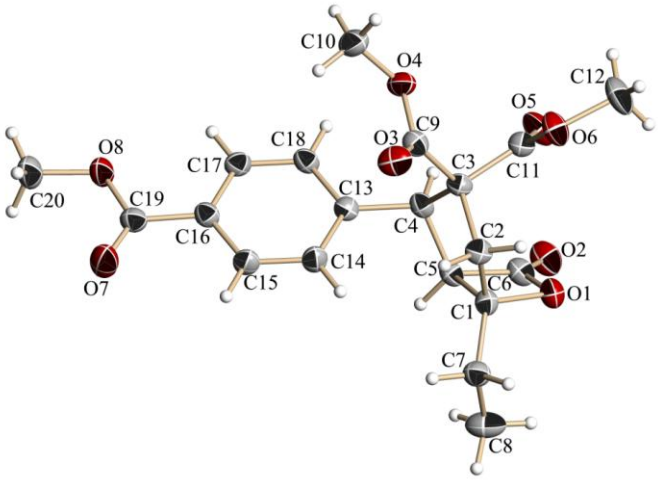


Figure 2.3: ORTEP of **45t** Showing Atom Numbering Scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

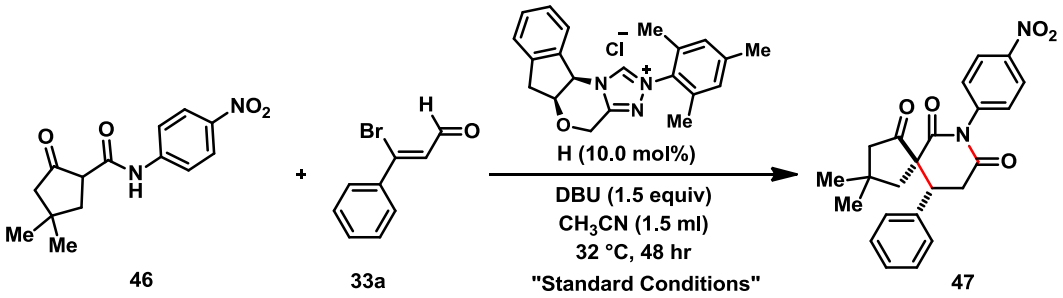
structure and stereochemistry of compound **45t** was determined by single-crystal X-ray analysis (Figure 2.3).[18] The highly selective formation of cyclopentane-fused β-lactone also sheds light on the proposed mechanism of the cyclopentene forming reaction (Scheme 2.16).

2.3.8. Synthesis of Spiroglutarimide Derivatives

Optimization Study

Finally, a cyclic β-ketoamide **46** was employed as α-substituted β-dicarbonyl compound for the reaction of α,β-unsaturated acyl azolium generated from 2-bromoenal. Having this strategy, we initiated our optimization study by the treatment of 2-bromocinnamaldehyde **33a** with cyclic β-ketoamide **46** in the presence of DBU base and CH_3CN solvent resulted the formation of spiroglutarimide derivative **47** in 34% yield, 10:1 dr and 92% ee (Table 2.2, entry 1).[21] The reaction afforded inferior yield of **47** when

Table 2.2. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	Yield of **47** (%)[b]	dr of **47**[c]	ee of **47** (%)[d]
1	none	34	10:1	92
2	reaction run at 0 °C instead of 32 °C	<5	n.d.	n.d.
3	Cs_2CO_3 instead of DBU	94	1:1	70
4	DMAP instead of DBU	75	8:1	74
5	DABCO instead of DBU	40	10:1	90
6	***i*-Pr_2NEt instead of DBU**	**50**	**10:1**	**90**
7	DCM instead of CH_3CN	30	4:1	87
8	DCE instead of CH_3CN	26	6:1	85
9	THF instead of CH_3CN	56	3:1	72
10	Toluene instead of CH_3CN	20	3:1	64

[a] Standard conditions: **33a** (0.15 mmol), **46** (0.1 mmol), **H** (10 mol %), DBU (1.5 equiv.), CH_3CN (1.5 mL), 32 °C and 48 h. [b] The yields were determined by ^{1}H NMR analysis of crude product using CH_2Br_2 as internal standrd. [c] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy prior to purification. [d] Determined by HPLC analysis on a chiral column.

performed at 0°C (entry 2). A rapid base screening revealed that in case of Cs_2CO_3 and DMAP the yield of the product **47** improved but the diastereoselectivity and enantioselectivity reduced (entry 3-4). But in the case of DABCO and *i*-Pr_2NEt, the yield of the product improved with a high level of diastereo- and enantioselectivity (entry 5-6). The screening of different solvent furnished the product in reduced yield and selectivity (entry 7-10). At this stage, entry 6 was found to be the best condition for this annulation reaction.

2.4. Conclusion

In conclusion, we have developed the NHC-catalyzed enantioselective synthesis of cyclopentene derivatives by the reaction of modified enals with malonic ester-derived nucleophiles.[22] The NHC-catalyzed generation of chiral α,β-unsaturated acyl azolium is the key for the success of this cascade reaction. Given the importance of functionalized cyclopentenes, the protocol presented herein is a practical method to synthesize these molecules. At the same time, the research group of Studer reported the enantioselective synthesis of highly substituted cyclopentane-fused β-lactone proceeding via the α,β-unsaturated acyl azoliums under oxidative NHC-catalysis.[23] Later, Ye and co-workers uncovered the asymmetric synthesis of spirocyclopentene-2-oxindole using bromoenal as α,β-unsaturated acyl azolium precoursor.[24]

2.5. Experimental Details

2.5.1. General Information

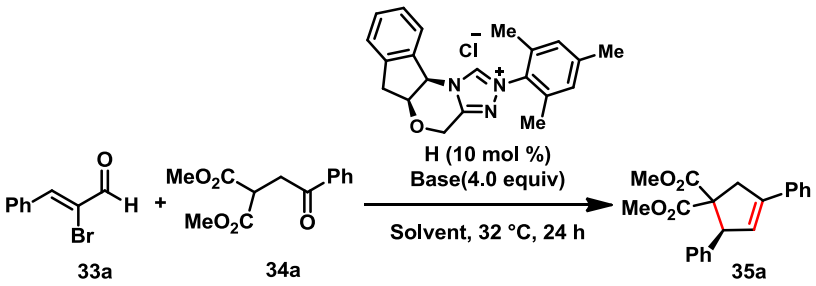
Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Dry DME was purchased from commercial sources and stored under argon over 4 Å molecular sieves. The 2-bromoenals were synthesized from the corresponding α,β-unsaturated aldehydes following the literature procedure.[25] All the malonic ester derivatives were prepared following the literature procedure.[26] The triazolium salt **H** was synthesized following the literature procedure.[17] Na_2CO_3 was dried by heating at 120 °C under high vacuum pump and cooling under argon atmosphere.

Analytical thin layer chromatography was performed on TLC Silica gel 60 F254. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions

followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet Ether-EtOAc solvent system.

All compounds were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infra-red spectra were recorded on a Bruker FT-IR (ATR mode) Infra-red Spectrophotometer. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS (ESI) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Optical rotation was measured with a JASCO P 2000 digital polarimeter at rt using 50 mm cell of 1 mL capacity. HPLC analysis was performed on Shimadzu Class-VP V6.12 SP5 with UV detector. X-ray intensity data were collected on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation at ambient temperature.

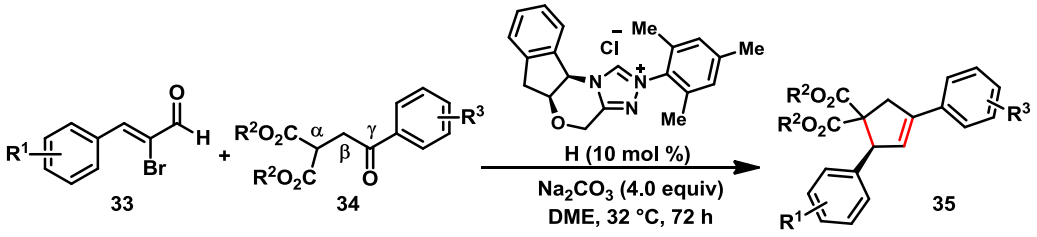
2.5.2. General Procedure for the Optimization of Reaction Conditions



33a 34a 35a

To a oven-dried Schlenk reaction vessel equipped with a magnetic stirr bar was taken the (*Z*)-2-bromo-3-phenylacrylaldehyde **33a** (0.080 g, 0.38 mmol), dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (0.062 g, 0.25 mmol) and base (1.00 mmol, 4.00 equiv) was added. The mixture was kept under argon atmosphere. To this mixture was added solvent (3.0 mL) under a positive pressure of argon, and the mixture was stirred at 32 °C. To this stirring solution was added the triazolium salt **H** (9.2 mg, 0.025 mmol, 10 mol %), and the resulting mixture was stirred at 32 °C for 24 h. Evaporation of the solvent followed by silica gel flash column chromatography afforded the cyclopentene derivative **35a**. The enantiomeric excess was determined by HPLC analysis on a chiral column.

2.5.3. General Procedure for the Enantioselective Synthesis of Functionalized Cyclopentenes



To an oven-dried Schlenk reaction vessel with a teflon screw cap was taken the 2-bromoenal **33** (0.75 mmol), the malonic ester derivative **34** (0.50 mmol), and Na_2CO_3 (212 mg, 2.0 mmol, 4.0 equiv). The mixture was kept under argon atmosphere, and dry DME (6.0 mL) was then introduced into the vessel by syringe under a positive pressure of argon, and the mixture was stirred at 32 °C. To this stirring solution was added the triazolium salt **H** (18.4 mg, 0.05 mmol), and the resulting mixture was stirred at 32 °C for 72 h. Evaporation of the solvent followed by silica gel flash column chromatography afforded the cyclopentene derivatives **35** in moderate to good yields with excellent enantioselectivity. [The racemic cyclopentenes were synthesized by treating **33** and **34** with IMes.HCl in the presence of Cs_2CO_3 (1.5 equiv) and NaH (1.0 equiv) in THF for 12 h at 32 °C].

2.5.4. X-ray Data of 35c and 45t

Single crystals of compound **35c**, obtained from dichloromethane. X-ray intensity data were collected on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation at ambient temperature. The X-ray generator was operated at 50 kV and 30 mA. Diffraction data were collected with a ω scan width of 0.5° and at different settings of φ and 2θ. The sample-to-detector distance was fixed at 5.00 cm. The X-ray data acquisition was monitored by APEX II program suite.[27] All the data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs integrated in APEX II program package. The structures were solved by direct method and refined by full matrix least squares, based on F^2, using SHELX-97.[28] All the H-atoms were placed in geometrically idealized position (C-H = 0.93 Å for the phenyl H-atom, C-H = 0.97 Å for the methylene H-atom, C-H = 0.98 Å for the methine H-atom and C-H = 0.96 Å for the methyl H-atom) and constrained to ride on their

parent atoms [U_{iso}(H) = 1.2U_{eq}(C) for the phenyl, methylene and methine group and U_{iso}(H) = 1.5 U_{eq}(C) for the methyl group]. ORTEP was generated using ORTEP-32 program.[29]

Crystallographic data for 35c ($C_{21}H_{19}O_4Br$): M = 415.27, Crystal dimensions 0.49 x 0.45 x 0.41 mm^3, trigonal, space group $P\,3_2$, a = 11.7082(7), b = 11.7082(7), c = 11.9217(8) Å, α = 90°, β = 90°, γ =120°, V = 1415.30(15) Å^3, Z = 3, ρ_{calcd} = 1.462 gcm^{-3}, μ (Mo-K$_\alpha$) = 2.201 mm^{-1}, *F(000)* = 636, 2θ_{max} = 67.22°, T = 296(2) K, 32442 reflections collected, 7324 unique (R_{int}=0.0360), 4525 observed ($I > 2\sigma$ (I)) reflections, 238 refined parameters, R value 0.0340, $wR2$ = 0.0730, (all data R = 0.0759, $wR2$ = 0.0838), S = 0.995, minimum and maximum transmission 0.412 and 0.466; maximum and minimum residual electron densities +0.44 and –0.43 e Å^{-3}. The absolute configuration was established by anomalous dispersion effect (Flack parameter of 0.0174(11)) in X-ray diffraction measurements which is caused by the presence of bromine atom in the molecule.

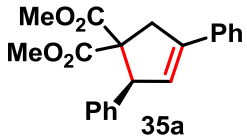
X-ray intensity data measurements of compound **45t** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK$_\alpha$= 0.71073Å) radiation at room temperature. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. ORTEP III3 views of both compounds were drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data of 45t ($C_{20}H_{22}O_8$): M = 390.38, colorless block, 0.39 x 0.09 x 0.06 mm^3, monoclinic, space group $C2$, a = 20.4540(10) Å, b = 7.1698(3) Å, c = 15.6356(8) Å, β = 121.607(6) °, V = 1952.84(16) Å^3, Z = 4, T = 296(2) K, 2θ_{max}=52.00°, D_{calc} (g cm^{-3}) = 1.328, F(*000*) = 824, μ (mm^{-1}) = 0.103, 11890 reflections collected, 3508 unique reflections (R_{int}=0.0436), 2708 observed ($I > 2\sigma$ (I)) reflections, multi-scan absorption correction,

T_{min} = 0.961, T_{max} = 0.994, 257 refined parameters, S = 1.095, $R1$ = 0.0515, $wR2$ = 0.0972 (all data R = 0.0722, $wR2$ = 0.1054), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.14, $\Delta\rho_{min}$= -0.17 (eÅ^{-3}).

2.5.5. Synthesis and Characterization of Functionalized Cyclopentenes

Dimethyl (*S*)-2,4-diphenylcyclopent-3-ene-1,1-dicarboxylate (35a)[30]



35a

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.3 mg, 0.75 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (125.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-2,4-diphenylcyclopent-3-ene-1,1-dicarboxylate **33a** as a light yellow solid (126.1 mg, 75%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.65.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 10.0 min, Minor: 13.3 min. 99% ee, $[\alpha]_D^{25}$ = -279.45 (c 0.4, $CHCl_3$).

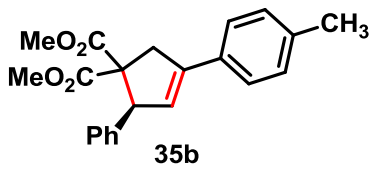
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.4 Hz, 2H, H_{ar}), 7.39 (t, J = 7.7 Hz, 2H, H_{ar}), 7.33-7.22 (m, 6H, H_{ar}), 6.16 (s, 1H, $H_{olefinic}$), 5.08 (s, 1H), 3.97-3.92 (m, 1H), 3.81 (s, 3H, CH_3), 3.21(d, J = 17.0 Hz, 1H), 3.18 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.56, 169.86, 140.39, 139.22, 135.09, 129.19, 128.62, 128.17, 127.99, 127.50, 126.39, 125.95, 65.22, 57.35, 53.11, 52.06, 40.83.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{20}O_4Na$: 359.1254, found: 359.1247.

FTIR (cm^{-1}) 3463, 3059, 3029, 2952, 2843, 2104, 1734, 1697, 1638, 1436, 1257, 1196, 1164, 1028, 964, 863, 697.

Dimethyl (*S*)-2-phenyl-4-(*p*-tolyl)cyclopent-3-ene-1,1-dicarboxylate (35b)



35b

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-oxo-2-(*p*-tolyl)ethyl)malonate **34b** (132.0 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to

afford dimethyl (*S*)-2-phenyl-4-(p-tolyl)cyclopent-3-ene-1,1-dicarboxylate **35b** as a white solid (96.4 mg, 55%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.67.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 11.4 min, Minor: 20.0 min. 99% ee, $[\alpha]_D^{25}$ = -250.61 (c 0.3, $CHCl_3$).

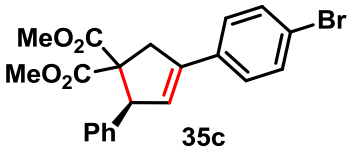
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 2H, H_{ar}), 7.32-7.25 (m, 5H, H_{ar}), 7.22 (d, *J* = 8.0, 2H, H_{ar}) 6.12 (s, 1H, $H_{olefinic}$), 5.09 (s, 1H), 3.97-3.93 (m, 1H), 3.82 (s, 3H, CH_3), 3.23-3.19 (m.4H), 2.41 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.57, 169.90, 140.25, 139.34, 137.84, 132.28, 129.28, 129.18, 128.13, 127.44, 125.86, 125.39, 65.21, 57.31, 53.08, 52.03, 40.83, 21.31.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_4Na$: 373.1410, found: 373.1401.

FTIR (cm^{-1}) 3427, 3028, 2951, 1734, 1634, 1514, 1492, 1435, 1262, 1222, 1196, 1164, 1058, 964, 903, 763, 668.

Dimethyl (*S*)-4-(4-bromophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35c)



35c

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(4-bromophenyl)-2-oxoethyl)malonate **34c** (164.5 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford Dimethyl (*S*)-4-(4-bromophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate **35c** as a white solid (176.0 mg, 85%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.64.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 13.8 min, Minor: 27.6 min. 99% ee, $[\alpha]_D^{25}$ = -203.02 (c 0.25, $CHCl_3$).

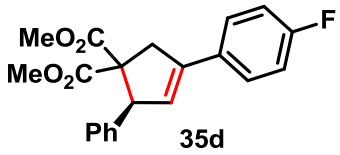
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H, H_{ar}), 7.40-7.38, (m, 2H, H_{ar}), 7.31-7.21 (m, 5H, H_{ar}), 6.16-6.14 (m, 1H, $H_{olefinic}$), 5.07 (s, 1H), 3.93-3.88 (m, 1H), 3.81 (s, 3H, CH_3), 3.18-3.14 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.43, 169.78, 139.41, 138.99, 134.02, 131.75, 129.16, 128.24, 127.61, 127.54, 127.24, 121.91, 65.22, 57.42, 53.19, 52.14, 40.83.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_4BrNa$: 437.0359, found: 437.0349.

FTIR (cm^{-1}) 3685, 3432, 3021, 2401, 2357, 1713, 1602, 1521, 1490, 1433, 1266, 1216, 1075, 929, 772, 670.

Dimethyl (*S*)-4-(4-fluorophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35d)



35d

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(4-fluorophenyl)-2-oxoethyl)malonate **34d** (134.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-4-(4-fluorophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate **35d** as a white solid (110.0 mg, 62%).

R_f (Pet. ether /EtOAc = 80/20): 0.62.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 12.6 min, Minor: 20.9 min. >99% ee, $[\alpha]_D^{25}$ = -234.52 (c 0.5, $CHCl_3$).

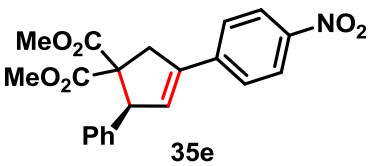
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H, H_{ar}), 7.31-7.23 (m, 5H, H_{ar}), 7.09-7.05 (m. 2H, H_{ar}), 6.08 (s, 1H, $H_{olefinic}$), 5.08 (s, 1H), 3.94-3.89 (m, 1H), 3.81 (s, 3H, CH3), 3.19-3.15 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.45, 169.80, 162.54 (d, *J* = 248.6 Hz), 139.22 (d, *J* = 18.7 Hz), 131.27 (d, *J* = 3.2 Hz), 129.12, 128.18, 127.62, 127.53, 126.07, 115.50 (d, *J* = 21.6 Hz), 65.20, 57.32, 53.13, 52.08, 40.97.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_4FNa$: 377.1160, found: 377.1150.

FTIR (cm^{-1}) 3466, 3027, 2953, 2845, 1732, 1638, 1603, 1511, 1436. 1224, 1099, 1059, 1023, 939, 834, 759.

Dimethyl (*S*)-4-(4-nitrophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35e)



35e

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(4-nitrophenyl)-2-oxoethyl)malonate **34e** (147.6 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 120 h followed by flash column chromatography (EtOAc-Pet. ether

10:90) to afford Dimethyl (*S*)-4-(4-nitrophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate **35e** as a yellow oil (134.0 mg, 70%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.48.

HPLC (Kromasil 5-AmyCoat, 80:20 Hexane / IPA, 0.7 mL/min.) Major: 19.6 min, Minor: 40.7 min. 99% ee, $[\alpha]_D^{25}$ = -217.42 (c 0.2, $CHCl_3$).

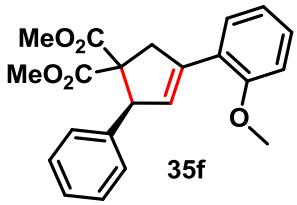
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 2H, H_{ar},), 7.64 (d, *J* = 8..8 Hz, 2H, H_{ar}), 7.29-7.20 (m, 5H, H_{ar}), 6.36 (s, 1H, $H_{olefine}$), 5.12 (S, 1H), 3.98-3.92 (m,1H), 3.82 (s, 3H, CH_3), 3.21 (d, *J* = 16.7 Hz, 1H), 3.16 (S, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.15, 169.53, 147.15, 141.26, 138.78, 138.36, 131.33, 129.07, 128.31, 127.77, 126.54, 123.98, 65.10, 57.51, 53.25, 52.20, 40.80.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_6NNa$: 404.1105, found: 404.1097.

FTIR (cm^{-1}) 3444, 3021, 2401, 2357, 1731, 1635, 1520, 1434, 1345, 1268, 1216, 1107, 929, 848, 771, 670.

Dimethyl (*S*)-4-(2-methoxyphenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35f)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(2-methoxyphenyl)-2-oxoethyl)malonate **34f** (104.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (DCM-Pet. ether 40:60) to afford dimethyl (*S*)-4-(2-methoxyphenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate **35f** as a white solid (124.5 mg, 68%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.57.

HPLC (Chiralcel OJ-H, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 17.3 min. >99% ee, $[\alpha]_D^{25}$ = -218.22 (c 0.25, $CHCl_3$).

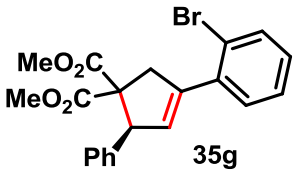
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J_1 = 1.56 Hz, J_2 = 7.56 Hz, 1H, H_{ar}), 7.29-7.20 (m, 6H, Har), 7.00-6.93 (m, 2H, H_{ar}), 6.40-6.39 (m, 1H, $H_{olefinic}$), 5.06 (s, 1H), 4.00-3.96 (m, 1H), 3.87 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.23 (d, *J* = 17.1 Hz, 1H), 3.17 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.14, 170.12, 157.97, 139.51, 137.32, 130.62, 129.26, 128.94, 128.75, 128.13, 127.36, 124.55, 120.55, 111.08, 64.65, 57.60, 55.38, 53.05, 52.03, 42.51.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_5Na$: 389.1359, found: 389.1348.

FTIR (cm^{-1}) 3433, 3022, 2953, 2839, 2402, 2108, 1730, 1629, 1601, 1458, 1437, 1218, 1166, 1057, 968, 870, 702.

Dimethyl (*S*)-4-(2-bromophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35g)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(2-bromophenyl)-2-oxoethyl)malonate **34g** (164.5 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (DCM-Pet. ether 40:90) to afford dimethyl (*S*)-4-(2-bromophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate **35g** as a colourless oil (135.0 mg, 65%).

R_f (Pet. ether /EtOAc = 80/20): 0.62.

HPLC (Kromasil 5-AmyCoat, 80:20 Hexane / IPA, 0.7 mL/min.) Major: 6.5 min, Minor: 8.0 min. >99% ee, $[\alpha]_D^{25}$ = -202.26 (c 0.2, $CHCl_3$).

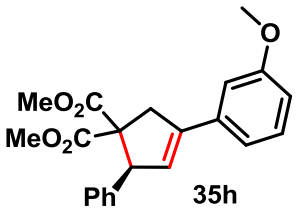
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 1H, H_{ar}), 7.39-7.26 (m, 7H, H_{ar}), 7.18 (t, *J* = 7.4 Hz, 1H, H_{ar}), 5.96 (s, 1H, $H_{olefinic}$), 5.07 (s, 1H), 3.96 (d, *J* = 17.1 Hz, 1H), 3.83 (s, 3H, CH_3), 3.25-3.19 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.44, 169.76, 141.32, 138.82, 137.82, 133.43, 131.68, 130.35, 129.24, 129.04, 128.25, 127.57, 127.41, 122.30, 65.52, 57.18, 53.13, 52.09, 43.14.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_4BrNa$: 437.0359, found: 437.0353.

FTIR (cm^{-1}) 3685, 3619, 3435, 3021, 2975, 2401, 2357, 1731, 1603, 1521, 1432, 1216, 1051, 929, 774, 670.

Dimethyl (*S*)-4-(3-methoxyphenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35h)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(3-methoxyphenyl)-2-oxoethyl)malonate **34h** (140.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture

at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-4-(3-methoxyphenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate 3**5h** as a light yellow oil (97 mg, 53%).

R_f (Pet. ether /EtOAc = 80/20): 0.64.

HPLC (Kromasil 5-AmyCoat, 80:20 Hexane / IPA, 0.7 mL/min.) Major: 8.2 min, Minor: 10.3 min. 99% ee, $[\alpha]_D^{25}$ = -195.5 (c 0.1, $CHCl_3$).

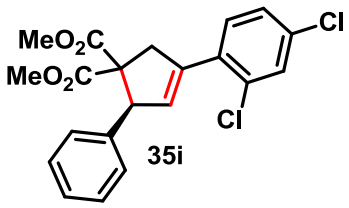
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 6H, H_{ar}), 7.14 (d, *J* = 7.7 Hz, 1H, H_{ar}), 7.06 (s, 1H, H_{ar}), 6.89-6.87 (m, 1H, H_{ar}), 6.16 (s, 1H, $H_{olefinic}$), 5.07 (s, 1H), 3.93 (d, *J* = 16.9 Hz, 1H), 3.86 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 3.21-3.18 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.55, 169.88, 159.87, 140.33, 139.14, 136.52, 129.62, 129.20, 128.21, 127.55, 126.83, 118.57, 113.63, 111.54, 65.19, 57.31, 55.41, 53.17, 52.12, 40.88.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_5Na$: 389.1359, found: 389.1353.

FTIR (cm^{-1}) 3021, 1731, 1599, 1433, 1264, 1214, 1170, 1052, 742, 668.

Dimethyl (*S*)-4-(2,4-dichlorophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35i)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(2,4-dichlorophenyl)-2-oxoethyl)malonate **34i** (158.2 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (dcm-Pet. ether 40:60) to afford dimethyl (*S*)-4-(2,4-dichlorophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate **35i** as a colourless oil (117.0 mg, 58%).

R_f (Pet. ether /EtOAc = 80/20): 0.78.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 8.5 min, Minor: 9.9 min. >99% ee, $[\alpha]_D^{25}$ = -191.90 (c 0.3, $CHCl_3$).

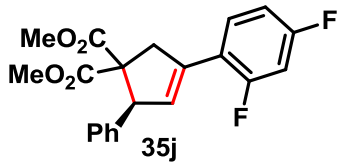
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 2.1 Hz, 1H, H_{ar}), 7.33-7.24 (m, 7H, H_{ar}), 6.09-6.07 (m, 1H, $H_{olefinic}$), 5.07 (s, 1H), 3.95-3.90 (m, 1H), 3.81 (s, 3H, CH_3), 3.20-3.16 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.29, 169.64, 138.59, 138.42, 133.85, 133.45, 132.58, 130.81, 130.12, 129.12, 128.26, 127.62, 127.14, 65.28, 57.26, 53.13, 52.11, 42.96.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{18}O_4Cl_2Na$: 427.0474, found: 427.0465.

FTIR (cm^{-1}) 3428, 3021, 2401, 2313, 1731, 1635, 1437, 1217, 1057, 769, 670.

Dimethyl (*S*)-4-(2,4-difluorophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate (35j)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and dimethyl 2-(2-(2,4-difluorophenyl)-2-oxoethyl)malonate **34j** (143.0 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-4-(2,4-difluorophenyl)-2-phenylcyclopent-3-ene-1,1-dicarboxylate **35j** as a white solid (143.0 mg, 77%).

R_f (Pet. ether /EtOAc = 80/20): 0.62

HPLC (Kromasil 5-AmyCoat, 99.3:0.7:0.1 Hexane / IPA/TFA, 0.5 mL/min.) Major: 20.2 min, Minor: 22.6 min. 99% ee, $[\alpha]_D^{25}$ = -249.26 (c 0.35, $CHCl_3$).

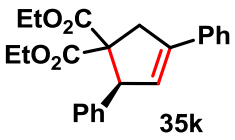
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.35 (m,1H, H_{ar}), 7.30-7.22 (m, 5H, H_{ar}), 6.92-6.83 (m, 2H, H_{ar}), 6.25 (s, 1H, $H_{olefine}$), 5.09 (s, 1H), 3.92 (d, *J* = 16.7 Hz, 1H), 3.80 (s, 3H, CH_3), 3.21-3.15 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.42, 169.83, 163.23 (dd, J_1 = 12.2 Hz, J_2 = 250.1 Hz), 161.58 (dd, J_1 = 11.7 Hz, J_2 = 254.5 Hz), 138.93, 134.08, 130.94 (d, *J* = 10.2 Hz), 129.66-129.51 (m), 129.15, 128.22, 127.57, 119.70 (dd, J_1 = 3.8 Hz, J_2 = 12.6 Hz), 111.33 (dd, J_1 = 3.4 Hz, J_2 = 21.2 Hz), 104.61 (t, *J* = 25.8 Hz), 64.57, 57.55, 53.17, 52.13, 42.08.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{18}O_4F_2Na$: 395.1065, found: 395.1058.

FTIR (cm^{-1}) 3430, 3023, 2954, 1731, 1619, 1502, 1271, 1217, 1162, 1141, 1105, 965, 854, 761, 702.

Diethyl (*S*) 2, 4-diphenylcyclopent-3-ene-1, 1-dicarboxylate (35k)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and diethyl 2-(2-oxo-2-phenylethyl)malonate **34k** (208.7 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet.

ether 10:90) to afford diethyl (*S*)-2,4-diphenylcyclopent-3-ene-1,1-dicarboxylate **35k** as a colourlass oil (110 mg, 61%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.69.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 10.5 min, Minor: 12.0 min. >99% ee, $[\alpha]_D^{25}$ = -265.10 (c 0.45, $CHCl_3$).

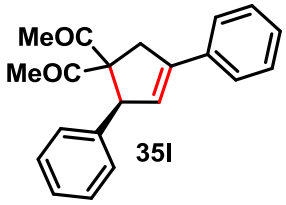
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 2H, H_{ar}), 7.40 (t, *J* = 7.4 Hz, 2H, H_{ar}), 7.33 (d, *J* = 7.4 Hz, 1H, H_{ar}), 7.31-7.22 (m, 5H, H_{ar}), 6.17 (s, 1H, $H_{olefinic}$), 5.09 (s, 1H), 4.38-4.30 (m, 1H), 4.27-4.19 (m, 1H), 3.81-3.73 (m, 1H), 3.55-3.47 (m, 1H), 3.21(d, *J* = 16.9 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3), 0.89 (t, *J* = 7.1 Hz, 3H, CH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.09, 169.53, 140.18, 139.44, 135.19, 129.34, 128.59, 128.13, 127.91, 127.43, 126.72, 125.95, 65.01, 61.85, 61.25, 57.18, 40.94, 14.14, 13.61.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{23}H_{24}O_4Na$: 387.1567, found: 387.1555.

FTIR (cm^{-1}) 3430, 3021, 2401, 1726, 1636, 1449, 1261, 1216, 1097, 928, 760, 669.

(*S*)-1,1'-(2,4-Diphenylcyclopent-3-ene-1,1-diyl)bis(ethan-1-one) (35l)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and 3-acetyl-1-phenylpentane-1,4-dione **34l** (109.0 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-1,1'-(2,4-diphenylcyclopent-3-ene-1,1-diyl)bis(ethan-1-one) **35l** as a white solid (76 mg, 50%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.53.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 11.1 min, Minor: 12.3 min. >99% ee, $[\alpha]_D^{25}$ = -406.95 (c 0.4, $CHCl_3$).

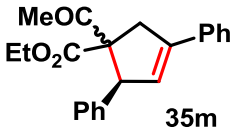
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H, H_{ar}), 7.37 (t, *J* = 7.1 Hz, 2H, H_{ar}), 7.32-7.18 (m, 6H, H_{ar}), 6.13 (s, 1H, $H_{olefinic}$), 5.06 (s, 1H), 4.06-4.00 (m, 1H), 2.94 (d, *J* = 17.0 Hz, 1H), 2.25 (s, 3H, CH_3), 1.63 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.43, 204.18, 139.68, 138.97, 135.10, 129.36, 128.74, 128.67, 128.06, 127.85, 127.62, 125.89, 79.24, 55.11, 38.22, 28.54, 26.81.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{20}O_2Na$: 327.1356, found: 327.1346.

FTIR (cm^{-1}) 3411, 3021, 2928, 2401, 1697, 1492, 1216, 1144, 1029, 760, 669, 622.

Ethyl (2*S*)-1-acetyl-2,4-diphenylcyclopent-3-ene-1-carboxylate (35m)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and ethyl 2-acetyl-4-oxo-4-phenylbutanoate **34m** (124 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford 3:1 diastereomeric mixture of ethyl (2*S*)-1-acetyl-2,4-diphenylcyclopent-3-ene-1-carboxylate **35m** as a white solid (Major isomer 67 mg yield 38% and minor isomer 23 mg yield 16%, diastereomeric ratio was determined by ^{1}H-NMR analysis of crude reaction mixture is 3:1).

Major Isomer

$\boldsymbol{R_f}$ (Pet. ether /EtOAc = 80/20): 0.61.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 10.5 min, Minor: 16.2 min. >99% ee, $[\alpha]_D^{25}$ = -359.98 (c 0.35, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H, H_{ar}), 7.39 (t, *J* = 7.8 Hz, 2H, H_{ar}), 7.33-7.22 (m, 6H, H_{ar}), 6.15 (s, 1H, $H_{olefinic}$), 5.06 (s, 1H), 4.01-3.96 (m, 1H), 3.81-3.75 (m, 1H), 3.54-3.48 (m, 1H), 2.98 (d, *J* = 16.6 Hz, 1H), 2.29 (s, 3H, CH_3), 0.88 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.74, 170.24, 139.83, 139.01, 135.08, 129.35, 128.57, 128.11, 127.90, 127.43, 127.30, 125.84, 71.31, 61.40, 55.25, 39.53, 26.36, 13.53.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_3Na$: 357.1461, found: 357.1456.

FTIR (cm^{-1}) 3429, 3022, 2401, 2311, 1711, 1636, 1491, 1358, 1217, 1090, 768, 670.

Minor Isomer

$\boldsymbol{R_f}$ (Pet. ether /EtOAc = 80/20): 0.64.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 10.4 min, Minor: 11.6 min. >99% ee, $[\alpha]_D^{25}$ = -326.84 (c 0.25, $CHCl_3$).

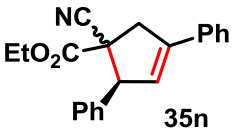
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H, H_{ar}), 7.38-7.35 (m, 2H, H_{ar}), 7.31-7.20 (m, 6H, H_{ar}), 6.09-6.08 (m,1H, $H_{olefinic}$), 5.08 (s, 1H), 4.32-4.22 (m, 2H), 4.01-3.96 (m, 1H), 3.05 (d, *J* = 17.0 Hz, 1H), 1.63 (s, 3H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.00, 173.09, 140.11, 139.24, 135.21, 129.47, 128.67, 128.61, 127.96, 127.72, 126.73, 125.99, 71.38, 62.13, 57.10, 39.63, 27.93, 14.16.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_3Na$: 357.1461, found: 357.1455.

FTIR (cm^{-1}) 3437, 3057, 3029, 2981, 1953, 1711, 1600, 1492, 1354, 1233, 1158, 1058, 840, 755.

Ethyl (2*S*)-1-cyano-2,4-diphenylcyclopent-3-ene-1-carboxylate (35n)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (158.2 mg, 0.75 mmol) and ethyl 2-cyano-4-oxo-4-phenylbutanoate **34w** (115.6 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford 3:1 diastereomeric mixture of ethyl (2*S*)-1-cyano-2,4-diphenylcyclopent-3-ene-1-carboxylate **35n** as a colourless oil (Major isomer 48 mg yield 30% and minor isomer 18 mg yield 12%, diastereomeric ratio was determined by ^{1}H-NMR analysis of crude reaction mixture is 3:1).

Major Isomer

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.55.

HPLC (Chiralcel OD-H, 95:05 Hexane / IPA, 0.7 mL/min.) Major: 22.9 min, Minor: 18.6 min. 85% ee, $[\alpha]_D^{25}$ = -43.86 (c 0.15, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.1 Hz, 2H, H_{ar}), 7.43-7.34 (m, 8H, H_{ar}), 6.20 (s, 1H, $H_{olefinic}$), 4.81 (s, 1H), 4.39-4.36 (m, 2H), 3.66 (d, *J* = 16.1 Hz, 1H), 3.54 (d, *J* = 16.1 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.83, 140.81, 137.99, 134.16, 128.83, 128.80, 128.70, 128.57, 128.55, 125.95, 125.31, 118.53, 63.39, 59.32, 55.02, 44.07, 14.15.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_2NNa$: 340.1308, found: 340.1304.

FTIR (cm^{-1}) 3440, 3021, 1740, 1635, 1493, 1499, 1216, 1074, 757, 897, 669.

Minor Isomer

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.64.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 14.1 min, Minor: 10.9 min. 95% ee, $[\alpha]_D^{25}$ = -95.71 (c 0.6, $CHCl_3$).

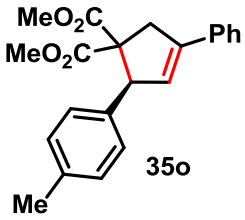
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.3 Hz, 2H, H_{ar}), 7.41 (t, *J* = 7.7 Hz, 2H, H_{ar}), 7.36-7.29 (m, 4H, H_{ar}), 7.23-7.21 (m, 2H, H_{ar}), 6.15 (d, *J* = 2.0 Hz, 1H, $H_{olefinic}$), 4.82 (s, 1H), 3.88-3.84 (m, 1H), 3.82-3.79 (m, 1H), 3.64-3.61 (m, 1H), 3.35 (d, *J* = 16.4 Hz, 1H), 0.93 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.37, 141.68, 136.81, 134.25, 129.05, 128.83, 128.65, 128.57, 126.13, 124.26, 121.68, 62.78, 62.52, 52.12, 41.99, 13.60.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_2NNa$: 340.1308, found: 340.1303.

FTIR (cm^{-1}) 3682, 3464, 3021, 2984, 2931, 2401, 1743, 1602, 1394, 1246, 1072, 774, 669.

Dimethyl (*S*)-4-phenyl-2-(*p*-tolyl)cyclopent-3-ene-1,1-dicarboxylate (35o)



Following the general procedure, treatment of (Z)-2-bromo-3-(*p*-tolyl)acrylaldehyde **33o** (168.8 mg, 0.75 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (125.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-4-phenyl-2-(*p*-tolyl)cyclopent-3-ene-1,1-dicarboxylate **35o** as a colourless oil (105.0 mg, 60%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.64.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 12.5 min, Minor: 24.4 min. >99% ee, $[\alpha]_D^{25}$ = -235.55 (c 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.4 Hz, 2H, H_{ar}), 7.37 (t, *J* = 7.2 Hz, 2H, H_{ar}), 7.30 (t, *J* = 7.3 Hz, 1H, H_{ar}), 7.12-7.06 (m, 4H, H_{ar}), 6.13 (s, 1H, $H_{olefinic}$), 5.02 (s, 1H), 3.94-3.89 (m, 1H), 3.79 (s, 3H, CH_3), 3.20-3.16 (m, 4H), 2.31 (s, 3H, CH_3).

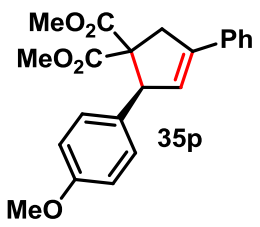
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.63, 169.95, 140.14, 137.12, 135.94, 135.15, 129.06, 128.89, 128.62, 127.95, 126.65, 125.95, 65.16, 56.97, 53.12, 52.12, 40.69, 21.19.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_4Na$: 373.1410, found: 373.1400.

FTIR (cm^{-1}) 3427, 3021, 2954, 1731, 1635, 1439, 1267, 1217, 768, 670.

Dimethyl (*S*)-2-(4-methoxyphenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (35p)

Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-methoxyphenyl)acrylaldehyde **33p** (180.8 mg, 0.75 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (125.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05



mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-2-(4-methoxyphenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate **35p** as a light yellow oil (110 mg, 60%).

R_f (Pet. ether /EtOAc = 80/20): 0.63.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 14.9 min, Minor: 28.8 min. 95% ee, $[\alpha]_D^{25}$ = -217.4 (c 0.25, $CHCl_3$).

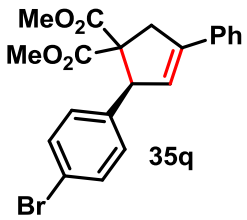
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H, H_{ar}), 7.37 (t, *J* = 7.1 Hz, 2H, H_{ar}), 7.30 (d, *J* = 7.2 Hz, 1H, H_{ar}), 7.13 (d, *J* = 8.7 Hz, 2H, H_{ar}), 6.80 (d, *J* = 8.7 Hz, 2H, H_{ar}), 6.11 (s, 1H, $H_{olefinic}$), 5.00 (s, 1H), 3.92-3.87 (m, 1H), 3.78-3.77 (m, 6H, $2CH_3$), 3.21 (s, 3H, CH_3), 3.16 (d, *J* = 16.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.66, 170.00, 159.03, 140.03, 135.15, 131.00, 130.25, 128.64, 127.97, 126.69, 125.95, 113.57, 65.11, 56.60, 55.35, 53.13, 52.21, 40.64.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{22}H_{22}O_5Na$: 389.1359, found: 389.1346.

FTIR (cm^{-1}) 3021, 1733, 1215, 908, 742, 669.

Dimethyl (*S*)-2-(4-bromophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (35q)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-bromophenyl)acrylaldehyde **33q** (108.7 mg, 0.38 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (62.5 mg, 0.25 mmol) with triazolium salt **H** (9.2 mg, 0.025 mmol), Na_2CO_3 (106 mg, 1.0 mmol) in DME (3.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-2-(4-bromophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate **35q** as a light yellow oil (65.4 mg, 63%).

R_f (Pet. ether /EtOAc = 80/20): 0.64.

HPLC (Kromasil 5-AmyCoat, 80:20 Hexane / IPA, 0.7 mL/min.) Major: 10.5 min, Minor: 16.3 min. >99% ee, $[\alpha]_D^{25}$ = -200.97 (c 0.45, $CHCl_3$).

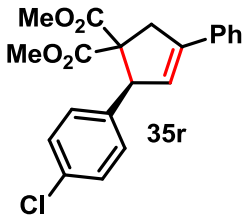
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H, H_{ar}), 7.41-7.36 (m, 4H, H_{ar}), 7.33-7.29 (m, 1H, H_{ar}), 7.11 (d, *J* = 8.4 Hz, 2H, H_{ar}), 6.08 (d, *J* = 1.5 Hz, 1H, $H_{olefinic}$), 5.03 (s, 1H), 3.92-3.88 (m, 1H), 3.79 (s, 3H, CH_3), 3.22-3.17 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.31, 169.70, 140.93, 138.31, 134.81, 131.28, 130.89, 128.66, 128.17, 125.97, 125.68, 121.47, 65.02, 56.67, 53.21, 52.26, 40.78.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_4BrNa$: 437.0359, found: 437.0355.

FTIR (cm^{-1}) 3436, 3022, 2954, 2401, 1732, 1636, 1437, 1267, 1216, 1167, 1073, 932, 758.

Dimethyl (*S*)-2-(4-chlorophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (35r)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-chlorophenyl)acrylaldehyde **33r** (92.0 mg, 0.38 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (62.5 mg, 0.25 mmol) with triazolium salt **H** (9.2 mg, 0.025 mmol), Na_2CO_3 (106.0 mg, 1.0 mmol) in THF (3.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-2-(4-chlorophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate **35r** as a light yellow oil (37.0 mg, 40%).

R_f (Pet. ether /EtOAc = 80/20): 0.65.

HPLC (Kromasil 5-AmyCoat, 80:20 Hexane / IPA, 0.7 mL/min.) Major: 10.1 min, Minor: 14.8 min. 99% ee, $[\alpha]_D^{25}$ = -334.60 (c 0.1, $CHCl_3$).

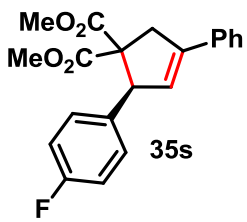
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2H, H_{ar}), 7.40 (t, *J* = 7.1 Hz, 2H, H_{ar}), 7.33 (t, *J* = 7.2 Hz, 1H, H_{ar}), 7.26 (d, *J* = 8.5 Hz, 2H, H_{ar}), 7.18 (d, *J* = 8.5 Hz, 2H, H_{ar}) 6.11 (s, 1H, $H_{olefinic}$), 5.06 (s, 1H), 3.94-3.89 (m, 1H), 3.81 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 3.21(d, *J* = 17.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.37, 169.75, 140.90, 137.79, 134.86, 133.36, 130.55, 128.68, 128.34, 128.19, 125.99, 125.79, 65.09, 56.63, 53.23, 52.26, 40.79.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_4ClNa$: 393.0864, found: 393.0859.

FTIR (cm^{-1}) 3435, 3021, 2955, 2401, 1732, 1635, 1489, 1437, 1267, 1216, 1169, 1091, 1017, 930, 770, 672.

Dimethyl (*S*)-2-(4-fluorophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (35s)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-fluorophenyl)acrylaldehyde **33s** (171.7 mg, 0.75 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (125.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h

followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-2-(4-fluorophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate **35s** as a light yellow oil (133.0 mg, 75%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.60.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 11.4 min, Minor: 17.4 min. 99% ee, $[\alpha]_D^{25}$ = -232.72 (c 0.15, $CHCl_3$).

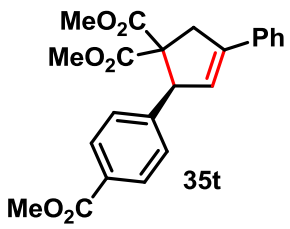
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H, H_{ar}), 7.38 (t, *J* = 7.1 Hz, 2H, H_{ar}), 7.31 (t, *J* = 7.3 Hz, 1H, H_{ar}), 7.22-7.18 (m, 2H, H_{ar}), 6.98-6.94 (m, 2H, H_{ar}), 6.11 (s, 1H, $H_{olefinic}$), 5.06 (s, 1H), 3.93-3.88 (m, 1H), 3.79 (s, 3H, CH_3), 3.21-3.17(m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.41, 169.80, 162.27 (d, *J* = 246.1 Hz), 140.61, 134.92, 130.74 (d, *J* = 8.0 Hz), 128.65, 128.11, 126.07, 125.96, 114.99 (d, *J* = 21.3 Hz), 65.09, 56.52, 53.15, 52.16, 40.74.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_4FNa$: 377.1160, found: 377.1154.

FTIR (cm^{-1}) 3441, 3028, 2053, 1734, 1636, 1604, 1507, 1438, 1265, 1224, 1098, 1018, 901, 841, 759.

Dimethyl (*S*)-2-(4-(methoxycarbonyl)phenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (35t)



Following the general procedure, treatment of methyl (*Z*)-4-(2-bromo-3-oxoprop-1-en-1-yl)benzoate **33t** (201.8 mg, 0.75 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (125.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-2-(4-(methoxycarbonyl)phenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate **35t** as a light yellow solid (110.4 mg, 56%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.44.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 27.3 min. >99% ee, $[\alpha]_D^{25}$ = -224.45 (c 0.55, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.50 (d, *J* = 7.4 Hz, 2H, H_{ar}), 7.37 (t, *J* = 7.3 Hz, 2H, H_{ar}), 7.31 (t, *J* = 6.9 Hz, 3H, H_{ar}), 6.10 (d, *J* = 1.5 Hz, 1H, $H_{olefinic}$),

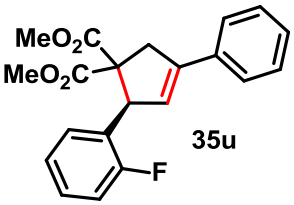
5.11 (s, 1H), 3.94-3.89 (m, 4H), 3.79 (s, 3H, CH_3), 3.21(d, *J* = 16.9 Hz, 1H), 3.15 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.28, 169.63, 167.03, 144.79, 141.17, 134.80, 129.47, 129.34, 129.24, 128.68, 128.22, 126.00, 125.53, 65.21, 57.12, 53.27, 52.24, 52.19, 40.91.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{23}H_{22}O_6Na$: 417.1309, found: 417.1300.

FTIR (cm^{-1}) 3426, 3021, 2401, 1729, 1617, 1439, 1281, 1217, 1113, 969, 766, 670.

Dimethyl (*R*)-2-(2-fluorophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (35u)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(2-fluorophenyl)acrylaldehyde **33u** (171.7 mg, 0.75 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (125.1 mg, 0.50 mmol) with triazolium salt **H** (18.4 mg, 0.05 mmol), Na_2CO_3 (212 mg, 2.0 mmol) in DME (6.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*R*)-2-(2-fluorophenyl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate **35u** as a colourless solid (90.3 mg, 51%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.59.

HPLC (Kromasil 5-AmyCoat, 90:10 Hexane / IPA, 0.7 mL/min.) Major: 10.5 min, Minor: 12.9 min. 94% ee, $[\alpha]_D^{25}$ = -167.96 (c 0.1, $CHCl_3$).

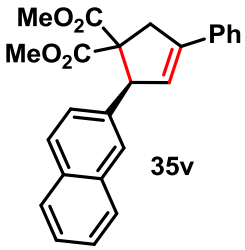
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H, H_{ar}), 7.37 (t, *J* = 7.1 Hz, 2H, H_{ar}), 7.32-7.28 (m, 1H, H_{ar}), 7.22-7.17 (m, 1H, H_{ar}), 7.10 (t, *J* = 6.2 Hz, 1H, H_{ar}), 7.02 (t, *J* = 8.6 Hz, 2H, H_{ar}), 6.05 (s, 1H, $H_{olefinic}$), 5.46 (s, 1H), 4.02-3.97 (m, 1H), 3.79 (s, 3H, CH_3), 3.22 (s, 3H, CH_3) 3.18 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.18, 169.90, 160.87 (d, *J* = 248.7 Hz), 140.86, 134.92, 130.38 (d, *J* = 3.4 Hz), 129.19 (d, *J* = 8.2 Hz), 128.67, 128.13, 126.52, 126.37, 126.00, 125.43, 123.96 (d, *J* = 3.3 Hz), 115.29 (d, *J* = 22.4 Hz), 64.54, 53.26, 52.24, 49.19 (d, *J* = 3.3 Hz), 41.01.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{19}O_4FNa$: 377.1160, found: 377.1152.

FTIR (cm^{-1}) 3685, 3619, 3434, 3021, 2401, 2358, 1733, 1605, 1521, 1491, 1435, 1216, 1049, 929,773, 670.

Dimethyl (*S*)-2-(naphthalen-2-yl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (35v)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(naphthalen-2-yl)acrylaldehyde **33v** (98.0 mg, 0.38 mmol) and dimethyl 2-(2-oxo-2-phenylethyl)malonate **34a** (62.5 mg, 0.25 mmol) with triazolium salt **H** (9.2 mg, 0.025 mmol), Na_2CO_3 (106 mg, 1.0 mmol) in DME (3.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*S*)-2-(naphthalen-2-yl)-4-phenylcyclopent-3-ene-1,1-dicarboxylate **35v** as a light yellow oil (55.0 mg, 57%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.64.

HPLC (Kromasil 5-AmyCoat, 80:20 Hexane / IPA, 0.7 mL/min.) Major: 14.6 min, Minor: 20.0 min. 99% ee, $[\alpha]_D^{25}$ = -200.97 (c 0.45, $CHCl_3$).

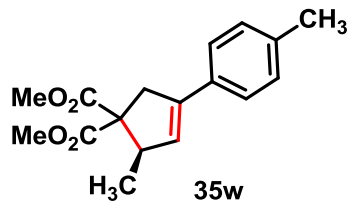
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.73 (m, 3H, H_{ar}), 7.68 (s, 1H, H_{ar}), 7.56 (d, *J* = 7.3 Hz, 2H, H_{ar}), 7.45-7.30 (m, 6H, H_{ar}), 6.21 (s, 1H, $H_{olefinic}$), 5.24 (s, 1H), 4.00 (d, *J* = 16.9 Hz, 1H), 3.81 (s, 3H, CH_3), 3.25 (d, *J* = 16.9 Hz, 1H), 3.03 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.62, 169.90, 140.57, 136.80, 135.11, 133.35, 132.89, 128.69, 128.09, 128.00, 127.93, 127.68, 127.42, 126.40, 126.10, 126.05, 125.92, 65.31, 57.44, 53.22, 52.14, 40.96.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{25}H_{22}O_4Na$: 409.1410, found: 409.1399.

FTIR (cm^{-1}) 3685, 3430, 3021, 2956, 2401, 2355, 1731, 1603, 1517, 1436, 1216, 1053, 928, 767.

Dimethyl (*R*) 2-methyl-4-(*p*-tolyl)cyclopent-3-ene-1,1-dicarboxylate (35w)



Following the general procedure, treatment of (*Z*)-2-bromobut-2-enal **33w** (28.0 mg, 0.188 mmol) and dimethyl 2-(2-oxo-2-(*p*-tolyl)ethyl)malonate **34b** (33.0 mg, 0.125 mmol) with triazolium salt **H** (4.6 mg, 0.0125 mmol), Na_2CO_3 (53.0 mg, 0.5 mmol) in DME (2.0 mL) and stirring the reaction mixture at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*R*) 2-methyl-4-(*p*-tolyl)cyclopent-3-ene-1,1-dicarboxylate **35w** as a light yellow oil (15.0 mg, 42%).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.70.

HPLC (Kromasil 5-AmyCoat, 95:05 Petroleum ether / IPA, 0.5 mL/min.) Major: 12.8 min, Minor: 14.5 min. 90% ee, $[\alpha]_D^{25}$ = -60.5 (c 0.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.12 (d, *J* = 8.0 Hz, 2H, H_{ar}), 5.93 (s, 1H), 3.79-3.76 (m, 1H), 3.75 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.70-3.66 (m, 1H), 3.09 (d, *J* = 16.5 Hz, 1H), 2.33 (s. 3H), 1.02 (d, *J* = 7.2 Hz, 3H).

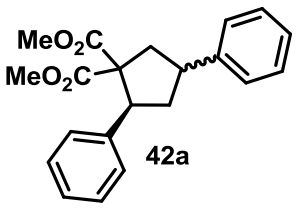
^{13}C NMR (125 MHz, $CDCl_3$) δ 172.78, 171.00, 137.90, 137.49, 132.61, 129.20, 127.84, 125.64, 63.47, 52.97, 52.51, 45.62, 40.12, 21.32, 16.09.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{20}O_4Na$: 311.1254, found: 311.1251.

FTIR (cm^{-1}) 3917, 3750, 3507, 3015, 2947, 2829, 2387, 2351, 1823, 1727, 1673, 1566, 1438, 1213, 1095, 1049, 949.

2.5.6. Diastereoselective Hydrogenation of 35a

Dimethyl (2*S*)-2,4-diphenylcyclopentane-1,1-dicarboxylate (42a)



42a

An oven dried round bottomed flask was charged with dimethyl (*S*)-2,4-diphenylcyclopent-3-ene-1,1-dicarboxylate **35a** (84.1 mg, 0.25 mmol, 1 equiv) and Pd 10% on activated carbon (10 mg, 0.03 equiv) in methanol (10 mL). The reaction mixture was kept stirring at 32 °C for 12 h under H_2 atmosphere (balloon pressure). Upon consumption of the starting material **35a** (TLC), the crude reaction mixture was passed through celite and concentrated under reduced pressure to get a sufficiently pure dimethyl (2*S*)-2,4-diphenylcyclopentane-1,1-dicarboxylate **42a** in 98% yield (82 mg, *dr* 20:1)

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.65.

HPLC (Kromasil 5-AmyCoat, 99:1 Hexane / IPA, 0.5 mL/min.) Major diastereomer (Major: 19.2 min, Minor: 20.7 min). Minor diastereomer (Major: 22.6 min, Minor: 25.5 min). $[\alpha]_D^{25}$ = -38.88 (c 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.39 (m, 6H, H_{ar}), 7.34-7.25 (m, 4H, H_{ar}), 4.37-4.33 (m, 1H), 3.82 (s, 3H, CH_3), 3.24-3.16 (m, 4H), 3.01 (d, *J* = 13.2 Hz, 1H), 2.64-2.59 (m, 1H), 2.46-2.32 (m, 2H).

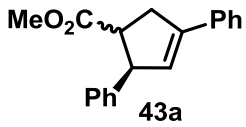
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.23, 171.23, 143.02, 140.08, 128.73, 128.62, 128.07, 127.30, 127.10, 126.65, 65.33, 52.89, 52.00, 50.90, 43.66, 42.48, 40.54.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{22}O_4Na$: 361.1410, found: 361.1404.

FTIR (cm^{-1}) 3463, 3061, 2952, 1728, 1603, 1455, 1365, 1096, 1046, 947, 752.

2.5.7. Decarboxylation of 35a

Methyl (2*R*)-2,4-diphenylcyclopent-3-ene-1-carboxylate (43a)



43a

To a microwave reaction tube was charged with **35a** (0.084 gm, 0.25 mmol) and LiCl (0.083 gm, 1.95 mmol, 7.8 equiv). Then the mixture was dissolved in DMSO (2.0 mL) : H_20 (1.5 mL). The reaction mixture was placed in a microwave reactor (Anton Paar, Monowave 300), and heated to 185 ^oC for 30 min. The resultant reaction mixture was quenched with saturated aq. solution of $NaHCO_3$ and extracted with Et_2O (3x10 mL). Then the organic layer was washed with brine, dried over Na_2SO_4, concentrated and the crude reaction mixture was purified by flash column chromatography to afford the diastereomeric mixture of methyl (2*R*)-2,4-diphenylcyclopent-3-ene-1-carboxylate **43a** in 51% yield (35 mg, *dr* 1:1).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.72.

$[\alpha]_D^{25}$ = +104.5 (c 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 2H, H_{ar}), 7.51 (d, *J* = 7.2 Hz, 2H, H_{ar}), 7.41-7.22 (m, 14H, H_{ar}), 7.20-7.17 (m, 2H, H_{ar}), 6.16 (s, 2H, $H_{olefinic}$), 4.45-4.42 (m, 2H), 3.80-3.73 (m, 4H), 3.49-3.41 (m, 1H), 3.26-3.14 (m, 6H), 2.96-2.89 (m, 1H).

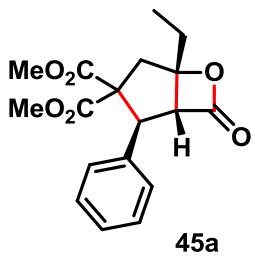
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.61, 173.36, 144.49, 142.67, 141.43, 140.24, 135.56, 128.75, 128.62, 128.20, 127.81, 127.65, 127.18, 126.93, 126.77, 126.00, 125.90, 55.27, 54.66, 52.27, 52.08, 51.25, 48.75, 37.14, 34.62.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{18}O_2Na$: 301.1199, found: 301.1196.

FTIR (cm^{-1}) 3021, 1745, 1379, 1214, 742, 669.

2.5.8. Synthesis and Characterization of Cyclopentane-Fused β-Lactones

Dimethyl *(1R,2S,5S)* 5-ethyl-7-oxo-2-phenyl-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate (45a)



45a

To an oven-dried Schlenk reaction vessel with a teflon screw cap was taken the (*Z*)-2-bromo 3-phenylacrylaldehye **33a** (79.1 mg, 0.38 mmol), the dimethyl 2-(2-oxobutyl)malonate **44** (50.0 mg, 0.25 mmol) and Na_2CO_3 (106 mg, 1.0 mmol, 4.0 equiv). The mixture was kept under argon atmosphere, and dry DME (3.0 mL) was then

introduced into the vessel by syringe under a positive pressure of argon, and the mixture was stirred at 32 °C. To this stirring solution was added the triazolium salt **H** (9.2 mg, 0.025 mmol), and the resulting mixture was stirred at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*1R,2S,5S*) 5-ethyl-7-oxo-2-phenyl-6-oxabicyclo[3.2.0] heptane-3,3-dicarboxylate **45a** as a white solid (38.0 mg, 46%).

R_f (Pet. ether /EtOAc = 80/20): 0.4.

HPLC (Chiralpak IA, 97:03 Petroleum ether / IPA, 0.5 mL/min, λ = 210 nm) Major: 18.7 min, Minor: 21.9 min. 99% ee, $[\alpha]_D^{25}$ = -188.7 (c 0.1, $CHCl_3$).

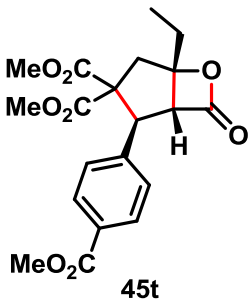
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 3H, H_{ar}), 6.99-6.97 (m, 2H, H_{ar}), 4.65 (s, 1H), 3.81 (s, 3H, CH_3), 3.70 (s, 1H), 3.31 (s, 3H, CH_3), 2.95-2.85 (m, 2H), 2.28-2.12 (m, 2H), 1.18 (t, *J* = 7.3 Hz, 3H, CH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.89, 168.36, 167.95, 138.52, 128.85, 128.10, 128.06, 90.77, 63.74, 53.65, 52.71, 50.68, 40.59, 28.57, 8.88.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{20}O_6Na$: 355.1152, found: 355.1150.

FTIR (cm^{-1}) 3118, 3022, 2430, 1827, 1734, 1780, 1556, 1445, 1035, 924.

Dimethyl (*1R,2S,5S*)-5-ethyl-2-(4-(methoxycarbonyl)phenyl)-7-oxo-6-oxabicyclo[3.2.0] heptane-3,3 dicarboxylate (45t)



45t

To an oven-dried Schlenk reaction vessel with a teflon screw cap was taken the (Z)-methyl-4-(2-bromo-3-oxoprop-1-en-1-yl)benzoate **33t** (101.0 mg, 0.38 mmol), the dimethyl 2-(2-oxobutyl)malonate **44** (50.0 mg, 0.25 mmol) and Na_2CO_3 (106 mg, 1.0 mmol, 4.0 equiv). The mixture was kept under argon atmosphere, and dry DME (3.0 mL) was then introduced into the vessel by syringe under a positive pressure of argon, and the mixture was stirred at 32 °C. To this stirring solution was added the triazolium salt **H** (9.2 mg, 0.025 mmol), and the resulting mixture was stirred at 32 °C for 72 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford dimethyl (*1R,2S,5S*) 5-ethyl-2-(4-(methoxycarbonyl) phenyl)-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3 dicarboxylate **45t** as a white solid (70.0 mg, 72%).

R_f (Pet. ether /EtOAc = 80/20): 0.23.

HPLC (Chiralpak IA, 97:03 Petroleum ether / IPA, 1.0 mL/min. λ = 210nm). Major: 15.8 min, Minor: 16.8 min. 99% ee, $[\alpha]_D^{25}$ = -74.1 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.06 (d, *J* = 8.2 Hz, 2H, H_{ar}), 4.71 (s, 1H), 3.90 (d, 3H, CH_3), 3.81 (s, 3H, CH_3), 3.69 (s, 1H), 3.31 (s, 3H, CH_3), 2.97-2.85 (m, 2H), 2.26-2.14 (m,2H), 1.19 (t, *J* = 7.5 Hz, 3H, CH_3).

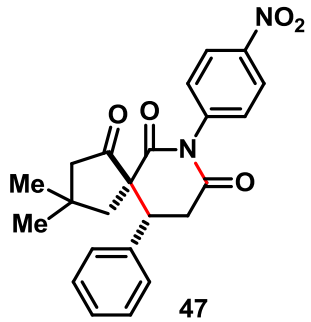
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.57, 167.85, 167.68, 166.50, 130.11, 128.16, 90.68, 66.62, 63.53, 53.77, 52.86, 52.38, 50.52, 40.65, 28.60, 8.88.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{22}O_8Na$: 413.1207, found: 413.1203.

FTIR (cm^{-1}) 2973, 2954, 1828, 1723, 1612, 1531, 1435, 1418, 1375, 1280, 1227, 1153, 1112, 1018, 900, 864, 810, 763, 707, 665.

2.5.9. Synthesis and characterization of Spiroglutarimide derivative

3,3-Dimethyl-7-(4-nitrophenyl)-10-phenyl-7-azaspiro[4.5]decane-1,6,8-trione (47)



47

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken the triazolium salt **H** (9.2 mg, 0.025 mmol, 10 mol %), 2-bromocinnamaldehyde **33a** (79.1 mg, 0.375 mmol, 1.5 equiv). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added CH_3CN (3.0 mL) under argon atmosphere followed by *i*-Pr_2NEt (48.4mg, 65 μl, 0.375 mmol, 1.5 equiv) and 4,4-dimethyl-N-(4-nitrophenyl)-2-oxocyclopentane-1-carboxamide **46** (69.0 mg, 0.25 mmol, 1.0 equiv) the mixture was kept stirring at 32°C for 48 hours. After completion of the reaction the crude reaction mixture was purified by flash column chromatography using 15% ethyl acetate-pet ether to afford 3,3-dimethyl-7-(4-nitrophenyl)-10-phenyl-7-azaspiro[4.5]decane-1,6,8-trione **47** as a light yellow solid (51.0 mg, 50% yield, diastereoselectivity determined by crude ^{1}H NMR is 10:1).

R_f (Pet. ether /EtOAc = 70/30): 0.62.

HPLC (Chiralcel OD-H, 50:50 Petroleum ether / EtOH, 0.7 mL/min. λ = 254nm). Major: 14.1 min, Minor: 11.5 min. 90% ee, $[\alpha]_D^{25}$ = -75.1 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.4 Hz, 2H), 7.41-7.32 (m, 5H), 7.16 (d, *J* = 7.3 Hz, 2H), 3.68 (t, *J* = 5.6 Hz, 1H), 3.50 (dd, J_1 = 17.6 Hz, J_2 = 5.8 Hz, 1H), 3.02 (dd, J_1 =

17.9 Hz, J_2 = 5.5 Hz, 1H), 2.57 (d, J = 14.1 Hz, 1H), 2.40 (d, J = 17.2 Hz, 1H), 2.25 (d, J = 17.4 Hz, 1H), 1.96 (d, J = 14.2 Hz, 1H), 1.12 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.64, 172.15, 170.64, 147.79, 141.24, 138.60, 129.88, 129.47, 128.38, 128.13, 124.64, 62.05, 53.58, 44.74, 42.85, 36.69, 33.59, 30.17, 29.40.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{23}H_{22}O_5N_2Na$: 429.1421, found: 429.1638.

FTIR (cm^{-1}) 3620, 3019, 2965, 2400, 1738, 1686, 1640, 1411, 1215, 1137, 1112, 850, 755, 669.

2.6. References

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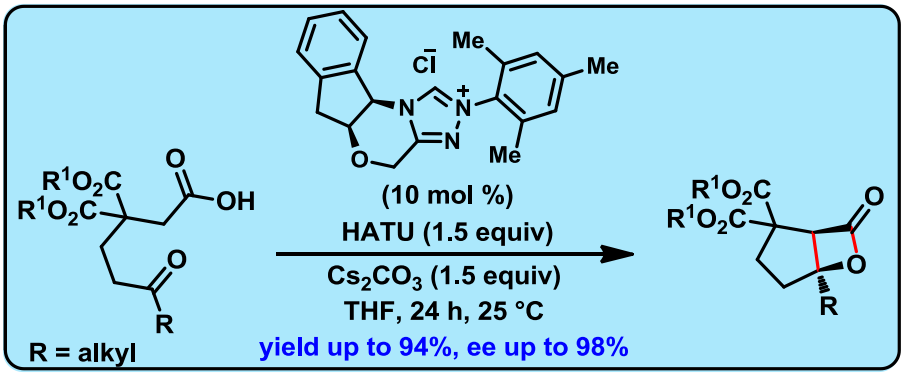
Chapter 3

Enantioselective Synthesis of Functionalized β-Lactones by NHC-Catalyzed Aldol Lactonization of Ketoacids

N-Heterocyclic carbene (NHC)-catalyzed intramolecular aldol lactonization of linear ketoacids resulting in the highly enantioselective synthesis of cyclopentane-fused β-lactones forms the central theme of this chapter. The reaction proceeds via the activation of acid in the presence of the peptide coupling reagent HATU followed by the generation of NHC-bound enolate intermediates under mild reaction conditions. An intramolecular aldol and a subsequent β-lactonization afforded the β-lactones in good yield and excellent enantioselectivity. Furthermore, the synthetic utility of the β-lactone products have been demonstrated.



J. Org. Chem. **2017**, *82*, 9223-9228.

3.1. Introduction

β-Lactone derivatives exhibit interesting biological properties and this core moiety is frequently found in numerous pharmaceutically important molecules.[1] This class of compounds show selective reactivity towards the active sites of several enzymes, and hence they are important in activity-based proteome profiling.[2] Among this family of compounds, the β-lactones fused to a five-membered ring are important candidates found in various natural products. For instance, the marine natural product spongiolactone shows antiproliferative activity towards the leukemia (K562) cell line (Figure 3.1).[3] Moreover, salinosporamide A is a potent proteasome inhibitor where the β-lactone moiety is fused to a γ- butyrolactam functionality,[4] and the rocaglate-derived *β*-lactone has been recently reported to have serine hydrolase activity.[5] Also omuralide is a member of this class of compound, isolated by Omura and co-workers from cultures of a terrestrial Streptomyces sp, a truly specific inhibitor of the proteasome.[6]

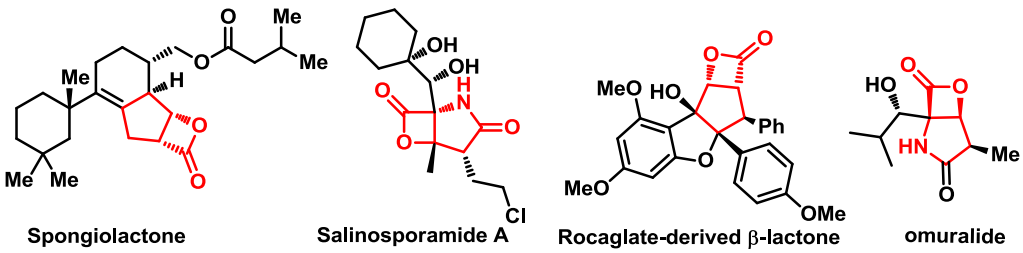
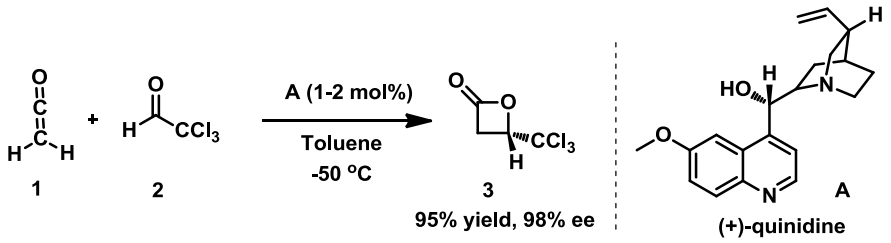


Figure 3.1: Selected Biologically Important β-Lactone-fused to Five-membered Rings

Due to the frequent occurrence of β-lactone moiety in biologically important molecules, development of mild, catalytic and enantioselective routes to these target molecules are of high importance. Two of the most widely used methods to construct this strained heterocycles are the [2+2] cycloaddition of ketene with various aldehyde or ketones and a tandem aldol lactonization with enolates.[7] In 1911, Staudinger first discovered the synthesis of β-lactones via the [2+2] cycloaddition of ketene and carbonyl compounds.[8] Later in 1982, Wynberg first introduced an efficient asymmetric synthesis of β-lactones proceeding through a proposed aldol lactonization process (Scheme3.1).[9] In presence of cinchona

Scheme 3.1: First Asymmetric β-Lactone Synthesis



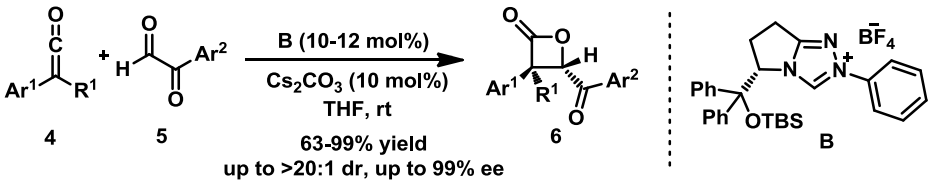
alkaloid (+) quinidine **A** as a catalyst, the formal [2+2] cycloaddition of ketene **1** and highly electrophilic carbonyl compound chloral **2** afforded the β-lactone product **3** in excellent yield and enantioselectivity.

NHC-Catalyzed Synthesis of β-Lactones

3.1.1. Synthesis of β-Lactone via Azolium Enolate Intermediate

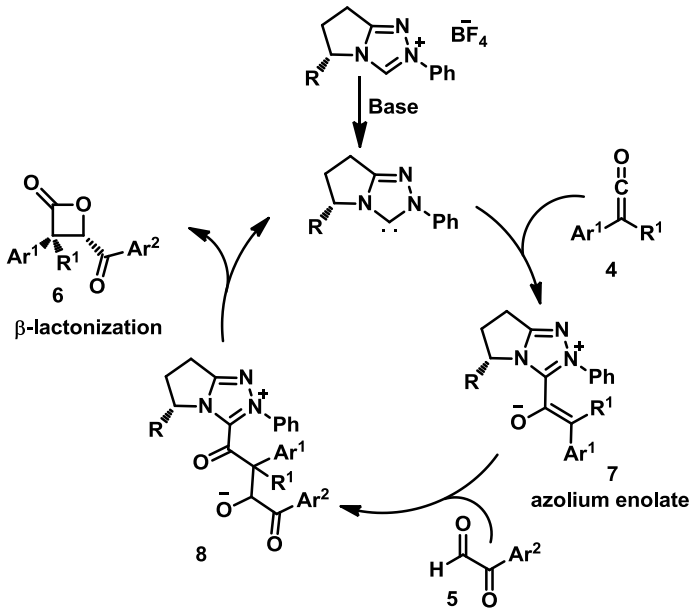
In 2008, Ye and co-workers developed the first NHC-catalyzed enantioselective synthesis of highly substituted β-lactones (Scheme 3.2).[10] In the presence of triazolium salt **B** as a catalyst precursor, the formal [2+2] cycloaddition reaction of disubstituted ketene **4** with 2-oxoaldehydes furnished the desired product in good yield, diastereoselectivity and excellent ee value. Both alkyl(aryl)ketenes and diarylketenes worked well under this reaction conditions.

Scheme 3.2: [2+2] Cycloaddition of Ketenes with Aldehydes



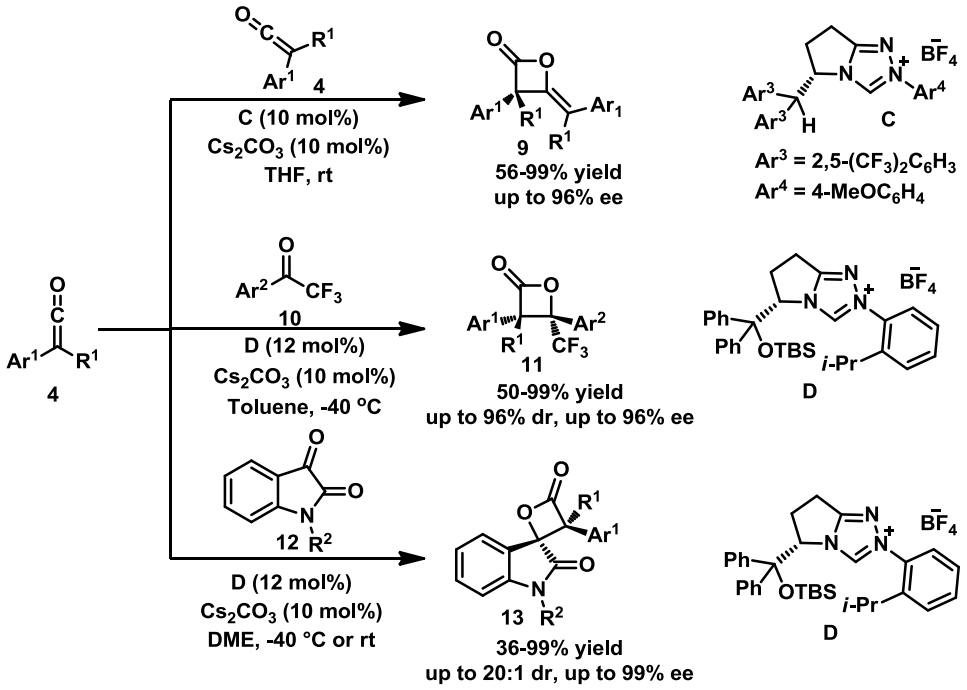
A possible mechanism for this cycloaddition reaction is represented in Scheme 3.3. The initial attack of NHC generated from triazolium precursor to ketene **4** forms azolium enolate intermediate **7**. A formal [2+2] cycloaddition of intermediate **7** with activated aldehyde afforded acyl azolium intermediate **8**. Finally, β-lactonization of **8** by the removal of free carbene furnished the desired product **6**.

Scheme 3.3: Mechanism of [2+2] Cycloaddition Reaction



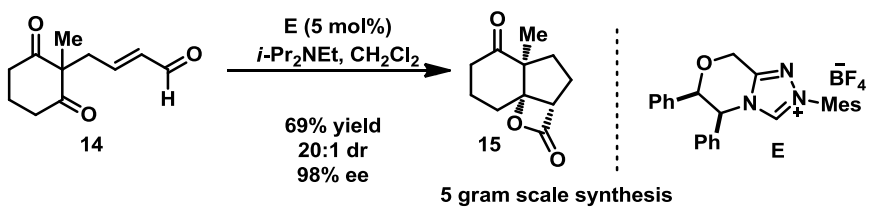
In a similar fashion, the same research group demonstrated the enantioselective synthesis of various other β-lactones employing different activated carbonyl compounds as an electrophilic reacting partner (Scheme 3.4).[11] All the cases, the expected product was formed in good to excellent yield and stereoselectivity. Recently, Smith and co-workers showed the similar strategy for β-lactone synthesis using 2-nitrobenzaldehyde and 2-pyridine carboxaldehyde as an electrophilic component.[12]

Scheme 3.4: [2+2] Cycloaddition of Ketenes with Activated Carbonyls



In 2010, Scheidt and co-workers uncovered the NHC-catalyzed desymmetrization of 1,3-diketones **14** for an enantioselective synthesis of tricyclic β-lactones **15** (Scheme 3.5).[13] Catalyzed by NHC generated from the chiral triazolium salt **E**, the expected product was formed in good yield with excellent enantio- and diastereoselectivity. The authors showed an application of this methodology for a gram scale asymmetric synthesis of Bakkenolides. Later, the same group demonstrated an enantioselective synthesis of cyclopentane-fused β-lactones using dynamic kinetic resolution strategy. For details see chapter 4, section 4.1.2, page 102.[14]

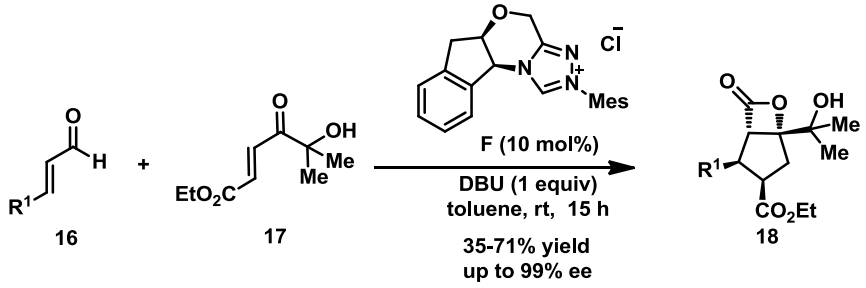
Scheme 3.5: Desymmetrization of a 1,3-Diketone



3.1.2. Synthesis of β-Lactone via Homoenolate Intermediates

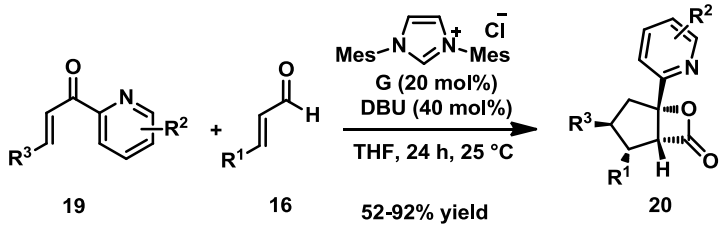
In 2010, Bode and co-workers disclosed a facile and highly enantioselective synthesis of β-lactones by the treatment of α,β-unsaturated aldehydes **16** with α-hydroxy enones **17** (Scheme 3.6).[15] The reaction proceeds via the generation of homoenolate intermediate in presence of NHC generated from chiral triazolium salt **F** followed by a Michael-aldol-β-lactonization sequence to afforded the desired product in good yield, diastereoselectivity and excellent enantioselectivity. Notably, using chiral imidazolium derived NHC-catalyst, the authors have shown the preferencial formation of γ-lactone over β-lactone.

Scheme 3.6: Annulation of α,β-Unsaturated Aldehydes and α-Hydroxy Enones



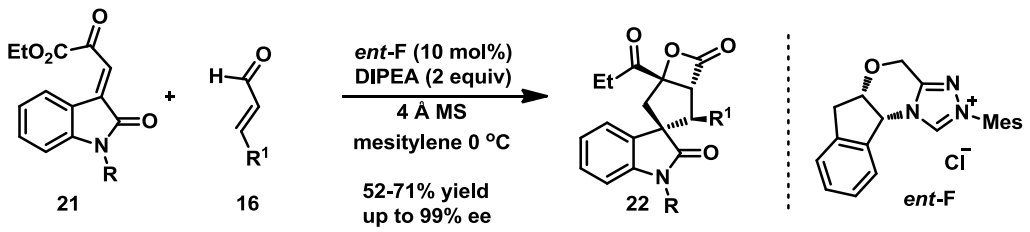
A diastereoselective homoenolate annulation of enals **16** with 2-enoylpyridine **19** for the synthesis of highly substituted cyclopentane-fused β-lactone was described by our group (Scheme 3.7).[16] The pyridine moiety in the enone plays an important role in stabilizing the β-lactone product. Under the mild reaction conditions, a wide variety of enals and 2-enoylpyridines are well tolerated and furnished the desired product in good to excellent yield and diastereoselectivity. Additionally, a preliminary investigation of the asymmetric version of this annulation reaction was also demonstrated.

Scheme 3.7: Annulation of α,β-Unsaturated Aldehydes and 2-Enoylpyridine



Very recently, Wang and co-workers reported the NHC-catalyzed asymmetric Michael-intramolecular aldol-lactonization cascade for enantioselective construction of β-propiolactone-fused spiro[cyclopentane-oxindoles] **22**.[17] In this reaction, the homoenolate generated from enal **16** will react with oxindolyl β,γ-unsaturated α-ketoesters **21** followed by aldol-lactonization to form the β-lactone product containing four contiguous stereocenters in moderate yields and excellent diastereoselectivities and enantioselectivities.

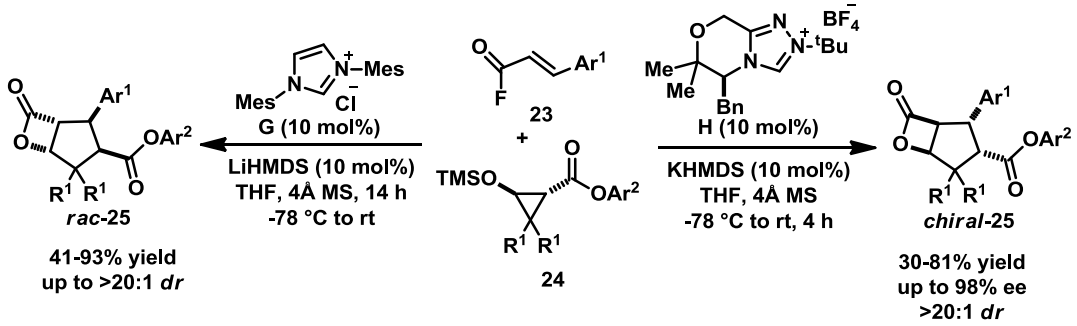
Scheme 3.8: Annulation of Enals with Oxindolyl β,γ-Unsaturated α-Ketoesters



3.1.3. Synthesis of β-Lactones via α,β-Unsaturated Acyl Azolium Intermediates

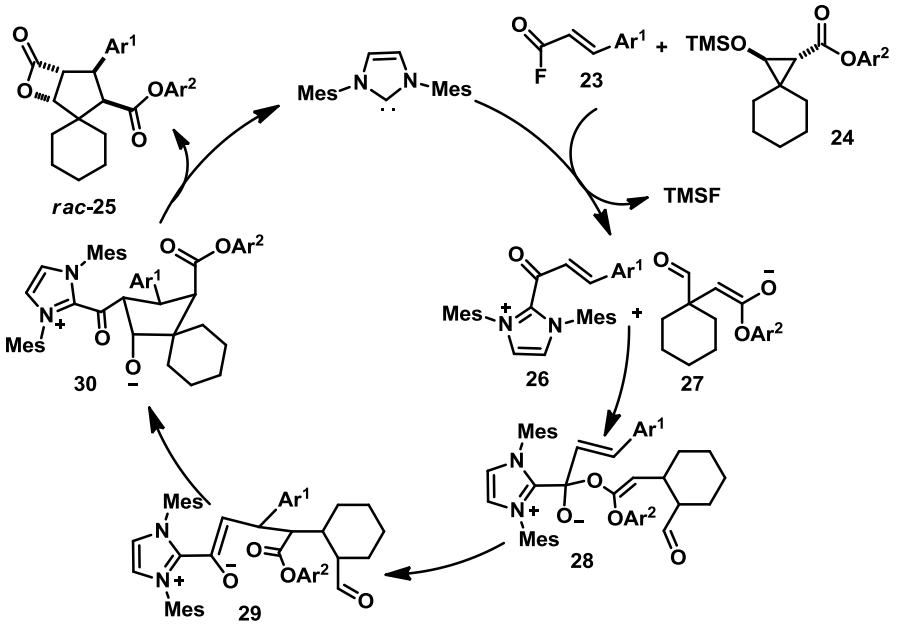
In 2012, the Lupton group reported the coupling reactions of α,β-unsaturated acyl fluorides **23** with silylated donor-acceptor cyclopropanes **24** via NHC-catalyzed Ireland-Coates-Claisen rearrangement. Under optimal conditions, electron-rich and electron-poor α,β-unsaturated acyl fluorides were well tolerated and highly functionalized β-lactones ***rac*-25** were synthesized in good yields (41-93%) with excellent stereoselectivity (>20:1 *dr* in all cases) (Scheme 3.9).[18] Moreover, the same research group developed the enantioselective version of this transformation using chiral triazolium precursor **H**, to afford corresponding functionalized β-lactones ***chiral*-25** in moderate to good enantioselectivity (55-98%).[19]

Scheme 3.9: Stereoselective Synthesis of β-Lactones



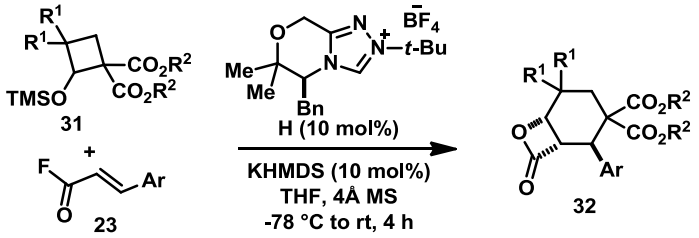
A tentative mechanism for this cascade reaction proposed in scheme 3.10. The NHC-catalyzed generation of α,β-unsaturated acylazolium ion **26** from α,β-unsaturated acid fluoride **23** by the liberation of fluoride ion, which is used for the desilylation of silylated donor-acceptor cyclopropanes **24** to form enolate **27**. 1,2-addition of the enolate **27** to α,β-unsaturated acylazolium **26** followed by a Ireland-Coates-Claisen rearrangement produced azolium enolate intermediate **29**. An intramolecular aldol followed by β-lactonization furnished the fused β-lactone product **rac-25**.

Scheme 3.10: Proposed Mechanism of the Reaction



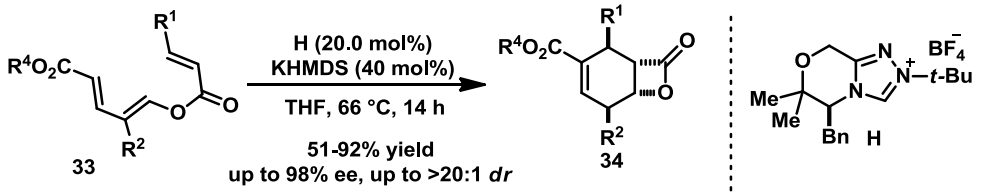
Recently, the same research group extended their methodology by introducing donor-acceptor cyclobutane **31** for NHC-catalyzed [4+2] annulation reaction with α,β-unsaturated acyl fluorides **23** (scheme 3.11).[20] This reaction proceeds via NHC-catalyzed deflourination-desilylation strategy. Employing NHC generated from chiral triazolium precursor **H**, various substitution on aryl group of α,β-unsaturated acyl fluoride **23** as well as substituted donor-acceptor cyclobutanes **31** underwent smooth annulation to furnish the expected cyclohexane-fused β-lactones **32** in good to excellent yield and excellent diastereo and enantioselectivity.

Scheme 3.11. Enantioselective (4+2) Annulation of Donor-Acceptor Cyclobutanes.



An enantioselective all carbon [4+2] annulation reaction of α,β-unsaturated dienyl ester **33** for the synthesis of cyclohexene-fused β-lactones **34** was uncovered by Lupton and co-workers (Scheme 3.12).[21] In the presence of catalyst precursor **H**, the in situ generated

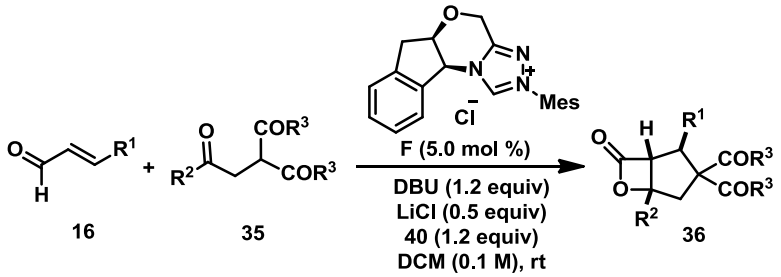
Scheme 3.12: Annulation Reactions of Dienyl Esters



dienolates undergoes cycloaddition reaction with α,β-unsaturated acylazolium in a vinylogous Michael-aldol-lactonization cascade fashion resulted the expected product **34** in good yields (upto 92%) with excellent enantioselectivity (upto 98%) and diastereoselectivity (upto >20:1).

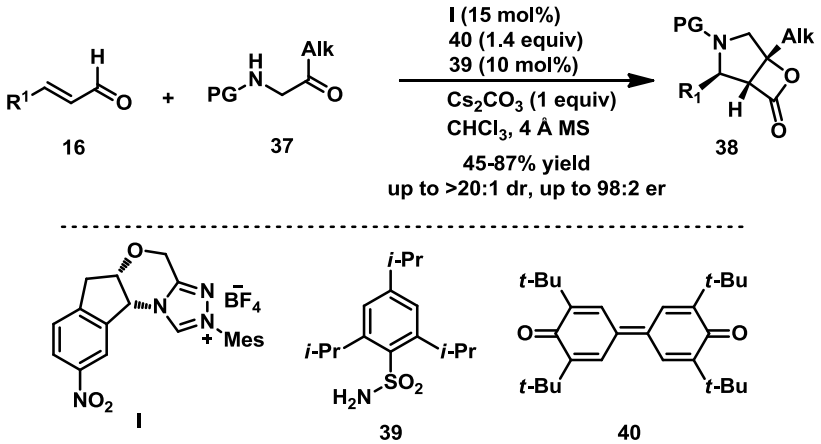
An enantioselective synthesis of highly substituted β-lactones through oxidative NHC catalysis with LiCl as cooperative Lewis acid was shown by Studer and co-workers (scheme 3.13).[22] The reaction of enals **16** with malonates **35** bearing a β-oxyalkyl substituent at the α-position in presence of chiral trizolium salt **F** and oxidant **40** afforded substituted β-lactone **36** in good yields (15-97%) and excellent selectivity (up to > 99% ee and >20:1 *dr*). The organocascade reaction proceeds via intermolecular Michael/aldol/ β-lactonization sequence to form β-lactone containing four contiguous stereogenic centers including two fully substituted stereocenters. Moreover, when the R^2-substituent of **35** is a phenyl group, this organocascade provided corresponding cyclopentene derivatives by the decarboxylation of corresponding β-lactones.

Scheme 3.13: Enantioselective Synthesis of Highly Substituted β-Lactones



Very recently, Chi and co-worker developed a practical method for the enantioselective synthesis of pyrrolidine-fused β-lactones (Scheme 3.14).[23] Under oxidative condition, the efficient cascade reaction between enals **16** and α-amino ketones **37**

Scheme 3.14: Enantioselective Synthesis of Pyrrolidine-fused β-Lactones

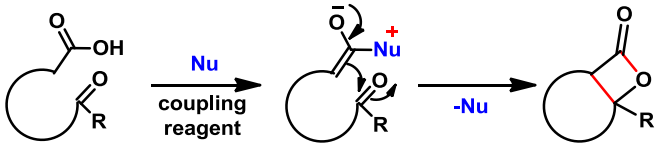


proceeds through intermolecular aza-Michael followed by intramolecular aldol-lactonization sequence. Notably, the use of sulfonyl amide **39** as an additive enhances the enantioselectivity of the product. A wide variety of enals and α-amino ketones tolerates this organocascade reaction and furnished the desired product **38** in good to excellent yield and stereoselectivity. Additionally, some interesting synthetic transformation of the pyrrolidine-fused β-lactone products and their application in secondary amine catalysis has been demonstrated.

3.2. Statement of the Problem

The nucleophile-catalyzed aldol lactonization (NCAL) of ketoacids is one of the well-established methods for the synthesis of β-lactone derivatives. A wide variety of highly stereoselective β-lactones synthesis using this strategy was extensively explored by the research group of Romo (Scheme 3.15).[24] Moreover the asymmetric version of NCAL process takes place in presence of isothiourea[25] or cinchona alkaloid[26] as an organocatalyst along with coupling reagent.

Scheme 3.15: NCAL of Ketoacids for the Synthesis of Bicyclic Lactones



In this context, we anticipated that a chiral NHC could be an organocatalyst for the aldol lactonization of ketoacids for the enantioselective synthesis of bicyclic β-lactones. Although NHCs are commonly used as organocatalysts for various transformations starting from aldehydes, the activation of carboxylic acids using NHCs has received only limited attention,[27] and the NHC-catalyzed aldol lactonization of ketoacids is rare. Herein, we describe the NHC-catalyzed aldol lactonization of ketoacids for the enantioselective synthesis of cyclopentane-fused β-lactones. The results of our studies are presented in the following sections.

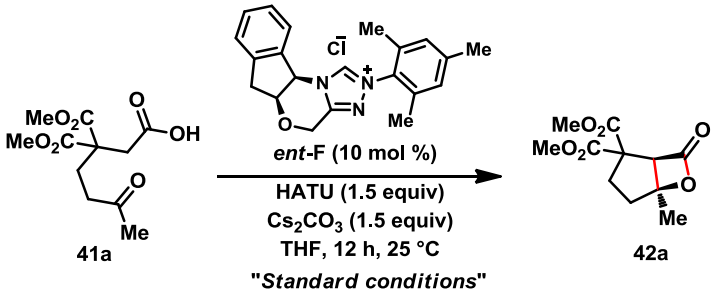
3.3. Results and Discussion

3.3.1. Optimization Studies

Considering the synthetic utility of functionalized β-lactones in organic synthesis, we initiated our investigation by the treatment of the ketoacid **41a** with the carbene generated from the chiral triazolium salt ***ent*-F**[28] using Cs_2CO_3 as base in presence of the peptide coupling reagent 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyl uronium

hexafluorophosphate (HATU). Intriguingly, under these reaction conditions, the cyclopentane-fused β-lactone **42a** was formed in 85% yield and 98% ee (Table 3.1, entry 1). The reaction was not working in the absence of activating reagent HATU (entry 2), and in the absence of the triazolium salt ***ent*-F**, 42% of racemic **42a** was observed (entry 3). Employment of other coupling reagents instead of HATU resulted in the formation of **42a** in low yields and ee values (entries 4-6). A rapid base screening revealed that Cs_2CO_3 is the best base for this transformation (entries 7-10). Notably, the reaction afforded only traces of **42a** when carried out in presence of Et_3N or DBU as the base. The reactivity was found to be better when performed in toluene instead of THF, but the ee value was slightly low (entry 12). The reactions performed in CH_2Cl_2 and DME furnished **42a** in moderate yield maintaining the excellent ee value (entries 11 and 13). Finally increasing the reaction time to 24 h afforded **42a** in 94% yield and 98% ee (entry 14).

Table 3.1: Optimization of the Reaction Conditions[a]

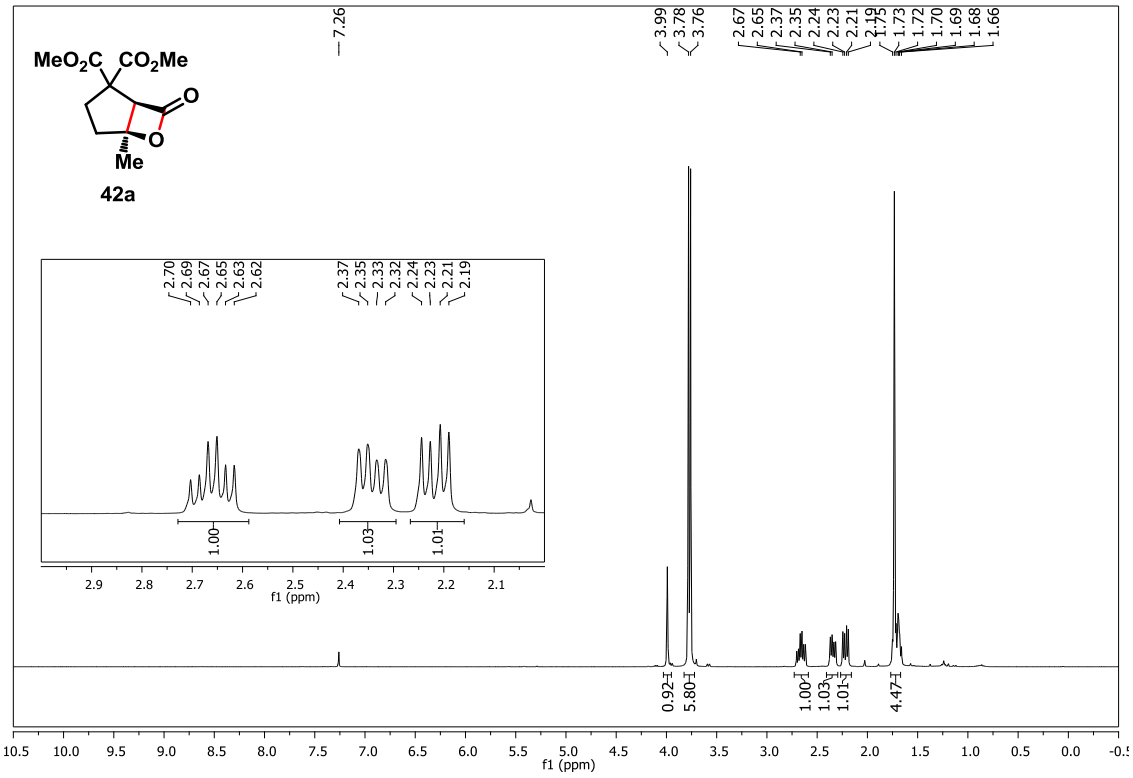


entry	variation of the standard conditions[a]	yield **42a** (%)[b]	ee **42a** (%)[c]
1	none	85	98
2	No HATU	<5	n.d.
3	No ***ent*-F**	42	n.d.
4	HBTU instead of HATU	61	89
5	CDI instead of HATU	<5	n.d.
6	Piv-Cl instead of HATU	78	96
7	Na_2CO_3 instead of Cs_2CO_3	65	88
8	Et_3N instead of Cs_2CO_3	<5	n.d.
9	DBU instead of Cs_2CO_3	<5	n.d.
10	KOt-Bu instead of Cs_2CO_3	20	64
11	CH_2Cl_2 instead of THF	68	98
12	toluene instead of THF	97	95
13	DME instead of THF	53	98
14	**Reaction time 24 h instead of 12 h**	**94**	**98**

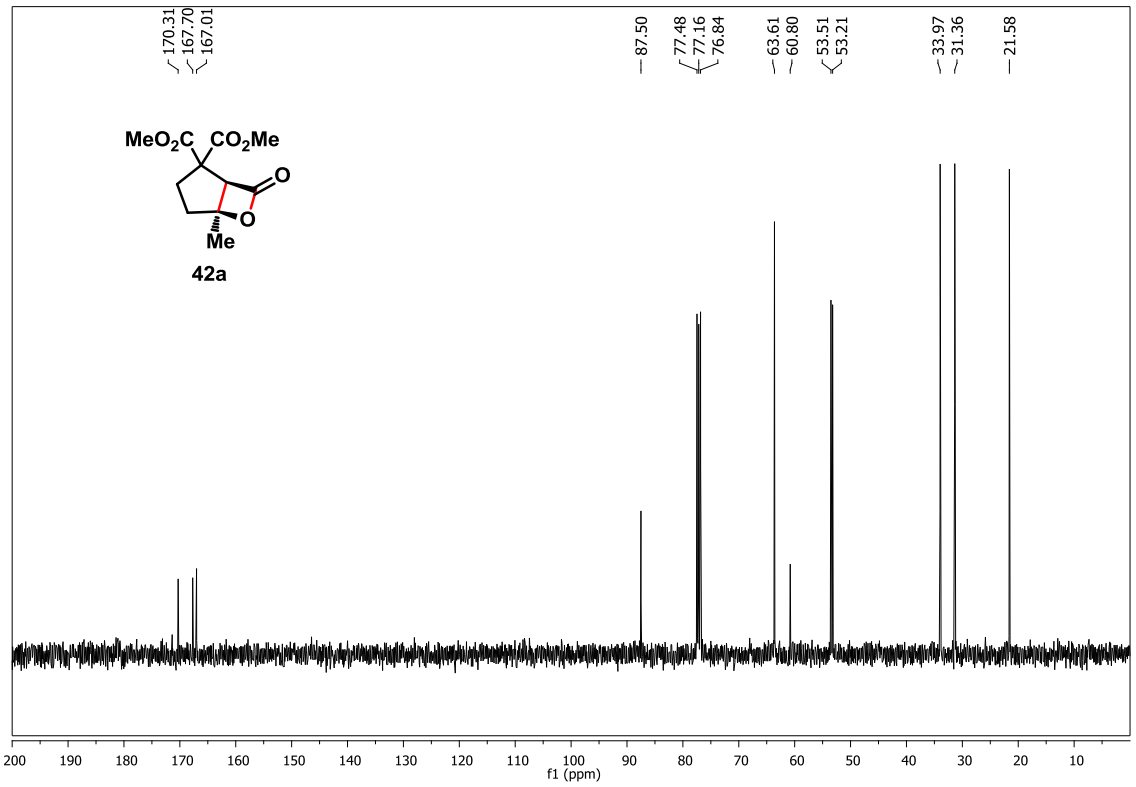
[a] Standard conditions: **41a** (0.25 mmol), ***ent*-F** (10 mol %), HATU (1.5 equiv), Cs_2CO_3 (1.5 equiv), THF (3.0 mL), 25 °C and 12 h. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis on a chiral column.

3.3.2. Spectral Data of 42a

^{1}H NMR Spectrum of 42a ($CDCl_3$)

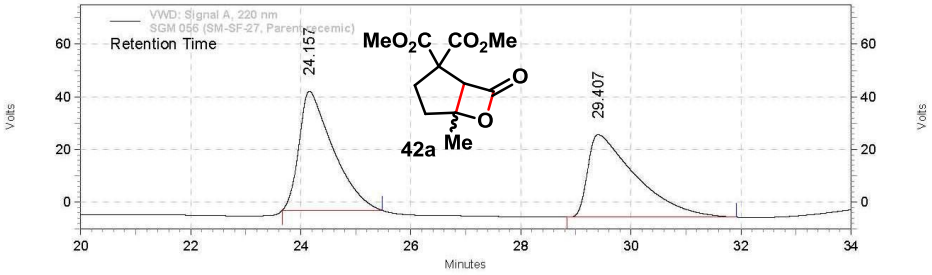


^{13}C NMR Spectrum of 42a ($CDCl_3$)



HPLC Chromatogram of Racemic- 42a

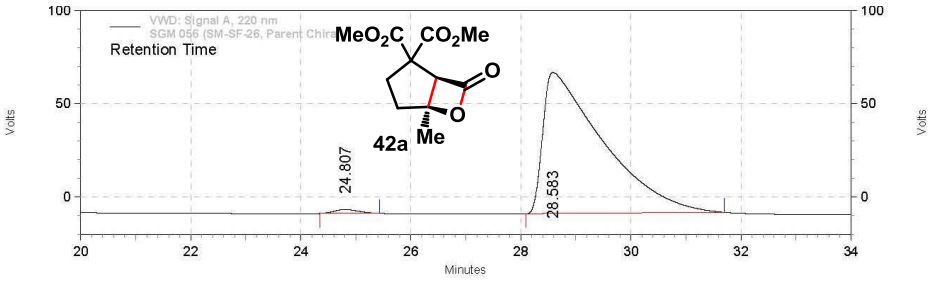
Data File: D:\BIJU\SGM\FINAL\Raw file\SGM 056 (SM-SF-27, Parent recemic).dat
Method: E:\cvr\106.met
Acquired: 11/6/2015 12:00:04 AM Printed: 4/10/2017 9:40:29 AM



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %
24.157	32732726	50.76
29.407	31750471	49.24
Totals	64483197	100.00

HPLC Chromatogram of Enantiomerically Pure-42a



VWD: Signal A, 220 nm Results

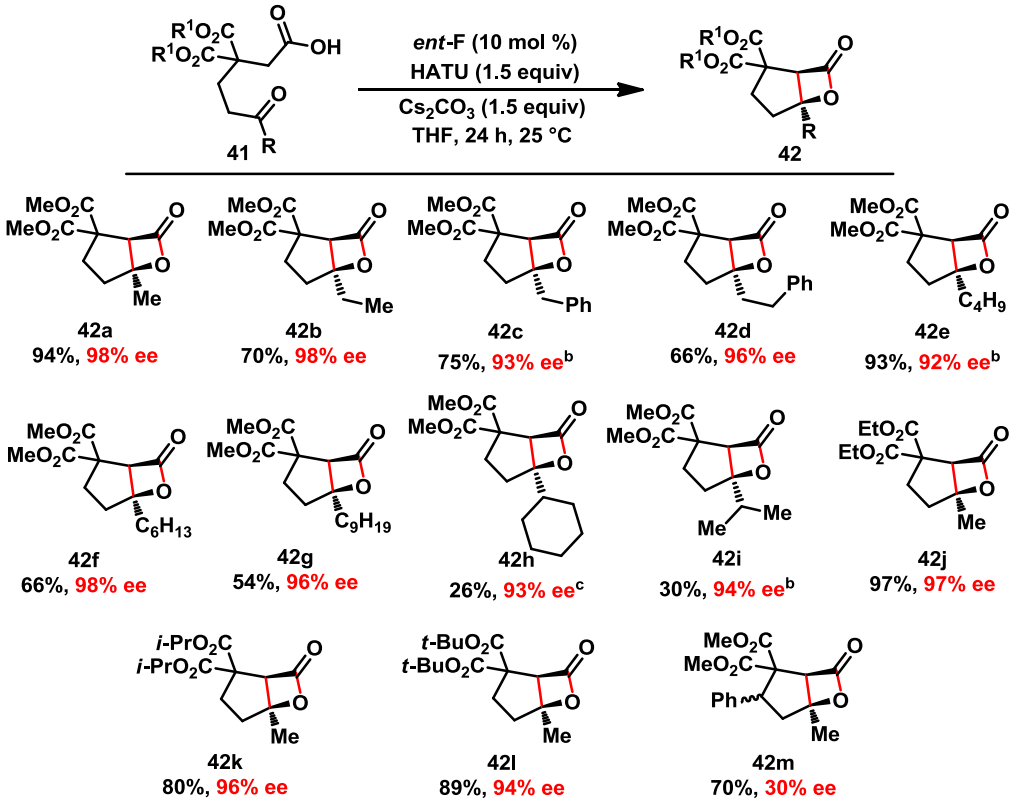
Retention Time	Area	Area %
24.807	1083534	1.11
28.583	96158253	98.89
Totals	97241787	100.00

Column : Chiralcel OJ-H
Eluent System : 93:7 (HEXANE:IPA)
Flow rate: 0.7 ml/min
Wavelength: 220 nm
Sample Conc: 1mg/ml

3.3.3. NHC-Catalyzed Aldol Lactonization of Ketoacids: Substrate Scope [a]

After optimizing the reaction conditions for the NHC-catalyzed aldol lactonization reaction, we examined the scope and limitation of this annulation reaction with various ketoacids (Scheme 3.16). A series of substrates having linear alkyl groups attached to the keto moiety smoothly underwent efficient aldol lactonization reaction under the present reaction conditions to deliver the cyclopentane-fused β-lactones in good yields and excellent ee values (**42a-42g**). Ketoacids containing branched alkyl groups attached to the keto group afforded the product in moderate yield, but with excellent ee values (**42h, 42i**). It may be mentioned

Scheme 3.16: Substrate Scope of the NHC-Catalyzed Aldol Lactonization Reaction[a]



[a] General reaction conditions: **41** (0.50 mmol), ***ent*-F** (10 mol %), HATU (1.5 equiv), Cs_2CO_3 (1.5 equiv), THF (6.0 mL), 25 °C and 24 h. Given are isolated yields and the ee was determined by HPLC analysis on a chiral column. [b] Reaction was run on 0.25 mmol scale. [c] Reaction carried out using 20 mol % of ***ent*-F**.

that the two ester groups at the β-position of acid was essential for high reactivity as well as enantioselectivity. The reactions performed using sterically different carboalkoxy groups did not affect the outcome of the reaction and in all cases tried, the desired product was formed in

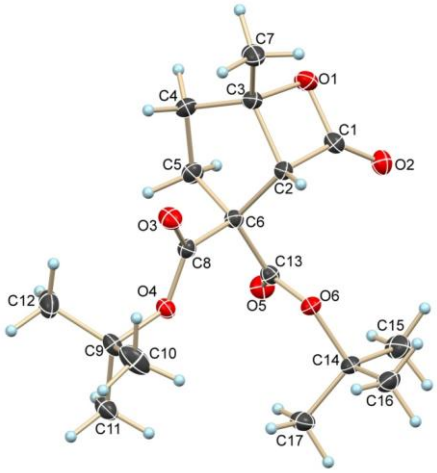


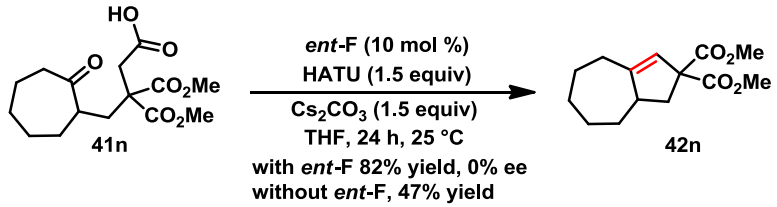
Figure 3.2: Crystal Structure of **42l** (Thermal Ellipsoids are Shown with 50% Probability).

good yields and excellent ee values (**42j**-**42l**). In the case of the *tert*-butyl ester **42l**, the structure and stereochemistry was determined using single crystal X-ray analysis (Figure

3.2).[29] Additionally, a linear ketoacid having a γ-phenyl ring subjected under optimized reaction condition, resulted the formation of expected product in good yield and moderate enantioselectivity (**42m**).

When this aldol lactonization reaction was performed under the optimized conditions on cycloheptanone-derived ketoacid **41n**, the bicyclic cyclopentene derivative **42m** was formed in 82% yield, and surprisingly, the product was a racemic mixture (Scheme 3.17). Notably, **42n** was formed in 47% yield when the reaction was carried out in the absence of triazolium salt ***ent*-F**. The cyclopentene **42n** was formed by the decarboxylation of the initially formed tricyclic β-lactone under the reaction conditions.

Scheme 3.17: Reaction using Cycloheptanone-derived Substrate



Finally, we attempted various other substrates for this annulation reaction. The use of substrate **41o** having an aryl group attached to the keto group, as well as the substrate **41p** with aldehyde moiety at the ε-position, this annulation reaction did not work (Figure 3.3). Moreover, when the acid and keto groups were interchanged (**41q**), the β-lactone product was not observed. In addition, our preliminary studies for the synthesis of cyclohexane-fused lactones by performing the reaction on substrate **41r** also failed.

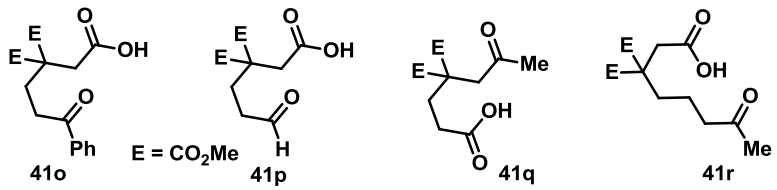
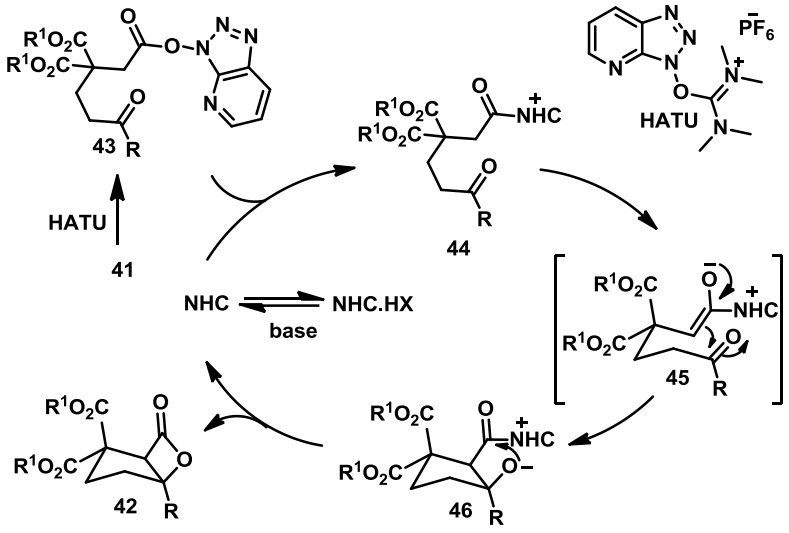


Figure 3.3: Unsuccessful Substrates in this Annulation

3.3.4. Proposed Mechanism

Mechanistically, the reaction proceeds via the generation of the HATU ester **43** by the addition of HATU to the ketoacid **41** (Scheme 3.18). The addition of free carbene generated from ***ent*-F** to the activated carboxylate **43** generates the NHC-acyl azolium intermediate **44**, which under basic conditions forms the key NHC-bound enolate intermediate **45**. Intramolecular aldol reaction results in the formation of NHC-acyl azolium **46**, which on β-lactonization with the release of free carbene resulted the β-lactone **42**.

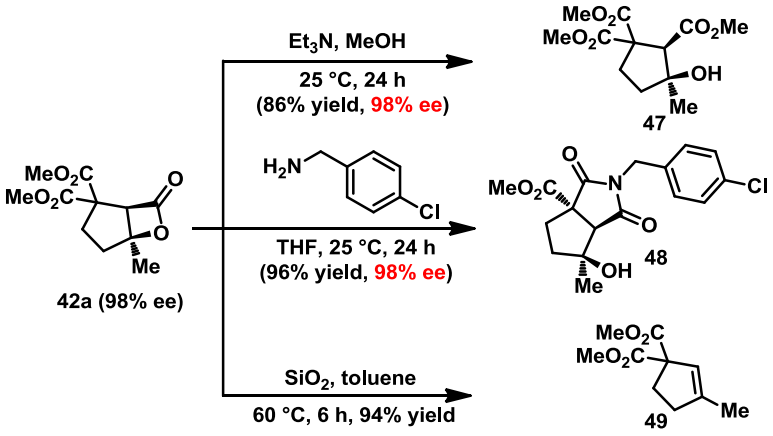
Scheme 3.18: Tentative Mechanism of the Reaction



3.3.5. Synthetic Transformations of Cyclopentane-fused β-Lactones

The enantiopure cyclopentane-fused β-lactones synthesized using the present method can undergo further synthetic transformations (Scheme 3.19). Nucleophilic opening of the β-lactone **42a** using MeOH in presence of Et_3N base afforded the cyclopentane **47** in 86% yield and 98% ee. When the nucleophile used was a 4-Chlorobenzyl amine, a tandem β-lactone opening-annulation reaction took place resulted the formation of the succinimide derivative **48** containing three contiguous stereocentres. The product **48** was obtained in 96% yield and 98% ee. Furthermore, heating the β-lactone **42a** at 60 °C in toluene for 6 h in the presence of SiO_2 furnished the cyclopentene **49** in 94% yield.

Scheme 3.19: Synthetic Transformations of Cyclopentane-fused β-Lactones



3.4. Conclusion

In conclusion, we have developed the NHC-catalyzed enantioselective synthesis of cyclopentane-fused β-lactones by the intramolecular aldol lactonization of ketoacids.[30] The

use of NHC generated from the aminoindanol-derived chiral triazolium salt along with HATU as an activating agent, afforded the β-lactones in moderate to good yields and excellent ee values. The β-lactones are converted into functionalized cyclopentanes and succinimide derivatives in high yields without the altering of ee values.

3.5. Experimental Details

3.5.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Dry THF were purchased from commercial sources and stored under argon over sodium wire. The triazolium salt ***ent*-F** was synthesized following the literature procedure.[28] Cs_2CO_3 was purchased from commercial sources and stored inside the glovebox.

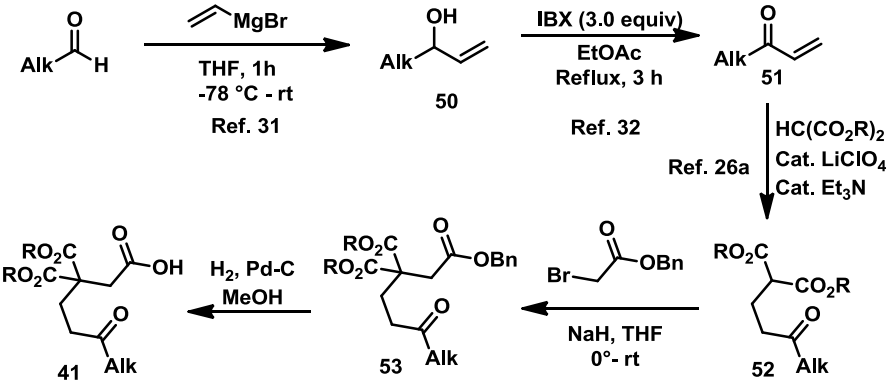
Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (100-200 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system.

All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400, in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS (ESI) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Optical rotation was measured with a JASCO P 2000 digital polarimeter at rt using 100 mm cell of 1 mL capacity. HPLC analysis was performed on Agilent Technologies 1260 Infinity with UV detector.

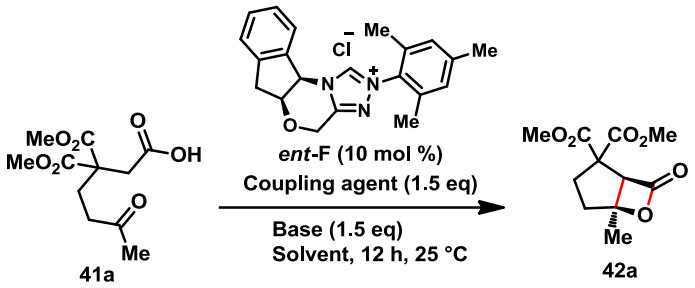
3.5.2. General Procedure for the Preparation of Ketoacids

The synthesis of the ketoacids used in the present study has been carried out starting from the aliphatic carboxaldehydes (scheme 3.20). The aldehyde was converted into the allylic alcohol **50** by reacting with vinyl magnesium bromide.[31] Oxidation of allylic alcohols **50** using IBX under reflux condition affords vinyl ketone **51**.[32] Michael addition of malonate ester to vinyl ketone followed by alkylation with benzyl bromoacetate and debenzylation furnished the keto acid substrates **41**.[26a]

Scheme 3.20: Synthesis of Ketoacids

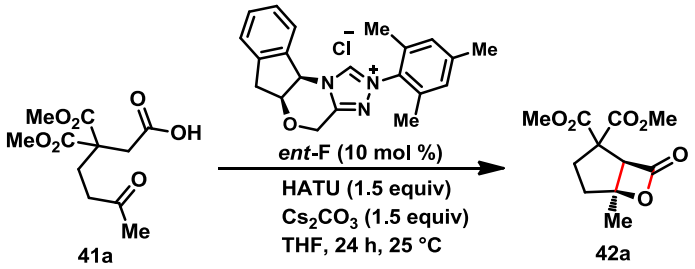


3.5.3. General Procedure for the Optimization of Reaction Conditions



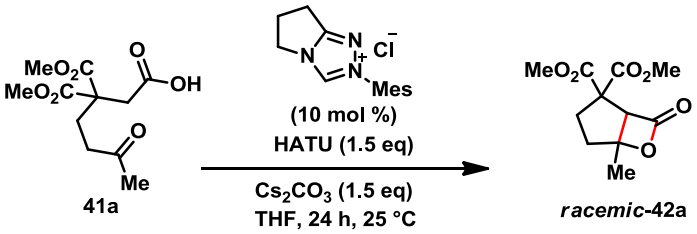
To a oven-dried Schlenk reaction vessel equipped with a magnetic stir bar was taken the 3,3-bis(methoxycarbonyl)-6-oxoheptanoic acid **41a** (65.0 mg, 0.25 mmol), coupling agent (0.375 mmol, 1.5 equiv), base (0.375 mmol, 1.5 equiv) and triazolium salt ***ent*-F** (9.2 mg, 0.025 mmol, 10 mol %). The mixture was kept under argon atmosphere. To this mixture was added solvent (3.0 mL) under a positive pressure of argon and the resulting mixture was stirred at 25 °C for 12 h. Evaporation of the solvent to obtain the crude product whose yield was determined after isolation by silica gel flash column chromatography. The enantiomeric excess was determined by HPLC analysis on a chiral column.

3.5.4. General Procedure for the Enantioselective Synthesis of Cyclopentane-fused β-Lactones



To a oven-dried Schlenk reaction vessel equipped with a magnetic stir bar was taken the 3,3-bis(methoxycarbonyl)-6-oxoheptanoic acid **41a** (130.0 mg, 0.50 mmol), HATU

(285.6 mg, 0.75 mmol, 1.5 equiv), Cs_2CO_3 (244.3 mg, 0.75 mmol, 1.5 equiv) and triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol, 10 mol %). The mixture was kept under argon atmosphere. To this mixture was added THF (6.0 mL) under a positive pressure of argon and the resulting mixture was stirred at 25 °C for 24 h. Evaporation of the solvent followed by silica gel flash column chromatography afforded the cyclopentane-fused β-lactone derivative **42a**. For compound **42a,** racemic sample was prepared using *N*-mesityl bicyclic triazolium salt as carbene precursor. All other racemic compounds were synthesized accordingly.



3.5.5. X-ray Data of 42l

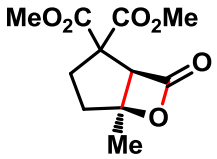
X-ray intensity data measurements of compound **42l** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Cu micro-focus sealed tube diffraction source (CuK_α= 1.54178 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.1 mA. A preliminary set of cell constants and an orientation matrix were calculated from two sets of 40 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[33] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT[34] and SADABS programs (Bruker, 2016). Using APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 [35] (Sheldrick, 2008) structure solution program, using direct methods. The model was refined with version of ShelXL-2014[36] (Sheldrick, 2014) using Least Squares minimisation. All the hydrogen atoms were placed in a geomerically idalized positions and constrained to ride on its parent atoms an *ORTEP* III [37] view of compound was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. The absolute configuration was established by anomalous dispersion effect (Flack parameter, 0.07(16)) in X-ray diffraction measurements carried out with Cu radiation. The single crystal X-ray diffraction data analysis clearly established that our synthesize compound has *R* and *S* configurations at C2 and C3 positions respectively. CCDC 1541484 (**42l**) contains the supplementary crystallographic

data for this paper. These data can be obtained free of charge from Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data of **42l** $C_{17}H_{26}O_6$, M = 326.38, colorless plate, 0.33 x 0.21 x 0.19 mm^3, monoclinic, chiral space group $P2_1$, a = 9.2074(17) Å, b = 11.5642(5) Å, c = 9.5785(18) Å, V = 118.017(11) $Å^3$, Z = 2, T = 100(2) K, $2\theta_{max}$=158.92°, D_{calc} (g cm^{-3}) = 1.204, $F(000)$ = 352, μ (mm^{-1}) = 0.748, 21833 reflections collected, 3654 unique reflections (R_{int}=0.0282), 3651 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.790, T_{max} = 0.871, 216 refined parameters, Good of Fit = S = 1.019, $R1$ = 0.0226, $wR2$ = 0.0652 (all data R = 0.0226, $wR2$ = 0.0653), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.201, $\Delta\rho_{min}$= -0.119 (e $Å^{-3}$).

3.5.6. Synthesis and Characterization of Functionalized Cyclopentane fused β-Lactones

Dimethyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42a)



42a

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxoheptanoic acid **41a** (130.0 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42a** as a colourless oil (114.0 mg, 94%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.58.

HPLC (Chiralcel OJ-H, 93:7 Hexane / IPA, 0.7 mL/min. 220 nm) Minor: 24.8 min, Major: 28.5 min. 98% ee, $[\alpha]_D^{25}$ = +53.74 (c 0.1, $CHCl_3$).

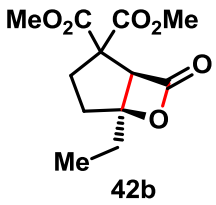
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 1H), 3.77 (d, J = 8.1 Hz, 6H), 2.66 (td, J_1= 13.9Hz, J_2 = 7.0 Hz, 1H), 2.34 (dd, J = 14.3, 7.2 Hz, 1H), 2.22 (dd, J = 14.8, 6.9 Hz, 1H), 1.75-1.68 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.31, 167.70, 167.01, 87.50, 63.61, 60.80, 53.51, 53.21, 33.97, 31.36, 21.58.

HRMS (ESI) calculated $[M+H]^+$ for $C_{11}H_{15}O_6$: 243.0863, found: 243.0858.

FTIR (cm^{-1}) 3022, 2978, 2957, 1820, 1734, 1436, 1386, 1295, 1270, 1216, 1155, 1138, 1059, 874, 816, 772.

Dimethyl (1*R*,5*S*)-5-ethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42b)



42b

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxooctanoic acid **41b** (137.1 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*S*)-5-ethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42b** as a colourless oil (90.0 mg, 70%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.63.

HPLC (Chiralcel OJ-H, 93:7 Hexane / IPA, 0.7 mL/min, 220 nm) Minor: 18.1 min, Major: 22.0 min. 98% ee, $[\alpha]_D^{25}$ = +68.10 (c 0.1, $CHCl_3$).

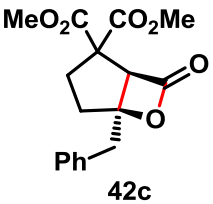
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.67 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.37 (dd, J_1 = 14.2 Hz, J_2 = 7.3 Hz, 1H), 2.20 (dd, J_1 = 14.7 Hz, J_2 = 6.9 Hz, 1H), 2.03 (q, J = 7.5 Hz, 2H), 1.68 (td, J_1 = 14.1 Hz, J_2 = 7.2 Hz, 1H), 1.07 (t, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.29, 167.80, 167.29, 90.84, 61.72, 60.53, 53.51, 53.25, 31.96, 31.04, 28.24, 8.53.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{12}H_{16}O_6Na$: 279.0839, found: 279.0840.

FTIR (cm^{-1}) 3023, 2975, 2956, 1821, 1734, 1461, 1436, 1291, 1264, 1217, 1194, 1174, 1154, 1139, 1089, 1061, 990, 815, 773, 668.

Dimethyl (1*R*,5*R*)-5-benzyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42c)



42c

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-7-phenylheptanoic acid **41c** (84.0 mg, 0.25 mmol) with triazolium salt ***ent*-F** (9.2 mg, 0.025 mmol), HATU (143.0 mg, 0.375mmol), and Cs_2CO_3 (122.0 mg, 0.375 mmol) in THF (3.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*R*)-5-benzyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42c** as a colourless oil (60.0 mg, 75%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.60.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 0.7 mL/min, 220 nm) Minor: 22.5 min, Major: 24.8 min. 93% ee, $[\alpha]_D^{25}$ = +47.94 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 5H), 3.99 (d, J = 1.0 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.31 (d, J = 14.6 Hz, 1H), 3.22 (d, J = 14.6 Hz, 1H), 2.65 (td, J_1 = 13.9 Hz, J_2 =

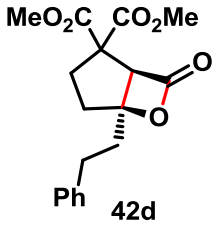
7.0 Hz, 1H), 2.37 (dd, J_1 = 14.3 Hz, J_2 = 7.2 Hz, 1H), 2.15 (dd, J_1 = 14.8 Hz, J_2 = 6.9 Hz, 1H), 1.82-1.75 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.28, 167.59, 166.63, 135.11, 130.16, 128.65, 127.37, 89.48, 61.74, 60.38, 53.54, 53.19, 41.14, 32.78, 31.12.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{19}O_6$: 319.1176, found: 319.1175.

FTIR (cm^{-1}) 3022, 2956, 1826, 1733, 1496, 1455, 1436, 1347, 1293, 1272, 1216, 1144, 1064, 994, 928, 772, 703, 668.

Dimethyl (1*R*,5*S*)-7-oxo-5-phenethyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42d)



42d

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-8-phenyloctanoic acid **41d** (175.0 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*S*)-7-oxo-5-phenethyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42d** as a colourless oil (110.0 mg, 66%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.68.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 0.7 mL/min, 220nm) Minor: 24.4 min, Minor: 33.1 min. 96% ee, $[\alpha]_D^{25}$ = +47.38 (c 0.1, $CHCl_3$).

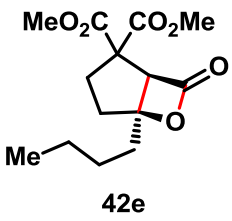
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.22-7.208 (m, 3H), 4.07 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.84-2.80 (m, 2H), 2.69 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.41-2.23 (m, 4H), 1.72 (td, J_1 = 14.1 Hz, J_2 = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.25, 167.68, 167.08, 140.71, 128.72, 128.39, 126.42, 89.75, 62.50, 60.44, 53.54, 53.26, 37.18, 32.44, 31.04, 30.53.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{20}O_6Na$: 355.1152, found: 355.1149.

FTIR (cm^{-1}) 3021, 2956, 1822, 1734, 1497, 1455, 1436, 1341, 1292, 1265, 1216, 1144, 1065, 1014, 992, 880, 814, 773, 701, 668.

Dimethyl (1*R*,5*S*)-5-butyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42e)



42e

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxodecanoic acid **41e** (75.0 mg, 0.25 mmol) with triazolium salt ***ent*-F** (9.2 mg, 0.025 mmol), HATU (143.0 mg, 0.375mmol), and Cs_2CO_3 (122.0 mg, 0.375 mmol) in THF (3.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column

chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*S*)-5-butyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42e** as a colourless oil (66.0 mg, 93%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.65.

HPLC (Chiralpak IA, 99:1 Hexane / IPA, 0.7 mL/min, 220 nm) Minor: 17.1min, Major: 19.4 min. 92% ee, $[\alpha]_D^{25}$ = +52.00 (c 0.1, $CHCl_3$).

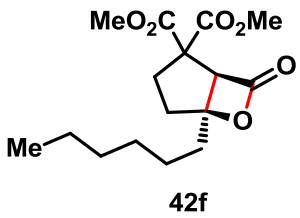
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (d, *J* = 1.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.66 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.36 (ddd, J_1 = 14.3 Hz, J_2 = 7.1 Hz, J_3 = 1.0 Hz, 1H), 2.21 (dd, J_1 = 14.7 Hz, J_2 = 6.9 Hz, 1H), 2.00-1.96 (m, 2H), 1.72-1.63 (m, 1H), 1.50-1.33 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.32, 167.79, 167.35, 90.40, 62.24, 60.49, 53.50, 53.23, 34.99, 32.32, 31.02, 26.37, 22.83, 13.99.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{14}H_{20}O_6Na$: 307.1152, found: 307.1149.

FTIR (cm^{-1}) 3022, 2958, 2937, 2872, 1821, 1734, 1461, 1436, 1292, 1267, 1216, 1171, 1153, 1107, 1064, 992, 878, 814, 773, 668.

Dimethyl (1*R*,5*S*)-5-hexyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42f)



42f

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxododecanoic acid **41f** (165.2 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*S*)-5-hexyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42f** as a colourless oil (103.0 mg, 66%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.71.

HPLC (Chiralcel OJ-H, 99:1 Hexane / IPA, 0.7 mL/min, 220 nm) Minor: 16.2 min, Major: 19.1 min. 98% ee, $[\alpha]_D^{25}$ = +52.92 (c 0.1, $CHCl_3$).

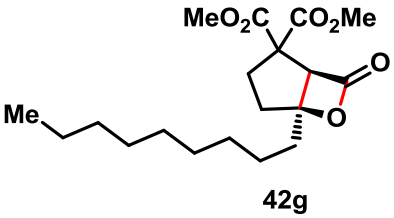
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (d, *J* = 1.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.66 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.36 (ddd, J_1 = 14.3 Hz, J_2 = 7.1 Hz, J_3 = 1.1 Hz, 1H), 2.24-2.18 (m, 1H), 1.99-1.95 (m, 2H), 1.72-7.63 (m, 1H), 1.51-1.43 (m, 2H), 1.38-1.25 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.32, 167.80, 167.36, 90.42, 62.25, 60.50, 53.51, 53.24, 35.31, 32.33, 31.70, 31.03, 29.37, 24.23, 22.63, 14.16.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{16}H_{24}O_6Na$: 335.1465, found: 335.1460.

FTIR (cm^{-1}) 3026, 2956, 2932, 2859, 1823, 1732, 1461, 1436, 1342, 1264, 1220, 1169, 1152, 1111, 1063, 992, 877, 815, 750, 668.

Dimethyl (1*R*,5*S*)-5-nonyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42g)



42g

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxopentadecanoic acid **41g** (186.0 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*S*)-5-nonyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42g** as a colourless oil (95.0 mg, 54%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.77.

HPLC (Chiralpak IA, 99:1 Hexane / IPA, 0.7 mL/min, 220 nm) Minor: 14.0 min, Major: 17.6 min. 96% ee, $[\alpha]_D^{25}$ = +49.52 (c 0.1, $CHCl_3$).

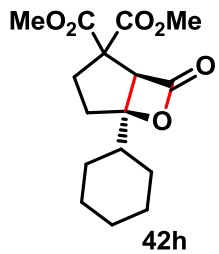
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.66 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.36 (dd, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 1H), 2.21 (dd, J_1 = 14.7 Hz, J_2 = 6.9 Hz, 1H), 1.99-1.95 (m, 2H), 1.68 (td, J_1 = 14.1 Hz, J_2 = 7.2 Hz, 1H), 1.48-1.44 (m, 2H), 1.34-1.26 (m, 12H), 0.87 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ170.31, 167.80, 167.38, 90.44, 62.21, 60.47, 53.51, 53.25, 35.30, 32.30, 31.98, 29.70, 29.57, 29.52, 29.39, 24.27, 22.80, 14.24.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{30}O_6Na$: 377.1935, found: 377.1930.

FTIR (cm^{-1}) 3024, 2955, 2928, 2856, 1822, 1734, 1461, 1436, 1342, 1292, 1264, 1217, 1152, 1108, 1065, 992, 814, 771, 668.

Dimethyl (1*R*,5*R*)-5-cyclohexyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42h)



42h

Following the general procedure, treatment of 6-cyclohexyl-3,3-bis(methoxycarbonyl)-6-oxohexanoic acid **41h** (164.2 mg, 0.50 mmol) with triazolium salt ***ent*-F** (36.8 mg, 0.1 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*R*)-5-cyclohexyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42h** as a colourless oil (41.0 mg, 26%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.71.

HPLC (Chiralcel OJ-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm) Minor: 8.9 min, Major: 11.5 min. 93% ee, $[\alpha]_D^{25}$ = +27.32 (c 0.1, $CHCl_3$).

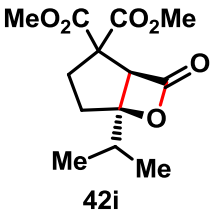
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.64 (td, J_1 = 13.8 Hz, J_2 = 6.9 Hz, 1H), 2.42-2.37 (m, 1H), 2.15 (dd, J_1 = 14.7 Hz, J_2 = 6.9 Hz, 1H), 1.86-1.80 (m, 5H), 1.73-1.66 (m, 2H), 1.33-1.19 (m, 4H), 1.16-1.07 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.17, 167.88, 167.62, 93.07, 60.47, 60.41, 53.49, 53.27, 42.29, 30.79, 30.22, 27.44, 27.34, 26.12, 26.06, 25.95.

HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{23}O_6$: 311.1489, found: 311.1487.

FTIR (cm^{-1}) 3403, 3021, 2932, 2856, 1820, 1734, 1678, 1450, 1435, 1337, 1264, 1216, 1149, 1067, 997, 814, 770, 668.

Dimethyl (1*R*,5*R*)-5-isopropyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42i)



42i

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-7-methyl-6-oxooctanoic acid **41i** (72.0 mg, 0.25 mmol) with triazolium salt ***ent*-F** (9.2 mg, 0.025 mmol), HATU (143.0 mg, 0.375mmol), and Cs_2CO_3 (122.0 mg, 0.375 mmol) in THF (3.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*R*)-5-isopropyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42i** as a colourless oil (20.0 mg, 30%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.64.

HPLC (Chiralcel OJ-H, 95:5 Hexane / IPA, 0.7 mL/min, 220 nm) Minor: 12.9 min, Major: 15.4 min. 94% ee, $[\alpha]_D^{25}$ = +49.36 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.66 (td, J_1 = 13.8 Hz, J_2 = 7.0 Hz, 1H), 2.41 (dd, J_1 = 14.2 Hz, J_1 = 7.2 Hz, 1H), 2.23-2.12 (m, 2H), 1.75-1.66 (m, 1H), 1.08 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H).

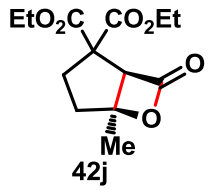
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.11, 167.84, 167.47, 93.49, 60.73, 60.60, 53.48, 53.26, 32.67, 30.92, 29.99, 17.36, 17.32.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{13}H_{18}O_6Na$: 293.0996, found: 293.0993.

FTIR (cm^{-1}) 3021. 2973, 1820, 1735, 1465, 1436, 1291, 1265, 1216, 1175, 1154, 1113, 1095, 1066, 1021, 991, 883, 814, 774, 668.

Diethyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42j)

Following the general procedure, treatment of 3,3-bis(ethoxycarbonyl)-6-oxoheptanoic acid **41j** (144.0 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the



42j

reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded diethyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42j** as a colourless oil (131.0 mg, 97%).

***R**f* (Pet. ether /EtOAc = 60/40): 0.69.

HPLC (Chiralcel OJ-H, 98:2 Hexane / IPA, 0.7 mL/min. 220 nm) Minor: 17.2 min, Major: 20.0 min. 97% ee, $[\alpha]_D^{25}$ = +75.96 (c 0.1, $CHCl_3$).

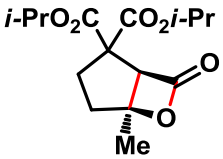
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27-4.16 (m, 4H), 3.99 (d, *J* = 1.4 Hz, 1H), 2.66 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.33 (ddd, J_1 = 14.3 Hz, J_2 = 7.1 Hz, J_3 = 1.2 Hz, 1H), 2.21 (dd, J_1 = 14.8 Hz, J_2 = 6.9 Hz, 1H), 1.73-1.67 (m, 4H), 1.29-1.24 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.96, 167.23, 167.04, 87.40, 63.62, 62.47, 62.28, 61.01, 34.02, 31.28, 21.60, 14.11, 14.08.

HRMS (ESI) calculated $[M+H]^+$ for $C_{13}H_{19}O_6$: 271.1176, found: 271.1169.

FTIR (cm^{-1}) 3026, 2983, 1829, 1724, 1465, 1477, 1387, 1368, 1302, 1265, 1221, 1182, 1155, 1098, 1025, 816, 749.

Diisopropyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42k)



42k

Following the general procedure, treatment of 3,3-bis(isopropoxycarbonyl)-6-oxoheptanoic acid **41k** (158.0 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded diisopropyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42k** as a colourless oil (120.0 mg, 80%).

***R**f* (Pet. ether /EtOAc = 60/40): 0.61.

HPLC (Chiralcel OD-H, 99:1 Hexane / IPA, 1.0 mL/min, 220nm) Major: 6.8 min, Minor: 8.9 min. 96% ee, $[\alpha]_D^{25}$ = +70.60 (c 0.1, $CHCl_3$).

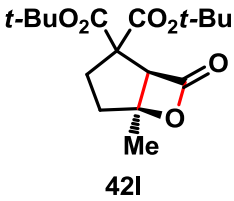
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16-5.01 (m, 2H), 3.97 (d, *J* = 1.2 Hz, 1H), 2.65 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.31-2.17 (m, 2H), 1.73-1.68 (m, 4H), 1.29-1.20 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.58, 167.12, 166.72, 87.39, 70.13, 69.93, 63.53, 61.09, 33.98, 31.15, 21.72, 21.61, 21.51.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{23}O_6$: 299.1489, found: 299.1482.

FTIR (cm^{-1}) 3402, 3020, 2982, 2400, 1822, 1723, 1603, 1524, 1425, 1387, 1295, 1266, 1215, 1107, 1047, 929, 776, 669.

Di-*tert*-butyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42l)



42l

Following the general procedure, treatment of 3,3-bis(*tert*-butoxycarbonyl)-6-oxoheptanoic acid **41l** (172.2 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded di-*tert*-butyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42l** as a white solid (145.0 mg, 89%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.79.

HPLC (Chiralcel OD-H, 98:2 Hexane / IPA, 0.7 mL/min, 220 nm) Major: 6.5 min, Minor: 7.3 min. 94% ee, $[\alpha]_D^{25}$ = +55.90 (c 0.1, $CHCl_3$).

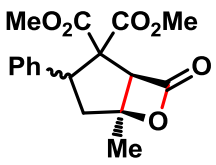
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (d, J = 1.3 Hz, 1H), 2.58 (td, J_1 = 13.9 Hz, J_2 = 7.0 Hz, 1H), 2.25-2.16 (m, 2H), 1.72 (s, 3H), 1.70-1.63 (m, 1H), 1.48 (s, 9H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.43, 167.43, 166.34, 87.31, 82.81, 82.66, 63.64, 62.34, 33.99, 31.06, 27.96, 27.89, 21.66.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{26}O_6Na$: 349.1622, found: 349.1614.

FTIR (cm^{-1}) 3402, 3020, 2979, 2934, 2400, 1820, 1722, 1602, 1523, 1424, 1391, 1370, 1307, 1215, 1047, 928, 775.

Dimethyl (1*R*,5*S*)-5-methyl-7-oxo-3-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (42m)



42m

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-4-phenylheptanoic acid **41m** (168.2 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,5*S*)-5-methyl-7-oxo-3-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42m** as a white solid (112.0 mg, 70%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.70.

HPLC (Chiralcel OD-H, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm) Major: 7.5 min, Minor: 9.0 min. 30% ee, $[\alpha]_D^{25}$ = +5.04 (c 0.1, $CHCl_3$).

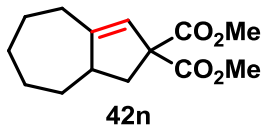
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 4.30 (dd, J_1 = 12.4 Hz, J_2 = 7.4 Hz, 1H), 4.01 (s, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 2.53-2.45 (m, 2H), 1.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.45, 167.77, 167.02, 136.02, 128.72, 128.35, 128.08, 86.18, 65.26, 65.17, 53.01, 52.60, 48.16, 40.01, 21.73.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{19}O_6$: 319.1176, found: 319.1169.

FTIR (cm^{-1}) 3402, 3020, 2977, 2400, 1818, 1755, 1727, 1602, 1523, 1477, 1275, 1215, 1130, 1044, 928, 775, 699.

Dimethyl 4,5,6,7,8,8a-hexahydroazulene-2,2(1*H*)-dicarboxylate (42n)



42n

Following the general procedure, treatment of 4-methoxy-3-(methoxycarbonyl)-4-oxo-3-((2-oxocycloheptyl)methyl)butanoic acid **41n** (157.0 mg, 0.50 mmol) with triazolium salt ***ent*-F** (18.4 mg, 0.05 mmol), HATU (285.6 mg, 0.75mmol), and Cs_2CO_3 (244.3 mg, 0.75 mmol) in THF (5.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl 4,5,6,7,8,8a-hexahydroazulene-2,2(1*H*)-dicarboxylate **42n** as a colourless oil (103.0 mg, 82%).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.79.

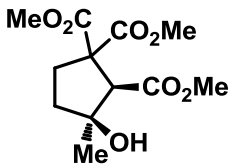
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (s, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 2.88-2.87 (m, 1H), 2.71 (dd, J_1 = 13.0 Hz, J_2 = 7.4 Hz, 1H), 2.35-2.32 (m, 2H), 1.85 (dd, J_1 = 13.0 Hz, J_2 = 8.4 Hz, 1H), 1.71-1.58 (m, 3H), 1.56-1.49 (m, 2H), 1.45-1.34 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.54, 171.92, 155.47, 121.71, 64.79, 52.62, 47.49, 40.55, 33.72, 31.22, 30.42, 27.77, 27.72.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{14}H_{20}O_4Na$: 275.1254, found: 275.1252.

FTIR (cm^{-1}) 3465, 3024, 2924, 2852, 1726, 1641, 1435, 1360, 1271, 1216, 1136, 1012, 854, 812, 752, 667.

Trimethyl (2*R*,3*S*)-3-hydroxy-3-methylcyclopentane-1,1,2-tricarboxylate (47)



47

An oven dried round bottomed flask was charged with dimethyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42a** (48.4 mg, 0.2 mmol,) (98% ee) and 1.0 ml of Et_3N in methanol (1.0 mL). The reaction mixture was stirred at 25 °C for 24 h under argon atmosphere. Evaporation of the solvent followed by silica gel flash column chromatography afforded trimethyl (2*R*,3*S*)-3-hydroxy-3-methylcyclopentane-1,1,2-tricarboxylate **47** as a colorless oil (47.0 mg, 86% yield).

***R*$_f$** (Pet. ether /EtOAc =70/30): 0.31.

HPLC (Chiralpak AD, 93:7 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 13.1 min, Minor: 13.9 min. 98% ee, $[\alpha]_D^{25}$ = +39.26 (c 0.1, $CHCl_3$).

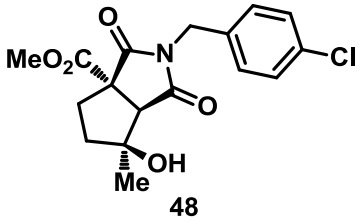
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74-3.71 (m, 9H), 3.26 (s, 1H), 2.81-2.74 (m, 1H), 2.12-2.04 (m, 1H), 1.99-1.92 (m, 1H), 1.80-1.73 (m, 1H), 1.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.48, 172.31, 171.31, 79.56, 62.89, 59.59, 53.23, 53.08, 52.12, 39.15, 32.62, 26.76.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{12}H_{18}O_7Na$: 297.0945, found: 297.0961.

FTIR (cm^{-1}) 3467, 3021, 2967, 2403, 1733, 1598, 1440, 1366, 1273, 1215, 1046, 759, 668.

Methyl (3a*S*,6*S*,6a*R*)-2-(4-chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxohexahydrocyclopenta[c]pyrrole-3a(1*H*)-carboxylate (48)



48

An oven dried round bottomed flask was charged with dimethyl (1*R*,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42a** (48.4 mg, 0.2 mmol,) (98% ee) and (4-chlorophenyl)methanamine (0.097 ml, 0.8 mmol, 4.0 equiv) in THF (2.0 mL). The reaction mixture was stirred at 25 °C for 24 h under argon atmosphere. Brine was added followed by EtOAc. The aqueous layer was extracted with EtOAc and combined organic layer were dried with Na_2SO_4, filtered and concentrated. The mixture was purified by flash chromatography (40% EtOAc- Pet ether) afforded methyl (3a*S*,6*S*,6a*R*)-2-(4-chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxohexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48** sticky liquid (67.0 mg, 96% yield, single diastereomer).

R_f (Pet. ether /EtOAc = 70/30): 0.23.

HPLC (Chiralpak AD, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Minor: 14.1 min, Major: 15.2 min. 98% ee, $[\alpha]_D^{25}$ = -48.40 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 4H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.56 (d, *J* = 14.6 Hz, 1H), 3.68 (s, 3H), 3.12 (s, 1H), 2.58-2.52 (m, 1H), 2.30-2.22 (m, 1H), 2.04 (bs, 1H), 1.88-1.81 (m, 2H), 1.50 (s, 3H).

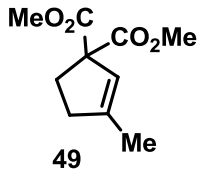
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.41, 174.77, 170.26, 133.91, 133.76, 129.63, 128.80, 80.60, 61.88, 61.23, 53.49, 42.39, 42.16, 30.08, 27.45.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{19}O_5NCl$: 352.0946, found: 352.0955.

FTIR (cm^{-1}) 3387, 3022, 2972, 2402, 1741, 1707, 1597, 1432, 1395, 1345, 1216, 1044. 930, 767, 699.

Dimethyl 3-methylcyclopent-2-ene-1,1-dicarboxylate (49)

An oven dried round bottomed flask was charged with dimethyl (1R,5*S*)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **42a** (48.4 mg, 0.2 mmol,) and 300 mg of silica in



49

toluene (3.0 mL). The reaction mixture was heated at 60 °C for 6 h under argon atmosphere. Upon consumption of the starting material **42a** (TLC), the crude reaction mixture was passed through celite and concentrated under reduced pressure to get a sufficiently pure dimethyl 3-methylcyclopent-2-ene-1,1-dicarboxylate **49** as a colorless oil (37.5 mg, 94% yield).

R_f (Pet. ether /EtOAc = 70/30): 0.70.

^{1}H NMR (400 MHz, $CDCl_3$) 5.41 (s, 1H), 3.70 (s, 6H), 2.47-2.43 (m, 2H), 2.38-2.35 (m, 2H), 1.76 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.32, 146.64, 122.60, 66.63, 52.67, 36.14, 32.31, 16.68.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{10}H_{14}O_4Na$: 221.0784, found: 221.0782.

FTIR (cm^{-1}) 3363, 3023, 2952, 2852, 2404, 1731, 1596, 1441, 1265, 1219, 1134, 1124, 1175, 922, 762, 996.

3.6. References

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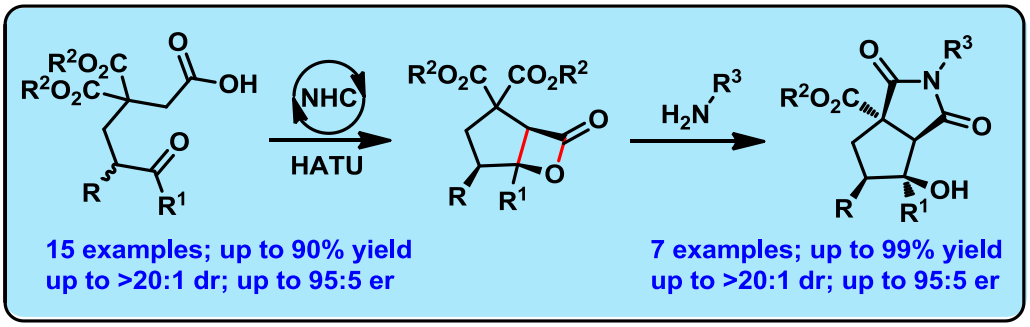
Chapter 4

N-Heterocyclic Carbene-Catalyzed Aldol-Lactonization of Ketoacids via Dynamic Kinetic Resolution

The dynamic kinetic resolution of acyclic ketoacids via an intramolecular aldol lactonization strategy is investigated in this chapter. The N-Heterocyclic carbene (NHC) generated from the chiral aminoindanol-derived triazolium salt in presence of LiCl as additive was the key for the success of this transformation. The reaction allows the diastereoselective and enantioselective synthesis of cyclopentane-fused β-lactones containing three contiguous stereocentres. Additionally, the reaction products are shown to undergo substrate-controlled β-lactone opening in presence of amines to afford succinimide derivatives with four contiguous stereocentres.

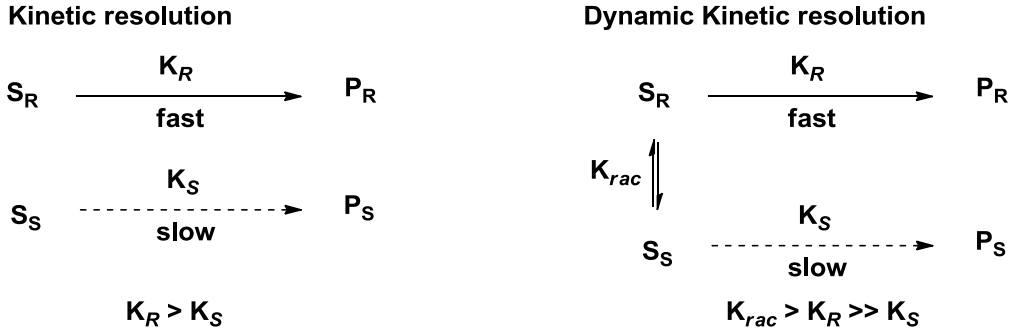


ACS. Catal. **2017**, *7*, 3995-3999.

4.1. Introduction

Resolution of a racemic compound to an enantiopure form is one of the major challenges in synthetic organic chemistry. In this context, kinetic resolution (KR) or dynamic kinetic resolution (DKR) are the widely used protocols for the preparation of the enantioenriched compounds.[1] The kinetic resolution is a process in which two enantiomers of a racemate are converted to the corresponding product enantiomers at different rates. In theory, KR represents a competitive reaction system in which two enantiomeric substrates compete for a single chiral catalyst. To get an efficient resolution, the reaction rate of one enantiomer has to be much higher than that of the other ($K_R >> K_S$) and a maximum 50% theoretical yield of the product is possible (Scheme 4.1).[2] On the other hand, in DKR process, there will be a constant equilibrium between the substrate enantiomers and allow both substrate enantiomer to form a single stereoisomeric product with 100% theoretical yield.[3]

Scheme 4.1: Representation of a KR and DKR Process

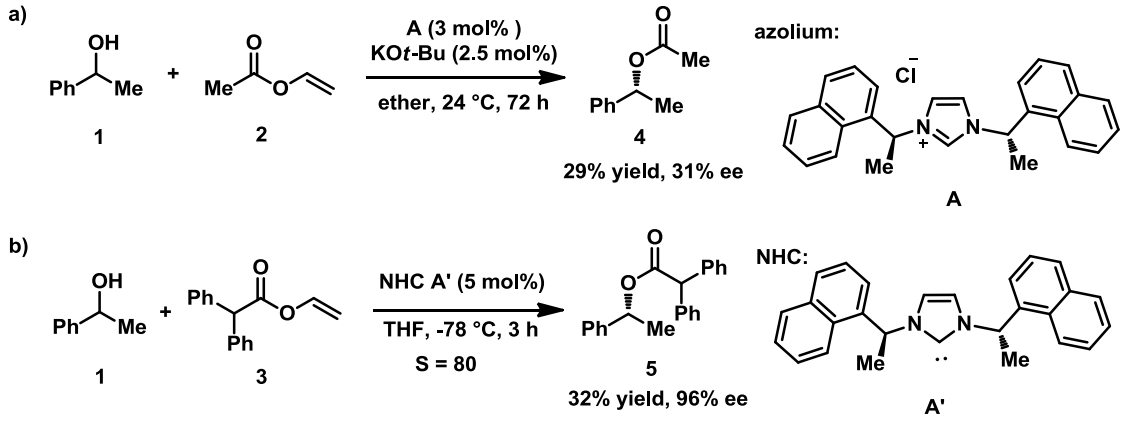


In recent days, N-heterocyclic carbenes (NHC)-catalyzed asymmetric synthesis has emerged as a powerful synthetic strategy for the construction of carbocycles and heterocycles. Apart from the conventional NHC-catalyzed asymmetric transformations, kinetic resolution and dynamic kinetic resolution using NHC-catalysis is also a growing field in this area. The details of NHC-catalyzed KR or DKR processes are described in the next two sections.

4.1.1. NHC-Catalyzed Kinetic Resolutions

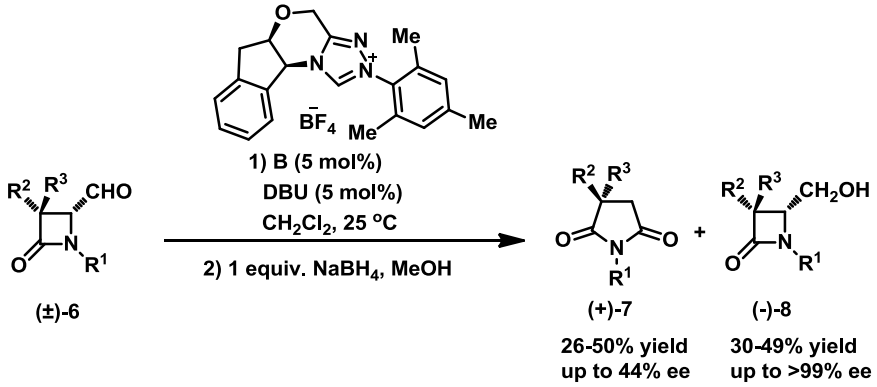
In 2004, Suzuki and co-workers demonstrated for the first time the NHC-catalyzed kinetic resolution of secondary alcohols (Scheme 4.2a).[4] In the presence of C_2-symmetric NHC-catalyst **A** and vinyl acetate **2** as an acylating agent, the resolution of arylethanols **1** afforded moderate enantioselectivity. Subsequently, Maruoka and co-workers demonstrated the better enantioselectivity for the secondary alcohol resolution, employing free carbene **A'** as a catalyst and a bulkier acylating agent **3** (Scheme 4.2b).[5]

Scheme 4.2: NHC-catalyzed kinetic resolution of alcohols via acyl transfer



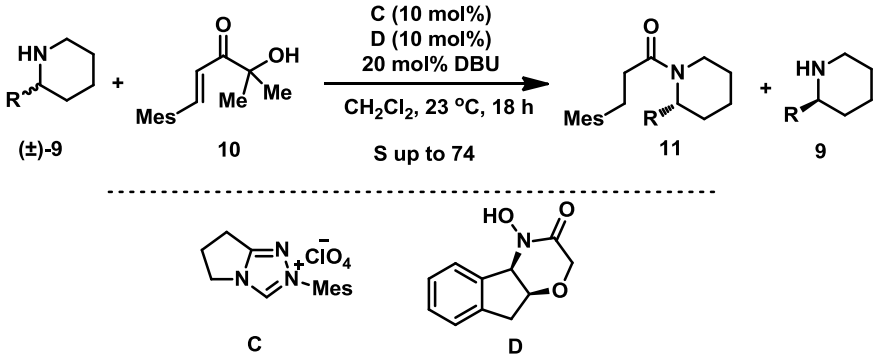
An efficient resolution of *cis*-4-formyl-β-lactams **6** by NHC-catalyzed ring expansion was reported by You and co-workers (Scheme 4.3).[6] Under the mild reaction condition, one enantiomer of **6** converted to succinimide **7**, while the other enantiomer remains unreacted and isolated as the reduced form **8** in moderate to excellent enantioselectivity. Also this reaction features the ready availability of both the substrate and the catalyst.

Scheme 4.3: NHC-Catalyzed Kinetic Resolution of β-Lactams



In 2011, Bode and co-workers developed the efficient kinetic resolution of racemic cyclic amines **9** by an enantioselective amidation reaction using the combination of an achiral

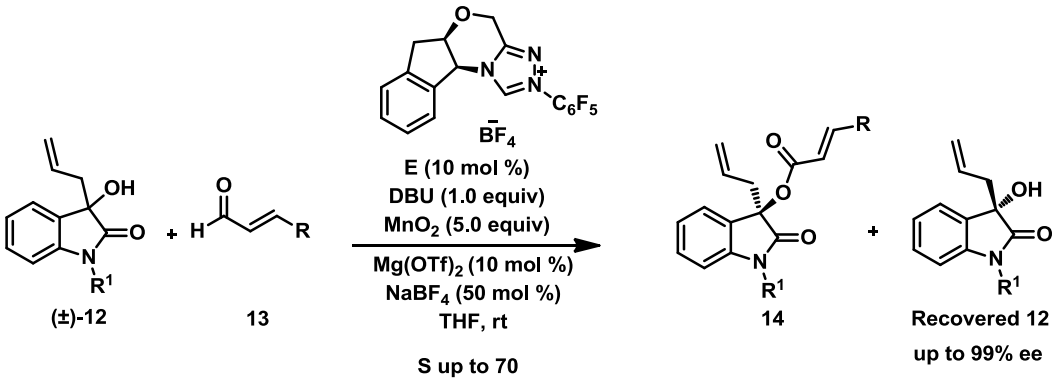
Scheme 4.4: NHC-Catalyzed Resolution of Cyclic Amines



NHC catalyst **C** and a new chiral hydroxamic acid co-catalyst **D** (Scheme 4.4).[7] This catalytic resolution of amine involved two independent catalytic cycles, which worked concertedly and both amine and amide product were obtained in high enantioselectivity under mild reaction condition. Detailed DFT calculations were also carried out to elucidate the reaction pathway and the origin of enantioselectivity for this catalytic system.

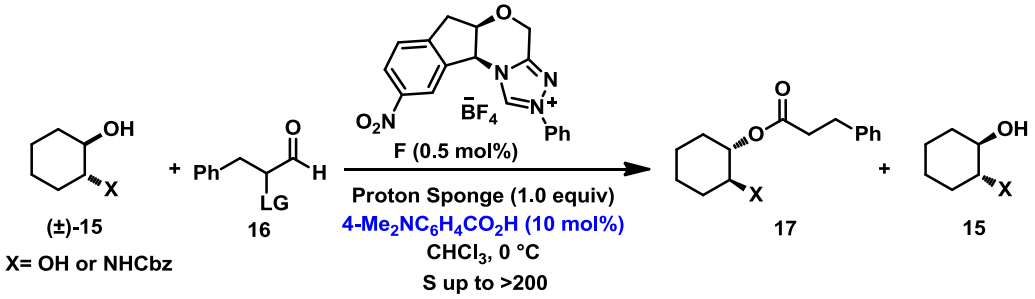
The NHC-catalyzed kinetic resolution of 3-hydroxy-3-substituted oxindole **12** under oxidative condition was discovered by Zhao and co-workers (Scheme 4.5).[8] The generation of chiral α,β-unsaturated acyl azolium ion from enal **13** and their interception with one of the enantiomer of the tertiary alcohol **12** to give ester **14** and enantiomerically pure tertiary alcohol **12**. A wide range of 3-substitution as well as electron-donating and electron-withdrawing groups on the oxindole backbone were tolerated well to afford ester **14** and recovered tertiary alcohol **12** in excellent enantioselectivity. It is noteworthy that the addition of Lewis acid co-catalyst proved to be beneficial for the reaction rate and selectivity. Later the same research group showed the NHC-catalyzed kinetic resolution of 1,1'-biaryl-2,2'-diols and amino alcohols.[9]

Scheme 4.5: Kinetic Resolution of Tertiary Alcohols



Also, the Takasu and Yamada group reported that the kinetic resolution of cyclic diols and amino alcohols **15** were achieved under NHC-catalysis with excellent enantioselectivity (scheme 4.6).[10] The rate and enantioselectivity of the NHC-catalyzed asymmetric acylation of

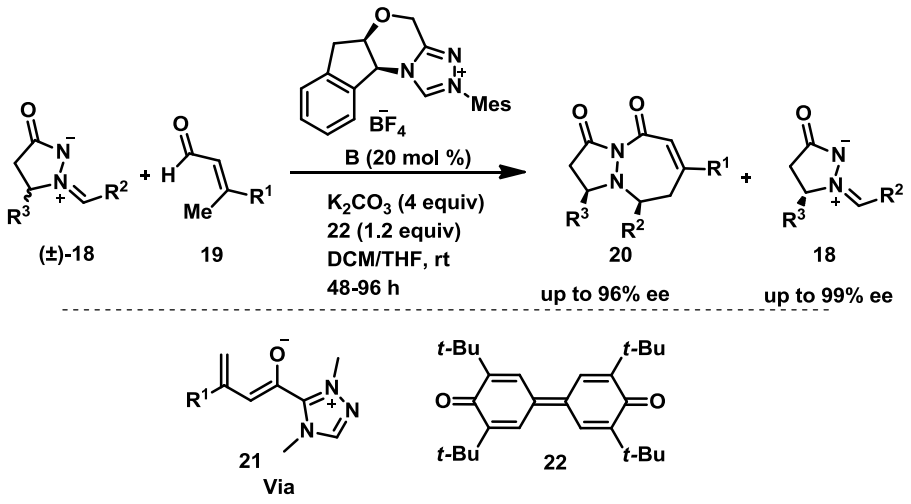
Scheme 4.6: KR of Cyclic Diols/Amino Alcohols



alcohols containing an adjacent H-bond donor functionality has been enhanced in the presence of a carboxylate co-catalyst. The degree of the enhancement is correlated with the basicity of the carboxylate. Based on the experimental as well as some computed data, a transition state was proposed, in which the carboxylate serves as a key hydrogen bond acceptor to interact with the substrate and accelerate the esterification reaction.

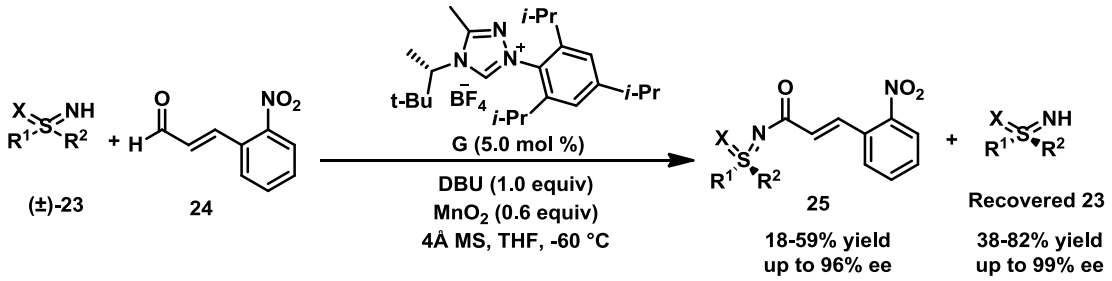
In 2014, Chi and co-workers illustrated a NHC-catalyzed highly enantioselective (up to 99%) and diastereoselective (up to >20:1) [3+4] cycloaddition of azomethine imine **18** with enals **19** (scheme 4.7).[11] Activation of remote sp^3 C-H bond under oxidative NHC-catalyzed conditions to generated vinyl enolate intermediate **21** and their cycloaddition reaction with racemic azomethine imine **18** to give dinitrogen-fused seven-membered heterocycles **20**. In the catalytic cycle, the NHC catalyst enabled kinetic resolution of azomethine imines although the chiral centre is remote to the NHC catalyst.

Scheme 4.7: Kinetic Resolution of Azomethine Imines



Very recently, Bolm and co-workers reported NHC-catalyzed kinetic resolution of sulfoximines **23** with enals **24** (Scheme 4.8).[12a] Notably, the stereoselective amidation proceeded without any additional acyl transfer agent.[12b,c] With the chiral triazolium salt **G**,

Scheme 4.8: Kinetic Resolution of Sulfoximines.

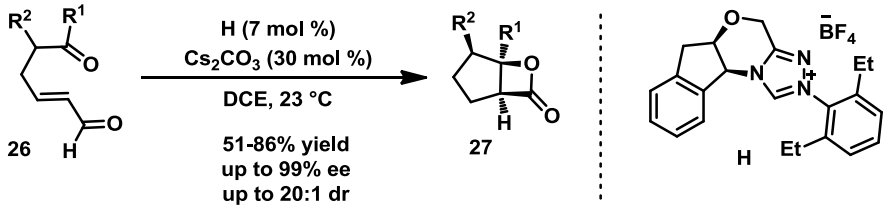


DBU as base and MnO_2 as a mild oxidant, both enantiomers of the sulfoximines **23** were obtained with excellent ee values (up to 99% ee).

4.1.2. NHC-Catalyzed Dynamic Kinetic Resolution

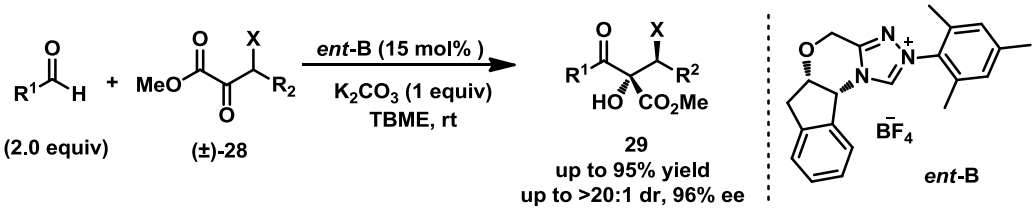
In 2012, Scheidt and co-workers demonstrated the first NHC-catalyzed intramolecular dynamic kinetic resolution of various α-substituted β-ketoesters **26** for the synthesis of cyclopentane-fused β-lactones **27** (Scheme 4.9).[13] Using NHC generated from the chiral triazolium salt **H**, the electron-deficient aromatic ketones led to desired β-lactones in good yield (64–88%) with good diastereoselectivity and excellent enantioselectivity (97–99%). In this organocatalytic DKR process, electron-rich aryl ketones furnished the cyclopentene products after a spontaneous decarboxylation of initially formed β-lactones. The authors envisioned that by making use of the basic environment needed to generate the active carbene species, they could achieve the epimerization of the substrate due to the presence of an acidic proton. By carrying out DFT calculations, they have shown two possible unconventional mechanisms of either a concerted formal [2+2] aldol lactonization process or a stepwise spiro-lactonization mechanism.[14]

Scheme 4.9: NHC-Catalyzed DKR of α- Substituted β-Ketoesters



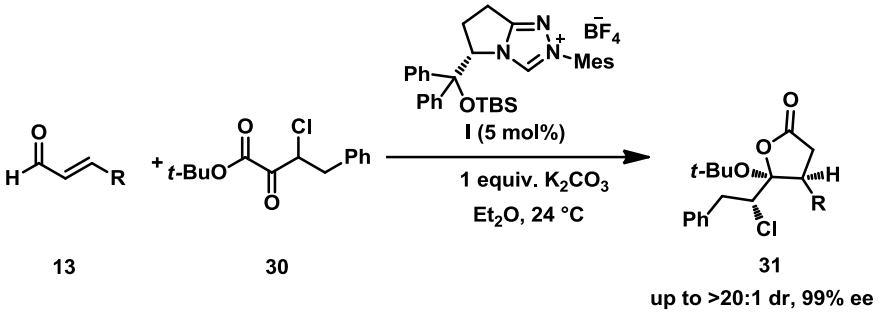
In 2014, the Johnson group reported the dynamic kinetic resolution of α-ketoesters **28** via an intermolecular cross-benzoin reaction (Scheme 4.10).[15] Such a process is highly challenging due to several competing reaction pathways. Remarkably, the desired cross benzoin product **29** could be formed in high yields, high enantioselectivity as well as diastereoselectivity. Due to the faster rate of racemization of the β-stereogenic center of the α-ketoester substrate than that of cross-benzoin reaction, the desired cross-benzoin product was obtained in high diastereo- and enantioselectivity.

Scheme 4.10: DKR by Benzoin Condensation



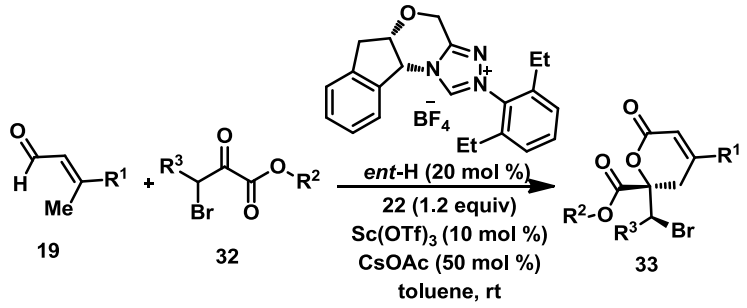
Subsequently, the same research group employed NHC-homoenolate annulation for the dynamic kinetic resolution of β-halo α-keto esters **30** (Scheme 4.11).[16] Under the optimized reaction condition, a rapid racemization of the chlorine containing β-stereogenic centre occurred and the homoenolate annulation to the ketone substrate affords γ-butyrolactone products **31** with three contiguous stereogenic centers.

Scheme 4.11: Annulation via Homoenolate Addition



In 2014, Wang and co-workers reported the first intermolecular dynamic kinetic resolution of α-keto ester **32** through NHC- Lewis acid cooperative catalysis (Scheme 4.12).[17] The reaction proceeds via the generation of NHC bound dienolate intermediate followed by [4+2] cycloaddition reaction with α-keto ester **32** containing an additional stereogenic centre to form enantiomerically pure δ-lactones **33** in moderate to good yield (35-88%) and excellent enantio- and diastereoselectivity. The authors proposed that the role of $Sc(OTf)_3$ was to bring the ketone electrophile in closer proximity with the nucleophile. This reaction could also be carried out on a gram scale without erosion in the stereoselectivity.

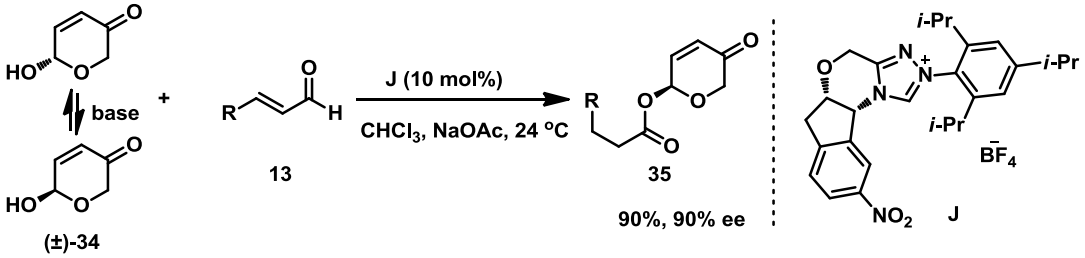
Scheme 4.12: Intermolecular Dynamic Kinetic Resolution of α-Keto Ester



Concurrently, the same research group developed NHC-catalyzed dynamic kinetic resolution of 6-hydroxypyranone (hemiacetal) **34** with α,β-unsaturated enals **13** through an asymmetric redox esterification (Scheme 4.13).[18] Under basic conditions, the hemiacetal substrates underwent facile racemization. The chiral NHC-catalyst promoted an efficient and enantioselective acylation of one isomer preferentially to deliver ester **35** in good to excellent

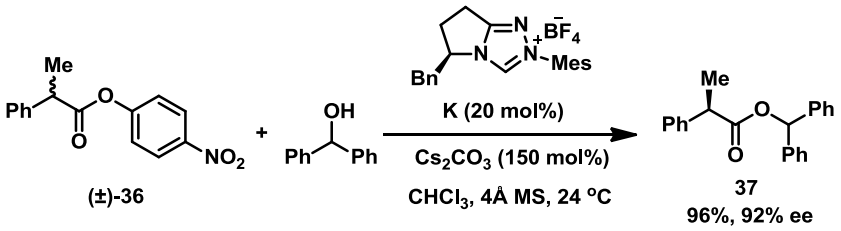
yields and with high levels of enantioselectivity. The derivatization of **35** to functionalized carbohydrate derivatives and natural products was also demonstrated in this report.

Scheme 4.13: DKR of Hemiacetals



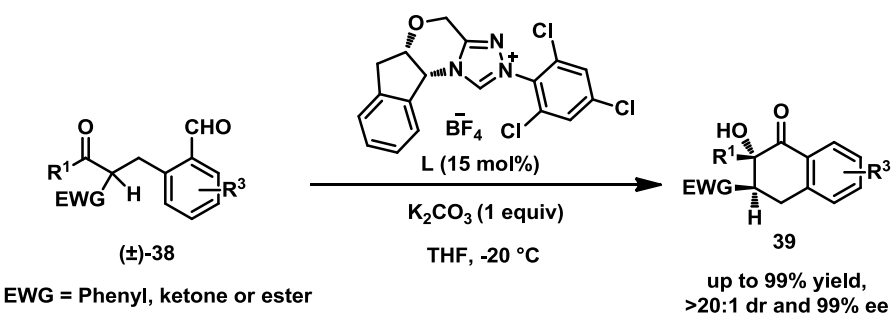
Recently, Chi and co-workers disclosed an elegant application of NHC-catalyzed transesterification of aryl esters with alcohols to a dynamic kinetic resolution of racemic α,α-disubstituted carboxylic esters **36** (Scheme 4.14).[19] The readily available racemic aryl esters were converted to highly enantioenriched products **37** in high yield and high ee. This reaction was applied to the preparation of certain important drug molecules such as Ibuprofen with high efficiency.

Scheme 4.14: DKR of Carboxylic Esters



Very recently, Fang and co-workers reported an example of dynamic kinetic resolution of β-ketoesters and 1,3-diketones **38** bearing a tethered aldehyde group in a highly enantio-, diastereo-, and regioselective fashion via intramolecular cross-benzoin reaction (Scheme 4.15).[20] The dynamic kinetic resolution of these substrates was successful due to the relatively acidic α- proton of the 1,3-dicarbonyl compounds. The products **39** bear highly

Scheme 4.15: DKR by Benzoin condensation



substituted tetralone backbone. Moreover, the authors found out that varying the electronic properties of the substituent on the azolium species helped to speed up the formation of the benzoin product over the corresponding competitive aldol reaction.

4.2. Statement of the Problem

Pioneered by Romo group,[21] the nucleophile-catalyzed aldol-lactonization is one of the convenient method for the synthesis of β-lactones and the asymmetric version of these reactions are well studied. Recently, our group has developed NHC-catalyzed aldol lactonization of acyclic ketoacids for the enantioselective synthesis of cyclopentane-fused β-lactones.[22] Although, NHC-catalysis is well known for asymmetric synthesis, NHC-catalyzed dynamic kinetic resolution has received limited attention. In this context, we envisaged the aldol lactonization of linear ketoacids containing an additional chiral centre and if successful, this could result the formation of fused β-lactones along with the resolution of the new chiral centre. The detailed study for the DKR of ketoacids is described in the following sections.

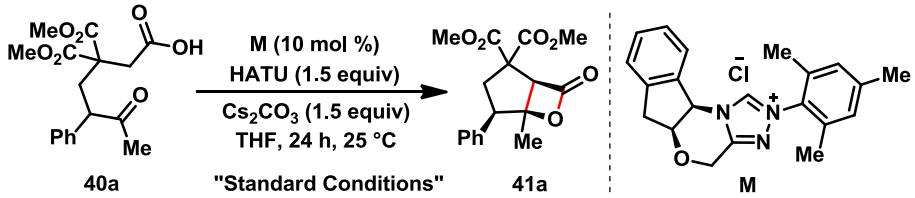
4.3. Results and Discussion

4.3.1. Optimization Studies

The present study was commenced by the treatment of the ketoacid **40a** with the triazolium salt **M**[23] in the presence of the peptide coupling reagent 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HATU) and Cs_2CO_3 as the base. To our delight, under these conditions, the cyclopentane-fused β-lactone **41a** was formed in 83% yield, 2:1 diastereomeric ratio and 93:7 enantiomeric ratio (Table 4.1, entry 1). The product **41a** was formed by the NHC-catalyzed aldol lactonization of **40a**, and the poor dr indicates that the both enantiomers of **40a** react under these conditions to afford the corresponding diastereomers. When the reaction was performed with pivaloyl chloride instead of HATU, the dr was slightly improved to 3:1, but the er dropped to 75:25 (entry 2). The use of carbonyl diimidazole instead of HATU returned only traces of **41a** (entry 3). The screening of different bases indicated that Cs_2CO_3 is optimal base for this transformation, and the reactions using other bases furnished inferior results (entries 4-7). Notably, the reaction using DABCO afforded **41a** in 89% yield and >20:1 dr, but the product was racemic (entry 6). The screening of different solvents revealed better reactivity affording **41a** in >82% yield, but the dr and er was not improving with variation in solvents (entries 8-11). At this stage, we considered the use of various additives. The addition of $Sc(OTf)_3$, AcOH, TFA and $LiOAc.2H_2O$ improved the dr, but provided less reactivity (entries 12-15). Moreover, the use

of other additives did not give satisfactory result in terms of diastereoselectivity (entries 16-22). Employing LiCl as the additive afforded **41a** in 68% yield, 5:1 dr and 94:6 er (entry 23).[24] Finally, performing the reaction in CH_2Cl_2 using 50 mol % of LiCl and 15 mol % of **M** furnished **41a** in 70% yield, 10:1 dr and 95:5 er (entry 14). This was the best reaction conditions identified for this transformation.

Table 4.1: Optimization of the Reaction Conditions[a]

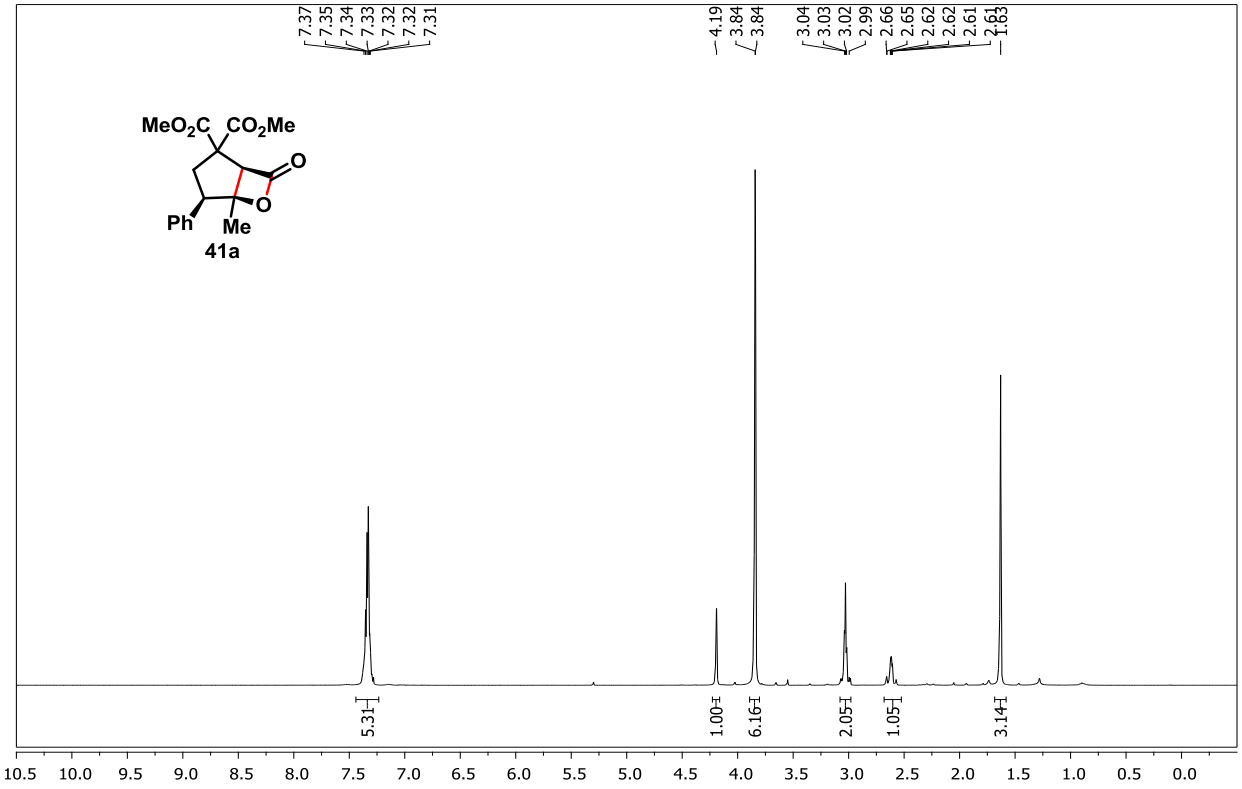


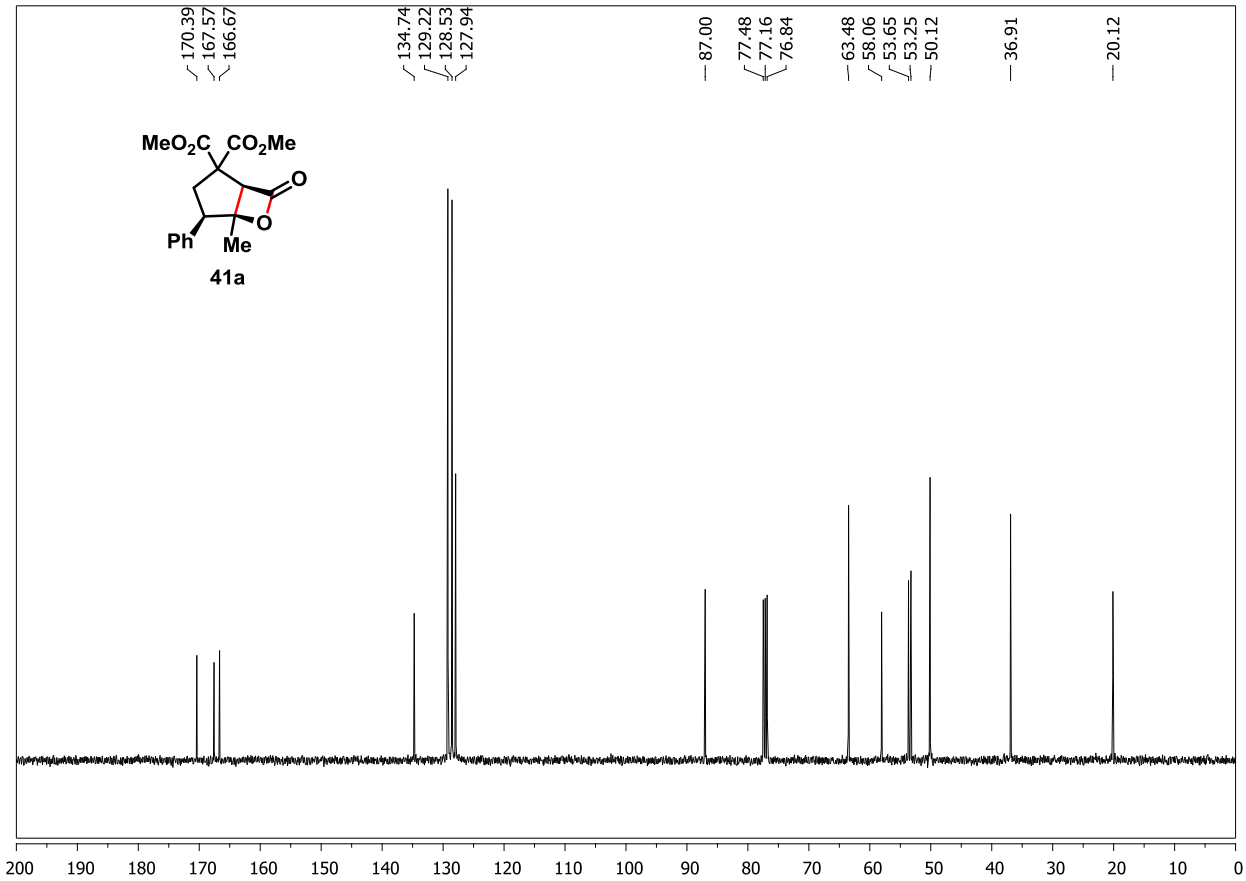
entry	variation of the standard conditions[a]	Yield of **41a** (%)[b]	dr of **41a**[c]	er of **41a** (%)[d]
1	none	83	2:1	93:7
2	PivCl instead of HATU	83	3:1	75:25
3	CDI instead of HATU	<5	n.d.	n.d.
4	Na_2CO_3 instead of Cs_2CO_3	49	5:1	85:15
5	KO*t*-Bu instead of Cs_2CO_3	<5	n.d.	n.d.
6	DABCO instead of Cs_2CO_3	89	>20:1	50:50
7	K_2CO_3 instead of Cs_2CO_3	<5	nd	n.d.
8	toluene instead of THF	96	1:1	90:10
9	DME instead of THF	92	2:1	88:12
10	1,4-Dioxane instead of THF	83	2:1	88:12
11	CH_2Cl_2 instead of THF	82	3:1	89:11
12	50 mol % $Sc(OTf)_3$ additive	20	10:1	93:7
13	50 mol % AcOH additive	40	16:1	78:22
14	50 mol% TFA	51	10:1	90:10
15	50 mol% $LiOAc.2H_2O$	35	6:1	95:5
16	50 mol% $Ti(OiPr)_4$	51	2.1	96:4
17	50 mol% $Mg(Ot\text{-}Bu)_2$	89	2:1	98:2
18	50 mol% NaCl	89	1:1	98:2
19	50 mol% Li_2CO_3	94	1:1	94:6
20	50 mol% LiO*t*-Bu	90	2:1	79:21
21	50 mol% $LiClO_4$	72	3:1	94:6
22	50 mol % LiBr additive	92	1:1	92:8
23	50 mol % LiCl additive	68	5:1	94:6
24	**50 mol % LiCl, 15 mol % of M, CH_2Cl_2 instead of THF**	**70**	**10:1**	**95:5**

[a] Standard conditions: **40a** (0.25 mmol), **M** (10 mol %), HATU (1.5 equiv), Cs_2CO_3 (1.5 equiv), THF (4.0 mL), 25 °C and 24 h. [b] The yields were determined by ^1H NMR analysis of crude product using CH_2Br_2 as the internal standard. [c] Ratio determined by ^1H NMR spectroscopy prior to purification. [d] Determined by HPLC analysis on a chiral column.

4.3.2. Spectral Data of 41a

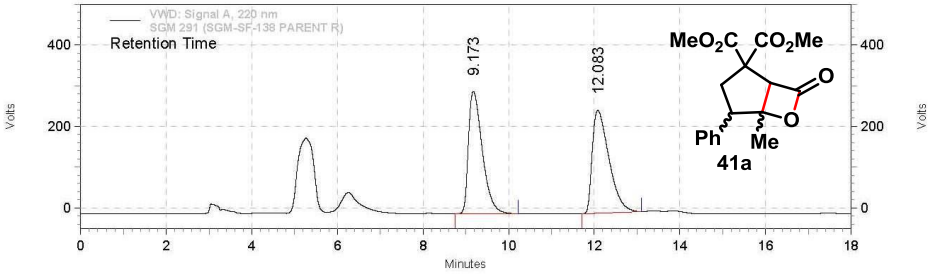
^{1}H NMR Spectrum of 41a ($CDCl_3$)





HPLC Chromatogram of Racemic- 41a

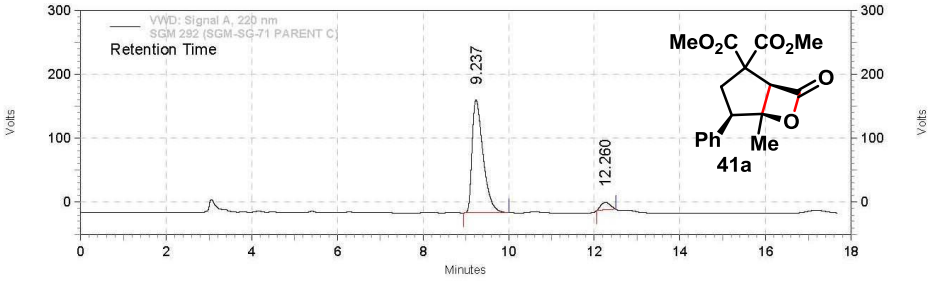
Data File: D:\BIJU\SGM\FINAL\Raw file\SGM 291 (SGM-SF-138 PARENT R).dat
Method: C:\Documents and Settings\admin\Desktop\Dr. D. S. Reddy\Vidya\99-1-30 min.met
Acquired: 3/9/2016 11:44:08 AM Printed: 3/9/2016 12:30:42 PM



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %
9.173	113627524	49.63
12.083	115337640	50.37
Totals	228965164	100.00

HPLC Chromatogram of Enantiomerically Pure-41a



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %
9.237	52967349	94.75
12.260	2936898	5.25
Totals	55904247	100.00

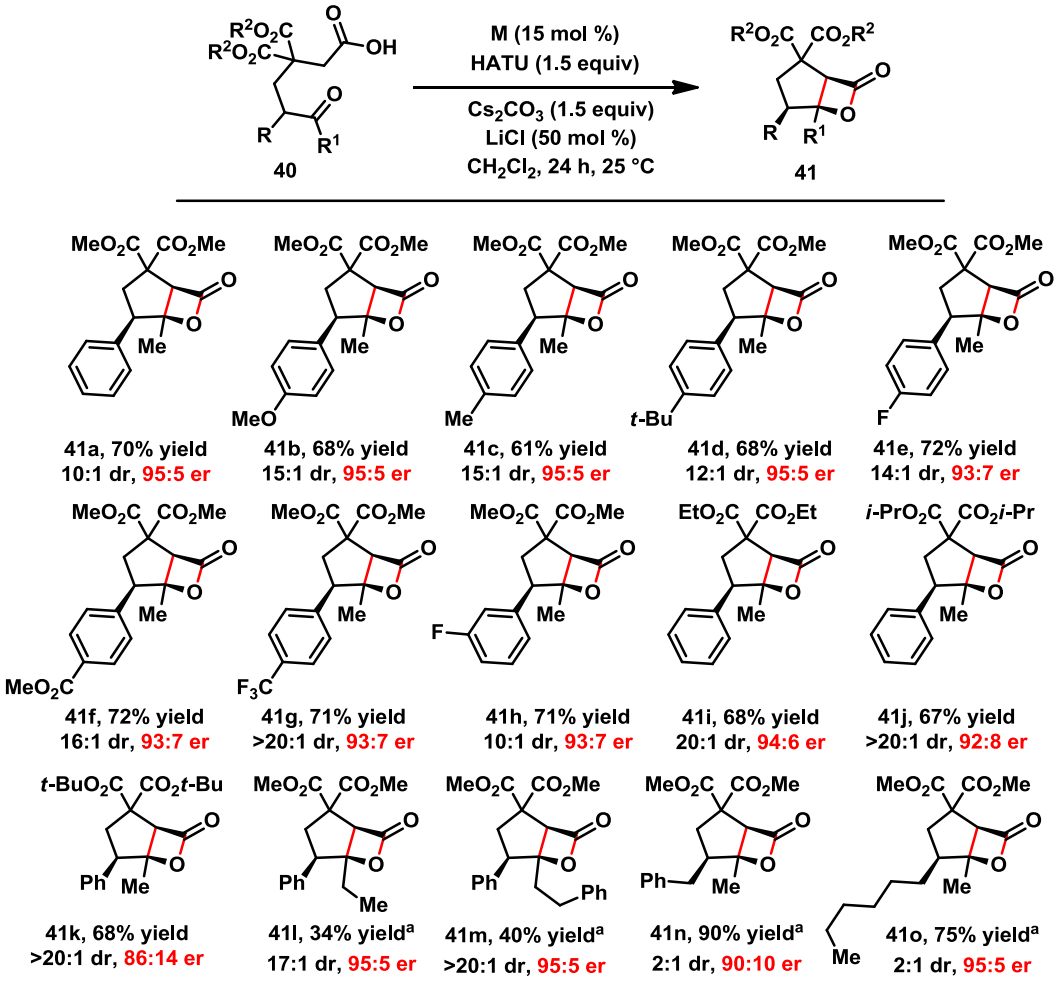
Column : Chiralcel OD-H
Eluent System : 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol..: 10ul
Wavelength: 220 nm
Sample Conc.: 1 mg/ ml

4.3.3. Aldol Lactonization of Ketoacids: Substrate Scope

With the reaction conditions in hand, we then expand the substrate scope of aldol β-lactonization reaction (Scheme 4.16). The parent ketoacid worked well and a series of electron-donating and -withdrawing groups on the aryl ring at the α-keto moiety in **40** are well tolerated and in all cases, the cyclopentane-fused β-lactone was formed in good yield, diastereoselectivity and enantioselectivity (**41a-41h**). It may be noted that the -CF_3 substituted substrate resulted in the formation of the β-lactone **41g** in 71% yield, >20:1 dr and

93:7 er. Moreover, ketoacids derived from various other malonate esters readily underwent smooth β-lactonization affording the desired products **41i-41k** with good yield, enantioselectivity and excellent diastereoselectivity. In addition, this annulation reaction is not limited to methyl ketones, but instead other alkyl ketones also worked well to furnish the functionalized β-lactones in moderate yields (**41l, 41m**). When the alkyl group fixed at the α-keto moiety instead of aryl group, the diastereoselectivity of the product dropped to 2:1 maintaining good yield and enantioselectivity (**41n, 41o**).

Scheme 4.16: Substrate Scope of the Aldol Lactonization Reaction



General reaction conditions: **40** (0.50 mmol), **M** (15 mol %), HATU (1.5 equiv), LiCl (50 mol %), Cs_2CO_3 (1.5 equiv), CH_2Cl_2 (7.0 mL), 25 °C and 24 h. The diastereomers are separable by column chromatography and given are combined yield of both diastereomers. The dr was determined by ^{1}H NMR spectroscopy of crude reaction mixture and er determined by HPLC analysis on a chiral column. [a] Reaction was run on 0.25 mmol scale.

4.3.4 Kinetic Study of the Aldol Lactonization Reaction

For a proper understanding of the reaction mechanism, we have studied the kinetics of the NHC-catalyzed intramolecular aldol lactonization of **40a** leading to the formation of **41a**.

The reaction proceeds very fast in the first 1 hour affording the major diastereomer **41a** in 34% yield. Then, the reaction proceeds relatively slower, and after 24 h, 62% of the major diastereomer were formed. Stirring the reaction mixture beyond 24 h did not improve the yield of **41a**. The kinetic profile of the reaction with the yield of major diastereomer as well as the combined yield against time is presented in Figure 4.1. The formation of the major diastereomer in 62% clearly indicates that the reaction proceeds via dynamic kinetic resolution strategy. The kinetic experiment also rules out the possibility of simple kinetic resolution operating in the β-lactonization reaction. It may be noted that the ketoacid **40a** was completely consumed under the present reaction conditions because of the fast conversion to the HATU ester.

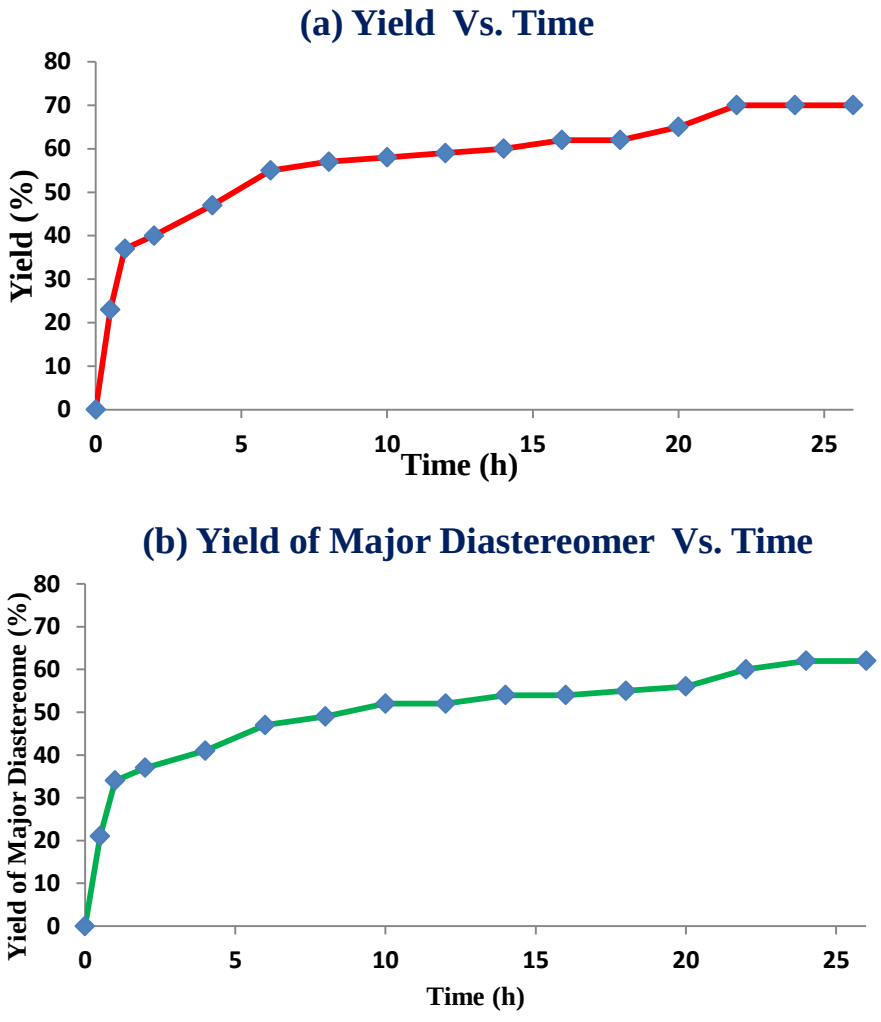
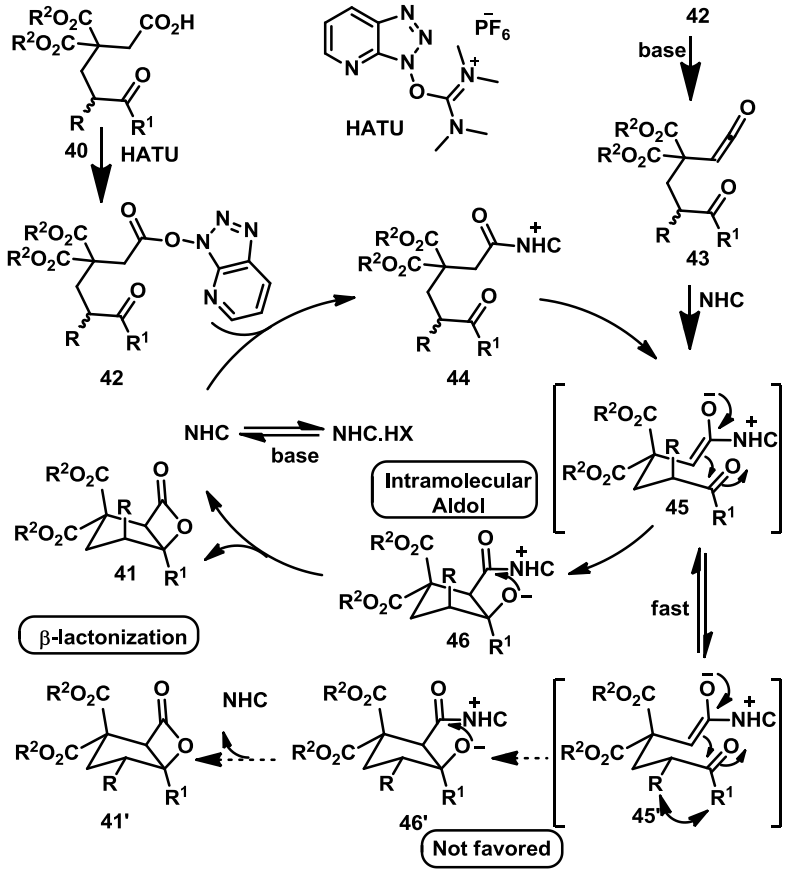


Figure 4.1: Kinetics Profile of the NHC-Catalyzed Aldol Lactonization Reaction. (a) Combined Yield of Two Diastereomers vs. Time Plot and (b)Major Diastereomer vs. Time Plot

4.3.5. Reaction Mechanism

A tentative mechanism for this aldol lactonization reaction is described in scheme 4.17. The initial activation of ketoacids **40** takes place in the presence of coupling agent HATU. The addition of NHC to the activated carboxylate **42** could generate the NHC-bound acyl azolium intermediate **44**, which under basic conditions generates the NHC-enolate **45**. Alternatively, it is also likely that the carboxylate **42** under basic conditions form the ketene intermediate **43**, which upon reaction with NHC form the NHC-enolate **45**. The intramolecular aldol reaction of enolate **45** could provide the cyclopentane intermediate **46**, which on β-lactonization affords the cyclopentane-fused β-lactone **41** with the regeneration of the NHC catalyst. It is also plausible that the cyclopentane alkoxide **46** adds to the azolium moiety (instead of β-lactonization) to generate the spirolactone intermediate as proposed by Scheidt[14] followed by ring contraction and carbene elimination results in the formation of **41**. The intermediates **45** and **45'** in a rapid equilibrium due to the basic reaction conditions

Scheme 4.17: Proposed Mechanism of the Reaction

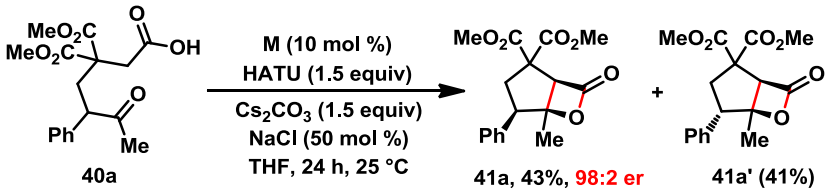


employed. It is likely that the major diastereomer **41** will be formed from **45** where R is in pseudo axial orientation. This conformation is more favourable than **45'**, which can lead to the minor diastereomer **41'** via the azolium intermediate **46'**. This may be because of the destabilization effect in **46'** due to the interaction of the aryl (R) and the alkyl (R^1) groups.

4.3.6. NHC-Catalyzed Parallel Kinetic Resolution of Ketoacid

Remarkably, when the reaction was carried out using NaCl (50 mol%) as the additive, the two diastereomers **41a** and **41a'** are formed in 43% and 41% yields respectively (scheme 4.18). Under these conditions, the products are expected to be formed by the stereodivergent parallel kinetic resolution (PKR).[25,26] The observation of PKR in the presence of NaCl is not clear. To examine the reversibility of the transformation, the PKR reaction mixture was subjected to LiCl conditions. Notably, even in the presence of 50 mol% LiCl, the products **41a** and **41a'** are formed in 1:1 ratio, indicating no observation of DKR under these conditions. This indicates that that **41a** and **41a'** are not interconvertible.

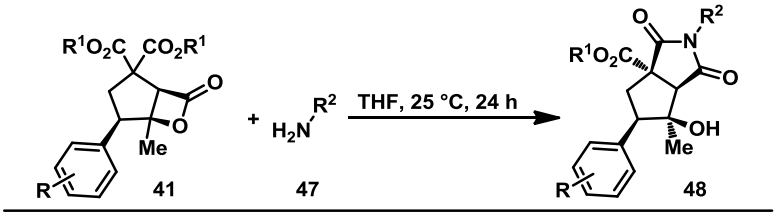
Scheme 4.18: Parallel Kinetic Resolution of Ketoacid

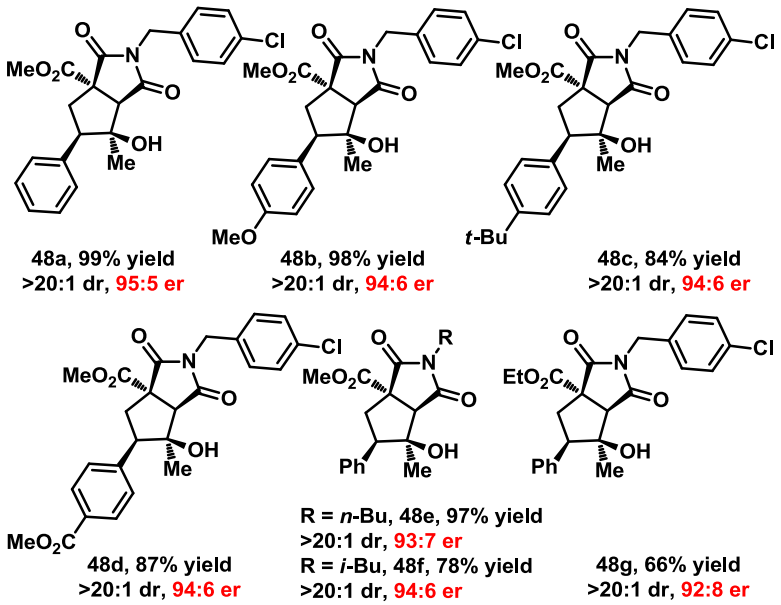


4.3.7. Functionalization of cyclopentane-fused β-lactone

A substrate controlled β-lactone ring opening followed by the intramolecular cyclization to one of the ester moiety for the synthesis of succinimide derivatives has been shown using various aliphatic primary amines. For example, treatment of **41a** with 4-chlorobenzyl amine afforded the cyclopentane-fused succinimide **48a** in 99% yield, >20 : 1 dr and 95:5 er (Scheme 4.19). The β-lactone having electronically different substituents at the 4-position of aryl ring furnished the succinimides bearing four contiguous stereocentres in excellent yield and diastereoselectivity and good enantiopurity (**48b-48d**). Moreover, this ring expansion reaction worked well with linear and branched aliphatic amines (**48e, 48f**).

Scheme 4.19: Substrate-controlled Conversion of β-Lactones to Succinimides in Presence of Amines





Additionally, in the case of reaction using the ethyl ester substituted β-lactone, the structure and stereochemistry of the succinimide **48g** was confirmed using single crystal X-ray analysis (Figure 4.2).[27] The absolute stereochemistry of the chiral centres in the β-lactones **41** (Scheme 4.16) were inferred in analogy with **48g**.

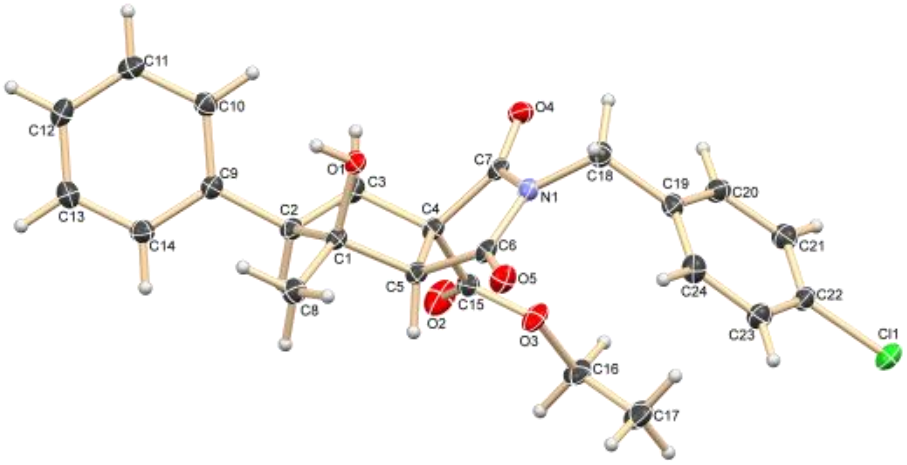
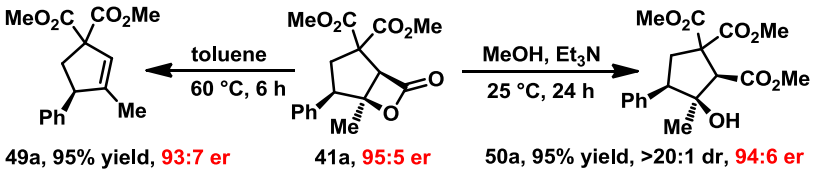


Figure 4.2. Crystal Structure of **48g** (Thermal Ellipsoids are Shown with 50% Probability).

Moreover, the ring-opening reactions of β-lactones were also performed. Heating **41a** in toluene at 60 °C in presence of SiO_2 afforded the cyclopentene **49a** in 95% yield and 93:7

Scheme 4.20: Stereoselective Functionalization to Cyclopentenes and Cyclopentanes



er proceeding via the decarboxylation (Scheme 4.20). Also, nucleophilic ring-opening of **41a** using methanol under basic condition furnished the functionalized cyclopentanol **50a** in 95% yield, >20:1 dr and 94:6 er.

4.4. Conclusion

In conclusion, we have demonstrated the NHC-catalyzed aldol-lactonization of acyclic ketoacids to furnish the cyclopentane-fused β-lactones having three contiguous stereocentres in moderate to good yields, diastereoselectivity and enantioselectivity.[28] The reaction proceeds via the DKR strategy. The NHC-bound azolium enolate generated under basic condition by the addition of NHC to the activated carboxylate (ketoacid-HATU adduct) in presence of LiCl is the key intermediate in this transformation. Additionally, the β-lactones are converted into succinimide derivatives with four contiguous stereocentres via the substrate-controlled β-lactone opening in presence of amines.

4.5. Experimental Details

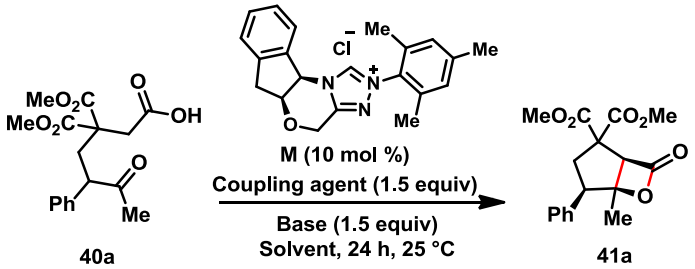
4.5.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with teflon screw caps. Dry DCM were purchased from commercial sources and stored under argon over 4 Å molecular sieves. The triazolium salt **M** was synthesized following the literature procedure.[23] Cs_2CO_3 and LiCl were purchased from commercial sources and stored inside the glovebox.

Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (100-200 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system.

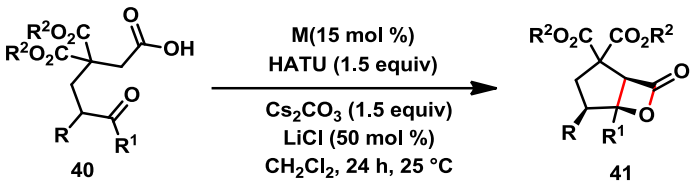
All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400, in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS (ESI) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Optical rotation was measured with a JASCO P 2000 digital polarimeter at rt using 50 mm cell of 1 mL capacity. HPLC analysis was performed on Agilent Technologies 1260 Infinity with UV detector, and HPLC analysis of compound **41o** was done on MERCK HITACHI with UV detector.

4.5.2. General Procedure for the Optimization of Reaction Conditions

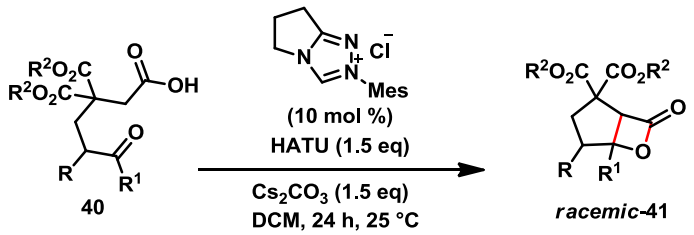


To a oven-dried Schlenk reaction vessel equipped with a magnetic stir bar was taken the 3,3-bis(methoxycarbonyl)-6-oxo-5-phenylheptanoic acid **40a** (84 mg, 0.25 mmol), coupling agent (0.375 mmol, 1.5 equiv) and base (0.375 mmol, 1.5 equiv) were added. The mixture was kept under argon atmosphere. To this mixture was added solvent (4.0 mL) under a positive pressure of argon, and the mixture was stirred at 25 °C for 15 min. To this stirring solution was added the triazolium salt **M** (9.2 mg, 0.025 mmol, 10 mol %), and the resulting mixture was stirred at 25 °C for 24 h. Evaporation of the solvent to obtain the crude product, whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard. The enantiomeric excess was determined by HPLC analysis on a chiral column.

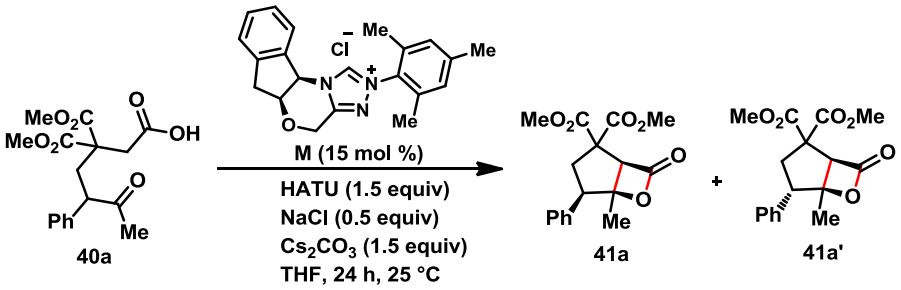
4.5.3. General Procedure for the Enantioselective Synthesis of Cyclopentane-fused β-Lactones



To a oven-dried Schlenk reaction vessel equipped with a magnetic stir bar was taken the ketoacid **40** (0.5 mmol), HATU (285.6 mg, 0.75 mmol, 1.5 equiv) and Cs_2CO_3 (244.3 mg, 0.75 mmol, 1.5 equiv) were added. The mixture was kept under argon atmosphere. To this mixture was added DCM (7.0 mL) under a positive pressure of argon, and the mixture was stirred at 25 °C for 15 min. To this stirring solution was added LiCl (10.6 mg, 0.25mmol, 50 mol%) followed by triazolium salt **M** (27.6 mg, 0.075 mmol, 15 mol %), and the resulting mixture was stirred at 25 °C for 24 h. Evaporation of the solvent followed by silica gel flash column chromatography afforded the cyclopentane-fused β-lactone derivative **41**. All racemic cyclopentane-fused β-lactones were prepared using by *N*-mesityl triazolium-derived carbenes.



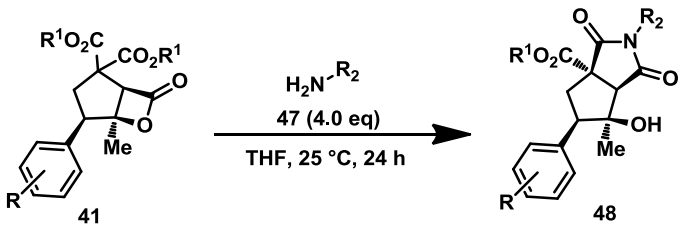
4.5.4. Procedure for Parallel Kinetic Resolution for Synthesis of Cyclopentane-fused β-Lactone



To a oven-dried Schlenk reaction vessel equipped with a magnetic stir bar was taken the 3,3-bis(methoxycarbonyl)-6-oxo-5-phenylheptanoic acid **40a** (84.0 mg, 0.25 mmol), HATU (142.0 mg, 0.375 mmol, 1.5 equiv), Cs_2CO_3 (122.0 mg, 0.375 mmol, 1.5 equiv) and NaCl (7.3 mg, 0.125mmol, 50 mol%) was added. The mixture was kept under argon atmosphere. To this mixture was added THF (4.0 mL) under a positive pressure of argon and the mixture was stirred at 25 °C. To this stirring solution was added triazolium salt **M** (9.2 mg, 0.075 mmol, 10 mol %), and the resulting mixture was stirred at 25 °C for 24 h. Evaporation of the solvent followed by silica gel flash column chromatography afforded the cyclopentane-fused β-lactone derivative **41a** (43% yield, 98:2 er) and **41a'** (41% yield; the er of the minor diastereomer was not determined due to the difficulty in preparing the racemic substrate. The performed racemic reactions always gave exclusively the diastereomer **41a**).

4.5.5. General Procedure for the Synthesis of Functionalized Succinimide Derivatives

An oven dried round bottomed flask was charged with cyclopentane fused β-lactone **41** (0.15 mmol,) and primary amine **4**7 (0.6 mmol, 4.0 equiv) in THF (1.0 mL). The reaction mixture was stirred at 25 °C for 24 h under argon atmosphere. Brine was added followed by EtOAc. The aqueous layer was extracted with EtOAc and combined organic layer were dried



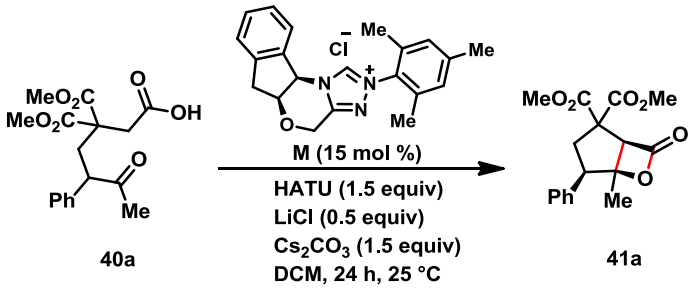
with Na_2SO_4, filtered and concentrated. The mixture was purified by flash chromatography (40% EtOAc- Pet ether) to afford desired product.

4.5.6. X-Ray Data of 48g

X-ray intensity data measurements of compound **48g** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Cu micro-focus sealed tube diffraction source (CuK_α= 1.54178 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.1 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 40 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[29] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[30] All the hydrogen atoms (except hydoxy H atoms) were placed in a geomerically idalized position (C-H = 0.95 Å for the phenyl H atoms, C-H = 0.98 for the methyl H atoms, C-H = 1.00 Å for the methine H atoms and C-H = 0.99 Å of the methylene H atoms) and constrained to ride on its parent atoms [Uiso(H) = 1.2Ueq(C) for phenyl, methine and methylene H atoms and Uiso(H) = 1.5Ueq(C) for methyl H atoms]. The hydroxy H atom (O1-H1) was located in the difference Fourier map and refined isotropically. An *ORTEP* III[31] view of compound was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. *The absolute configuration was established by anomalous dispersion effect (Flack parameter, 0.044(11)) in X-ray diffraction measurements carried out with Cu radiation.* The single crystal X-ray diffraction data analysis clearly established that our synthesize compound has *S, R, S, R* configurations at C1, C2, C4 and C5 positions respectively. CCDC 1524579 (**48g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data of **48g :** $C_{24}H_{24}ClNO_5$, M = 441.89, colorless needle, 0.40 x 0.08 x 0.06 mm^3, monoclinic, chiral space group $P2_1$, a = 9.9750(2) Å, b = 8.9417(2) Å, c = 12.2426(3) Å, β = 101.0430(10)°, V = 1071.74(4) $Å^3$, 2 = 4, T = 100(2) K, $2\theta_{max}$=156.96°, D_{calc} (g cm^{-3}) = 1.369, $F(000)$ = 464, μ (mm^{-1}) = 1.886, 25563 reflections collected, 4372 unique reflections (R_{int}=0.0267), 4349 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.519, T_{max} = 0.895, 287 refined parameters, number of restraints = 1, Good of Fit = S = 1.036, $R1$ = 0.0223, $wR2$ = 0.0572 (all data R = 0.0224, $wR2$ = 0.0573), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.233, $\Delta\rho_{min}$= -0.145 ($eÅ^{-3}$).

4.5.7. Kinetics Study



Sixteen reactions were carried out in parallel. To each of oven-dried Schlenk reaction vessel equipped with a magnetic stir bar was taken the 3,3-bis(methoxycarbonyl)-6-oxo-5-phenylheptanoic acid **40a** (34.0 mg, 0.1 mmol), HATU (57.0 mg, 0.15 mmol, 1.5 equiv) and

Table 4.2: Kinetics of the Reaction

Entry	Time (h)	Yield (%)	Yield of Major Diastereomer (%)
1	0	0	0
2	0.5	23	21
3	1	37	34
4	2	40	37
5	4	47	41
6	6	55	47
7	8	57	49
8	10	58	52
9	12	59	52
10	14	60	54
11	16	62	54
12	18	62	55
13	20	65	56
14	22	70	60
15	24	70	62
16	26	70	62

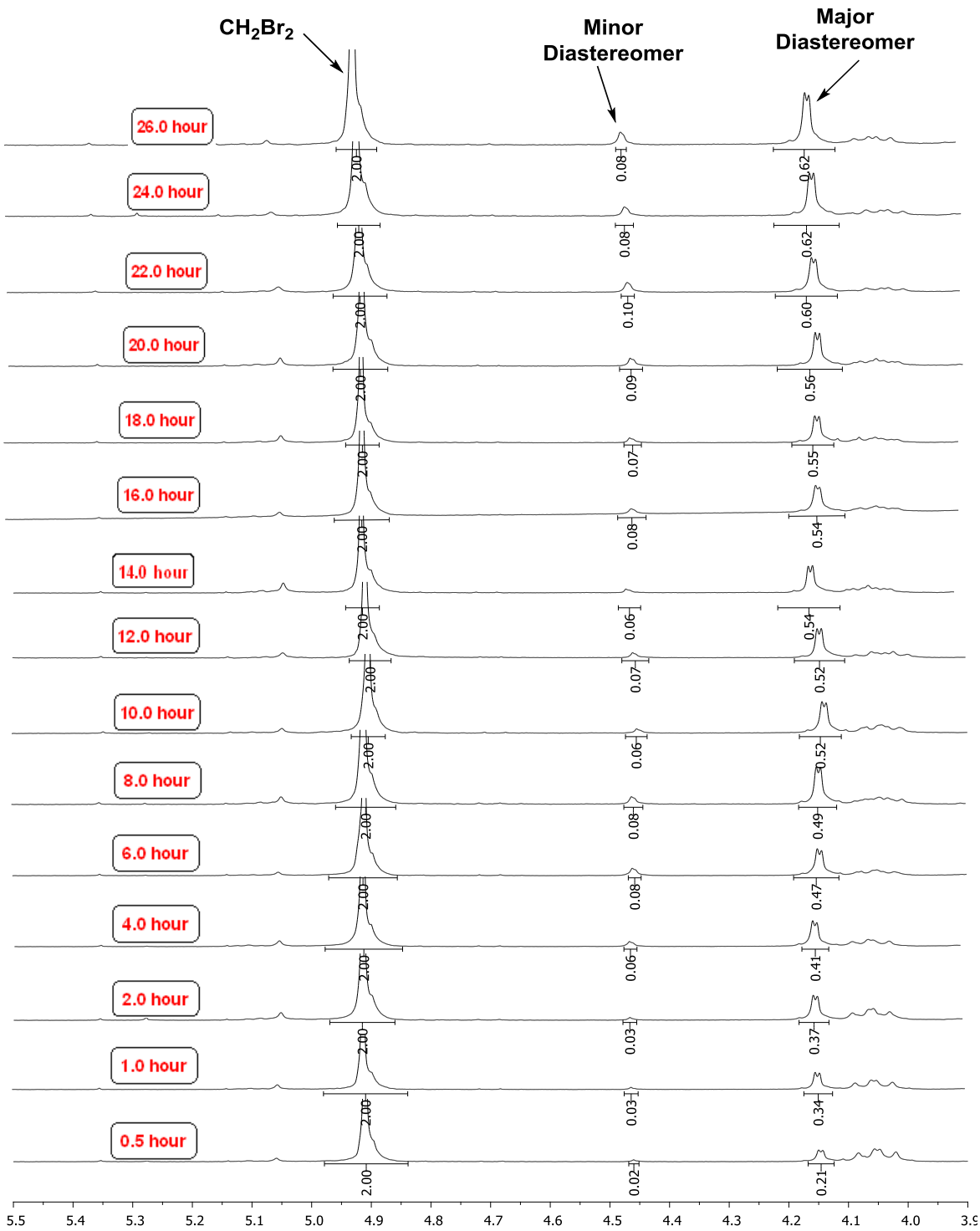


Figure 4.3: ^{1}H NMR Spectra of Crude Reaction Mixture (Recorded at Different Time) Using CH_2Br_2 as an Internal Standard.

Cs_2CO_3 (49.0 mg, 0.15 mmol, 1.5 equiv) was added. The mixture was kept under argon atmosphere. To this mixture was added DCM (1.5 mL) under a positive pressure of argon, and the mixture was stirred at 25 °C for 15 min. To this stirring solution was added LiCl (2.0 mg, 0.05mmol, 50 mol %) followed by triazolium salt **M** (5.5 mg, 0.015 mmol, 15 mol %),

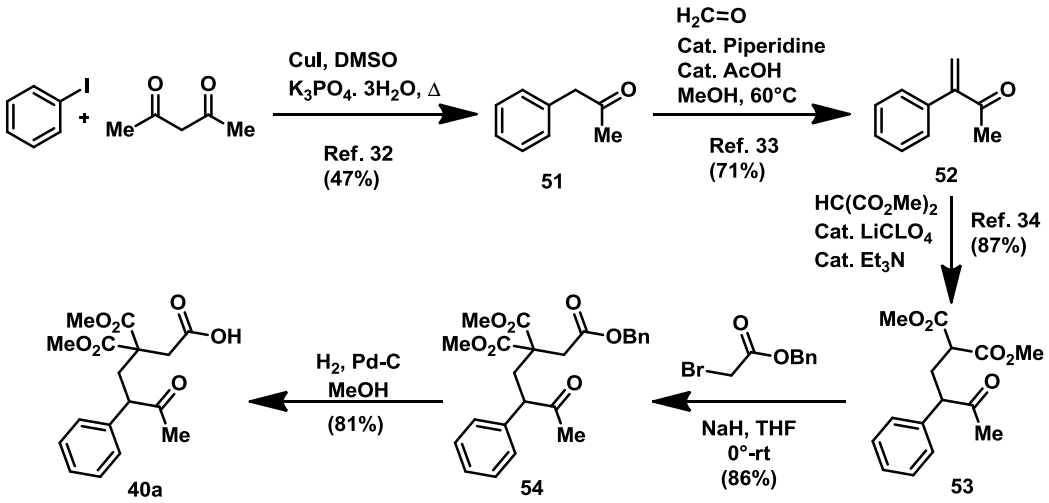
and the resulting mixture was stirred at 25 °C for the time mentioned in Table 4.2. The reactions are quenched and filtered through a short pad of silica and eluted with EtOAc. The solvent was evaporated to obtain the crude product, which was analyzed by ^{1}H NMR using CH_2Br_2 as an internal standard.

More than 50 % yield after 6 hour clearly indicates that the reaction proceeds via dynamic kinetic resolution strategy.

4.5.8. Synthesis and Characterization of Ketoacids

3,3-Bis(methoxycarbonyl)-6-oxo-5-phenylheptanoic acid (40a)

The synthesis of the ketoacids used in the present study has been achieved starting from phenyl iodide and acetyl acetone following the known procedure. Synthesis of phenyl acetone **51** by Cu catalyzed coupling of phenyl iodide with acetylacetone.[32] α-olefination of **51** using paraformaldehyde and catalytic piperidine and acetic acid affords **52**.[33] Michael addition of dimethyl malonate to **52** followed by ayalkylation with benzyl bromoacetate and debenzylation furnished the keto acid substrates **40a**.[34]



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.22 (m, 3H), 7.18 (d, *J* = 7.3 Hz, 2H), 4.01-3.98 (m, 1H), 3.62 (d, *J* = 28.2 Hz, 6H), 3.06-2.91 (m, 3H), 2.30 (dd, J_1 = 14.7 HZ, J_2 = 4.8 Hz, 1H), 2.02 (s, 3H).

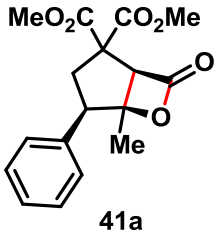
^{13}C NMR (100 MHz, $CDCl_3$) δ 206.97, 175.69, 170.60, 170.37, 138.67, 129.23, 128.55, 127.74, 55.22, 54.31, 53.04, 52.89, 38.67, 35.26, 29.04.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{20}O_7Na$: 359.1101, found: 359.1098.

FTIR (cm^{-1}) 3021, 2955, 2401, 1735, 1719, 1494, 1437, 1356, 1216, 1066, 928, 875, 772, 701, 668.

4.5.9. Synthesis and Characterization of Functionalized Cyclopentane fused β-Lactones

Dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41a)



41a

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-5-phenylheptanoic acid **40a** (168.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41a** as a colourless oil (111.0 mg, 70% yield, *dr* 10:1).

***R**f* (Pet. ether /EtOAc = 70/30): 0.45.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 9.2 min, Minor: 12.2 min. er = 95:5, $[\alpha]_D^{25}$ = -27.37 (c 0.1, $CHCl_3$).

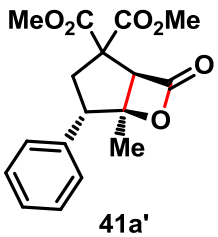
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 4.19 (s, 1H), 3.84 (d, *J* = 1.0 Hz, 6H), 3.07-2.98 (m, 2H), 2.66-2.57 (m, 1H), 1.63 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.39, 167.57, 166.67, 134.74, 129.22, 128.53, 127.94, 87.00, 63.48, 58.06, 53.65, 53.25, 50.12, 36.91, 20.12.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{19}O_6$: 319.1176, found: 319.1175.

FTIR (cm^{-1}) 3121, 2980, 2956, 1821, 1735, 1455, 1436, 1385, 1272, 1216, 1166, 1139, 1109, 1059, 1037, 1018, 771, 668.

Dimethyl (1*R*,4*S*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41a')



41a'

***R**f* (Pet. ether /EtOAc = 70/30): 0.49.

$[\alpha]_D^{25}$ = -39.37 (c 0.1, $CHCl_3$).

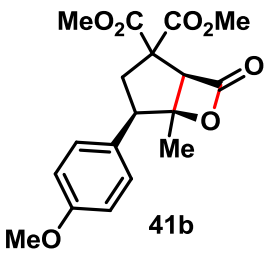
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 -7.25 (m, 3H), 7.03-7.02 (m, 2H), 4.48 (s, 1H), 3.87 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.45 (dd, J_1 = 15.0 Hz, J_2 = 9.1 Hz, 1H), 2.72- 2.67 (m, 1H), 1.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.79, 168.23, 167.53, 138.89, 128.83, 128.32, 127.47, 91.11, 65.42, 60.59, 53.68, 53.59, 52.50, 40.20, 20.65.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{19}O_6$: 319.1176, found: 319.1175.

FTIR (cm^{-1}) 3128, 2976, 2802, 1825, 1730, 1466, 1420, 1395, 1232, 1216, 1166, 1139, 1169, 1019, 1027, 1018, 770, 669.

Dimethyl (1*R*,4*R*,5*S*)-4-(4-methoxyphenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41b)



41b

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-5-(4-methoxyphenyl)-6-oxoheptanoic acid **40b** (183.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-4-(4-methoxyphenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41b** as a colourless oil (118.0 mg, 68% yield, *dr* 15:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.40.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 12.8 min, Minor: 17.4 min. er = 95:5, $[\alpha]_D^{25}$ = -27.8 (c 0.1, $CHCl_3$).

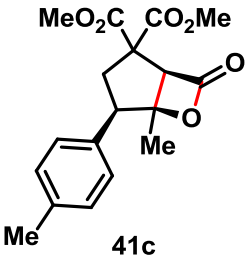
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.14 (s, 1H), 3.82-3.77 (m, 9H), 2.99- 2.90 (m, 2H), 2.60-2.51 (m, 1H), 1.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.49, 167.67, 166.80, 159.38, 130.25, 126.67, 113.98, 87.08, 63.35, 58.02, 55.34, 53.67, 53.29, 49.44, 37.12, 20.12.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{20}O_7Na$: 371.1101, found: 371.1091.

FTIR (cm^{-1}) 3021, 2957, 1821, 1735, 1514, 1459, 1437, 1272, 1252, 1217, 1182, 1108, 1066, 1037, 829, 771, 668.

Dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-(*p*-tolyl)-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41c)



41c

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-5-(*p*-tolyl)heptanoic acid **40c** (175.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet.

ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-(*p*-tolyl)-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41c** as a colourless oil (101.0 mg, 61% yield, *dr* 15:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.5.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 7.9 min, Minor: 11.0 min. er = 95:5, $[\alpha]_D^{25}$ = -39.55 (c 0.1, $CHCl_3$).

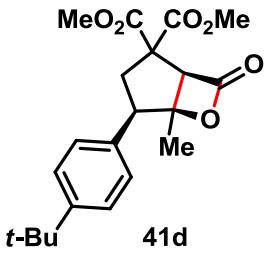
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.13 (m, 4H), 4.15 (s, 1H), 3.82 (s, 6H), 3.03-2.94 (m, 2H), 2.61-2.52 (m, 1H), 2.33 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.46, 167.65, 166.77, 137.67, 131.65, 129.26, 129.08, 87.05, 63.43, 58.06, 53.65, 53.27, 49.79, 36.97, 21.13, 20.13.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{20}O_6Na$: 355.1152, found: 355.1146.

FTIR (cm^{-1}) 3021, 2956, 1821, 1735, 1515, 1436, 1384, 1272, 1216, 1166, 1139, 1108, 1065, 1040, 1021, 754, 668.

Dimethyl (1*R*,4*R*,5*S*)-4-(4-(*tert*-butyl)phenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41d)



41d

Following the general procedure, treatment of 5-(4-(*tert*-butyl)phenyl)-3,3-bis(methoxycarbonyl)-6-oxoheptanoic acid **40d** (196.2 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-4-(4-(*tert*-butyl)phenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41d** as a white foam (126.0 mg, 68% yield, *dr* 12:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.59.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 7.4 min, Minor: 8.5 min. er = 95:5, $[\alpha]_D^{25}$ = -51.77 (c 0.1, $CHCl_3$).

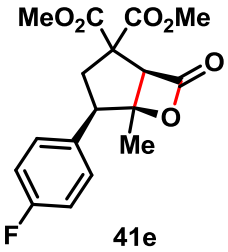
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.26-7.22 (m, 2H), 4.16 (s, 1H), 3.82 (d, *J* = 2.9 Hz, 6H), 3.04-2.96 (m, 2H), 2.62-2.53 (m, 1H), 1.62 (s, 3H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.49, 167.66, 166.77, 150.84, 131.64, 128.87, 125.49, 87.12, 63.49, 58.10, 53.65, 53.28, 49.71, 36.97, 34.58, 31.39, 20.21.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{26}O_6Na$: 397.1622, found: 397.1614.

FTIR (cm^{-1}) 3022, 2960, 2906, 2870, 1821, 1735, 1458, 1436, 1272, 1217, 1140, 1108, 1065, 1040, 1021, 846, 826, 770, 668.

Dimethyl (1*R*,4*R*,5*S*)-4-(4-fluorophenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41e)



41e

Following the general procedure, treatment of 5-(4-fluorophenyl)-3,3-bis(methoxycarbonyl)-6-oxoheptanoic acid **40e** (177.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-4-(4-fluorophenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41e** as a colourless oil (120.3 mg, 72% yield, *dr* 14:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.46.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 10.8 min, Minor: 13.8min. er = 93:7, $[\alpha]_D^{25}$ = -27.10 (c 0.1, $CHCl_3$).

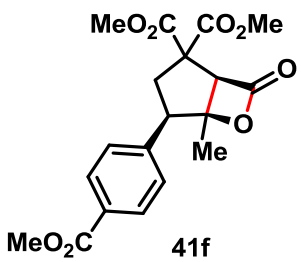
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.03 (t, *J* = 8.4 Hz, 2H), 4.17 (s, 1H), 3.83 (s, 6H), 3.03-2.91 (m, 2H), 2.59 (dd, J_1 = 12.4 Hz, J_2 = 4.5 Hz, 1H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.38, 167.52, 166.54, 162.57 (d, *J* = 246.8 Hz), 130.8 (d, *J* = 8.1 Hz), 130.55 (d, *J* = 3.1 Hz), 115.50 (d, *J* = 21.3 Hz), 86.89, 63.46, 58.03, 53.72, 53.33, 49.46, 37.18, 20.09.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{17}O_6FNa$: 359.0901, found: 359.0893.

FTIR (cm^{-1}) 3025, 2957, 1823, 1736, 1512, 1437, 1296, 1271, 1218, 1194, 1163, 1105, 1065, 1039, 847, 830, 811, 757, 668.

Dimethyl (1*R*,4*R*,5*S*)-4-(4-(methoxycarbonyl)phenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0] heptane-2,2-dicarboxylate (41f)



41f

Following the general procedure, treatment of 3,3 bis(methoxycarbonyl)-5-(4-(methoxycarbonyl)phenyl)-6-oxoheptanoic acid **40f** (197.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-4-(4-

(methoxycarbonyl)phenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41f** as a colourless oil (136.0 mg, 72% yield, *dr* 16:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.33.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 23.9 min, Minor: 35.3 min. er = 93:7, $[\alpha]_D^{25}$ = -41.20 (c 0.1, $CHCl_3$).

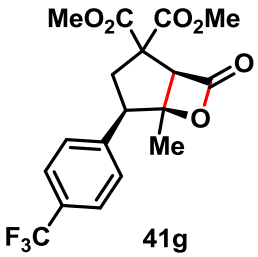
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 4.17 (s, 1H), 3.89 (s, 3H), 3.81 (s, 6H), 3.09-2.96 (m, 2H), 2.59 (dd, J_1 = 12.9 Hz, J_2 = 5.0 Hz, 1H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.28, 167.41, 166.82, 166.38, 140.07, 129.86, 129.76, 129.32, 86.88, 63.68, 58.14, 53.75, 53.35, 52.23, 50.09, 36.85, 20.17.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{20}O_8Na$: 399.1050, found: 399.1040.

FTIR (cm^{-1}) 3410, 3020, 2965, 2401, 1823, 1733, 1612, 1515, 1437, 1387, 1281, 1216, 1113, 1040, 1020, 772, 668.

Dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-(4-(trifluoromethyl)phenyl)-6-oxabicyclo[3.2.0] heptane-2,2-dicarboxylate (41g)



41g

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-5-(4-(trifluoromethyl)phenyl)heptanoic acid **40g** (202.17 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-(4-(trifluoromethyl)phenyl)-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41g** as a colourless oil (136.0 mg, 71% yield, *dr* >20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.44.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 11.8 min, Minor: 13.8 min. er = 93:7, $[\alpha]_D^{25}$ = -27.58 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 2H), 4.18 (s, 1H), 3.82 (s, 6H), 3.10 – 2.95 (m, 2H), 2.60 (dd, J_1 = 13.4 Hz, J_2 = 5.6 Hz, 1H), 1.61 (s, 3H).

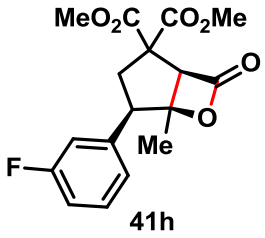
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.28, 167.40, 166.28, 139.06, 130.72, 130.39, 130.07, 129.69, 128.19, 125.50, 125.47, 122.78, 86.82, 63.72, 58.14, 53.77, 53.36, 49.96, 36.95, 20.13.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.63.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{17}O_6F_3Na$: 409.0869, found: 409.0859.

FTIR (cm^{-1}) 3022, 2986, 1824, 1736, 1437, 1327, 1297, 1272, 1218, 1188, 1167, 1129, 1069, 1040, 1019, 829, 754, 667.

Dimethyl (1*R*,4*R*,5*S*)-4-(3-fluorophenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41h)



41h

Following the general procedure, treatment of 5-(3-fluorophenyl)-3,3-bis(methoxycarbonyl)-6-oxoheptanoic acid **40h** (177.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-4-(3-fluorophenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41h** as a colourless oil (119.0 mg, 71% yield, *dr* 10:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.45.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 11.1 min, Minor: 12.9 min. er = 93:7, $[\alpha]_D^{25}$ = -21.39 (c 0.1, $CHCl_3$).

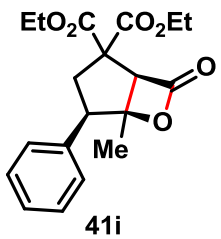
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 1H), 7.08 – 6.98 (m, 3H), 4.17 (s, 1H), 3.82 (s, 6H), 3.03-2.91 (m, 2H), 2.59 (dd, J_1 = 12.1 Hz, J_2 = 4.1 Hz, 1H), 1.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.37, 167.47, 166.43, 162.87 (d, *J* = 245.6 Hz), 137.39 (d, *J* = 7.3 Hz), 130.06 (d, *J* = 8.2 Hz), 125.00 (d, *J* = 2.6 Hz), 116.27 (d, *J* = 22.2 Hz), 114.99 (d, *J* = 21.3 Hz), 86.83, 76.84, 63.66, 58.08, 53.77, 53.39, 49.89, 37.04, 20.20.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{17}O_6FNa$: 359.0901, found: 359.0891.

FTIR (cm^{-1}) 3022, 3025, 1823, 1736, 1590, 1491, 1450, 1437, 1271, 1217, 1191, 1154, 1108, 1039, 813,754, 698, 668.

Diethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41i)



41i

Following the general procedure, treatment of 3,3-bis(ethoxycarbonyl)-6-oxo-5-phenylheptanoic acid **40i** (182.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash

column chromatography (EtOAc-Pet. ether 30:70) afforded diethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41i** as a colourless oil (117.0 mg, 68% yield, *dr* 20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.62.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 6.9 min, Minor: 9.8 min. er = 94:6, $[\alpha]_D^{25}$ = -15.26 (c 0.1, $CHCl_3$).

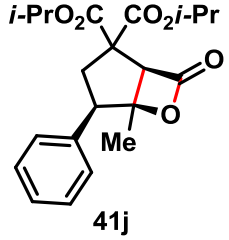
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (m, 5H), 4.36 – 4.23 (m, 4H), 4.19 (s, 1H), 3.07-2.98 (m, 2H), 2.64-2.55 (m, 1H), 1.63 (s, 3H), 1.35-1.29 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.06, 167.11, 166.73, 134.90, 129.25, 128.54, 127.92, 86.93, 63.46, 62.64, 62.38, 58.23, 50.16, 36.85, 20.16, 14.10, 14.06.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{22}O_6Na$: 369.1309, found: 369.1299.

FTIR (cm^{-1}) 3026, 2983, 1823, 1730, 1385, 1386, 1298, 1268, 1215, 1194, 1164, 1138, 1105, 1058, 1036, 835, 753, 700, 668.

Diisopropyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41j)



41j

Following the general procedure, treatment of 3,3-bis(isopropoxycarbonyl)-6-oxo-5-phenylheptanoic acid **40j** (196.2.0 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded diisopropyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41j** as a colourless oil (125.0 mg, 67% yield, *dr* >20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.72.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 4.7 min, Minor: 7.0 min. er = 92:8, $[\alpha]_D^{25}$ = -7.01 (c 0.1, $CHCl_3$).

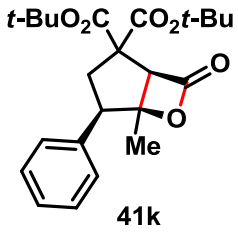
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.19-5.08 (m, 2H), 4.14 (s, 1H), 3.04 – 2.95 (m, 2H), 2.57 – 2.49 (m, 1H), 1.61 (s, 3H), 1.33-1.20 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.71, 166.78, 166.59, 135.03, 129.27, 128.55, 127.91, 86.89, 70.34, 70.09, 63.45, 58.35, 50.17, 36.77, 21.71, 21.61, 21.50, 20.18.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{21}H_{26}O_6Na$: 397.1622, found: 397.1611.

FTIR (cm^{-1}) 3410, 3020, 2983, 24001822, 1723, 1658, 1527, 1425, 1386, 1270, 1216, 1099, 1036, 928, 771, 689.

Di-*tert*-butyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41k)



41k

Following the general procedure, treatment of 3,3-bis(*tert*-butoxycarbonyl)-6-oxo-5-phenylheptanoic acid **40k** (210.2 mg, 0.50 mmol) with triazolium salt **M** (27.6 mg, 0.075 mmol), HATU (285.6 mg, 0.75mmol), Cs_2CO_3 (244.3 mg, 0.75 mmol), and LiCl (10.6 mg, 0.25mmol) in CH_2Cl_2 (7.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded di-*tert*-butyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41k** as a colourless oil (136.0 mg, 68% yield, *dr* >20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.72.

HPLC (Chiralcel OD-H, 99:1 Hexane / IPA, 0.7 mL/min, 220 nm wavelength.) Major: 6.6 min, Minor: 10.8 min. er = 86:14, $[\alpha]_D^{25}$ = +1.33 (c 0.1, $CHCl_3$).

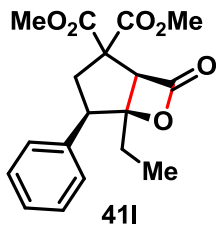
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 4.07 (s, 1H), 3.00-2.89 (m, 2H), 2.53-2.42 (m, 1H), 1.60 (s, 3H), 1.50 (d, *J* = 10.7 Hz, 18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.57, 167.14, 166.24, 135.25, 129.28, 128.53, 127.86, 86.87, 83.05, 82.88, 63.53, 59.56, 50.17, 36.71, 27.95, 27.89, 20.22.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{23}H_{30}O_6Na$: 425.1935, found: 425.1929.

FTIR (cm^{-1}) 3023, 2980, 2934, 1822, 1723, 1456, 1392, 1370, 1301, 1274, 1217, 1150, 1112, 1035, 842, 821, 769, 700, 668.

Dimethyl (1*R*,4*R*,5*S*)-5-ethyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41l)



41l

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-5-phenyloctanoic acid **40l** (88.0 mg, 0.25 mmol) with triazolium salt **M** (13.8 mg, 0.0375 mmol), HATU (142.6 mg, 0.375mmol), Cs_2CO_3 (122.0 mg, 0.375 mmol), and LiCl (5.3 mg, 0.125mmol) in CH_2Cl_2 (4.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-5-ethyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41l** as a colourless oil (28.0 mg, 34% yield, *dr* 17:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.56.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 8.2 min, Minor: 11.1 min. er = 95:5, $[\alpha]_D^{25}$ = -26.51 (c 0.1, $CHCl_3$).

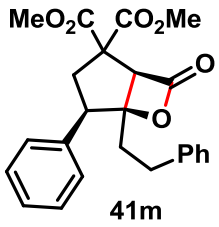
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 4.24 (s, 1H), 3.83 (d, *J* = 4.4 Hz, 6H), 3.07-2.97 (m, 2H), 2.67-2.57 (m, 1H), 1.96-1.84 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.39, 167.73, 166.88, 135.22, 129.34, 128.61, 127.97, 90.23, 60.75, 58.08, 53.69, 53.37, 48.71, 37.16, 26.10, 8.44.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{20}O_6Na$: 355.1152, found: 355.1144.

FTIR (cm^{-1}) 3384, 3020, 2400, 1823, 1735, 1602, 1436, 1215, 1058, 929, 771, 669.

Dimethyl (1*R*,4*R*,5*S*)-7-oxo-5-phenethyl-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41m)



41m

Following the general procedure, treatment of 3,3-bis(methoxycarbonyl)-6-oxo-5,8-diphenyloctanoic acid **40m** (106.6 mg, 0.25 mmol) with triazolium salt **M** (13.8 mg, 0.0375 mmol), HATU (142.6 mg, 0.375mmol), Cs_2CO_3 (122.0 mg, 0.375 mmol), and LiCl (5.3 mg, 0.125mmol) in CH_2Cl_2 (4.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*R*,5*S*)-7-oxo-5-phenethyl-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41m** as a colourless oil (41.0 mg, 40% yield, *dr* >20:1).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.54.

HPLC (Chiralcel OD-H, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 24.0 min, Minor: 10.7 min. er = 95:5, $[\alpha]_D^{25}$ = +22.02 (c 0.1, $CHCl_3$).

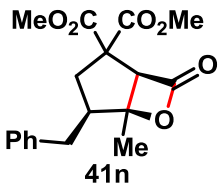
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 7H), 7.22-7.15 (m, 3H), 4.30 (s, 1H), 3.85 (d, *J* = 2.6 Hz, 6H), 3.11-2.99 (m, 2H), 2.82-2.61 (m, 3H), 2.22-2.18 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.42, 167.61, 166.68, 140.60, 135.09, 129.39, 128.69, 128.68, 128.38, 128.06, 126.42, 89.23, 61.38, 58.13, 53.73, 53.38, 49.40, 37.15, 35.09, 30.32.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{24}H_{24}O_6Na$: 431.1465, found: 431.1464.

FTIR (cm^{-1}) 3385, 3020, 2400, 1824, 1736, 1658, 1529, 1433, 1216, 1030, 926, 762, 669.

Dimethyl (1*R*,4*S*,5*S*)-4-benzyl-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41n)



41n

Following the general procedure, treatment of 5-benzyl-3,3-bis(methoxycarbonyl)-6-oxoheptanoic acid **40n** (88.0 mg, 0.25 mmol) with triazolium salt **M** (13.8 mg, 0.0375 mmol), HATU (142.6 mg, 0.375mmol), Cs_2CO_3 (122.0 mg, 0.375 mmol), and LiCl (5.3 mg, 0.125mmol) in CH_2Cl_2 (4.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*S*,5*S*)-4-

benzyl-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41n** as a colourless oil (75.0 mg, 90% yield, *dr* 2:1).

R_f (Pet. ether /EtOAc = 70/30): 0.48.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 12.1 min, Minor: 13.4 min. er = 90:10, $[\alpha]_D^{25}$ = +32.33 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) Major isomer δ 7.32-7.18 (m, 5H), 4.06 (s, 1H), 3.76 (d, *J* = 24.3 Hz, 6H), 2.95 (dd, J_1 = 13.6 Hz, J_2 = 5.5 Hz, 1H), 2.67 (dd, J_1 = 13.6 Hz, J_2 = 9.4 Hz, 1H), 2.84-2.41 (m, 1H), 2.32-2.25 (m, 1H), 2.21-2.09 (m, 1H), 1.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 167.65, 167.11, 139.36, 128.92, 128.73, 126.59, 87.70, 64.51, 58.59, 53.52, 53.18, 46.29, 37.18, 34.32, 20.48.

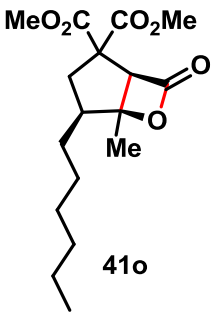
Representative peak for minor isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (s,1H), 3.82 (d, *J* = 41.5 Hz), 2.88-2.76 (m), 1.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.57, 176.60, 167.37, 138.83, 128.82, 128.79, 126.75, 89.87, 65.45, 60.24, 55.54, 53.34, 46.31, 35.54, 34.68, 19.34.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{20}O_6Na$: 355.1152, found: 355.1145.

FTIR (cm^{-1}) 3409, 3020, 2956, 2401, 1820, 1735, 1603, 1436, 1386, 1270, 1216, 1152, 1112, 1051, 928, 769, 668.

Dimethyl (1*R*,4*S*,5*S*)-4-hexyl-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate (41o)



Following the general procedure, treatment of 5-acetyl-3,3-bis(methoxycarbonyl)undecanoic acid **40o** (86.1 mg, 0.25 mmol) with triazolium salt **M** (14.0 mg, 0.0375 mmol), HATU (142.0 mg, 0.375mmol), Cs_2CO_3 (122.0 mg, 0.375 mmol), and LiCl (5.3 mg, 0.25mmol) in CH_2Cl_2 (4.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded dimethyl (1*R*,4*S*,5*S*)-4-hexyl-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41o** as a colourless oil (61.0 mg, 75% yield, *dr* 2:1).

R_f (Pet. ether /EtOAc = 70/30): 0.65.

HPLC (Chiralcel OD-RH, 50:50 Acetonitrile: H_2O, 0.5 mL/min, 220 nm wavelength.) Major: 22.8 min, Minor: 25.3 min. er = 94:6, $[\alpha]_D^{25}$ = +33.81 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 1H)**,** 3.78-3.76 (m, 6H), 2.52-2.43 (m, 1H), 2.33-2.27 (m, 1H), 1.84-1.76 (m, 1H), 1.67 (s, 3H), 1.41-1.27 (m, 10H), 0.89-0.86 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.63, 167.85, 167.29, 88.18, 64.03, 58.83, 53.55, 53.22, 44.47, 37.05, 31.77, 29.56, 28.25, 27.58, 22.68, 20.24, 14.17.

Representative peak for minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 1.66 (s, 3H).

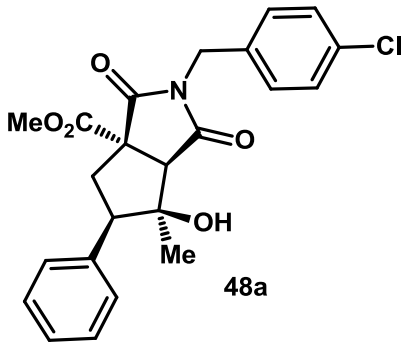
^{13}C NMR (100 MHz, $CDCl_3$) 171.25, 167.63, 90.32, 63.91, 60.41, 55.52, 53.40, 44.91, 34.96, 31.74, 29.30, 29.18, 27.95, 19.22.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{26}O_6Na$: 349.1622, found: 349.1610.

FTIR (cm^{-1}) 3022, 3021, 2957, 2931, 2859, 1818, 1735, 1675, 1459, 1436, 1270, 1216, 1135, 1104, 1049, 771, 668.

4.5.10. Synthesis and Characterization of Functionalized Succinimide Derivatives

Methyl (3*aS*,5*R*,6*S*,6*aR*)-2-(4-chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate (48a)



48a

Following the general procedure, treatment of dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41a** (48 mg, 0.15 mmol,) (>20:1 dr, 95:5 er) and (4-chlorophenyl)methanamine (0.073 ml, 0.6 mmol, 4.0 equiv) in THF (1.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded methyl (3*aS*,5*R*,6*S*,6*aR*)-2-(4-chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48a** as a white solid (64.0 mg, 99% yield, >20:1 *dr*).

R_f (Pet. ether /EtOAc = 70/30): 0.47.

HPLC (Chiralpak-IA, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 37.0 min, Minor: 49.0 min. er = 95:5, $[\alpha]_D^{25}$ = -37.55 (c 0.1, $CHCl_3$).

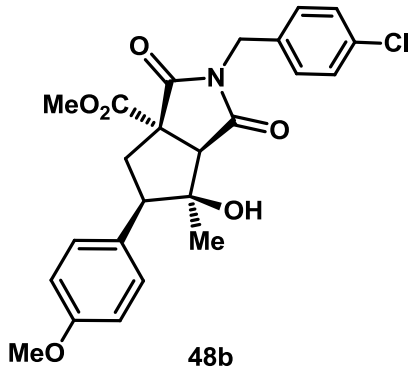
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 9H), 4.73 (d, J = 4.6 Hz, 1H), 4.64 (d, J = 4.6 Hz, 1H), 3.74 (s, 3H), 3.33 (s, 1H), 3.16 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 2.89-2.84 (m, 1H), 2.71 (t, J = 13.3 Hz, 1H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.32, 174.10, 170.64, 135.53, 134.07, 133.74, 129.76, 129.12, 128.96, 128.79, 128.74, 128.06, 80.88, 61.89, 59.23, 57.74, 53.61, 42.25, 34.36, 25.25.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{23}H_{22}O_5NClNa$: 450.1079, found: 450.1075.

FTIR (cm^{-1}) 3686, 3620, 3019, 2975, 2400, 1745, 1708, 1525, 1494, 1433, 1395, 1342, 1300, 1215, 1174, 1093, 1047, 928, 770, 669.

Methyl (3*aS*,5*R*,6*S*,6*aR*)-2-(4-chlorobenzyl)-6-hydroxy-5-(4-methoxyphenyl)-6-methyl-1,3-dioxohexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate (48b)



48b

Following the general procedure, treatment of dimethyl (1*R*,4*R*,5*S*)-4-(4-methoxyphenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41b** (35.0 mg, 0.10 mmol,) (>20:1 dr, 95:5. er) and (4-chlorophenyl)methanamine (0.049 ml, 0.4 mmol, 4.0 equiv) in THF (1.0 mL) and stirring the reaction mixture at 25°C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded methyl (3*aS*,5*R*,6*S*,6*aR*)-2-(4-chlorobenzyl)-6-hydroxy-5-(4-methoxyphenyl)-6-methyl-1,3-dioxohexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48b** as a white solid (45.0 mg, 98% yield, >20:1 *dr*).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.34.

HPLC (Chiralpak AD, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 31.6 min, Minor: 37.5 min. er = 94:6, $[\alpha]_D^{25}$ = -31.74 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.74 (d, *J* = 14.6 Hz, 1H), 4.64 (d, *J* = 14.6 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.33 (s, 1H), 3.13 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 2.85 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 2.66 (t, *J* = 13.3 Hz, 1H), 1.37 (s, 3H).

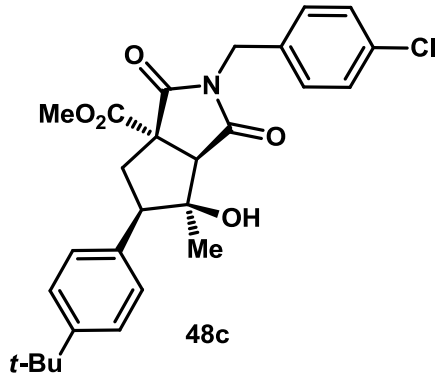
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.37, 174.18, 170.65, 159.38, 134.07, 133.69, 130.08, 129.73, 128.76, 127.40, 114.10, 80.73, 61.78, 59.14, 56.98, 55.39, 53.57, 42.21, 34.51, 25.18.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{24}H_{24}O_6NClNa$: 480.1184, found: 480.1191.

FTIR (cm^{-1}) 3019, 2973, 2400, 1745, 1708, 1612, 1514, 1493, 1434, 1395, 1343, 1301, 1249, 1215, 1181, 1092, 834, 755, 699.

Methyl (3*aS*,5*R*,6*S*,6*aR*)-5-(4-(*tert*-butyl)phenyl)-2-(4-chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxohexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate (48c)

Following the general procedure, treatment of dimethyl (1*R*,4*R*,5*S*)-4-(4-(*tert*-butyl)phenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41d** (37 mg, 0.10 mmol,) (>20:1 dr, 95:5 er) and (4-chlorophenyl)methanamine (0.049 ml, 0.4 mmol, 4.0 equiv) in THF (1.0 mL) and stirring the reaction mixture at 25°C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded methyl (3*aS*,5*R*,6*S*,6*aR*)-5-(4-(*tert*-



butyl)phenyl)-2-(4-chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxohexahydro cyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48c** as a white solid (41.0 mg, 84% yield, >20:1 *dr*).

***R**f* (Pet. ether /EtOAc = 70/30): 0.53.

HPLC (Chiralpak AD, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 9.8 min, Minor: 20.4 min. er = 94:6, $[\alpha]_D^{25}$ = -40.65 (c 0.1, $CHCl_3$).

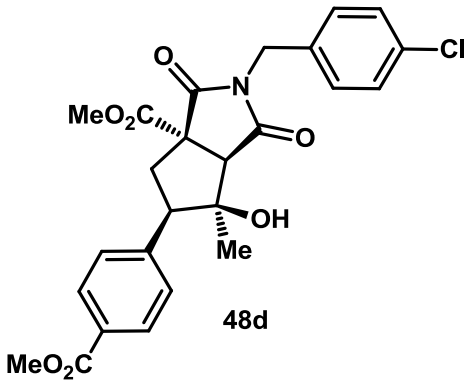
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.33-7.26 (m, 4H), 7.16 (d, *J* = 8.2 Hz, 2H), 4.73 (d, *J* = 14.6 Hz, 1H), 4.64 (d, *J* = 14.6 Hz, 1H), 3.74 (s, 3H), 3.32 (s, 1H), 3.15 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 2.85 (dd, J_1 = 13.2 Hz, J_2 = 6.9 Hz, 1H), 2.70 (t, *J* = 13.3 Hz, 1H), 1.38 (s, 3H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.40, 174.15, 170.68, 151.02, 134.10, 133.71, 132.34, 129.75, 128.77, 128.76, 125.69, 80.88, 61.87, 59.26, 57.30, 53.58, 42.25, 34.66, 34.32, 31.43, 25.27.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{27}H_{30}O_5NClNa$: 506.1705, found: 506.1718.

FTIR (cm^{-1}) 3682, 3621, 3019, 2972, 2400, 2349, 1745, 1708, 1604, 1515, 1477, 1431, 1395, 1217, 1046, 928, 772, 669.

Methyl (3a*S*,5*R*,6*S*,6a*R*)-2-(4-chlorobenzyl)-6-hydroxy-5-(4-(methoxycarbonyl)phenyl)-6-methyl-1,3-dioxohexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate (48d)



Following the general procedure, treatment of dimethyl (1*R*,4*R*,5*S*)-4-(4-(methoxycarbonyl)phenyl)-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41f** (38 mg, 0.10 mmol,) (>20:1 dr, 93:7 er) and (4-chlorophenyl)methanamine (0.049 ml, 0.4 mmol, 4.0 equiv) in THF (1.0 mL) and stirring the reaction mixture at 25°C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded methyl (3a*S*,5*R*,6*S*,6a*R*)-2-(4-chlorobenzyl)-6-hydroxy-5-(4-(methoxycarbonyl)phenyl)-6-methyl-1,3-dioxohexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48d** as a white solid (42.0 mg, 87% yield, >20:1 *dr*).

***R**f* (Pet. ether /EtOAc = 70/30): 0.24.

HPLC (Chiralpak AD, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 43.8 min, Minor: 37.5 min. er = 94:6, $[\alpha]_D^{25}$ = -27.33 (c 0.1, $CHCl_3$).

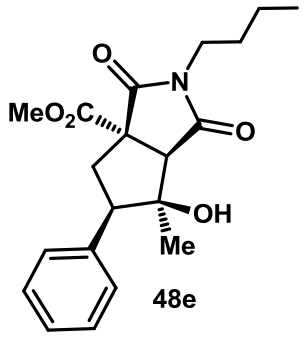
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.35-7.28 (m, 6H), 4.72 (d, *J* = 14.6 Hz, 1H), 4.65 (d, *J* = 14.6 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.35 (s, 1H), 3.20 (dd, *J* = 13.2, 6.7 Hz, 1H), 2.90 (dd, *J* = 13.2, 6.7 Hz, 1H), 2.73 (t, *J* = 13.2 Hz, 1H), 1.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.11, 173.99, 170.49, 166.90, 141.06, 133.98, 133.79, 129.76, 129.74, 129.30, 128.80, 81.01, 62.04, 59.19, 57.68, 53.65, 52.29, 42.27, 34.57, 25.18.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{25}H_{24}O_7NClNa$: 508.1134, found: 508.1144.

FTIR (cm^{-1}) 3020, 2956, 2400, 1745, 1709, 1612, 1528, 1493, 1436, 1396, 1343, 1268, 1174, 1145. 1114, 1093, 1018, 771, 669.

Methyl (3*aS*,5*R*,6*S*,6*aR*)-2-butyl-6-hydroxy-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate (48e)



48e

Following the general procedure, treatment of dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41a** (32 mg, 0.10 mmol,) (>20:1 dr, 95:5 er) and butan-1-amine (0.040 ml, 0.4 mmol, 4.0 equiv) in THF (1.0 mL) and stirring the reaction mixture at 32°C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded methyl (3*aS*,5*R*,6*S*,6*aR*)-2-butyl-6-hydroxy-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48e** as a white solid (35.0 mg, 97% yield, >20:1 *dr*).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.48.

HPLC (Chiralpak AD, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 7.9 min, Minor: 10.6 min. er = 93:7, $[\alpha]_D^{25}$ = -38.09 (c 0.1, $CHCl_3$).

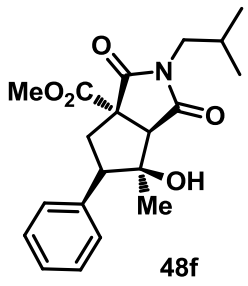
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 3.77 (s, 3H), 3.54 (t, *J* = 7.2 Hz, 2H), 3.30 (s, 1H), 3.14 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 2.86 (dd, J_1 = 13.3 Hz, J_2 = 6.8 Hz, 1H), 2.70 (t, *J* = 13.3 Hz, 1H), 1.61-1.56(m, 2H), 1.42 (s, 1H), 1.37-1.34 (m, 4H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.72, 174.59, 170.86, 135.73, 129.14, 128.62, 127.91, 80.61, 61.77, 59.05, 57.69, 53.53, 39.15, 34.48, 29.60, 25.29, 19.96, 13.75.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{25}O_5NNa$: 382.1625, found: 382.1625.

FTIR (cm^{-1}) 3020, 2961, 2875, 1778, 1744, 1702, 1453, 1438, 1401, 1379, 1361, 1347, 1294, 1155, 1114, 776, 703, 668.

Methyl (3*aS*,5*R*,6*S*,6*aR*)-6-hydroxy-2-isobutyl-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate (48f)



48f

Following the general procedure, treatment of dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41a** (32 mg, 0.10 mmol,) (>20:1 dr, 95:5 er) and 2-methylpropan-1-amine (0.040 ml, 0.4 mmol, 4.0 equiv) in THF (1.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded methyl (3*aS*,5*R*,6*S*,6*aR*)-6-hydroxy-2-isobutyl-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48f** as a white solid (28.0 mg, 78% yield, >20:1 *dr*).

R_f (Pet. ether /EtOAc = 70/30): 0.47.

HPLC (Chiralpak AD, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 13.3 min, Minor: 18.0 min. er = 94:6, $[\alpha]_D^{25}$ = -47.52 (c 0.1, $CHCl_3$).

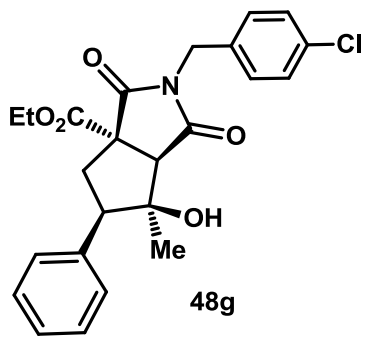
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 3H), 7.23-7.21 (m, 2H), 3.75 (s, 3H), 3.34 (dd, J_1 = 7.3 Hz, J_2 = 2.2 Hz, 2H), 3.28 (s, 1H), 3.12 (dd, J_1 = 13.3 Hz, J_2 = 6.7 Hz, 1H), 2.85 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 2.67 (t, J = 13.3 Hz, 1H), 2.10-2.01 (m, 1H), 1.35 (s, 3H), 0.90 (d, J = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.94, 174.78, 170.88, 135.73, 129.15, 128.65, 127.94, 80.60, 61.76, 59.03, 57.72, 53.51, 46.63, 34.48, 27.21, 25.39, 20.09, 20.05.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{25}O_5NNa$: 382.1625, found: 382.1628.

FTIR (cm^{-1}) 3589, 3019, 2964, 2935, 2874, 1744, 1703, 1452, 1436, 1402, 1388, 1349, 1326, 1297, 1217, 1050, 772, 704, 669.

Ethyl (3*aS*,5*R*,6*S*,6*aR*)-2-(4-chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate (48g)



48g

Following the general procedure, treatment of diethyl 5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41i** (35 mg, 0.10 mmol,) (>20:1 dr, 94:6 er) and (4-chlorophenyl)methanamine (0.049 ml, 0.4 mmol, 4.0 equiv) in THF (1.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (EtOAc-Pet. ether 30:70) afforded ethyl (3*aS*,5*R*,6*S*,6*aR*)-2-(4-

chlorobenzyl)-6-hydroxy-6-methyl-1,3-dioxo-5-phenylhexahydrocyclopenta[*c*]pyrrole-3a(1*H*)-carboxylate **48g** as a white solid (29.0 mg, 66% yield, >20:1 *dr*).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.48.

HPLC (Chiralpak-IA, 90:10 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 14.3 min, Minor: 17.4 min. er = 92:8, $[\alpha]_D^{25}$ = -48.90 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 9H), 4.73 (d, *J* = 14.6 Hz, 1H), 4.66 (d, *J* = 14.6 Hz, 1H), 4.25-4.12 (m, 2H), 3.32 (s, 1H), 3.17 (dd, J_1 = 13.2 Hz, J_1 = 6.8 Hz, 1H), 2.89 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H), 2.71 (t, *J* = 13.3 Hz, 1H), 1.39 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

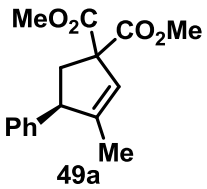
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.43, 174.22, 170.08, 135.61, 134.13, 133.71, 129.78, 129.13, 128.75, 128.69, 128.00, 80.83, 62.74, 61.97, 59.27, 57.74, 42.12, 34.11, 25.21, 13.95.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{24}H_{24}O_5NClNa$: 464.1235, found: 464.1253.

FTIR (cm^{-1}) 3683, 3621, 3019, 2976, 2400, 2349, 1741, 1708, 1524, 1494, 1477, 1428, 1396, 1342, 1215, 147, 928, 849, 769, 669.

Decarboxylation of 41a

Dimethyl (*S*)-3-methyl-4-phenylcyclopent-2-ene-1,1-dicarboxylate (49a)



49a

An oven dried round bottomed flask was charged with dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41a** (48 mg, 0.15 mmol,) (>20:1 dr, 95:5 er) and 300 mg of silica in toluene (3.0 mL). The reaction mixture was heated at 60 °C for 6 h under argon atmosphere. Upon consumption of the starting material **41a** (TLC), the crude reaction mixture was passed through celite and concentrated under reduced pressure to get a sufficiently pure dimethyl (*S*)-3-methyl-4-phenylcyclopent-2-ene-1,1-dicarboxylate **49a** as a colorless oil (39 mg, 95% yield).

***R*$_f$** (Pet. ether /EtOAc = 70/30): 0.75.

HPLC (Chiralpak IA, 99:1 Hexane / IPA, 0.5 mL/min, 220 nm wavelength.) Major: 13.1 min, Minor: 14.9 min. er = 93:7, $[\alpha]_D^{25}$ = -123.84 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 2H), 5.66 (s, 1H), 3.86 (t, *J* = 7.7 Hz, 1H), 3.75 (s, 6H), 3.14 (dd, J_1 = 14.0 Hz, J_2 =8.5 Hz, 1H), 2.30 (dd, J_1 = 14.0 Hz, J_1 = 7.1 Hz, 1H), 1.55 (s, 3H).

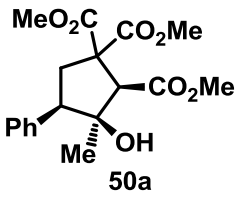
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.36, 171.91, 148.45, 143.31, 128.72, 128.04, 126.78, 124.28, 65.48, 54.31, 52.87, 52.79, 42.20, 15.28.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{16}H_{18}O_4Na$: 297.1097, found: 297.1095.

FTIR (cm^{-1}) 3063, 3025, 2954, 2916, 1724, 1493, 1436, 1276, 1215, 1171, 1132, 1081, 1061, 1033, 1010, 842, 772, 703, 688.

Ring Opening of 41a

Trimethyl (2*R*,3*S*,4*R*)-3-hydroxy-3-methyl-4-phenylcyclopentane-1,1,2-tricarboxylate (50a)



50a

An oven dried round bottomed flask was charged with dimethyl (1*R*,4*R*,5*S*)-5-methyl-7-oxo-4-phenyl-6-oxabicyclo[3.2.0]heptane-2,2-dicarboxylate **41a** (48 mg, 0.15 mmol,) (>20:1 dr, 95:5 er) and 1.0 ml of Et_3N in methanol (1.0 mL). The reaction mixture was stirred at 25 °C for 24 h under argon atmosphere. Evaporation of the solvent followed by silica gel flash column chromatography afforded trimethyl 3-hydroxy-3-methyl-4-phenylcyclopentane-1,1,2-tricarboxylate **50a** as a colorless oil (50 mg, 95% yield, >20:1 *dr*).

R$_f$ (Pet. ether /EtOAc =70/30): 0.36.

HPLC (Chiralpak-IA, 95:5 Hexane / IPA, 1.0 mL/min, 220 nm wavelength.) Major: 24.9 min, Minor: 19.4 min. er = 94:6, $[\alpha]_D^{25}$ = +12.40 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 3.78 – 3.74 (m, 9H), 3.60 (s, 1H), 3.44 (s, 1H), 3.28 – 3.22 (m, 1H), 2.90 (dd, J_1 = 11.8 Hz, J_2 = 8.6 Hz, 1H), 2.49 (dd, J_1 = 13.7 Hz, J_2 = 8.4 Hz, 1H), 1.25 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.80, 172.52, 171.05, 137.01, 129.81, 128.16, 127.37, 80.03, 60.86, 59.65, 54.47, 53.51, 53.24, 52.21, 39.46, 24.55.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{22}O_7Na$: 373.1258, found: 373.1253.

FTIR (cm^{-1}) 3522, 3020, 2955, 2846, 1733, 1497, 1454, 1436, 1375, 1269, 1217, 1177, 1103, 1055, 1019, 886, 771, 702, 668.

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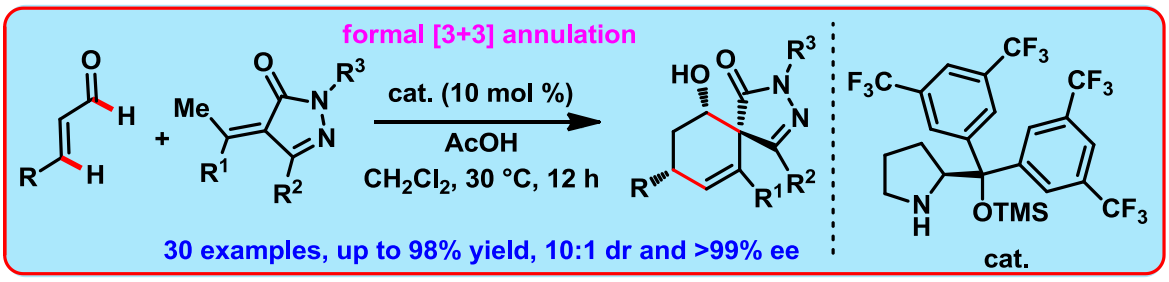
Chapter 5

Organocatalytic Enantioselective Vinylogous Michael-Aldol Cascade for the Synthesis of Spirocyclic Compounds

The focal theme of this chapter is the secondary amine-catalyzed cascade reaction of α,β-unsaturated aldehydes with α-arylidene pyrazolinones for the enantioselective synthesis of pyrazolone-fused spirocyclohexenols. This formal [3+3] organocascade reaction proceeds through a vinylogous Michael/aldol sequence to furnish the spiroheterocycles with three stereocentres including an all-carbon quaternary centre in good yields and selectivities. The catalytic generation of α,β-unsaturated iminium from enals and tandem dienolate/enolate formation from pyrazolinones are the key for the success of this spiroannulation reaction.

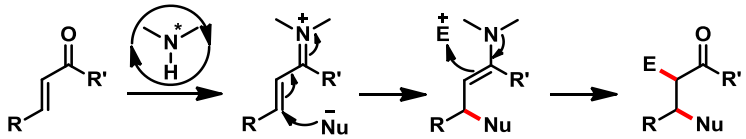


Org. Lett. **2017**, *19*, 4367−4370.

5.1. Introduction

Organocatalytic cascade or domino reaction is one of the fast-growing fields in asymmetric catalysis for the construction of complex chiral molecular architectures from simple starting materials with high yields and selectivity in a metal-free environment.[1] These processes are challenging and have several advantages from economic and environmental points of view, by avoiding costly protecting groups and time-consuming purification procedures after each step.[2] Tietze has defined a domino/cascade reaction as a reaction involving two or more bond-forming transformations, which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.[3] In many of the secondary amine-catalyzed cascade reactions, a catalytically generated α,β-unsaturated iminium ion formed from α,β–unsaturated aldehyde or ketone and the chiral catalyst will be intercepted at the β-position by a nucleophile followed by the subsequent addition of electrophile at the α-position (Scheme 5.1).[4] A detailed discussion on various secondary amine-catalyzed cascade reactions are described in the following sections.

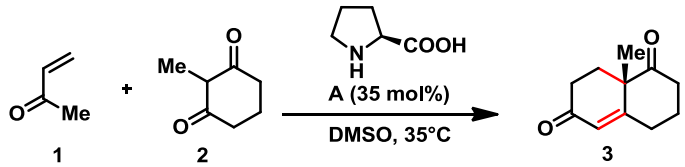
Scheme 5.1: Organocascade via the Iminium Ion/Enamine Activation Mode



5.1.1 Organocatalytic Enantioselective Michael-Aldol Cascade

Although, enantioselective Michael and aldol reaction using proline based secondary amine catalyst was developed in early 1970s,[5] but it was in 2000, Barbas and co-workers introduced the first asymmetric Michael/aldol condensation cascade for Robinson annulation reaction (Scheme 5.2).[6] The reaction between vinyl ketone **1** and 2-methylcyclohexane-1,3-dione **2** in presence of L-proline **A**, led to the formation of the condensation product **3,** which was isolated in 49% yield and 76% enantiomeric excess.

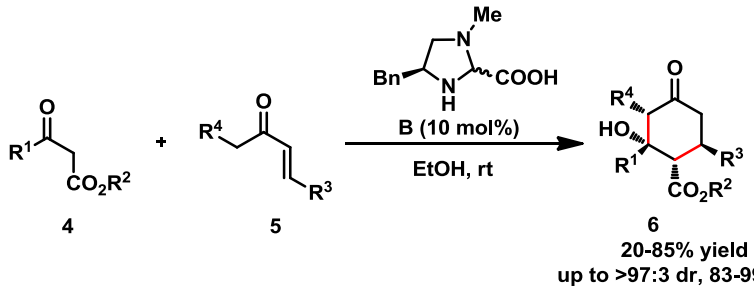
Scheme 5.2: Organocatalyzed Robinson Annulation



In 2004, Jørgensen and co-workers developed the highly general enantio- and diastereoselective organocatalytic Michael/aldol cascade reaction (Scheme 5.3).[7] Optically

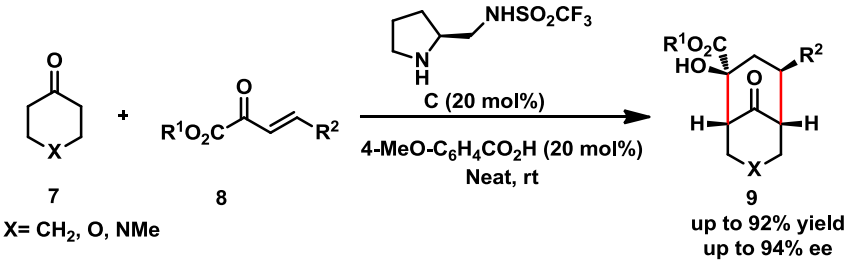
active cyclohexanone derivatives **6** with up to four stereogenic centers were obtained in excellent enantioselectivity by the reaction of β-ketoesters **4** and α,β-unsaturated ketones **5**. Protic solvents gave the best results in terms of both yield and stereoselectivity. Interestingly, no chromatography was required and the optically active cyclohexanone **6** was obtained as a single diastereomer by simple filtration and washing.

Scheme 5.3: Enantiselective Michael/Aldol Cascade Reaction



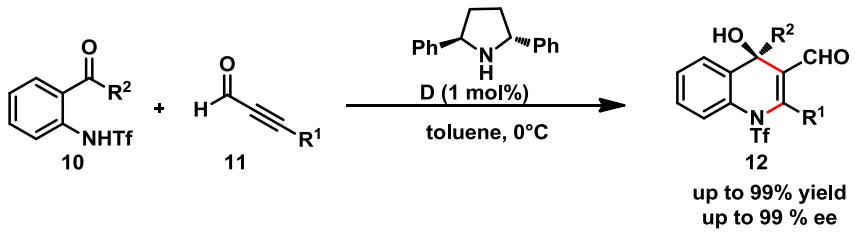
An enantioselective formal [3+3] annulation reaction proceeding via Michael/aldol cascade was described by Tang and co-workers (Scheme 5.4).[8] The reaction of cyclic ketones **7** with β,γ-unsaturated keto ester **8** afforded the bicyclic compound **9** having four stereogenic centers in excellent enantioselectivity under mild reaction condition. Notably, the reaction generates two new C−C bonds and four new stereogenic centers.

Scheme 5.4: Michael/Aldol Cascade for the Construction of Bicyclic Skeletons



In 2012, Wang and co-workers disclosed an enantioselective synthesis of dihydroquinoline through an aza-Michael/aldol cascade reaction (Scheme 5.5).[9] In the presence of secondary amine catalyst **D**, a wide variety of ynal **11** and 2'-(trifluoromethanesulfonyl)amino ketones **10** were tolerated under the reaction condition and

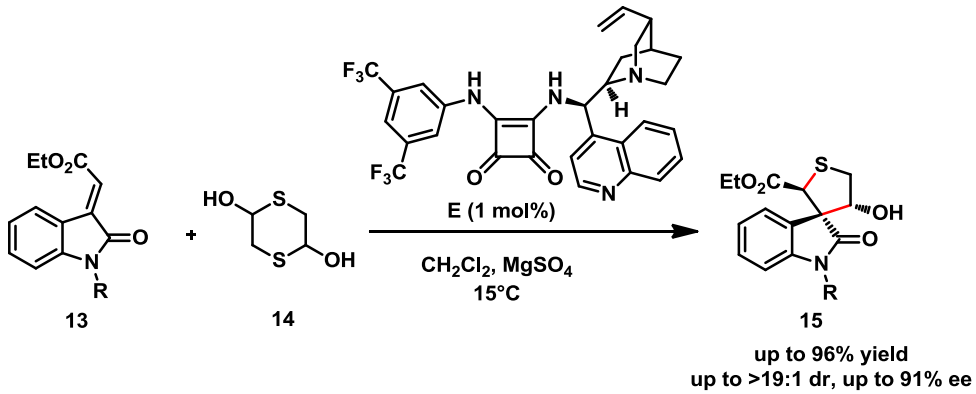
Scheme 5.5: Enantioselective Organocatalytic Aza-Michael/Aldol Cascade Reaction



the desired product **12** was formed in excellent yield and enentiselectivity. Also, the authors have found that the outcome of the reaction depends upon the sulfonyl protecting group. Electron-donating aryl sulfonamides facilitate the dehydration-aromatization of the aza-Michael/aldol adducts to give quinolines. However, when the strongly electron-withdrawing Tf group is used, chiral 1,4-dihydroquinolines are obtained.

At the same time, the Xiao group demonstrated an efficient organocatalytic Michael-aldol cascade for the construction of enantioenriched spirocyclic oxindoles fused with tetrahydrothiophenes **15** (Scheme 5.6).[10] Employing squaramide-based H-bonding catalyst **E**, the organocascade between 3-ylideneoxindoles **13** and 1,4-dithiane-2,5-diol **14** provided an easy access to a new family of tetrahydrothiophene-fused spirooxindoles **15** bearing three consecutive stereocenters with one all-carbon quarternary stereocentre. Moreover, organocascade reactions involving Michael-aldol sequence were reported by several other research groups.[11]

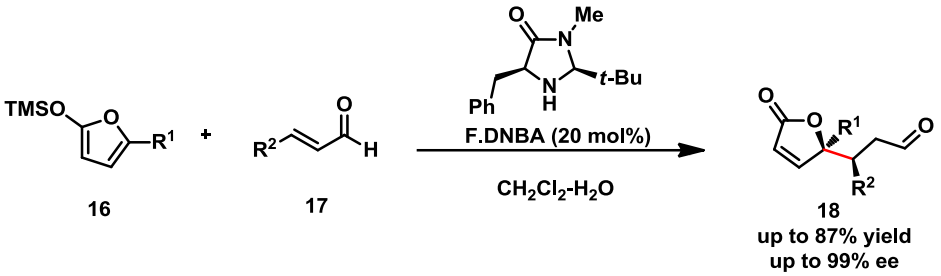
Scheme 5.6: Enantioselective Michael-Aldol Cascade for the Synthesis of Spirocyclic Compounds



5.1.2 Organocatalytic Enantioselective Vinylogous Michael Reaction

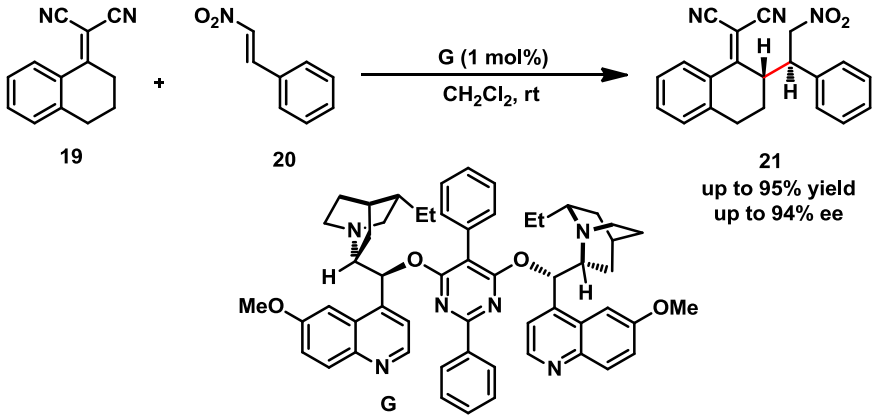
The vinylogous reactivity in an organocascade process is growing as an essential tool for remote C-H functionalization.[12] This can be achieved either by the use of vinylogous enolate-type nucleophile or by generation of catalyst-bound vinylogous enamine intermediates (dienamines).[13] In 2003, the Macmillan research group developed the enantioselective organocatalytic Mukaiyama-Michael reaction of silyloxy furan **16** with α,β-unsaturated aldehydes **17** (Scheme 5.7).[14] Employing the secondary amine catalyst **F**, the vinylogous Michael reaction furnished the γ-butenolide product **18** in good to excellent yield and enantioselectivity. The use of inexpensive bench stable catalyst, aerobic reaction environment and less sensitive reaction condition are the noteworthy features of this transformation.

Scheme 5.7: Organocatalyzed Mukaiyama-Michael Reaction



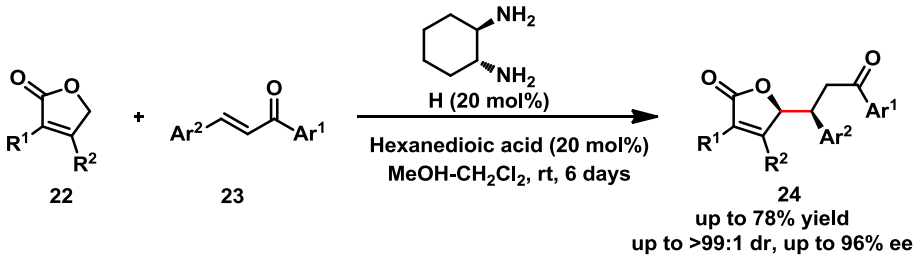
An asymmetric direct vinylogous Michael reaction between electron-deficient vinyl malononitriles **19** and nitroolefins **20** was reported by Deng and co-workers (Scheme 5.8).[15] The exclusive γ-selective Michael reaction afforded the expected product **21** containing two vicinal chiral centers in high yield and stereoselectivity.

Scheme 5.8: Enantioselective Vinylogous Michael Addition of Vinyl Malononitriles



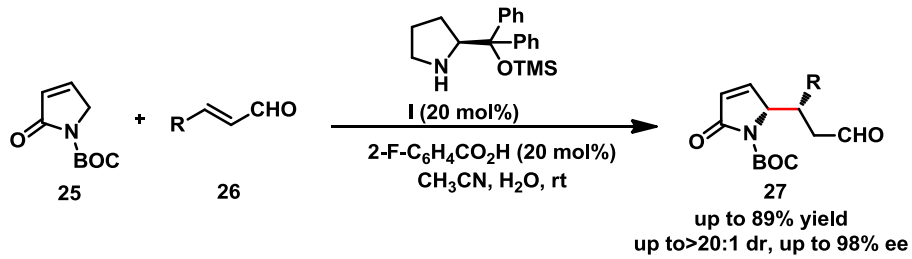
In 2010, Li and co-workers introduced γ-butenolides **22** for the first time in organocatalytic vinylogous Michael reaction with chalcones **23** (Scheme 5.9).[16] Using chiral 1,2-diaminocyclohexane as a novel organocatalyst, the desired Michael product **24** were formed in good yields and high stereoselectivities. Based on the background literature, the authors proposed that chalcones were activated by the catalyst via the di-iminium transition state which in turn led to the *syn* selective Michael product.

Scheme 5.9: Asymmetric Vinylogous Michael Reactions of γ-Butenolides



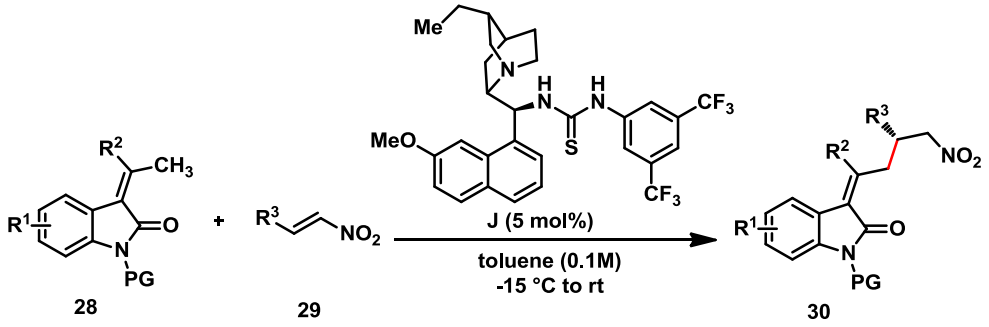
Subsequently, Chen and co-workers employed N-Boc α,β-unsaturated γ-butyrolactam **25** as a vinylogous Michael donor to α,β-unsaturated aldehydes **26** for the enantioselective synthesis of 5-substituted γ-butyrolactam **27** (Scheme 5.10).[17] A wide variety of electronically different cinnamaldehyde derivatives as well as heteroaromatic enals and aliphatic enals were well tolerated and the corresponding product was formed in moderate to good yield and diastereoselectivity with excellent enantioselectivity. Moreover, the authors have demonstrated the synthetic utility of this methodology by preparing some enantioenriched drug like scaffolds.

Scheme 5.10: Asymmetric Vinylogous Michael Reactions of γ-Butyrolactam



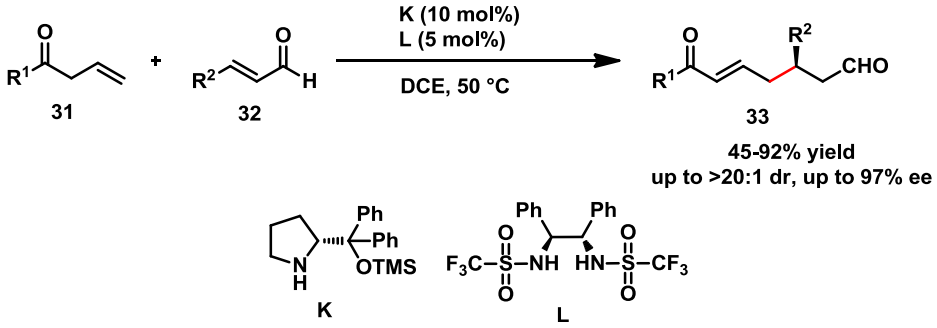
In 2012, Casiraghi and co-workers explored 3-alkylidene oxindoles **28** as vinylogous carbon nucleophiles for asymmetric vinylogous Michael reaction with nitroolefins **29** (Scheme 5.11).[18] Using bifunctional cinchona alkaloid-thiourea catalyst **J**, enantiopure γ-substituted 3-alkylidene oxindoles **30** are formed in excellent yields and stereoselectivities.

Scheme 5.11: Asymmetric Vinylogous Michael Reactions of 3-Alkylidene Oxindoles



Recently, Xu and co-workers disclosed an unprecedented vinylogous Michael reaction of linear enones **31** with α,β-unsaturated aldehydes **32** (Scheme 5.12).[19] This type of linear enones in vinylogous Michael reaction are very challenging due to the poor reactivity and the considerable difficulty in controlling the regioselectivity. By employing a well-designed multifunctional supramolecular iminium catalysis strategy, the direct vinylogous Michael addition affords chiral 1,7-dioxo compounds **33** with good yields and excellent regio- as well as enantioselectivity. Moreover, the organocatalyzed vinylogous Michael reaction was extensively studied by several other research group.[20]

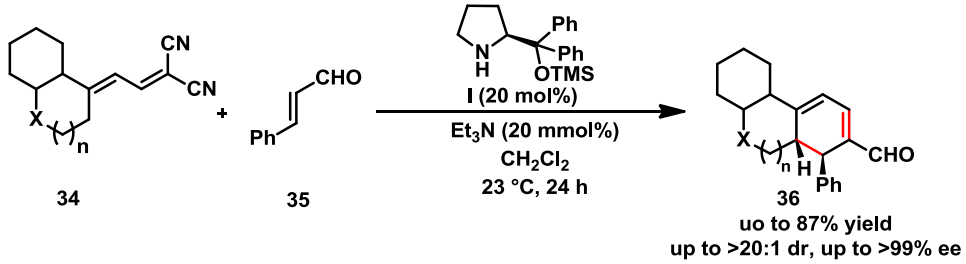
Scheme 5.12: Asymmetric Vinylogous Michael Reactions of Linear Enones



5.1.3 Organocatalytic Enantioselective Vinylogous Michael Involving Cascade Reaction

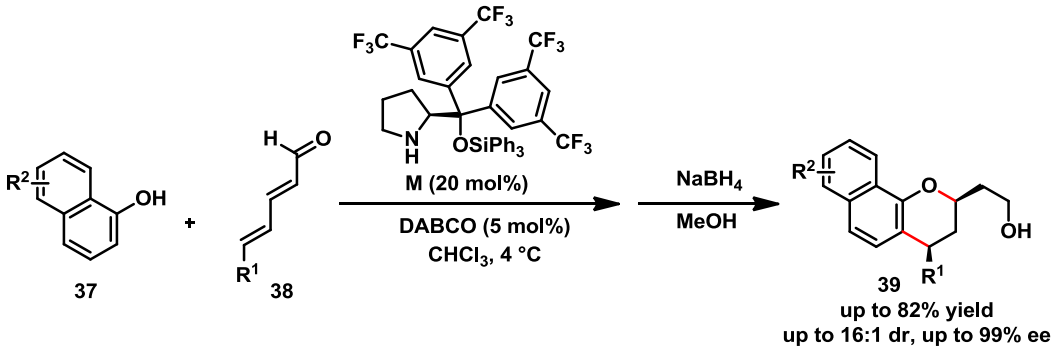
Organocatalytic vinylogous Michael-cascade reactions have drawn remarkable attention because of their multiple bond forming ability in an operationally simple procedure.[1] In 2015, Zanardi and co-workers developed a bisvinylogous Michael/Michael/retro-Michael cascade reaction for the asymmetric synthesis of highly substituted polycyclic carbaldehydes **36** (Scheme 5.13).[21] They used remotely enolizable π-extended allylidenemalononitriles **34** as electron-rich 1,3-diene precursors and α,β-unsaturated iminium ion as a dienophile in presence of prolinol catalyst **I**. The direct eliminative [4+2] cycloaddition reaction affords the desired product in moderate to good yields and excellent level of chemo-, regio-, diastereo-, and enantioselectivity.

Scheme 5.13: Secondary Amine-Catalyzed Vinylogous Asymmetric [4+2] Cycloaddition Reaction



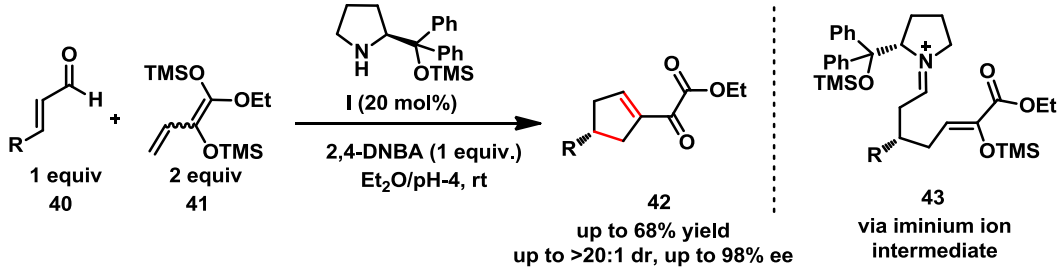
Subsequently, an asymmetric organocatalytic 1,6-addition/1,4-addition cascade reaction to 2,4-dienal **38** was described by Jørgensen and co-workers (Scheme 5.14).[22] The reaction proceeds via the 1,6-Friedel-Crafts addition of hydroxyarene **37** to 2,4-dienal **38** followed by 1,4-oxa-Michael to furnish the chromans product **39** out of four possible regioisomer in high yield and stereoselectivity. The authors proposed the mechanism based on computational study and showed an excellent synthetic transformation for the formation of an optically active macrocyclic lactam.

Scheme 5.14: Organocatalytic Asymmetric 1,6-Friedel-Crafts/1,4-Oxa-Michael Cascade Reaction



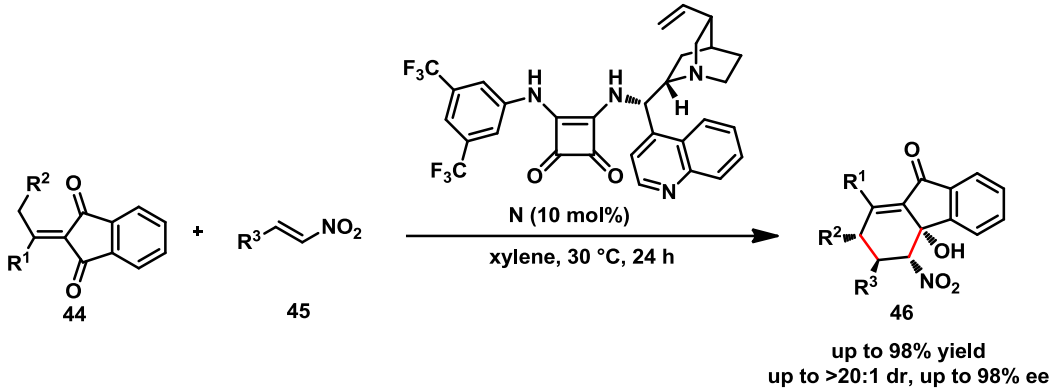
Schneider and co-workers reported an enantioselective secondary amine-catalyzed synthesis of 1-cyclopentenyl-α-keto esters **42** via a vinylogous Michael-intramolecular Knoevenagel-type cascade reaction (Scheme 5.15).[23] The use of a simple bis-silyl-1,3-dienediolate **41** as a vinylogous Michael donor and their interception with α,β-unsaturated aldehyde **40** afforded the cyclopentene derivatives in moderate to good yield and high stereoselectivity.

Scheme 5.15: Organocatalytic Asymmetric Vinylogous Michael-Intramolecular Knoevenagel- Cascade



Recently, Lin and co-workers showed an organocatalytic enantioselective vinylogous Michael addition/Henry cyclization cascade reaction for the synthesis of highly substituted tetrahydrofluoren-9-ones **46** (Scheme 5.16).[24] Employing 1,3-indandione derived vinylogous Michael donor **44** to nitroalkene **45**, the expected product **46** was formed with four contiguous stereocentre in good to excellent yields and stereoselectivity. Also, organocatalytic enantioselective vinylogous Michael-cascade reaction was developed by several other groups.[25]

Scheme 5.16: Organocatalytic Vinylogous Michael /Henry Cascade



5.2. Statement of the Problem

As discussed in the previous section, the vinylogous Michael reaction has been developed widely, but organocascade reaction involving vinylogous Michael is very limited. Moreover, the vinylogous Michael/aldol cascade reaction involving the tandem generation of dienolate and enolate from same substrate is not known to the best of our knowledge. We have recently employed α-arylidene pyrazolinones as bisnucleophiles for the tandem generation of dienolate/enolate under basic conditions and the subsequent interception with chiral α,β-unsaturated acylazoliums generated under oxidative N-heterocyclic carbene catalysis.[26] These reactions afforded spirocyclohexadienones in good yields and high ee values. Inspired by this work, we envisioned that the tandem dienolate/enolate generated from α-arylidene pyrazolinones[27] could be intercepted with catalytically generated α,β-unsaturated iminiums, and if successful, this could result in the synthesis of spirocyclohexenols with multiple stereocentres. A detailed account for the reaction of α-arylidene pyrazolinones with α,β-unsaturated aldehyde in presence of chiral secondary amine catalyst for the enantioselective synthesis of spirocyclohexenols is described in the following sections.

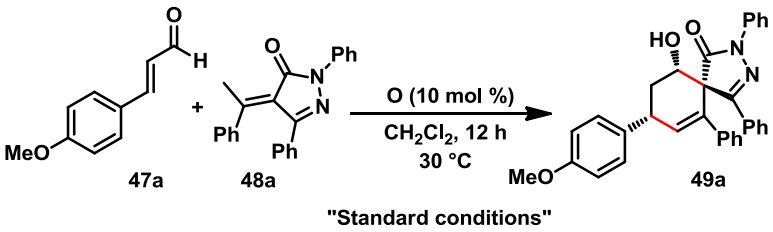
5.3. Results and Discussion

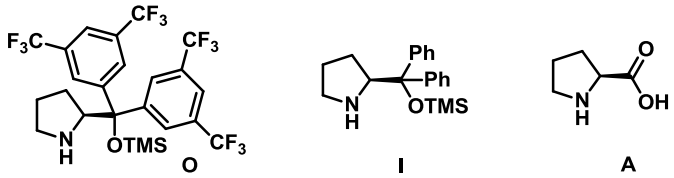
5.3.1. Optimization Studies

The present studies were initiated by treating 3-(4-methoxyphenyl)propenal **47a** with α-arylidene pyrazolinone **48a** in the presence of the secondary amine catalyst **O**[28] in CH_2Cl_2 at 30 °C. Interestingly, under these conditions, the spirocyclohexenol **49a** was formed in 23%

yield and 5:1 dr and 94% ee (Table 5.1, entry 1). With this initial result, the optimization of reaction conditions for this spiroannulation was undertaken. Compared to the catalyst **O**, the use of TMS-protected diphenyl prolinol **I** and L-proline **A** showed better reactivity but very poor enantioselectivity (entries 2-3). A rapid solvent screening indicated that CH_3CN and $CHCl_3$ resulted in comparable results (entries 4-5), but the reaction returned only traces of **49a** when performed in 1,4-dioxane (entry 6). In order to improve the reactivity and selectivity of this organocascade reaction, we envisaged to use various Brønsted acid additives. Notably, the use of 1.0 equiv BzOH as additive improved the yield to 89% and ee to 97% maintaining the 5:1 dr (entry 7). The use of trifluoroacetic acid (TFA) was not helpful in this spiroannulation (entry 8). The use of 1.0 equiv AcOH as additive slightly improved the dr and ee (entry 9). Finally, with the use of 5.0 equiv of AcOH, the spirocompound **49a** was isolated in 94% yield, 10:1 dr and 98% ee (entry 10).

Table 5.1. Optimization of the Reaction Conditions



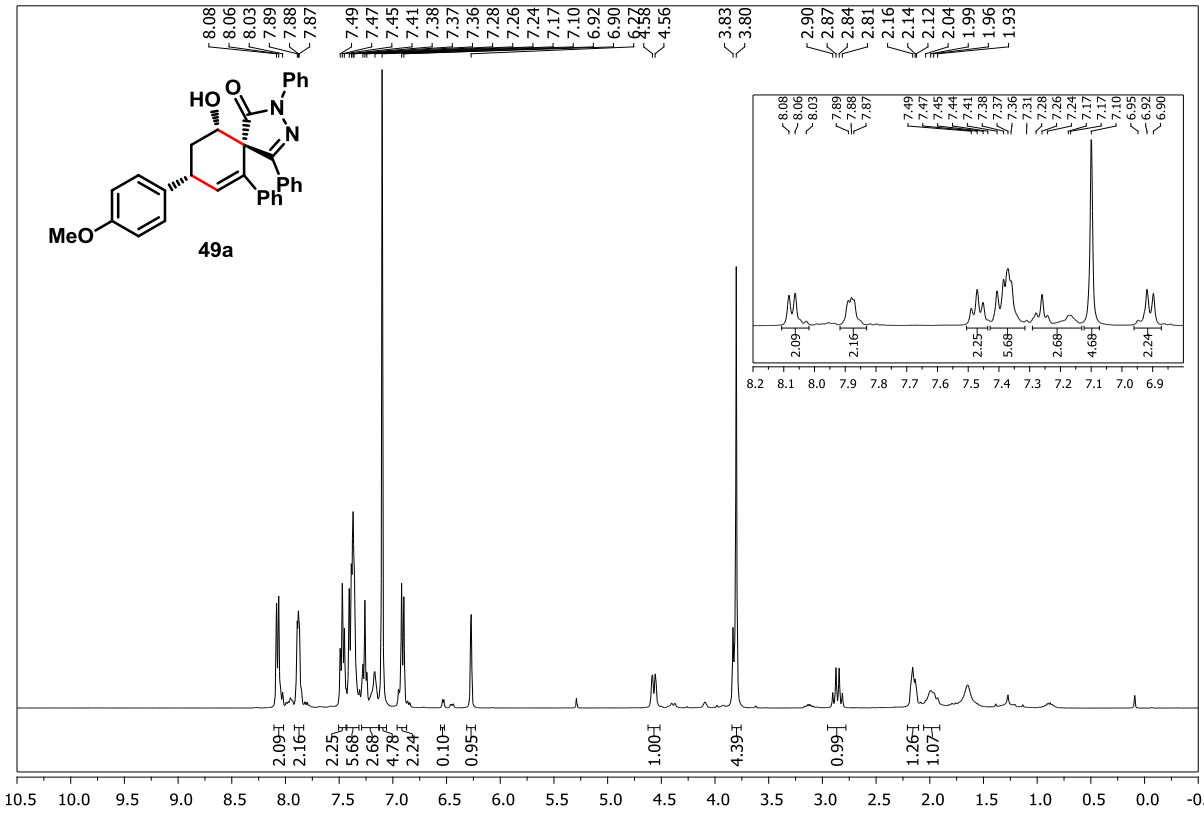


entry	variation of the standard conditions[a]	yield **49a** (%)[b]	dr of **49a** [c]	ee **49a** (%)[d]
1	none	23	5:1	94
2	5 instead of 4	82	5:1	40
3	6 instead of 4	46	6:1	00
4	CH_3CN instead of CH_2Cl_2	26	5:1	84
5	$CHCl_3$ instead of CH_2Cl_2	25	5:1	94
6	1,4-dioxane instead of CH_2Cl_2	<5	n.d.	n.d.
7	1.0 equiv of BzOH additive	89	5:1	97
8	1.0 equiv of TFA additive	<5	n.d.	n.d.
9	1.0 equiv of AcOH additive	82	6:1	98
10	5.0 equiv of AcOH additive	94	10:1	98

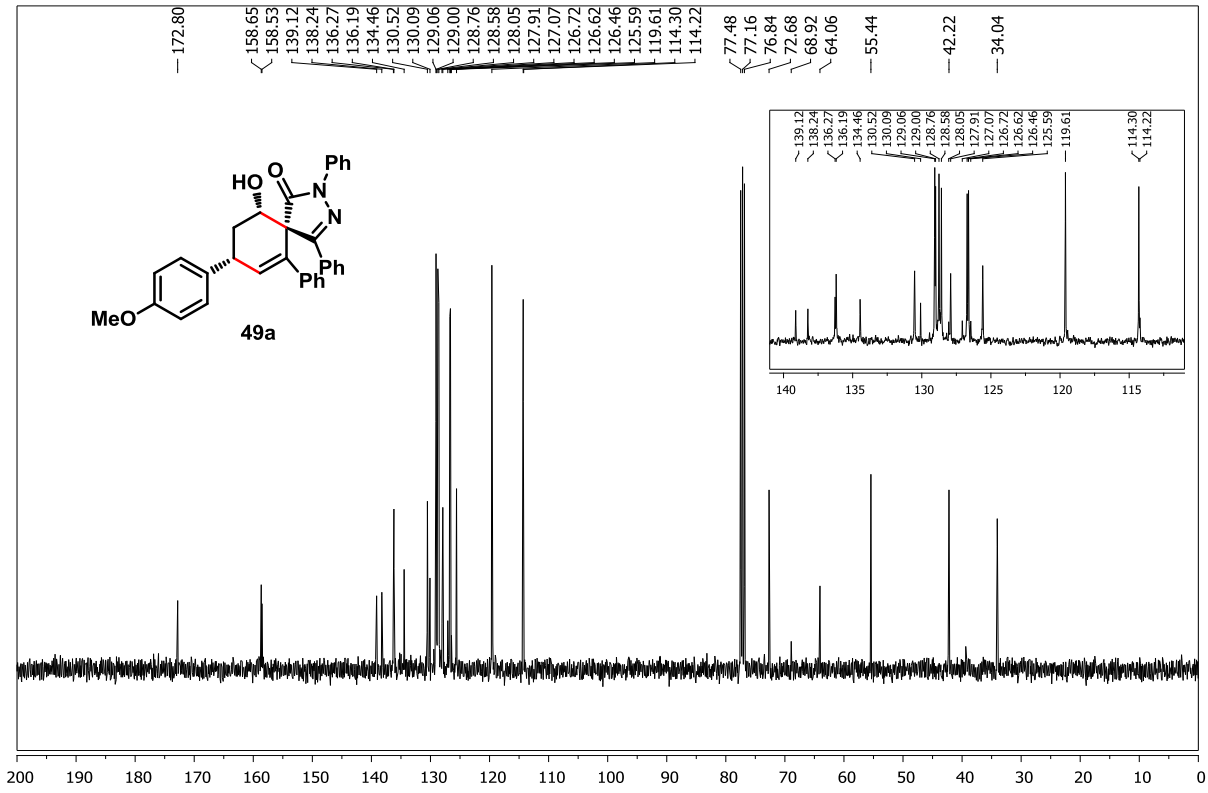
[a]Standard conditions: **47a** (0.10 mmol), **48a** (0.10 mmol), **O** (10 mol %), CH_2Cl_2 (1.5 mL), 30 °C and 12 h. [b]The yields were determined by ^{1}H NMR analysis of crude product using CH_2Br_2 as the internal standard. [c]Ratio determined by ^{1}H NMR spectroscopy prior to purification. [d]Determined by HPLC analysis on a chiral column.

5.3.2. Spectral Data of 49a

^{1}H NMR Spectrum of 49a ($CDCl_3$)

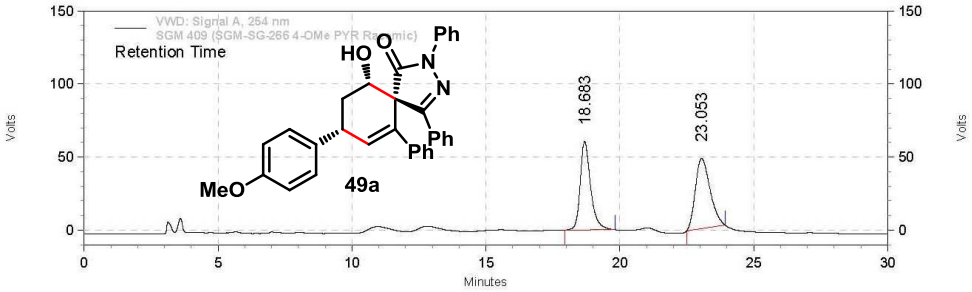


^{13}C NMR Spectrum of 49a ($CDCl_3$)



HPLC Chromatogram of Racemic- 49a

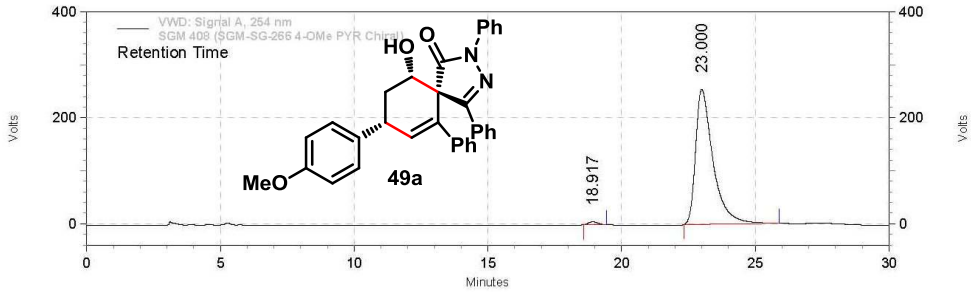
Data File: D:\BIJU\SGM\FINAL\Raw file\SGM 409 (SGM-SG-266 4-OMe PYR Racemic).dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\cvr1 2.met
Acquired: 10/4/2016 12:53:21 AM Printed: 10/13/2016 8:03:25 PM



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %
18.683	27547143	47.33
23.053	30657267	52.67
Totals	58204410	100.00

HPLC Chromatogram of Enantiomerically Pure-49a



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %
18.917	2249686	1.15
23.000	193211348	98.85
Totals	195461034	100.00

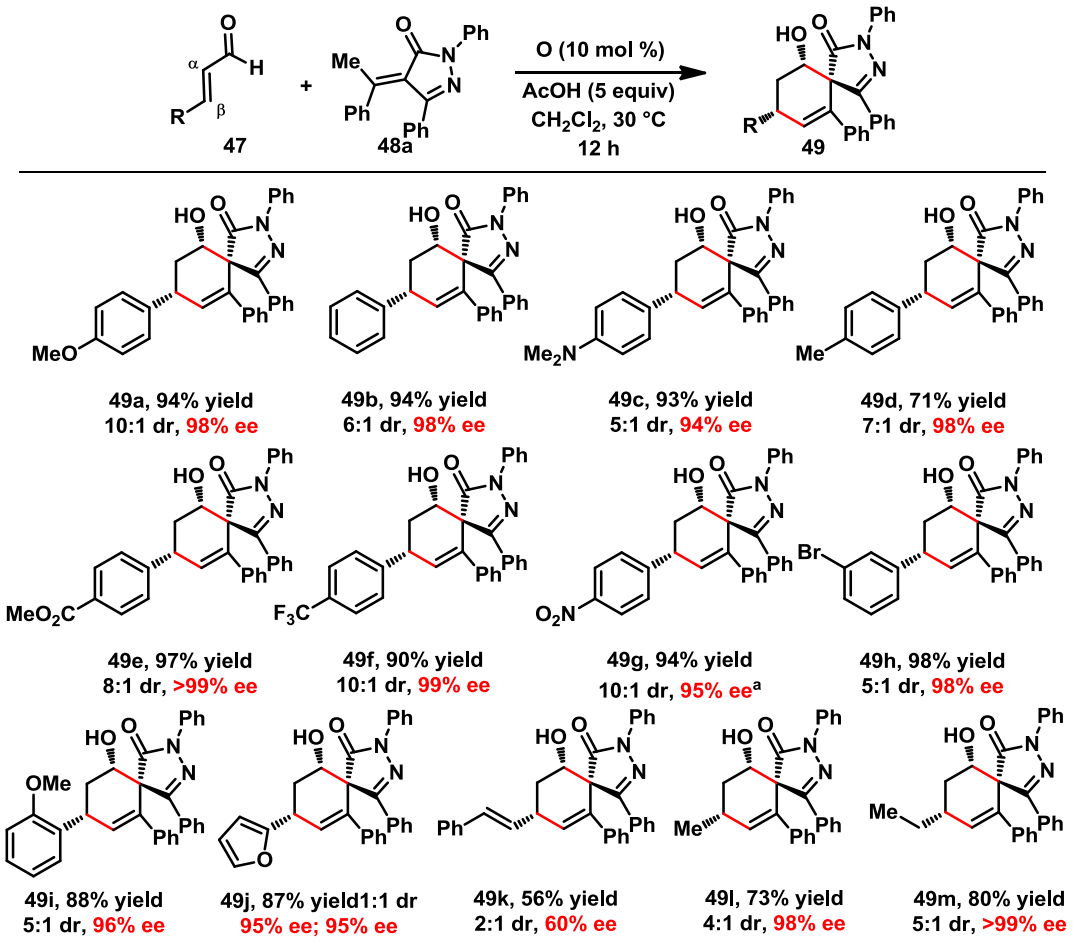
Column : Chiralpak IB
Eluent System : 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol..: 10ul
Wavelength: 254 nm

5.3.3. Enantioselective Synthesis of Spirocyclohexenols from α,β-Unsaturated Enals

The substrate scope of the reaction with respect to the various α,β-unsaturated aldehydes was explored using α-arylidene pyrazolinone **48a** as a reacting partner (Scheme 5.17). The unsubstituted enal worked well (**49b**) and a series of enals with electron- donating and -withdrawing groups at the 4-position of the β-aryl ring underwent smooth annulation under secondary amine catalysis, and in all cases, the pyrazolone-fused spiro cyclohexenols

were isolated in high yields and ee values and moderate to good diastereoselectivity (**49a-49g**). The structure and stereochemistry of the nitro derivative **49g** was determined by single crystal X-ray analysis, and other derivatives were assigned by analogy (Figure 5.1).[29] Moreover, substitution at the 3-position and 2-position of the β-aryl ring did not affect the outcome of this annulation reaction and the desired products are formed in high yields (**49h, 49i**). Additionally, heteroaryl moiety at the β-position of **47** was also worked well and the furyl substituted spirocyclohexenol (**49j**) was formed in 87% yield, 1:1 dr and excellent ee

Scheme 5.17. Scope of the α,β-Unsaturated Aldehydes



General conditions: **47** (0.25 mmol), **48a** (0.25 mmol),**O** (10 mol %), AcOH (5 equiv), CH_2Cl_2 (3.0 mL), 30 °C and 12 h. Yields of isolated products are given. The dr was determined by ^{1}H NMR spectroscopy of the crude reaction mixture and the ee value was determined by HPLC analysis on a chiral column. [a]Structure and stereochemistry confirmed by X-ray analysis.

values. The substrate having an extended conjugation at the β-position of **47** furnished the expected product **49k** in moderate yield and selectivity. Notably, the present methodology is not limited to aromatic enals. Interestingly, aliphatic enals also furnished the spirocyclic cyclohexenols in moderate diastereoselectivity and excellent yield and ee values thus showing the versatile nature of this formal [3+3] annulation (**49l, 49m**).

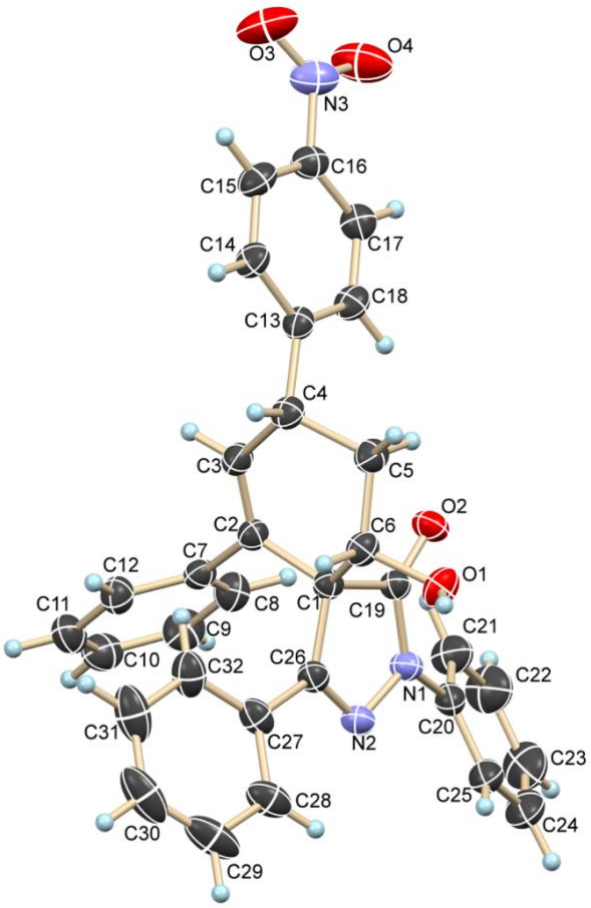
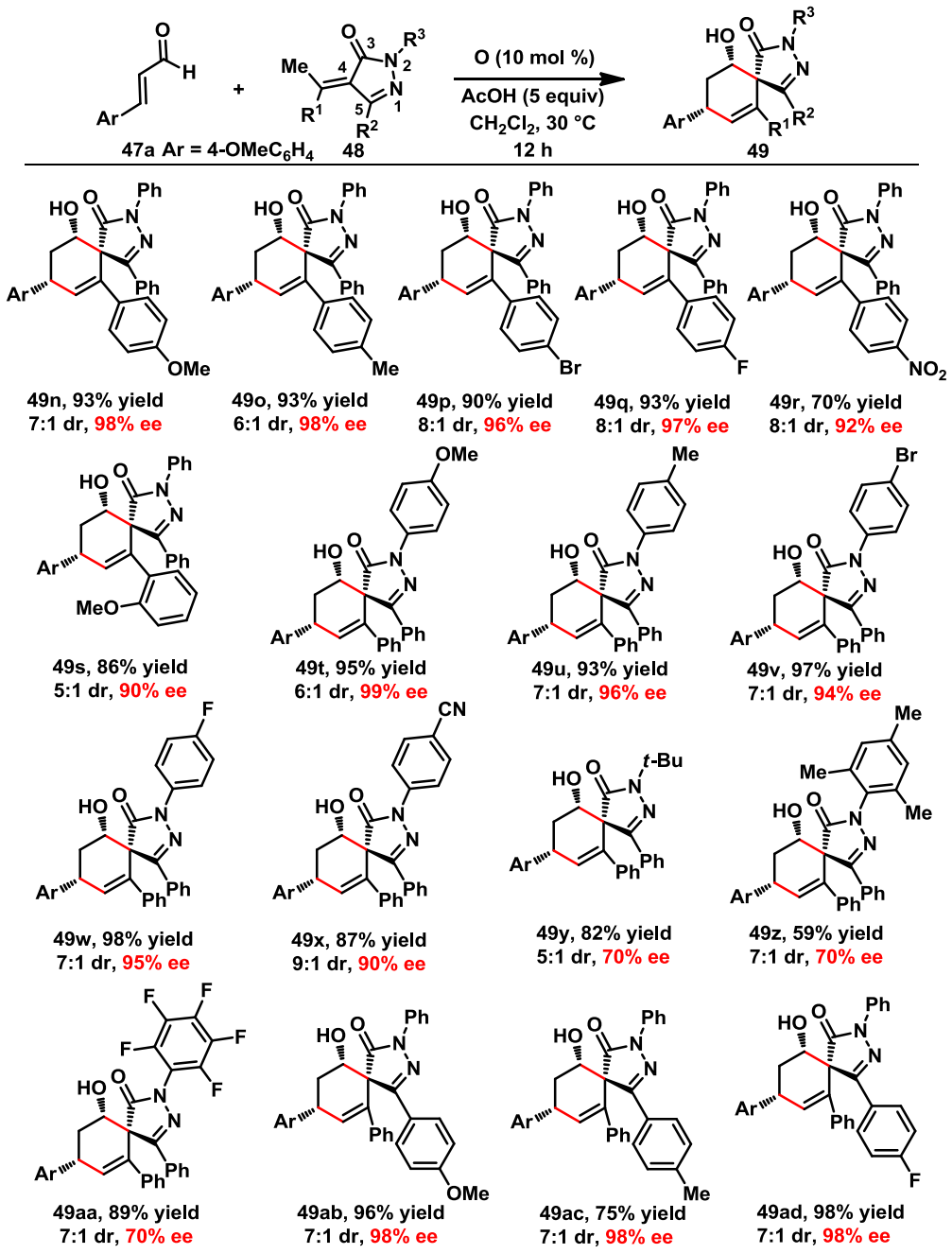


Figure 5.1. Crystal Structure of **49g** (Thermal Ellipsoids are Shown with 30% Probability).

5.3.4. Enantioselective Synthesis of Spirocyclohexenols from α-arylidene pyrazolinone

Next, we evaluated the tolerence of this reaction with differently substituted α-arylidene pyrazolinones (Scheme 5.18). Notably, electron-donating and -withdrawing groups on the arylidine moiety of **48** (R^1) worked smoothly under the present conditions to furnish the spirocyclohexenols in good yields and selectivity (**49n-49s**). Moreover, substrates having differently substituted *N*-aryl moiety (R^3) and *N*-*tert*-Butyl group (**48y**) underwent efficient [3+3] annulation to afford the desired compounds in excellent yields of >82% in all cases (**49t-49y**). It is noteworthy that the substrates having sterically demanding Mesityl and electron-withdrawing C_6F_5 afforded the desired products in moderate ee values (**49z,49aa**). Additionally, electronically different substituent on aryl ring at 5-position of **2** (R^2) were well tolerated and the corresponding products obtained in high yields and selectivity (**49ab-49ad**).

Scheme 5.18. Scope of the α-Arylidene Pyrazolinone



General conditions: **47a** (0.25 mmol), **48** (0.25 mmol), **O** (10 mol %), AcOH (5 equiv), CH_2Cl_2 (3.0 mL), 30 °C and 12 h. Yields of isolated products are given. The dr was determined by ^{1}H NMR spectroscopy of the crude reaction mixture and the *ee* value was determined by HPLC analysis on a chiral column.

We have tested various other α,β-unsaturated aldehydes and dienolate precoursors for this formal [3+3] annulation reaction (Figure 5.2). But the reactions returned unsatisfactory result. For example, enals with α and β substitution (**50**-**52**) as well as hexadienal **53** and ynal **54** failed to give the desired product under this reation condition. Also dienolate precoursor like isatilidine **55** and β-methyl chalcone **56** did not work under this condition. Moreover, the

reaction performed using pyrazolinone having C_5 methyl (**57**) did not afford the expected product and α-alkylidine pyrazolinone **58** also failed.

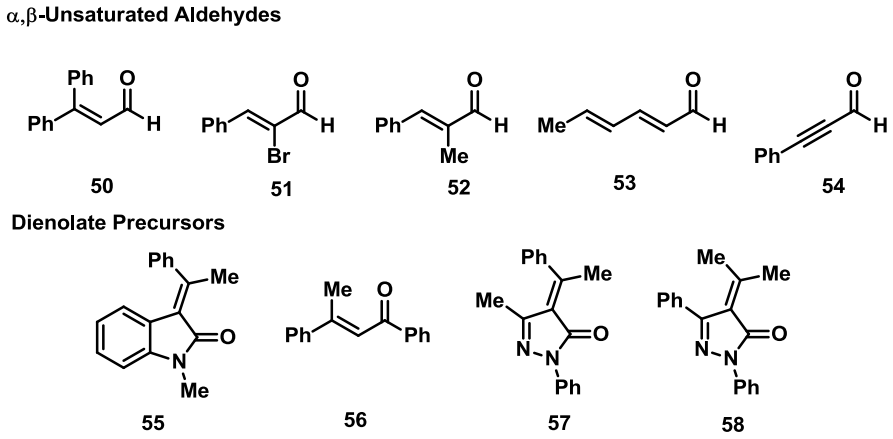
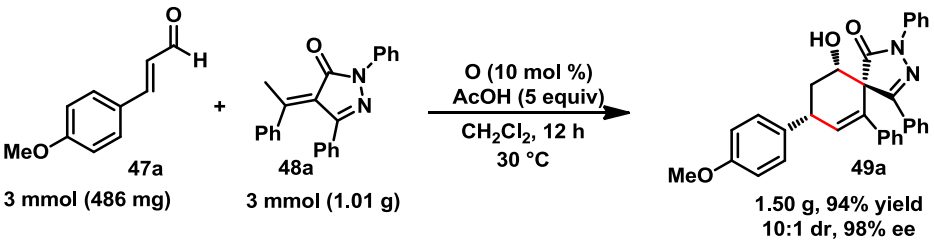


Figure 5.2: Unsuccessful Substrate in this Annulation Reaction

5.3.5. Enantioselective Gram Scale Synthesis of Pyrazolone-fused Spirocyclohexenols

In a scale up experiment, we have demonstrated a gram scale synthesis of pyrazolone-fused spirocyclohexenols (scheme 5.19). Under the optimized reaction condition the desired product formed in 94% yield with same lavel of stereoselectivity (10:1 dr, 98% ee).

Scheme 5.19: Gram Scale Synthesis of Pyrazolone-fused Spirocyclohexenols

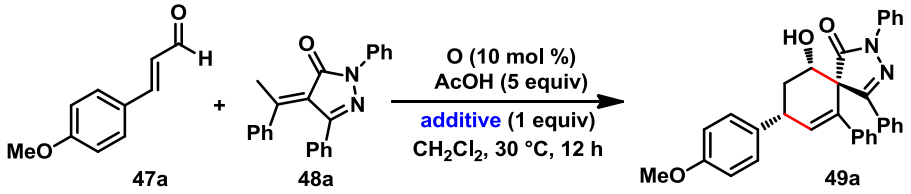


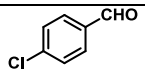
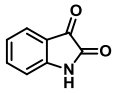
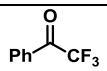
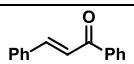
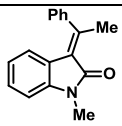
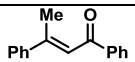
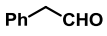
5.3.6 Robustness Screen of the Spiroannulation Reaction

We also studied the robustness of this annulation reaction with common electrophiles/nucleophiles.[30] Satisfyingly, the commonly used electrophiles in organocatalysis such as aldehyde, *N*-unprotected isatin, trifluoroacetophenone and chalcone survived under the present reaction conditions and are isolated in good yields after the reaction showing that these electrophiles are not decomposing/interfering the course of this annulation under the present conditions (Table 5.2, entries 2-5). The spirocyclohexenol **49a** was isolated in high yield and selectivity in all cases. In addition, the tolerance of this reaction with dienolate precursors such as isatilidene and β-methyl chalcone were tested and both cases, **49a** was isolated in high yields and the additive was isolated in good yields

(entries 6,7). But the use of phenyl acetaldehyde reduced the yield of **49a** to 54% maintaining the high ee, and only 20% of the aldehyde was recovered after the reaction (entry 8).

Table 5.2: Effect of Common Electrophiles/Nucleophiles in this Reaction.



Entry	Additive	yield of **49a**(%)[b]	ee of **49a**(%)[b]	additive remaining (%)
1	none	94	98	---
2		91	98	80[a]
3		92	98	90[c]
4		86	98	94[d]
5		95	98	99[c]
6		86	98	99[c]
7		83	98	84[a]
8		54	99	20[a]

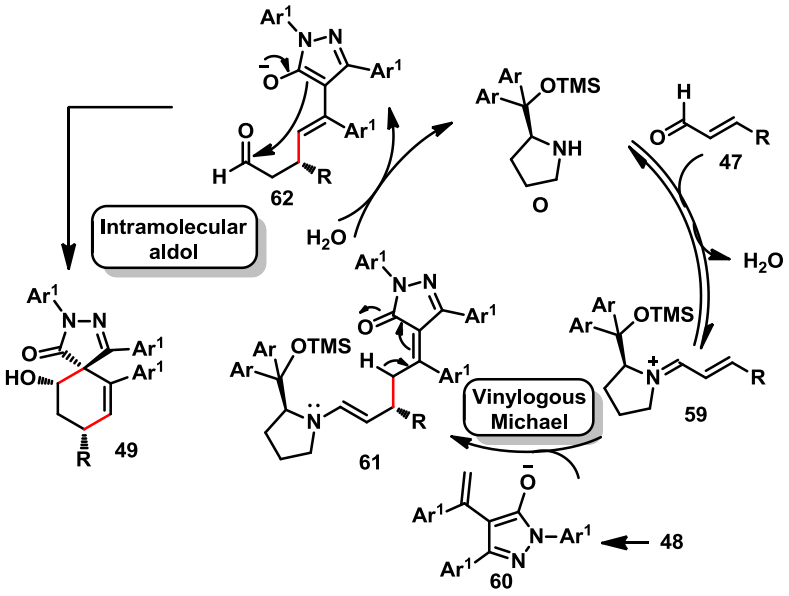
Standard conditions: **47a** (0.125 mmol), **48a** (0.125 mmol), additive (0.125 mmol), **O** (10 mol %), AcOH (5 equiv), CH_2Cl_2 (1.5 mL), 30 °C and 12 h. The dr determined by ^{1}H NMR of crude reaction was found to be 10:1 in all cases. [a] Determined by ^{1}H NMR of crude products using CH_2Br_2 as the internal standard. [b] Determined by HPLC analysis on a chiral column. [c] Isolated yield. [d] Additive remaining determined by GC.

5.3.7. Reaction Mechanism

Mechanistically, the reaction proceeds via the generation of the α,β-unsaturated iminium ion **59** from the enal **47** and catalyst **O**, which undergoes a vinylogous Michael addition with the dienolate **60** generated from **48** to form the catalyst bound enamine intermediate **61** (Scheme 5.20). At this stage, hydrolysis of the intermediate **61** affords the

aldehyde, which on intermolecular deprotonation generates the dienolate containing aldehyde **62**, and a subsequent intramolecular aldol reaction affords the spirocyclohexenol **49**. The high stereoselectivity observed in the intramolecular aldol reaction leading to the construction of spirocentre is noteworthy, and related spiroannulation was recently uncovered by Jørgensen and co-workers.[31]

Scheme 5.20: Proposed Mechanism of the Reaction



5.4. Conclusion

In conclusion, we have developed a secondary amine-catalyzed enantioselective vinylogous Michael/aldol cascade for the synthesis of pyrazolone-fused spirocyclohexenols by the reaction of enals with α-arylidene pyrazolinones.[32] The interception of the tandem generated dienolate/enolate intermediate from pyrazolinone to the catalytically generated α,β-unsaturated iminium was the key for the reaction, and the products are usually formed in excellent yields and ee values with moderate to good diastereoselectivity. The present method was found to be robust as evident from the tolerance with commonly used electrophiles and other sources of dienolates. Mild, scalability and broad substrate scope are the noteworthy features of this annulation reaction. Simultaneously, the research group of Guo[33] and Xu[34] employed α-arylidene pyrazolinone substrates for the tandem generation of dienolate/enolate intermediate and their subsequent reaction with Morita-Baylis−Hillman carbonates and (*E*)-2-nitroallylic acetates respectively for the enantioselective synthesis of spirocyclohexene derivatives. Moreover, Li and co-workers observed the similar reactivity for the synthesis of pyrazolone-fused spirocyclohexenols, employing TBS protected prolinol catalyst.[35]

5.5. Experimental Details

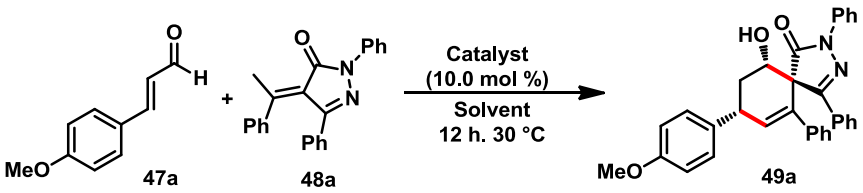
5.5.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Dry DCM were purchased from commercial sources and stored under argon over 4 Å molecular sieves. The α,β-unsaturated aldehydes **47a**, **47b**, **47c**, **47g**, **47i, 47j, 47l, 47m** were purchased from commercial sources and was used without further purification, and **47d**, **47e**, **47f**, **47h**, **47k** were synthesized by following the literature procedure.[36] α -Arylidene pyrazolinone derivatives were synthesized by following the literature procedure.[26] The secondary amine catalysts **O, I** and **A** were purchased from commercial sources.

Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (100-200 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system.

All compounds were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400, in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Infrared spectra were recorded on a Perkin-Elmer 1615 FT Infrared Spectrophotometer Model 60B. The wave numbers (n) of recorded IR-signals are quoted in cm^{-1}. HRMS (ESI) data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Optical rotation was measured with a JASCO P 2000 digital polarimeter at rt using 100 mm cell of 1 mL capacity. HPLC analysis was performed on Agilent Technologies 1260 Infinity with UV detector.

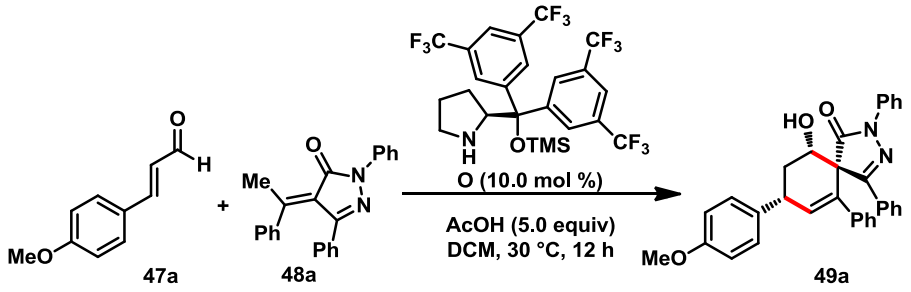
5.5.2. General Procedure for the Optimization of Reaction Conditions



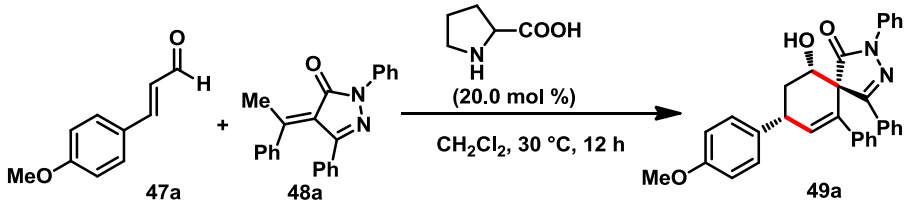
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (16 mg, 0.1 mmol, 1.0 equiv), (*E*)-1,3-diphenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **48a** (34.0 mg, 0.1 mmol, 1.0 equiv) and secondary amine catalyst (0.01 mmol, 10 mol%). To this mixture was added solvent (1.5 mL) under argon atmosphere and mixture was kept stirring at 30 °C for 12 h. Evaporation of the

solvent to obtain the crude product, whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (7.0 µL, 0.1 mmol) as the internal standard. The enantiomeric excess was determined by HPLC analysis on a chiral column.

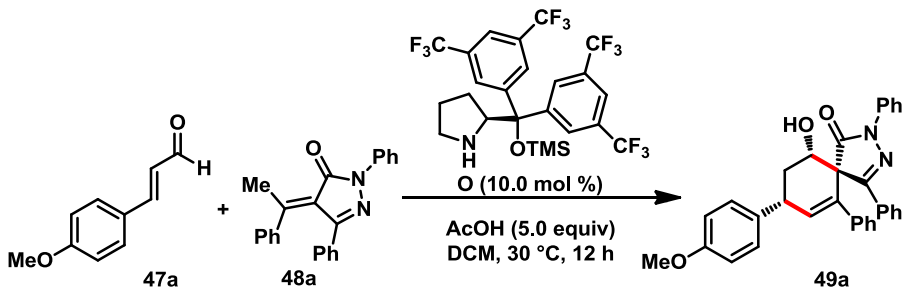
5.5.3. General Procedure for the Enantioselective Synthesis of Pyrazolone-fused Spirocyclohexenols



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol, 1.0 equiv), (*E*)-1,3-diphenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **48a** (84.6 mg, 0.25 mmol, 1.0 equiv) and secondary amine catalyst **O** (15.0 mg, 0.025 mmol, 10 mol%). To this mixture was added dry CH_2Cl_2 (3.0 mL) under argon atmosphere followed by AcOH (75.0 mg, 71 µL, 1.25 mmol, 5.0 equiv) and mixture was kept stirring at 30 °C for 12 h. Evaporation of the solvent followed by silica gel flash column chromatography afforded the corresponding pyrazolone-fused spirocyclohexenol **49a**. All racemic pyrazolone-fused spiro cyclohexenol were prepared using racemic proline catalyst.

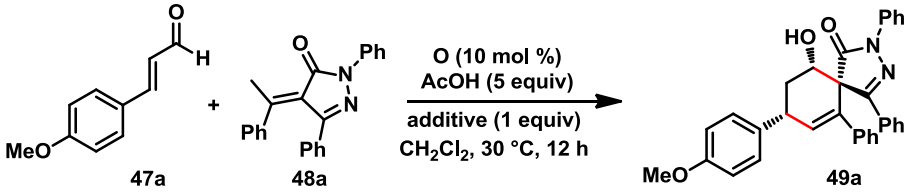


5.5.4. Procedure for the Gram Scale Synthesis of Pyrazolone-fused Spirocyclohexenols



To a flame-dried screw-capped schlenk tube equipped with a magnetic stir bar was taken (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (486.0 mg, 3.0 mmol, 1.0 equiv), (*E*)-1,3-diphenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **48a** (1.01 g, 3.0 mmol, 1.0 equiv) and secondary amine catalyst **O** (179.0 mg, 0.3 mmol, 10 mol%). To this mixture was added dry CH_2Cl_2 (35.0 mL) under argon atmosphere followed by AcOH (900.0 mg, 860.0 µL, 15.0 mmol, 5.0 equiv) and mixture was kept stirring at 30 °C for 12 h. Evaporation of the solvent followed by silica gel flash column chromatography afforded the corresponding pyrazolone-fused spirocyclohexenol **49a** as off white foam solid (1.50 g, 94% yield, 10:1 *dr*, 98% ee).

5.5.5. General Procedure for the Additive Reactions



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (20.3 mg, 0.125 mmol, 1.0 equiv), (*E*)-1,3-diphenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **48a** (42.3 mg, 0.125 mmol, 1.0 equiv) and secondary amine catalyst **O** (7.5 mg, 0.0125 mmol, 10 mol%). To this mixture was added dry CH_2Cl_2 (1.5 mL) under argon atmosphere followed by AcOH (36 µl, 37 mg, 0.0625 mmol, 5.0 equiv) and additive (1.0 equiv) and mixture was kept stirring at 30 °C for 12 h. Evaporation of the solvent to obtain the crude product, whose yield was determined by ^{1}H NMR analysis using CH_2Br_2 (9.0 µL, 0.125 mmol) as the internal standard. The enantiomeric excess was determined by HPLC analysis on a chiral column.

5.5.6. X-Ray Data of 49g

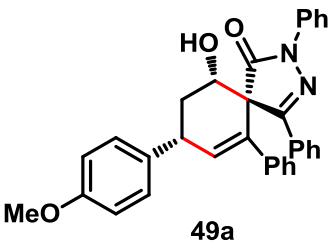
X-ray intensity data measurements of compound **49g** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Cu micro-focus sealed tube diffraction source (CuK_α= 1.54178 Å) at 296(2) K temperature. The X-ray generator was operated at 50 kV and 1.1 mA. A preliminary set of cell constants and an orientation matrix were calculated from two sets of 40 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[37] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). SHELX-97 was

used for structure solution and full matrix least-squares refinement on F^2.[38] All the hydrogen atoms were placed in a geomerically idalized positions and constrained to ride on its parent atoms An *ORTEP* III[39] view of compound was drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. The absolute configuration was established by anomalous dispersion effect (Flack parameter, -0.05(5)) in X-ray diffraction measurements carried out with Cu radiation. The single crystal X-ray diffraction data analysis clearly established that our synthesize compound has *S*, *R*, and *S*, configurations at C1, C4, and C6 positions respectively. CCDC 1537812 (**49g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data of **49g** $C_{32}H_{25}N_3O_4$, M = 515.55, colorless plate, 0.27 x 0.26 x 0.16 mm^3, orthorhombic, chiral space group $P2_12_12_1$, a = 9.9278(8) Å, b = 13.8213(12) Å, c = 19.0453(15) Å, V = 2613.3(4) $Å^3$, Z = 4, T = 296(2) K, $2\theta_{max}$=156.55°, D_{calc} (g cm^{-3}) = 1.310, $F(000)$ = 1080, μ (mm^{-1}) = 0.708, 23261 reflections collected, 5209 unique reflections (R_{int}=0.0282), 5023 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.832, T_{max} = 0.895, 355 refined parameters, Good of Fit = S = 1.017, $R1$ = 0.0327, $wR2$ = 0.0834 (all data R = 0.0339, $wR2$ = 0.0846), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.124, $\Delta\rho_{min}$= -0.102 (e $Å^{-3}$).

5.6.7. Synthesis and Characterization of Spirocyclohexenols

(5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49a)



49a

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-8-(4-methoxyphenyl)-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49a** as an off white foam solid (118.0 mg, 94% yield; diastereoselectivity determined by crude ^{1}H NMR is 10:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.57.

HPLC (Chiralpak IB, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 18.9 min, *Major*: 23.0 min. ee = 98%, $[\alpha]_D^{25}$ = +90.3 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.03 (m, 2H), 7.89-7.87 (m, 2H), 7.49-7.44 (m, 2H), 7.41-7.36 (m, 5H), 7.28-7.17 (m, 2H), 7.10 (s, 4H), 6.95-6.90 (m, 2H), 6.27 (s, 1H), 4.58-4.56 (m, 1H), 3.83-3.80 (m, 4H), 2.85 (q, *J* = 11.9 Hz, 1H), 2.16-2.12 (m, 1H), 2.04-1.93 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.80, 158.65, 158.53, 139.12, 138.24, 136.27, 136.19, 134.46, 130.52, 130.09, 129.06, 129.00, 128.76, 128.58, 127.91, 126.72, 126.62, 125.59, 119.61, 114.30, 72.68, 64.06, 55.44, 42.22, 34.04.

Representative peak for minor diastereomer:

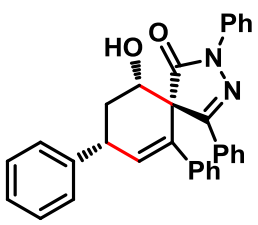
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, *J* = 4.5 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 128.05, 127.07, 126.46, 114.22, 68.92.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{29}O_3N_2$: 501.2173, found: 501.2159.

FTIR (cm^{-1}) 3619, 3376, 3019, 2976, 2401, 1596, 1424, 1216, 1121, 1044, 774, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-2,4,6,8-tetraphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49b)



49b

Following the general procedure, treatment of cinnamaldehyde **47b** (33.0 mg, 31.5 µL, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-2,4,6,8-tetraphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49b** as an off white foam solid (110.0 mg, 94% yield; diastereoselectivity determined by crude ^{1}H NMR is 6:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.66.

HPLC (Chiralpak IB, 90:10 Hexane / IPA, 1.0 mL/min) *Minor*: 8.5 min, *Major*: 10.2 min. ee = 98%, $[\alpha]_D^{25}$ = +75.2 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.92-7.89 (m, 2H), 7.51-7.47 (m, 4H), 7.41-7.37 (m, 5H), 7.31-7.26 (m, 2H), 7.22-7.18 (m, 1H), 7.12 (s, 4H), 6.31 (d, J = 1.6 Hz, 1H), 4.59 (dd, J_1 = 12.2 Hz, J_2 = 3.5Hz, 1H), 3.88-3.84 (m, 1H), 2.90 (q, *J* = 12Hz, 1H), 2.20-2.15 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.77, 158.50, 144.9, 139.07, 138.23,135.77, 134.77, 130.51, 130.10, 129.05, 128.93, 128.74, 128.57, 128.02, 127.93, 127.04, 126.71, 126.63, 125.58, 119.61, 72.62, 64.06, 43.02, 33.87.

Representative peak for minor diastereomer:

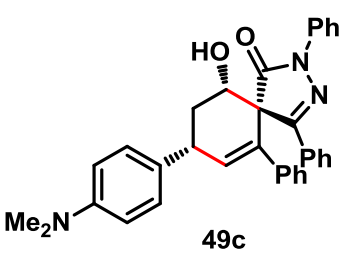
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, J = 4.7 Hz, 1H), 4.40 (dd, J_1 = 11.6 Hz, J_2 = 3.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.08, 128.84, 128.64, 127.88, 126.46, 74.50, 68.87, 40.13.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{27}O_2N_2$: 471.2067, found: 471.2055.

FTIR (cm^{-1}) 3681, 3619, 3377, 3019, 2976, 2401, 1596, 1424, 1216, 1044, 928, 774, 669.

(5*S*,8*R*,10*S*)-8-(4-(Dimethylamino)phenyl)-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49c)



49c

Following the general procedure, treatment of (*E*)-3-(4-(dimethylamino)phenyl)acrylaldehyde **47c** (44.0 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-8-(4-(dimethylamino)phenyl)-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49c** as an off white foam solid (119.0 mg, 93% yield; diastereoselectivity determined by crude ^{1}H NMR is 5:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.54.

HPLC (Chiralpak IB, 92:8 Hexane / IPA, 1.0 mL/min) *Minor*: 15.3 min, *Major*: 18.4 min. ee = 94%, $[\alpha]_D^{25}$ = +77.9 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.07 (m, 2H), 7.91 (bs, 2H), 7.51-7.47 (m, 2H), 7.39-7.37 (m, 5H), 7.29-7.27 (m, 1H), 7.20-7.17 (m, 1H), 7.12 (s, 4H), 6.81 (d, J = 7.8 Hz, 2H), 6.31 (s, 1H), 4.57 (dd, J_1 = 12.1 Hz, J_2 = 3.3 Hz, 1H), 3.80-3.76(m, 1H), 2.95 (s, 6H), 2.90-2.84 (m, 1H), 2.16-2.13 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.85, 158.60, 149.87, 139.23, 138.13, 136.80, 134.09, 132.15, 130.47, 129.04, 128.74, 128.62, 128.53, 127.80, 126.74, 126.66, 125.52, 119.60, 113.29, 72.14, 64.11, 42.12, 40.94, 34.05.

Representative peak for minor diastereomer:

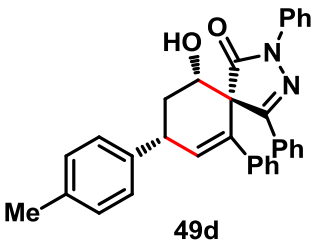
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, J = 4.7 Hz, 1H), 4.45 (dd, J_1 = 11.7 Hz, J_2 = 3.3 Hz, 1H), 4.09 (bs, 1H), 2.99 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.63, 134.89, 130.18, 127.10, 126.47, 125.58, 113.04, 69.05, 64.33, 40.88, 39.36, 32.51.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{32}O_2N_3$: 514.2489, found: 514.2479.

FTIR (cm^{-1}) 3681, 3619, 3347, 3019, 2976, 2401, 1596, 1525, 1424, 1216, 1121, 1044, 774, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-2,4,6-triphenyl-8-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49d)



49d

Following the general procedure, treatment of (*E*)-3-(*p*-tolyl)acrylaldehyde **47d** (40.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-2,4,6-triphenyl-8-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49d** as an off white foam solid (86.0 mg, 71% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.69.

HPLC (Chiralpak IB, 97:3 Hexane / IPA, 1.0 mL/min) *Minor*: 20.1 min, *Major*: 24.9 min. ee = 98%, $[\alpha]_D^{25}$ = +71.1 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz 2H), 7.93-7.91 (m, 2H), 7.50 (t, *J* = 7.7 Hz 2H), 7.41-7.39 (m, 4H), 7.29 (t, *J* = 7.4 Hz 2H), 7.23-7.19 (m, 3H), 7.14 (s, 4H), 6.32 (d, *J* = 1.6 Hz 1H), 4.59 (dd, J_1= 12.1, J_2= 3.4 Hz, 1H), 3.85-3.81 (m, 1H), 2.91 (q, *J* = 12.1 Hz, 1H), 2.39 (s, 1H), 2.19-2.13 (m. 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.79, 158.52, 141.08, 139.09, 138.22, 136.57, 136.07, 134.55, 130.47, 130.64, 129.57, 129.03, 128.72, 128.53, 128.64, 127.87, 126.70, 126.62, 125.55, 119.60, 72.64, 64.05, 42.60, 33.90, 21.19.

Representative peak for minor diastereomer:

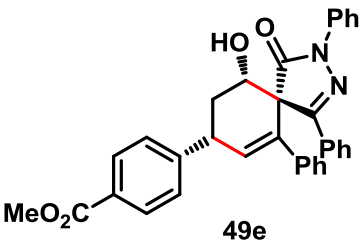
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.32, 129.47, 128.61, 127.75, 126.44, 68.88, 39.76, 32.25, 21.11.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{29}O_2N_2$: 485.2224, found: 485.2212.

FTIR (cm^{-1}) 3377, 3019, 2927, 2401, 1707, 1596, 1496, 1445, 1382, 1319, 1303, 1216, 927, 771, 669.

Methyl 4-((5*S*,8*R*,10*S*)-10-hydroxy-4-oxo-1,3,6-triphenyl-2,3-diazaspiro[4.5]deca-1,6-dien-8-yl)benzoate (49e)



49e

Following the general procedure, treatment of methyl (*E*)-4-(3-oxoprop-1-en-1-yl)benzoate **47e** (47.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford methyl 4-((5*S*,8*R*,10*S*)-10-hydroxy-4-oxo-1,3,6-triphenyl-2,3-diazaspiro[4.5]deca-1,6-dien-8-yl)benzoate **49e** as an off white foam solid (128.0 mg, 97% yield; diastereoselectivity determined by crude ^{1}H NMR is 8:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.48.

HPLC (Chiralpak IB, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 32.6 min, *Major*: 35.0 min. ee = >99%, $[\alpha]_D^{25}$ = +90.2 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.04 (m, 4H), 7.89-7.87 (m, 2H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.51-7.47 (m, 2H), 7.39-7.38 (m, 3H), 7.30-7.27 (m, 1H), 7.19 (bs, 1H), 7.12 (s, 4H), 6.27 (s, 1H), 4.63 (dd, J_1 = 11.8 Hz, J_2 = 2.6 Hz, 1H), 3.97-3.92 (m, 4H), 2.91 (q, *J* = 12.0 Hz, 1H), 2.21-2.18 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.66, 167.16, 158.37, 149.37, 138.89, 138.18, 135.54, 134.57, 130.57, 130.31, 130.01, 129.08, 128.78, 128.64, 128.10, 126.69, 126.61, 125.66, 119.61, 72.43, 64.02, 52.21, 42.99, 33.53.

Representative peak for minor diastereomer:

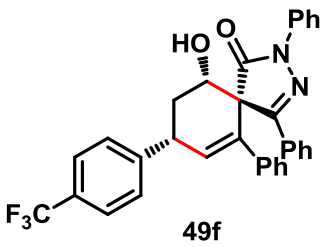
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, J = 4.4 Hz, 1H), 4.39-4.36 (m, 1H), 4.21 (bs, 1H), 3.95 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.17, 130.69, 130.16, 128.98, 127.89, 127.51, 127.02, 126.45, 68.78, 52.31, 40.17, 31.88.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{29}O_4N_2$: 529.2122, found: 529.2115.

FTIR (cm^{-1}) 3346, 3019, 2976, 2401, 1595, 1423, 1216, 1120, 1044, 773, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-2,4,6-triphenyl-8-(4-(trifluoromethyl)phenyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49f)



49f

Following the general procedure, treatment of (*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde **47f** (50.0 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column

chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-Hydroxy-2,4,6-triphenyl-8-(4-(trifluoromethyl)phenyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49f** as an off white foam solid (120.0 mg, 90% yield; diastereoselectivity determined by crude ^{1}H NMR is 10:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.72.

HPLC (Chiralpak IB, 97:3 Hexane / IPA, 1.0 mL/min) *Major*: 19.0 min, *Minor*: 24.9 min. ee = 99%, $[\alpha]_D^{25}$ = +79.4 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.10 (m, 2H), 7.95-7.93 (m, 2H), 7.74-7.69 (m, 4H), 7.57-7.34 (m, 8H), 7.18 (s, 4H), 6.31 (s, 1H), 4.70-4.66 (m, 1H), 4.03-3.99 (m, 1H), 2.96 (q, *J* = 11.9 Hz, 1H), 2.27-2.20 (m. 1H), 2.11-1.99 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.65, 158.36, 148.16, 138.82, 138.14, 135.63, 134.41, 130.63, 129.96, 129.11, 128.80, 128.67, 128.47, 128.21, 128.16, 126.70, 126.57, 125.92, 125.89, 125.73, 119.63, 72.38, 63.99, 42.81, 33.53.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.35.

Representative peak for minor diastereomer:

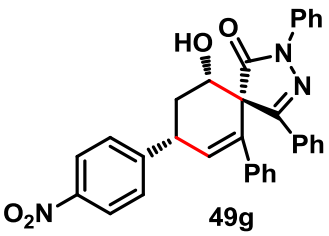
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58(d, *J* = 4.4 Hz, 1H), 4.44-4.41 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.03, 129.54, 127.05, 126.42, 68.72, 40.00.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{26}O_2N_2F_3$: 539.1941, found: 539.1928.

FTIR (cm^{-1}) 3682, 3619, 3357, 3020, 2976, 2401, 1596, 1424, 1216, 1044, 928, 774, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-nitrophenyl)-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49g)



49g

Following the general procedure, treatment of (*E*)-3-(4-nitrophenyl)acrylaldehyde **47g** (44.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-8-(4-nitrophenyl)-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49g** as an off white foam solid (122.0 mg, 94% yield; diastereoselectivity determined by crude ^{1}H NMR is 10:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.6.

HPLC (Chiralpak IB, 95:5 Hexane / IPA, 1.0 mL/min) *Major*: 35.1 min, *Minor*: 44.0 min. ee = 95%, $[\alpha]_D^{25}$ = +116.1 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz 2H), 8.12 (d, *J* = 8.0 Hz 2H), 7.93-7.91 (m, 2H), 7.69 (d, *J* = 8.4 Hz 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.45-7.44 (m, 3H), 7.35-7.26 (m, 2H), 7.19 (s, 5H), 6.26 (s, 1H), 4.65 (d, *J* = 10.0 Hz 1H), 4.02-3.99 (m, 1H), 2.90 (q, *J* = 12.0 Hz, 1H), 2.58 (s, 1H), 2.23-2.19 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.58, 158.32, 151.68, 147.02, 138.63, 138.02, 136.07, 133.44, 130.63, 129.79, 129.06, 128.96, 128.74, 128.66, 128.21, 126.61, 126.45, 125.71, 124.15, 123.97, 119.57, 72.10, 63.85, 42.65, 33.22.

Representative peak for minor diastereomer:

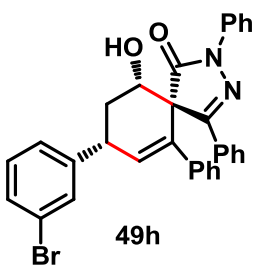
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, *J* = 4.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 126.94, 126.32, 68.54, 39.93.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{26}O_4N_3$: 516.1918, found: 516.1907.

FTIR (cm^{-1}) 3347, 3020, 2403, 1596, 1218, 1122, 1044, 928, 854, 772, 669.

(5*S*,8*R*,10*S*)-8-(3-Bromophenyl)-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49h)



49h

Following the general procedure, treatment of (*E*)-3-(3-bromophenyl)acrylaldehyde **47h** (52.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-8-(3-bromophenyl)-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49h** as an off white foam solid (134.0 mg, 98% yield; diastereoselectivity determined by crude ^{1}H NMR is 5:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.6.

HPLC (Chiralpak IF, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 19.5 min, *Major*: 28.3 min. ee = 98%, $[\alpha]_D^{25}$ = +103.3 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz 2H), 7.88-7.86 (m, 2H), 7.59 (s, 1H), 7.50-7.37 (m, 7H), 7.32-7.23 (m, 3H), 7.20 (s, 1H), 7.12 (s, 4H), 6.25 (s, 1H), 4.58 (dd, J_1= 11.9, J_2= 2.8 Hz, 1H), 3.84-3.80 (m, 1H), 2.87 (q, *J* = 12.0 Hz, 1H), 2.18-2.13 (m. 1H), 2.09-2.06 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.60, 158.34, 146.38, 138.87, 138.17, 135.44, 134.70, 131.08, 130.64, 130.58, 130.23, 130.0, 129.09, 128.78, 128.64, 128.10, 126.75, 126.69, 126.61, 125.68, 122.76, 119.64, 72.44, 63.96, 42.70, 33.62.

Representative peak for minor diastereomer:

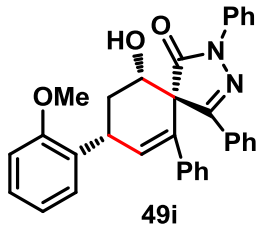
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, *J* = 4.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.05, 130.92, 128.90, 128.27, 127.03, 126.48, 68.66, 39.92.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{26}O_2N_2Br$: 549.1172, found: 549.1165.

FTIR (cm^{-1}) 3618, 3358, 3019, 2976, 2401, 1707, 1595, 1497, 1424, 1216, 1121, 1045, 928, 773, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-8-(2-methoxyphenyl)-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49i)



49i

Following the general procedure, treatment of (*E*)-3-(2-methoxyphenyl)acrylaldehyde **47i** (40.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether-EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-8-(2-methoxyphenyl)-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49i** as an off white foam solid (110.0 mg, 88% yield; diastereoselectivity determined by crude ^{1}H NMR is 5:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.48.

HPLC (Chiralpak IB, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 13.4 min, *Major*: 21.3 min. ee = 96%, $[\alpha]_D^{25}$ = +73.7 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz 2H), 7.90-7.89 (m, 2H), 7.54 (d, *J* = 7.7 Hz 1H), 7.45 (t, *J* = 7.8 Hz, 3H), 7.36-7.35 (m, 4H), 7.26-7.14 (m, 4H), 7.10 (s, 5H), 7.0 (t, *J* = 7.4 Hz, 1H), 6.94-6.90 (m, 1H), 6.28 (s, 1H), 4.62-4.58 (m, 1H), 4.45-4.41 (m, 1H), 3.89 (s, 3H), 2.76 (q, *J* = 11.9 Hz, 1H), 2.22-2.17 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.83, 158.62, 156.44, 139.58, 138.29, 136.20, 134.69, 132.11, 130.44, 130.14, 129.02, 128.72, 128.53, 127.88, 127.79, 126.74, 126.64, 125.49, 121.46, 119.58, 110.45, 72.81, 64.16, 55.59, 34.77, 32.38.

Representative peak for minor diastereomer:

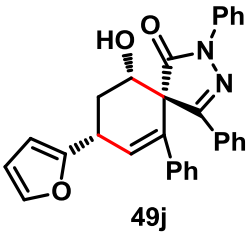
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 4.6 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.14, 139.58, 135.40, 134.41, 127.05, 126.39, 120.17, 110.82, 69.55, 55.45, 34.67.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{29}O_3N_2$: 501.2173, found: 501.2162.

FTIR (cm^{-1}) 3681, 3618, 3375, 3019, 2976, 2401, 1706, 1597, 1523, 1496, 1424, 1349, 1216, 928, 774, 669.

(5*S*,8*R*,10*S*)-8-(Furan-2-yl)-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49j)



49j

Following the general procedure, treatment of (*E*)-3-(furan-2-yl)acrylaldehyde **47j** (31.0 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-8-(furan-2-yl)-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49j** as an off white foam solid (100.0 mg, 87% yield; diastereoselectivity determined by crude ^{1}NMR is 1:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.63.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min) Diastereomer 1- *Major*: 15.9 min, *Minor*: 21.3 min, Diastereomer 2- *Major*: 19.2 min, *Minor*: 25.7 min. Diastereomer 1: 95% ee, Diastereomer 2: 95% ee, $[\alpha]_D^{25}$ = +16.7 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, *J* = 7.7 Hz 2H), 7.93-7.91 (m, 2H), 7.47-7.42 (m, 3H), 7.40-7.31 (m, 4H), 7.26-7.19 (m, 2H), 7.11 (d, *J* = 7.0 Hz 5H), 6.42-6.40 (m, 1H), 6.24 (dd, J_1= 13.1, J_2= 2.8 Hz, 1H), 4.65 (d, *J* = 11.1 Hz 1H), 4.03-3.99 (m, 1H), 3.12-3.04 (m, 1H), 2.14 (d, *J* = 13.2 Hz 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.52, 158.52, 156.24, 141.94, 139.02, 138.15, 136.01, 132.68, 130.98, 130.55, 130.03, 129.05, 128.59, 128.09, 126.92, 126.74, 125.63, 119.60, 110.51, 105.91, 69.37, 64.20, 35.10, 29.48.

Representative peak for minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 6.35-6.835 (m, 1H), 4.56 (d, *J* = 11.3 Hz, 1H) 4.16-4.14 (m, 1H), 3.04-2.95 (m, 1H), 2.27-2.24 (m, 1H).

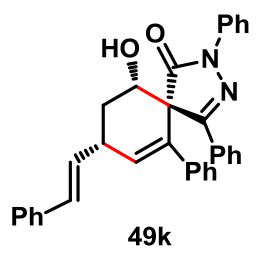
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.40, 158.19, 156.05, 141.69, 138.83, 138.20, 135.20, 130.07, 128.81, 126.78, 126.68, 125.56, 119.51, 110.54, 105.09, 72.20, 64.17, 36.21, 29.99.

HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{25}O_3N_2$: 461.1860, found: 461.1849.

FTIR (cm^{-1}) 3345, 3020, 2925, 2400, 1594, 1421, 1318, 1214, 1122, 1043, 928, 756, 667.

(5*S*,8*S*,10*S*)-10-Hydroxy-2,4,6-triphenyl-8-((*E*)-styryl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49k)

Following the general procedure, treatment of (2*E*,4*E*)-5-phenylpenta-2,4-dienal **47k** (39.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71



49k

μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether-EtOAc: 80:20) to afford (5*S*,8*S*,10*S*)-10-hydroxy-2,4,6-triphenyl-8-((*E*)-styryl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49k** as an off white foam solid (70.0 mg, 56% yield; diastereoselectivity determined by crude ^{1}H NMR is 2:1).

***R**f* (Pet. ether /EtOAc = 60/40): 0.62.

HPLC (Chiralpak AD, 90:10 Hexane / IPA, 1.0 mL/min) *Minor*: 26.9 min, *Major*: 41.9 min. ee = 60%, $[\alpha]_D^{25}$ = +7.9 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.03 (m, 2H), 7.93-7.88 (m, 2H), 7.49-7.32 (m, 10H), 7.27 (bs, 2H), 7.15-7.12 (m, 5H), 6.65-6.61 (m, 1H), 6.43-6.47 (m, 2H), 4.56-4.48 (m, 1H), 3.48-3.44 (m, 1H), 2.80-2.71 (m, 1H), 2.09-2.05 (m, 1H), 1.91-1.88(m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.61**,** 158.44, 139.07, 138.24, 137.17, 135.35, 134.99, 133.45, 131.92, 130.85, 130.53, 130.10, 129.05, 128.70, 128.59, 127.98, 127.58, 126.70, 126.44, 125.57, 119.53, 72.30, 64.17, 40.19, 31.38.

Representative peak for minor diastereomer:

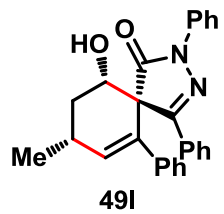
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66-3.64 (m, 1H), 3.08-3.01 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.63, 139.21, 138.15, 137.07, 135.29, 134.96, 131.64, 131.15, 130.59, 130.25, 128.87. 128.77, 128.65, 128.05, 127.79, 126.82, 126.31. 125.63, 119.61, 69.22, 64.50, 38.01, 30.09.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{29}O_2N_2$: 497.2224, found: 497.2227.

FTIR (cm^{-1}) 3619, 3360, 3019, 2976, 2401, 1596, 1424, 1216, 1044, 928, 774, 669.

5*S*,8*R*,10*S*)-10-Hydroxy-8-methyl-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49l)



49l

Following the general procedure, treatment of (*E*)-but-2-enal **47l** (17.5 mg, 21 μL, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-8-methyl-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49l** as an off white foam solid (74.0 mg, 73% yield; diastereoselectivity determined by crude ^{1}H NMR is 4:1).

***R**f* (Pet. ether /EtOAc = 60/40): 0.58.

HPLC (Chiralcel OD-H, 97:3 Hexane / IPA, 1.0 mL/min) *Major*: 18.7 min, *Minor*: 25.3 min. ee = 98%, $[\alpha]_D^{25}$ = -12.3 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz 2H), 7.88-7.86 (m, 2H), 7.47 (t, *J* = 7.6 Hz 2H), 7.37-7.34 (m, 3H), 7.28-7.21 (m, 2H), 7.12-7.08 (m, 4H), 6.18 (d, *J* = 1.5 Hz 1H), 4.45 (dd, J_1= 12.2, J_2= 2.8 Hz, 1H), 2.71-2.68 (m, 1H), 2.45 (q, *J* = 11.7 Hz, 1H), 1.97-1.94 (m. 1H), 1.30 (d, *J* = 7.1 Hz 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.84, 158.62, 139.26, 138.36, 133.69, 130.41, 128.99, 128.68, 128.50, 127.55, 126.80, 126.71, 126.66, 126.55, 125.45, 119.50, 72.60, 64.37, 33.27, 31.12, 21.46.

Representative peak for minor diastereomer:

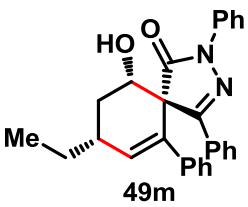
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.26, 137.60, 130.17, 128.55, 119.55, 69.05, 31.25, 29.83, 20.91.

HRMS (ESI) calculated $[M+H]^+$ for $C_{27}H_{25}O_2N_2$: 409.1911, found: 409.1899.

FTIR (cm^{-1}) 3682, 3619, 3359, 3019, 2975, 2401, 1707, 1596, 1424, 1216, 928, 774, 669.

(5*S*,8*R*,10*S*)-8-Ethyl-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49m)



49m

Following the general procedure, treatment of (*E*)-pent-2-enal **47m** (21.0 mg, 25 µL, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48a** (84.6 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-8-ethyl-10-hydroxy-2,4,6-triphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49m** as an off white foam solid (85. mg, 80% yield; diastereoselectivity determined by crude ^{1}H NMR is 5:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.66.

HPLC (Chiralcel OD-H, 97:3 Hexane / IPA, 0.7 mL/min) *Major*: 21.6 min, *Minor*: 30.3 min. ee = >99%, $[\alpha]_D^{25}$ = -15.9 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.06 (m, 2H), 7.88-7.86 (m, 2H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.37 (bs, 3H), 7.28-7.25 (m, 1H), 7.11-7.10 (m, 5H), 6.24 (s, 1H), 4.49-4.45 (m, 1H), 2.56-2.43 (m, 2H), 1.99-1.95 (m, 1H), 1.77-1.64 (m, 2H), 1.13-1.08 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.85, 158.58, 139.39, 138.28, 137.04, 034.05, 130.44, 129.01, 128.70, 128.52, 127.76, 126.73, 126.70, 125.47, 119.51, 72.75, 64.61, 37.60, 30.81, 28.76, 11.28.

Representative peak for minor diastereomer:

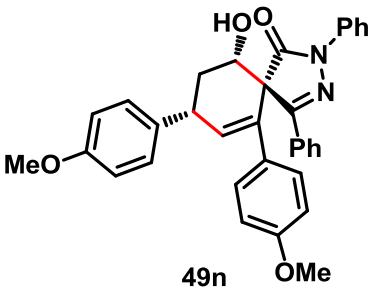
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 4.6 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$) δ 236.58, 130.18, 128.59, 126.84, 126.62, 125.57, 119.56, 69.41, 64.53, 36.74, 28.84, 28.37, 12.68.

HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{27}O_2N_2$: 423.2067, found: 423.2058.

FTIR (cm^{-1}) 3682, 3620, 3377, 3019, 2976, 2401, 1596, 1425. 1216, 1044, 928, 775, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-6,8-bis(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49n)



49n

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (E)-4-(1-(4-methoxyphenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one **48n** (92.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-6,8-bis(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49n** as an off white foam solid (123.0 mg, 93% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.59.

HPLC (Chiralpak IB, 93:7 Hexane / IPA, 1.0 mL/min) *Minor*: 21.8 min, *Major*: 27.1 min. ee = 98%, $[\alpha]_D^{25}$ = +73.8 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.9 Hz 2H), 7.92-7.90 (m, 2H), 7.51-7.47 (m, 2H), 7.42-7.40 (m, 5H), 7.32-7.28 (m, 1H), 7.06-7.04 (m, 2H), 6.94-6.92 (m, 2H), 6.65-6.63 (m, 2H), 6.22 (s, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 3.83-3.79 (m, 4H), 3.66 (s, 3H), 2.86 (q, *J* = 12.1 Hz, 1H), 2.16-2.13 (m, 1H), 1.96-1.93 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.86, 159.19, 158.72, 158.63, 138.29, 136.46, 135.13, 133.97, 131.68, 130.50, 130.16, 129.05, 128.98, 128.76, 127.80, 126.76, 125.53, 119.55, 114.29, 113.93, 72.68, 64.22, 55.43, 55.19, 42.13, 34.14.

Representative peak for minor diastereomer:

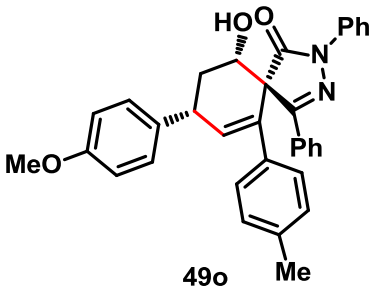
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (s, 1H), 3.85 (d, *J* = 1.8 Hz, 3H), 3.70 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.92, 136.26, 133.24, 131.95, 130.42, 128.84, 128.67, 127.64, 127.11, 114.19, 114.09, 68.90, 64.46, 39.35, 32.45.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{31}O_4N_2$: 531.2278, found: 531.2280.

FTIR (cm^{-1}) 3448, 3009, 2930, 2841, 1706, 1605, 1505, 1452, 1378, 1290, 1247, 1178, 1137, 1035, 831, 758, 691.

(5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-2,4-diphenyl-6-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49o)



49o

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-2,5-diphenyl-4-(1-(*p*-tolyl)ethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48o** (88.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-2,4-diphenyl-6-(*p*-tolyl)-2,3-diazaspiro[4.5] deca-3,6-dien-1-on**e 49o** as an off white foam solid (120.0 mg, 93% yield; diastereoselectivity determined by crude ^{1}H NMR is 6:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.60.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 28.3 min, *Major*: 34.9 min. ee = 98%, $[\alpha]_D^{25}$ = +73.9 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 2H), 7.92-7.90 (m, 2H), 7.50-7.46 (m, 2H), 7.41-7.35 (m, 5H), 7.29-7.26 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.92 (d, J = 8.3 Hz, 4H), 6.25 (d, J = 1.4 Hz, 1H), 4.54 (dd, J_1 = 12.1 Hz, J_2 = 3.4 Hz, 1H), 3.80-3.76 (m, 4H), 2.84(q, *J* = 12.0 Hz, 1H), 2.18 (s, 1H), 2.14-2.10 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.87, 158.68, 158.55, 138.26, 137.59, 136.41, 136.26, 135.56, 134.33, 130.43, 130.13, 129.24, 129.01, 128.96, 128.69, 126.74, 126.40, 125.49, 119.55, 114.23, 72.61, 64.06, 55.37, 42.12, 34.07, 21.03.

Representative peak for minor diastereomer:

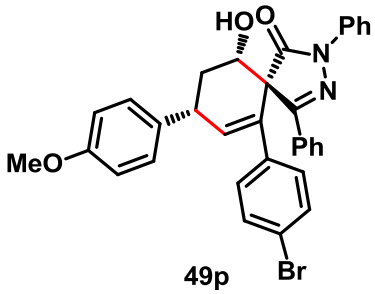
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49(d, *J* = 4.8 Hz, 1H), 3.84 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.73, 130.35, 129.41, 128.81, 128.60, 127.08, 126.24, 125.56, 114.14, 68.85, 64.35, 55.43, 39.31, 32.36, 21.08.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{31}O_3N_2$: 515.2329, found: 515.2335.

FTIR (cm^{-1}) 3348, 3019, 2976, 2400, 1596, 1513, 1423, 1216, 1044, 928, 772, 669.

(5*S*,8*R*,10*S*)-6-(4-Bromophenyl)-10-hydroxy-8-(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49p)



49p

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-4-(1-(4-bromophenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one **48p** (104.3 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-6-(4-bromophenyl)-10-hydroxy-8-(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49p** as an off white foam solid (130.0 mg, 90% yield; diastereoselectivity determined by crude ^{1}H NMR is 8:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.54.

HPLC (Chiralpak IB, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 23.2 min, *Major*: 28.0 min. ee = 96%, $[\alpha]_D^{25}$ = +78.5 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2H), 7.87-7.85 (m, 2H), 7.49-7.45 (m, 2H), 7.38-7.36 (m, 5H), 7.28-7.21 (m, 3H), 6.93 (dd, J_1 = 17.7 Hz, J_2 = 8.3 Hz, 4H), 6.25 (s, 1H), 4.57 (dd, J_1 = 12.1 Hz, J_2 = 3.3 Hz, 1H), 3.80 (bs, 4H), 2.85 (q, *J* = 11.8 Hz, 1H), 2.17-2.12 (m. 1H), 1.96-1.93 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.58, 158.72, 158.20, 138.11, 138.05, 136.74, 135.96, 133.50, 131.72, 130.69, 129.93, 129.10, 128.96, 128.86, 128.27, 126.60, 125.71, 122.02, 119.37, 114.36, 72.59, 63.84, 55.44, 42.21, 33.95.

Representative peak for minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, *J* = 4.7 Hz, 1H), 3.83 (s, 3H).

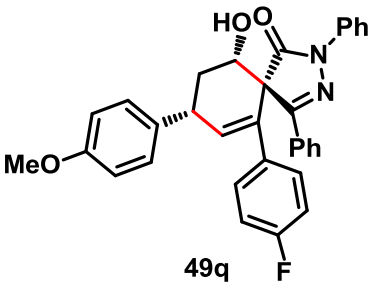
^{13}C NMR (100 MHz, $CDCl_3$) δ 135.02, 131.88, 128.76, 128.12, 126.92, 125.77, 119.54, 114.28, 68.87, m64.09, 55.49, 39.41, 32.26.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{28}O_3N_2Br$: 579.1278, found: 579.1256.

FTIR (cm^{-1}) 3351, 3019, 2976, 2401, 1595, 1424, 1216, 1121, 1044, 773, 669.

(5*S*,8*R*,10*S*)-6-(4-Fluorophenyl)-10-hydroxy-8-(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49q)

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-4-(1-(4-fluorophenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one **48q** (89.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30



49q

°C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-6-(4-fluorophenyl)-10-hydroxy-8-(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49q** as an off white foam solid (120.0 mg, 93% yield; diastereoselectivity determined by crude ^{1}H NMR is 8:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.57.

HPLC (Chiralpak IB, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 22.2 min, *Major*: 25.5 min. ee = 97%, $[\alpha]_D^{25}$ = +73.7 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.88-7.86 (m, 2H), 7.46 (t, *J* = 7.7 Hz 2H), 7.39-7.35 (m, 5H), 7.29-7.24 (m, 1H), 7.07-7.03 (m, 2H), 6.95-6.90 (m, 2H), 6.78 (t, J = 8.5 Hz, 2H), 6.22 (s, 1H), 4.58 (dd, J_1 = 12.1 Hz, J_2 = 3.3 Hz, 1H), 3.80 (bs, 4H), 2.85 (q, *J* = 11.9 Hz, 1H), 2.17-2.13 (m. 1H), 1.97-1.93 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.68, 162.36 (d, *J* = 247.5 Hz), 158.72, 158.33, 138.15, 136.36, 136.12, 135.18 (d, *J* = 3.1 Hz), 133.55, 130.65, 130.03, 129.09, 128.97, 128.84, 128.45 (d, *J* = 8.0 Hz), 126.63, 125.68, 119.56, 115.50 (d, *J* = 21.5 Hz), 114.36, 72.61, 64.14, 55.44, 42.51, 34.04.

Representative peak for minor diastereomer:

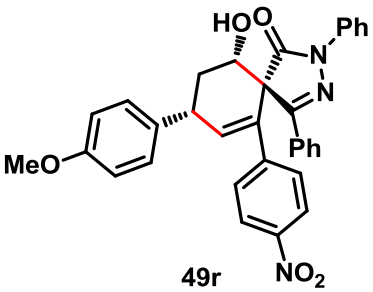
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 4.7 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.56, 128.79, 128.74, 126.96, 115.78, 115.57, 114.27, 68.68, 64.37, 55.50, 39.36, 32.33.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{28}O_3N_2F$: 519.2078, found: 519.2083.

FTIR (cm^{-1}) 3346, 3019, 2401, 1596, 1512, 1423, 1216, 1122, 1043, 771, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-6-(4-nitrophenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49r)



49r

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-4-(1-(4-nitrophenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one **48r** (95.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-8-(4-methoxyphenyl)-6-(4-nitrophenyl)-2,4-

diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49r** as an off white foam solid (96.0 mg, 70% yield; diastereoselectivity determined by crude ^{1}H NMR is 8:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.48.

HPLC (Chiralpak IB, 90:10 Hexane / IPA, 1.0 mL/min) *Minor*: 24.7 min, *Major*: 28.2 min. ee = 92%, $[\alpha]_D^{25}$ = +112.9 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.9 Hz, 2H), 7.95 (d, *J* = 8.7 Hz, 2H), 7.85-7.81 (m, 2H), 7.50-7.46 (m, 2H), 7.40-7.35 (m, 5H), 7.30-7.28 (m, 1H), 7.22 (d, J = 8.7 Hz, 2H), 6.94-6.91 (m, 2H), 6.39 (d, J = 1.5 Hz, 1H), 4.62 (dd, J_1 = 11.9 Hz, J_2 = 3.2 Hz, 1H), 3.87-3.84 (m, 1H), 3.80 (s, 3H), 2.93-2.84 (m, 1H), 2.21-2.15 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.32, 158.87, 157.73, 147.27, 145.59, 138.97, 137.98, 135.40, 132.86, 130.91, 129.19, 128.98, 127.46, 126.41, 125.92, 123.96, 119.51, 114.46, 72.60, 63.58, 55.45, 42.42, 33.68.

Representative peak for minor diastereomer:

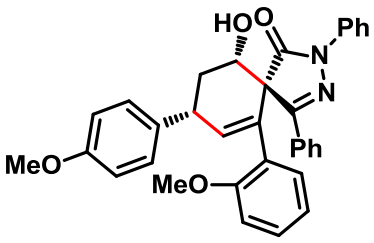
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, *J* = 4.7 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 129.65, 128.90, 128.72, 127.34, 126.71, 125.97, 124.10, 55.51, 32.04.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{28}O_5N_3$: 546.2023, found: 546.2015.

FTIR (cm^{-1}) 3681, 3359, 3020, 2976, 2401, 1597, 1515, 1424, 1348, 1216, 1120, 1043, 928, 773, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-6-(2-methoxyphenyl)-8-(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49s)



49s

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (E)-4-(1-(2-methoxyphenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one **48s** (92.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-6-(2-methoxyphenyl)-8-(4-methoxyphenyl)-2,4-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49s** as an off white foam solid (114.0 mg, 86% yield; diastereoselectivity determined by crude ^{1}H NMR is 5:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.63.

HPLC (Chiralpak AD, 90:10 Hexane / IPA, 1.0 mL/min) *Minor*: 27.9 min, *Major*: 31.3 min. ee = 90%, $[\alpha]_D^{25}$ = +95.1 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.1 Hz, 2H), 7.90-7.88 (m, 2H), 7.48-7.43 (m, 4H), 7.32 (s, 3H), 7.25-7.21 (m, 1H), 7.08-7.00 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.67 (t, J = 7.7 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 6.23 (d, J = 1.8 Hz, 1H) 4.60 (dd, J_1 = 12.0 Hz, J_2 = 3.3 Hz, 1H), 3.85-3.82 (m, 1H), 3.79 (s, 3H), 3.44 (s, 3H), 2.95 (q, *J* = 11.9 Hz, 1H), 2.16-2.12 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.48, 158.46, 157.52, 156.52, 138.70, 137.71, 136.38, 130.74, 130.04, 130.01, 129.09, 128.93, 128.23, 126.79, 124.82, 120.22, 118.84, 114.15, 110.39, 72.96, 63.79, 55.34, 55.03. 42.49, 33.31.

Representative peak for minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, *J* = 4.1 Hz, 1H), 3.52 (s, 3H).

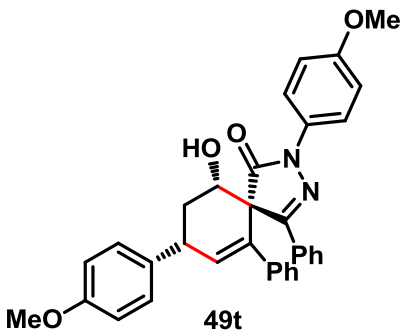
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.21, 158.16, 156.29, 138.56, 137.04, 136.31, 130.04, 129.42, 128.37, 126.94, 124.98, 120.39, 110.50, 69.04, 64.41, 54.39, 54.71, 39.77, 32.44.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{31}O_4N_2$: 531.2278, found: 531.2282.

FTIR (cm^{-1}) 3439, 3062, 3012, 2931, 2839, 1710, 1597, 1500, 1454, 1378, 1307, 1248, 1177, 1135, 1032, 927, 755, 690.

(5*S*,8*R*,10*S*)-10-Hydroxy-2,8-bis(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49t)

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-2-(4-methoxyphenyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3H-pyrazol-3-one **48t** (92.1 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-2,8-bis(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5] deca-3,6-dien-1-one **49t** as an off white foam solid (126.0 mg, 95% yield; diastereoselectivity determined by crude ^{1}H NMR is 6:1).



49t

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.54.

HPLC (Chiralcel OD-H, 93:7 Hexane / IPA, 1.0 mL/min) *Minor*: 45.4 min, *Major*: 57.3 min. ee = 99%, $[\alpha]_D^{25}$ = +88.4 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.8 Hz, 2H), 7.88-7.85 (m, 2H), 7.40-7.35 (m, 5H), 7.18-7.17 (m, 1H), 7.10 (s, 4H), 6.99 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 6.26 (s, 1H), 4.56 (dd, J_1 = 12.0 Hz, J_2 = 2.9 Hz, 1H), 3.84-3.78 (m, 7H), 2.86 (q, J = 11.9 Hz, 1H), 2.15-2.11 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.49, 158.63, 158.39, 157.47, 139.17, 136.31, 136.10, 134.55, 131.61, 130.40, 130.16, 129.00, 128.72, 128.53, 127.87, 126.66, 121.47, 72.63, 63.89, 55.66, 55.42, 42.22, 32.04.

Representative peak for minor diastereomer:

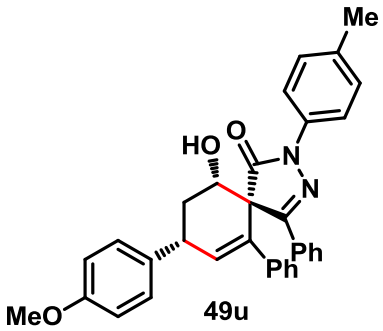
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, J = 4.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.38, 128.82, 128.64, 128.01, 127.03, 126.49, 114.29, 114.22, 68.88, 64.07, 55.48, 39.55, 32.41.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{31}O_4N_2$: 531.2278, found: 531.2266.

FTIR (cm^{-1}) 3357, 3020, 2976, 2401, 1595, 1512, 1424, 1216, 1121, 1046, 773, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49u)



49u

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-5-phenyl-4-(1-phenylethylidene)-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one **48u** (88.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2-(p-tolyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49u** as an off white foam solid (120.0 mg, 93% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.66.

HPLC (Chiralpak IB, 97:3 Hexane / IPA, 1.0 mL/min) *Minor*: 41.7 min, *Major*: 52.0 min. ee = 96%, $[\alpha]_D^{25}$ = +57.1 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz 2H), 7.91-7.87 (m, 2H), 7.42-7.37 (m, 5H), 7.32-7.26 (m, 2H), 7.22-7.16 (m, 1H), 7.12 (s, 4H), 6.93 (d, J = 8.5 Hz 2H), 6.28 (d, J = 1.8 Hz 1H), 4.57 (dd, J_1= 12.1, J_2= 3.4 Hz, 1H), 3.82 (s, 3H), 2.88 (dd, J_1= 23.8, J_2= 3.4 Hz, 1H), 2.42 (s, 3H), 2.16-2.12 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.63, 158.63, 158.38, 139.16, 136.32, 136.11, 135.85, 135.29, 134.53, 130.41, 130.16, 129.55, 128.99, 128.82, 128.71, 128.53, 127.86, 126.68, 126.63, 114.29, 72.63, 63.99, 55.41, 42.22, 34.03, 21.14.

Representative peak for minor diastereomer:

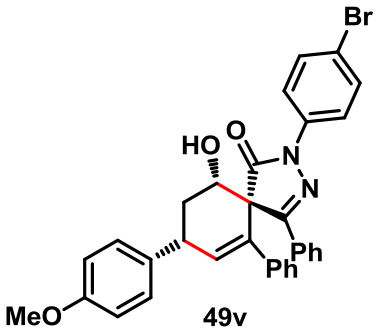
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 127.05, 126.47, 114.20, 39.35.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{31}O_3N_2$: 515.2329, found: 515.2333.

FTIR (cm^{-1}) 3682, 3618, 3019, 2400, 1708, 1597, 1215, 1044, 928, 771, 669.

(5*S*,8*R*,10*S*)-2-(4-Bromophenyl)-10-hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49v)



49v

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (20.0 mg, 0.125 mmol) and (*E*)-2-(4-bromophenyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48v** (52.0 mg, 0.125 mmol) with catalyst **O** (7.5 mg, 0.0125 mmol), and AcOH (37.5 mg, 36 μL, 0.625 mmol) in DCM (1.5 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-2-(4-Bromophenyl)-10-hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49v** as an off white foam solid (70.0 mg, 97% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

***R**$_f$* (Pet. ether /EtOAc = 60/40): 0.57.

HPLC (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 50.6 min, *Major*: 61.3 min. ee = 94%, $[\alpha]_D^{25}$ = +61.8 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.6 Hz, 2H), 7.88-7.86 (m, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.38-7.34 (m, 5H), 7.15 (s, 1H), 7.10-7.07 (m, 4H), 6.91 (d, J = 8.4 Hz, 2H), 6.27 (s, 1H), 4.55 (dd, J_1 = 12.1 Hz, J_2 = 3.4 Hz, 1H), 3.80-3.78 (m, 4H), 2.81 (q, *J* = 12.0 Hz, 1H), 2.15-2.10 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.79, 158.89, 158.65, 138.99, 137.29, 136.33, 136.14, 134.30, 132.02, 130.70, 129.99, 128.94, 128.78, 128.59, 127.96, 126.75, 126.57, 120.83, 118.37, 114.32, 72.65, 64.12, 55.42, 42.14, 34.08.

Representative peak for minor diastereomer:

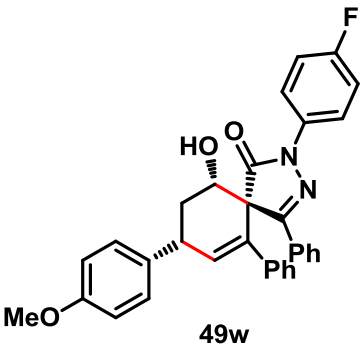
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, *J* = 4.8 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.17, 135.97, 134.49, 131.86, 130.08, 128.69, 128.41, 128.09, 127.04, 126.42, 114.23, 68.87, 64.41, 55.48, 39.36, 32.37.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{28}O_3N_2Br$: 579.1278, found: 579.1284.

FTIR (cm^{-1}) 3619, 3377, 3020, 2976, 2401, 1709, 1591, 1513, 1489, 1216, 1044, 928, 774, 669.

(5*S*,8*R*,10*S*)-2-(4-Fluorophenyl)-10-hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49w)



49w

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-2-(4-Fluorophenyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48w** (89.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-2-(4-fluorophenyl)-10-hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49w** as an off white foam solid (127.0 mg, 98% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.63.

HPLC (Chiralpak IF, 90:10 Hexane / IPA, 1.0 mL/min) *Major*: 21.9 min, *Minor*: 32.7 min. ee = 95%, $[\alpha]_D^{25}$ = +73.6 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.01 (m, 2H), 7.88-7.87 (m, 2H), 7.39-7.38 (m, 5H), 7.17-7.10 (m, 7H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.27 (s, 1H), 4.56 (dd, J_1= 12.1, J_2= 3.3 Hz, 1H), 3.80-3.78 (m, 4H), 2.84 (q, *J* = 12.1 Hz, 1H), 2.14-2.11 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.66, 160.14 (d, *J* = 245.1 Hz), 158.72, 158.66, 139.07, 136.27, 136.20, 134.38, 130.61, 128.96, 128.78, 128.58, 127.95, 126.67 (d, *J* = 9.2 Hz), 121.37, 121.29, 115.75 (d, *J* = 22.4 Hz), 114.32, 72.65, 64.01, 55.42, 42.18, 34.09.

Representative peak for minor diastereomer:

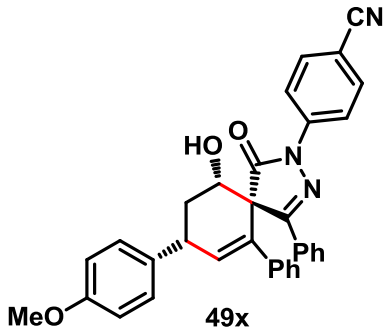
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, *J* = 4.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 129.98, 128.69, 128.24, 127.04, 126.46, 114.23, 68.88, 39.37.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{28}O_3N_2F$: 519.2078, found: 519.2084.

FTIR (cm^{-1}) 3681, 3617, 3377, 3019, 2401, 1599, 1510, 1216, 1043, 928, 773, 669.

4-((5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-1-oxo-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-2-yl)benzonitrile (49x)



49x

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-4-(5-oxo-3-phenyl-4-(1-phenylethylidene)-4,5-dihydro-1H-pyrazol-1-yl)benzonitrile **48x** (90.8 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford 4-((5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-1-oxo-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-2-yl)benzonitrile **49x** as an off white foam solid (114.0 mg, 87% yield; diastereoselectivity determined by crude ^{1}H NMR is 9:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.52.

HPLC (Chiralcel OD-H, 85:15 Hexane / IPA, 1.0 mL/min) *Minor*: 28.2 min, *Major*: 33.9 min. ee = 90%, $[\alpha]_D^{25}$ = +87.0 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz 2H), 7.89 (d, *J* = 7.3 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.40-7.37 (m, 5H), 7.10-7.04 (m, 5H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.29 (s, 1H), 4.60 (dd, J_1 = 12.1 Hz, J_2 = 3.1 Hz, 1H), 3.84-3.81 (m, 4H), 2.81 (q, *J* = 11.9 Hz, 1H), 2.18-2.15 (m, 1H), 2.03-1.96 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.29, 159.54, 158.73, 141.62, 138.85, 136.61, 135.98, 134.06, 133.27, 131.04, 129.62, 128.91, 128.87, 128.81, 128.77, 128.65, 128.07, 126.88, 126.55, 118.90, 114.37, 108.07, 72.74, 64.31, 55.45, 42.11, 34.16.

Representative peak for minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, *J* = 4.7 Hz, 1H).

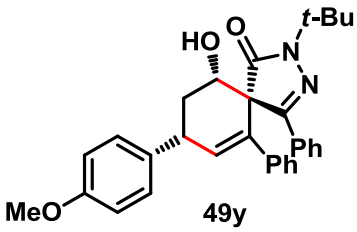
^{13}C NMR (100 MHz, $CDCl_3$) δ 128.20, 127.12, 126.41, 119.01, 114.29, 68.93.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{28}O_3N_3$: 526.2125, found: 526.2128.

FTIR (cm^{-1}) 3419, 2927, 2226, 1718, 1607, 1506, 1447, 1378, 1310, 1248, 1178, 1041, 931, 835, 760, 696, 666.

(5*S*,8*R*,10*S*)-2-(*tert*-butyl)-10-hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49y)

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-2-(*tert*-butyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48y** (80.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and



49y

AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-2-(*tert*-butyl)-10-hydroxy-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49y** as an off white foam solid (98.0 mg, 82% yield; diastereoselectivity determined by crude ^{1}H NMR is 5:1).

***R**f* (Pet. ether /EtOAc = 60/40): 0.66.

HPLC (Chiralpak IB, 93:7 Hexane / IPA, 0.7 mL/min) *Minor*: 11.4 min, *Major*: 12.2 min. ee = 70%, $[\alpha]_D^{25}$ = +28.5 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.77 (m, 2H), 7.37-7.32 (m, 5H), 7.12 (s, 5H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.18 (s, 4H), 4.47 (dd, J_1 = 11.8 Hz, J_2 = 2.5 Hz, 1H), 3.79-3.73 (m, 4H), 2.80 (q, *J* = 11.9 Hz, 1H), 2.10-2.07 (m, 1H), 1.85-1.82 (m, 1H), 1.61 (s, 9H)**.**

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.91, 158.57, 155.73, 139.36, 136.53, 135.62, 135.12, 130.90, 129.69, 128.96, 128.61, 128.20, 127.71, 127.01, 126.23, 114.24, 72.35, 63.93, 58.41, 55.41, 42.13, 34.06, 28.39.

Representative peak for minor diastereomer:

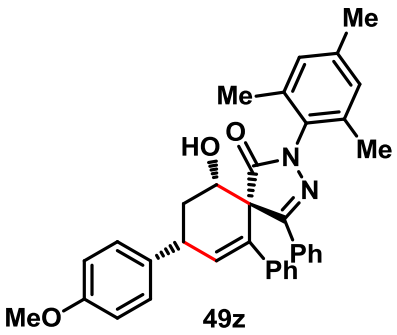
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45(d, *J* = 4.0 Hz, 1H), 3.82 (s, 3H), 1.57 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.41, 139.79, 136.31, 134.71, 134.22, 131.52, 129.83, 129.46, 128.86, 128.56, 128.43, 127.84, 126.95, 126.75, 114.13, 68.76, 63.62, 58.48, 39.03, 32.50, 28.31.

HRMS (ESI) calculated $[M+H]^+$ for $C_{31}H_{33}O_3N_2$: 481.2486, found: 481.2488.

FTIR (cm^{-1}) 3449, 3060, 3009, 2973, 2932, 1689, 1614, 1508, 1450, 1365, 1290, 1249, 1219, 1178, 1136, 1033, 940, 833, 757, 694.

(5*S*,8*R*,10*S*)-10-Hydroxy-2-mesityl-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49z)



49z

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (20.3 mg, 0.125 mmol) and (*E*)-2-mesityl-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **48z** (47.5 mg, 0.125 mmol) with catalyst **O** (7.5 mg, 0.0125 mmol), and AcOH (37.5 mg, 36 µL, 0.625 mmol) in DCM (1.5 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column

chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-Hydroxy-2-mesityl-8-(4-methoxyphenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49z** as an off white foam solid (40 mg, 59% yield; diastereoselectivity determined by crude ^{1}H NMR is 7.1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.63.

HPLC (Chiralpak IF, 92:8 Hexane / IPA, 1.0 mL/min) *Major*: 37.7 min, *Minor*: 65.9 min. ee = 70%, $[\alpha]_D^{25}$ = -2.2 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.46-7.40 (m, 5H), 7.24-7.22 (m, 2H), 7.19-7.14 (m, 3H), 6.93-6.91 (m, 3H), 6.80 (s, 1H), 6.17 (s, 1H), 4.66 (d, J = 10.8 Hz, 1H), 3.81 (s, 4H), 2.82 (q, *J* = 11.9 Hz, 1H), 2.26 (d, J = 4.4 Hz, 6H), 2.12-2.09 (m, 1H), 1.95(bs, 1H), 1.51 (s, 3H) .

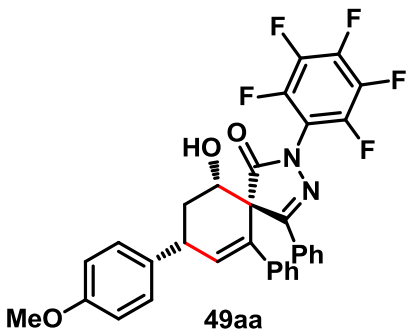
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.56, 158.63, 157.93, 139.25, 136.69, 136.76, 136.71, 136.54, 136.51, 135.42, 132.17, 131.26, 130.36, 129.25, 129.14, 129.04, 128.98, 128.72, 128.38, 128.08, 126.78, 114.31, 72.54, 63.17, 55.43, 41.93, 34.62, 21.13, 18.87, 14.46.

Representative peak for minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, *J* = 4.1 Hz, 1H), **^{13}C NMR (100 MHz, $CDCl_3$)** δ 128.62, 127.40, 114.12.

HRMS (ESI) calculated $[M+H]^+$ for $C_{36}H_{35}O_3N_2$: 543.2642, found: 543.2651.

FTIR (cm^{-1}) 3853, 3815, 3746, 3731, 3685, 3616, 3020, 2977, 2401, 1704, 1596, 1424, 1216, 1121, 1044, 774, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-2-(perfluorophenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49aa)



49aa

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (20.3 mg, 0.125 mmol) and (E)-2-(perfluorophenyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3H-pyrazol-3-one **48aa** (54.0 mg, 0.125 mmol) with catalyst **O** (7.5 mg, 0.0125 mmol), and AcOH (37.5 mg, 36 µL, 0.625 mmol) in DCM (1.5 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-2-(perfluorophenyl)-4,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49aa** as an off white foam solid (66.0 mg, 89% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.63.

HPLC (Chiralpak IB, 92:8 Hexane / IPA, 1.0 mL/min) *Minor*: 10.7 min, *Major*: 12.8 min. ee = 70%, $[\alpha]_D^{25}$ = +44.4 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.80 (m, 2H), 7.37-7.35 (m, 5H), 7.20-7.17 (m, 5H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.31 (s, 1H), 4.61-4.58 (m, 1H), 3.83-3.79 (m, 4H), 2.77 (q, *J* = 11.9 Hz, 1H), 2.20-2.17 (m, 1H), 1.87 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.34, 160.46**,** 158.75, 144.24 (d, *J* = 257 Hz) 138.81, 136.72, 133.95, 133.76, 130.96, 129.62, 128.97, 128.86, 128.77, 128.62, 128.15, 128.76, 126.70, 114.34, 72.51, 62.56, 55.43, 42.17, 34.01.

Representative peak for minor diastereomer:

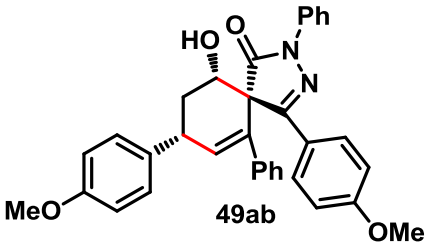
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, *J* = 4.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.20, 128.45, 127.05, 126.57.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{24}O_3N_2F_5$: 591.1702, found: 591.1702.

FTIR (cm^{-1}) 3615, 3020, 2976, 2410, 1733, 1611, 1515, 1465, 1218, 1113, 1056, 774, 669.

(5*S*,8*R*,10*S*)-10-Hydroxy-4,8-bis(4-methoxyphenyl)-2,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49ab)



49ab

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-5-(4-Methoxyphenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3H-pyrazol-3-one **48ab** (92.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-10-hydroxy-4,8-bis(4-methoxyphenyl)-2,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49ab** as an off white foam solid (128.0 mg, 96% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.45.

HPLC (Chiralpak IF, 88:12 Hexane / IPA, 1.0 mL/min) *Major*: 40.9 min, *Minor*: 44.5 min. ee = 98%, $[\alpha]_D^{25}$ = +66.6 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz 2H), 7.85 (d, *J* = 8.8 Hz 2H), 7.47 (t, *J* = 7.7 Hz 2H), 7.41 (d, *J* = 8.2 Hz 2H), 7.31-7.24 (m, 1H), 7.18 (s, 1H), 7.12 (s, 4H), 6.95-6.84 (m, 4H), 6.28 (s, 4H), 4.55 (d, *J* = 11.4 Hz 1H), 3.81 (s, 6H), 2.87 (q, *J* = 12.0 Hz, 1H), 2.16-2.13 (m. 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.65, 161.31, 158.60, 158.31, 139.16, 138.32, 136.31, 136.05, 134.54, 128.98, 128.52, 128.31, 127.82, 126.59, 126.43, 125.38, 122.75, 119.52, 114.27, 114.14, 72.81, 69.04, 64.03, 55.40, 42.20, 33.99.

Representative peak for minor diastereomer:

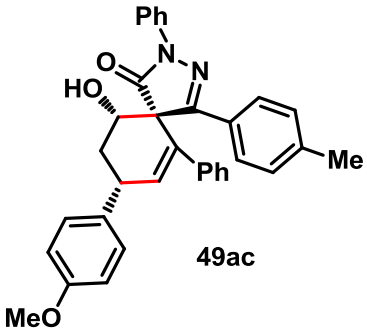
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, *J* = 4.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 128.76, 128.68, 39.33, 32.23.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{31}O_4N_2$: 531.2278, found: 531.2285.

FTIR (cm^{-1}) 3347, 3019, 2401,1597, 1514, 1214, 1216, 928, 772, 669.

((5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-2,6-diphenyl-4-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49ac)



49ac

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a** (40.5 mg, 0.25 mmol) and (*E*)-2-phenyl-4-(1-phenylethylidene)-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one **48ac** (88.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 μL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford ((5*S*,8*R*,10*S*)-10-Hydroxy-8-(4-methoxyphenyl)-2,6-diphenyl-4-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49ac** as an off white foam solid (96.0 mg, 75% yield; diastereoselectivity determined by crude ^{1}H NMR is 7:1).

R_f (Pet. ether /EtOAc = 60/40): 0.62.

HPLC (Chiralpak IB, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 19.5 min, *Major*: 27.4 min. ee = 98%, $[\alpha]_D^{25}$ = +69.6 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.80-7.76 (m, 2H), 7.49 (t, J = 7.7 Hz, 2H), 7.41 (d, *J* = 7.3 Hz 5H), 7.28-7.24 (m, 1H), 7.18 (d, *J* = 7.7 Hz, 3H), 7.11 (s, 4H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.27 (s, 1H), 4.56 (dd, J_1 = 12.1 Hz, J_2 = 3.4 Hz, 1H), 3.85-3.81 (m, 4H), 2.86 (q, *J* = 12.0 Hz, 1H), 2.36 (s, 3H), 2.18-2.12 (m. 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.76, 158.65, 158.60, 140.85, 139.19, 138.31, 136.34, 136.10, 134.55, 129.49, 129.03, 129.01, 128.55, 127.86, 127.36, 126.67, 126.65, 125.49, 119.60, 114.30, 72.77, 64.08, 55.43, 42.24, 34.04, 21.61.

Representative peak for minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, *J* = 4.6 Hz, 1H), 3.85 (s, 3H).

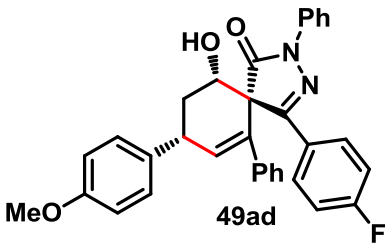
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.46, 136.25, 134.30, 129.39, 128.83, 128.71, 126.99, 126.49, 114.23, 69.01, 64.29, 55.51, 39.40, 32.37.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{31}O_3N_2$: 515.2329, found: 515.2332.

FTIR (cm^{-1}) 3682, 3619, 3377, 3019, 2976, 2400, 1706, 1597, 1513, 1423, 1215, 1044, 928, 774, 669.

(5*S*,8*R*,10*S*)-4-(4-Fluorophenyl)-10-hydroxy-8-(4-methoxyphenyl)-2,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one (49ad)

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **47a**



49ad

(40.5 mg, 0.25 mmol) and (*E*)-5-(4-Fluorophenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3H-pyrazol-3-one **48ad** (89.0 mg, 0.25 mmol) with catalyst **O** (15.0 mg, 0.025 mmol), and AcOH (75.0 mg, 71 µL, 1.25 mmol) in DCM (3.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 80:20) to afford (5*S*,8*R*,10*S*)-4-(4-fluorophenyl)-10-hydroxy-8-(4-methoxyphenyl)-2,6-diphenyl-2,3-diazaspiro[4.5]deca-3,6-dien-1-one **49ad** as an off white foam solid (128.0 mg, 98% yield; diastereoselectivity determined by crude ^{1}NMR is 7:1).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.57; ee = 98%, $[\alpha]_D^{25}$ = +75.0 (c 0.1, $CHCl_3$). **HPLC** (Chiralcel OD-H, 95:5 Hexane / IPA, 1.0 mL/min) *Minor*: 33.5 min, *Major*: 41.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.86-7.83 (m, 2H), 7.44 (t, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.24-7.22 (m, 1H), 7.14 (s, 1H), 7.09-6.99 (m, 6H), 6.89 6(d, *J* = 8.6 Hz, 2H), 6.26 (d, *J* = 1.7 Hz, 1H), 4.48 (dd, J_1= 12.1, J_2= 3.2 Hz, 1H), 3.78 (s, 3H), 2.82 (q, *J* = 12.2 Hz, 1H), 2.11-2.07 (m. 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.65, 163.92 (d, *J* = 251.9 Hz), 158.62, 157.65, 138.98, 138.15, 136.35, 136.12, 134.18, 129.05, 128.96, 128.72 (d, *J* = 8.4 Hz), 128.61, 127.96, 126.47, 125.61, 119.55, 115.98, 115.88 (d, *J* = 21.8 Hz), 114.29, 72.62, 63.93, 55.39, 42.17, 33.97. **Representative peak for minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.48 (d, *J* = 4.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.17, 162.67, 134.54, 128.76, 128.10, 126.34, 114.23, 68.82, 39.26, 32.24. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{33}H_{28}O_3N_2F$: 519.2078, found: 519.2084. **FTIR (cm^{-1})** 3350, 3019, 2403, 1596, 1423, 1217, 1042, 928, 772, 669.

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