Enantioselective Construction of Six-Membered Heterocycles and Carbocycles Using N-Heterocyclic Carbene (NHC)-Organocatalysis

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

BY

Santhi Vardhana Reddy Y
(Registration Number: 10CC11A26033)

Under the guidance of
Dr. A. T. Biju

Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune-411008, India.

April 2016

Dedicated to

My Beloved Parents

सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग, पुणे - 411 008. भारत
CSIR-NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

Dr. A. T. Biju
Senior Scientist
at.biju@ncl.res.in
Organic Chemistry Division

+91 20 2590 2441

Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Enantioselective Construction of Six-Membered Heterocycles and Carbocycles Using N-Heterocyclic Carbene (NHC)-Organocatalysis"** submitted by **Mr. Santhi Vardhana Reddy Y** 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.

Santhi Vardhana Reddy

Santhi Vardhana Reddy Y
(Research Student)

Dr. A. T. Biju
(Research Supervisor)

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Enantioselective Construction of Six-Membered Heterocycles and Carbocycles Using N-Heterocyclic Carbene (NHC)-Organocatalysis"** 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.

Santhi Vardhana Reddy

April 2016
CSIR-National Chemical Laboratory
Pune-411 008

Santhi Vardhana Reddy Y
(Research Student)

ACKNOWLEDGEMENT

During the long period of my research work, I have been acquainted, accompanied and supported by many people. It is a pleasant aspect that I have now the opportunity to express my gratitude for all of them.

It is my great privilege to express my deepest sense of gratitude to my teacher and research supervisor ***Dr. A. T. Biju*** *for excellent guidance, constant encouragement, and constructive criticism during my doctoral research. I consider extremely fortunate to have an advisor who not only educated me in chemistry but also taught me discipline and shown unique ways to achieve my goals. I sincerely acknowledge the freedom rendered by him in the laboratory for the independent thinking, planning and execution of the research. I believe the better way of thanking him would be through my future contribution to the scientific community.*

I owe to thank my DAC members, Dr. M. V. Badiger, Dr. Pradeep Kumar and Dr. G. J. Sanjayan for their continued support, guidance and suggestions. I am grateful to Prof. Dr. Ashwini K. Nangia, Director, NCL, Dr. Vijayamohanan K. Pillai and Prof. Dr. Sourav Pal (Former Directors, NCL), Dr. Pradeep Kumar, Head, Division of Organic Chemistry, and Dr. R. A. Joshi and Dr. Ganesh Pandey (Former HoDs, Organic Chemistry Division) for giving me this opportunity and providing all necessary infrastructure and facilities.

I would like to extend my thanks to Mrs. Sunitha S. Kunte for excellent HPLC support, Dr. P. R. Rajamohanan, Amol, Kavya, Shrikant, Dinesh for their timely help with NMR spectra recording, Dr. Rajesh Gonnade, Dr. Eringathodi Suresh, Shridhar for the X-ray analysis, Mrs. Shantakumari for Mass/HRMS facility and Dr. Kumar Vanka and Dr. Manoj Mane for theoretical calculations.

My sincere thanks to Dr. C. V. Ramana, Dr. D. S. Reddy, Dr. H. B. Borate, Dr. Nitin Patil, Dr. S. P. Chavan, Dr. Shashidhar, Dr. Argade, Dr. Muthukrishnan and all other scientists of NCL for their motivation, constant encouragement and support.

It is my pleasure to thank all my lab mates Sachin, Anup, Trinadh, Atanu, Tony, Manikandan, Santigopal, Subrata, Dnyaneshwar, and Tamal for devoting their precious time and made many valuable suggestions, which indeed helped me during this research work. A special thank goes to Anup Bhunia, Trinadh Kaicharla, Atanu Patra, Tony Roy, Santigopal Mondal, Subrata Mukherjee and past summer research fellows Kuruva Balanna and Naseef for their help in various projects.

I would like to acknowledge my senior colleagues for their helping hands and friendly affection including Dr. Chandrababu Naidu, Dr. Venu, Dr. Ramesh, Dr. Rambabu, Dr. Ramireddy, Dr. Yadagiri, Dr. Suneel, Dr. Chitanya Kiran, Dr. Manoj, Dr. Chitanya, Dr. Balanagulu, Dr. Rajendar Reddy, Dr. Vilas, Dr. Narasimha, Dr. Gowri, Dr. Sangram, Dr. Arup, Dr. Roshna and Vijay Thorat.

No words are sufficient to acknowledge my prized friends in and out of NCL who have helped me at various stages of my work in NCL. I wish to thank Rajendra, director Innaih Kumar, Narendraprasad, Curious Chitanya Krishna, Srikanth Dama, Srinu, Nagendra, Laxmi prasad, Sathish Battu, Suresh, Deva Dutta, Viswanath, Trinadh, Bhasker, Tarun, Sathish, Seetharam Singh, Kashinath, Kumarraja, Hanuman, Nookaraju, Eeswar, Venkannababu, prabhaker, Praveen, Sagar, Swamy, Naresh Killi, Bhuma Naesh, Ramu. I always enjoy their company and they are my strength for many things. I am lucky to have such a big family, which I have got kind gift in NCL. I also thank my friends in NCL with special mention to Ashok, Vasu, Mohan, Lenin, Manoj, Sanjeev Kheria, Amol, Thukaram, Manzoor, Wahid, Manoj V mane. I would like to thank my UG and PG friends Krishna Reddy, Ayaz, Mrs. Aruna, Rekha, Ravindra, Rajendra, Ramakrishna, Rajesh, Satya, Rama, Pravallika, Kishore, Damodar, Swamy, Ramana for their motivation and support.

Without the funding I received, this Ph.D would not have been possible and I would like to express my sincere appreciation to Council of Scientific & Industrial Research (CSIR)-New Delhi for awarding JRF and SRF.

My family is always source of inspiration and great moral support for me in perceiving my education, I used thank god of almighty for providing me such a beautiful family. I take this opportunity to my sense of gratitude to my parents Pushpavathi (mother) and Yedukondalu (father) for their tons of love, sacrifice, blessings, unconditional support and encouragement. I always love my elder brother Rajareddy, sisterin-law sravanthi and my little angels Srujana and Sanjana. I find no words to express my feelings for my dear brother Ravi kiran for his enormous love, and affection, you have always made me admire you.

I wish to thank the great scientific community whose achievements are constant source of inspiration for me.

Above all, I thank God Almighty for His enormous blessings.

Santhi Vardhana Reddy Y

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

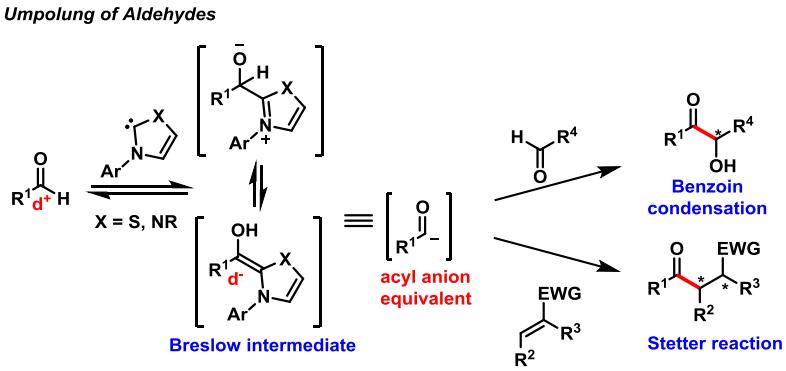
Synopsis

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. Santhi Vardhana Reddy Y
Degree Enrolment No. & Date	Ph. D in Chemical Sciences (10CC11A26033); August 2011
Title of the Thesis	Enantioselective Construction of Six-Membered Heterocycles and Carbocycles Using N-Heterocyclic Carbene (NHC)-Organocatalysis
Research Supervisor	Dr. Akkattu T. Biju (AcSIR, CSIR-NCL, Pune)

The proposed thesis envisions the enantioselective N-heterocyclic carbene (NHC)-based organocatalysis for the synthesis of various six-membered heterocycles and carbocycles such as dihydropyranones, dihydropyridinones, pyrazole-fused pyranones, and spirocyclohexadienones.

Introduction

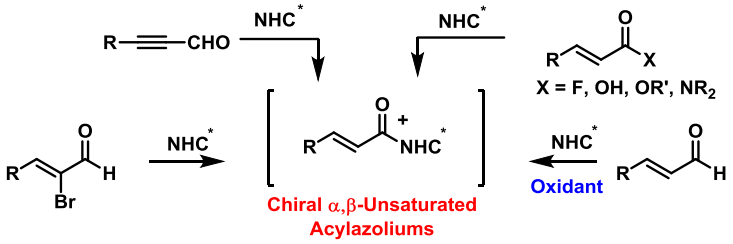
Over the past two decades, the chemistry of NHCs has witnessed tremendous development in carbon-carbon and carbon-heteroatom bond-forming reactions.[1] The benzoin and Stetter reactions proceed via the umpolung of aldehydes catalyzed by NHCs. In benzoin condensation, an aldehyde reacts with a second aldehyde to provide the α-hydroxy ketone product. The Stetter reaction is the NHC-catalyzed conjugate addition of an aldehyde to a Michael acceptor.[1b] The key intermediate in these transformations is the formation of Breslow intermediate and it is achieved by the umpolung of the aldehyde with an NHC.



Statement of the Problem

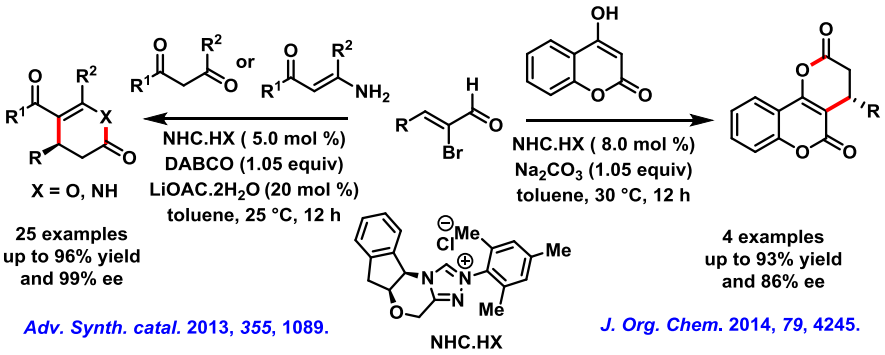
NHCs are also used in catalytic transformations proceeding via the normal mode (*non-umpolung*) of reactivity. One specific example is the generation of α,β-unsaturated acyl azolium intermediates using NHCs. The important methods for the generation of chiral α,β-unsaturated acylazoliums include (*i*) the reaction of α,β-unsaturated enol esters or acyl fluorides with NHCs,[2a,b] (*ii*) treatment of enals with NHCs followed by stoichiometric oxidation of the generated Breslow intermediate,[2c] (*iii*) reaction of ynals with NHCs[2d] (*iv*) the reaction of 2-bromoenals with NHCs.[2e] and more recently (*v*) from *α,β*-unsaturated acids[2f] and amides[2g]. Although the generation of chiral α,β-unsaturated acylazoliums is well established, their generation from stable

starting materials and development of asymmetric transformations using various bifunctional nucleophiles appears challenging as well as interesting. This constitutes the focal theme of the present thesis.



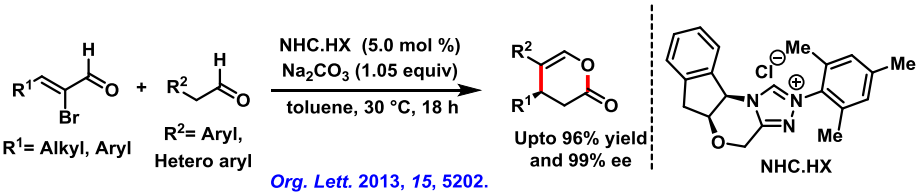
Noteworthy Findings

Enantioselective Synthesis of Dihydropyranones and Dihydropyridinones: In the context of our interest in asymmetric organocatalysis for carbon–carbon and carbon-heteroatom bond-forming reactions, recently, we have developed the NHC-organocatalyzed annulation of 2-bromoenals with readily available 1, 3-dicarbonyl compounds and enamines, which furnished the enantioselective synthesis of dihydropyranones and dihydropyridinones. Additionally we have provided reasonable rationalization for the mechanistic scenario and the mode of enantioinduction by DFT calculations.[3] Furthermore we introduced 4-hydroxycoumarin as a bifunctional cyclic nucleophile in α,β-unsaturated acyl azolium chemistry, thereby coumarin-fused dihydropyranones were synthesized in good yield and enantioselectivity.[4]



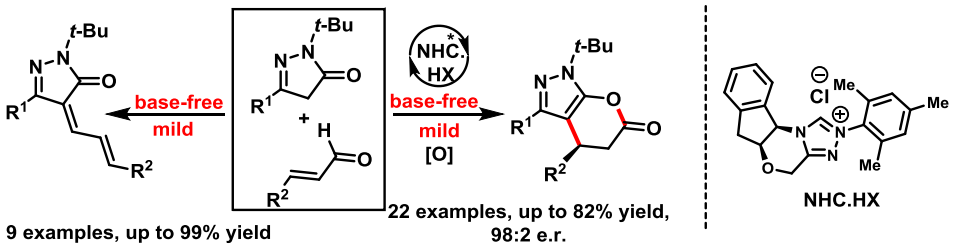
Adv. Synth. catal. 2013, *355*, 1089. *J. Org. Chem.* 2014, *79*, 4245.

NHC-Catalyzed Cross-Coupling of Aldehydes: We have also disclosed a highly enantioselective NHC-organocatalyzed lactonization of 2-bromoenals with enolizable aldehydes via chiral α,β-unsaturated acylazolium intermediates. The reaction resulted in the asymmetric synthesis of synthetically important 4,5-disubstituted dihydropyranones.[5]



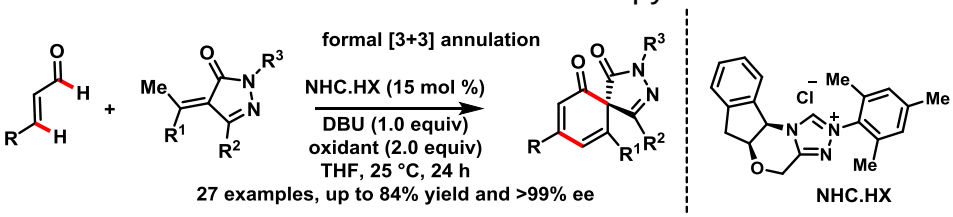
Org. Lett. 2013, *15*, 5202.

Pyrazolones in Asymmetric Transformations: An operationally simple and base-free protocol for the nucleophilic addition of pyrazolones to enals under NHC-catalysis has been developed. Knoevenagel condensation products were obtained in excellent yields under mild and base-free conditions by simple mixing of pyrazolones with α,β-unsaturated aldehydes. Intriguingly, the selectivity was completely switched in the presence of a triazolium salt under oxidative conditions resulting in the formation of dihydropyranone-fused pyrazoles in good yield and enantioselectivity with broad substrate scope.[6]



Org. Lett. 2015, *17*,1417.

Vinylogous Reactivity in NHC-Catalysis: Recently, we have uncovered the atom-economic and NHC-organocatalyzed reaction of enals with α-arylidene pyrazolinones under oxidative conditions. This annulation reaction proceeds via a vinylogous Michael addition/spiroannulation/dehydrogenation cascade affording the spirocyclic compounds having an all-carbon quaternary stereocentre in moderate to good yields and excellent ee values. Key to success for the present reaction is the cooperative NHC catalyzed generation of chiral α,β-unsaturated acyl azoliums from enals, and base-mediated tandem generation of dienolate/enolate intermediates from pyrazolinones.[7]



Angew. Chem., Int. Ed. 2016, *55*, 268.

Selected references

1. (a) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A. Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (b) Yetra, S. R.; Patra, A.; Biju, A. T. *Synthesis*. **201**5, *47*, 1357.
2. (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (b) Cheng, J.; Huang, Z.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8592. (c) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett*. **2007**, *9*, 371. (d) Zeitler, K. *Org. Lett*. **2006**, *8*, 637. (e) Sun, F.-G.; Sun, L.-H.; Ye, S. *Adv. Synth. Catal*. **2011**, *353*, 3134. (f) Chen, X.-Y.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S. *Angew. Chem., Int. Ed.* **2014**, *5*, 11611. (g) Ni, Q.; Xiong, J.; Song, X.; Raabe, G.; Enders, D. *Chem Commun.* **2015**, 51, 14628.
3. Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. *Adv. Synth. Catal.* **2013**, *355*, 1089.
4. Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A.T. *J. Org. Chem*. **2014,** *79*, 4245.
5. Yetra, S. R.; Trinadh, K.; Kunte, S.S.; Gonade, R. G.; Biju, A. T. *Org. Lett*. **2013**, *15*, 5202.
6. Yetra, S. R.; Mondal S.; Suresh E.; Biju, A. T. *Org. Lett*. **2015**, *17*, 1417.
7. Yetra, S. R.; Mondal, S.; Mukherjee, S.; Biju, A. T. *Angew. Chem., Int. Ed*. **2015,** *55*, 268.

TABLE OF CONTENTS

Chapter 1: N-Heterocyclic Carbene (NHC)-Catalyzed Reactions Proceeding Via *α*,*β*-Unsaturated Acylazolium Intermediates

Chapter 2: N-Heterocyclic carbene (NHC)-Catalyzed Enantioselective Synthesis of Dihydropyranones and Dihydropyridinones

Chapter 3: Enantioselective N-Heterocyclic carbene (NHC)-Catalyzed Annulation of Modified Enals with Enolizable Aldehydes

Chapter 4: Enantioselective Synthesis of Functionalized Pyrazoles by N-Heterocyclic Carbene (NHC)-Catalyzed Reaction of Pyrazolones with α,β- Unsaturated Aldehydes

Chapter 5: Enantioselective Synthesis of Spirocyclohexadienones by NHC-Catalyzed Formal [3+3] Annulation Reaction of Enals

CHAPTER 1

N-Heterocyclic Carbene (NHC)-Catalyzed Transformations Involving *α,β*-Unsaturated Acylazolium Intermediates

1.1. Introduction

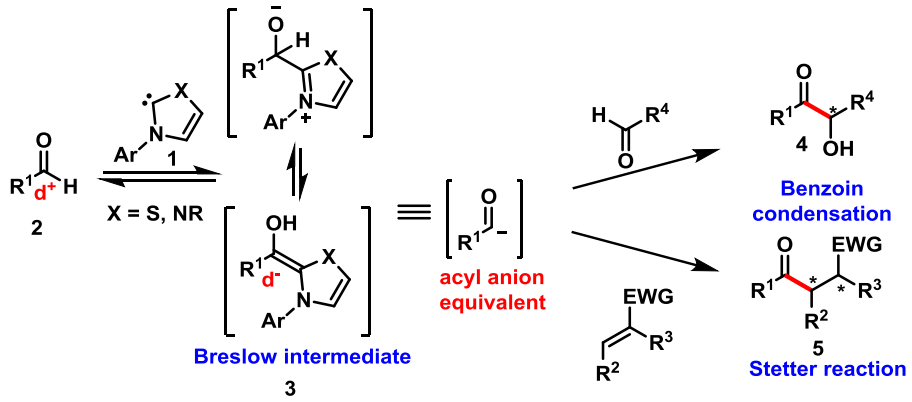
Transition metal mediated/catalyzed reaction is a powerful method for carbon-carbon and carbon-heteroatom bond-forming reactions, but it has some inherent drawbacks like cost of catalyst and toxicity of the metals. Transition-metal-free reactions represent an attractive alternative and, in some cases, offer transformations unparalleled in metal catalysis. In this context, organocatalysis is an emerging area as a useful method for the synthesis of variety of organic compounds. Organocatalysis utilizes small organic molecules to accelerate chemical reactions. Organocatalysts have major advantages like their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which awards a huge direct benefit in the production of pharmaceutical intermediates when compared with (transition)metal catalysts.

Among organocatalysis, one area which has been widely explored in the last two decades is N-heterocyclic carbene (NHC)-organocatalysis, which is versatile and for which a number of modes of actions are known. NHCs belong to one of the most investigated reactive species in the field of organic chemistry. They are neutral species and possess a bivalent carbon atom with an electron sextet. In organocatalysis, NHCs are mainly known for umpolung of aldehydes. The umpolung strategy encompasses all the methods that make organic molecules react in an inverse manner compared to their natural polarity-driven reactivity. This concept entered the field of organocatalysis when it was recognized that NHCs can provide catalytic access to acyl anion equivalents. Since then, tremendous efforts have followed to develop a broad variety of NHC-catalyzed reactions.[1]

The benzoin and Stetter reactions are the most prominent reactions in NHC-catalysis, which proceed via the umpolung of aldehydes. In benzoin condensation, the NHC **1** enables the aldehyde **2** to react with a second aldehyde to provide the *α*-hydroxy ketone product **4** (Scheme 1.1).[2] The Stetter reaction is the NHC-catalyzed conjugate

addition of an aldehyde to a Michael acceptor leading to the formation of 1,4-bifunctional compounds **5**.[3] The key intermediate in these transformations is the formation of Breslow intermediate **3**[2d] and it is achieved by the umpolung of the aldehyde with an NHC. The Breslow intermediates are acyl anion equivalents.

Scheme 1.1: Umpolung of Aldehydes



1.1.1 Important Intermediates in NHC-Catalysis

The majority of organocatalyzed transformations that are proceeding through umpolung are catalyzed by NHCs. NHCs possess several modes of action in which it forms six-important intermediates.

(1) Breslow intermediate (umpolung)

(2) Homoenolate equivalents (conjugate umpolung)

(3) Enolate

(4) Dienolate

(5) Allenoate

(6) Acylazolium and *α,β*-unsaturated acylazolium

It is assumed that the azolium salt is deprotonated in the reaction mixture to afford a nucleophilic carbene **1** (Figure 1.1). Addition of an aldehyde **2** followed by proton transfer affords an enamine type intermediate **3**, referred to as the Breslow intermediate[2], in which the originally electrophilic carbon atom of the aldehyde has gained nucleophilic character. It can then attack a second molecule of aldehyde or a Michael acceptor to furnish the benzoin/Stetter products. However, when an *α,β*-unsaturated aldehyde reacts with NHC, the electrophilic *β*-carbon of the enal can become nucleophilic (homoenolate) **6**,[4] as a result of the presence of conjugated alkene, and react in an a^3 to d^3 umpolung, generating *β*-functionalized carbonyl compounds. In addition to the chemistry of Breslow intermediates, homoenolate intermediate **6** (a three carbon synthon) is the highly explored modes in NHC-catalysis, which allows facile

preparation of diverse ranges of annulated products. Moreover, reactions of α-halo aldehydes and ketenes with NHC affords the enolate intermediate **7** which is a two-carbon synthon normally gives [2+2] and [3+2] annulations.[1i] In some cases where a γ-proton is available on the α,β-unsaturated carbonyl compounds and enals with leaving groups generates NHC-bound dienolate intermediates **8**. These four-carbon synthons normally undergoes [4+x] cyclizations.[5] Furthermore, the reaction of ynals with NHC affords allenoate intermediate **9**, which is a three-carbon synthon and normally participates in [3+2] annulations.[1a] Under external oxidant conditions, reactions of aldehydes with NHC affords electrophilic (normal mode) acylazoliums **10** and α,β-unsaturated acylazolium intermediates **11**, which usually shows esterification and annulation reactions.[6]

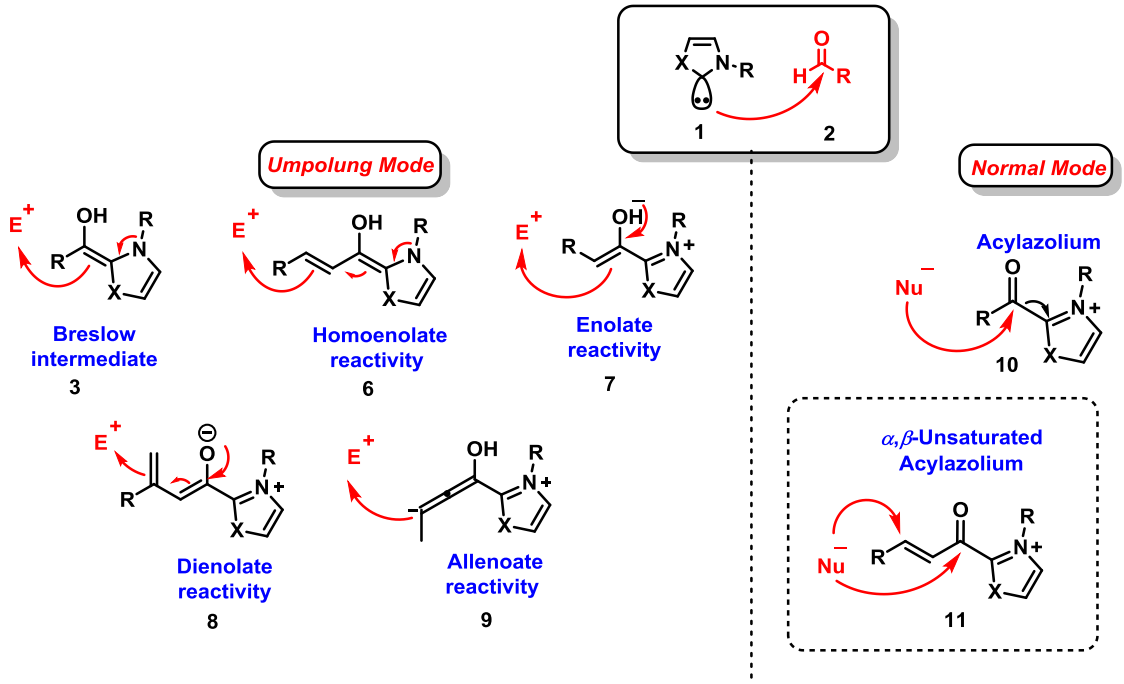
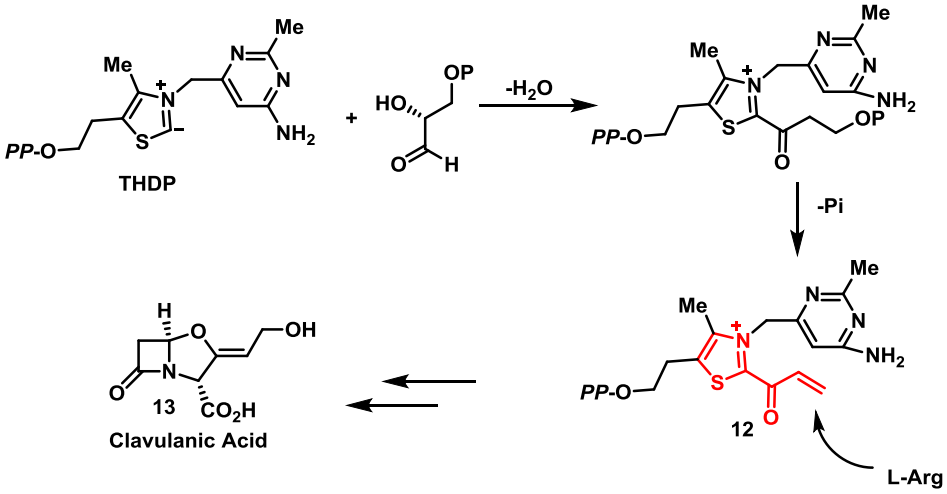


Fig 1.1: Most Prominent Intermediates in NHC-Organocatalysis

1.2. Reactions of α,β-Unsaturated Acylazoliums

In addition to umpolung chemistry, NHCs are also used in catalytic transformations proceeding via the normal mode (*non-umpolung*) of reactivity. One specific example is the generation of α,β-unsaturated acylazolium intermediates using NHCs. Notably, these α,β-unsaturated acylazoliums are the important intermediates in the biosynthesis of clavulanic acid. Townsend and co-workers successfully demonstrated that the conjugate additions of L-arginine to a thiamine diphosphate (ThDP, vitamin B1)-derived α,β-unsaturated acylazolium ion **12** is a key step in the biosynthesis of clavulanic acid **13**, a potent β-lactamase inhibitor (Scheme 1.2).[7]

Scheme 1.2: Biosynthesis of Clavulanic Acid



The important methods for the generation of *α,β*-unsaturated acylazoliums **11** include (*i*) treatment of enals **14** and saturated aldehydes **15** with NHCs followed by stoichiometric oxidation of the generated Breslow intermediate,[8-29] (*ii*) reaction of ynals **21** with NHCs[30-38] (*iii*) the reaction of *α,β*-unsaturated esters **17** or acyl fluorides **20** with NHCs,[39-47] (*iv*) the reaction of 2-bromoenals **16** with NHCs (explained in detail in Chapter 2) and more recently (*v*) from *α,β*-unsaturated acids[48] **18** and amides[49] **19** (Fig 1.2). The methods for the generation of *α,β*-unsaturated acylazoliums and subsequent reactions are presented in the following sections.

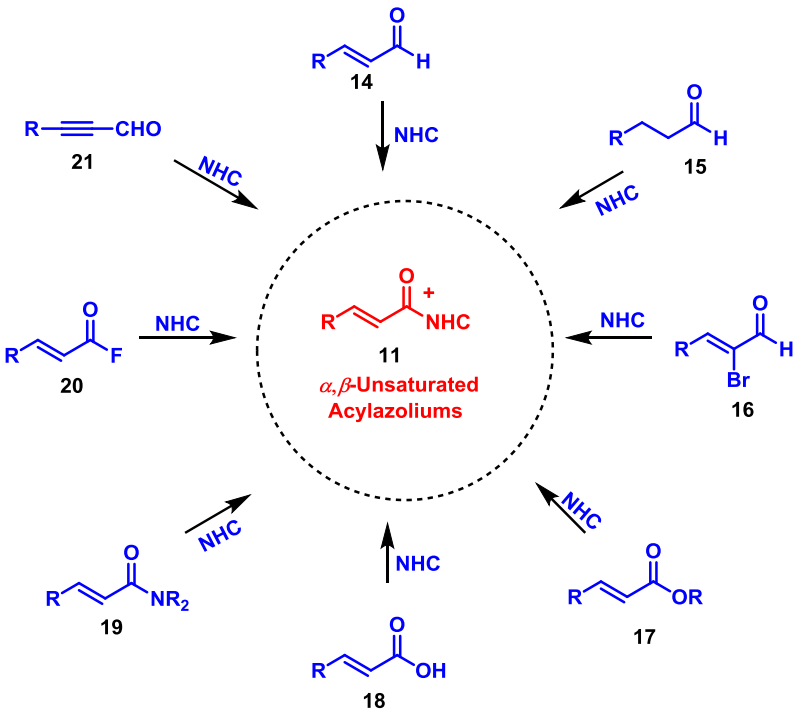
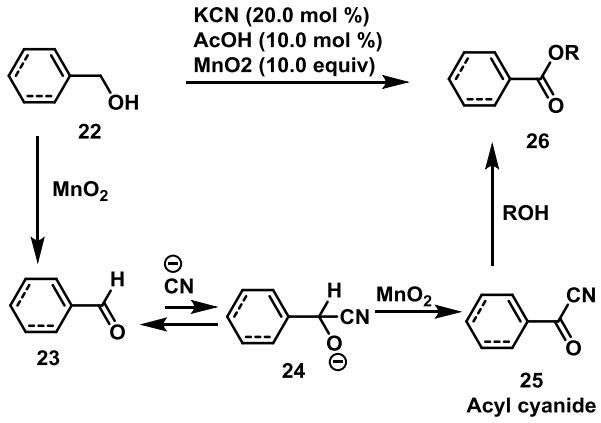


Fig 1.2: Generation of *α,β*-Unsaturated Acylazoliums

1.3. α,β-Unsaturated Acylazoliums from Enals under Oxidative Conditions:

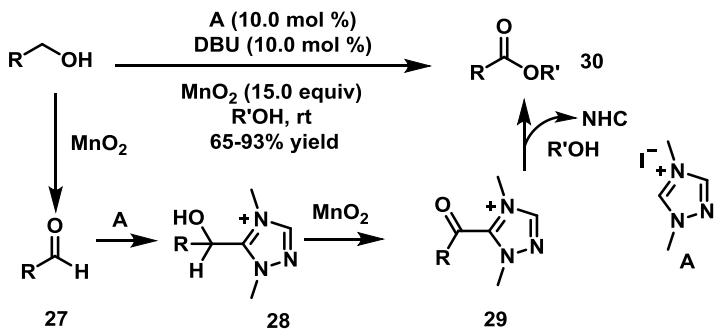
In 1983 Corey and co-workers reported the cyanide-catalyzed oxidation of allylic or benzylic alcohols **22** to esters **26**. Mechanistically, the reaction proceeds via the nucleophilic addition of cyanide ion to α,β-unsaturated aldehyde **23** to generate tetrahedral intermediate **24**. MnO_2 oxidation of **24** furnishes (α,β-unsaturated) acylcyanide **25**, and a subsequent nucleophilic interception of **25** with alcohol gives corresponding ester **26** (Scheme 1.3).[50]

Scheme 1.3: Cyanide-Catalyzed Oxidations



Scheidt and co-workers found that the NHC generated from **A** can efficiently play the role of cyanide in oxidative esterification reactions (Scheme 1.4).[8] A variety of unsaturated esters **30** were prepared from the corresponding allylic, benzylic, and propargylic alcohols in good to excellent yields (65-93%). Notably, desymmetrization of meso-diol gave encouraging results (80% ee) when a chiral triazolium was employed as a catalyst with similar optimized conditions.

Scheme 1.4: NHC-Catalyzed Oxidative Esterifications

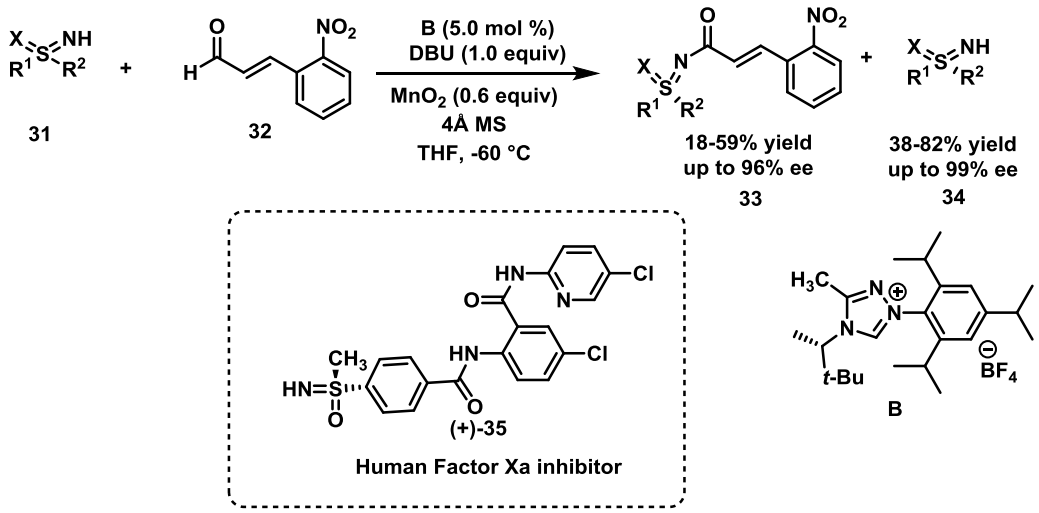


Similar to cyanide ion catalysis, this mechanism involves two oxidation steps: first step involves oxidation of alcohol to aldehyde **27**. Nucleophilic addition of NHC derived from **A** to aldehyde **27** furnishes a transient benzylic alcohol **28**. Oxidation of

28 delivers an activated (*α,β*-unsaturated) acyl azolium **29**, trapping of **29** with an alcohol gives corresponding ester **30** followed by regeneration of the NHC catalyst.

Very recently, Bolm and co-workers reported NHC-catalyzed kinetic resolution of sulfoximines **31** with enals **32** (Scheme 1.5).[9] Notably, the stereoselective amidation proceeds without any additional acyl transfer agent. With the chiral triazolium salt **B**, DBU as base and MnO_2 as oxidant, both enantiomers of the sulfoximines **33** were obtained with excellent ee values (up to 99% ee). Moreover, using the recovered sulfoximine **34** they performed the catalysis on a gram scale and accomplished the asymmetric synthesis of (+)-**35**, which is a human factor Xa inhibitor.

Scheme 1.5: Kinetic Resolution of Sulfoximines

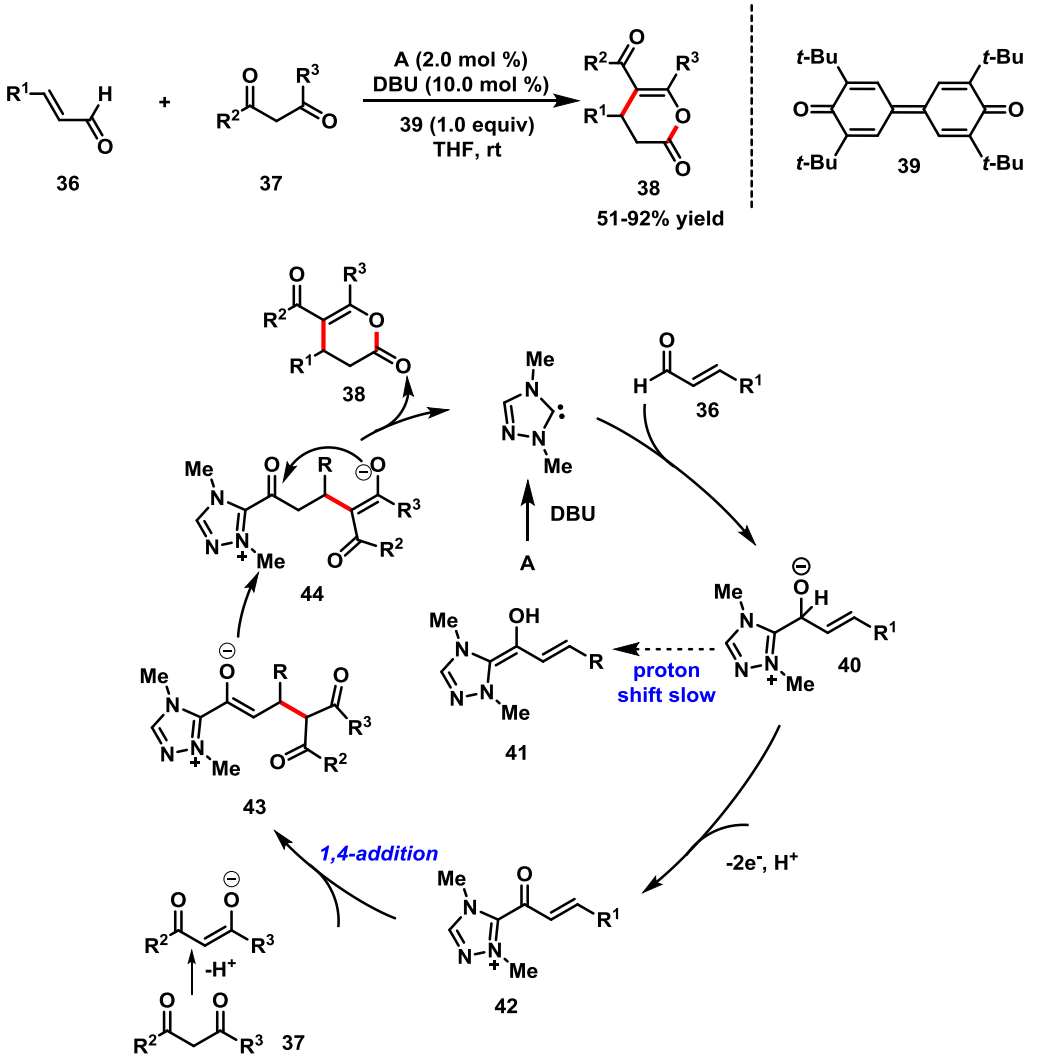


In 2010, Studer and co-workers disclosed the conjugate addition of soft carbon nucleophiles to catalytically generated *α,β*-unsaturated acylazolium ions **42** (Scheme 1.6).[10] Functionalized dihydropyranones **38** were synthesized in good to excellent yields (51-92%). For the first time, they had proposed the oxidation of in situ generated tetrahedral intermediate **40** to the corresponding *α,β*-unsaturated acylazolium species **42** with mild organic oxidant **39** and also they proposed that under optimal conditions, this oxidation is faster than the proton transfer that would lead to the extended Breslow intermediate **41**. Enals **36** with phenyl ring having electron-releasing and -withdrawing groups, heteroaryl, alkyl groups are well tolerated whereas nucleophiles like *β*-diketo and *β*-keto esters were found to be competent to afford desired products. Importantly, quaternary carbon centres were build-up with low catalyst loading (2.0 mol %) and mild reaction conditions (Scheme 1.6). Moreover they had performed experimental and theoretical investigations on mode of addition of nucleophiles to *α,β*-unsaturated

acylazolium ions and found that conjugate addition is more preferable than 1,2-addition.[11]

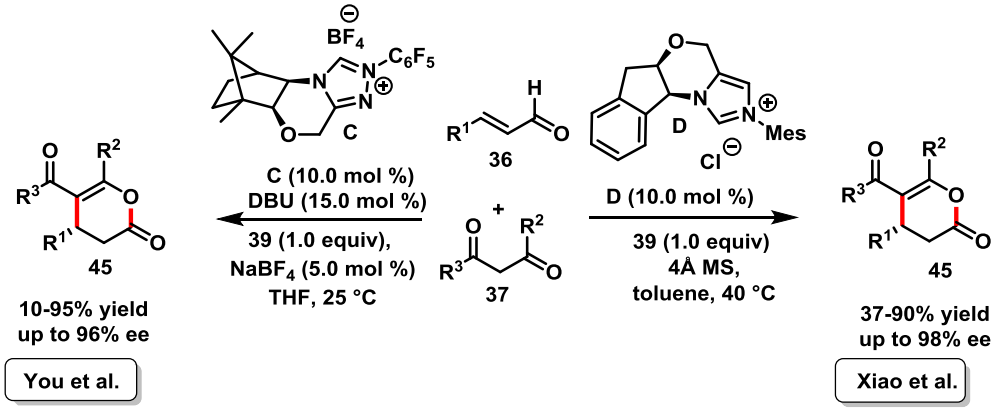
You and Xiao groups independently reported the enantioselective reactions of enals **36** with 1,3-dicarbonyl compounds **37** under oxidative conditions (**39**) (Scheme 1.7).[12] You and co-workers employed *D*-camphor derived precatalyst **C**, DBU as base and $NaBF_4$ as an additive to furnish dihydropyranones in low to good yields (10-95%) and high ee (up to 96%) values.

Scheme 1.6: Synthesis of Dihydropyranone Derivatives.



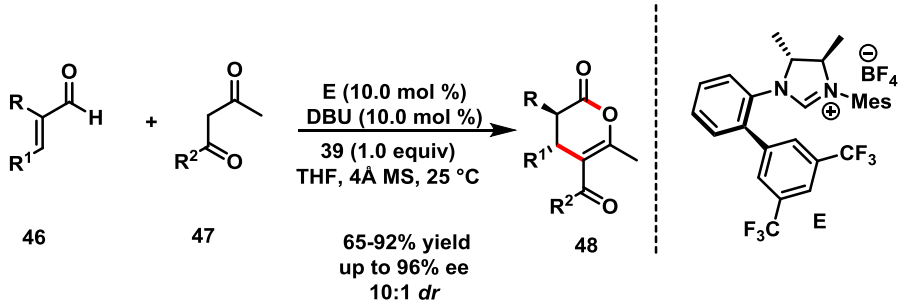
On the other hand, Xiao and co-workers used aminoindanol derived chiral triazolium salt **D** and 4Å MS as an additive to obtain desired products in good yields with excellent selectivities (up to 98%).[13] Interestingly, without addition of base they observed excellent results.

Scheme 1.7: Enantioselective Synthesis of Dihydropyranone Derivatives.



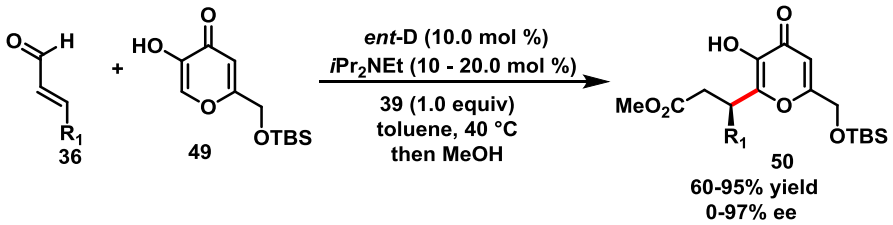
Xu and co-workers generated chiral *α,β*-unsaturated acylazolium species from the challenging *α*-aryl substituted *α,β*-disubstituted unsaturated aldehydes **46** via oxidative NHC-catalysis (Scheme 1.8).[14] With the newly developed C1-symmetric biaryl-saturated imidazolium **E** and DBU as base, various substituted enals **46** and 1,3-dicarbonyl compounds **47** are well tolerated. A broad range of products are accessible with excellent yields (65-92%) and good enantioselectivity (up to 96% ee) with moderate dr values (10:1).

Scheme 1.8: Enantioselective Synthesis of Functionalized Dihydropyranones.



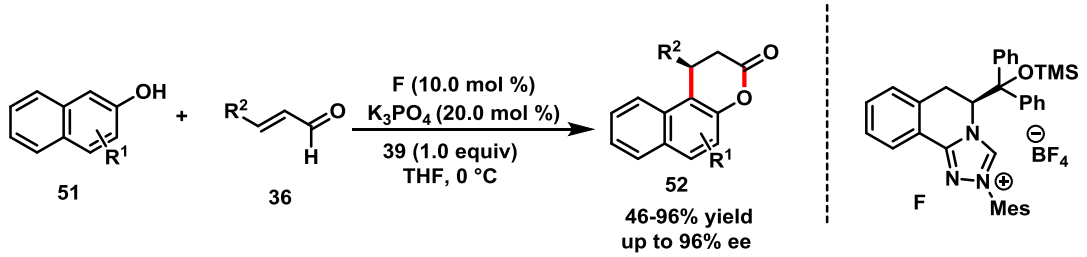
Bode and co-workers utilized kojic acid **49** and naphthol derivatives as nucleophiles in oxidative NHC-catalysis and the corresponding products **50** were obtained in good yields (60-95%) with excellent ee values (up to 97%). Due to instability, the kojic acid products were converted to the stable methyl esters (Scheme 1.9).[15]

Scheme 1.9: Synthesis of Stable Methyl Esters from Kojic Acid Derivatives.



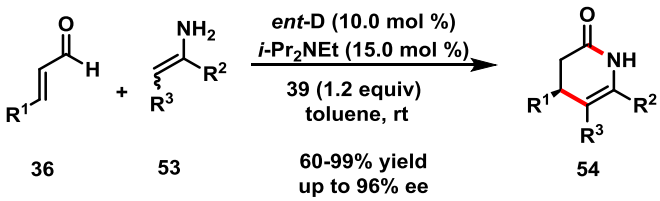
You and co-workers synthesized a series of novel chiral triazolium salts from *L*-phenylalanine derivatives and they successfully demonstrated the application of carbene precursor **F** in an enantioselective annulation of enals **36** with *β*-naphthols **51** (Scheme 1.10).[16] Under the optimized conditions, using chiral triazolium **F** as the carbene precursor, K_3PO_4 as base and **39** as an oxidant, various 2-naphthols **51** reacted with *α,β*-unsaturated aldehydes **36** to form the naphthalene-fused dihydropyranones in good yields (46-96%) and high enantioselectivity (up to 96% ee).

Scheme 1.10: Enantioselective Annulations of Enals with *β*-Naphthols.



Bode and co-workers successfully trapped vinylogous amides **53** with *α,β*-unsaturated acylazolium ions for the enantioselective synthesis of dihydropyridinones **54** via aza-Claisen rearrangement (Scheme 1.11).[17] A variety of enals **36** (aliphatic, alkenyl and aromatic), in combination with the chiral triazolium salt ***ent-D*** and oxidant **39**, served as suitable *α,β*-unsaturated acylazolium precursors and their interception with a large number of unprotected conjugated enamines **53** smoothly afforded 3,4-dihydropyridinones **54** in good yields (60-99%) and high enantioselectivity (up to 96% ee). Moreover, *α′*-hydroxy enones were employed as enal surrogates to expand the scope of this NHC-catalyzed aza-Claisen rearrangement.

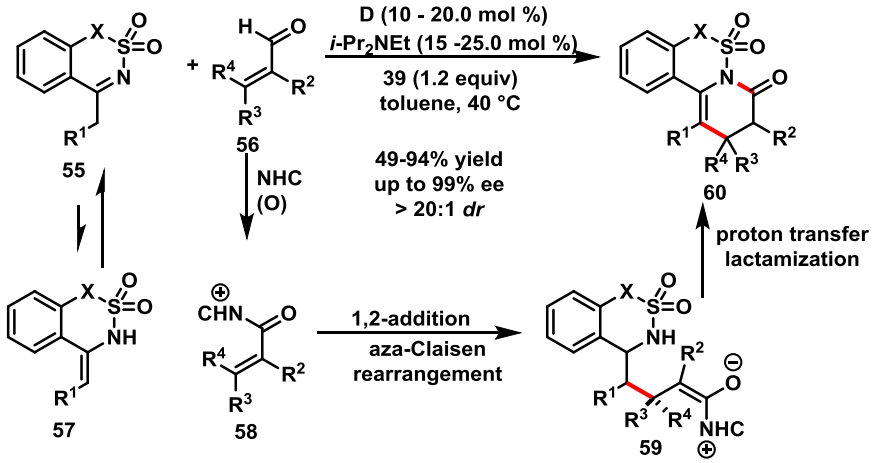
Scheme 1.11: Enantioselective Synthesis of Dihydropyridinone Derivatives.



Later in 2012, the same research group expanded the scope of the reaction with cyclic *N*-sulfonylimines **55** as nucleophilic coupling partners for oxidatively generated *α,β*-unsaturated acylazoliums **58** (Scheme 1.12).[18] Generation of enamine intermediate **57** through tautomerization makes cyclic *N*-sulfonylimines **55** as potent nucleophiles in various Michael addition reactions. Using chiral triazolium salt **D** and Hunig's base under oxidative conditions (**39**), a number of aromatic as well as aliphatic enals acted as

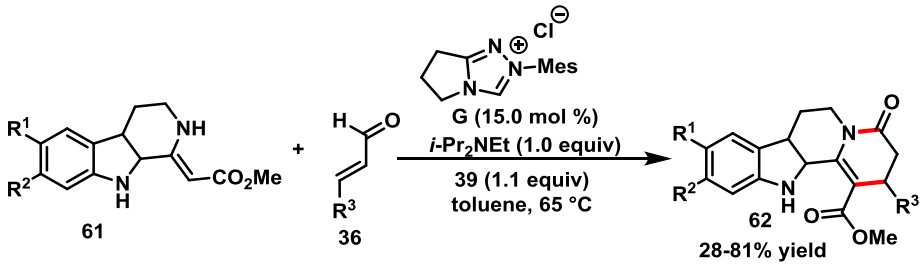
competent precursors for *α*,*β*-unsaturated acylazolium ions. Notably, with this catalytic system, they achieved highly enantio- (up to 99% ee) and diastereoselective (>20:1) "Claisen-type" annulation of *α*-substituted and *β*,*β′*-disubstituted enals. Interestingly, the high levels of diastereoselectivity were explained by substrate-directed protonation, rather than catalyst-directed protonation.

Scheme 1.12: Enantioselective Reactions of Cyclic *N*-Sulfonylimines



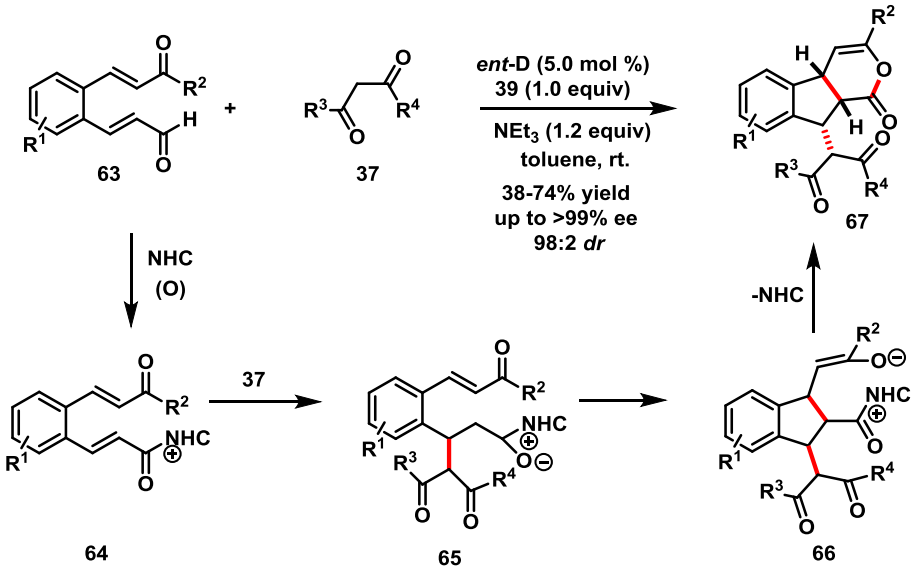
Recently, Du, Lu and co-workers reported similar aza-Claisen type annulation by employing cyclic *β*-enamino esters **61** as nucleophilic coupling partner (Scheme 1.13).[19] Using analogous reaction conditions using mesityl-triazolium salt **G**, the corresponding dihydropyridinones **62** were obtained in good yields (28-81%).

Scheme 1.13: Synthesis of Dihydropyridinone Derivatives.



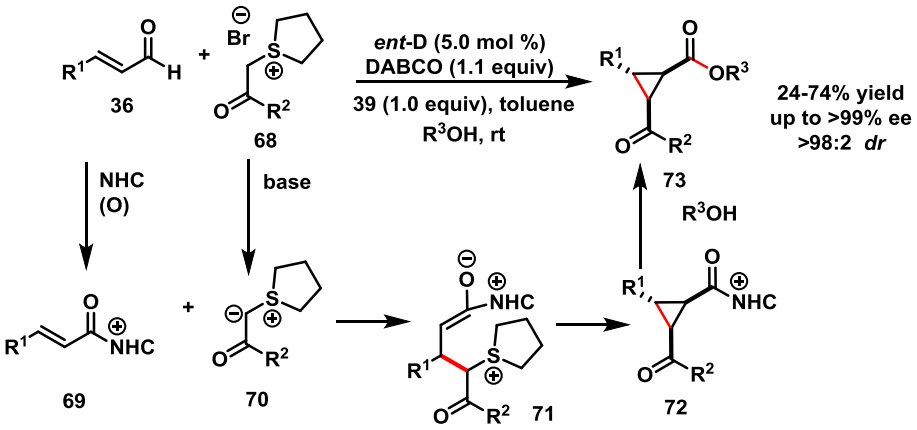
Highly enantio- and diastereo selective synthesis of functionalized indane derivatives **67** was reported by the Studer group (Scheme 1.14).[20] Cascade reaction of enals **63** with *β*-diketones **37** under oxidative NHC-catalysis furnished the products **67** with all three substituents were oriented *cis* to each other. The reaction proceeds via the generation of *α*,*β*-unsaturated acylazolium **64** from enal **63** and NHC generated from **D** in presence of oxidant **39**. Michael addition of **37** to **64** forms enolate intermediate **65** followed by intramolecular Michael addition and subsequent lactonization delivers **67** with regeneration of the NHC. Overall, this cascade includes two sequential C-C bond formations followed by a lactonization.

Scheme 1.14: Enantioselective Synthesis of Indane Derivatives.



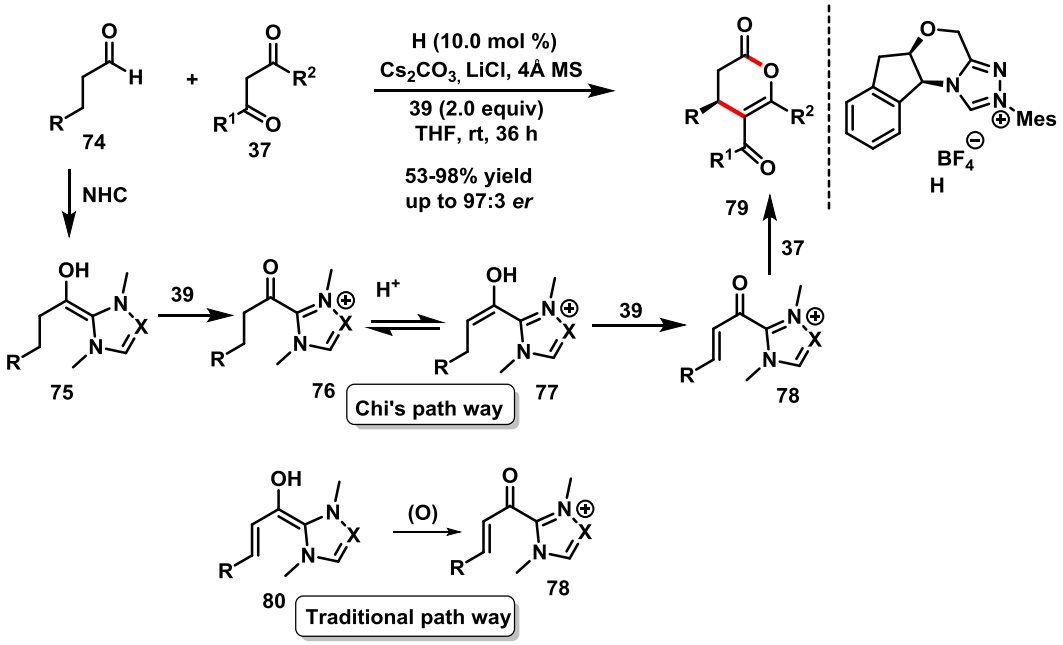
Later, the same group successfully employed oxidative NHC catalysis for enantioselective cyclopropanation reactions (Scheme 1.15).[21] This protocol allows the reaction of enals **36** with sulphur ylides **68** using chiral NHC ***ent*-D** and DABCO as base to form cyclopropyl carboxylic esters **73** in good yields (24-74%) with excellent selectivities. The interception of acylazolium ion **69** with in situ generated sulfur ylide **70** provides enolate **71**. Cyclization of this enol intermediate **71** affords acylazoliun **72**, and interception of **72** by alcohol delivers the product **73**.

Scheme 1.15: Enantioselective Synthesis of Cyclopropyl Carboxylic Esters.



In 2013, Chi and co-workers disclosed the direct functionalization of *β*-carbon atom of saturated aldehydes **74** through oxidative NHC catalysis (Scheme 1.16).[22] The initially formed Breslow intermediate **75** was oxidized to azolium intermediate **76**. The oxidation of NHC-bound enolate intermediate **77** using **39** resulted in the generation of *α*,*β*-unsaturated acylazolium intermediates **78**.

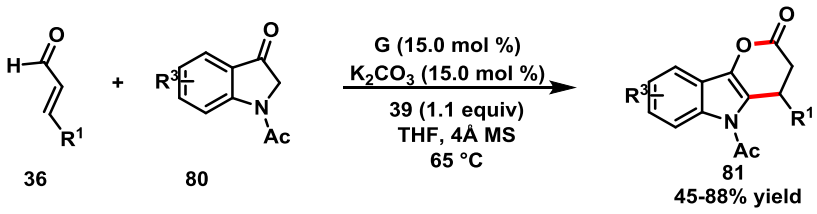
Scheme 1.16: Direct Functionalization of *β*-Carbon Atom of Saturated Aldehydes.



Chi's approach differs from the traditional pathway of oxidation of extended Breslow intermediate **80** to *α*,*β*-unsaturated acylazolium intermediates **78**. In this context, oxidation of the saturated Breslow intermediate **75** provides NHC-bound acylazolium ion **76**, subsequent deprotonation of *α*-CH protons of **76** affords an azolium enolate **77**. Final oxidative process transforms the ester enolate intermediate to **78**. Interception of these *α*,*β*-unsaturated acylazolium intermediates **78**, generated oxidatively from saturated aldehydes, with enolic 1,3- dicarbonyl compounds **37** afforded dihydropyranones in good yields (53-98%) with good ee values (up to 94%).

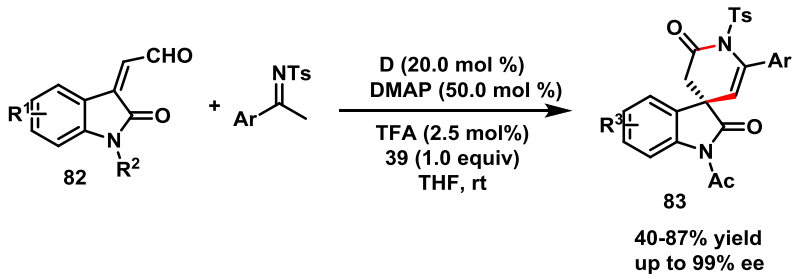
Lu and co-workers described an effective strategy for the synthesis of functionalized 3,4-dihydropyranones **81** via NHC-catalyzed annulation of enals and ynals with indolin-3ones **80** (Scheme 1.17).[23] The reactions proceed smoothly in moderate to high yields with wide substrate compatibility. The reaction using enals **36** with oxidant **39** seems to be more advantageous than the one using ynals without oxidant.

Scheme 1.17: Synthesis of Functionalized Indoles.



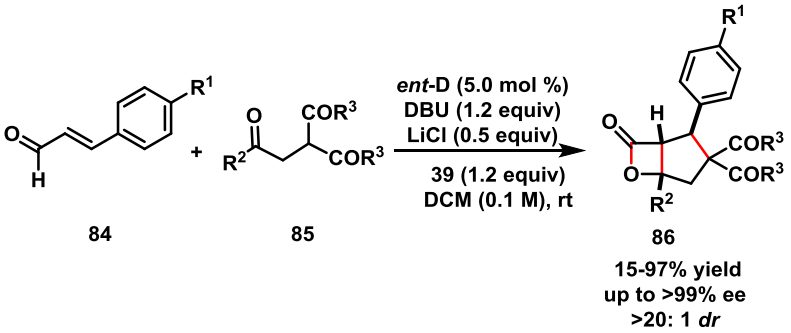
In 2015, Zhong and co-workers introduced oxindole- derived enals **82** as a precursors for the generation of *α,β*-unsaturated acylazolium intermediates under oxidative conditions (Scheme 1.18).[24] Interestingly, better results were obtained with catalytic amounts of TFA. Using aminoindanol derived chiral traizolium salt **D** and DMAP as base in the presence of oxidant **39** resulted in the formation of the spirocylic oxindoles **83** in good yields (40-87%) and excellent enantioselectivity in less than one hour of reaction time.

Scheme 1.18: Enantioselective Synthesis of Spirocompounds



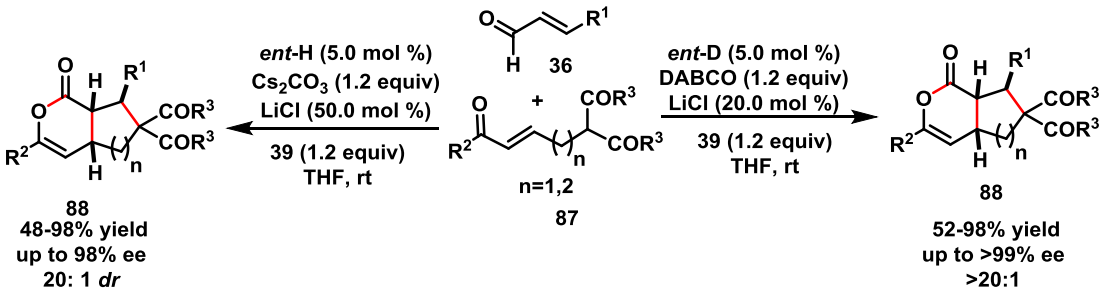
A highly enantioselective synthesis of *β*-lactones through oxidative NHC-catalysis with LiCl as cooperative Lewis acid was disclosed by Studer and co-workers (Scheme 1.19).[25] In these reactions, *α,β*-unsaturated aldehydes **84** are used for the generation of the *α,β*-unsaturated acylazoliums under oxidative conditions, which can then be intercepted with *β*-diketones, *β*-ketoesters, and malonates bearing a *β*-oxyalkyl substituent at the *α*-position **85** to produce desired lactones **86**. The substrate scope was limited to aromatic enals **84**. Enals with phenyl ring bearing both electron-withdrawing and -donating groups underwent efficient Michael additions followed by aldol lactonizations to accomplish *β*-lactones in good yields (15-97%) and excellent selectivity (up to > 99% ee and >20:1 *dr*). Notably, this organocascade comprises two C-C bond formations and one C-O bond formation leading to four contiguous stereogenic centers including two fully substituted stereocenters. Moreover, when the R^2-substituent is a phenyl group, this organocascade provided corresponding cyclopentene derivatives by the decarboxylation of corresponding *β*-lactones. Independent investigations by our group provided a detailed study on the enantioselective synthesis of functionalized cyclopentenes starting from 2-bromoenals as a precursors for the generation of *α,β*-unsaturated acylazoliums.[26]

Scheme 1.19: Enantioselective Synthesis of *β*-Lactones



Very recently the same Studer group expanded the scope of the nucleophile to unsaturated malonate derivatives **87** for the enantioselective synthesis of substituted *δ*-lactones (Scheme1.20).[27] A wide variety of enals **36** and malonate derivatives **87** are well tolerated under optimized conditions using chiral triazolium salt ***ent*-H** as catalyst and LiCl as additive resulting in the synthesis of complex cylcopentane- or cyclohexane-fused *δ*-lactones **88** in high yields (52-98%) with excellent selectivities (up to >99% ee and >99:1 *dr*). Concurrently, Ye and co-workers demonstrated enantioselective synthesis of *δ*-lactones by cooperative NHC-catalysis using chiral catalyst ***ent*-D**, Cs_2CO_3 as base and LiCl as additive under oxidative conditions.[28]

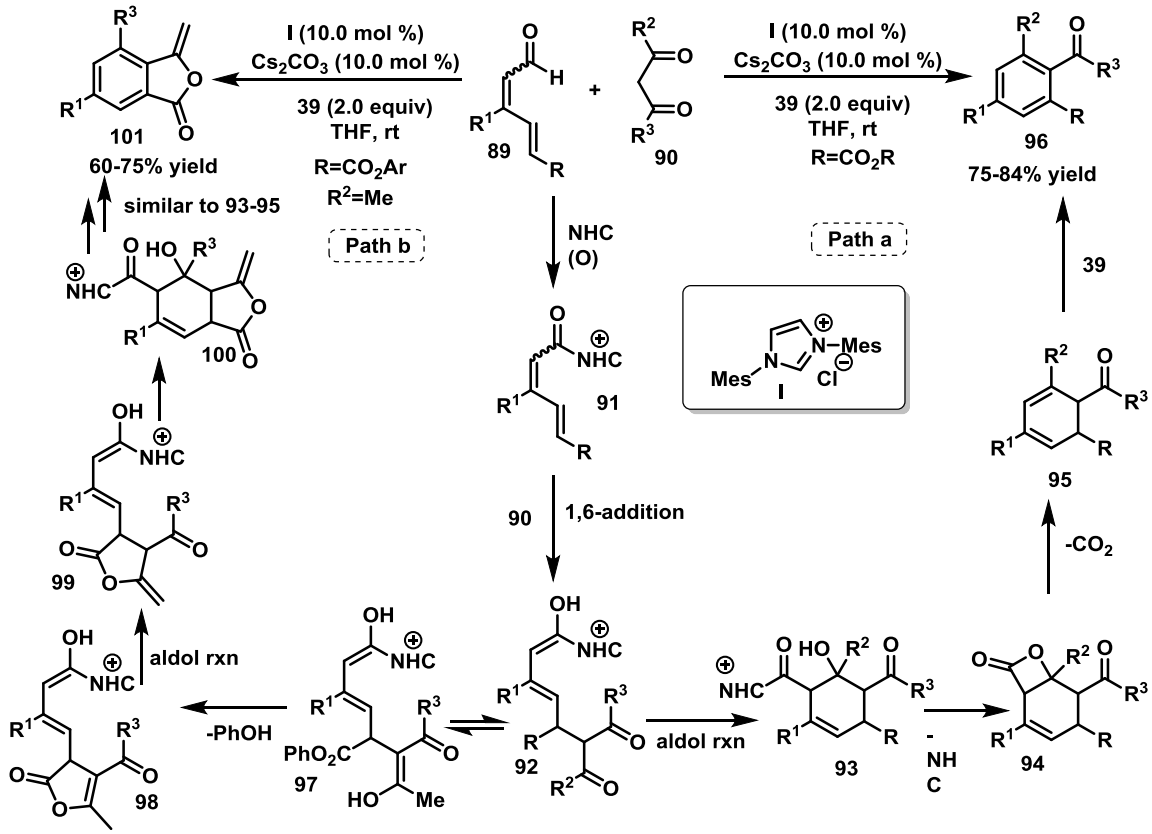
Scheme 1.20: Enantioselective Synthesis of *δ* -Lactones



The synthetic potential of NHC-catalyzed reactions of aldehydes was significantly expanded by introducing additional conjugated C=C bonds to enals, the first NHC-catalyzed activation of the *δ*-carbon of *α*,*β*-*γ*,*δ*-diunsaturated aldehydes **89** was reported by Chi and co-workers (Scheme 1.21).[29] The chemoselectivity issue between the *β*- and *δ*-carbons was addressed by introducing a substituent to block the reactivity of the *β*-carbon. This *δ*-LUMO activated enals under oxidative conditions reacts with 1,3-carbonyls **90** in formal [4+2] path way to afford multi-substituted arenes. The proposed catalytic cycle include oxidative conversion of unsaturated aldehyde **89** to unsaturated acylazolium intermediate **91**. The 1,6-addition of 1,3-diketone **90** to **91** leads to enol intermediate **92**, and a subsequent aldol reaction and

lactonization affords bicyclic adduct **94**, with the regeneration of NHC catalyst. This can then undergo decarboxylation followed by spontaneous oxidative aromatization to provide the multi-substituted benzene product **96**. Whereas, when R is a reactive aryl ester unit (Scheme 1.21, path b), intramolecular transesterification of enol intermediate **97** forms 5-memberd lactone (**97** to **98**). Followed by isomerization (**98** to **99**) and aldol reaction yields **100**, this can undergo further transformations to form the 3-ylidenephthalide product **101** via a process similar to the conversion of **93** to **95**.

Scheme 1.21: NHC-Catalyzed *δ*-Carbon Activation of the Unsaturated Aldehydes

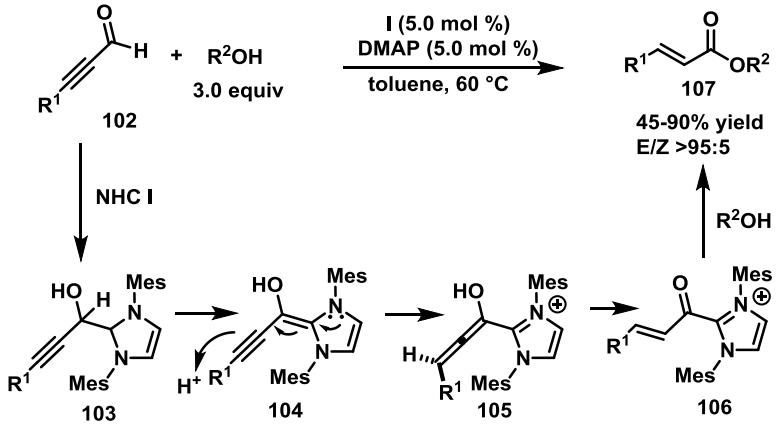


1.4. *α,β*-Unsaturated Acylazoliums from Ynals:

In 2006, Zeitler introduced ynals as precursors for the NHC-catalyzed generation of *α,β*-unsaturated acylazoliums **106**, and reported redox esterification of ynals **102** to provide *α,β*-unsaturated esters **107** (Scheme 1.22).[30] Under optimized reaction conditions, various aryl and aliphatic ynals as well as a range of primary alcohols are well tolerated to furnish desired unsaturated esters in good yields (45-90%) with good selectivity. The proposed mechanism involves the generation of tetrahedral intermediate **103** by 1,2-addition of **I** to ynal **102**. This can then generate the unsaturated Breslow intermediate **104** by tautomerization, followed by protonation results allenol

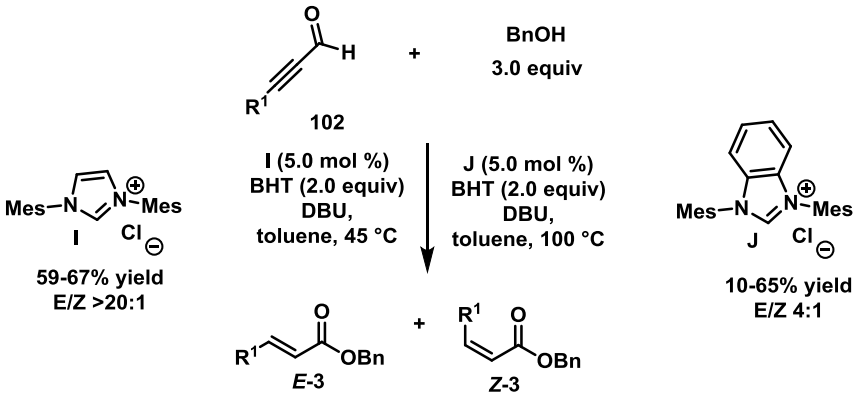
intermediate **105**. The allenol **105** can undergo rapid tautomerization to afford *α,β*-unsaturated acylazolium **106**. Interception of **106** with alcohol provides the corresponding unsaturated esters **107**.

Scheme 1.22: Redox Esterification of Ynals



Moreover, the effect of catalyst on the yield and stereoselectivity in analogous NHC-catalyzed esterification reactions was demonstrated by Scheidt and co-workers (Scheme 1.23).[31] Using imidazolium salt **I** and a bulky proton source (BHT = 2,6-di-tert-butyl-4-methylphenol), the desired unsaturated esters **107** were obtained in good yields (59-67%) and high selectivity (*E*/*Z* >20:1).

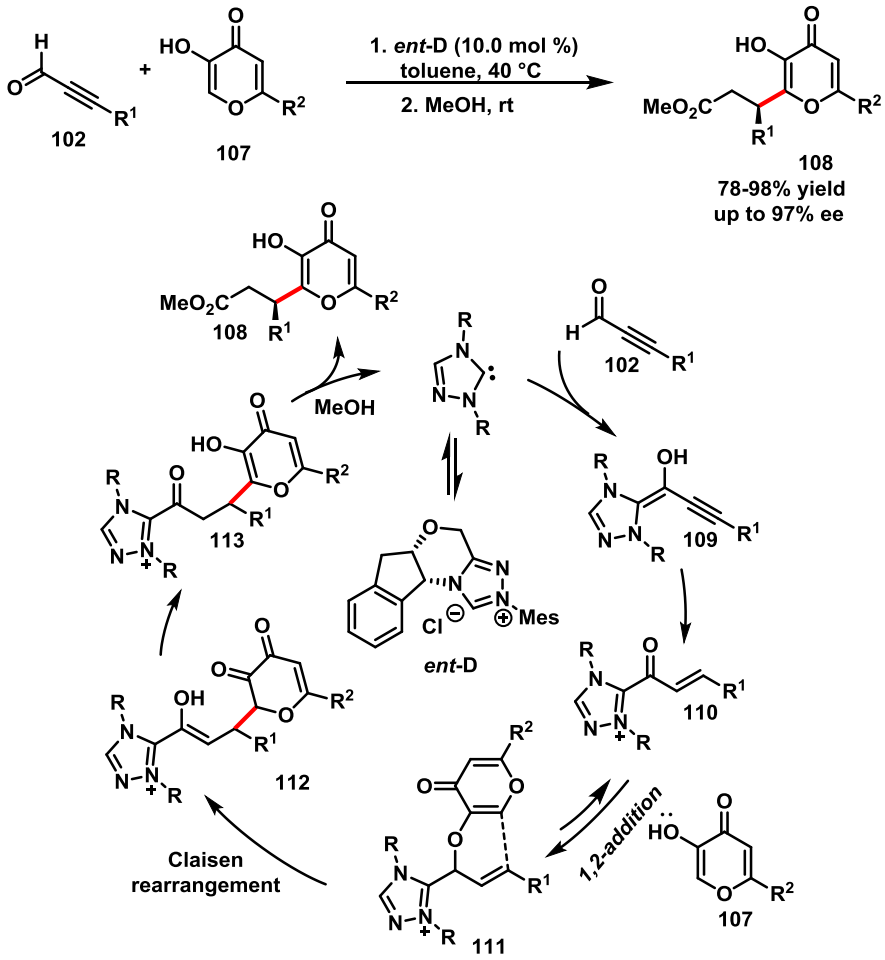
Scheme 1.23: Synthesis of Unsaturated Esters



Bode and co-workers reported coupling of ynals to enolic C-nucleophiles such as kojic acids with good enantioselectivity (Scheme 1.24).[32] With chiral triazolium salt ***ent*-D**, various aliphatic and aryl ynals **102** as well as aliphatic groups on the kojic acid component **107** are well tolerated (78-98%). Interestingly, studies on the effect of the counterion of the triazolium precatalyst showed that with more basic counterions like Cl^- and AcO^- ,the free carbene will generate to some extent without any added base.

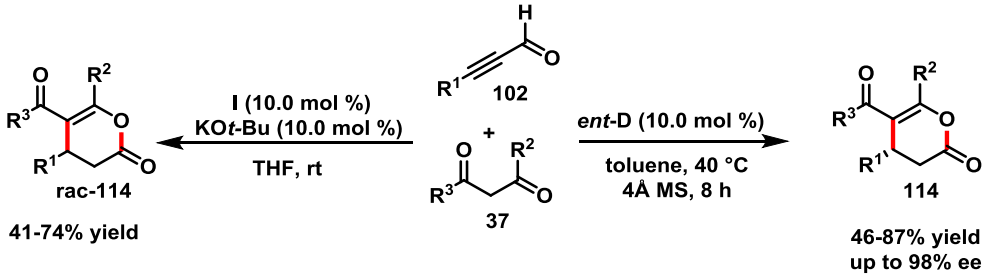
Based on kinetic studies, the authors proposed initial formation of the Breslow intermediate **109**, followed by protonation to provide *α,β*-unsaturated acylazolium **110**. Reversible 1,2-addition of enol **107** to **110** affords a kinetically important hemiacetal intermediate **111**. This intermediate **111** undergoes a [3,3]-sigmatropic Coates-Claisen rearrangement to give **112**, tautomerization and lactonization of **112** provides dihydropyranone which upon methanolysis (work up) gives corresponding product **108**. Moreover, theoretical investigations on mode of addition of nucleophile to *α,β*-unsaturated acylazolium proved that 1,2-addition is more favoured than 1,4-additions unlike related reports by the Studer group.[33,34]

Scheme 1.24: Reactions of Kojic Acid Derivatives



Xiao and co-workers developed a synthetically useful annulation reaction between ynals **102** and 1,3-dicarbonyl compounds **37** for the mild construction of 3,4-dihydropyranones **114** in moderate to good yields (41-74%) (Scheme 1.25).[35]

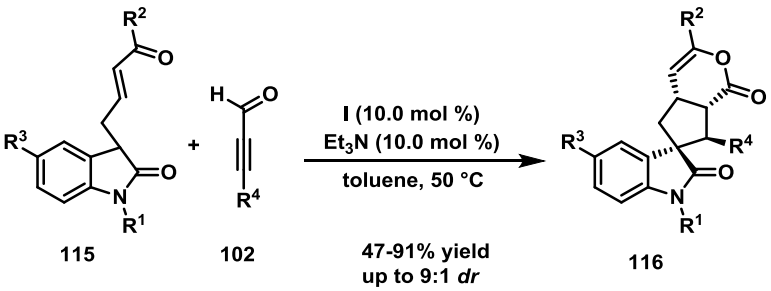
Scheme 1.25: Synthesis of Dihydropyranones from Ynals



Notably, with the enantiopure aminoindanol derived triazolium salt ***ent*-D**, a variety of substrates (aryl and aliphatic) were well tolerated to afford the desired 3,4-dihydropyranones **114** in good yields (46−87%) and high enantioselectivity (up to 98% ee, Scheme 1.25).[13] Moreover, use of 4 Å molecular sieves as additive improved the yields as the intermediate *α*,*β*-unsaturated acylazolium species is highly sensitive to residual moisture. Similar to Bode and co-workers observation, they found that use of base was not necessary to generate the active carbene species.

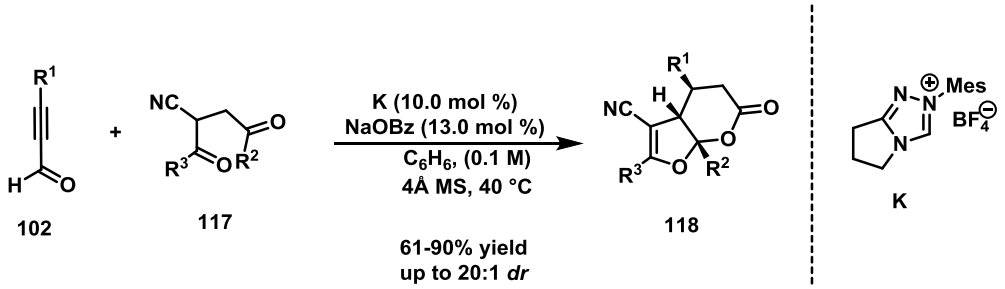
Li and co-workers designed a Michael donor-acceptor oxindole synthon **115** and developed an NHC-organocatalytic Michael/Michael/lactonization cascade reaction (Scheme 1.26).[36] A variety of ynals **102** and oxindole derivatives **115** are competent in this reaction, providing spirocompounds **116** in good yields (47-91%) with moderate selectivity. Notably, this cascade process afforded tricyclic oxindole system with four contiguous stereogenic centers, including an all-carbon spiro quaternary center.

Scheme 1.26: Synthesis Spirocompounds from Ynals



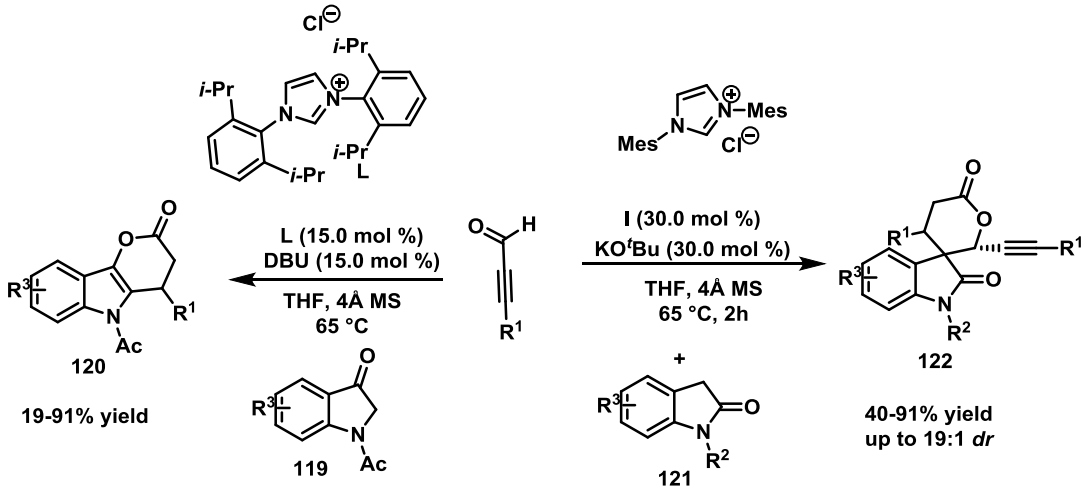
α-Cyano-1,4-diketones **117** were employed as nucleophilic coupling partners to *α*,*β*-unsaturated acylazolium species generated from ynals **102** by Alexakis and co-workers (Scheme 1.27).[37] Using a bicyclic mesityl triazolium precursor **K** and NaOBz as base, a wide range of substrates gave the 4,5-dihydro-3*H*-(furo)pyran-6-one **118** products in good yields (61-90%) and good diastereoselectivity (up to 20:1 *dr*).

Scheme 1.27: Reaction of Ynals with *α*-Cyano -1,4-Diketones



Du, Lu, and co-workers reported the synthesis of chiral spirooxindole derivatives **122** by the reaction of oxindoles **121** with ynals (Scheme 1.28).[38] Using IMes.HCl **I** and KO*t*-Bu as optimal conditions, substrates with different substitution patterns on both the ynal and oxindole are well tolerated, spirooxindoles were obtained in moderate to high yields (40-91%) and good diastereoselectivity (up to 19:1 *dr*).

Scheme 1.28: Selective Reactions of Ynals with Indolinones



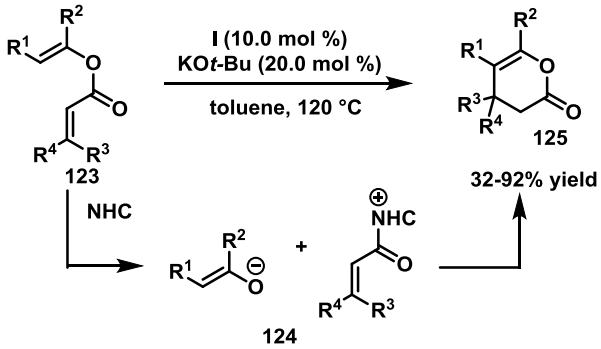
Moreover, the same research group employed the isomeric indolin-3-ones **119** as nucleophilic reaction partners in an annulations with *α,β*-unsaturated acylazolium ions (Scheme 1.28).[23] With imidazolium carbene precursor **L** and DBU as base, the reaction tolerates a variety of aryl-substituted ynals and afforded the desired tricyclic indole products **120** in moderate-to-good yields (19-91%).

1.5. *α,β*-Unsaturated Acylazoliums from *α,β*-Unsaturated Enol Esters and *α,β*-Unsaturated Acyl Fluorides:

In 2009, Lupton and co-workers reported the generation of *α,β*-unsaturated acylazolium species from a carbene-induced fragmentation of *α,β*-unsaturated enol esters **123** (Scheme 1.29).[39] The recombination of corresponding acylazolium/enolate ion pair **124** furnished 2,3-dihydropyranones **125**. Aromatic, heteroaromatic, and

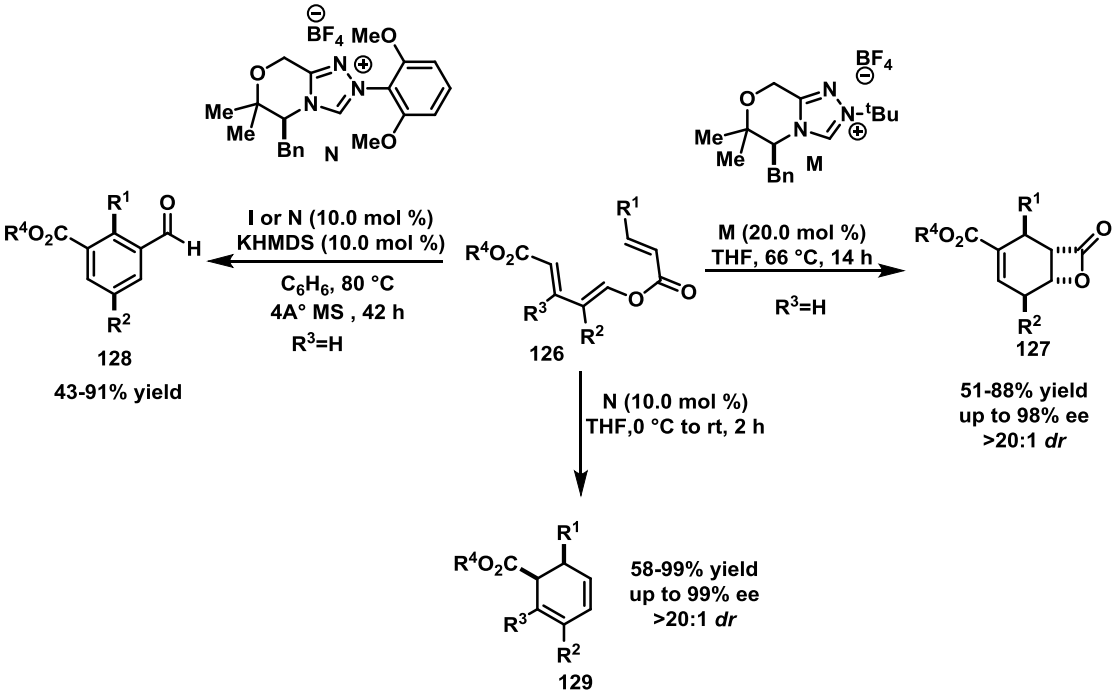
aliphatic α,β-unsaturated esters **123** underwent efficient annulation to the corresponding dihydropyranones. Notably, *β*-disubstituted enol esters reacted smoothly for the construction of quaternary carbon centres.

Scheme 1.29: Annulation of *α,β*-Unsaturated Enol Esters



Moreover, when they extended the scope of *α,β*-unsaturated enol esters **124** to dienyl esters **126** different reactivity pattern was observed depending on substitution pattern and carbene precursors (Scheme 1.30).

Scheme 1.30: Annulation Reactions of Dienyl Esters

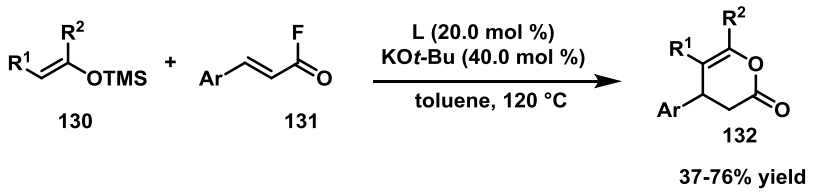


The underlying principle of these transformations was the interception of in situ generated *α,β*-unsaturated acylazoliums with dienolates. When dienyl esters **126** were treated with chiral *N*-alkyl triazolium precursor **M,** these reactions underwent all-carbon [4+2] annulation to afford cyclohexyl *β*-lactones **127** in good yields with excellent selectivities.[40] Notably, change of reaction conditions to *N*-aryl triazolium precursor **N**, KHMDS as base and benzene as solvent under reflux, the reaction selectively afforded

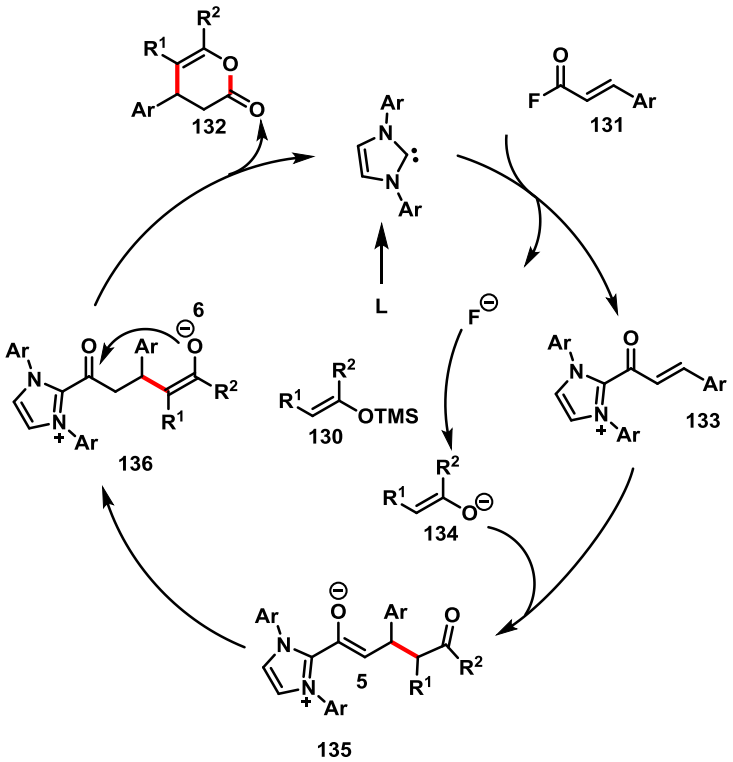
benzaldehyde derivatives **128** in excellent yields (43-91%).[41] Very recently, they reported NHC-catalyzed regenerative [4+2] annulations with substituted (R^3) dienyl esters **126**. Using chiral NHC generated from **N** under mild reaction conditions, cyclohexadienes **129** were furnished in excellent selectivities (up to 99% ee, >20:1 *dr*).[42]

Interestingly, the same research group successfully accessed *α,β*-unsaturated acylazolium species from a combination of *α,β*-unsaturated acyl fluorides **131** and TMS enol ethers **130** (Scheme 1.31).[39,43-45] Aromatic *α,β*-unsaturated acyl fluorides and cyclic enol ethers underwent smooth conversions to the corresponding dihydropyranones **132** in presence of carbene precursor **L** and KO*t*-Bu in good yields (37-76%).

Scheme 1.31: Synthesis of Dihydropyranones from Unsaturated Acyl Fluorides



Scheme 1.32: Proposed Mechanism for the Synthesis of Dihydropyranones

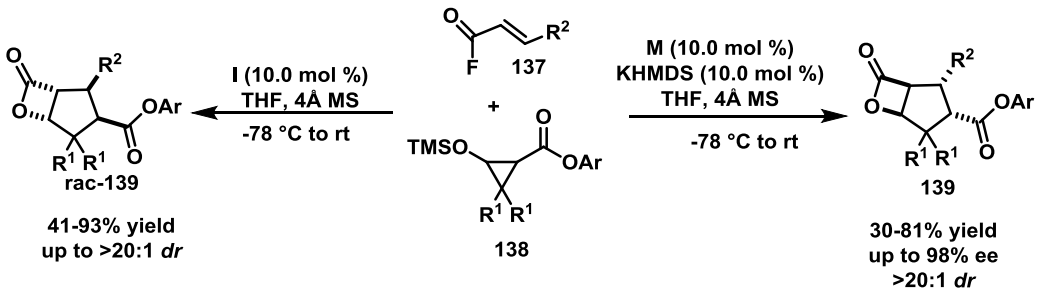


The proposed a mechanism for this transformation is shown in (Scheme 1.32). Initial interception of NHC to acyl fluoride generates the *α,β*-unsaturated acylazolium

species **133**, by liberating a fluoride ion. Fluoride ion induced desilylation of the TMS enol ether **130** affords enolate **134**. This can then undergo 1,4-addition to **133** to furnish azolium enolate **135**. The latter can undergo tautomerization to give acylazolium **136**, subsequent lactonization provides the desired dihydropyranone product **132** and regenerate the carbene catalyst.

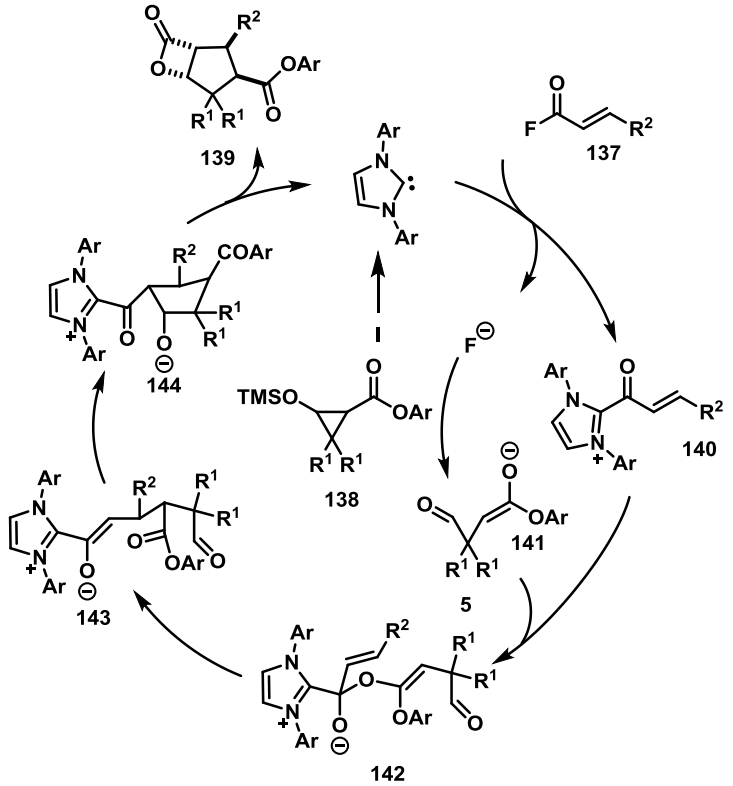
Recently, the Lupton group reported the coupling reactions of *α*,*β*-unsaturated acyl fluorides **137** with silylated push-pull cyclopropanes **138** via NHC-catalyzed Ireland-Coates-Claisen rearrangement. Under optimal conditions, electron-rich and electron-poor α,*β*-unsaturated acyl fluorides are well tolerated, highly functionalized *β*-lactones **rac-139** were synthesized in good yields (41-93%) with excellent stereo selectivity (>20:1 *dr* in all cases) (Scheme 1.33).[46,47]Moreover, they reported the enantioselective variant of this transformation using chiral triazolium precursor **M**. The corresponding functionalized *β*-lactones **139** were accomplished in moderate to good enantioselectivity (up to 98% ee).

Scheme 1.33: Stereoselective Synthesis of *β*-Lactones



The proposed mechanism involves the addition of the free carbene to *α*,*β*-unsaturated acyl fluoride **137** to form the corresponding *α*,*β*-unsaturated acylazolium **140** (Scheme 1.34). Fluoride induced desilylation followed by retro-aldol reaction affords bifunctional enolate **141**. This can then intercepts with the acylazolium to form hemiacetal **142**. Ireland−Coates−Claisen rearrangement of **142** result the alkoxide **143**, which can undergo aldol cyclization followed by lactonization to afford the desired product **139** and regenerate free carbene.

Scheme 1.34: Proposed Mechanism for *β*-Lactones

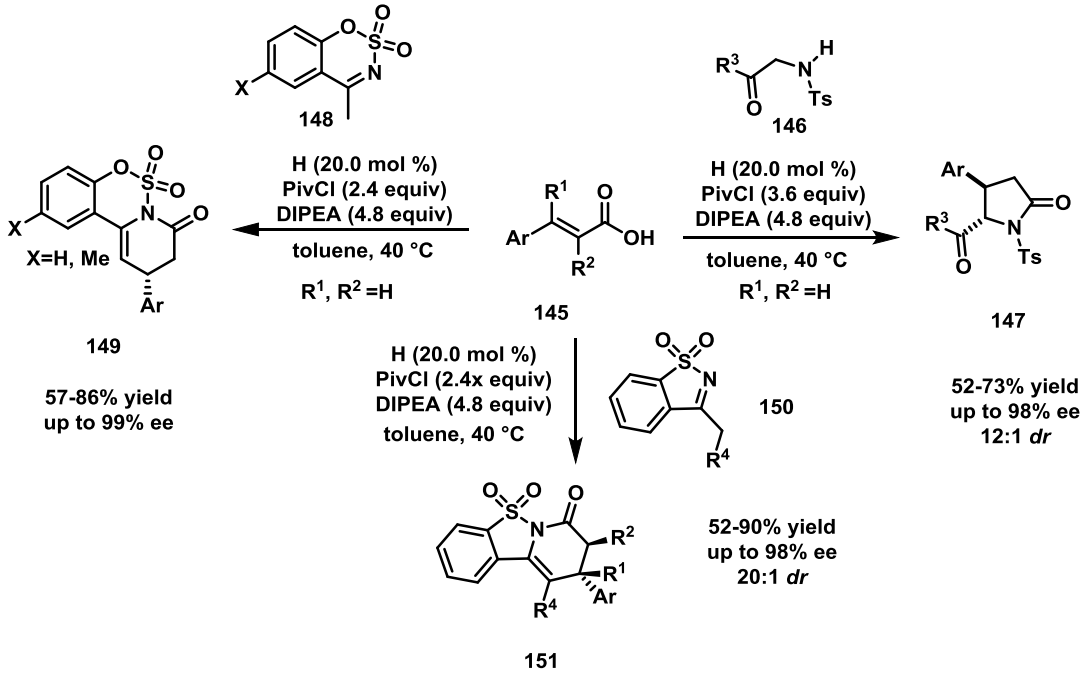


1.6. *α,β*-Unsaturated Acylazoliums from *α,β*-Unsaturated Acids

Recently, Ye and co-workers introduced *α,β*-unsaturated carboxylic acids **145** as *α,β*-unsaturated acylazolium precursors (Scheme 1.35).[48] They reported the enantioselective synthesis of *γ*-butyrolactams by employing *α*-amino ketones **146** as 1,2-bis(nucleophiles). Using chiral catalyst **H**, PivCl as coupling agent, the desired *γ*-butyrolactams **147** were synthesized in good yields (52-73%) moderate selectivity (up to 12:1 *dr*) and high ee value (up to 98% ee). Furthermore, sulfamate-derived cyclic imines **148** as 1,3-bis(nucleophiles) afforded the corresponding dihydropyranones **149** in good yields (57-86%) and excellent enantioselectivity (up to 99%) with same optimized conditions.

Finally, sultam-derived cyclic imines **150** were also successfully employed as potential substrates for the [3 + 3] cyclocondensation with *α,β*-unsaturated acids. A range of α,β-unsaturated carboxylic acids tolerated to provide the desired tricyclic sultams **151** in good yields (52-90%) and with high enantioselectivity (up to 98% ee). Noatably, *β,β*-disubstituted and *α,β*-disubstituted acids also reacted to furnish the products with quaternary carbon centers or multiple stereogenic centers, respectively.

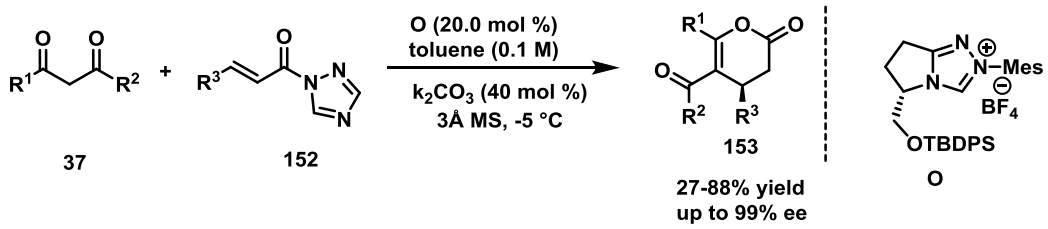
Scheme 1.35: Enantioselective Annulations of *α,β*-Unsaturated Carboxylic Acids



1.7. *α,β*-Unsaturated Acylazoliums from *α,β*-Unsaturated Amides

Very recently, Enders and co-workers disclosed the activation of *α,β*-unsaturated *N*-acyltriazoles **152** for the generation of *α,β*-unsaturated acylazolium intermediates (Scheme 1.36).[49] This allows enantioselective synthesis of dihydropyranones **153** through [3+3] cycloaddition with 1,3-dicarbonyl compounds **37**. Under optimized conditions the corresponding products were formed in good yields (27-88%) with high enantioselectivities (up to 99% ee)

Scheme 1.36: Enantioselective Annulations of *α,β*-unsaturated Amides



1.8. *α,β*-Unsaturated Acylazoliums from 2-Bromoenals

Generation of α,β-unsaturated acylazolium intermediates from 2-bromoenals has been explained in details in Chapter 2 (Section 2.2.2).

1.9. Focal Theme of the Thesis

With the broad diversity of chemistry discussed above, it is clear that the *α,β*-unsaturated acylazolium chemistry is an emerging area in NHC-organocatalysis. The success of *α,β*-unsaturated acylazolium chemistry is attributed to their mild methods of generation and versatility in the starting materials. More importantly, use of chiral *α,β*-unsaturated acylazoliums can lead to the construction of complex chiral molecules from simple starting materials. The focal theme of this thesis is the interception of chiral *α,β*-unsaturated acylazoliums with various bifunctional nucleophiles. If successful, this can result in the enantioselective construction of various six-membered heterocycles and carbocycles.

Dihydropyranones and dihydropyridinones are important core moieties present various biologically active compounds. However, their enantioselective synthesis had some drawbacks such as stability of starting materials and low enantioselectivity. More importantly enantioselective synthesis of both dihydropyranones and dihydropyridinones from the same stable starting materials to the best our knowledge is unknown. The detailed study on enantioselective coupling reaction of 1,3-dicarbonyl compounds, enamides and 4-hydroxycoumarins for the synthesis of both dihydropyranones and dihydropyridinones has been provided in Chapter 2.

Moreover, NHC-catalyzed coupling reactions of aldehydes can lead to either benzoin products or *γ*-buterolactones. Use of enolizable aldehydes as nucleophilic coupling partners to the electrophilic *α,β*-unsaturated acylazoliums generated from stable 2-bromoenals for the enantioselective synthesis of 4,5-disubstituted dihydropyranones has been presented in Chapter 3.

Pyrazole and pyrazolone derivatives are the important building blocks of various biologically active compounds. In view of their biological importance, we envisioned the utility of pyrazolones in asymmetric NHC-catalysis. We have observed the switchable selectivity in the nucleophilic addition of pyrazolones to *α,β*-unsaturated acylazoliums. This study also provided the enantioselective synthesis of functionalized pyrazolones. These details are presented in Chapter 4 of the thesis.

Interestingly, vinologous Michael-additions have received only scant attention in *α,β*-unsaturated acylazolium chemistry. In this context, use of *α*-arylidene pyrazolinones as dienolate precursors in *α,β*-unsaturated acylazoliums chemistry has been investigated. An unexpected reactivity in coupling reactions of *α*-arylidene

pyrazolinones with enals leading to the enantioselective synthesis of spirocyclohexadienones has been documented in Chapter 5.

1.10. References

1. For recent reviews on NHC catalysis: (a) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F.; *Nature* **2014**, *510*, 485. (c) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (d) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (e) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (f) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 351. (g) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. (h) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53. (i) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (j) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295. (k) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res*. **2011**, *44*, 1182. (l) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (m) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5606.
2. For early reports on Benzoin: (a) Wohler, F.; Liebig. J. *Ann. Pharm.* **1832,** *3*, 249. (b) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995. (c) Ugai, T.; Tanaka, S.; Dokawa, S.; Yakugaku Zasshi. **1943**, *63*, 296. (d) Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.
3. For selected reviews on Stetter reactions see: (a) Yetra, S. R.; Patra, A.; Biju, A. T. *Synthesis* **2015**, *47*, 1357. (b) Read de Alaniz, J.; Rovis, T. *Synlett*. **2009**, 1189. (c) Rovis, T. *Chem. Lett*. **2008**, *37*, 2. (d) Stetter, H. *Angew. Chem. Int. Ed. Engl*. **1976**, *15*, 639.
4. For initial reports on NHC-catalyzed homoenolate chemistry, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370; (b) Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed*. **2004**, *43*, 6205.
5. For related reports on NHC-bound dienolates see: (a) Shen, L.-T.; Shao, P.-L.; Ye, S. *Adv. Synth. Catal*. **2011**, *353*, 1943. (b) Mo, J.; Shen, L.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810. (c) Chen, X.; Yang, S.; Song, B. A.; Chi, Y. R. *Angew. Chem., Int., Ed.* **2013**, *52*, 11134. (d) Zhu, T.; Zheng, P.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. *Nat. Commun*. **2014,** *5*, 5027.
6. For reviews on oxidative NHC-catalysis, see: (a) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. Eur. J.* **2013**, *19*, 4664. (b) Knappke, C. E. I.;

Imami, A.; Jacobi von Wangelin, A. *ChemCatChem*, **2012**, *4*, 937. for an account of azolium chemistry, see: (c) Mahatthananchai, J.; Bode, J.W. *Acc. Chem. Res*. **2014**, *47*, 696.

7. (a) Khaleeli, N.; Li, R.; Townsend, C. A. *J. Am. Chem. Soc*. **1999**, *121*, 9223. (b) Merski, M.; Townsend, C. A. *J. Am. Chem. Soc*. **2007**, *129*, 15750.
8. Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett*. **2007**, *9*, 371.
9. Dong, S.; Frings, M.; cheng, H.; Wen, J.; Zhang, D.; Raabe, G.; Bolm, C. *J. Am. Chem. Soc*. **2016**, *138*, 2166.
10. De Sarkar, S.;Studer, A. *Angew. Chem., Int., Ed.* **2010**, *49*, 9266.
11. Samantha, R. C.; Maji, B.; De Sarkar, S.; Bergander, K.; Fröhlich, R.; Mück-Lichtenfeld, C.; Mayr, H.; Studer, A. *Angew. Chem., Int., Ed.* **2012**, *51*, 5234.
12. Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett*. **2011**, *13*, 4080.
13. Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun*. **2011**, *47*, 8670.
14. Lu, H.; Liu, J-Y.; Li, C-G.; Lin, J-B.; Liang, Y-M.; Xu, P-F *Chem. Commun*. **2015**, *51*, 4473.
15. Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494.
16. Li, G-T.; Gu, Q.; You S-L *Chem. Sci.* **2015**, *6*, 4278.
17. Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378.
18. Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433.
19. Hu, S.; Wang, B.; Zhang, Y.; Tang, W.; Fang, M.; Lu, T.; Du D. *Org. Biomol. Chem*. **2015**, *13*, 4661.
20. Biswas, A.; De Sarkar, S.; Fröhlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966.
21. Biswas, A.; De Sarkar, S.; Tebben, L.; Studer, A. *Chem. Commun.* **2012**, 48, 5190.
22. Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem., Int. Ed*. **2013**, *52*, 8588.
23. Lu, Y.; Tang, W.; Zhang, Y.; Du, D.; Lu, T.; *Adv. Synth. Catal.* **2013**, *355*, 321.
24. Xie, D.; Yang, L.; Lin, Y.; Zhang, Z.; Chen, D. Zeng, X.; Zhong G. *Org. Lett.* **2015**, *17*, 2318.
25. Bera, S.; Samanta, R. C.; Daniliuc C. G.; Studer, A. *Angew. Chem., Int. Ed*. **2014**, *53*, 9622.
26. Mondal, S.; Yetra, S. R.; Patra, A.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. *Chem. Commun.* **2014**, *50*, 14539.

27. Bera, S.; Daniliuc C. G.; Studer, A. *Org. Lett.* **2015**, *17*, 4940.
28. Liang, Z-Q.; Wang, D-L.; Zhang, H-M.; Ye, S. *Org. Lett.* **2015**, *17*, 5140.
29. Zhu, T.; Mou, C.; Li, B.; Smetankova, M.; Song, B-A.; Chi,Y. R. *J. Am. Chem. Soc*. **2015**, *137*, 5658.
30. Zeitler, K. *Org. Lett*. **2006**, *8*, 637.
31. Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett*. **2007**, *9*, 371.
32. Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc*. **2010**, *132*, 8810.
33. Lyngvi, E.; Bode, J. W.; Schoenebeck, F. *Chem. Sci.* **2012**, *3*, 2346.
34. Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem., Int. Ed*. **2011**, *50*, 1673.
35. Zhu, Z.-Q.; Xiao, J.-C. *Adv. Synth. Catal*. **2010**, *352*, 2455.
36. Zhou, B.; Luo, Z.; Li, Y. *Chem. Eur. J*. **2013**, *19*, 4428.
37. Romanov-Michailidis, R.; Besnard, C.; Alexakis, A. *Org. Lett*. **2012**, *14*, 4906.
38. Du, D.; Hu, Z.; Jin, J.; Lu, Y.; Tang, W.; Wang, B.; Lu, T. *Org. Lett.* **2012**, *14*, 1274.
39. Ryan, S. J.; Candish, L.; Lupton, D. W. J. *Am. Chem. Soc.* **2009**, *131*, 14176.
40. Candish, L.; Levens, A.; Lupton, D. W. *J. Am. Chem. Soc.* **2014**, 136, 14397.
41. Candish, L.; Levens, A.; Lupton, D. W. *Chem. Sci*. **2015**, *6*, 2366.
42. Levens, A.; Zhang, C; Candish, L.; Forsyth, C. M.; Lupton, D. W. *Org. Lett*. **2015**, *17*, 5332.
43. Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 4694.
44. Ryan, S. J.; Candish, L.; Lupton, D. W. *Synlett.* **2011**, 2275.
45. Ryan, S. J.; Stasch, A.; Paddon-Row, M. N.; Lupton, D. W. *J. Org. Chem.* **2011**, *77*, 1113.
46. Candish, L.; Lupton, D. W. *J. Am. Chem. Soc*. **2013**, *135*, 58.
47. Candish, L.; Forsyth, C. M.; Lupton, D. W. *Angew. Chem., Int. Ed*. **2013**, *52*, 9149.
48. Zhang, C.-L.; Wang, Z.-X.; Ye, S. *Angew. Chem., Int. Ed*. **2014**, *53*, 11611.
49. Ni, Q.; Xiong, J.; Song, X.; Raabe, Ge.; Enders D. *Chem. Commun*. **2015**, *51*, 14628.
50. Corey. E. J.; Gilman N. W.; Ganem B. E.; *J. Am. Chem. Soc*. **1968**, *90*, 5616.

CHAPTER 2

N-Heterocyclic Carbene (NHC)-Catalyzed Enantioselective Synthesis of Dihydropyranones and Dihydropyridinones

2.1. Introduction

Six-membered oxygen-containing heterocycles or substituted enol δ-lactones are better known as 3,4-dihydropyranones, and are widely recognized as useful building blocks for the synthesis of various biologically active compounds (Fig 2.1).[1] They are useful synthetic intermediates for the preparation of γ-lactones, cyclic enamines, 2-pyranones, etc.

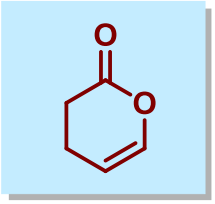


Fig 2.1: 3,4-Dihydropyranone

Isocoumarins are a family of naturally occurring compounds containing 3,4-dihydropyran-2-ones as subunits, that show broad spectrum of pharmacological activities such as anti-inflammatory, antifungal, antimicrobial, and cytotoxic (Fig 2.2). For example, cytogenin is a natural product containing dihydropyranone moiety and exhibits antitumor activity.[2] NM-3 is an analog of cytogenin, which inhibits the growth of tumour-angiogenesis in human tumour xenograft models and human hendotelial cells in culture.[3] The 3,4-dihydropyran-2-one fragment is also a component in rubromycin, which possesses antitumor and antibiotic activity.[4] (-)7-Deoxyloganin containing dihydropyranone moiety is a member of iridoids known for their medicinal property.[5] Englerin A, a guaiane sesquiterpene can be synthesized starting from nepetalactone, which inhibits the growth of renal cancer cell lines.[6]

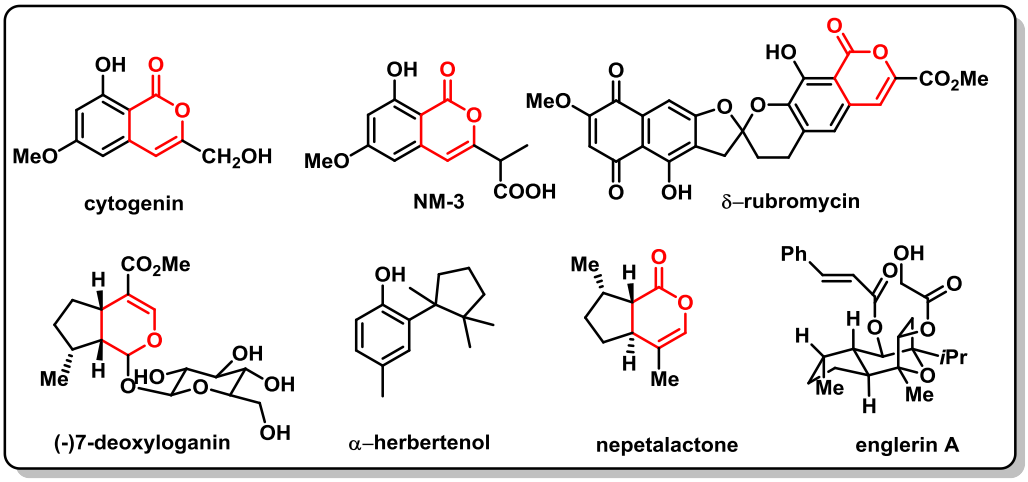


Fig 2.2: Selected Biologically Active Compounds with 3,4-Dihydropyranone Core

In addition, 3,4-dihydropyridinone is the nitrogen analog of dihydropyanone, an important motif present in various bioactive natural and unnatural compounds (Fig 2.3).[7] Aza-Diels-Alder reaction of imines with dienes allows a classical and straightforward approach to dihydropyridinones.

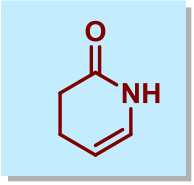


Fig 2.3: 3,4-Dihydropyridinone

Homoclausenamides are 3,4-dihydropyridin-2-one alkaloids, used for the treatment of the gastrointestinal disorder, influenza, dermatological diseases, and viral hepatitis (Fig 2.4).[8] These 3,4-dihydropyridin-2-one derivatives act as potential calcium-channel modulators.[9] They also act as Rho kinase (ROCK1) inhibitors, which mediate vascular smooth muscle contraction and also a potential target for the treatment of hypertension and related disorders.[10]

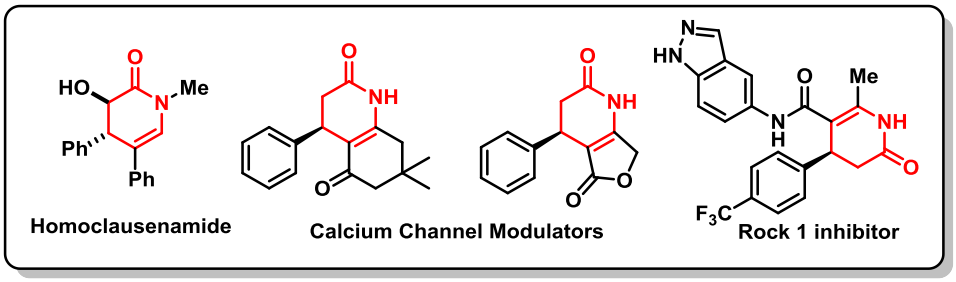


Fig 2.4: Selected Biologically Active Compounds with 3,4-Dihydropyridinone Core

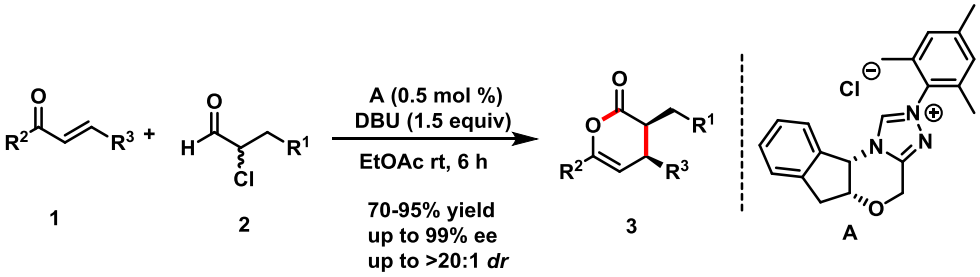
2.2. NHC-Catalyzed Synthesis of Dihydropyranones:

In view of the biological importance, the synthesis of dihydropyranones is of great importance and interest to synthetic chemists. Recently, NHC-catalysis has emerged as a powerful strategy for the synthesis of dihydropyranones.[1] In particular, NHC-bound azolium enolates and α,β-unsaturated acylazolium ions are two reactive species involved in the synthesis of dihydropyranones. Azolium enolates proceed via [4 + 2] cycloaddition reactions and α,β-unsaturated acylazolium ions involve [3 + 3] annulation reactions for the synthesis of dihydropyranones.

2.2.1. Synthesis of Dihydropyranones via Azolium Enolates

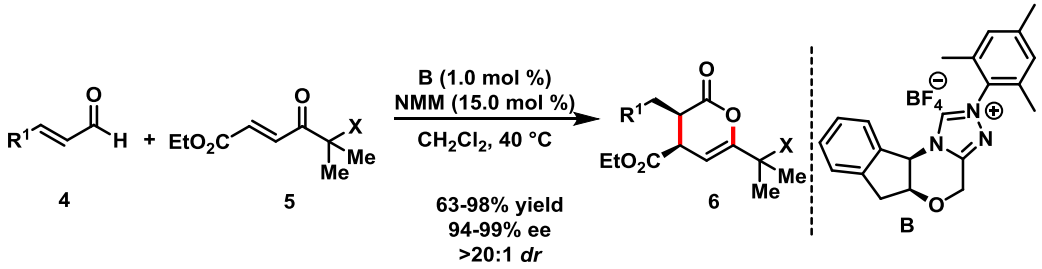
In 2006, Bode and co-workers reported the enantioselective synthesis of dihydropyranones by NHC-catalyzed Diels-Alder reaction of racemic α-chloro aldehydes with enones. Aromatic and aliphatic α-chloro aldehydes **2** when treated with electron-withdrawing enones **1** furnished the desired products under mild reaction conditions (Scheme 2.1). The reaction proceeds with low catalyst loading of NHC precursor **A** and provides the dihydropyranones **3** in good yield and excellent diastereoselectivity and enantioselectivity. Formation of the (*Z*)-enolate and its preference to react in an *endo* cycloaddition mode with the enone attributed *cis*-diastereoselectivity.[11]

Scheme 2.1: Diels-Alder Reaction of α-Chloro aldehydes with Enones



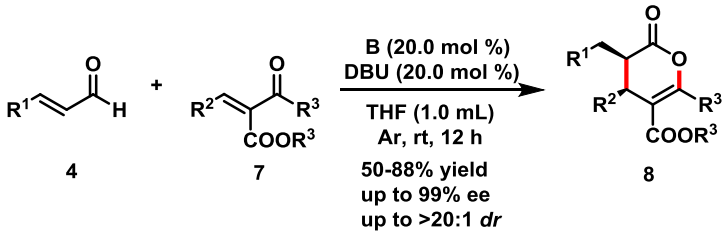
Later, they have found that enals **4** can also be used for the enantioselective synthesis of dihydropyranones. Enolate equivalents can be generated from enals and NHC generated from **B** in the presence of weak base such as *N*-methylmorpholine (NMM) followed by a hetero-Diels-Alder reaction with a variety of α-hydroxy enones or α-amino enones **5** to afford pyranone **6** (Scheme 2.2). Furthermore, the high level of enantioselectivity was explained by computational experiments which suggest the formation of a non-conjugated complex with azolium and the enolate olefin.[12]

Scheme 2.2: Diels-Alder Reaction of Enals with α-Hydroxy Enones



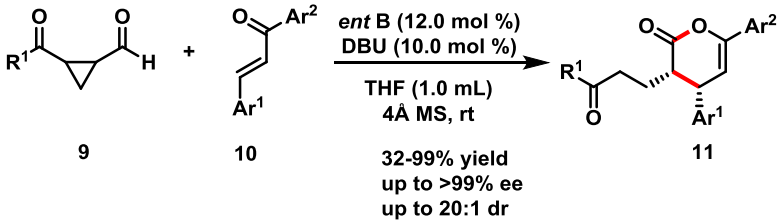
Recently, Chi and co-workers developed the NHC-catalyzed enantioselective Diels-Alder reaction of enals **4** and alkylidene diketones **7** (Scheme 2.3). They have found the enolate reactivity of enals under NHC catalysis when they introduced an electron-withdrawing group at the α-position of the chalcones. The scope of enals include both aromatic as well as hetero-aromatic systems resulting in the formation of the products **8** using NHC derived from **B** in good yields and high selectivities.[13]

Scheme 2.3: Diels-Alder Reaction of Enals with Alkylidene Diketones



Further, they described the enantioselective synthesis of dihydropyranones via formal hetero Diels-Alder reactions of formyl cyclopropanes **9** and chalcones **10** (Scheme 2.4). In this work, the NHC-bound enolate intermediate generated from formyl cyclopropane was intercepted with chalcones. The dihydropyranone products **11** can easily be transformed to highly substituted cyclohexanes in good yields and excellent stereoselectivities.[14]

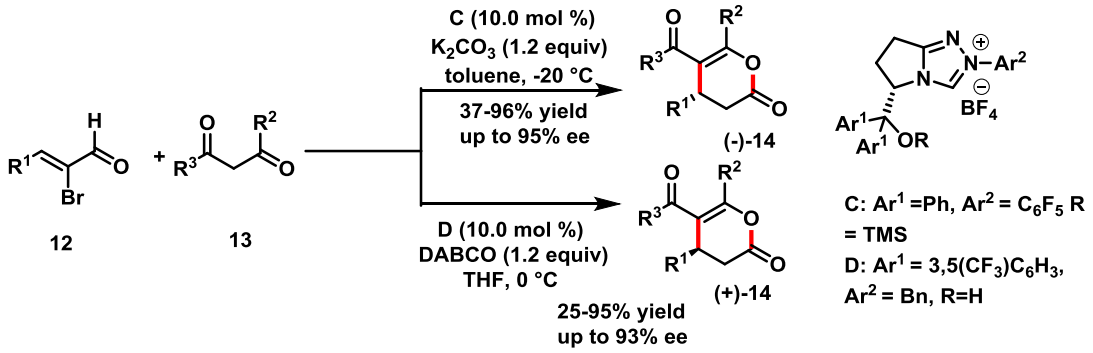
Scheme 2.4: Diels-Alder Reaction of Formylcyclopropanes with Chalcones



2.2.2. Synthesis of Dihydropyranones via *α,β*-Unsaturated Acylazolium Ion

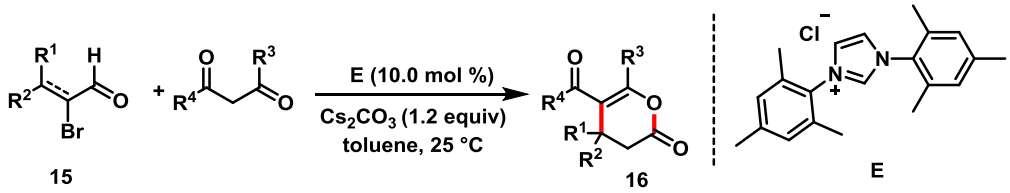
In 2011, Ye and co-workers reported the generation of chiral *α,β*-unsaturated acylazolium ions from bench stable 2-bromoenals **12** and NHC generated from **C** or **D**. Michael addition of 1,3-dicarbonyl compounds **13** to these intermediates afford the dihydropyranones **14** in optically pure form (Scheme 2.5). Interestingly, both enantiomers can be synthesized depending on the structure of the catalyst and the nature of the base. Additionally, the stereochemical outcome of the reaction was explained by DFT-studies.[15]

Scheme 2.5: Annulation of 2-Bromoenals with 1,3-Dicarbonyl Compounds



Independently, Yao and co-workers reported the annulation of 2-bromoenal with 1,3-dicarbonyl compounds in the presence of imidazolium salt **E** and Cs_2CO_3 to furnish racemic dihydropyranones **16** (Scheme 2.6).[16] Moreover, *α,β*-dibromoaldehydes **15** were also employed as precursors for the generation of *α,β*-unsaturated acylazolium ions.

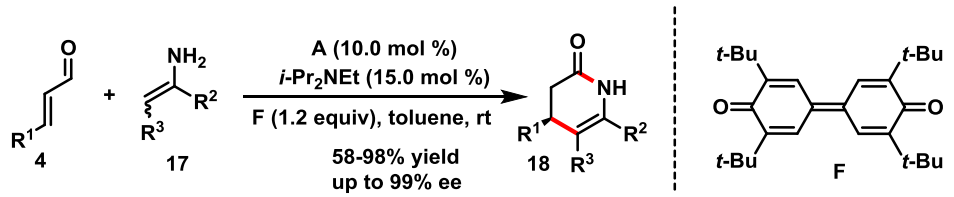
Scheme 2.6: Racemic Synthesis of Dihydropyranones



2.3. NHC-Catalyzed Synthesis of Dihydropyridinones:

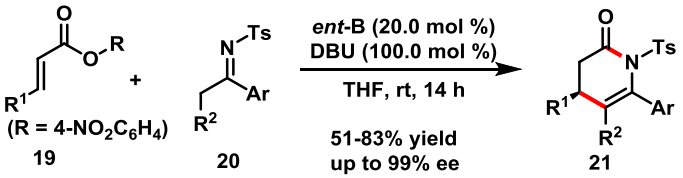
NHC-catalyzed aza-Claisen annulation of vinylogous amides **17** with enals **4** or *α*-hydroxyenones was reported by Bode and co-workers. The reaction affords synthetically useful dihydropyridinones **18** in good yields and enantioselectivities (Scheme 2.7). It is noteworthy that readily available vinylogous amides with no nitrogen protecting groups are employed for this annulation reaction.[17]

Scheme 2.7: Aza-Claisen Cyclization of Enals with Vinylogous Amides



In 2013, Chi and co-workers developed the LUMO activation of α,β-unsaturated esters **19** via NHC-organocatalytic strategy for the enantioselective synthesis of 3,4-dihydropyridinones **21** (Scheme 2.8). The enolizable imines **20** were used as the nucleophilic source in the reaction. The use of β,β-disubstituted esters furnished optically enriched lactam products containing a quaternary stereogenic center. These products were successfully transformed to various nitrogen heterocycles by further synthetic transformations.[18]

Scheme 2.8: LUMO Activation of α,β-Unsaturated Esters



2.4. Statement of the Problem

As discussed earlier, dihydropyranones and dihydropyridinones are two privileged moieties present in various biologically active natural products. Notably, NHC-catalyzed enantioselective synthesis of dihydropyranones and dihydropyridinones although known in the literature, but suffers from major limitations such as the use of stoichiometric oxidants, stability of starting materials and high catalyst loadings. Moreover, there is no general method for the enantioselective synthesis of both dihydropyranones and dihydropyridinones from a common precursor. In addition, despite the knowledge on the generation of α,β-unsaturated acylazolium under NHC-catalysis, the application of *chiral* α,β-unsaturated acylazolium intermediates are limited. Hence, we envisioned the generation of chiral α,β-unsaturated acylazolium intermediates from 2-bromoenals and NHCs followed by their interception with 1,3-dicarbonyl compounds/enamines could result in the enantioselective synthesis of dihydropyranones and unprotected dihydropyridinones.

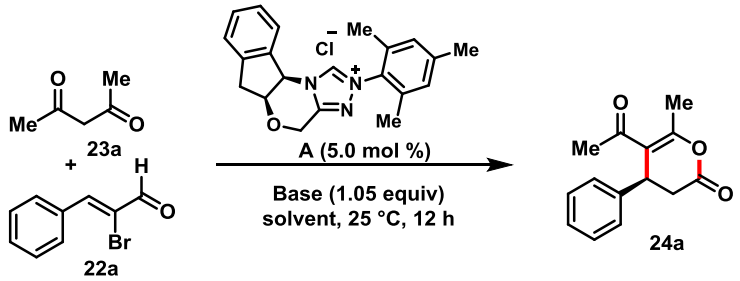
2.5. Results and Discussion

2.5.1. Optimization Studies

In a pilot experiment, treatment of α-bromo cinnamaldehyde (**22a**) and acetyl acetone (**23a**) with the triazolium salt **A** (5 mol%) and 1.05 equiv of KO*t*-Bu as base resulted in the formation of dihydropyranone derivative **24a** in 35% yield (based on ^{1}H NMR spectroscopy) and 37% ee. (Table 1, entry 1). A brief survey of bases revealed that bases such as K_2CO_3, DBU, Et_3N, *i*-Pr_2NH, DIPEA, and Na_2CO_3 afforded **24a** either in reduced yield or selectivity (entries 2-8). DMAP improved the yield to 80% and selectivity to 82% ee (entry 9). Interestingly, when the reaction was carried out using DABCO as base, the selectivity was improved to 88% ee, with 66% yield of the product (entry 10). Notably, bases like TMEDA, NaOAc, $KHCO_3$, and $NaHCO_3$ gave comparable selectivity and poor yields (entries 11-14). Among the lithium bases, LiOAc.$2H_2O$ and Li_2CO_3, showed excellent selectivity (>90% ee) but in low yields (entries 18-22). Overall, DABCO and DMAP appear to be optimal bases with good yields as well as selectivities in the base screening. Furthermore, variation of the reaction temperature was not beneficial (entries 23 and 24). Later, we have performed solvent screening with optimal bases. When DABCO was used as base, THF and 1,4-dioxane resulted in reduced selectivity (entries 25 and 26), whereas non-polar solvents including xylene and mesitylene returned similar results (entries 27 and 28). Solvent screening using DMAP as base did not improve the outcome (entries 29-35). Additionally, we have checked the role of additives in this transformation. Additives like 4Å MS, $NaBF_4$, Ti(O*i*-Pr)$_4$, with various bases did not affect the selectivity (entries 36-44).

At this stage, we thought of using a combination of base along with additive. Delightfully, when the reaction was carried out using a combination of 1.05 equiv of DABCO and 20 mol% LiOAc.$2H_2O$, along with 4Å MS, the desired product was formed in 82% isolated yield and 96% ee (entry 45). To investigate the role of lithium source in selectivity, the reaction was performed using other lithium sources such as Li_2CO_3 and LiBr as co-bases along with 4Å MS, but these reactions returned inferior results (entries 46 and 47). Additionally, use of NaOAc and AcOH along with DABCO and 4Å MS as additive gave reduced yield and selectivity (entries 48 and 49). The spectral data of **24a** is given in Section 2.5.2.

Table 1. Optimization of the Reaction Conditions[a]



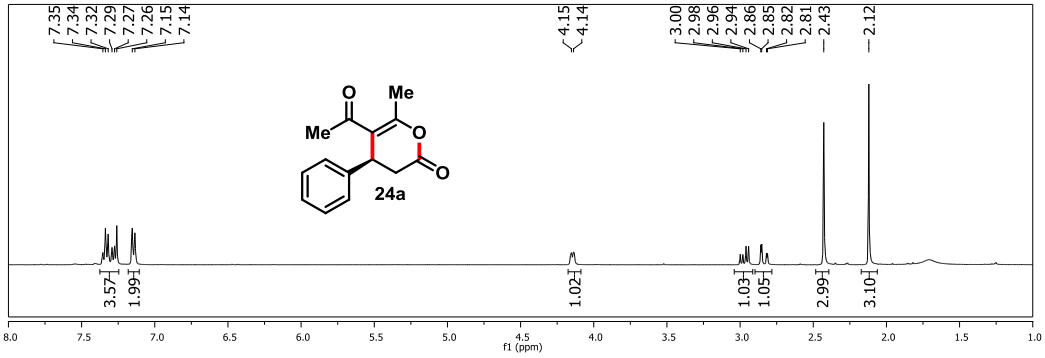
entry	**Base**	**Solvent**	**Additive**	yield of **24a** (%)[b]	ee of **24a** (%)[c]
1[d]	KO*t*-Bu	toluene	-	35	37
2[d]	K_2CO_3	toluene	-	36	64
3[d]	DBU	toluene	-	54	10
4[d]	Cs_2CO_3	toluene	-	57	20
5	Et_3N	toluene	-	66	63
6	*i*-Pr_2NH	toluene	-	83	33
7	DIPEA	toluene	-	70	75
8	Na_2CO_3	toluene	-	40	82
9	DMAP	toluene	-	80	82
10	DABCO	toluene	-	62	88
11	TMEDA	toluene	-	48	84
12	NaOAc	toluene	-	14	84
13	$KHCO_3$	toluene	-	27	81
14	$NaHCO_3$	toluene	-	12	87
15	Imidazole	toluene	-	39	64
16	K_3PO_4	toluene	-	79	64
17	Pyridine	toluene	-	5	79
18	LiOAc	toluene	-	10	81
19	LiHMDS	toluene	-	18	38
20	LiOAc.$2H_2O$	toluene	-	25	90
21	Li_2CO_3	toluene	-	20	92
22	LiH	toluene	-	17	26
23	DABCO (at 0 °C)	toluene	-	51	86
24	DABCO(at 40 °C)	toluene	-	58	85

25	DABCO	THF	-	70	60
26	DABCO	1,4-dioxane	-	50	80
27	DABCO	xylene	-	61	87
28	DABCO	mesitylene	-	61	88
29	DMAP	DCM	-	80	23
30	DMAP	1, 4-dioxane	-	86	74
31	DMAP	THF	-	90	48
32	DMAP	DME	-	88	42
33	DMAP	Benzene	-	72	74
34	DMAP	m-xylene	-	34	85
35	DMAP	mesitylene	-	62	88
36	KO*t*-Bu	toluene	4Å MS	60	30
37	Na_2CO_3	toluene	4Å MS	43	82
38	Na_2CO_3	toluene	$NaBF_4$	40	78
39	DMAP	toluene	4Å MS	81	77
40	DMAP	toluene	$NaBF_4$	80	75
41	$LiOAc.2H_2O$	toluene	4Å MS	40	90
42	Li_2CO_3	toluene	4Å MS	35	90
43	$LiOAc.2H_2O$	toluene	Ti (O*i*-Pr)$_4$	24	86
44	DABCO	toluene	Ti (O*i*-Pr)$_4$	55	86
45	**DABCO**	**toluene**	**20 mol % $LiOAc.2H_2O$, 4Å MS**	**80**	**96**
46	DABCO	toluene	20 mol % Li_2CO_3 and 4Å MS	59	80
47	DABCO	toluene	20 mol % LiBr and 4Å MS	40	80
48	DABCO	toluene	20 mol % NaOAc and 4Å MS	79	79
49	DABCO	toluene	20 mol % AcOH and 4Å MS	53	86

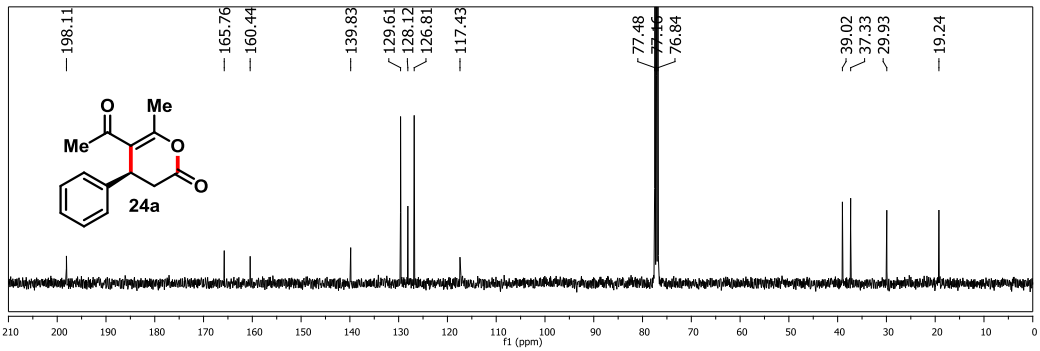
[a] Standard conditions: **22a** (0.25 mmol), **23a** (0.25 mmol), **A** (5 mol %), Base (1.05 equiv), toluene (1.0 mL), 25 °C and 12 h. [b] The yields were determined by ^{1}H-NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield in parentheses. [c] Determined by HPLC analysis on a chiral column. [d] Reaction carried out using 10 mol % **A** and 1.10 equiv of base.

2.5.2. Spectral Data of 24a

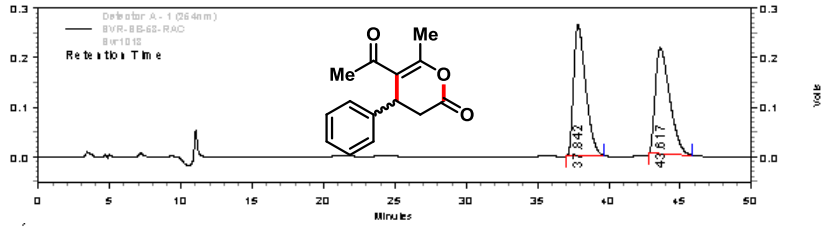
^{1}H NMR Spectrum of 24a ($CDCl_3$)



^{13}C NMR Spectrum of 24a ($CDCl_3$)

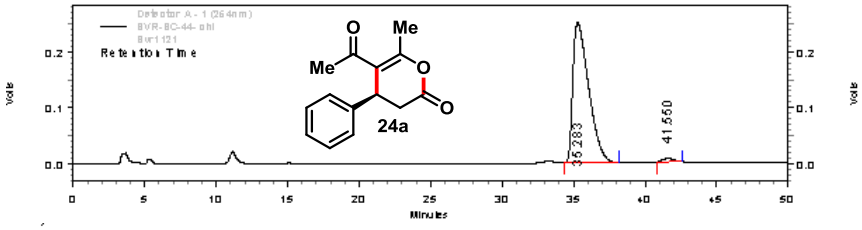


HPLC Chromatogram of Racemic-24a



Retention Time	C Area	Area %
37.842	15567219	50.790
43.617	15083179	49.210
Totals	30650398	100.000

HPLC Chromatogram of Enantiomerically pure-24a



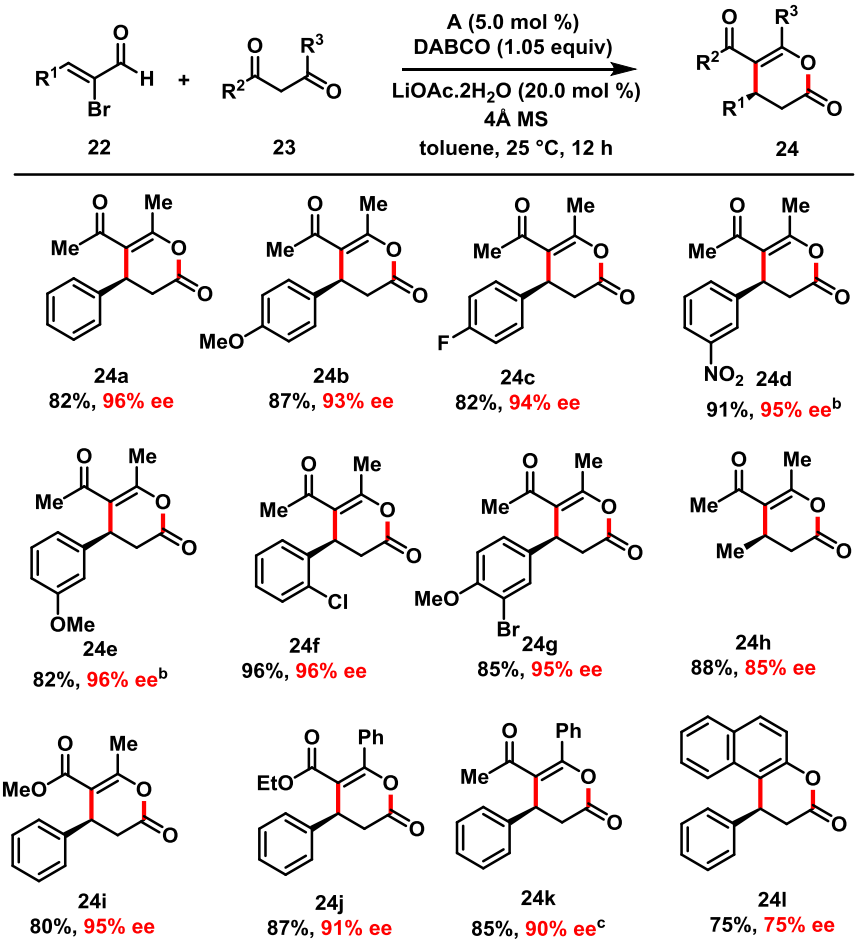
Retention Time	C Area	Area %
35.283	19367956	98.083
41.550	378442	1.917
Totals	19746398	100.000

The optimization studies gave clear indication that, there is no role of Lewis acid activation by the lithium source as well as any counterion effect induced by the acetate anions in selectivity.[19] In addition, lowering the amount of catalyst below 5 mol % resulted in reduced yield of the product.

2.5.3. Enantioselective Synthesis of Dihydropyranones

After optimizing the reaction conditions, we examined the substrate scope of this NHC-catalyzed annulation reaction (Scheme 2.9). First, tolerance of this reaction with various 2-bromoenals has been tested. The unsubstituted parent system worked well, and electron-donating and -withdrawing groups at the 4-position of the aromatic ring were well tolerated, leading to dihydropyranones in good yields and with excellent ee values (**24a-24c**). Moreover, substitution at 3-position of the benzene ring of **22** having electron-

Scheme 2.9: Substrate Scope for the Enantioselective Synthesis of Dihydropyranones[a]



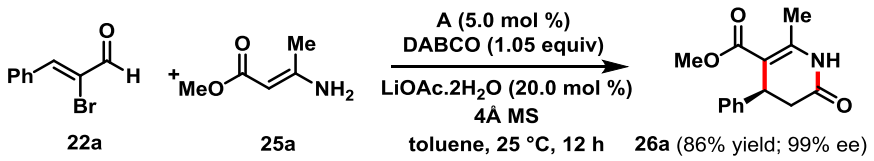
[a] General reaction conditions: **22** (0.50 mmol), **23** (0.50 mmol), **A** (5.0 mol%), DABCO (1.05 equiv) LiOAc.$2H_2O$ (20 mol %), and 4Å MS (100 mg) in toluene (2.0 mL) at 25 °C for 12 h. [b] Reaction run on 0.25 mmol scale. [c] <5% of the other regioisomer was also formed.

releasing and -withdrawing groups furnished the product in good yield and high enantioselectivity (**24d-24g**). In addition, halides such as bromide in 3-position (**24g**) or chloride in 2-position (**24f**) were well tolerated. It is noteworthy that the corresponding products could undergo further functionalization by traditional cross-coupling reactions for the construction of more complex molecules. Interestingly, challenging aliphatic aldehydes such as (*Z*)-2-bromobut-2-enal also resulted in the smooth conversion to desired product in good yield and moderate enantioselectivity, thus further expanding the scope of this annulation reaction (**24h**). Later, we evaluated the scope of the reaction with various 1,3-dicarbonyl compounds. Variation of *β*-ketoesters as well as unsymmetrical *β*-diketones resulted in the smooth formation of dihydropyranone derivatives in good yields and enantioselectivity (**24i-24k**). Gratifyingly, *β*-naphthol can also be used as a coupling partner furnishing chiral benzochromen-3-one **24l** in moderate yield and selectivity.[20] In all cases, the absolute configuration of the major enantiomer was assigned as *S* by comparison of optical rotation of same compounds described previously.[21]

2.5.4. Enantioselective Synthesis of Dihydropyridinones

Encouraged by these interesting results, we then focused our attention on another class of bisnucleophiles, the primary vinylogous amides or enamines with the objective to synthesize nitrogen heterocycles. To our delight, under the optimized reaction conditions, treatment of 2-bromoenal **22a** with the enamine **25a** afforded the dihydropyridinone derivative **26a** in 86% yield and 99% ee (Scheme 2.10). The spectral data of **26a** is given in Section 2.5.5.

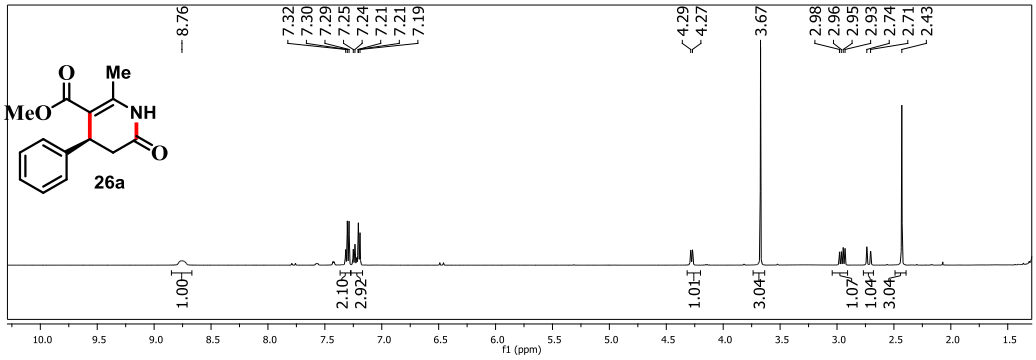
Scheme 2.10: Enantioselective Synthesis of Dihydropyridinone



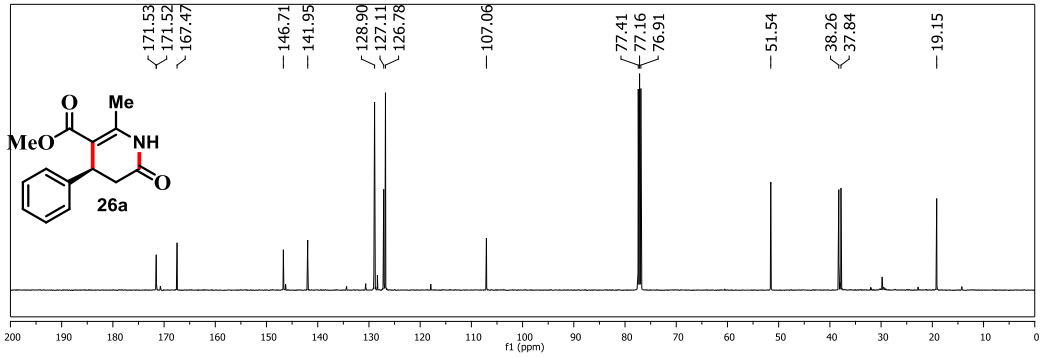
Notably, no nitrogen protecting group was employed for this annulation and the reaction delivered the medicinally and synthetically valuable dihydropyridinones. Interestingly, under the optimized reaction conditions, the competing amide-bond formation was not observed.[22] With this result, we examined the scope of the reaction (Scheme 2.11). Substrates with substitution at the benzene ring of 2-bromoenal **22** underwent efficient annulation leading to the product formation of dihydropyridinones

2.5.5. Spectral Data of 26a

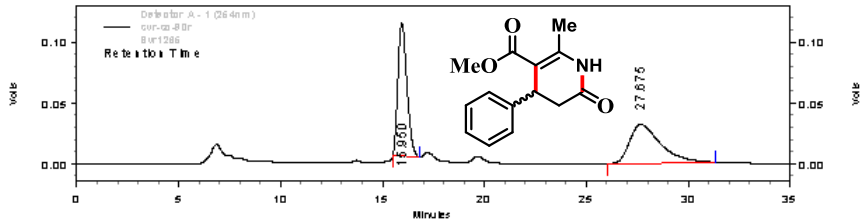
^{1}H NMR Spectrum of 26a ($CDCl_3$)



^{13}C NMR Spectrum of 26a ($CDCl_3$)

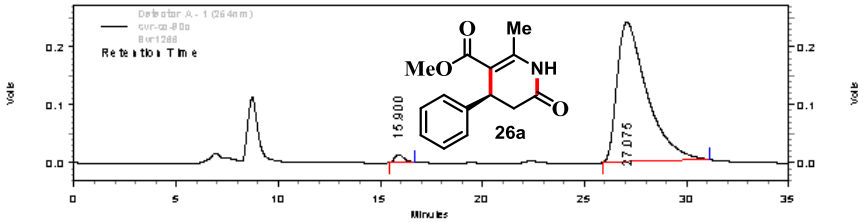


HPLC Chromatogram of Racemic-26a



Retention Time	C Area	Area %
15.950	3379173	50.099
27.675	3365765	49.901
Totals	6744938	100.000

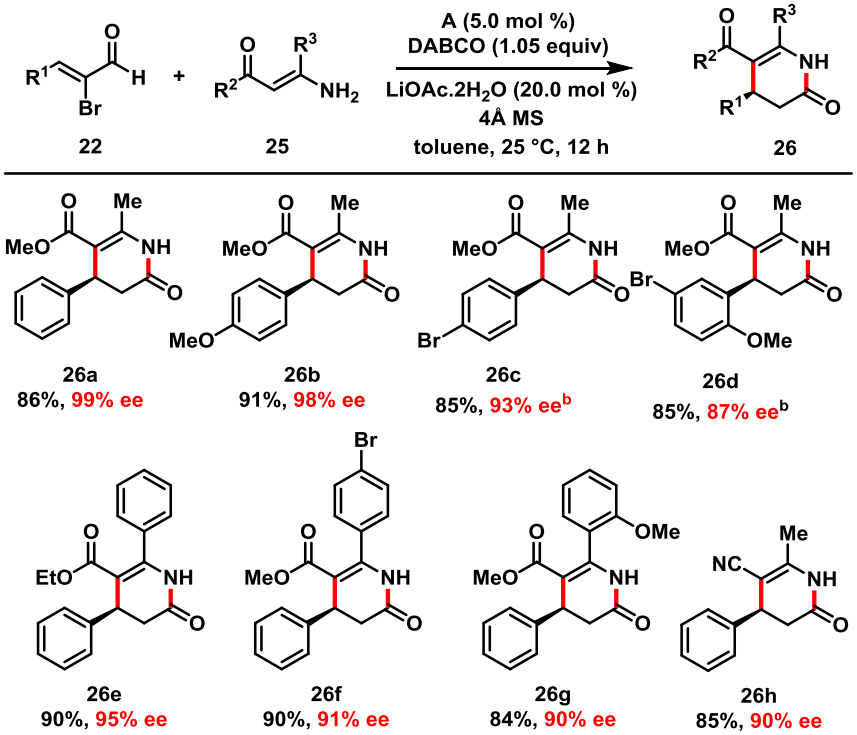
HPLC Chromatogram of Enantiomerically pure-26a



Retention Time	C Area	Area %
15.900	104364	0.395
27.075	26294133	99.605
Totals	26398497	100.000

in good yield and excellent ee values (**26b-26d**). Moreover, a number of stable, unprotected and substituted enamines underwent smooth conversions to the desired products (**26e-26g**). Furthermore, the vinylogous amide containing cyano group was well tolerated leading to the expected product **26h** in 85% yield and 90% ee.

Scheme 2.11: Substrate Scope for the Enantioselective Synthesis of Dihydropyridinones[a]

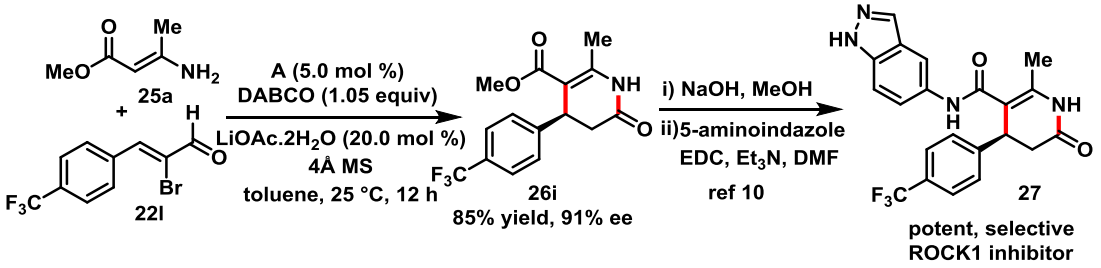


[a] General reaction conditions: **22** (0.50 mmol), **25** (0.50 mmol), **A** (5.0 mol %), DABCO (1.05 equiv) $LiOAc.2H_2O$ (20 mol %), and 4Å MS (100 mg) in toluene (2.0 mL) at 25 °C for 12 h. [b] Reaction run on 0.25 mmol scale.

2.5.6. Synthetic Utility of Dihydropyridinones

To show the versatility of the present method, the synthetic utility of dihydropyridinones **26** was demonstrated via the formal synthesis of ROCK1 inhibitor. The synthesis of the trifluoromethyl substituted dihydropyridinone **26i** starting from the 2-bromoenal **22l** and enamine **25a** was achieved in 85% yield and 91% ee under the optimized conditions. The potent and selective ROCK1 inhibitor **27** can easily synthesized in two steps from the product **26i** following the literature procedure (Scheme 2.12).[10]

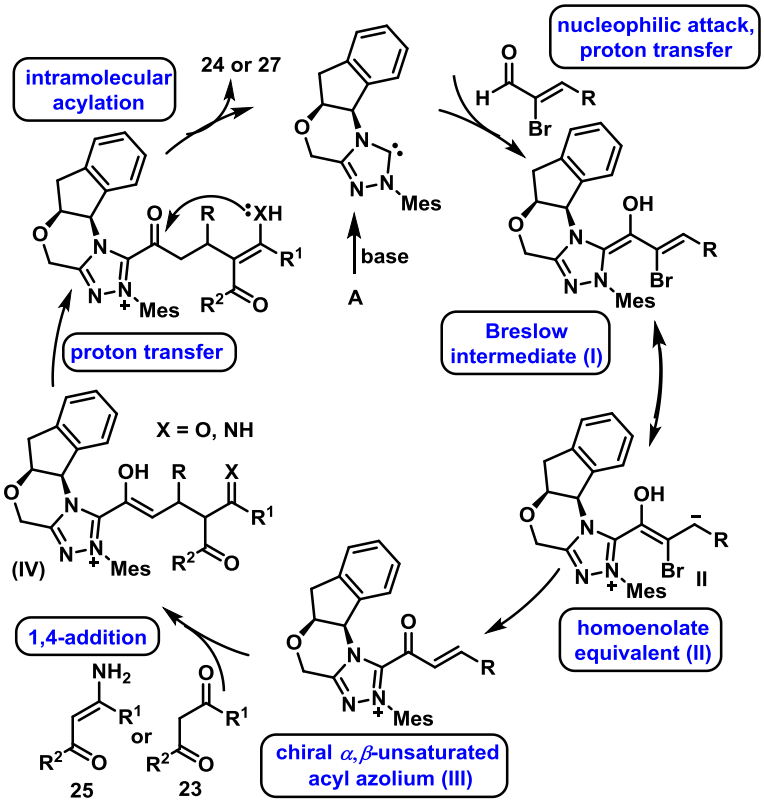
Scheme 2.12: Formal Synthesis of ROCK1 Inhibitor



2.5.7. Proposed Mechanism

The plausible mechanism for this NHC-catalyzed annulation reaction is shown in Scheme 2.13. The 1,2-addition of the NHC generated from **A** to 2-bromoenal **22** will initiate the reaction, subsequent proton transfer to generate the nucleophilic Breslow intermediate **I**,[23] which is in resonance with the homoenolate equivalent **II**. This is followed by a rapid debromination of **II** to the key α,β-unsaturated acylazolium intermediate **III**.[24] The bifunctional nucleophile **23** or **25** will undergo Michel addition[25] to **III** and delivers the enol intermediate **IV**, which upon proton transfer and intramolecular acylation lead to the final product **24** or **27**.

Scheme 2.13: Proposed Mechanism of the NHC-Catalyzed Annulation of 2-Bromoenals.



2.5.8. Theoretical Investigation

To shed light on the mechanism as well as the induction of enantioselectivity in the present reaction, high level quantum chemical calculations have been done using density functional theory (DFT), employing the TZVP[2]/PBE[3] approach with Turbomole 6.4.[26] The initial focus of the computational study was on the addition of the substrate **23a** to the chiral α,β-unsaturated acylazolium (**III**). As shown in Fig 2.5., this can occur through two approaches: from above the plane containing the triazolium moiety (pathway a), or from below the plane (pathway b). The calculated energy of the two complexes **IVa** and **IVb** thus formed indicate that pathway b is energetically preferred in comparison to pathway a, by 4.0 kcal/mol. This is due to the fact that nucleophilic attack from below the plane containing the triazolium moiety can lead to a favorable hydrogen bonding interaction between the enolic and carbonyl moieties, a possibility that does not exist in the case of the approach from above the plane. The hydrogen bonding O-H distance is found to be 1.69 Å, while the O-H-O angle is found to be 154.7°, both values falling in the range of typical hydrogen bonding interactions.

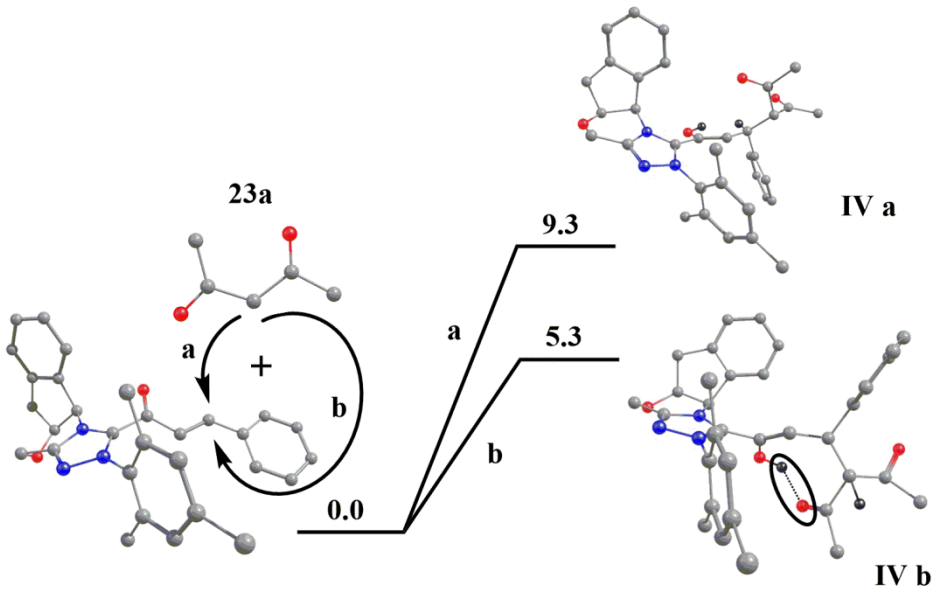


Fig 2.5. Two possible pathways for the approach of acetyl acetone **23a** towards **III** leading to two different intermediates **IVa** and **IVb**; intermediate **IVb** is stabilized by intramolecular hydrogen bonding (encircled in the figure); all structures shown are fully optimized geometries obtained from DFT; the color scheme is as follows: carbon: gray, nitrogen: blue, oxygen: red, hydrogen atoms are omitted for the purpose of clarity – only the hydrogen taking part in hydrogen bonding is shown; the reported energies are in kcal/mol.

Subsequent steps leading to the formation of **24a** are delineated in Fig 2.6. The complex **IVb** can undergo enol-keto, and keto-enol transformations to yield the intermediate **V**. The energy for such a conversion has been calculated to be endergonic by 12.5 kcal/mol. At this point, the cationic species **V** can be converted to the neutral species **VI** through the abstraction of the proton by the acetate anion released from the lithium acetate in solution. This is found to be a highly favorable process, being exothermic by -41.8 kcal/mol. This also indicates the role of lithium acetate in the catalytic process, and the calculations seem to indicate that DABCO is ineffective for the proton abstraction process, the energy for its proton abstraction has been found to be endothermic by 20.7 kcal/mol. This is due to the fact that the proton abstraction by DABCO involves the conversion of the neutral DABCO species to the cation $(DABCO)(H)^+$, a less favorable process than the conversion of the anionic acetate species to acetic acid. Calculations also indicate that the use of $LiOAc.2H_2O$ base in place of LiOAc (thus generating the acetate di-hydrate anion) would also be effective, though slightly less, the proton abstraction in this case being exothermic by -22.6 kcal/mol. The

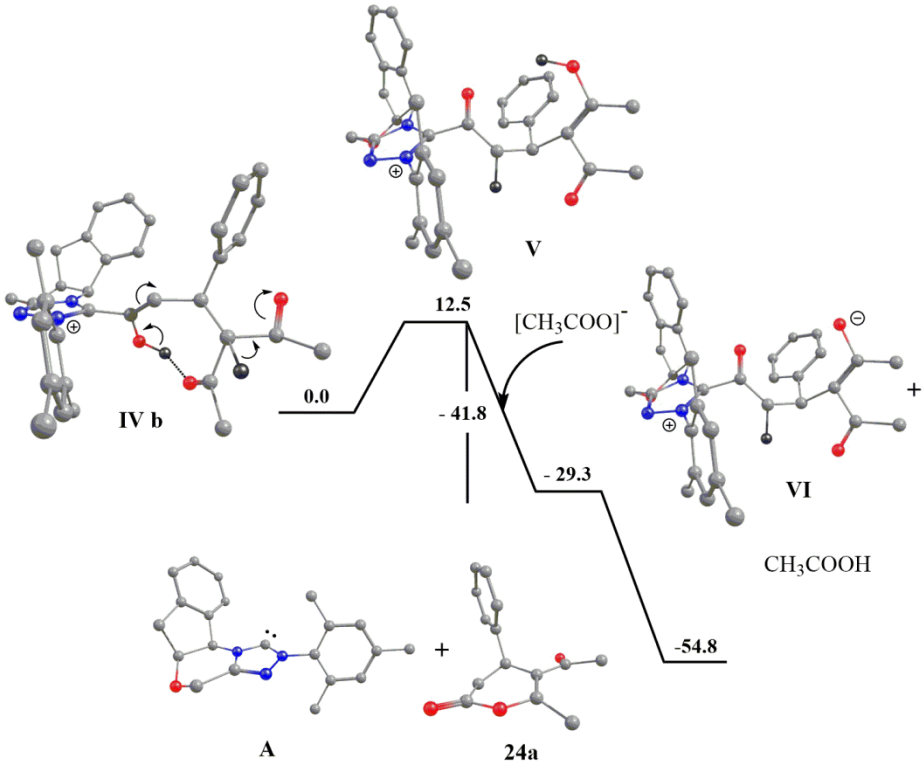


Fig 2.6 The steps converting the intermediate **IVb** to **A** and **24a**; all values reported are in kcal/mol.

neutral complex **VI** thus formed can then undergo intramolecular acylation to give rise to **A** and **24a**.This step has been calculated to be exergonic by -25.5 kcal/mol. The fact that this step is entropically favorable, converting the single intermediate species **VI** to two moieties **A** and **24a**, helps to explain its exergonicity. Therefore, taken together, the conversion of **IV** to **A** and **24a** is favorably exothermic by -54.8 kcal/mol (considered for the case of the lithium acetate base). This therefore helps to explain why product **24a** is formed in high yield and high enantioselectivity.

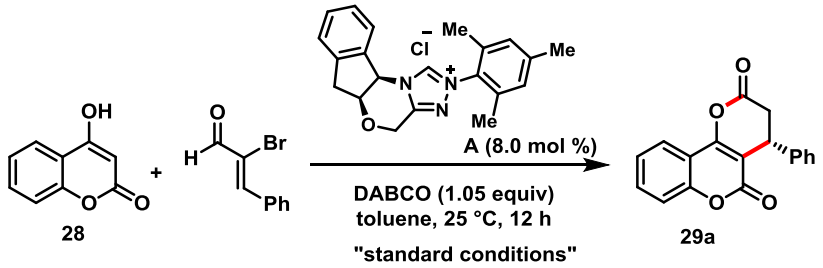
2.6. Reactions with Heterocyclic C-H Acids

Inspired by the successful development of mild and efficient method for the enantioselective synthesis of both dihydropyranones and dihydropyridinones through annulation reaction of 2-bromoenals with acyclic bisnucleophiles, we then focused our attention on interception of cyclic bifunctional nucleophiles with chiral α,β-unsaturated acylazoliums.

2.6.1. Optimization Studies for Coumarin-fused Dihydropyranones

The optimization study was commenced with the treatment of α-bromo cinnamaldehyde (**22a**) and 4-hydroxycoumarin (**28**) with the triazolium salt **A** and 1.05 equiv of DABCO (1,4-diazabicyclo [2.2.2]octane) as the base. Delightfully, the reaction afforded the functionalized pyrano[3,2-c]chromene-2,5-dione derivative **29a** in 65% yield (based on ^{1}H NMR spectroscopy) and 72% ee (Table 1, entry 1). Solvent screening revealed that non-polar solvents like xylene and mesitylene furnished comparable results (entries 2 and 3). Polar solvent like THF resulted in reduced selectivity (entry 4). Base screening revealed that K_2CO_3 returned comparable results (entry 5), but other bases such as DMAP and DIPEA, afforded either reduced reactivity or selectivity (entries 6-7). From our previous experience, using LiOAc.2H_2O as an additive gave comparable selectivity but the yield of the product was reduced to 54% (entry 8). Interestingly, when the reaction was carried out using a Na_2CO_3 as a base, the desired product was formed in 71% isolated yield and 86% ee (entry 9). The spectral data of **29a** is given Section 2.6.3.

Table 2. Optimization of the Reaction Conditions[a]



Entry	Variation of the standard conditions	Yield of **29a** (%)	ee of **29a** (%)
1	None	65	72
2	mesitylene instead of toluene	70	64
3	xylene instead of toluene	72	60
4	THF instead of toluene	55	50
5	K_2CO_3 instead of DABCO	65	70
6	DMAP instead of DABCO	55	64
7	DIPEA instead of DABCO	63	56
8	DABCO and LiOAc.$2H_2O$ instead of DABCO	54	66
9	Na_2CO_3 instead of DABCO	71	86

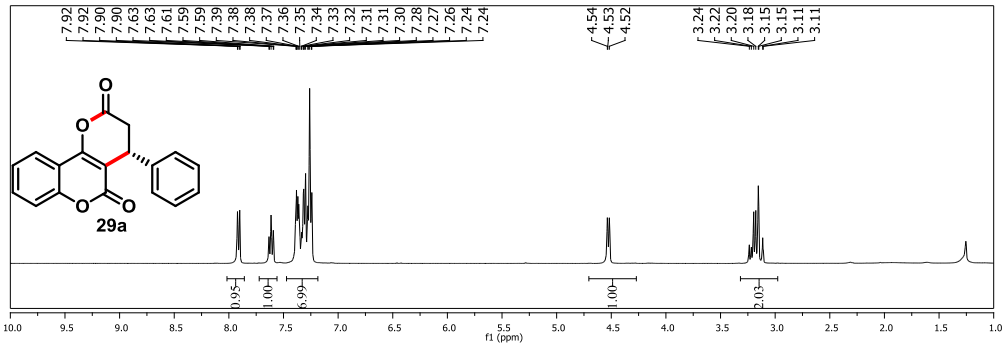
[a] General reaction conditions: **22** (0.25 mmol), **28** (0.25 mmol), **A** (8.0 mol %), Na_2CO_3 (1.2 equiv), toluene (1.0 mL), 30 °C and 12 h.

2.6.2. Enantioselective Synthesis of Coumarin-Fused Dihydropyranones

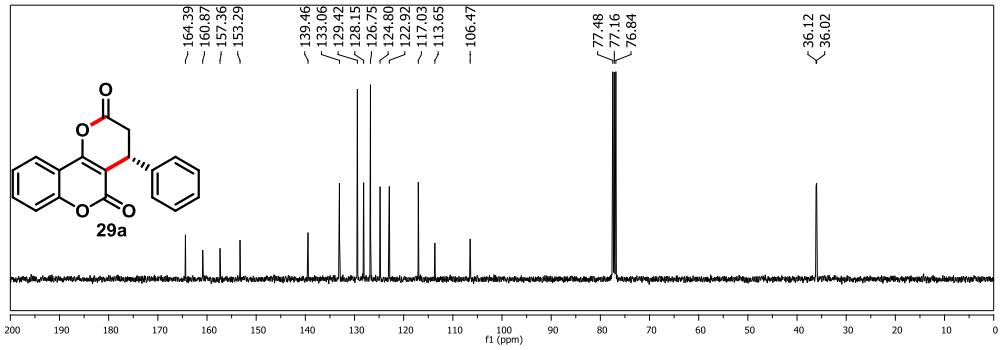
With the optimized reaction conditions in hand, we then studied the substrate scope of this interesting NHC-catalyzed annulation reaction by evaluating various bromoenals (Scheme 2.14). The unsubstituted parent system worked well, and electron -donating or -withdrawing groups at the 4-position of the *β*-aromatic ring of **22** were well tolerated, to form coumarin fused-dihydropyranones in good yields and with moderate ee values (**29b, 29c**). Moreover, substitution at 2-position of *β*-aryl was also well tolerated with excellent yield and moderate enantioselectivity (**29d**). The absolute configuration of the major enantiomer was assigned as *R* by comparison of the optical rotation of same compounds described previously.[27]

2.6.3. Spectral Data of 29a

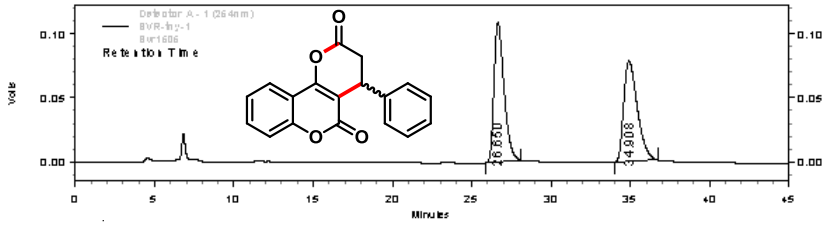
^{1}H NMR Spectrum of 29a ($CDCl_3$)



^{13}C NMR Spectrum of 29a ($CDCl_3$)

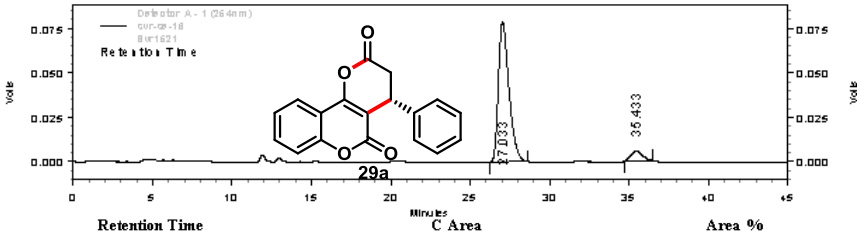


HPLC Chromatogram of Racemic-29a



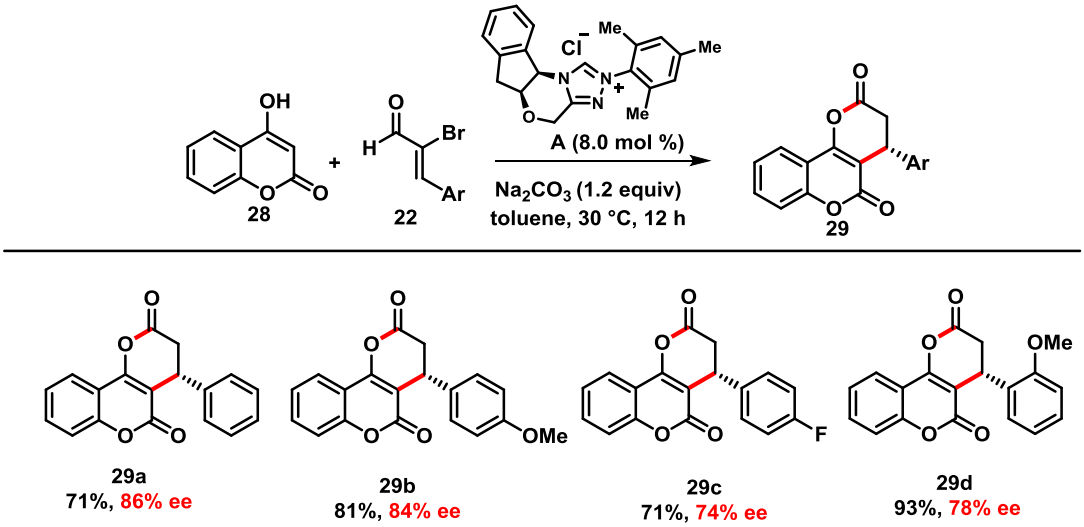
Retention Time	C Area	Area %
26.650	4808253	50.292
34.908	4752364	49.708
Totals	9560617	100.000

HPLC Chromatogram of Enantiomerically Pure-29a



Retention Time	C Area	Area %
27.033	3645064	92.916
35.433	277901	7.084
Totals	3922965	100.000

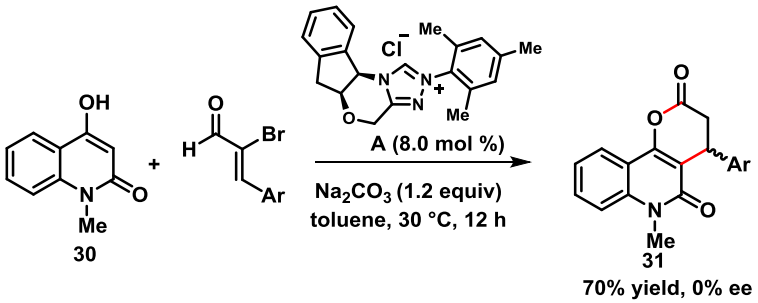
Scheme 2.14: Enantioselective Synthesis of Functionalized Coumarins[a]



[a] General reaction conditions: **28** (0.25 mmol), **22** (0.25 mmol), **A** (8 mol %), Na_2CO_3 (1.2 equiv), toluene (1.0 mL), 30 °C and 12 h.

Next, we focused our attention on another class of heterocyclic C-H acid, namely 4-hydroxy-1-methylquinolin-2 (1*H*)-one **30,** an *N*-analog of 4-hydroxycoumarin **28** with a view to construct quinolinone-fused dihydropyranones. Treatment of 2-bromoenal **22a** with **30** in the presence of carbene generated from **A** using Na_2CO_3 as base afforded the 2*H*-pyrano[3,2-c]quinoline-2,5(3*H*)-dione **31** in 70% yield. Disappointingly under these reaction conditions we did not observe any enantioselectivity (0% ee, Scheme 2.15)

Scheme 2.15: Synthesis of Quinolinone Fused Dihydropyranones



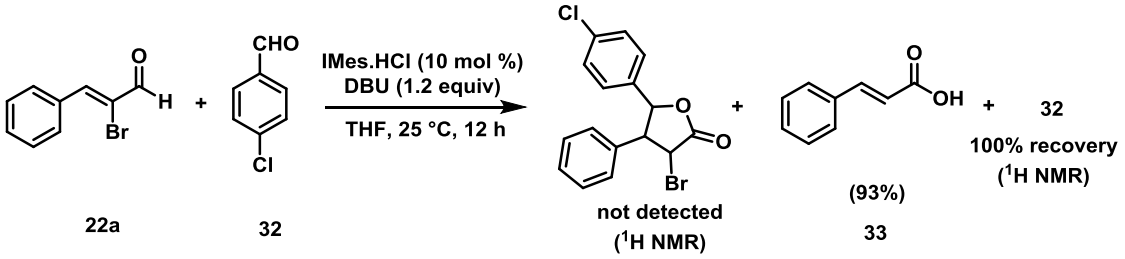
2.7. Mechanistic Experiments

2.7.1. Experiment to Intercept the Homoenolate Intermediate (II) with Aldehydes

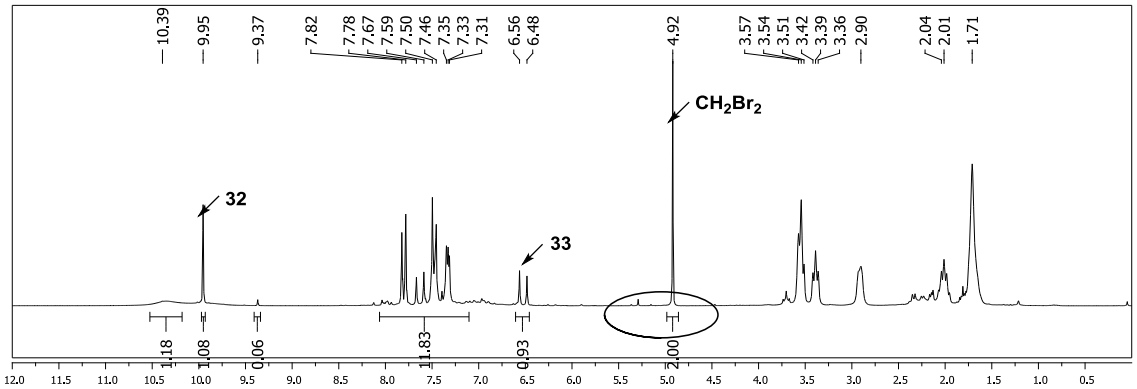
A mechanistic experiment to intercept the homoenolate intermediate **II** was performed. For this purpose, we carried out ^{1}H NMR analysis of crude reaction mixture

using CH_2Br_2 as the internal standard to determine the yield of products. Treatment of bromoenal **22a** with 4-chloro benzaldehyde **32** and 10 mol % of imidazolium salt (IMes. HCl) and 1.2 equiv of DBU did not furnish any desired lactone product (Scheme 2.16). Notably, 2-bromoenal was converted into corresponding acid **33** and 4-chloro benzaldehyde was recovered quantitatively. This experiment shows that the homoenolate intermediate **II** generated in the reaction mixture cannot be trapped by aldehydes. In other words, this sheds light on the fast debromination of **II** leading to the generation of α,β-unsaturated acylazolium **III.**

Scheme 2.16: Experiment to Intercept the Homoenolate Intermediate (II) with Aldehydes



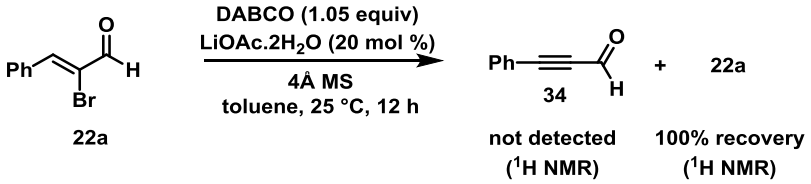
^{1}H NMR Spectrum of the Crude Reaction Mixture (Scheme 2.16)



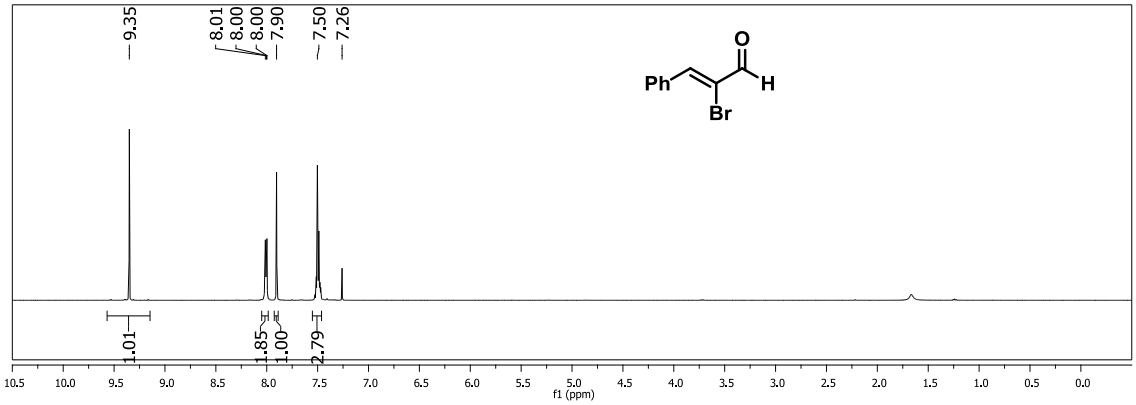
2.7.2. Reaction of 2-Bromoenal under Basic Conditions

We have performed another experiment to confirm whether the reaction was proceeding via ynal formation via the dehydrobromination of bromoenal **22a** under basic conditions. For this purpose, we treated the bromoenal **22a** under optimized conditions without NHC catalyst. We did not observe the formation ynal **34**, and recovered the starting material (Scheme 2.17). This experiment rules out the initial dehydrobromination of **22a** to **34** and subsequent generation of α,β-unsaturated acylazolium intermediate.

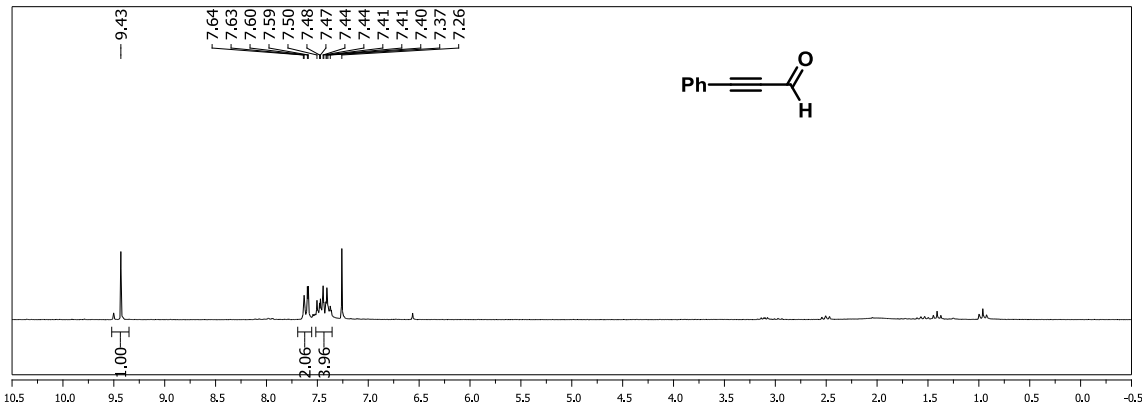
Scheme 2.17: Reaction of 2-Bromoenal under Basic Conditions



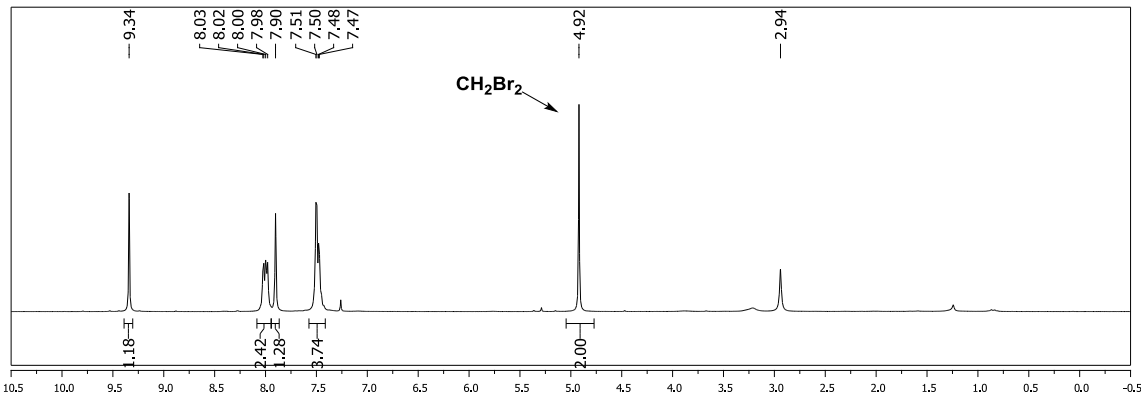
^{1}H NMR Spectrum of 2-Bromoenal 22a in $CDCl_3$



^{1}H NMR Spectrum of Ynal 34 in $CDCl_3$



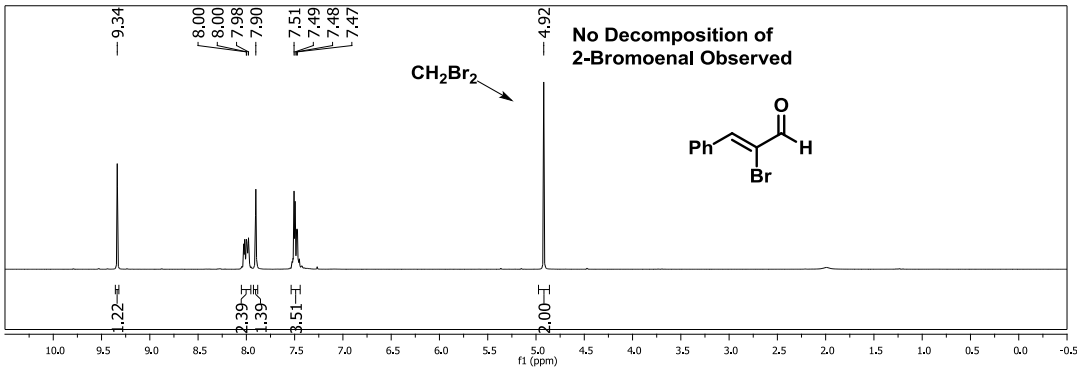
^{1}H NMR Spectrum of the Crude Reaction Mixture in $CDCl_3$ (Scheme 2.17)



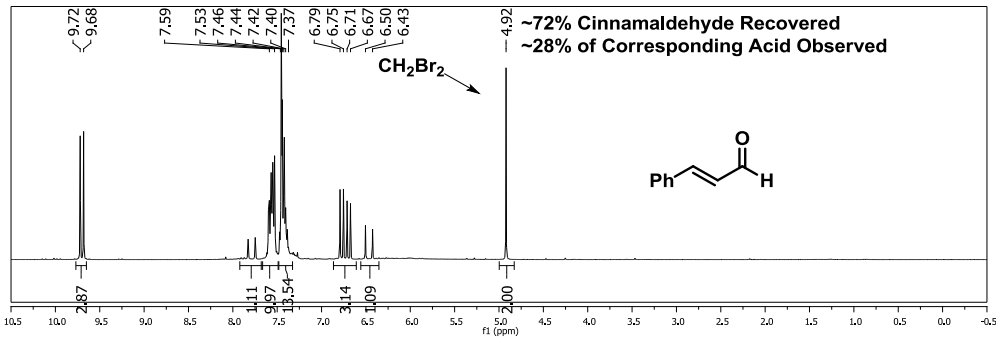
2.7.3. Stability Experiment

Further, we performed stability experiment by exposing cinnamaledyde and 2-bromoenal to open air for 12 h. This experiment shows that 2-bromoenal is very stable to air at rt and is not sensitive to oxidation. But cinnamaldehyde partially (~28% when exposed 12 h) oxidized in air to the corresponding acid. This sheds light on the enhanced stability of 2-bromoenals over enals.

^{1}H NMR Spectrum of the 2-Bromoenal 22a after Exposing in Air for 12 h



^{1}H NMR Spectrum of the Cinnamaldehyde after Exposing in Air for 12 h



2.8. Conclusion

In conclusion, we have developed the NHC-organocatalyzed annulation of 2-bromoenals with readily available 1,3-dicarbonyl compounds or enamines proceeding via the chiral α,β-unsaturated acyl azolium intermediates. The reaction furnished an enantioselective synthesis of dihydropyranones and dihydropyridinones, which takes place without the use of external oxidants, under mild conditions with broad substrate scope.[28] Moreover, based on DFT calculations, we have provided a reasonable rationalization for the mechanistic scenario and the mode of enantioinduction. Furthermore, we introduced 4-hydroxycoumarin as a bifunctional cyclic nucleophile in *α,β*-unsaturated acylazolium

chemistry; thereby coumarin-fused dihydropyranones were synthesized in good yield and enantioselectivity.[29]

2.9. Experimental Details

2.9.1. 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 toluene was purchased from commercial sources and stored under argon over sodium wire. The 2-bromoenals were synthesized from the corresponding α,β-unsaturated aldehydes following the literature procedure.[30] Acetyl acetone was purchased from commercial sources and was distilled, prior to use. The enamine derivatives were synthesized from the corresponding β-ketoesters following the literature procedure.[31] DABCO was purchased from Acros and was recrystallized from distilled Pet. Ether, prior to use. $LiOAc.2H_2O$ was purchased from Aldrich and was used without further purification. 4Å molecular sieves were powdered and activated in furnace (300 °C) before use. The triazolium salt **A** was synthesized following the literature procedure.[32]

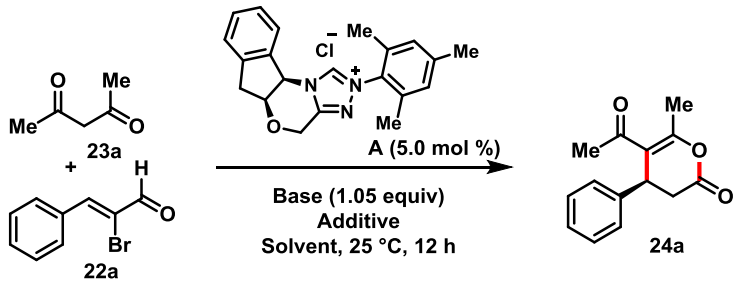
Analytical thin layer chromatography was performed on TLC Silica gel 60 F_{254}. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system.

All compounds were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400, in $CDCl_3$ 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 Shimadzu Class-VP V6.12 SP5 with UV detector.

Full quantum chemical (QM) calculations have been performed using density functional theory (DFT). The Turbomole 6.4 suites of programs have been utilized for this purpose.[33] The TZVP[34] basis set and the PBE functional[35] have been employed.The resolution of

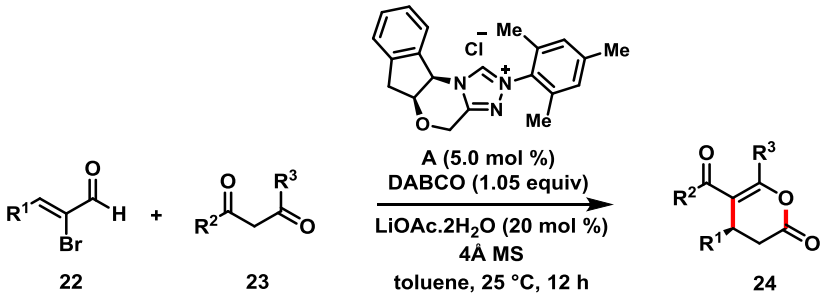
identity (ri), along with the multipole accelerated resolution of identity (marij) approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. Solvent effects were incorporated using the COSMO model, with toluene (ε = 2.4) as the solvent. The resolutions of identity (RI)[36] along with the multipole accelerated resolution of identity (marij)[37] approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. It is also to be noted that for the structures **IVa, IVb** and **V**, a conformational search was first done using molecular mechanics as implemented in the Hyperchem software.[38] The best geometries obtained from the conformational search by Hyperchem were then optimized through DFT. The contributions of internal energy and entropy were obtainedfrom frequency calculations done on the DFT structures at 298.15 K: thus, the energies reported in the figures are the ΔG values.

2.9.2. Procedure for the Optimization of Reaction Conditions



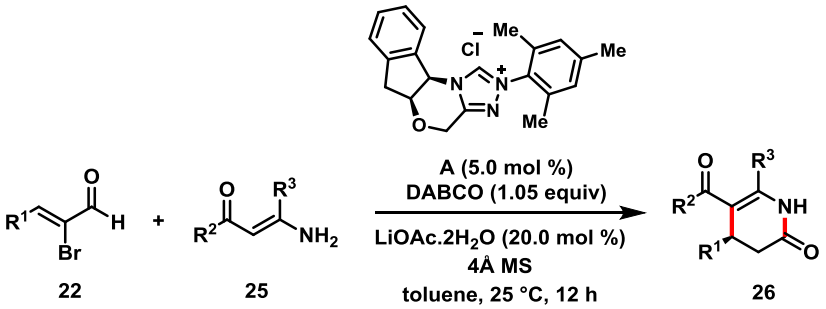
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (4.6 mg, 0.0125 mmol, 5 mol%), and base (0.264 mmol, 1.05 equiv), was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added solvent (1.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C for 10 min. To this mixture was added the 2-bromoenal **22a** (0.25 mmol) followed by acetyl acetone **23a** (0.25 mmol). Then the reaction mixture was stirred at 25° C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated 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.

2.9.3. Procedure for the Enantioselective Synthesis of Dihydropyranones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (9.1 mg, 0.025 mmol), and DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C for 10 min. To this mixture was added the 2-bromoenal **22** (0.50 mmol) followed by 1,3-dicarbonyl compound **23** (0.5 mmol). Then the reaction mixture was stirred at 25° C for 12 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding dihydropyranones.

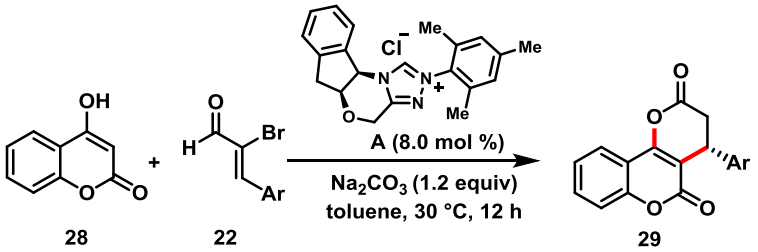
2.9.4. Procedure for the Enantioselective Synthesis of Dihydropyridinones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (9.1 mg, 0.025 mmol), and DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C for 10 min. To this mixture was added the 2-bromoenal **22** (0.50 mmol) followed by enamine derivative **25** (0.5 mmol). Then the reaction mixture was stirred at 25°

C for 12 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding dihydropyridinones.

2.9.5. Procedure for the Enantioselective Synthesis of Coumarin-Fused Dihydropyranones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (7.4 mg, 0.02 mmol), and 2-bromoenal **22** (0.25 mmol), followed by 4-hydroxy-2H-chromen-2-one **28** (0.25 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere and mixture was kept stirring at 30 °C. To this stirring solution was added the Na_2CO_3 (1.2 equiv). Then the reaction mixture was stirred at 30 °C for 12 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding functionalized coumarins (**29**).

2.10. Procedure for the Mechanistic Experiments

2.10.1. Homoenolate Interception with Aldehyde (Scheme 2.16)

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken imidazolium salt (IMes.HCl, 8.5 mg, 0.025 mmol, 0.10 equiv), (*Z*)-2-bromo 3-phenyl acrylaldehye **22a** (52.7 mg, 0.25 mmol 1.0 equiv) and 4-chlorobenzaldehyde **30** (35.1 mg, 0.25mmol, 1.0 equiv). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added THF (1.0 mL) under argon atmosphere followed by the addition of DBU (45 µL, 0.30 mmol, 1.2 equiv). Then the reaction mixture was stirred at 25° C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated 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.

2.10.2. 2-Bromoenal Reaction under Basic Conditions (Scheme 2.17)

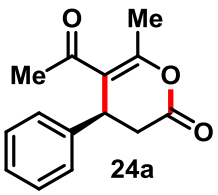
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (52.7 mg, 0.25 mmol) DABCO (29.4 mg, 0.26 mmol), lithium acetate dihydrate (5.1 mg, 0.05 mmol), and activated, powdered 4Å molecular sieves (50 mg). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (1.0 mL) under argon atmosphere. Then the reaction mixture was stirred at 25° C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated 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.

2.10.3. Stability Experiment

Cinnamaldehyde (128μl, 1.0 mmol) and (*Z*)-2-bromo 3-phenylacrylaldehye (52.7 mg, 0.25 mmol) were carefully taken in two petri dish separately and kept in air at 25 °C for 12h. The extent of air oxidation was determined by ^{1}H NMR analysis in $CDCl_3$ using CH_2Br_2 (18.0 μL, 0.25 mmol) as the internal standard.

2.11. Synthesis and Characterization of Dihydropyranones

(*S*)-5-Acetyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (24a)[15a]



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and acetyl acetone **23a** (50.1 mg, 51 μL, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 h followed by flash chromatography to afford (*S*)-5-acetyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **24a** as a white solid (94.0 mg, 82% yield).

R_f (Pet. ether /EtOAc = 60/40): 0.60.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min.) Major: 35.3 min, Minor: 41.5 min. 96% ee, $[\alpha]_D^{25}$ = +103.20 (c 0.1, $CHCl_3$).

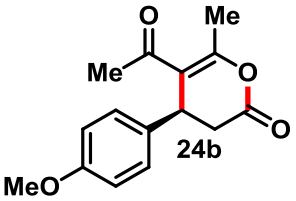
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 3H), 7.15 (d, J = 7.1 Hz, 2H), 4.15 (d, J = 6.1 Hz, 1H), 3.00 (dd, J_1 = 7.1 Hz, J_2 = 15.6 Hz, 1H,), 2.86 (dd, J_1 = 2.6 Hz, J_2 =15.6 Hz, 1H), 2.43 (s, 3H) 2.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.11, 165.76, 160.44, 139.83, 129.61, 128.12, 126.81, 117.43, 39.02, 37.33, 29.93, 19.24.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{15}O_3$: 231.1016, found: 231.1020.

FTIR (cm^{-1}) 2924, 2857, 1733, 1699, 1358, 1255, 1176, 1149, 1030, 943, 764, 702.

(*S*)-5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (24b)[15a]



Following the general procedure, treatment of (*Z*)-2-bromo -3-(4-methoxyphenyl) acrylaldehye **22b** (120.5 mg, 0.50 mmol) and acetyl acetone **23a** (50.1 mg, 51 μL, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-5-acetyl-4-(4-methxyphenyl)-6- methyl-3,4-dihydro-2*H*-pyran-2-one **24b** as a white solid (113.0 mg, 87% yield).

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

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min.) Major: 39.5 min, Minor: 44.4 min. 93% ee, $[\alpha]_D^{25}$ = +143.08 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.05 (m, 2H), 6.87-6.84 (m, 2H), 4.15 (d, J = 6.3 Hz, 1H), 3.78 (s, 3H), 2.96 (dd, J_1 = 7.1 Hz, J_2 = 15.6 Hz, 1H,), 2.82 (dd, J_1 = 2.6 Hz, J_2 =15.6 Hz, 1H), 2.41 (s, 3H) 2.12 (s, 3H).

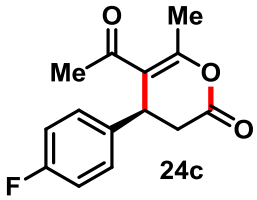
^{13}C NMR (100 MHz, $CDCl_3$) δ 198.25, 165.92, 160.19, 159.36, 131.67, 127.92, 117.68, 114.94, 55.43, 38.27, 37.57, 29.84, 19.18.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{17}O_4$: 261.1121, found: 261.1122.

FTIR (cm^{-1}) 2924, 2857, 1733, 1699, 1358, 1255, 1176, 1149, 1030, 943, 764, 702. 1280, 1178, 1033.

(*S*)-5-Acetyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (24c)

Following the general procedure, treatment of (Z)-2-bromo-3-(3-fluorophenyl)acrylaldehyde **22e** (114.5 mg, 0.50 mmol) and acetyl acetone **23a** (50.1 mg, 51 μL, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr



followed by flash chromatography to afford (*S*)-5-acetyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-pyran-2-one **24c** as a light yellow solid (102.0 mg, 82% yield).

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

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 0.8 mL/min.) Major: 38.8 min, Minor: 56.2 min. 94% ee, $[\alpha]_D^{25}$ = +132.1 (c 0.1, $CHCl_3$).

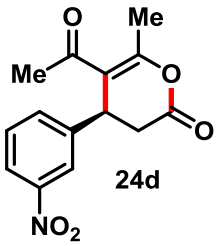
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13-7.10 (m, 2H), 7.04-7.00 (m, 2H), 4.15 (d, *J* = 6.3 Hz, 1H), 2.95 (dd, J_1 = 7.2 Hz, J_2 = 15.8 Hz, 1H,), 2.81 (dd, J_1 = 2.5 Hz, J_2 =15.8 Hz, 1H), 2.42 (s, 3H, CH_3) 2.14 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.73, 165.57, 162.43 (*J* = 251.8 Hz), 160.62, 135.55 (*J* = 3.8 Hz), 128.49 (*J* = 8.5 Hz), 117.52, 116.32 (*J* = 21.8 Hz), 38.20, 37.32, 29.98, 29.83, 19.32.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{14}O_3F$: 249.0921, found: 249.0921.

FTIR (cm^{-1}) 3020, 2927, 2854, 1728, 1692, 1634, 1450, 1416, 1311, 1284, 1216, 1026, 981, 757, 700, 669.

(*S*)- 5-Acetyl-3,4-dihydro-6-methyl-4-(3-nitrophenyl)pyran-2-one (24d)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(3-nitrophenyl)acrylaldehyde **22f** (64 mg, 0.25 mmol) and acetyl acetone **23a** (25.0 mg, 26 μL, 0.25 mmol) with triazolium salt **A** (4.6 mg, 0.0125 mmol), DABCO (29.4 mg, 0.2625 mmol), lithium acetate dihydrate (5.1 mg, 0.05 mmol), and activated, powdered 4Å molecular sieves (50 mg) in toluene (1.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-5-acetyl-3,4-dihydro-6-methyl-4-(3-nitrophenyl)pyran-2-one **24d** as a colourless oil (62.7 mg, 91% yield).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.40.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / EtOH, 0.6 mL/min.) Major: 46.7 min, Minor: 63.5 min. 95% ee, $[\alpha]_D^{25}$ = +130.50 (c 0.1, $CHCl_3$).

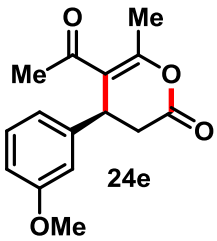
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.76 Hz, 1H), 8.02 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 4.35 (d, *J* = 6.8 Hz, 1H), 3.02 (dd, J_1 = 7.2 Hz, J_2 = 15.8 Hz, 1H), 2.88 (dd, J_1 = 1.7 Hz, J_2 =15.7 Hz, 1H), 2.47 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.80, 164.99, 161.64, 148.90, 142.15, 132.83, 130.66, 123.16, 122.04, 117.09, 38.22, 36.67, 30.37, 19.66.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{14}H_{13}O_5NNa$: 298.0686, found: 298.0685.

FTIR (cm^{-1}) 3071, 3021, 2960, 2871, 1789, 1692, 1634, 1532, 1422, 1350, 1291, 1181, 1119, 1027, 980, 945, 889, 861, 809, 793, 753, 684, 621.

(*S*)- 5-Acetyl-3,4-dihydro-4-(3-methoxyphenyl)-6-methylpyran-2-one (24e)



Following the general procedure, treatment of (Z)-2-bromo-3-(3-methoxyphenyl)acrylaldehyde **22g** (60 mg, 0.25 mmol) and acetyl acetone **23a** (25.03 mg, 26 µL, 0.25 mmol) with triazolium salt **A** (4.6 mg, 0.0125 mmol), DABCO (29.4 mg, 0.2625 mmol), lithium acetate dihydrate (5.1 mg, 0.05 mmol), and activated, powdered 4Å molecular sieves (50 mg) in toluene (1.0 mL) and stirring the reaction mixture for 12 h followed by flash chromatography to afford (*S*)-5-Acetyl-3,4-dihydro-4-(3-methoxyphenyl)-6-methylpyran-2-one **24e** as a white solid (53.6 mg, 82% yield).

R$_f$ (Pet. ether /EtOAc = 60/40): 0.50.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 0.8 mL/min.) Major: 52.3 min, Minor: 66.7 min. 96% ee, $[\alpha]_D^{25}$ = +62.30 (c 0.1, $CHCl_3$).

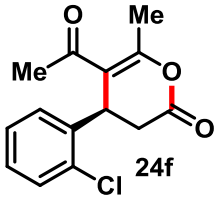
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.15 (m, 1H), 6.76-6.60 (m, 3H), 4.04 (dd, J_1 = 6.7 Hz, J_2 = 2.2 Hz, 1H), 3.71 (s, 3H), 2.95 (dd, J_1 = 7.6 Hz, J_2 = 15.9 Hz, 1H) 2.79 (dd, J_1 = 3.3 Hz, J_2 = 15.9 Hz, 1H) 2.35 (s, 3H) 2.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.17, 165.74, 160.51, 160.42, 141.43, 130.69, 118.97, 117.24, 113.09, 112.78, 55.35, 38.96, 37.24, 29.88, 19.21.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{17}O_4$: 261.1121, found: 261.1123.

FTIR (cm^{-1}) 3062, 3029, 2925, 1780, 1645, 1597, 1579, 1494, 1448, 1319, 1118, 946, 900, 763, 696.

(*S*)- 4-Acetyl-5-(2-chlorophenyl)-3-methylcyclohex-3-enone (24f)[15a]



Following the general procedure, treatment of (*Z*)-2-bromo-3-(2-chlorophenyl)acrylaldehyde **22h** (122.7 mg, 0.50 mmol) and acetyl acetone **23a** (50.1 mg, 51 µL, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate

dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)- 4-acetyl-5-(2-chlorophenyl)-3-methylcyclohex-3-enone **24f** as a white solid (126.4 mg, 96% yield).

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

HPLC (Chiralcel OD-H, 85:15 Pet.ether / IPA, 0.5 mL/min.) Major: 19.4 min, Minor: 21.0 min. 96% ee, $[\alpha]_D^{25}$ = +139.16 (c 0.1, $CHCl_3$).

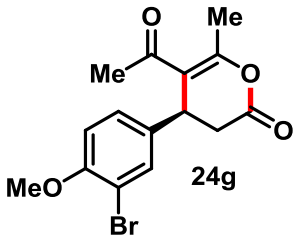
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 1H), 7.28-7.24 (m, 2H), 7.08-7.06 (m, 1H), 4.67 (d, *J* = 4.4 Hz, 1H), 3.01-2.90 (m, 2H,), 2.49 (s, 3H), 2.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.71, 165.44, 161.73, 136.40, 133.25, 130.69, 129.60, 128.07, 127.50, 116.08, 35.69, 35.05, 29.41, 19.23.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{14}O_3Cl$: 265.0626, found: 265.0626.

FTIR (cm^{-1}) 2924, 1788, 1693, 1614, 1471, 1443, 1423, 1379, 1360, 1287, 1174, 1116, 1026, 940, 862, 762, 693.

(*S*)-5-Acetyl-4-(3-bromo-4-methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (24g)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(3-bromo-4-methoxyphenyl)acrylaldehyde **22j** (160 mg, 0.50 mmol) and acetyl acetone **23a** (50.1 mg, 51 µL, 0.50 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.1 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-5-acetyl-4-(3-bromo-4-methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one **24g** as a white oil (144.0 mg, 85% yield).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.40.

HPLC (Chiralcel OD-H, 95:05 Pet.ether / IPA, 0.5 mL/min.) Major: 26.3 min, Minor:33.1 min. 95% ee, $[\alpha]_D^{25}$ = +130.40 (c 0.1, $CHCl_3$).

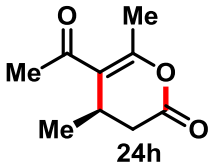
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.3 (m, 1H), 7.03-7.01 (m, 1H), 6.83-6.81, (m, 1H), 4.07 (d, *J* = 6.4 Hz, 1H), 3.84(s, 3H), 2.95 (dd, J_1 = 7.4 Hz, J_2 = 15.6 Hz, 1H,), 2.76 (m, 2H), 2.43 (s, 3H) 2.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.71, 165.53, 160.73155.56, 133.08, 131.74, 126.66, 117.1, 112.58, 112.55, 56.35, 37.64, 37.24, 29.91, 19.28.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{16}O_4Br$: 339.0226, found: 339.0225.

FTIR (cm^{-1}) 2923, 2825, 1786, 1697, 1604, 1498, 1462, 1286, 1260, 1182, 1146, 1054, 1020, 949, 816, 760.

(*R*)-5-Acetyl-4,6-dimethyl-3,4-dihydro-2*H*-pyran-2-one (24h)



Following the general procedure, treatment of (*Z*)-2-bromobut-2-enal **22k** (74.4 mg, 0.50 mmol) and acetyl acetone **23a** (50.1 mg, 51 μL, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*R*)-5-acetyl-4,6-dimethyl-3,4-dihydro-2*H*-pyran-2-one **24h** as a white solid (74.0 mg, 88% yield).

R$_f$ (Pet. ether /EtOAc = 60/40): 0.56.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 0.8 mL/min.) Major: 16.34 min, Minor: 19.9 min. 85% ee, $[\alpha]_D^{25}$ = +10.1 (c 0.1, $CHCl_3$).

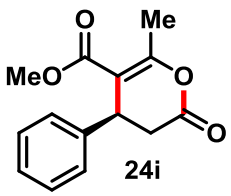
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04-3.00 (m, 1H), 2.67 (dd, J_1 = 5.6 Hz, J_2 = 15.9 Hz, 1H), 2.57 (dd, J_1 = 2.2 Hz, J_2 =15.9 Hz, 1H), 2.33 (s, 3H) 2.25 (s, 3H), 1.12 (d, J = 6.94 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.67, 167.01, 159.17, 120.72, 35.87, 27.55, 19.44, 19.40.

HRMS (ESI) calculated $[M+H^+]$ for $C_9H_{13}O_3$: 169.0859, found: 169.0861.

FTIR (cm^{-1}) 3674, 3523, 3021, 2967, 2928, 1779, 1687, 1608, 1516, 1457, 1420, 1384, 1367, 1294, 1216, 1132, 1082, 953, 918, 754, 667.

(*S*)-Methyl 6-methyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (24i)[15b]



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and methyl acetoacetate **23l** (58.1 mg, 54 μL, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash

chromatography to afford (*S*)-methyl 6-methyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate **24i** as a white oil (98.0 mg, 80% yield)

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.41.

HPLC (Chiralcel OD-H, 95:05 Pet.ether / IPA, 1.0 mL/min.) Major: 11.24 min, Minor: 21.84 min, 95% ee, $[\alpha]_D^{25}$ = +103.20 (c 0.1, $CHCl_3$).

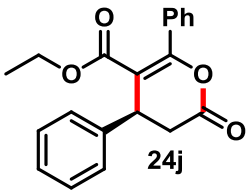
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 3H), 7.16-7.14 (m, 2H), 4.29 (d, J = 6.6 Hz, 1H), 3.69 (s, 3H), 2.99 (dd, J_1 = 7.7 Hz, J_2 = 16.0 Hz, 1H,), 2.86 (dd, J_1 = 2.1 Hz, J_2 =16.0 Hz, 1H), 2.5 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.49, 166.15, 161.84, 140.42, 129.13, 127.60, 126.61, 109.73, 52.01, 37.72, 36.51, 18.98.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{15}O_4$: 247.0965, found: 247.0965.

FTIR (cm^{-1} 3019, 2925, 2846, 1783, 1733, 1718, 1637, 1304, 1497, 1360, 1216, 1157, 1119, 1075, 941, 897, 757, 699, 669.

(*S*)-Ethyl 2-oxo-4,6-diphenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (24j)[15b]



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and ethyl 3-oxo-3-phenylpropanoate **23n** (96.1 mg, 87 μL, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-ethyl 2-oxo-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carboxylate **24j** as a white solid (148.0 mg, 92% yield).

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

HPLC (Chiralcel OD-H, 85:15 Pet.ether / IPA, 0.5 mL/min.) Major: 16.2 min, Minor: 18.3 min. 91% ee, $[\alpha]_D^{25}$ = +5.0 (c 0.1, $CHCl_3$).

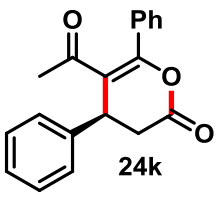
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H), 7.50-7.41 (m, 3H), 7.39-7.25(m, 5H), 4.45 (dd, J_1 = 2.6 Hz, J_2 = 7.4 Hz, 1H), 3.97 (q, J_1 = 7.2 Hz, J_2 = 14.3 Hz, 2H, CH_2), 3.14 (dd, J_1 = 7.5 Hz, J_2 = 15.9 Hz, 1H), 2.96 (dd, J_1 = 2.9 Hz, J_2 =15.9 Hz, 1H), 0.91 (t, J = 7.2 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.32, 166.03, 158.52, 139.92, 139.09, 130.10, 129.16, 128.62, 127.97, 127.70, 126.73, 111.67, 60.95, 38.78, 36.25, 13.41.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{19}O_4$: 323.1278, found: 323.1273.

FTIR (cm^{-1}) 3025, 2927, 2846, 2599, 1731, 1683, 1633, 1492, 1450, 1421, 1315, 1288, 1217, 1177, 1026, 985, 934, 873, 757, 705.

(*S*)-5-Benzoyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (24k)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and 1-phenylbutane-1,3-dione **23o** (81.1 mg, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-5-benzoyl-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-2-one **24k** as a white solid (124.0 mg, 85% yield). It should be noted that <5% of the other regioisomer was also formed under the reaction conditions.

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

HPLC (Chiralcel OJ-H, 90:10 Pet.ether / EtOH, 0.7 mL/min.) Minor: 49.2 min, Major: 62.7 min. 90% ee, $[\alpha]_D^{25}$ = +9.1 (c 0.1, $CHCl_3$).

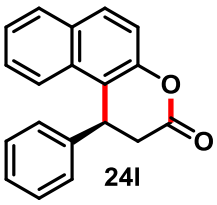
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.3 Hz, 2H, H_{ar}), 7.46-7.41 (m, 1H, H_{ar}), 7.32 (t, J = 7.8 Hz, 2H, H_{ar}), 7.23-7.11 (m, 3H, H_{ar}), 7.08-7.06 (m, 2H, H_{ar}), 4.24 (dd, J_1 = 3.1 Hz, J_2 = 7.0 Hz, 1H, CH), 2.99 (dd, J_1 = 7.6 Hz, J_2 = 16.1 Hz, 1H, CH), 2.85 (dd, J_1 = 3.6 Hz, J_2 =16.1 Hz, 1H, CH), 1.82 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.95, 166.68, 154.91, 140.06, 138.48, 133.21, 129.24, 129.06, 129.03, 128.91, 128.84, 127.73, 126.86, 117.82, 39.47, 36.29, 19.14.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{17}O_3$: 293.1172, found: 293.1175.

FTIR (cm^{-1}) 3360, 2922, 2851, 1783, 1719, 1664, 1632, 1597, 1449, 1359, 1267, 1171, 1117, 1023, 979, 764, 700.

(*R*)-1-Phenyl-1*H*-benzo[f]chromen-3(2*H*)-one (24l)[20]



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and naphthalen-2-ol **23p** (72.0 mg, 0.50 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular

sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*R)*-1-phenyl-1H-benzo[f]chromen-3(2H)-one **24l** as a white solid (102.0 mg, 75% yield).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.75.

HPLC (Kromasil 5-Amycoat, 85:15 Pet.ether / IPA, 0.5 mL/min.) Major: 26.3 min, Minor: 21.7 min. 75% ee, $[\alpha]_D^{25}$ = +24.0 (c 0.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H), 7.81 (d, 1H, *J* = 8.5 Hz), 7.50-7.43 (m, 2H), 7.37 (d, 1H, *J* = 7.0 Hz), 7.29-7.26 (m, 2H), 7.24-7.21 (m, 1H), 7.14 (d, 2H, *J* = 7.5 Hz), 4.97 (d, 1H, *J* = 6.5 Hz), 3.25-3.15 (m, 2H).

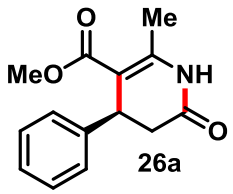
^{13}C NMR (125 MHz, $CDCl_3$) δ 167.28, 149.91, 140.65, 131.21, 131.11, 130.06, 129.35, 128.88, 127.71, 127.59, 127.05, 125.39, 123.17, 117.71, 37.75, 37.59.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{15}O_2$: 275.1067, found: 275.1068.

FTIR (cm^{-1}) 3021, 2968, 2929, 1780, 1687, 1635, 1609, 1457, 1420, 1385, 1361, 1326, 1294, 1216, 1132, 1082, 1042, 1005, 984, 953, 919, 872, 843, 759, 668, 625.

2.12. Synthesis and Characterization of Dihydropyridinones

(*S*)-Methyl 2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (26a)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and (Z)-methyl 3-aminobut-2-enoate **25a** (57.5 mg, 0.50 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-methyl 2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydro pyridine-3-carboxylate **26a** as a white solid (98.0 mg, 86% yield).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.46.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / IPA, 0.5 mL/min.) Minor: 15.9 min, Major: 27.0 min. 99% ee, $[\alpha]_D^{25}$ = +120.04 (c 0.1, $CHCl_3$).

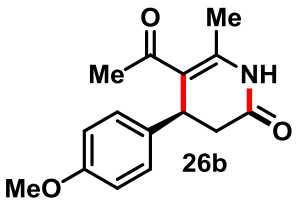
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (bs, 1H), 7.32-7.29 (m, 2H), 7.25-7.19 (m, 3H), 4.29 (d, *J* = 7.9 Hz, 1H), 3.67 (s, 3H), 2.98 (dd, J_1 = 7.9 Hz, J_2 = 16.2 Hz, 1H), 2.74 (d, *J* = 16.2 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.53, 167.47, 146.47, 141.95, 128.90, 127.1, 126.7, 107.0, 51.54, 38.26, 37.84, 19.15.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{16}O_3N$: 246.1125, found: 246.1124.

FTIR (cm^{-1}) 3242, 3027, 2925, 2854, 1694, 1455, 1367, 1286, 1202, 1091, 1031, 789, 764, 697, 648, 467.

(*S*)-5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyridin-2(1*H*)-one (26b)



Following the general procedure, treatment of (*Z*)-2-bromo -3-(4-methoxyphenyl) acrylaldehye **22b** (120.5 mg, 0.5 mmol) and (Z)-methyl 3-aminobut-2-enoate **25a** (57.5 mg, 0.50 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-5-acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyridin-2(1*H*)-one **26b** as a white solid (125.0 mg, 91% yield).

R$_f$ (Pet. ether /EtOAc = 60/40): 0.33.

HPLC (Chiralcel OJ-H, 60:40 Pet.ether / IPA, 0.5 mL/min.) Major: 24.6 min, Minor: 14.6 min. 98% ee, $[\alpha]_D^{25}$ = +74.12 (c 0.1, $CHCl_3$).

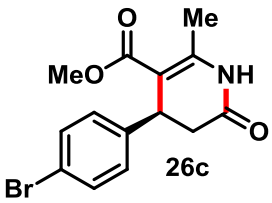
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (bs, 1H), 7.10-7.07 (d, *J* = 8.5 Hz, 2H), 6.82-6.79 (d, *J* = 8.5 Hz, 2H), 4.20 (d, *J* = 7.4 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.92 (dd, J_1 = 7.8 Hz, J_2 = 16.4 Hz, 1H,), 2.67 (d, *J* = 16.4 Hz, 1H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.74, 167.52, 158.62, 146.48, 133.97, 127.80, 114.23, 107.40, 55.37, 51.53, 38.41, 37.00, 19.11.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{15}H_{17}O_4NNa$: 298.1050, found: 298.1049.

FTIR (cm^{-1}) 3237, 3130, 2924, 2853, 1701, 1631, 1510, 1377, 1287, 1200, 1089, 1034, 830, 803, 721, 700, 664.

(*S*)-Methyl 4-(4-bromophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (26c)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-bromophenyl)acrylaldehyde **22j** (72.4 mg, 0.25 mmol) and (*Z*)-methyl 3-aminobut-2-enoate **25a** (28.76 mg, 0.5 mmol) with

triazolium salt **A** (4.6 mg, 0.0125 mmol), DABCO (29.4 mg, 0.2625 mmol), lithium acetate dihydrate (5.1 mg, 0.05 mmol), and activated, powdered 4Å molecular sieves (50 mg) in toluene (1.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (**(***S***)**-Methyl 4-(4-bromophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro pyridine-3-carboxylate **26c** as a white solid (65.0 mg, 85% yield).

R*f* (Pet. ether /EtOAc = 60/40): 0.42.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / IPA, 0.5 mL/min.) Minor: 15.0 min, Major: 25.7 min. 93% ee, $[\alpha]_D^{25}$ = +45.56 (c 0.1, $CHCl_3$).

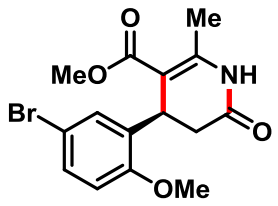
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 4.22 (d, *J* = 7.4 Hz, 1H), 3.65 (s, 3H), 2.95 (dd, J_1 = 8.0 Hz, J_2 = 16.6 Hz, 1H), 2.67 (d, *J* = 16.6 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.74, 167.24, 146.79, 140.97, 132.65, 128.61, 121.02, 106.72, 51.67, 38.06, 37.48, 19.36.

HRMS (ESI) calculated $[M+H]^+$ for $C_{14}H_{15}O_3NBr$: 324.0230, found: 324.0230.

FTIR (cm^{-1}) 3404, 3019, 2927, 2854, 1780, 1702, 1634, 1518, 1488, 1425, 1285, 1216, 1093, 1030, 929, 849, 771, 669, 625.

(*S*)-Methyl 4-(3-bromo-2-methoxyphenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (26d)



26d

Following the general procedure, treatment of (*Z*)-2-bromo-3-(3-bromo-2-methoxyphenyl)acrylaldehyde **22k** (80 mg, 0.25 mmol) and (*Z*)-methyl 3-aminobut-2-enoate **25a** (28.7 mg, 0.25 mmol) with triazolium salt **A** (4.6 mg, 0.01 mmol), DABCO (29.4 mg, 0.26 mmol), lithium acetate dihydrate (5.1 mg, 0.05 mmol), and activated, powdered 4Å molecular sieves (50 mg) in toluene (1.0 mL) and stirring the reaction mixture for 12 h followed by flash chromatography to afford (*S*)-methyl 4-(3-bromo-2- ethoxyphenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate **26d** as a white solid (75.0 mg, 85% yield).

R*f* (Pet. ether /EtOAc = 60/40): 0.37.

HPLC (Chiralcel OJ-H, 85:15 Pet.ether / EtOH, 0.5 mL/min.) Major: 19.53 min, Minor: 21.55 min. 87% ee, $[\alpha]_D^{25}$ = +80.34 (c 0.1, $CHCl_3$).

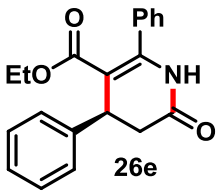
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.30 (dd, J_1 = 2.86 Hz, J_2 = 8.78 Hz, 1H), 6.99 (d, J = 2.43 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 4.52 (d, J = 8.1 Hz, 1H), 3.82 (s, 3H), 2.83 (dd, J_1 = 8.1 Hz, J_2 = 16.4 Hz, 1H,), 2.71 (d, J = 16.6 Hz, 1H), 2.46 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.76, 167.29, 156.11, 147.54, 131.17, 131.04, 129.88, 113.02, 112.56, 105.26, 55.59, 51.66, 36.25, 32.56, 19.53.

HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{17}O_4NBr$: 354.0335, found: 354.0331.

FTIR (cm^{-1}) 3526, 3019, 2967, 2940, 2842, 1781, 1689, 1610, 1487, 1280, 1216, 1243, 1243, 1028, 944, 757, 668, 624.

(*S*)-Ethyl 6-oxo-2,4-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (26e)[17]



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and (*Z*)-ethyl 3-amino-3-phenylacrylate **25e** (95.5 mg, 0.50 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 h followed by flash chromatography to afford (*S*)-ethyl 6-oxo-2,4-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate **26e** as a white solid (145.0 mg, 90% yield).

R$_f$ (Pet. ether /EtOAc = 60/40): 0.57.

HPLC (Chiralcel OJ-H, 85:15 Pet.ether / IPA, 1.0 mL/min.) Minor: 48.98 min, Major: 55.02 min. 95% ee, $[\alpha]_D^{25}$ = +46.38 (c 1.0, $CHCl_3$).

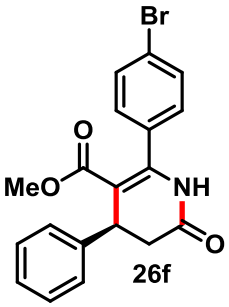
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.18 (m, 11H), 4.28 (dd, J_1 = 2.8 Hz, J_2= 8.3 Hz, 1H), 3.80 (q , J = 7.3 Hz, 2H), 3.03 (dd, J_1 = 8.1 Hz, J_2 = 16.2 Hz, 1H), 2.75 (dd, J_1 = 2.8 Hz, J_2 = 16.2Hz, 1H), 0.78 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.81, 166.75, 146.66, 141.82, 135.85, 129.69, 129.03, 128.60, 127.97, 127.28, 126.88, 108.88, 60.34, 38.71, 38.16, 13.64.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{19}O_3NNa$: 344.1257, found: 344.1255.

FTIR (cm^{-1}) 3246, 3027, 2924, 2853, 1690, 1638, 1600, 1492, 1453, 1366, 1286, 1204, 1097, 1629, 1008, 861, 764, 698, 647.

(*S*)-Ethyl 2-(4-bromophenyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (26f)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and (*Z*)-methyl 3-amino-3-(4-bromophenyl)acrylate **25f** (128.0 mg, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 h followed by flash chromatography to afford (*S*)-ethyl 2-(4-bromophenyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate **26f** as a white solid (167.0 mg, 90% yield).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.62.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / EtOH, 0.6 mL/min.) Minor: 82.9 min, Minor: 121.7 min. 91% ee, $[\alpha]_D^{25}$ = +22.90 (c 0.1, $CHCl_3$).

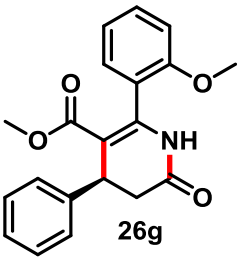
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.56-7.53 (m, 2H), 7.38-7.19 (m, 7H), 4.36 (dd, J_1= 2.0 Hz, J_2= 8.1 Hz , 1H), 3.46 (s, 3H), 3.08(dd, J_1= 7.86 Hz, J_2= 16.2 Hz , 1H), 2.79 (d, J = 16.2 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.32, 166.85, 146.30, 141.33, 134.16, 131.65, 129.70, 129.01, 127.31, 126.71, 123.92, 108.57, 51.52, 38.40, 38.03.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{17}O_3NBr$: 386.0386, found: 386.0386.

FTIR (cm^{-1}) 3398, 3019, 2927, 2854, 1702, 1635, 1589, 1489, 1440, 1360, 1287, 1215, 1174, 1094, 1073, 1013, 759, 668.

(*S*)-Methyl 2-(2-methoxyphenyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (26g)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and (*Z*)-methyl 3-amino-3-(2-methoxyphenyl)acrylate **25g** (104.0 mg, 0.50 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 h followed by flash chromatography to afford

(*S*)-methyl 2-(2-methoxyphenyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate **26g** as a yellow solid (142.0 mg, 84% yield).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.42.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / EtOH, 0.6 mL/min.) Major: 66.9 min, Minor: 45.7 min. 90% ee, $[\alpha]_D^{25}$ = +3.6 (c 0.1, $CHCl_3$).

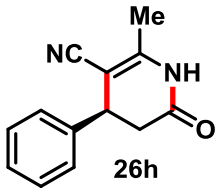
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (bs, 1H, NH), 7.44-7.40 (m, 3H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.29-7.26 (m, 2H), 7.05-6.98 (m, 2H), 4.38 (d, *J* = 6.7 Hz, 1H, CH), 3.85 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 3.11 (dd, J_1 = 8.0 Hz, J_2 =16.8 Hz, 1H, CH), 2.87 (d, *J* = 16.8 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.91, 166.82, 156.33, 144.44, 141.51, 130.98, 129.52, 128.97, 128.27, 127.12, 127.02, 124.52, 120.65, 111.08, 109.34, 55.71, 51.41, 38.55, 38.45.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{20}H_{19}O_4Na$: 360.1206, found: 360.1204.

FTIR (cm^{-1}) 3402, 3019, 2927, 2855, 1697, 1641, 1600, 1494, 1439, 1360, 1289, 1215, 1094, 1049, 1028, 929, 668, 624.

(*S*)-2-Methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (26h)[17]



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (105.5 mg, 0.50 mmol) and (*Z*)-methyl 3-aminobut-2-enoate **25h** (41.0 mg, 0.50 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4Å molecular sieves (100 mg) in toluene (2.0 mL) and stirring the reaction mixture for 12 h followed by flash chromatography to afford (*S*)-methyl 2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate **26h** as a white solid (90.0 mg, 85% yield).

***R*$_f$** (Pet. ether /EtOAc = 60/40): 0.26.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / IPA, 0.5 mL/min.) Minor: 25.60 min, Major: 35.90 min. 90% ee, $[\alpha]_D^{25}$ = +125.7 (c 1.0, $CHCl_3$).

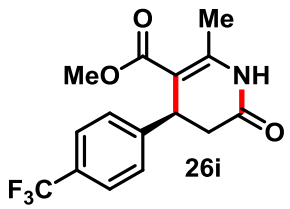
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (bs, 1H), 7.42-7.21 (m, 5H), 3.90 (t, *J* = 7.5 Hz, 1H), 2.97 (dd, J_1 = 7.5 Hz, J_2 = 16.1 Hz, 1H,), 2.80 (dd, J_1= 5.3 Hz, J_2 = 16.1 Hz, 1H), 2.23 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.06, 148.31, 139.80, 129.36, 128.13, 126.32, 118.27, 89.58, 39.28, 37.52, 19.03.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{13}H_{12}ON_2Na$: 235.0842, found: 235.0842.

FTIR (cm^{-1}) 3249, 3136, 2925, 2854, 2205, 1698, 1646, 1491, 1434, 1385, 1360, 1270, 1159, 1078, 1003, 887, 763, 701.

(*S*)-Methyl 2-methyl-6-oxo-4-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridine -3-carboxylate (26i)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-(trifluoromethyl)phenyl)acrylaldehyde **22l** (69.8 mg, 0.25 mmol) and (*Z*)-methyl 3-aminobut-2-enoate **25a** (28.7 mg, 0.25 mmol) with triazolium salt **A** (4.6 mg, 0.0125 mmol), DABCO (29.4 mg, 0.26 mmol), lithium acetate dihydrate (5.1 mg, 0.05 mmol), and activated, powdered 4Å molecular sieves (50 mg) in toluene (1.0 mL) and stirring the reaction mixture for 12 hr followed by flash chromatography to afford (*S*)-methyl 2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate **26i** as a white solid (67.0 mg, 85% yield).

R_f (Pet. ether /EtOAc = 60/40): 0.35.

HPLC (Chiralcel OJ-H, 90:10 Pet.ether / EtOH, 0.5 mL/min.) Minor: 19.58 min, Major: 28.49 min. 91% ee, $[\alpha]_D^{25}$ = +78.24 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (bs, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.32 (d, *J* = 7.8Hz, 1H), 3.66 (s, 3H), 2.99 (dd, J_1 = 8.0 Hz, J_2 = 16.4 Hz, 1H,), 2.70(d, *J* = 16.4 Hz, 1H), 2.43 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.20, 167.16, 147.00, 146.0, 127.27, 126.02, 125.99 (d, J_{C-F} = 3.3 Hz), 125.95, 106.41, 51.74, 37.97, 37.90, 19.49.

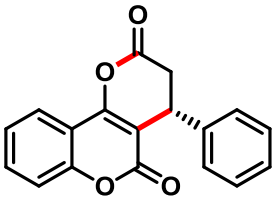
HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{15}O_3NF_3$: 314.0999, found: 314.0998.

FTIR (cm^{-1}) 3404, 3020, 2927, 2855, 1703, 1635, 1520, 1422, 1326, 1215, 1129, 765, 669.

2.13. Synthesis and Characterization of Coumarin-fused Dihydropyranones

(*R*)-4-Phenyl-3,4-dihydropyrano[3,2-c]chromene-2,5-dione (29a)[27]

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **22a** (53 mg, 0.25 mmol) and 4-hydroxy-2*H*-chromen-2-one **28** (41 mg, 0.25 mmol) with triazolium salt **A** (7.4 mg, 0.02 mmol), Na_2CO_3 (32 mg, 0.75 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography to afford



29a

(*R*)-4-phenyl-3,4-dihydropyrano[3,2-c]chromene-2,5-dione **29a** as a white solid (55.1 mg, 75%).

R_f (Pet. ether /EtOAc = 70/30): 0.60.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / EtOH, 1.0 mL/min.) Major: 27.0 min, Minor: 35.4 min. 93:7 er, $[\alpha]_D^{25}$ = -159.30 (c 0.1, $CHCl_3$).

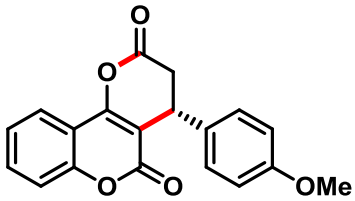
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J_1 = 1.7 Hz, J_2 = 8.2 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.39-7.24 (m, 7H), 4.53 (d, *J* = 7.3 Hz, 1H) 3.24-3.11 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.39, 160.87, 157.36, 153.29, 139.46, 133.06, 129.42, 128.15, 126.75, 124.80, 122.92, 117.03, 113.65, 106.47, 36.12, 36.02.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{12}O_4Na$: 315.0628, found: 315.0624.

FTIR (cm^{-1}) 3065, 3028, 2924, 1793, 1722, 1645, 1609, 1578, 1456, 1328, 1108, 906, 757, 699, 637.

(*R*)-4-(4-Methoxyphenyl)-3,4-dihydro-2*H*,5*H*-pyrano[3,2-c]chromene-2,5-dione (29b)



29b

Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-methoxyphenyl)acrylaldehyde **22b** (60.2 mg, 0.25 mmol) and 4-hydroxy-2*H*-chromen-2-one **1a** (41 mg, 0.25 mmol) with triazolium salt **A** (7.4 mg, 0.02 mmol), Na_2CO_3 (32 mg, 0.75 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography to afford (*R*)-4-(4-methoxyphenyl)-3,4-dihydro-2*H*,5*H*-pyrano[3,2-c]chromene-2,5-dione **29b** as a white solid (65.0 mg, 81%).

R_f (Pet. ether /EtOAc = 70/30): 0.46.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / EtOH, 0.7 mL/min.) Major: 30.7 min, Minor: 46.0 min. 92:8 er, $[\alpha]_D^{25}$ = -165.30 (c 0.1, $CHCl_3$).

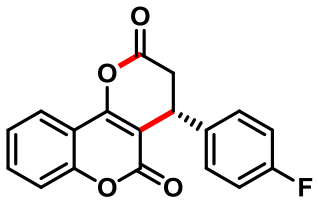
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91(dd, J_1 = 8.3 Hz, J_2 = 8.3 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.39-7.35 (m, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.48 (d, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 3.21-3.09 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.56, 160.91, 159.37, 157.11, 153.25, 132.99, 131.46, 127.88, 124.77, 122.89, 117.01, 114.74, 113.69, 106.82, 55.40, 36.32, 35.27.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{14}O_5Na$: 345.0731, found: 345.0729.

FTIR (cm^{-1}) 2925, 2853, 1792, 1721, 1644, 1609, 1379, 1251, 1105, 1034, 983, 760, 637.

(*R*)-4-(4-Fluorophenyl)-3,4-dihydropyrano[3,2-c]chromene-2,5-dione (29c)



29c

Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-fluorophenyl)acrylaldehyde **22e** (57.3 mg, 0.25 mmol) and 4-hydroxy-2*H*-chromen-2-one **28** (41 mg, 0.25 mmol) with triazolium salt **A** (7.4 mg, 0.02 mmol), Na_2CO_3 (32 mg, 0.75 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography to afford (*R*)-4-(4-fluorophenyl)-3,4-dihydropyrano[3,2-c]chromene-2,5-dione **29c** as a white solid (55.0 mg, 71%).

R$_f$ (Pet. ether /EtOAc = 70/30): 0.56.

HPLC (Chiralcel OJ-H, 70:30 Pet.ether / EtOH, 1.0 mL/min.) Major: 22.6 min, Minor: 30.10min. 87:13 er, $[\alpha]_D^{25}$ = -170.20 (c 0.1, $CHCl_3$).

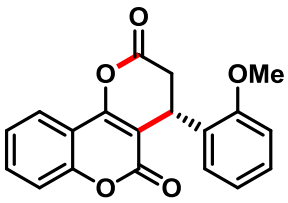
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J_1 = 1.9 Hz, J_2 = 10.2 Hz, 1H), 8.24-8.19 (m, 1H), 7.94-7.88 (m, 2H), 7.74-7.70 (m, 2H), 7.47-7.41 (m, 2H), 4.35 (dd, J_1 = 2.0 Hz, J_2 = 9.5 Hz, 1H), 2.74 (dd, J_1 = 9.5 Hz, J_2 = 20.0 Hz, 1H), 2.61 (dd, J_1 = 2.0 Hz, J_2 = 20.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.94, 185.23 (d, *J* = 310.2), 181.72, 177.43, 172.30, 149.73 (d, *J* = 4.26), 147.20, 141.30 (d, *J* = 9.8), 136.79, 134.38, 127.04, 126.24, 125.97, 122.63, 113.55, 25.95, 24.92.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{11}FO_4Na$: 333.0534, found: 333.0527.

FTIR (cm^{-1}) 3065, 3028, 2924, 1793, 1722, 1645, 1609, 1578, 1456, 1328, 1108, 906, 757, 699, 637.

(*R*)-4-(2-Methoxyphenyl)-3,4-dihydro-2*H*,5*H*-pyrano[3,2-c]chromene-2,5-dione (29d)



29d

Following the general procedure, treatment of (Z)-2-bromo-3-(3-methoxyphenyl)acrylaldehyde **22m** (60.2 mg, 0.25 mmol) and 4-hydroxy-2*H*-chromen-2-one **28** (41 mg, 0.25 mmol) with triazolium salt **A** (7.4 mg, 0.02 mmol), Na_2CO_3 (32 mg, 0.75 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 12 h followed by flash column chromatography to afford (*R*)-4-(2-Methoxyphenyl)-3,4-dihydro-2*H*,5*H*-pyrano[3,2-c]chromene-2,5-dione **29d** as a white solid (75.0 mg, 93%).

R$_f$ (Pet. ether /EtOAc = 70/30): 0.56.

HPLC (Chiralcel OJ-H, 95:05 n-hexane / EtOH, 1.0 mL/min.) Minor: 61.6 min, Major: 67.0 min. 89:11 er, $[\alpha]_D^{25}$ = -173.5 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 8.6 Hz, 1H), 7.39-7.31 (m, 3H), 7.28-7.24 (m, 1H), 6.93 (t, *J* = 7.0 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 4.52 (d, J = 8.5 Hz, 1H), 3.74 (s, 3H), 3.20-3.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.23, 160.97, 157.12, 156.83, 153.11, 132.58, 129.34, 127.28, 124.53, 122.85, 120.87, 116.84, 113.91, 110.78, 104.00, 54.34, 34.47, 34.15.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{14}O_5Na$: 345.0733, found: 345.0726.

FTIR (cm^{-1}) 3070, 3014, 2926, 2841, 1792, 1722, 1645, 1609, 1490, 1456, 1378, 1248, 1108, 992, 906, 810, 758, 638.

2.14. References

1. Albanese, D. C. M.; Gaggero, N. *Eur. J. Org. Chem.* **2014**, 5631
2. Kumagai, H.; Masuda, T.; Ishizuka, M.; Takeuchi, T. *J. Antibiotics.* **1995**, *48*, 177.
3. Nakashima, T.; Hirano, S.-i.; Agata, N.; Kumagai, H.; Isshiki, K.; Yoshioka, T.; Ishizuka, M.; Maeda, K.; Takeuchi, T. *J. Antibiotics.* **1999**, *52*, 426.
4. Brasholz, M.; Sörgel, S.; Azap, C.; Reißig, H.-U. *Eur. J. Org.Chem.* **2007**, 3801
5. Candish, L.; Lupton, D. W. *Org. Lett.* **2010**, *12*, 4836
6. Willot, M.; Radtke, L.; Konning, D.; Forhlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9105.
7. (a) Sorkin, E. M.; Clissold S. P.; Brogden, R. N. *Drugs*, **1985**, *30*, 182. (b) Janis, R. A.; Silver P. J.; Triggle, D. *J. Adv. Drug Res*, **1987**, *16*, 309. (c) Lewis, J. R. *Nat. Prod. Rep*, **1994**, *11*, 329. (d) Pettit, G. R.; Groszek, G.; Backhaus, R. A.; Doubek, D. L.; Barr R. J.; Meerow, A. W. *J. Nat. Prod*, **1995**, *58*, 756.
8. Yang, M.-H.; Chen, Y.-Y.; Huang, L. *Phytochemistry* **1988**, *27*, 445.
9. (a) Ochoa, E.; Suarez, M.; Verdecia, Y.; Pita, B.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Duque, J.; Pomes, R. *Tetrahedron*,**1998**, *54*, 12409. (b) Suarez, M.; Ochoa, E.; Verdecia, Y.; Pita, B.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; H. Novoa, Blaton, N.; Peeters, O. *Tetrahedron* **1999**, *55*, 875.
10. Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.;

Jung, D. K.; Wright,L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. *J. Med. Chem*. **2006**, *50*, 6.

11. He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc*. **2006**, *128*, 15088.
12. Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*, 20661.
13. Fang, X.; Chen, X.; Chi, R. Y. *Org. Lett*. **2011**, *13*, 4708.
14. Lv, H.; Mo, J.; Fang, X.; Chen, X.; Chi, R. Y. *Org. Lett*. **2011**, *13*, 5366.
15. (a) Sun, F.-G.; Sun, L.-H.; Ye, S. *Adv. Synth. Catal*. **2011**, *353*, 3134. (b) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun*. **2011**, *47*, 8670. (c) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett*. **2011**, *13*, 4080.
16. Yao, C.; Wang, D.; Lu, J.; Li, T.; Jiao, W.; Yu, C. *Chem. Eur. J*. **2012**, *18*, 1914.
17. Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378.
18. Cheng, J.; Huang, Z.; Chi, Y. R. *Angew. Chem., Int., Ed.* **2013**, *52*, 8592.
19. For review on cooperative Lewis acid/NHC-catalysis, see: (a) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53. For a recent report on cooperative Brønsted acid/NHC-catalysis, see: (b) Zhao, X.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466.
20. Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810.
21. (a) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun*. **2011**, *47*, 8670. (b) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett*. **2011**, *13*, 4080.
22. Zhang, B.; Feng, P.; Cui, Y.; Jiao, N. *Chem. Commun*. **2012**, *48*, 7280.
23. For the seminar report on this concept, see: Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
24. For the successful interception of homoenolate intermediates with aldehydes, see (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, 43, 6205. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, 126, 14370.
25. Utilizing high level DFT calculations and kinetic experiments, Studer and co-workers recently reported that nucleophilic addition of enols and enamines to α,β-unsaturated acyl azoliums proceed via 1,4-type addition reaction. For details, see Samantha, R. C.;

Maji, B.; De Sarkar, S.; Bergander, K.; Fröhlich, R.; Mück-Lichtenfeld, C.; Mayr, H.; Studer, A. *Angew. Chem. Int., Ed.* **2012**, *51*, 5234.

26. Ahlrichs, R.; Bär, M.; Häser, M.; Horn, H.; Kölmel, C. *Chem. Phys. Lett*. **1989**, *162*, 165.
27. Singh, V. K.; Molleti, N.; Singh, P. K.; Ray, S. K. *J. Org. Chem*. **2012,** *77*, 8802.
28. Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. *Adv. Synth. Catal*. **2013**, *355*, 1089.
29. Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A. T. *J. Org. Chem.* **2014**, *79*, 4245.
30. (a) Allen, C. F. H.; Edens, Jr. C. O. *Org. Synth.* **1945**, *25*, 92. (b) Li, W.; Li, J.; Wan, Z.-K.; Wu, J.; Massefski, W. *Org. Lett.* **2007**, *9*, 4607.
31. Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis*, **1983**, 902.
32. Struble, J. R.; Bode, J. W. *Org. Synth.* **2010,** *87*,362.
33. Ahlrichs, R.; Bär, M.; Häser, M.; Horn, H.; Kölmel, C. Electronic structure calculations on workstation computers: The program system turbomole. *Chem. Phys. Lett.* **1989**, *162*, 165.
34. Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571.
35. Perdew, J. P.; Burke, K.; Ernzerhof, M. Generalized Gradient Approximation Made Simple. *Phys. Rev. Lett.* **1996**, *77*, 3865.
36. Eichkorn, K.; Treutler, O.; Öhm, H.; Häser, M.; Ahlrichs, R. Auxiliary basis sets to approximate Coulomb potentials. *Chem. Phys.Lett.* **1995**, *240*, 283.
37. Sierka, M.; Hogekamp, A.; Ahlrichs, R. *J. Chem. Phys*. **2003**, *118*, 9136.
38. Hyperchem (version 5); Hypercube: Gainesville, FL, 32601.

CHAPTER 3

Enantioselective N-Heterocyclic Carbene (NHC)-Catalyzed Annulation of Modified Enals with Enolizable Aldehydes

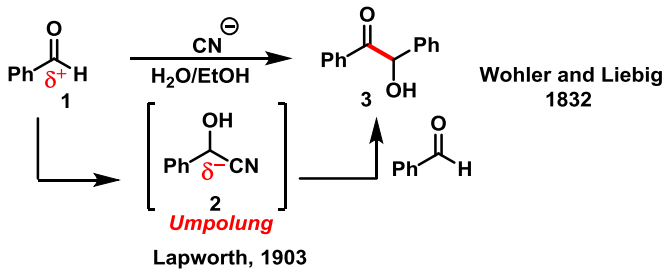
3.1. Introduction

The focal theme of this chapter is the N-heterocyclic carbene (NHC)-catalyzed cross-coupling between two aldehydes resulting in the enantioselective synthesis of 4,5-disubstituted dihydropyranones in spite of several selectivity issues. Before going into the details, NHC-catalyzed aldehyde-aldehyde coupling reactions are explained below.

3.1.1. Benzoin Condensation:

In 1832, Wöhler and Liebig discovered the coupling reaction of two aldehydes via cyanide-catalyzed condensation of benzaldehyde **1** to form benzoin **3** (Scheme 3.1).[1] This transformation allows the preparation of α-hydroxyketones through the condensation of various aromatic aldehydes. Later in 1903, Lapworth postulated a mechanism for this condensation reaction. The mechanism involves the formation of a carbinol intermediate **2** by hydrogen cyanide addition to benzaldehyde followed by protonation.[2] Notably, the electrophilic aldehyde carbon property was inverted to nucleophilic reactivity upon addition of cyanide. This nucleophilic "active aldehyde" intermediate exemplifies the "*Umpolung*" concept, which was first described by Wittig in 1951 and later popularized by Seebach and co-workers.[3]

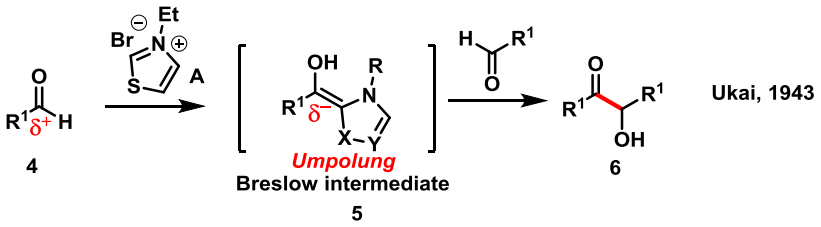
Scheme 3.1: Cyanide Catalyzed Benzoin Condensation



NHC-catalysis has been extensively investigated for benzoin condensation.[4] In 1943, thiazolium salts were recognized as useful catalysts in the benzoin condensation by

Ukai and co-workers.[5] On the basis of Lapworth's work, Breslow proposed a mechanistic model for the thiazolium salt-catalyzed benzoin condensation (Scheme 3.2).[6] In this mechanism, Breslow proposed the formation of nucleophilic intermediate **5** from electrophilic aldehyde **4** and carbene generated from **A**. This intermediate is well recognised as "Breslow intermediate" **5** and its reaction with another molecule of aldehyde can afford the benzoin product **6**.

Scheme 3.2: NHC-Catalyzed Benzoin Condensation



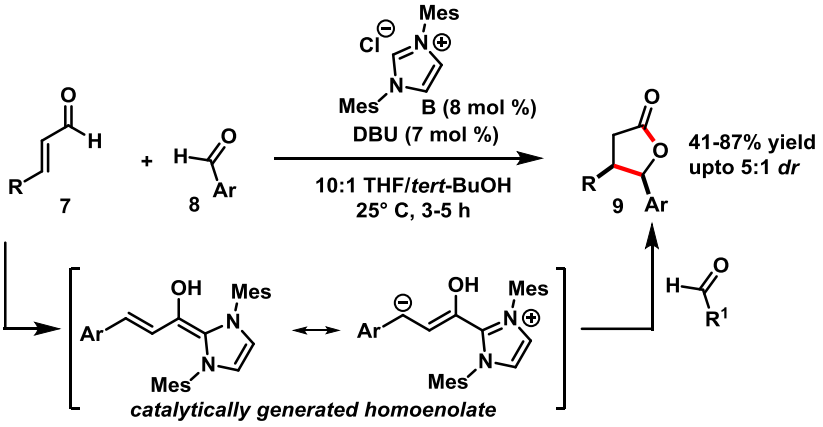
3.1.2. Reactions of Enals with Aldehydes:

Similar to aryl and aliphatic aldehydes, *α*,*β*-unsaturated aldehydes are often competent coupling partners in acyl-anion reactivity following the benzoin pathway or the Stetter reaction. Interestingly enals possess unique reactivity under NHC-catalysis, i.e. typically electrophilic *β*-carbon of the enal can become nucleophilic (extended Breslow/homoenolate equivalent/ conjugate umpolung). In 1964, Walia and co-workers reported this type of extended umpolung reactivity in the context of cyanide-catalyzed transformation. It was found that *α*,*β*-unsaturated aldimines and enals are transformed to the corresponding saturated amides and methyl esters in the presence of a catalytic amount of cyanide.[7]

After 40 years, the Bode[8] and Glorius[9] groups independently reported the NHC-catalyzed homoenolate generation from enals. With these seminal reports, the field of NHC-catalyzed extended umpolung or homoenolate reactivity has blossomed and resulted in plethora of methods to synthesize useful molecules starting from simple enals. The imidazolium salt (IMes.HCl) **B** was found to be efficient for this annulation and a variety of aryl and propargyl enals **7** underwent coupling with aryl aldehydes **8** affording the desired γ-lactone products **9** in moderate to good yields (41-87%) and moderate diastereoselectivity (up to5:1 *dr*) (Scheme 3.3). The addition of NHC generated from B to enal generates the nucleophilic extended Breslow intermediate, which is a resonance form of the homoenolate

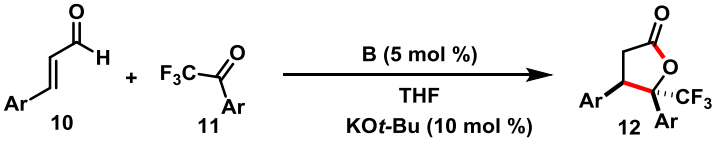
equivalent. In Bode's work DBU was the base used for the generation of carbenes whereas KO*t*-Bu was used as the base in Glorius procedure.

Scheme 3.3: NHC- Catalyzed Annulations of Enals with Aromatic Aldehydes



Glorius and co-workers found that this reaction is not limited to aromatic aldehydes, but worked well with activated ketones. For instance, the reaction of enals **10** with trifluoromethyl ketone **11** as the carbonyl component afforded the corresponding γ-lactones **12** in good yields and moderate diastereoselectivity (Scheme 3.4).

Scheme 3.4: NHC- Catalyzed Annulation of Enals with Trifluoromethyl ketones

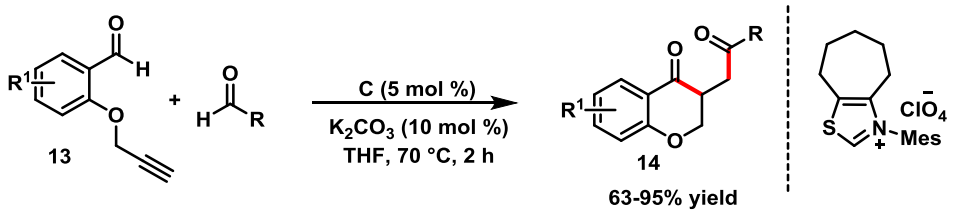


Recently, Glorius and co-workers disclosed the NHC-catalyzed hydroacylation reaction of unactivated terminal alkynes followed by a second NHC-catalyzed Stetter reaction in a cascade process. 2-Propargyloxy aldehydes **13** upon treatment with a different coupling aldehyde using NHC generated from **C** resulted in the formation of chromanone **14** with a 1,4-diketone motif in good to excellent yields (Scheme 3.5).[10] NHC generation under mild base was a key factor for this reaction. Low catalyst loading (5 mol %) and high levels of selectivity are the noteworthy features this reaction. Additionally, benzopyranopyrrole derivatives can be synthesized with this methodology by a hydroacylation-Stetter cascade followed by reaction with aniline derivative in a one-pot operation.

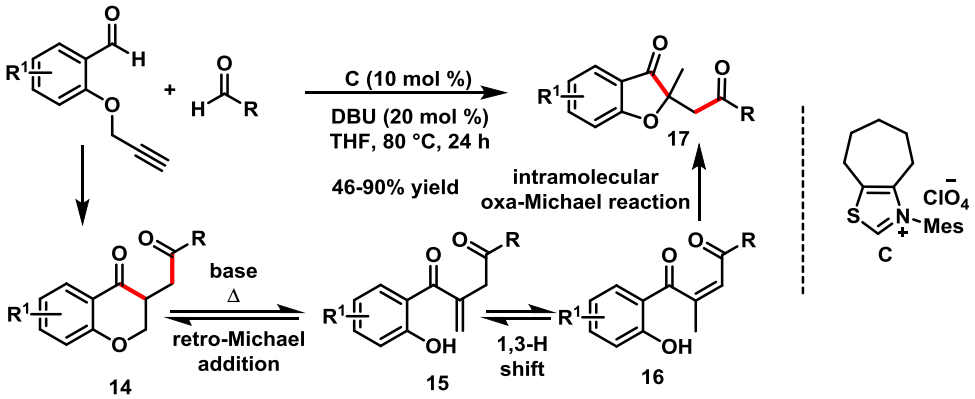
It was found that the NHC-catalyzed hydroacylation-Stetter cascade was indeed very sensitive to the base employed and the reaction temperature. When DBU was used as

the base and the reaction performed at 80 °C, the initially formed chromanone **14** undergoes retro-Michael addition to generate the phenol **15,** which undergoes a 1,3-H shift followed by intramolecular oxa-Michael reaction to afford the 2,2-disubstituted benzofuranone derivative **17** (Scheme 3.6).[11]

Scheme 3.5: NHC- Catalyzed Hydroacylation of Unactivated Alkynes

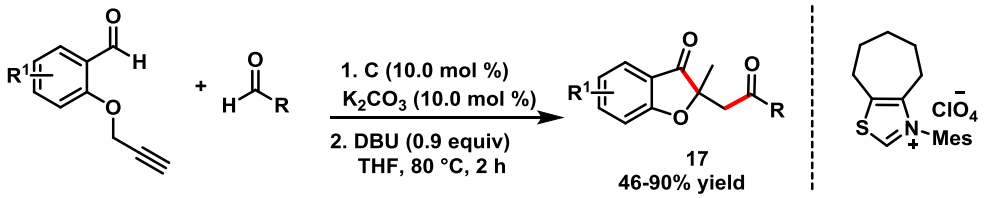


Scheme 3.6: NHC/Base- Catalyzed Hydroacylation-Stetter Cascade



Independently, Zeitler and co-workers demonstrated the similar strategy using almost identical conditions to give a mixture of the chromanone and benzofuranone products (Scheme 3.7). They used a one-pot two step protocol for the synthesis of benzofuranones **17**.[12]

Scheme 3.7: NHC/Base-Catalyzed Synthesis of Benzofuranones



3.2. Statement of the Problem

NHC-Catalysis is well known for the umpolung of aldehydes. When the two coupling partners are aromatic aldehydes, the reaction affords benzoin products through acylanion mode (umpolung) of activity. Whereas when the coupling partners are enals and

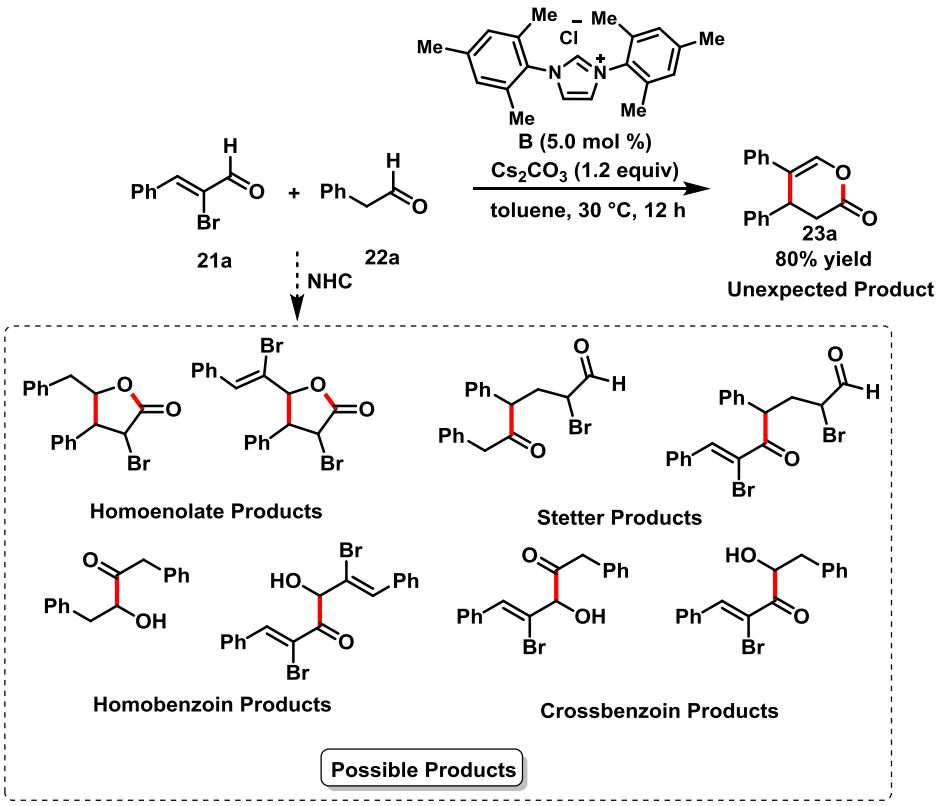
aromatic aldehydes the reaction can proceed via the benzoin pathway, or homoenolate pathway resulting in the formation of γ-lactones (conjugate umpolung). However, NHC-catalyzed transformations can also proceed via the normal mode of reactivity. In this context, we envisioned the cross-coupling of enals with enolizable aldehydes proceeding via the α,β-unsaturated acylazolium intermediates. Notably, the challenges include the undesired benzoin, Stetter and homoenolate pathways. The results of our studies on NHC-catalyzed cross-coupling reactions of 2-bromoenals with enolizable aldehydes resulting in the enantioselective synthesis of 4,5-disubstituted dihydropyranones are presented in the following sections.

3.3. Results and Discussion

3.3.1. Optimization Studies

In a pilot experiment, treatment of α-bromo cinnamaldehyde (**21a**) and 2-phenylacetaldehyde (**22a**) in the presence of NHC-generated from IMes.HCl (**B**) and 1.2 equiv of Cs_2CO_3 in toluene resulted in a facile reaction leading to the formation of 4,5-diaryl dihydropyranone (**23a**) in 80% yield (Scheme 3.8).

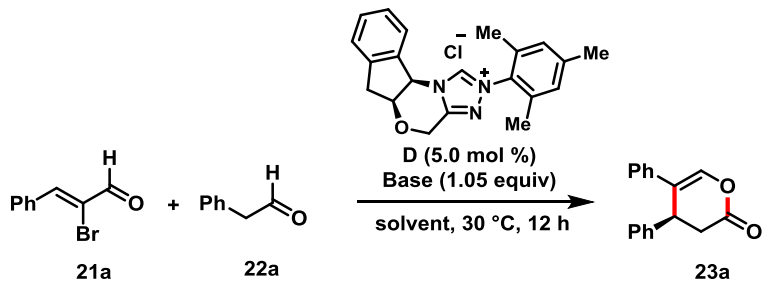
Scheme 3.8: NHC-Catalyzed Reactions of Aldehydes.



In this context, it is noteworthy that NHC-catalyzed coupling of two different aldehydes can always arise various selectivity issues. For example, the competing homoenolate reactivity (two γ-butyrolactones) as well as the acylanion reactivity i.e. benzoin (four benzoin products) and Stetter reaction (two Stetter products) pathways were largely suppressed under the present reaction conditions (Scheme 3.8).

With this initial result, we focused our attention on asymmetric version of this reaction. Gratifyingly, treatment of **21a** and **22a** with 1.05 equiv of Na_2CO_3 and aminoindanol-derived triazolium salt **D**[14]furnished the desired product 23a in 63% yield (based on ^{1}H-NMR spectroscopy) and 98% ee (Table 1, entry 1). As expected, in the absence of the triazolium salt **D** (entry 2) the reaction failed to furnish the product. A quick variation of bases revealed that the bases like DABCO, DBU, DMAP and Cs_2CO_3 provided the desired product in either reduced yields or diminished selectivities (entries 3-6).

Table 1. Optimization of the Reaction Conditions[a]

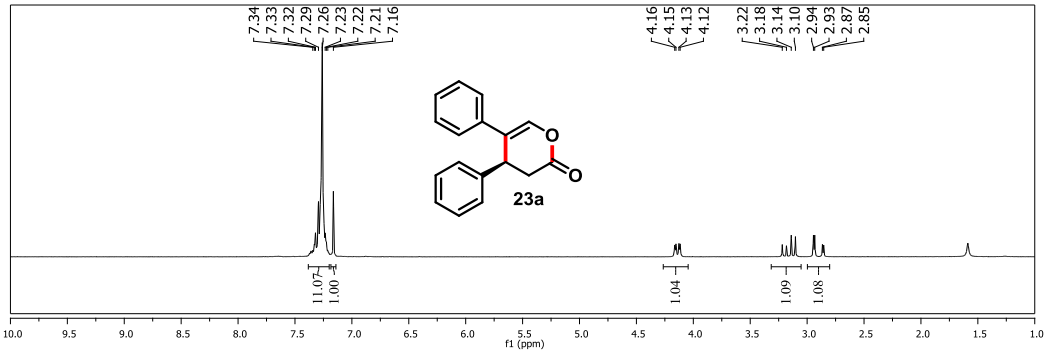


entry	Base	Solvent	yield of **23a** (%)[b]	ee of **23a** (%)[c]
1	Na_2CO_3	toluene	63	98
2	Na_2CO_3 (reaction without **D)**	toluene	<1	nd
3	DABCO	toluene	27	98
4	DMAP	toluene	82	93
5	DBU	toluene	49	43
6	Cs_2CO_3	toluene	79	82
7	Na_2CO_3	1,4-dioxane	70	95
8	Na_2CO_3	THF	85	87
9	Na_2CO_3	CH_2Cl_2	44	89
10	**Na_2CO_3 (reaction time 18 h instead of 12 h)**	**toluene**	**78 (75)**	**99**

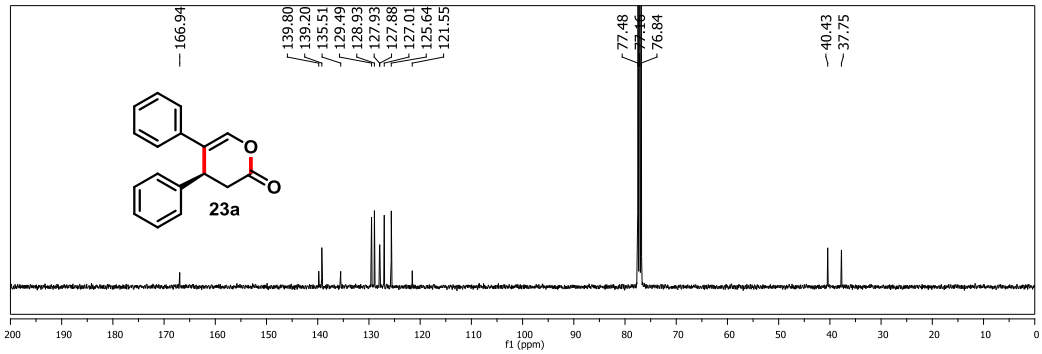
[a] Standard conditions: **21a** (0.25 mmol), **22a** (0.25 mmol), **D** (5 mol %), Base (1.05 equiv), toluene (1.0 mL), 30 °C and 12 h. [b] The yields were determined by ^{1}H-NMR analysis of crude products using CH_2Br_2 as the internal standard, isolated yield in parentheses. [c] Determined by HPLC analysis on a chiral column.

3.3.2. Spectral Data of 23a

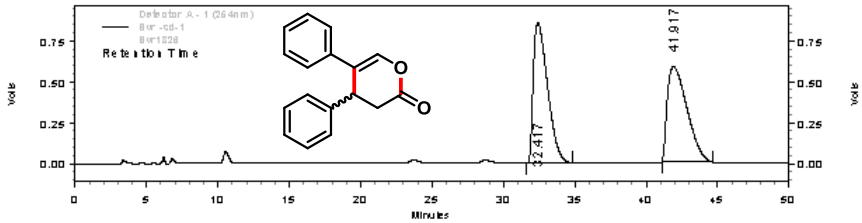
^{1}H NMR Spectrum of 23a ($CDCl_3$)



^{13}C NMR Spectrum of 23a ($CDCl_3$)



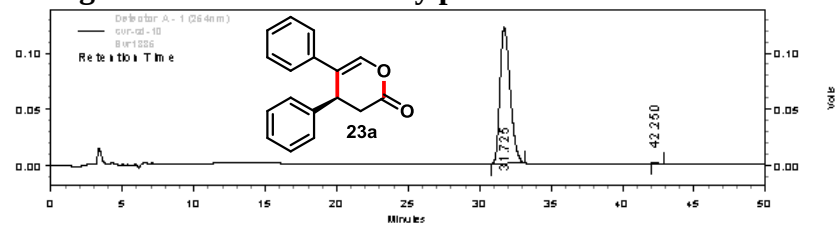
HPLC Chromatogram of Racemic-23a



(254nm)

Retention Time	C Area	Area %
32.417	58950920	50.824
41.917	57038917	49.176
Totals	115989837	100.000

HPLC Chromatogram of Enantiomerically pure-23a



(254nm)

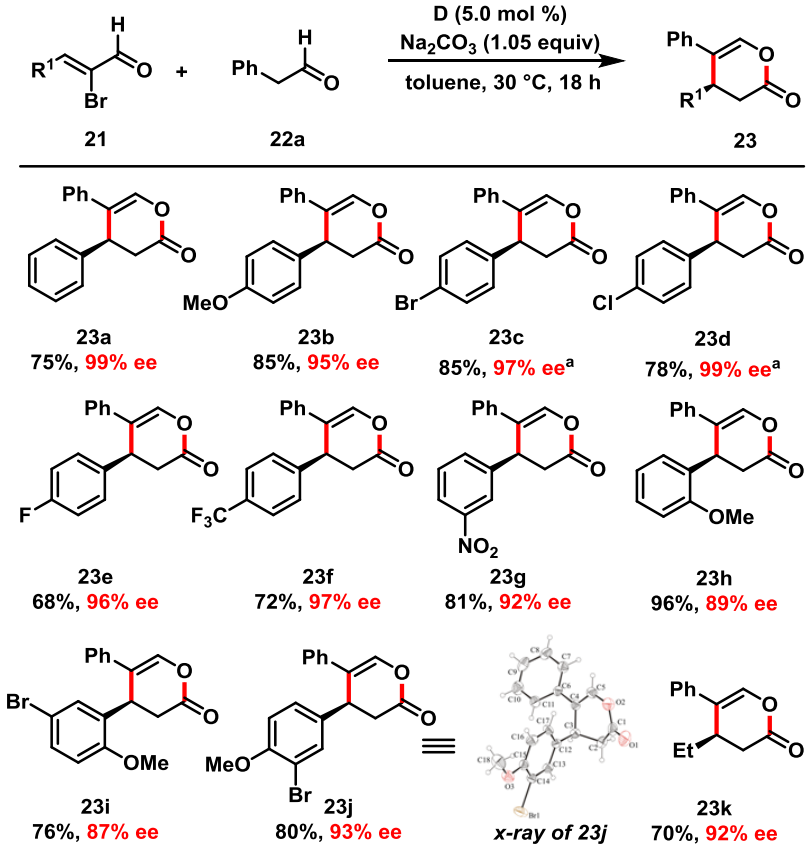
Retention Time	C Area	Area %
31.725	5978118	99.880
42.250	7206	0.120
Totals	5985324	100.000

The solvent screening revealed that 1, 4-dioxane returned comparable selectivity and yield improved to 70% (entry 7), whereas polar solvents like THF and CH_2Cl_2 resulted in reduced selectivities (entry 8, 9). At last, increasing the reaction time to 18 h improved the isolated yield (75%) as well as the enantioselectivity was enhanced to 99% (entry 10). The spectral data of **23a** is given in Section 3.3.2.

3.3.3. Enantioselective Synthesis of 4,5-Disubstituted Dihydropyranones from 2-Bromoenals

Based on the above optimization (Table 1, entry 10), the substrate scope of this interesting aldehyde coupling reaction was investigated. In the beginning, we examined various 2-bromoenals (Scheme 3.9).

Scheme 3.9: Variation of the 2-Bromoenal Moiety.



General reaction conditions: **21** (0.50 mmol), **22a** (0.50 mmol), **D** (5.0 mol %), Na_2CO_3 (1.05 equiv.), toluene (2.0 mL) at 30 °C for 18 h. The ee values were determined by HPLC analysis on a chiral column. [a] Reaction was run on 0.25 mmol scale.

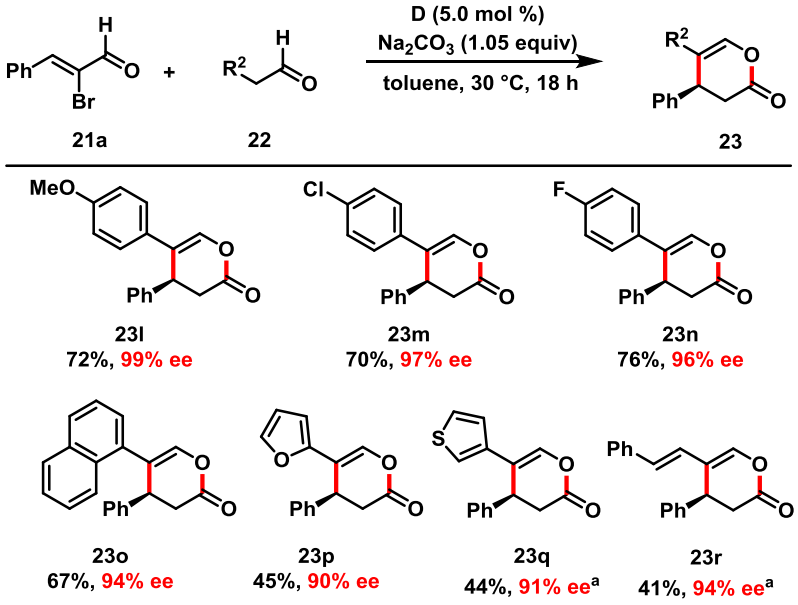
The unsubstituted 2-bromoenal worked well and a variety of electron-donating and -withdrawing groups at the 4-position of the aromatic ring underwent smooth conversion,

leading to desired products in good yields and with excellent ee values over 95% in all cases (**23a-23f**). Furthermore, substitution at 3-position as well as at 2-position of the *β*-aryl ring were well tolerated and furnished the 4,5-disubstituted dihydropyranones (**23g**, **23h**) in good yield and high enantioselectivity. Moreover, disubstituted bromo enals also afforded the expected product in good yield and selectivity (**23i**, **23j**). The structure and stereochemistry of **23j** was unequivocally confirmed by single-crystal X-ray analysis.[15] Interestingly, challenging aliphatic aldehydes such as (*Z*)-2-bromopent-2-enal also furnished the product in good yield and high enantioselectivity, further expanding the scope of this annulation reaction (**23k**).

3.3.4. Enantioselective Synthesis of 4,5-Disubstituted Dihydropyranones from Enolizable Aldehydes

Next, we turned our attention to variation of enolizable aldehydes (Scheme 3.10). We observed that substrates with electron-releasing and -withdrawing groups at 4-position of the aromatic ring underwent efficient annulation reaction affording the desired products in good yields and excellent selectivities (**23l-23n**).

Scheme 3.10: Variation of the Enolizable Aldehyde Moiety



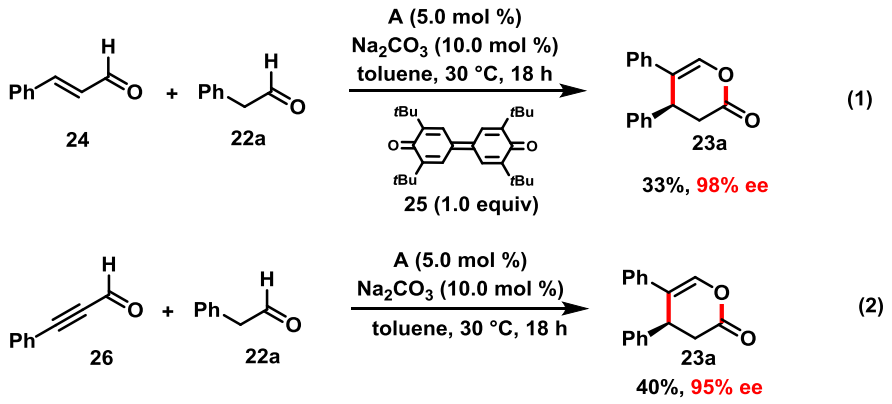
General reaction conditions: **21a** (0.50 mmol), **22** (0.50 mmol), **D** (5.0 mol %), Na_2CO_3 (1.05 equiv.), toluene (2.0 mL) at 30 °C for 18 h. The ee values were determined by HPLC analysis on a chiral column. [a] Reaction was run on 0.25 mmol scale.

Furthermore, the naphthyl acetaldehyde furnished the desired product in 64% yield and 94% ee (**23o**). Moreover, the heterocyclic acetaldehyde derivatives afforded the desired products in moderate yield with high ee, further expanding the scope of this reaction (**23p, 23q**). Interestingly, this reaction is not limited to aromatic acetaldehyde derivatives. (*E*)-4-Phenylbut-3-enal can also be used as a coupling partner to afford the 5-styryl 4-phenyl dihydropyranone **23r** in 41% yield and 94% ee. Disappointingly linear aliphatic aldehydes such as *n*-heptanal and less enolizable aldehydes such as 3-phenylpropanal did not show reactivity with α,β-unsaturated acylazoliums under the present optimized conditions.

3.3.5. Synthesis of 4,5-Disubstituted Dihydropyranones from Enals and Ynals

To demonstrate the advantages of generating α,β-unsaturated acylazoliums from 2-bromoenals, we have carried out additional experiments starting from enals and ynals. Treatment of cinnamaldehyde **24** with enolizable aldehyde **22a** under the reaction conditions using oxidant **25** afforded the desired product **23a** in 33% yield and 98% ee (Scheme 3.11, eq 1). Moreover, the reaction of 3-phenylpropiolaldehyde **26** with **22a** in the presence of carbene precursor **D** and Na_2CO_3 furnished **23a** in 40% yield and 95% ee (eq 2). Although the enantioselectivity is comparable, the reactivity is lower in both cases compared to reaction with 2-bromoenals. These experiments indicates that the generation of α,β-unsaturated acylazoliums from 2-bromoenals affords the dihydropyranones in better yields compared to the generation of the same intermediate either from enal or ynal.

Scheme 3.11: Reaction Using Enals and Ynals

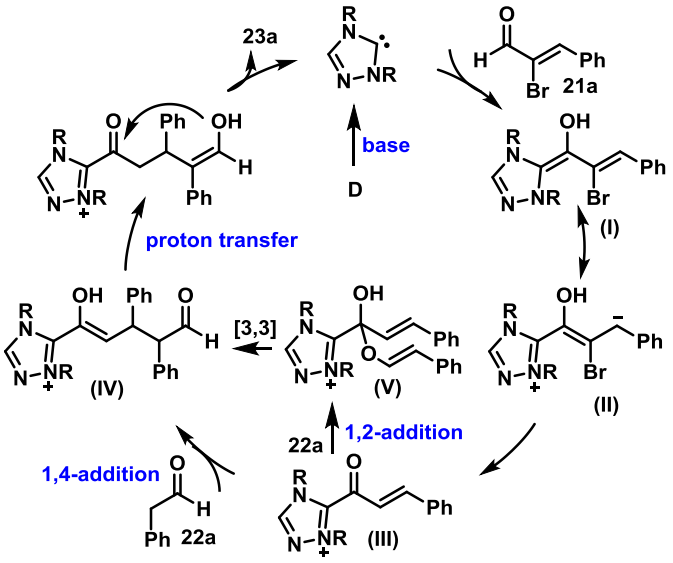


3.3.6. Tentative Mechanism

A tentative mechanism for this NHC-catalyzed annulation reaction is shown in Scheme 3.12. The nucleophilic addition of NHC to 2-bromoenal **21a** will generate

nucleophilic Breslow intermediate (**I**),[6] which can be converted into the key α,β-unsaturated acylazolium intermediate **III** by the rapid debromination of the homoenolate equivalent **II**.[14] Nucleophilic addition of **22a** to **III** can proceed in a 1,4-fashion[16] or in a 1,2-pathway.[17] The 1,4-addition can directly generate the enol intermediate **IV**. On the other hand, the 1,2-addition of **22a** to **III** can form the hemiacetal intermediate **V**, which can undergo [3,3] sigmatropic rearrangement to furnish **IV**.[18] Proton transfer of intermediate **IV** followed by intramolecular cyclization lead to the product **23a.**

Scheme 3.12. Tentative Mechanism of the NHC-Catalyzed Annulation of 2-Bromoenals



3.4. Conclusion

In conclusion, we have developed a highly enantioselective NHC-organocatalyzed coupling reaction of two different aldehydes. 2-Bromoenals underwent an efficientt lactonization reaction with enolizable aldehydes under NHC-catalysis proceeding via the chiral α,β-unsaturated acylazolium intermediates. The reaction resulted in the synthesis of 4,5-disubstituted dihydropyranones in good yield and excellent enantioselectivity.[19] It is noteworthy that the present dihydropyranone formation took place in spite of several selectivity issues.

3.5. Experimental Details

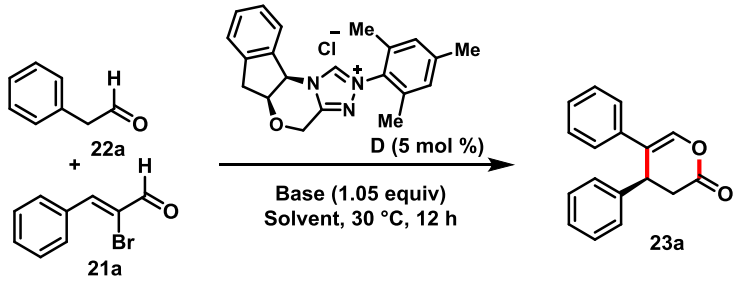
3.5.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Dry toluene was purchased from commercial sources and stored under argon over sodium wire. The 2-bromoenals were synthesized from the corresponding α,β-unsaturated aldehydes following the literature procedure.[20] Phenyl acetaldehyde was purchased from Across Organics and was used without further purification. Other phenyl acetaldehyde derivatives were prepared following the literature procedure.[21] The triazolium salt **D** was synthesized following the literature procedure.[14a] Na_2CO_3 was dried by heating at 120 °C under vacuum and cooling under argon.

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 (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system.

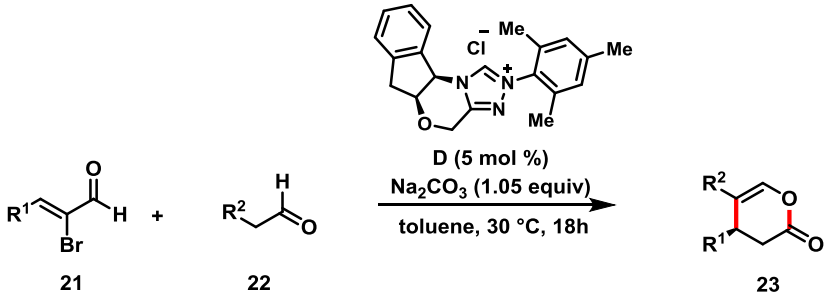
All compounds were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400, in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 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 Shimadzu Class-VP V6.12 SP5 with UV detector.

3.5.2. Procedure for the Optimization of Reaction Conditions



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **D** (4.6 mg, 0.0125 mmol, 5 mol %), and base (0.264 mmol, 1.05 equiv), was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added solvent (1.0 mL) under argon atmosphere and mixture was kept stirring at 30 °C for 10 min. To this mixture was added the 2-bromoenal **21a** (0.25 mmol) followed by phenyl acetaldehyde **22a** (0.25 mmol). Then the reaction mixture was stirred at 30° C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated 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.

3.5.3. Procedure for the Enantioselective Synthesis of Dihydropyranones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **D** (9.1 mg, 0.025 mmol), and Na_2CO_3 (56 mg, 0.525 mmol), was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere and mixture was kept stirring at 30 °C for 10 min. To this mixture was added the 2-bromoenal **21** (0.50 mmol) followed by phenyl acetaldehyde **22** (0.5 mmol). Then the reaction mixture was stirred at 30° C for 18 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding dihydropyranones.

3.5.4. X-ray Data of 23j

X-ray intensity data measurements of **23j** was carried out on a Bruker SMART Apex2 CCD diffractometer with graphite-monochromatized (MoK$_\alpha$= 0.71073Å) radiation at 296 (2) K. 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 168 reflections harvested

from three sets of 36 frames (12 frames from each set). The optimized strategy used for data collection consisted of four ω scan sets, with 0.5° steps in φ or ω; completeness achieved was 100% with redundancy 3.98. Data were collected with a frame time of 10 sec keeping the sample-to-detector distance fixed at 5.00 cm. A total of 1111 frames were collected. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[22] Final unit cell parameters were obtained from 2149 reflections after integration.

Crystal data of **23j**: $C_{18}H_{15}O_3Br$, M = 359.21, colorless prism, 0.41 x 0.29 x 0.12 mm^3, monoclinic, space group $P2_1$, a = 6.2782(7), b = 9.3617(12), c = 13.9272(17) Å, β = -100.666(9)°, V = 804.42(17) $Å^3$, Z = 2, T = 297(2) K, $2\theta_{max}$=56.62°, D_{calc} (g cm^{-3}) = 1.483, $F(000)$ = 364, μ (mm^{-1}) = 2.564, 7532 reflections collected, 3230 unique reflections (R_{int} = 0.0503), 1969 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.4195, T_{max} = 0.7484, 200 refined parameters, S = 0.943, $R1$ = 0.0416, $wR2$ = 0.0852 (all data R = 0.0906, $wR2$ = 0.1007), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.37, $\Delta\rho_{min}$= -0.23 ($eÅ^{-3}$).

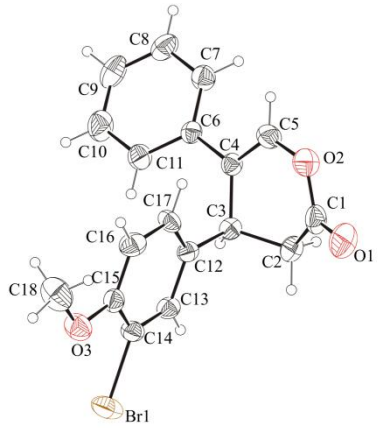


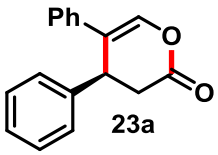
Fig 3.1. ORTEP of **23j** showing atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Apex2, Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[23] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. The absolute configuration established by anomalous dispersion effects in diffraction measurements on

the crystal which could become possible due to the presence of heavy atom Br in the molecule. The absolute configuration of the molecule was found by refining Flack parameter. A value of Flack parameter of 0.012(13) established that the configuration of atom C3 is *S*.

3.5.5. Synthesis and Characterization of Dihydropyranones

(*S*)-4,5-Diphenyl-3,4-dihydro-2*H*-pyran-2-one (23a)[24]



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (105.5 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4,5-diphenyl-3,4-dihydro-2*H*-pyran-2-one **23a** as a white solid (94.3 mg, 75% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.56.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min.) Major: 31.7 min, Minor: 42.2 min. 99% ee, $[\alpha]_D^{25}$ = +339.80 (c 0.1, $CHCl_3$).

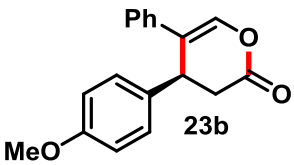
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 10H), 7.16 (s, 1H), 4.16 (dd, J_1 = 2.2 Hz, J_2 = 7.3 Hz, 1H), 3.22 (dd, J_1 = 7.3 Hz, J_2 = 15.7 Hz, 1H), 2.94 (dd, J_1 = 2.2 Hz, J_2 =15.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.94, 139.80, 139.20, 135.51, 129.49, 128.93, 127.93, 127.88, 127.01, 125.64, 121.55, 40.43, 37.75.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{14}O_2Na$: 273.0886, found: 273.0882.

FTIR (cm^{-1}) 3650, 3368, 3020, 2855, 2400, 1774, 1646, 1215, 1143, 1029, 758, 698, 669.

(*S*)-4-(4-Methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23b)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-methoxyphenyl)acrylaldehyde **21b** (120.5 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4-(4-methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23b** as a colourless oil (119.4 mg, 85% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.51.

HPLC (Chiralcel OD-H, 70:30 Pet.ether / IPA, 1.0 mL/min.) Major: 21.7 min, Minor: 45.5 min. 95% ee, $[\alpha]_D^{25}$ = +252.60 (c 0.1, $CHCl_3$).

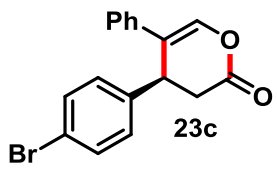
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.23 (m, 5H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.08 (d, *J* = 7.1 Hz, 1H), 3.75 (s, 3H), 3.13 (dd, J_1 = 7.3 Hz, J_2 = 15.7 Hz, 1H), 2.87 (d, *J* =15.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.04, 159.14, 138.92, 135.53, 131.70, 128.84, 128.03, 127.82, 125.57, 121.84, 114.76, 55.31, 39.57, 37.88.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{16}O_3Na$: 303.0992, found: 303.0985.

FTIR (cm^{-1}) 3019, 2925, 2400, 1771, 1701, 1645, 1492, 1415, 1325, 1218, 1143, 926, 771, 668.

(*S*)-4-(4-Bromophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23c)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-bromophenyl)acrylaldehyde **21c** (72.5 mg, 0.25 mmol) and 2-phenylacetaldehyde **22a** (30 mg, 29 μL, 0.25 mmol) with triazolium salt **D** (4.6 mg, 0.0125 mmol), Na_2CO_3 (28 mg, 0.2625 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4-(4-bromophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23c** as a white solid (70.3 mg, 85% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.59.

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 1.0 mL/min.) Major: 13.4 min, Minor: 16.3 min. 97% ee, $[\alpha]_D^{25}$ = +242.60 (c 0.1, $CHCl_3$).

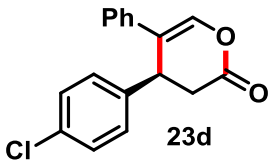
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-6.95 (m, 10H), 3.93 (dd, J_1 = 2.2 Hz, J_2 = 7.3 Hz, 1H), 3.02 (dd, J_1 = 7.3 Hz, J_2 = 15.6 Hz, 1H), 2.75 (dd, J_1 = 2.2 Hz, J_2 =15.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.51, 139.39, 138.86, 135.14, 132.63, 129.02, 128.79, 128.11, 125.59, 121.85, 121.18, 39.90, 37.48.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{13}O_2BrNa$: 350.9991, found: 350.9987.

FTIR (cm^{-1}) 3684, 3019, 2400, 1768, 1735, 1648, 1476, 1217, 928, 771, 669.

(*S*)-4-(4-Chlorophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23d)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-chlorophenyl)acrylaldehyde **21d** (61.4 mg, 0.25 mmol) and 2-phenylacetaldehyde **22a** (30 mg, 29 μL, 0.25 mmol) with triazolium salt **D** (4.6 mg, 0.0125 mmol), Na_2CO_3 (28 mg, 0.2625 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4-(4-chlorophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23d** as a white solid (55.3 mg, 78% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.54.

HPLC (Chiralcel OJ-H, 90:10 Pet.ether / EtOH, 1.0 mL/min.) Major: 18.3 min, Minor: 23.1 min. 99% ee, $[\alpha]_D^{25}$ = +185.00 (c 0.1, $CHCl_3$).

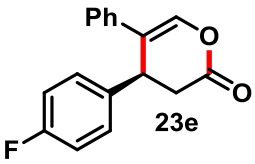
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 10H), 4.13 (dd, J_1 = 2.3 Hz, J_2 = 7.3 Hz, 1H), 3.20 (dd, J_1 = 7.3 Hz, J_2 = 15.8 Hz, 1H), 2.90 (dd, J_1 = 2.3Hz, J_2 =15.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.55, 139.36, 138.31, 135.16, 133.76, 129.67, 129.07, 128.44, 128.10, 125.58, 121.25, 39.82, 37.56.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{13}O_2ClNa$: 307.0496, found: 307.0494.

FTIR (cm^{-1}) 3029, 2932, 1770, 1747, 1607, 1514, 1493, 1253, 1183, 1141, 1030, 963, 829, 803, 770, 702.

(*S*)-4-(4-Fluorophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23e)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-fluorophenyl)acrylaldehyde **21e** (114.5 mg, 0.50 mmol) and 2-phenylacetaldehyde **22e** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4-(4-fluorophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23e** as a white solid (91.0 mg, 68% yield).

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

HPLC (Chiralcel OJ-H, 90:10 Pet.ether / EtOH, 1.0 mL/min.) Major: 24.2 min, Minor: 34.2 min.96% ee, $[\alpha]_D^{25}$ = +457.2 (c 0.1, $CHCl_3$).

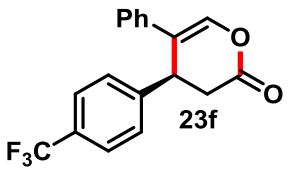
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.75 (m, 7H), 7.68 (s, 1H), 7.53-7.47 (m, 2H), 3.93 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 2.72 (dd, J_1 = 9.4 Hz, J_2 =20 Hz, 1H), 2.37 (dd, J_1 = 2.8 Hz, J_2 =19.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.04, 183.60 (d, J = 308.5 Hz), 154.72, 150.05 (d, J = 4.2 Hz), 149.74, 141.91, 141.52 (d, J = 9.9 Hz), 140.74, 137.68, 132.61, 126.17 (d, J = 27.5 Hz), 30.32, 27.93.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{13}FO_2Na$: 291.0792, found: 291.0788.

FTIR (cm^{-1}) 3372, 3023, 2929, 1767, 1619, 1496, 1416, 1326, 1019, 843, 764.

(*S*)-5-Phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyran-2-one (23f)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(4-(trifluoromethyl)phenyl)acrylaldehyde **21f** (138.5 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (S)-5-phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyran-2-one **23f** as a white solid (115.3 mg, 72% yield).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.41.

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 1.0 mL/min.) Major: 9.2 min, Minor: 11.5 min.97% ee, $[\alpha]_D^{25}$ = +302.0 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.35-7.25 (m, 5H), 7.22 (s, 1H), 4.26 (dd, J_1 = 1.4 Hz, J_2 = 7.4 Hz, 1H), 3.25 (dd, J_1 = 7.4 Hz, J_2 = 16.1 Hz, 1H), 2.95 (dd, J_1 = 2 Hz, J_2 =15.8 Hz, 1H).

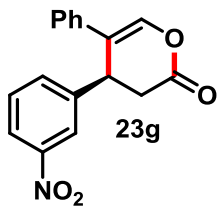
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.27, 143.91, 139.62, 135.0, 130.31 (q, J = 32.9 Hz), 130.09, 128.22, 127.52, 126.53 (q, J = 3.7 Hz), 125.62, 125.14, 120.97, 40.22, 37.55.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{14}O_2F_3Na$: 319.0940, found: 319.0936.

FTIR (cm^{-1}) 3022, 2255, 1778, 1646, 1538, 1351, 1216, 1097, 911, 743.

(*S*)-4-(3-Nitrophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23g)

Following the general procedure, treatment of (*Z*)-2-bromo-3-(3-nitrophenyl)acrylaldehyde **21g** (128.0 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL)



and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4-(3-Nitrophenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23g** as a white solid (119.4 mg, 81% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.32; 92% ee, $[\alpha]_D^{25}$ = +236.2 (c 0.1, $CHCl_3$).

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 1.0 mL/min.) Major: 63.4 min, Minor: 73.1 min.

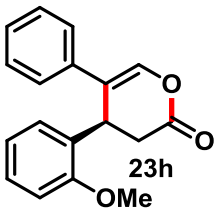
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.14 (m, 2H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.54 (t, J = 8.7 Hz, 1H), 7.35-7.26 (m, 6H), 4.36 (d, *J* = 7.4 Hz, 1H), 3.30 (dd, J_1 = 7.4 Hz, J_2 = 16.0 Hz, 1H), 2.99 (dd, J_1 = 2.1 Hz, J_2 = 16.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 148.93, 141.96, 139.88, 134.54, 133.12, 130.56, 129.09, 128.28, 125.55, 123.01, 122.28, 120.48, 39.84, 37.24.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{13}O_4NNa$: 318.0737, found: 318.0735.

FTIR (cm^{-1}) 3087, 1769, 1729, 1645, 1599, 1529, 1495, 1349, 1192, 1142, 1083,988, 969, 762, 741, 6936.

(*R*)-4-(2-Methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23h)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(2-methoxyphenyl)acrylaldehyde **21h** (120.5 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 15:85) to afford **(*R*)**-4-(2-Methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23h** as white solid.(134.2 mg, 96% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.51.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min.) Major: 25.3 min, Minor: 46.9 min. 89% ee, $[\alpha]_D^{25}$ = +311.60 (c 0.1, $CHCl_3$).

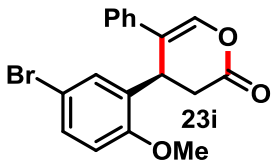
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.15 (m, 8H), 6.91-6.84 (m, 2H), 4.54 (d, *J* = 7.4 Hz, 1H), 3.86 (s, 3H), 3.08 (dd, J_1 = 7.5 Hz, J_2 = 16.0 Hz, 1H), 2.99 (dd, J_1 = 2.3 Hz, J_2

=15.16.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.59, 156.69, 139.41, 135.51, 128.95, 128.75, 127.68, 127.65, 126.95, 125.55, 120.99, 120.77, 110.78, 55.23, 35.41, 34.27.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{16}O_3Na$: 303.0992, found: 303.0990.

FTIR (cm^{-1}) 3965**,** 3784, 3021, 2854, 1766, 1624, 1419, 1325, 1216, 1143, 1019, 770, 462.

(*R*)-4-(5-Bromo-2-methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23i)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(5-bromo-2-methoxyphenyl)acrylaldehyde **21i** (160.0 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*R*)-4-(5-bromo-2-methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23i** as a white solid (137 mg, 76% yield).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.46.

HPLC (Chiralcel OD-H, 95:05 n-Hexane / EtOH, 0.5 mL/min.) Minor: 29.3 min, Major: 32.6 min. 87% ee, $[\alpha]_D^{25}$ = +93.20 (c 0.1, $CHCl_3$).

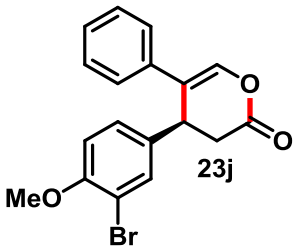
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 8H), 6.80 (d, J = 8.6 Hz, 1H), 4.49 (d, J = 7.5 Hz, 1H), 3.88 (s, 3H), 3.10 (dd, J_1 = 7.6 Hz, J_2 = 16.0 Hz, 1H), 2.99 (dd, J_1 = 2.3 Hz, J_2 =16.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.13, 155.94, 139.82, 135.15, 131.81, 130.50, 129.36, 128.93, 127.95, 125.56, 120.14, 113.47, 112.65, 55.63, 35.18, 34.25.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{15}O_3BrNa$: 381.0097, found: 381.0097.

FTIR (cm^{-1}) 3394, 3020, 2400, 1769, 1647, 1594, 1486, 1462, 1443, 1244, 1

(*S*)-4-(3-Bromo-4-methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23j)



Following the general procedure, treatment of (*Z*)-2-bromo-3-(3-bromo-4-methoxyphenyl)acrylaldehyde **21j** (160 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4-(3-bromo-4-methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyran-2-one

23j as a white solid (144.4 mg, 80% yield). CCDC- 943669 **(23j)** contains the supplementary crystallographic data.

R_f (Pet. ether /EtOAc = 80/20): 0.39.

HPLC (Chiralcel OJ-H, 60:40 Pet.ether / IPA, 1.0 mL/min.) Minor: 51.4 min, Major: 58.6 min. 93% ee, $[\alpha]_D^{25}$ = +200.40 (c 0.1, $CHCl_3$).

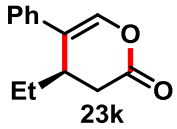
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H) 7.41-7.32 (m, 5H), 7.27-7.24 (m, 2H), 6.93 (d, *J* = 8.29 Hz, 1H) 4.16 (d, *J* = 7.5 Hz, 1H), 3.95 (s, 3H), 3.25 (dd, J_1 = 7.5 Hz, J_2 = 16.1 Hz, 1H), 2.98 (d, *J* = 16.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.62, 155.57, 139.31, 135.19, 133.18, 132.04, 129.01, 128.07, 126.92, 125.53, 121.23, 112.67, 112.57, 56.41, 39.30, 37.83.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{15}O_3BrNa$: 381.0097, found: 381.0096.

FTIR (cm^{-1}) 3372, 2924, 1769, 1645, 1600, 1491, 1325, 1217, 1143, 1028, 760, 697, 475.

(*R*)-4-Ethyl-5-phenyl-3,4-dihydro-2*H*-pyran-2-one (23k)



Following the general procedure, treatment of (*Z*)-2-bromopent-2-enal **21k** (82.0 mg, 0.50 mmol) and 2-phenylacetaldehyde **22a** (60 mg, 58 μL, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*R*)-4-Ethyl-5-phenyl-3,4-dihydro-2*H*-pyran-2-one **23k** as a colourless oil (71.3 mg, 70% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.59.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min.) Major: 13.1 min, Minor: 17.8 min. 92% ee, $[\alpha]_D^{25}$ = +162.00 (c 0.1, $CHCl_3$).

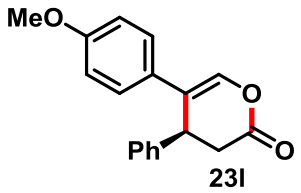
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (m, 5H), 6.85 (s, 1H), 2.94-2.91 (m, 1H), 2.84-2.83 (m, 2H), 1.67-1.60 (m, 1H), 1.49-1.42 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.39, 137.70, 135.6, 128.92, 127.84, 125.99, 123.79, 35.14, 33.36, 26.08, 10.98.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{13}H_{14}O_2Na$: 225.0886, found: 225.0886.

FTIR (cm^{-1}) 3019, 2625, 2400, 1763, 1679, 1522, 1421, 1217, 1146, 1109, 928, 771.

(*S*)-5-(4-Methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (23l)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (105.5 mg, 0.50 mmol) and 2-(4-methoxyphenyl)acetaldehyde **22l** (75 mg, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-5-(4-Methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **23l** as a white solid (101.4 mg, 72% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.39

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 1.0 mL/min.) Major: 24.3 min, Minor: 37.4 min. 99% ee, $[\alpha]_D^{25}$ = +100.00 (c 0.1, $CHCl_3$).

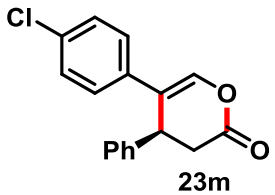
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (m, 7H), 7.08 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.11 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 3.17 (dd, J_1 = 7.7 Hz, J_2 = 15.9 Hz, 1H), 2.91 (dd, J_1 = 2.1 Hz, J_2 =16.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.06, 159.39, 139.88, 138.04. 129.41, 127.79, 127.00, 126.84, 121.17, 114.31, 55.39, 40.48, 37.65.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{18}H_{16}O_3Na$: 303.0992, found: 303.0992.

FTIR (cm^{-1}) 3365, 2922, 1775, 1747, 1645, 1415, 1218, 1141, 1034, 771.

(*S*)-5-(4-Chlorophenyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (23m)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (105.5 mg, 0.50 mmol) and 2-(4-chlorophenyl)acetaldehyde **22m** (77.2 mg, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-5-(4-Chlorophenyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **23m** as a white solid (99.3 mg, 70% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.46.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min.) Major: 29.2 min, Minor: 39.1 min. 97% ee, $[\alpha]_D^{25}$ = +55.60 (c 0.1, $CHCl_3$).

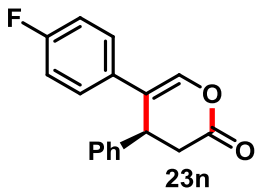
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.17 (m, 10H), 4.12 (d, J = 7.2 Hz, 1H), 3.21 (dd, J_1 = 7.7 Hz, J_2 = 15.7 Hz, 1H), 2.95 (dd, J_1 = 2.3 Hz, J_2 =15.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.57, 139.49, 139.41, 133.97, 133.70, 129.54, 129.06, 128.74, 128.69, 127.99, 126.90, 126.62, 120.57, 40.36, 37.56.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{17}H_{13}O_2ClNa$: 307.0496, found: 307.0493.

FTIR (cm^{-1}) 3020, 2926, 2400, 1772, 1650, 1491, 1459, 1216, 1145, 981, 769, 669.

(*S*)-5-(4-Fluorophenyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (23n)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (105.5 mg, 0.50 mmol) and 2-(4-fluorophenyl)acetaldehyde **22n** (69.1 mg, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-5-(4-Fluorophenyl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **23n** as a white solid (102.2 mg, 76% yield).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.51.

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 1.0 mL/min.) Major: 14.2 min, Minor: 17.3 min. 96% ee, $[\alpha]_D^{25}$ = +390.2(c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.27-7.22 (m, 5H), 7.13 (s, 1H), 6.99 (t, J = 8.4 Hz, 2H), 4.11 (d, J = 6.9 Hz, 1H), 3.21 (dd, J_1 = 7.5 Hz, J_2 = 15.8 Hz, 1H), 2.93 (d, J = 15.9 Hz, 1H).

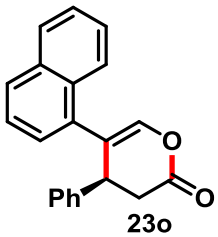
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.68, 162.48 (d, J = 247.2 Hz), 139.62, 139.03, 131.64 (d = 3.2 Hz), 129.54, 127.98, 127.41 (d, J = 7.92 Hz), 126.98, 120.79, 115.89 (d, J = 21.64 Hz), 40.69, 37.63.

HRMS (ESI) calculated $[M+Na]^+$ for $C17H13O_2FNa$: 291.0792, found: 291.0792.

FTIR (cm^{-1}) 3020, 2925, 1771, 1646, 1511, 1217, 1143, 1032, 929, 771, 668.

(*S*)-5-(naphthalen-1-yl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (23o)

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (105.5 mg, 0.50 mmol) and 2-(naphthalen-1-yl)acetaldehyde **22o** (85.1 mg, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column



chromatography (EtOAc-Pet. ether 10:90) to afford(*S*)-5-(naphthalen-1-yl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **23o** as a white solid (101.6 mg, 67% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.56.

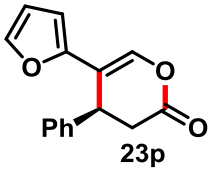
HPLC (Chiralcel OJ-H, 70:30 Pet.ether / EtOH, 1.0 mL/min.) Major: 19.8 min, Minor: 23.7 min. 94% ee, $[\alpha]_D^{25}$ = +10.6 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.90-7.88 (m, 1H), 7.80 (d, *J* = 8.33 Hz, 1H), 7.59-7.52 (m, 2H),7.36-7.24 (m, 4H), 7.18-7.13 (m, 3H), 6.88 (s, 1H), 4.14 (dd, J_1 = 2.4 Hz, J_2 = 7.5 Hz, 1H), 3.47 (dd, J_1 = 7.66 Hz, J_2 = 16.1 Hz, 1H), 3.07(dd, J_1 = 2.4 Hz, J_2 =15.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.19, 140.37, 139.74, 133.88, 133.43, 131.90, 129.19, 128.89, 128.83, 128.64, 127.73, 127.46, 127.18, 126.60, 126.12, 125.33, 124.91, 121.40, 42.82, 37.06. **HRMS (ESI)** calculated $[M+Na]^+$ for $C_{17}H_{16}O_2Na$: 323.1043, found: 323.1042.

FTIR (cm^{-1}) 3021, 2356, 1768, 1715, 1660, 1138, 1101, 1079, 802, 763, 667.

(*S*)-5-(Furan-2-yl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (23p)



Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (52.7 mg, 0.25 mmol) and 2-(furan-2-yl)acetaldehyde **22p** (27.5 mg, 0.25 mmol) with triazolium salt **D** (4.6 mg, 0.0125 mmol), Na_2CO_3 (27.8 mg, 0.2625 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-5-(Furan-2-yl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **(3p)** as a white solid (27.0 mg, 45% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.54.

HPLC (Chiralcel OJ-H, 90:10 Pet.ether / IPA, 1.0 mL/min.) Major: 10.2 min, Minor: 25.7 min. 90% ee, $[\alpha]_D^{25}$ = +64.2 (c 0.1, $CHCl_3$).

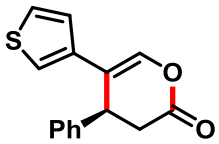
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.13 (m, 7H), 6.25 (m, 1H), 6.04 (d, *J* = 3.35 Hz, 1H), 4.0 (dd, J_1 = 2.07 Hz, J_2 = 7.5 Hz, 1H), 3.10 (dd, J_1 = 7.8 Hz, J_2 = 15.5 Hz, 1H), 2.85 (dd, J_1 = 2.13 Hz, J_2 =15.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.60, 149.52, 142.09, 139.78, 138.03, 129.38, 127.93, 126.81, 113.25, 111.44, 107.10, 38.42, 37.12.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{15}H_{12}O_3Na$: 263.0679, found: 263.0679.

FTIR (cm^{-1}) 3020, 2400, 1768, 1734, 1602, 1218, 1143, 929, 772, 668.

(*S*)-4-Phenyl-5-(thiophen-3-yl)-3,4-dihydro-2*H*-pyran-2-one (23q)



23q

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (105.5 mg, 0.50 mmol) and 2-(thien-2-yl)acetaldehyde **22q** (63.1mg, 0.50 mmol) with triazolium salt **D** (9.1 mg, 0.025 mmol), Na_2CO_3 (56 mg, 0.525 mmol) in toluene (2.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*)-4-Phenyl-5-(thiophen-3-yl)-3,4-dihydro-2*H*-pyran-2-one **23q** as a white solid (56.4 mg, 44% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.51.

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / IPA 1.0 mL/min.) Major: 39.8 min, Minor: 43.9 min. 91% ee, $[\alpha]_D^{25}$ = +219 (c 0.1, $CHCl_3$).

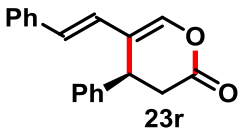
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.11 (m, 7H), 7.12 (d, *J* = 4.7 Hz, 1H), 7.05 (d, *J* = 1.7 Hz, 1H), 4.13 (d, *J* = 6.6 Hz, 1H), 3.20 (dd, J_1 = 7.7 Hz, J_2 = 16.0 Hz, 1H), 2.92 (d, *J* = 15.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.70, 139.81, 138.83, 136.33, 129.46, 127.91, 126.94, 126.68, 124.37, 120.69, 117.44, 40.48, 37.42.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{15}H_{12}O_2NaS$: 279.0450, found: 279.0449.

FTIR (cm^{-1}) 3021, 2927, 2400, 1774, 1648, 1216, 1143, 1033, 760, 669.

(*S*,*E*)-4-Phenyl-5-styryl-3,4-dihydro-2*H*-pyran-2-one (23r)



23r

Following the general procedure, treatment of (*Z*)-2-bromo 3-phenylacrylaldehye **21a** (52.7 mg, 0.25 mmol) and (E)-4-phenylbut-3-enal **22r** (36.5 mg, 0.25 mmol) with triazolium salt **D** (4.6 mg, 0.01 mmol), Na_2CO_3 (56 mg, 0.26 mmol) in toluene (1.0 mL) and stirring the reaction mixture at 30 °C for 18 h followed by flash column chromatography (EtOAc-Pet. ether 10:90) to afford (*S*,*E*)-4-Phenyl-5-styryl-3,4-dihydro-2*H*-pyran-2-one (**23r**) as a white solid (28.3 mg, 41% yield).

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

HPLC (Chiralcel OJ-H, 85:15 Pet.ether / EtOH, 1.0 mL/min.) Major: 16.0 min, Minor: 18.0 min. 94% ee, $[\alpha]_D^{25}$ = +310.0 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.32-7.27 (m, 5H), 7.24-7.21 (m,1H), 7.05 (s, 1H), 6.75 (d, J = 16.5 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 4.15 (d, J = 6.7 Hz, 1H), 3.13 (dd, J_1 = 7.6 Hz, J_2 = 16.0 Hz, 1H), 2.93 (d, J = 15.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.94, 142.11, 139.67, 136.82, 129.44, 129.15, 128.82, 128.78, 126.86, 126.35, 123.0, 120.94, 37.41, 37.28.

HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{16}O_2Na$: 299.1043, found: 299.1043.

FTIR (cm^{-1}) 3346, 2925, 1773, 1644, 1491, 1325, 1143, 1028, 771, 696.

3.6. References

1. (a) Wohler, F.; Liebig. J. *Ann. Pharm.* **1832,** *3,* 249. For review on NHC-catalyzed benzoin reactions see (b) Menon, R. S.; Biju. A. T.; Nair, V. *Beilstein J. Org. Chem*. **2016**, *12*, 444.
2. Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.
3. (a) Bugaut, X.; Glorius, F. *Chem. Soc. Rev*. **2012**, *41*, 3511. (b) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239.
4. Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A. Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.
5. Ukai, T.; Tanaka, S.; Dokawa, S.; Yakugaku Zasshi. **1943**, *63*, 296.
6. Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.
7. (a) Walia, J. S.; Rao, D. H.; Singh, M. *Indian J. Chem*. **1964**, *2*, 437. (b) Walia, J. S.; Hanumantha, R.; Singh, M.; Nath, R. *Chem. Ind*. **1967**, 583.(c) Singh, G.; Mandal, A. K. *Heterocycles* **1982**, *18*, 291.
8. Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.
9. Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed*. **2004**, *43*, 6205.
10. Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970.
11. Padmanaban, M.; Biju, A. T.; Glorius, F. *Org. Lett*. **2011**, *13*, 5624.
12. Franz, J. F.; Fuchs, P. J. W.; Zeitler, K. *Tetrahedron Lett.* **2011**, *52*, 6952.
13. Riveira, M. J.; Mischne, M. P. *Chem. Eur. J*. **2012**, *18*, 2382.
14. (a) Struble, J. R.; Bode, J. W. *Org. Synth.* **2010,** *87*,362. (b) Mahatthananchai, J.; Bode, J. W. *Chem. Sci*. **2012**, *3*, 192.
15. CCDC- 943669

16. (a) Samantha, R. C.; Maji, B.; De Sarkar, S.; Bergander, K.; Fröhlich, R.; Mück-Lichtenfeld, C.; Mayr, H.; Studer, A. *Angew. Chem., Int., Ed.* **2012**, *51*, 5234. (b) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266.
17. (a) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433. (b) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494. (c) Lyngvi, E.; Bode, J. W.; Schoenebeck, F. *Chem. Sci.* **2012**, *3*, 2346. (d) Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem., Int. Ed*. **2011**, *50*, 1673. (e) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378.
18. Based on detailed kinetic and theoretical studies, Studer and co-workers proposed the conjugate addition of nucleophiles to α, β-unsaturated acylazoliums. Depending on the nucleophile and the structure of the α, β-unsaturated acylazolium ion, Bode and co-workers invoked the initial 1,2- addition followed by [3,3]-sigmatropic rearrangement.
19. Yetra, S. R.; Trinadh, K.; Kunte, S.S.; Gonade, R. G.; Biju, A. T. *Org. Lett*. **2013**, *15*, 5202.
20. Allen, C. F. H.; Edens, Jr. C. O. *Org. Synth.* **1945**, *25*, 92. (b) Li, W.; Li, J.; Wan, Z.-K.; Wu, J.; Massefski, W. *Org. Lett.* **2007**, *9*, 4607.
21. Treu, M.; Jordis, U. *Molecules* **2002**, *7*, 374.
22. Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
23. Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112.
24. Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176.

CHAPTER 4

Enantioselective Synthesis of Functionalized Pyrazoles by N-Heterocyclic Carbene (NHC)-Catalyzed Reaction of Pyrazolones with α,β- Unsaturated Aldehydes

4.1. Introduction

Pyrazoles and their derivatives are one of the most important classes of bioactive heterocyclic compounds. These nitrogen-containing five-membered heterocycles have attracted tremendous attention in recent years due to their widespread applications as synthetic scaffolds in combinatorial and medicinal chemistry, pharmaceutical agents, chelating agents in coordination chemistry, photographic couplers and agrochemical products.[1]

The pyrazole unit is a building block of various bioactive compounds. For example, the pyranopyrazol-6-one derivative **1** was known to have analgesic and anti-inflammatory activity,[2] and the pyrazole derivative of type **2** exhibits antiplatelet activity (Figure 4.1).[3] Moreover, the annulated pyranopyrazole of the type **3** is known to possess fungicide activity,[4] whereas the trifluoromethylated analogue **4** has AMPA receptor activity enhancer property.[5]

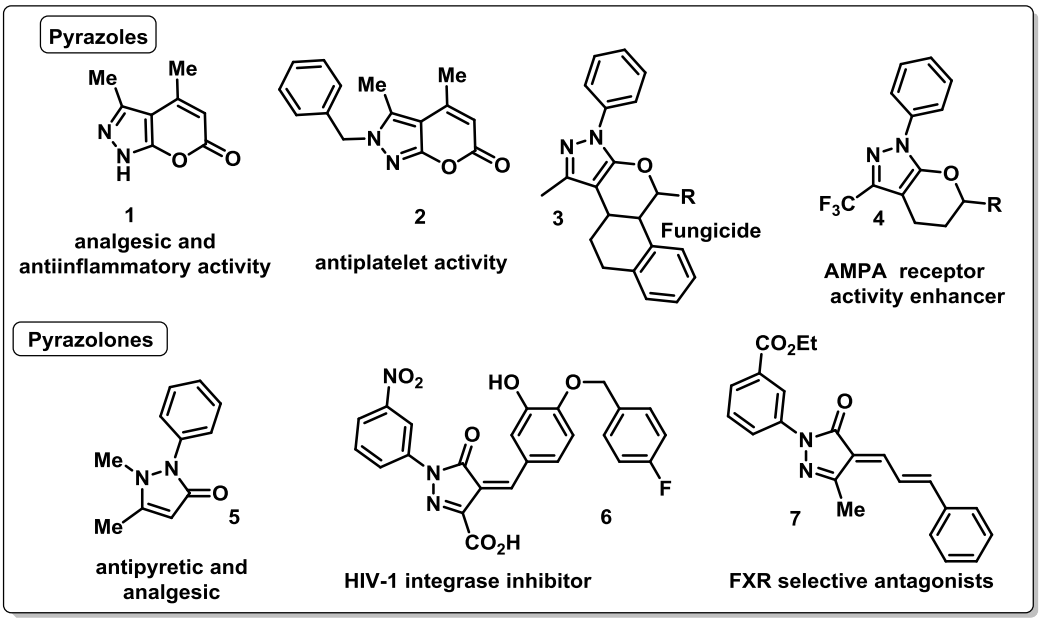


Fig 4.1: Biologically active functionalized pyrazoles

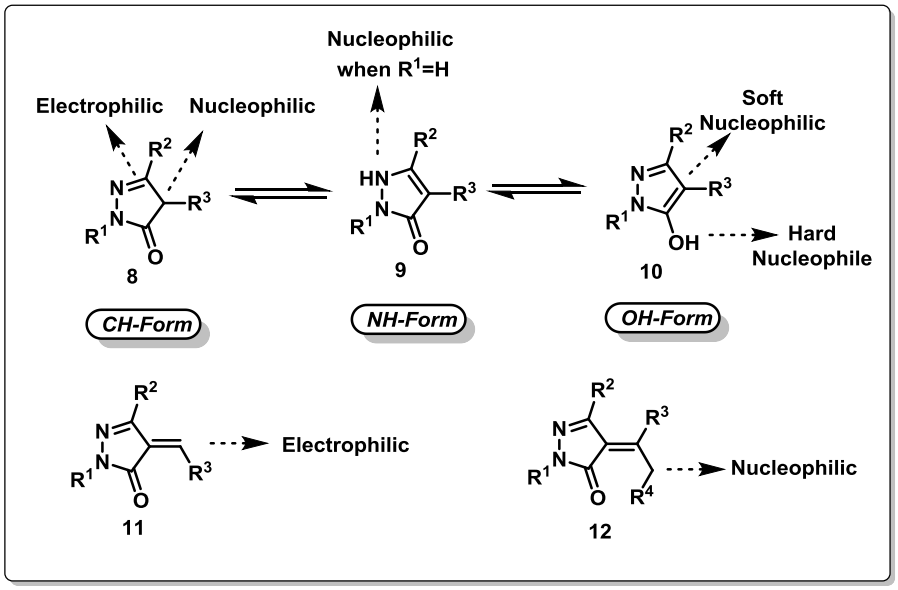
Among various possible pyrazole derivatives, pyrazolones are another important heterocycles possessing significant biological properties and they have been known for

more than a century.[6] In 1883, Ludwig Knorr synthesized the simple pyrazolone derivative phenazone (**5**),[7] which is the first synthetic antipyretic and analgesic drug. The pyrazolone carboxylic acid derivative **6** shows HIV inhibition activity,[8] and the linearly conjugated pyrazolone ester **7** exhibits FXR selective antagonist activity.[9]

4.2. Reactions of Pyrazolones

In recent times, pyrazolin-5-one derivatives **8** are successfully employed in various asymmetric organo- and metal-catalyzed strategies for the synthesis of bioactive enantiopure pyrazolone and pyrazole derivatives.[10] The availability of many reactive centres is a special feature of pyrazolin-5-one substrates and the products obtained from **8** can be further manipulated in order to get valuable compounds. The pyrazolin-5-ones can exist in three tautomeric forms **8**, **9** and **10** (Scheme 4.1). In general, pyrazolin-5-ones **8** will undergo nucleophilic addition from C-4 to various acceptors to afford all-carbon quaternary stereocentre bearing pyrazolones (when R^3=alkyl, aryl), or pyrazole derivatives (when R^3=H). The *N*1-unsubstituted pyrazolin-5-one derivatives **9** (R^1=H) are suitable substrates for aza-Michael addition reactions. Moreover, the enol form **10** can undergo cyclization reaction through the C-4 and the C-5 -OH functionality.

Scheme 4.1: Various Reactive Centers of Pyrazolin-5-ones

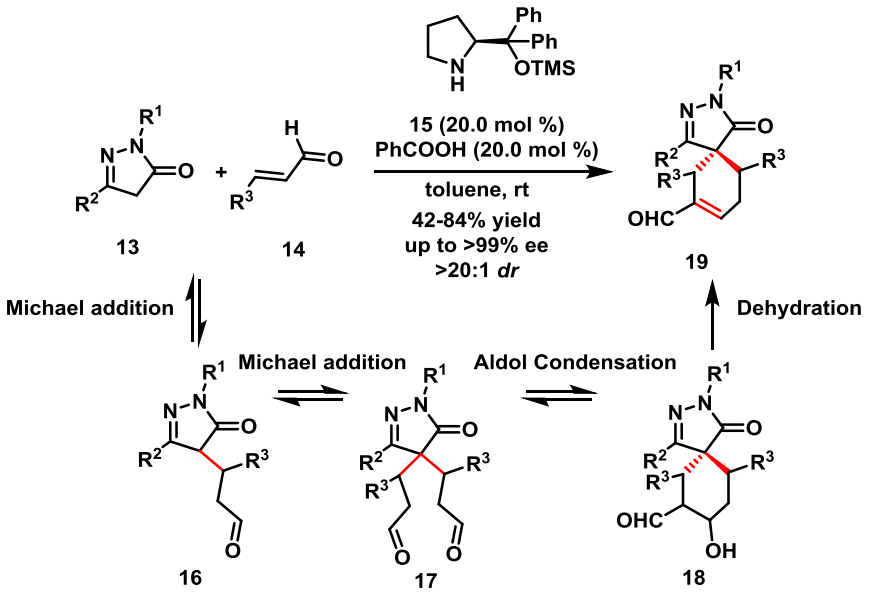


The α,β-unsaturated pyrazolones such as **11**, acts as powerful Michael acceptors for various nucleophiles and will undergo subsequent cascade sequences through C-4 additions and *O*-cyclizations. Very recently, the α,β-unsaturated pyrazolones **12** bearing a γ-hydrogen have been exploited in asymmetric vinylogous γ-addition reactions.

4.3. Reactions of Pyrazolones with *α,β*-Unsaturated Carbonyl Compounds

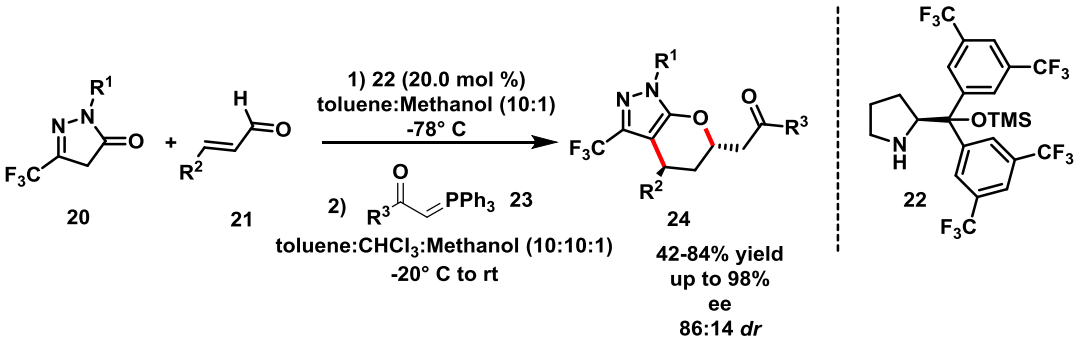
In 2011, Rios and co-workers developed an organocatalyzed triple domino Michael/Michael/aldol reaction between pyrazolones **13** and two molecules of enals **14** to afford highly functionalized spiropyrazolone derivatives **19** (Scheme 4.2).[11] With the Jorgensen–Hayashi catalyst **15** and benzoic acid as an additive, the spiropyrazolones **19** could be obtained in good yields and good to excellent stereoselectivities. In this triple cascade sequence, various aryl or alkyl enals are well tolerated to furnish substituted pyrazolones. The triple domino sequence was initiated by the Michael addition of pyrazolone to iminium ion generated from catalyst **15** and the enal **14**. The resulting Michael adduct **16** then undergoes a second Michael addition to iminium ion generated from the second molecule of the enal to afford a disubstituted pyrazolone **17**. An intramolecular aldol reaction via the enamine intermediate provides **18**, which on dehydration provides the desired spiropyrazolone **19**.

Scheme 4.2: Triple Domino Reactions of Pyrazolones with Enals



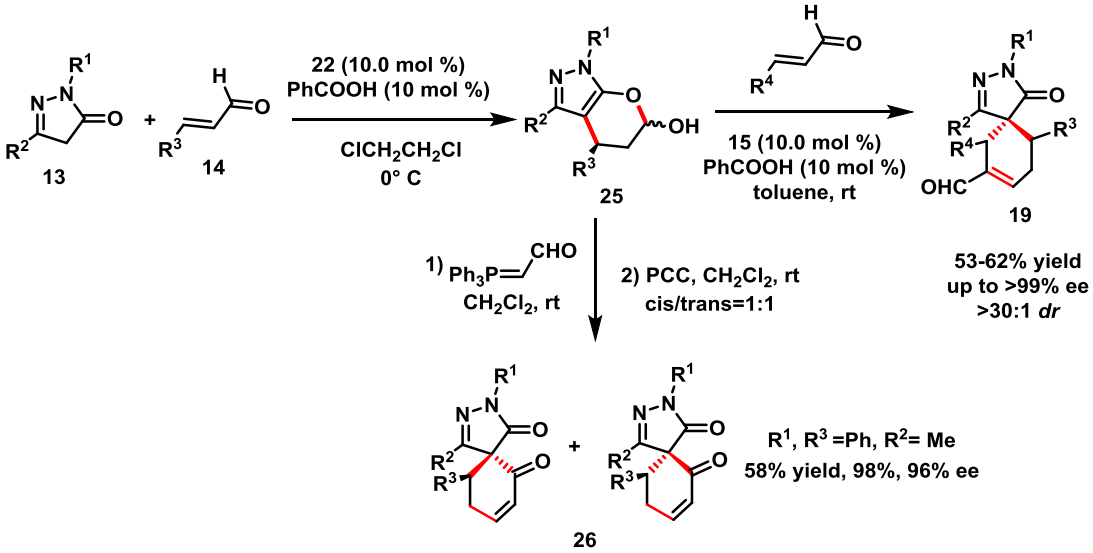
Enders and co-workers achieved an efficient asymmetric synthesis of tetrahydropyrano pyrazoles **24** via a one-pot Michael/Wittig/oxa-Michael reaction (Scheme 4.3).[12] The reaction proceeds via the secondary amine **22**-catalyzed Michael addition of 3-trifluoromethyl pyrazolones **20** to α,β-unsaturated aldehydes **21**, followed by the addition of the Wittig reagent **23**. The subsequent Wittig/oxa-Michael reaction accomplishes the biologically active tetrahydropyrano pyrazoles **24**.

Scheme 4.3: Enantioselective Synthesis of Tetrahydropyrano Pyrazoles



Very recently, Wang and co-workers reported that benzoic acid as an additive can afford the enantioselective synthesis of tetrahydropyrano pyrazol-6-ols **25** (normally unstable in Enders case) through a Michael addition/hemiacetalization sequence using the secondary amine catalyst **22** (Scheme 4.4).[13] Both pyrazolol-5-ones **13** and enals **14** underwent efficient annulation to furnish products in good yields (71-91%) and good to high enantioselectivities. Moreover, treatment of **25** with enals in presence of amine catalyst **15** the spirocompound **19** was obtained (Rios product). Treatment of **25** with Wittig reagent did not afford **24** but instead resulted in the formation of the spirocompound **26** (1:1 *dr*) with good enantioselectivity.

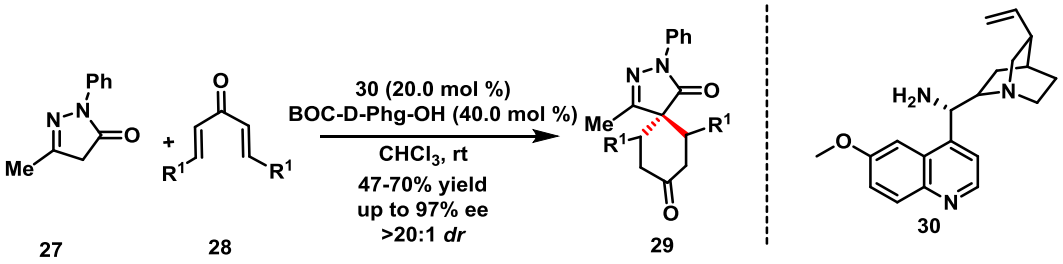
Scheme 4.4: Enantioselective Reactions of Pyrazolones with Enals



Wang and co-workers demonstrated the enantioselective reaction of *N*-phenyl protected pyrazolones **27** with divinyl ketones **28** catalyzed by 9-amino-9-deoxyepiquinine **30** using *N*-Boc-*D*-phenylglycine as an acidic additive to furnish the spirocyclohexanone- fused pyrazolones **29** in moderate to good yields (Scheme 4.5).[14]

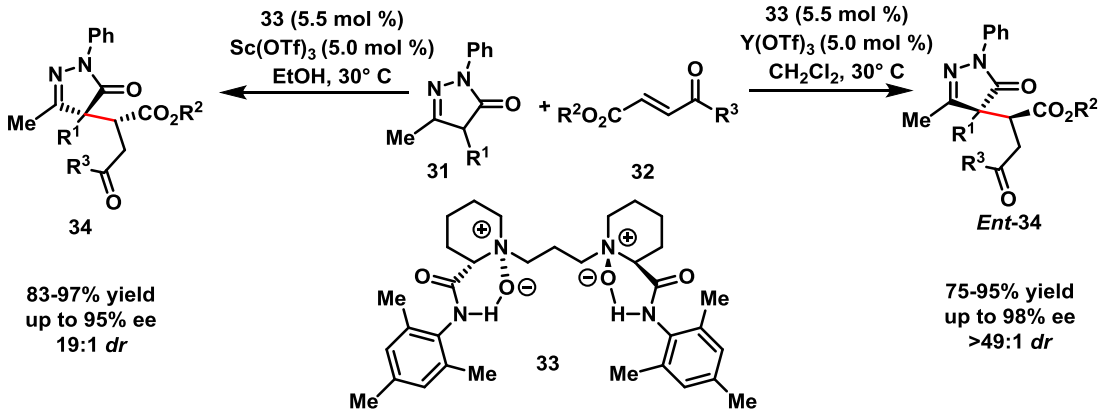
The reaction proceeds in a double Michael addition pattern resulting in excellent diastereoselectivity and high ee values.

Scheme 4.5: Enantioselective Reactions of Pyrazolones with Divinyl Ketones



Feng and co-workers disclosed the chiral metal/*NN'*-dioxide complexes catalyzed enantioselective Michael addition of 4-substituted pyrazolones **31** to the 4-oxo-4-arylbutenoates **32** to afford a range of 4-substituted-5- pyrazolone derivatives **34** (Scheme 4.6).[15] Notably, both enantiomers of the products could be synthesized using the same ligand **33** by switching the metal (Sc or Y). Moreover, the scale-up reaction proceeded with excellent ee and yields, thus indicating the preparative value of this catalyst system. Ethanol was best for the reactivity as well as enantioselectivity in Sc(III)-catalyzed reactions. However, ethanol lowered the enantioselectivity in the case of Y(III)-catalyzed reactions. This is due to the coordination of alcohol with Sc(III) (smaller ionic radius) and enolized pyrazolone.

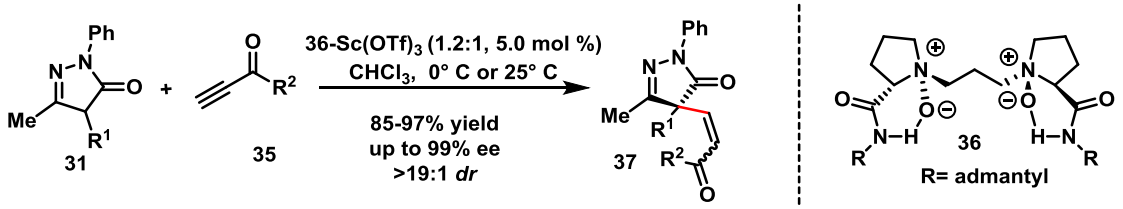
Scheme 4.6: Enantioselective Reactions of Pyrazolones with 4-*oxo*-4-Arylbutenoates



Later in 2012, Feng and co-workers developed a highly *Z*-selective asymmetric 1,4-addition reaction of 4-substituted pyrazolones **31** to alkynones **35**. The chiral *N,N'*-dioxide–Sc(III) complex catalyzed the reaction to afford the enantiomerically pure 4-alkenyl-pyrazol-5-ones **37** in high geometric control (*Z*/*E* up to >19:1), with high yields (up to 97%), and excellent enantioselectivities (up to 99% ee). Moreover, the procedure

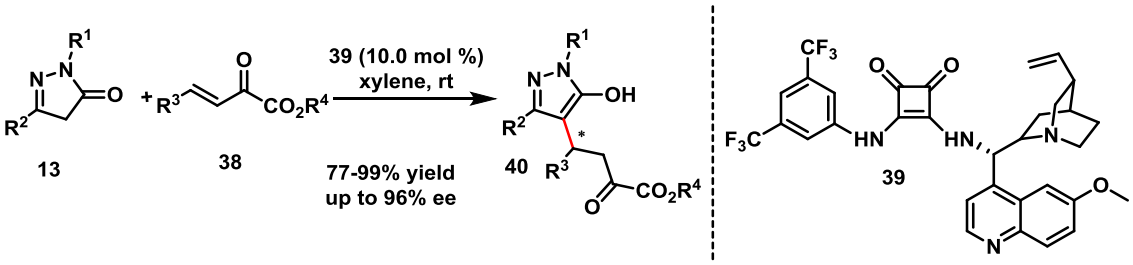
tolerates a wide range of substrates, and excellent results obtained on a gram scale (Scheme 4.7).[16]

Scheme 4.7: Enantioselective Reactions of Pyrazolones with 4-*oxo*-4-Arylbutenoates



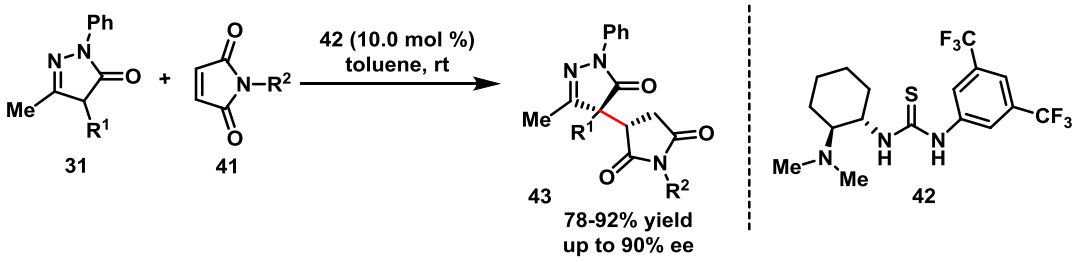
Asymmetric Michael addition reaction of pyrazolin-5-ones **13** to aryl substituted β,γ-unsaturated α-ketoesters **38** catalyzed by an aminosquaramide **39** resulted in a straightforward access to the optically active pyrazolone derivatives **40** in good to excellent yields and high enantioselectivities (Scheme 4.8).[17]

Scheme 4.8: Enantioselective Reaction of Pyrazolones with β,γ-Unsaturated α-Ketoesters



A bifunctional aminothiourea **42** promoted the enantioselective Michael addition of pyrazolones **31** to *N*-aryl maleimides **41** to afford the corresponding functionalized pyrazolones **43** bearing vicinal quaternary and tertiary stereocenters in excellent yields (up to 92%), and good enantioselectivities (Scheme 4.9).[18]

Scheme 4.9: Enantioselective Reactions of Pyrazolones with *N*-Aryl Maleimides

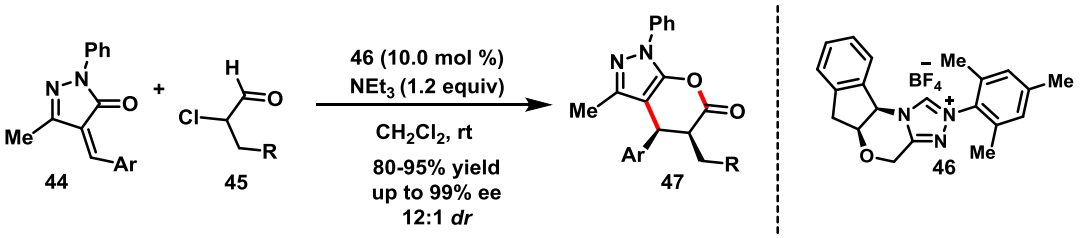


4.4. NHC-Catalyzed Reactions of Pyrazolones with Aldehydes

Ye and co-workers reported NHC-catalyzed reaction of chloroaldehydes **45** with unsaturated pyrazolones **44** (Scheme 4.10).[19] The reaction proceeded via NHC-bound enolate generated from triazolium salt **46** and chloroaldehydes **45** followed by their

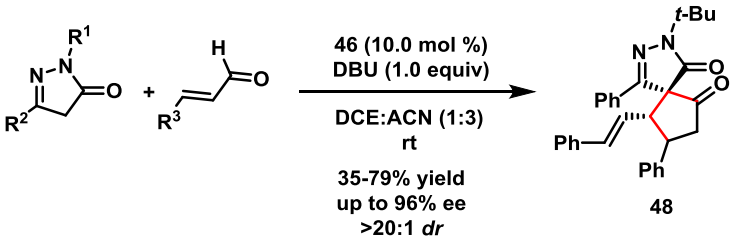
addition to pyrazolones **44**, to furnish the dihydropyrano[2,3-c]pyrazol-6-(1*H*)-ones **47** in high yields with good diastereoselectivities and excellent enantioselectivities.

Scheme 4.10: NHC-Catalyzed Reactions of Chloroaldehydes with Unsaturated Pyrazolones



Very recently, Enders and co-workers reported a one-pot three-component method for the diastereo- and enantioselective synthesis of spiropyrazolones **48** (Scheme 4.11).[20]The reaction involves the NHC- bound homoenolate addition to in situ generated *α*,*β*-unsaturated pyrazolones. This NHC-catalyzed [3+2] annulation furnished the desired spirocyclopentane pyrazolones in moderate to good yields and good to excellent stereoselectivities (up to 96% ee and >20:1 *dr*).

Scheme 4.11: NHC-Catalyzed Reactions of Enals with Pyrazolones



4.5. Statement of the Problem

From the above discussion, it is clear that the utility of pyrazolone derivatives, which are core moieties present in various biologically active compounds are known in various enantioselective transformations under organocatalytic conditions. However, the use of pyrazolones in NHC-organocatalysis is underexplored. Although pyrazolones are well-known as excellent nucleophiles in various Michael addition reactions, surprisingly, however, the use of pyrazolones as bifunctional nucleophiles in NHC-catalysis is limited. In this context, we envisioned the utilization of pyrazolones as bisnucleophiles to intercept the chiral *α*,*β*-unsaturated acylazolium generated under NHC-catalyzed reaction conditions. The results of our studies leading to the highly enantioselective synthesis of pyrazole-fused dihydropyranones using asymmetric NHC-catalyzed reaction of enals with pyrazolones under oxidative conditions are presented in the following sections. Notably, these reactions proceed under base-free conditions.

While doing this work, we also uncovered a base-free Knoevenagel condensation between enals and pyrazolones resulting in the synthesis of trisubstituted pyrazolone derivatives.

4.6. Results and Discussion

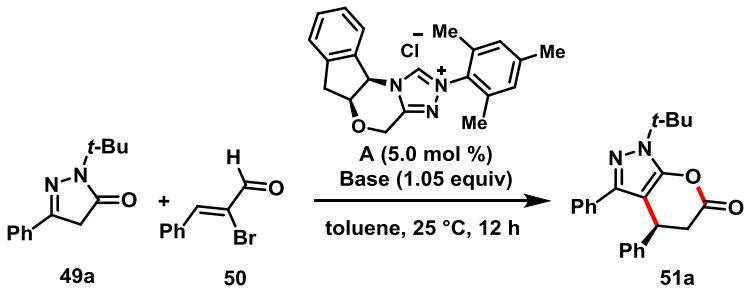
4.6.1. Reactions of Pyrazolones with 2-Bromoenals

Due to the excellent biological importance of pyrazolones and their derivatives, we envisioned their enantioselective synthesis by asymmetric NHC-organocatalysis. Continuation to our ongoing interest in the N-heterocyclic carbene (NHC)-organocatalyzed addition of nucleophiles to α,β-unsaturated electrophilic systems,[21] herein, we envisioned pyrazolone as a nucleophilic coupling partner. It is noteworthy that in NHC-catalysis pyrazolones are known as electrophiles in (3+2) annulations and our aim is to introducing them as nucleophiles.

4.6.2. Optimization Studies with 2-Bromoenals

The optimization studies began by the treatment of 5-aryl pyrazolone **49a** and α-bromo cinnamaldehyde (**50**) with the triazolium salt **A** and 1.05 equiv of Na_2CO_3 as the base. Delightfully, the reaction furnished the functionalized dihydropyranone-fused pyrazole **51a** in 91% yield (based on ^{1}H-NMR spectroscopy) and 58:42 er (Table 1, entry 1). DABCO and TMEDA as bases improved the selectivity with same yield (entries 2,4).

Table 1. Optimization of the Reaction Conditions[a]



entry	Base	yield of **51a** (%)[b]	er of **51a**[c]
1	Na_2CO_3	91	58:42
2	DABCO	91	73:27
3	DMAP	99	70:30
4	TMEDA	90	65:35
5	DABCO (0° C to 25 °C)	91	71:29
6	DMAP (0° C to 25 °C)	99	69:31

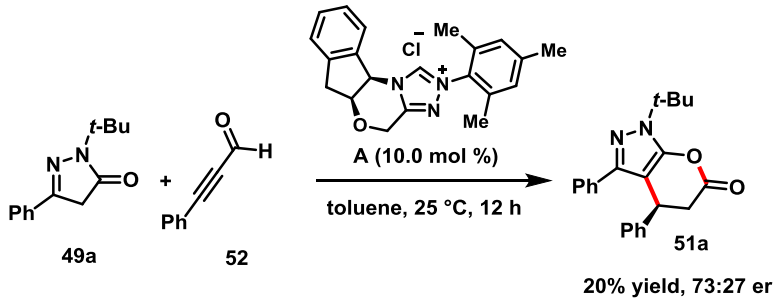
[a] Standard conditions: **49a** (0.125 mmol), **50** (0.125 mmol), **A** (5.0 mol %), Base (1.05 equiv), toluene (2.0 mL), 25 °C and 12 h. [b] The yields were determined by ^{1}H-NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield in parentheses. [c] Determined by HPLC analysis on a chiral column.

Interestingly, DMAP gave excellent yield of **51a** (99%) but with poor selectivity compared to DABCO (Table 1, entry 3). Lowering the reaction temperature gave comparable yields with reduced selectivities (entries 5,6). So far DABCO and DMAP are considered as optimal bases for the asymmetric synthesis of functionalized dihydropyranone-fused pyrazole **51a** from 2-bromoenal **50**.

4.6.3. Reactions of Pyrazolones with Ynals

The interception of 5-aryl pyrazolone **49a** with chiral α,β-unsaturated acylazoliums generated from ynal **52** and NHC (in situ generated from carbene precursor **A)** afforded dihydropyranone-fused pyrazole **51a** in 20% yield with 73:27 er. Although this method giving comparable selectivity like 2-bromoenal **50** (Table 1, entry 2), but the yield of **51a** was very low (Scheme 4.12).

Scheme 4.12: NHC-Catalyzed Reactions of Ynals with Pyrazolones



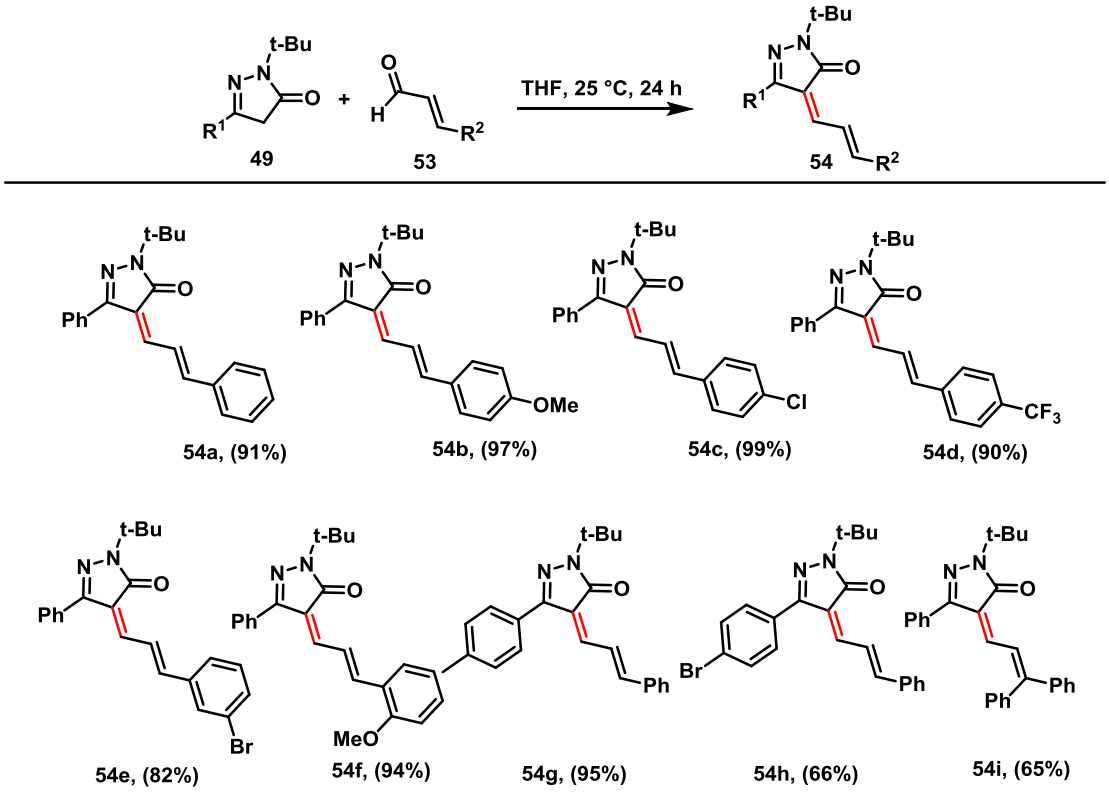
4.6.4. Reactions of Pyrazolones with Enals

Finally we selected cinnamaldehyde as a coupling partner for the generation of chiral α,β-unsaturated acylazoliums. We initiated our reaction by the treatment of 5-aryl pyrazolone **49a** with cinnamaldehyde **53a** in toluene at 25 °C. Surprisingly, before the addition of oxidant and carbene precursor we observed change in the color of reaction mixture to red, and the reaction resulted in the formation of the trisubstituted pyrazolone **54a** in 20% yield. It is noteworthy that the Knoevenagel condensation between enals and pyrazolones took place in the absence of base. Possibly, the pyrazolones can act as the base to initiate the reaction. Changing the solvent to THF and reaction time to 24 h improved the yield of **54a** to 91%. Notably, the reaction worked well under mild conditions and in the absence of base and microwave conditions.

As the conjugated pyrazolones are known to exhibit interesting biological properties (for example compounds **5**,**6**) we planned their synthesis with our mild and base free approach (Scheme 4.13). We evaluated scope of this Knoevenagel reaction, electron-releasing and -withdrawing groups at the 4-position of the β-aryl ring of enals

53 are well tolerated and resulted in the formation of trisubstituted pyrazolones in excellent yield (**54a-54d**). Furthermore, substitution at the 3- and 2-position of *β*-aryl ring was well tolerated (**54e**, **54f**). Additionally, substrates with substitution at the 5-aryl ring, and a *β*,*β*-diphenyl enal underwent smooth condensation reaction furnishing the desired products in good yields (**54g, 54i**).

Scheme 4.13: Mild and Base-free Reaction of 4-Unsubstituted Pyrazolones with *α*,*β*-Unsaturated Aldehydes



General reaction conditions: **49a** (0.25 mmol), **53** (0.25 mmol), THF (2.0 mL) 25 °C and 24 h. Yields of isolated products are given.

4.6.5. Reactions of Pyrazolones with Enals under NHC-Catalysis

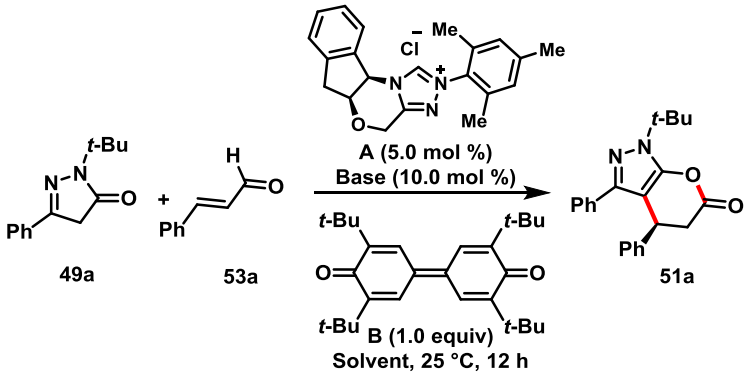
Coming back to our main focus, we examined the reaction of pyrazolones with enals under NHC-catalyzed conditions. Generation of chiral *α*,*β*-unsaturated acylazoliums by the reaction of enals with NHCs under oxidative conditions followed by their interception with pyrazolones was the underlying principle of this reaction.

4.6.6. Optimization Studies with Enals

We started our optimization studies by the treatment of pyrazolone **49a** with cinnamaldehyde **53a** and carbene generated from the chiral triazolium salt **A** using Na_2CO_3 as the base and with oxidant **B**, the reaction resulted in the enantioselective synthesis of dihydropyranone-fused pyrazole **51a** in 54% yield (based on ^{1}H-NMR

spectroscopy) and excellent enantiomer ratio (er) of 98:2 (Table 2, entry 1). A quick solvent screening revealed that non-polar solvents such as mesitylene and xylene resulted in comparable selectivity but with poor yield (entries 2, 3), whereas THF resulted in reduced selectivity and yield (entry 4). A brief survey of bases revealed that the bases like DABCO, DMAP, and DIPEA furnished the desired product in slightly improved yields and diminished selectivities (entries 5-7). Screening of lithium derived bases did not improve the yield (entries 8-11). Base screening clearly indicated that base has no impact on reactivity and selectivity. This observation prompted us to proceed further reactions under base-free reactions. Surprisingly, the reaction afforded the desired product in same yield and selectivity in the absence of base (entry 12).[22]

Table 2. Optimization of the Reaction Conditions[a]

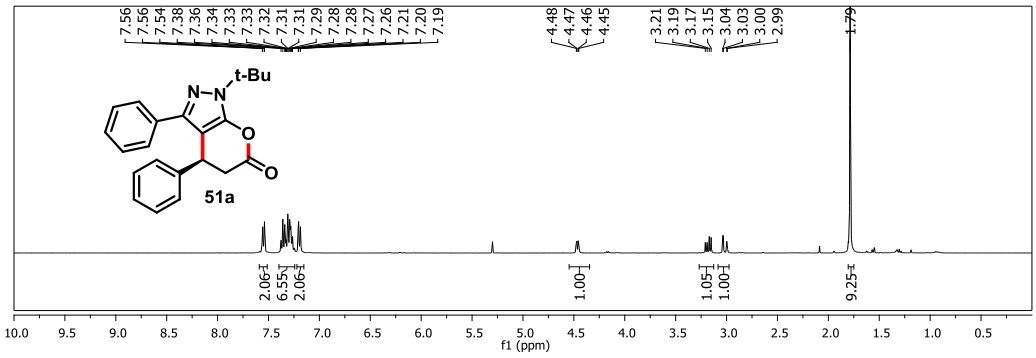


entry	Base	Solvent	yield of **51a** (%)[b]	er of **51a**[c]
1	Na_2CO_3	toluene	54	98:2
2	Na_2CO_3	mesitylene	50	98:2
3	Na_2CO_3	xylene	49	98:2
4	Na_2CO_3	THF	45	92:7
5	DABCO	toluene	54	97:4
6	DMAP	toluene	55	97:3
7	DIPEA	toluene	63	96:5
8	Li_2CO_3	toluene	65	97:3
9	LiOAc.$2H_2O$+4Å MS	toluene	57	97:3
10	LiO*t*-Bu	toluene	57	97:4
11	LiCl	toluene	53	98:2
12	No Base	toluene	55	98:2
13	***No Base, 1.5 equiv of 49a***	**toluene**	***82(81)***	***98:2***

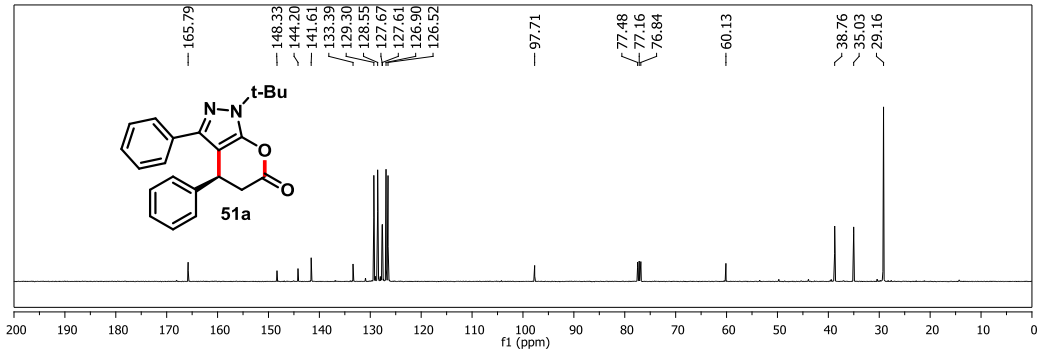
[a] Standard conditions: **49a** (0.125 mmol), **53a** (0.125 mmol), **A** (5.0 mol %), Base (10.0 mol %), **B** (1.0 equiv), Solvent (2.0 mL), 25 °C and 12 h. [b] The yields were determined by ^{1}H-NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield in parentheses. [c] Determined by HPLC analysis on a chiral column.

4.6.7. Spectral Data of 51a

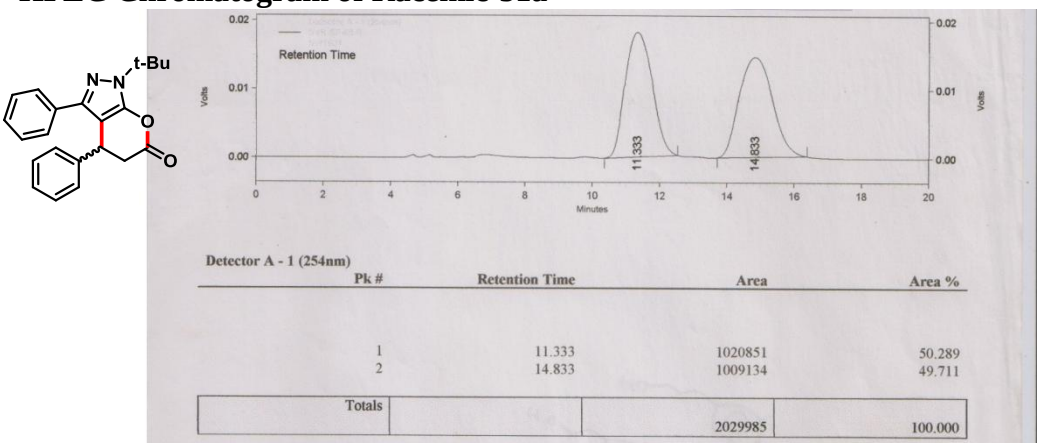
^{1}H NMR Spectrum of 51a ($CDCl_3$)



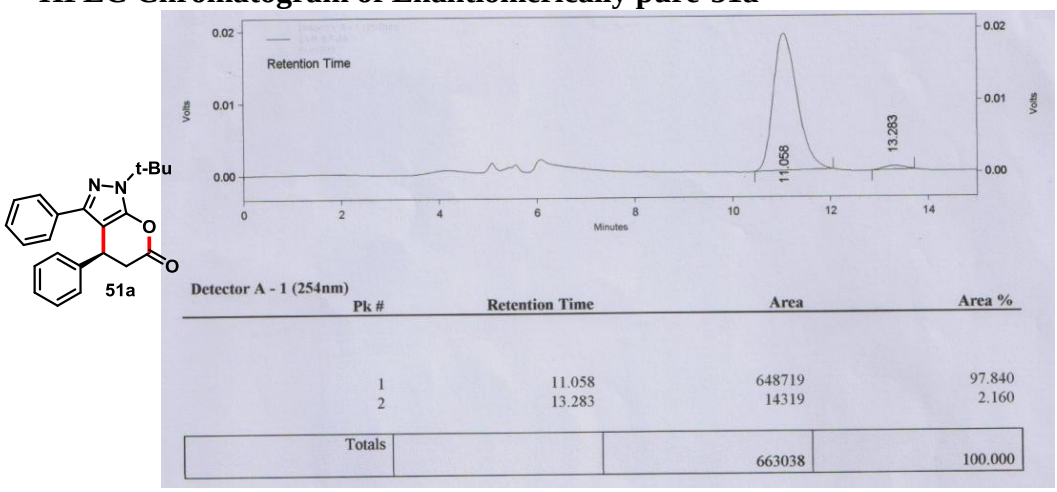
^{13}C NMR Spectrum of 51a ($CDCl_3$)



HPLC Chromatogram of Racemic-51a



HPLC Chromatogram of Enantiomerically pure-51a



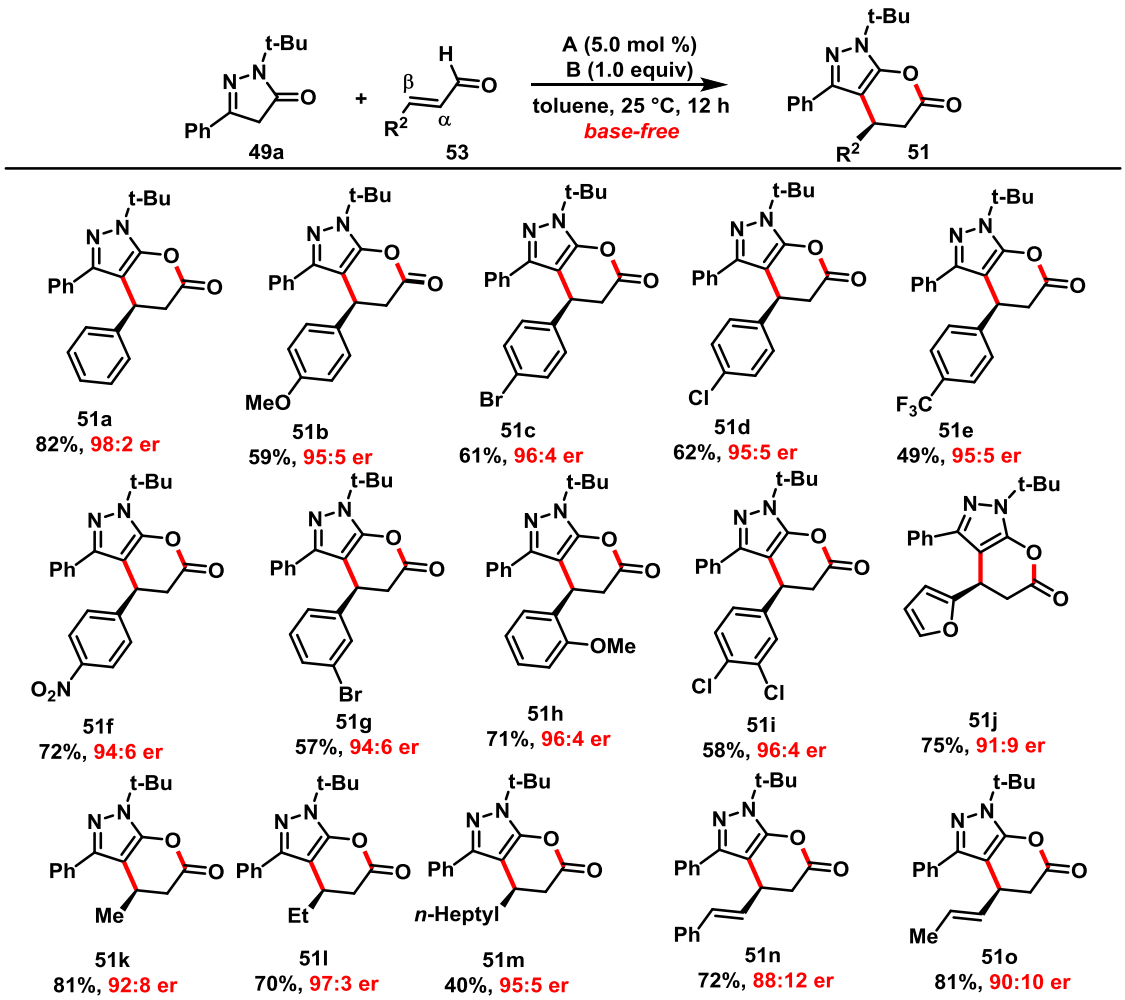
Here, it is reasonable to believe that the chloride counterion in **A** acts as a base in generating traces of free NHC, which immediately reacts with **53a** to begin the catalytic cycle (it could be also possible that the pyrazolone acts as the base to generate the free NHC to initiate the catalytic cycle).[23] Finally, increasing the amount of pyrazolone **49a** to 1.5 equiv improved the yield of **51a** to 82% with 98:2 er (entry 13). In this context It is worthy to note that the condensation product between **49a** and **53a** was not observed under the optimized conditions. The spectral data of **51a** is given in Section 4.6.7.

4.6.8. Enantioselective Synthesis of Pyrazole-Fused Dihydropyranones from Enals

With the optimized conditions in hand, we examined the substrate scope of this NHC-catalyzed annulation reaction (Scheme 4.14). First, the scope of this reaction with various α,β-unsaturated aldehydes has been evaluated. The unsubstituted parent system worked well, and various electron-donating and -withdrawing groups at the 4-position of the β-aryl ring were well tolerated and afforded the dihydropyrano pyrazolones in moderate to good yields and with good er values (**51a-51f**). In addition, substitution at the *meta*-position and *ortho*-position of β-aryl ring of **53** as well as disubstitution resulted in the smooth conversion to the products in good yield and good enantioselectivity (**51g-51i**). Moreover, β-furyl enal as a coupling partner furnished the desired product **51j** in 75% yield and 91:9 er. It is noteworthy

that the enantiomeric ratio of **51j** was improved to >99.9:0.1 upon single crystallization in 2-propanol. The structure of **51j** was further confirmed by single crystal X-ray analysis.[24] Notably, various linear aliphatic α,β-unsaturated aldehydes gave the expected dihydropyranone-fused pyrazoles in good yields and er values (**51k-m**). Gratifyingly, enals with extended conjugation at the β-position afforded the target vinyl dihydropyranopyrazole in good yield and moderate er values (**51n**, **51o**)

Scheme 4.14. Substrate Scope of the NHC-Catalyzed Enantioselective Synthesis of Pyranone-fused Pyrazoles: Variation of Enals.

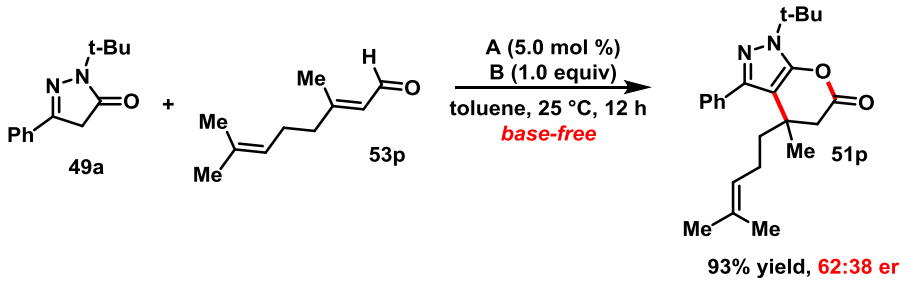


General reaction conditions: **49a** (0.75 mmol), **53** (0.50 mmol), **A** (5.0 mol %), **B** (1.0 equiv), toluene (5.0 mL) 25 °C and 12 h. Yields of isolated products are given.

4.6.9. Reactions of Pyrazolones with *β,β*-Disubstituted Enal

Interestingly, when the NHC-catalyzed reaction of pyrazolone **49a** was carried out using a *β,β*-disubstituted enal (citral, **53p**) as a coupling partner, the desired dihydropyranone-fused pyrazole **51p** was isolated in a high yield of 93% and a moderate er of 62:38 (Scheme 4.15). Variation of reaction temperature and solvents did not improve the er values. The high reactivity in this case is an indication of the probable 1,2-addition of **49a** to the *α,β*-unsaturated acyl azolium intermediate formed from **53p** and **A**.[25]

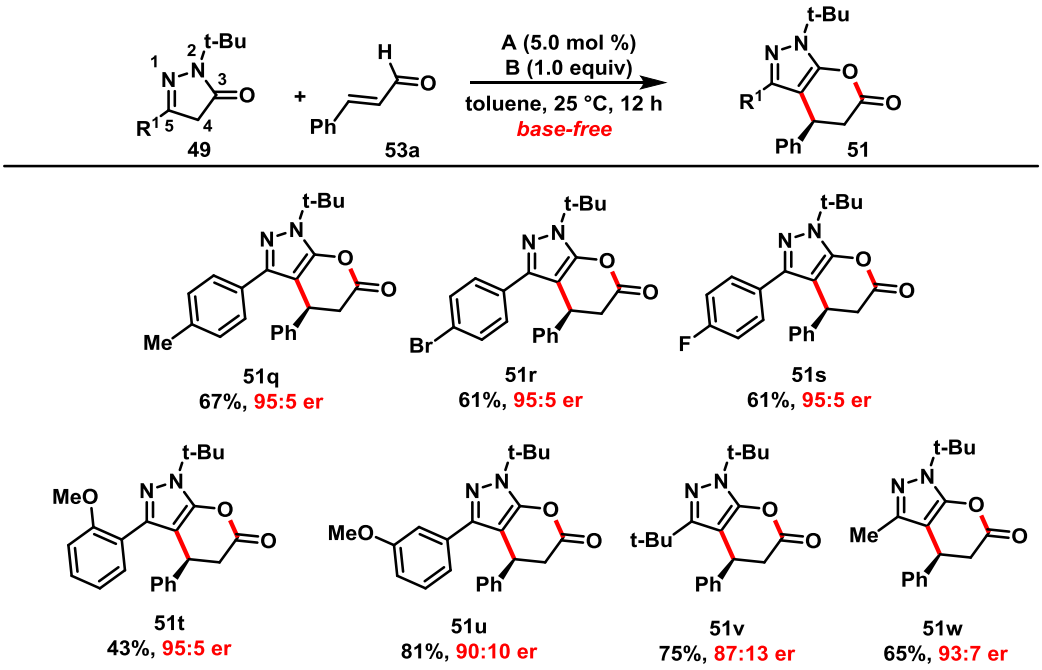
Scheme 4.15. Reaction of the Pyrazolone with Citral



4.7. Enantioselective Synthesis of Pyrazole-Fused Dihydropyranones from Pyrazolones

Next, we focussed our attention on the variation of the 4-unsubstituted pyrazolones moiety (Scheme 4.16). Pyrazolones having electron-rich and electron-poor substituents at *para*-position of 5-aryl ring readily furnished the desired pyrazoles in good yield and er values (**51q-51s**). Furthermore, methoxy substitution at the *ortho* and *meta*-position of 5-aryl ring were well tolerated (**51t, 51u**). Moreover, alkyl substitution at the 5-position of **49** also furnished the expected products (**51v, 51w**). Notably, the 5-*tert*-butyl substituted pyrazolone resulted in smooth conversion to the product **51v** in 75% yield, but in moderate er of 87:13. It is worthy of note that the *tert*-butyl group at the 2-position of pyrazolone **49** was found to be crucial for good reactivity.

Scheme 4.16. Variation of the Pyrazolones Moiety[a]



[a] General reaction conditions: **49** (0.75 mmol), **53a** (0.50 mmol), **A** (5.0 mol %), **B** (1.0 equiv), toluene (5.0 mL) 25 °C and 12 h. Yields of isolated products are given.

4.7.1 Unsuccessful Heterocyclic Bifunctional Nucleophiles and Enals

Disappointingly, the reaction of pyrazolones with α-substituted enals did not afford the expected dihydropyranone-fused pyrazoles under the present reaction conditions (Fig 4.2). Moreover, attempted reactions using oxazolones and α-angelicalactone as bifunctional nucleophiles instead of pyrazolone were also unsuccessful.

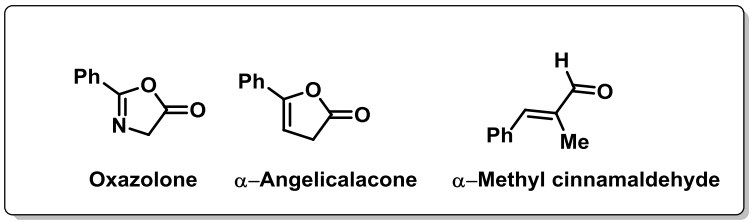
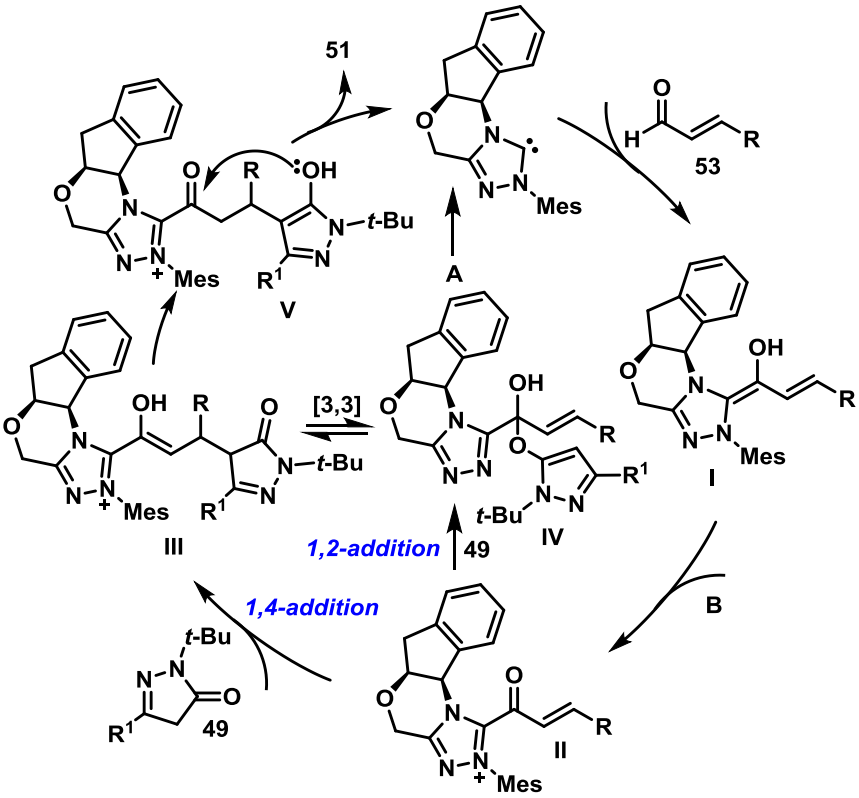


Fig 4.2: Unsuccessful Substrates

4.8. Plausible Mechanism

A plausible pathway for this NHC-catalyzed annulation reaction of enals and pyrazolones is shown in Scheme 4.17. The free NHC generated with the aid of the chloride counterion (or using the pyrazolone substrate),[23] will undergo nucleophilic 1,2-addition to enal **53** to generate the nucleophilic Breslow intermediate **I**.[26]

Scheme 4.17. Proposed Mechanism of the NHC-Catalyzed Annulation of Enals.



In the presence of oxidant **B**, the enaminol **I** will transform to the key α,β-unsaturated acylazolium intermediate **II**. It is likely that the nucleophilic addition of **1** to **II** can proceed in a 1,4-fashion[27] or in a 1,2-pathway.[28] The 1,4-addition can directly generate the enol intermediate **III**. Considering the minor amount of 3-hydroxypyrazole form of **49** in solution, a 1,2- addition of **49** to **II** can also be invoked. This can generate the hemiacetal intermediate **IV,** which can undergo a [3,3] sigmatropic rearrangement to furnish **III**. The enol intermediate **III** undergoes proton transfer generating the acylazolium intermediate **V**, and an intramolecular acylation results in the formation of the desired product **51** with the release of free carbene.

4.9. Conclusion

In conclusion, we have developed an operationally simple and base-free method for the nucleophilic addition of pyrazolones to enals.[29] Knoevenagel condensation products were obtained in excellent yields and selectivity under mild and base-free conditions by simple mixing of pyrazolones with α,β-unsaturated aldehydes. Intriguingly, when the reaction was performed in the presence of a triazolium salt under oxidative conditions, the dihydropyranone-fused pyrazoles were formed in good yield and high enantioselectivity with broad substrate scope.

4.10. Experimental Details

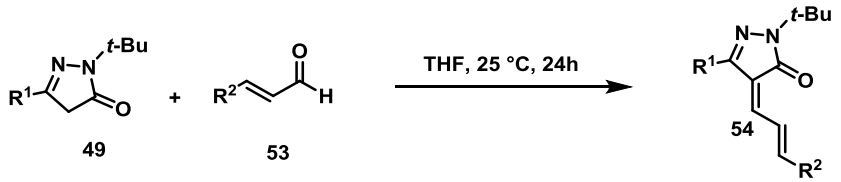
4.10.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Dry toluene and THF were purchased from commercial sources and stored under argon over sodium wire. The *α,β*-unsaturated aldehydes **53a**, **53b**, **53h**, **53j**, **53k**, **53l**, **53m**, **53o** were purchased from commercial sources and was used without further purification, and **53c**, **53d**, **53e**, **53f**, **53g**, **53n** were synthesized by following the literature procedure.[30] Pyrazolone derivatives were synthesized by following the literature procedure. [31]The triazolium salt **A** was synthesized following the literature procedure.[32]

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. Fast column is needed to avoid decomposition of products.

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 50 mm cell of 1 mL capacity. HPLC analysis was performed on Shimadzu Class-VP V6.12 SP5 with UV detector.

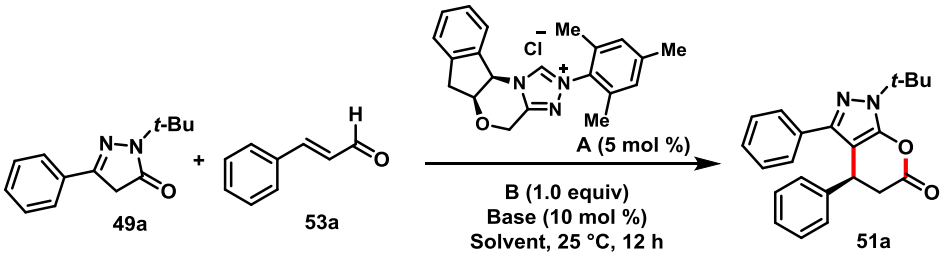
4.10.2. Procedure for the Synthesis of Functionalized 2,4-dihydro-3*H*-pyrazol-3-ones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken enal **53** (0. 25 mmol), and Pyrazolone derivative **49** (0.25 mmol), were added. Then the

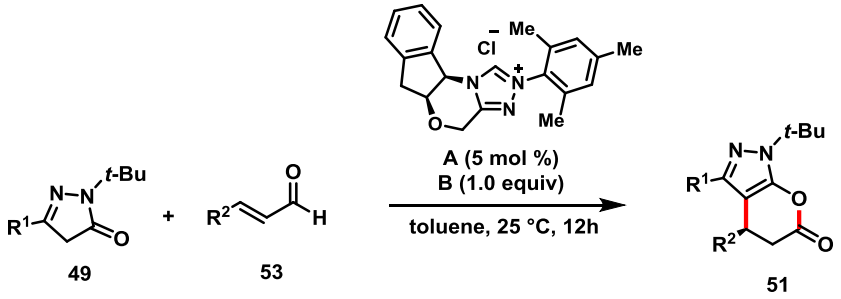
screw-capped tube was evacuated and backfilled with argon. To this mixture was added THF (2.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C for 24 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding functionalized 2,4-dihydro-3*H*-pyrazol-3-ones **54**.

4.10.3. Procedure for the Optimization of Reaction Conditions



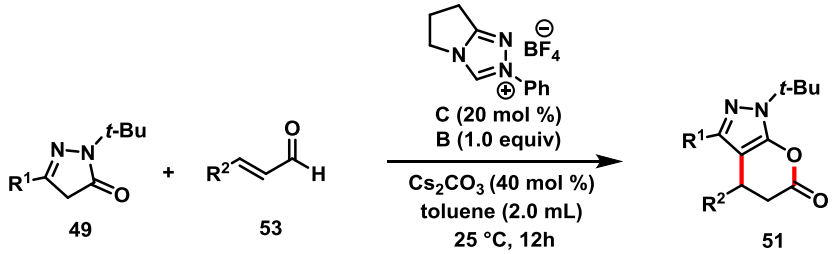
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (2.3 mg, 0.006 mmol, 5 mol%), and base (0.012 mmol, 10 mol %), oxidant **B** (0.125mmol) was added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added solvent (1.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C. To this mixture was added the Cinnamaldehyde **53a** (0.125 mmol) followed by 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (0.125 mmol). Then the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with CH_2Cl_2 (10.0 mL). The solvent was evaporated 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.

4.10.4. Procedure for the Enantioselective Synthesis of Functionalized Pyrazoles



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (9.1 mg, 0.025 mmol), and **B** (202 mg, 1.0 equiv), were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture

was added toluene (5.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C. To this mixture was added the enal **53** (0.50 mmol) followed by Pyrazolone drivative **49** (0.75 mmol). Then the reaction mixture was stirred at 25° C for 12 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding dihydropyranopyrazols. Racemic samples were prepared by using the carbene precurser **C.**



4.10.5. X-ray crystallography:

Crystal of suitable size was selected from the mother liquor and then mounted on the tip of a glass fiber and cemented using epoxy resin. Intensity data for both the crystals were collected using MoK_{α} (λ=0.71073 Å) radiation on a Bruker SMART APEX diffractometer equipped with CCD area detector at 150K. The data integration and reduction were processed with SAINT software.[33]An empirical absorption correction was applied to the collected reflections with SADABS.[34]The structures were solved by direct methods using SHELXTL and were refined on F^2 by the full-matrix least-squares technique using the program SHELXL-97. [35,36]

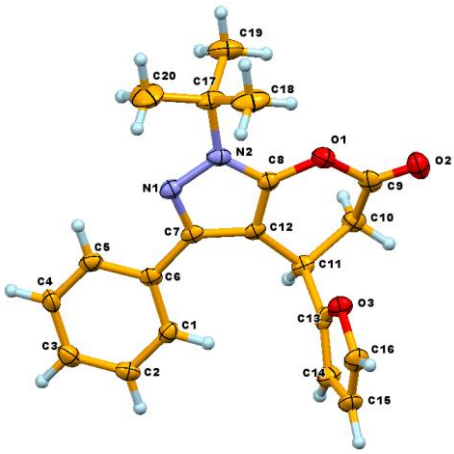
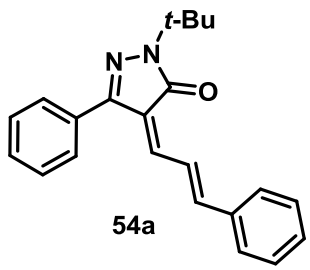


Fig 4.3: ORTEP diagram of **51j** with atom numbering scheme (50% probability for the thermal ellipsoids)

All non-hydrogen atoms were refined anisotropically till convergence is reached. Hydrogen atoms attached to the organic moieties are either located from the difference Fourier map or stereochemically fixed in all the compounds (Fig 4.3). X-ray crystal structure analysis of **51j**: Molecular formula $C_{20}H_{20}N_2O_3$, Formula weight (M) = 336.38, colorless crystal obtained by recrystallization from isopropanol, 0.37 x 0.27 x 0.16 mm, a = 9.8991(11), b = 10.1513(11), c = 17.5003(19)Å, a=b=g= 90°, V =1758.6(3) $Å^3$, ρ calc=1.271gcm^{-3}, μ=0.086 mm^{-1}, Z = 4, Orthorhombic, Space group $P2_12_12_1$, T= 150(2)K, Reflections collected= 9511, Independent reflections= 3445 (R_{int} = 0.0346), Completeness of data = 99.8 %, Number of parameters= 229, F(000) =712, GOF on F^2 = 1.210, Final R indices [I ≥ 2σ(I)] R1 = 0.0612, wR2 = 0.1235, R indices (all data) R1 = 0.0683, wR2 = 0.1261, Absolute structure parameter -0.2(17), Residual electron density 0.233 e.Å^{-3}. CCDC 1029784 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.

4.10.6. Synthesis and Characterization of Functionalized 2,4-dihydro-3*H*-pyrazol-3-ones

(*Z*)-2-(*tert*-Butyl)-5-phenyl-4-((*E*)-3-phenylallylidene)-2,4-dihydro-3*H*-pyrazol-3-one (54a)



Following the general procedure, treatment of cinnamaldehyde **53a** (33 mg, 32 μL, 0.25 mmol) and 2-(*tert*-butyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-pyrazol-3-one **49a** (54 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*Z*)-2-(tert-butyl)-5-phenyl-4-((*E*)-3-phenylallylidene)-2,4-dihydro-3*H*-pyrazol-3-one **54a** as a red oil (75.0 mg, 91% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.66.

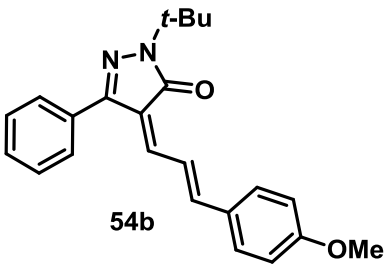
^{1}H NMR (400 MHz, CDCl3) δ 8.69 (dd, J_1 = 15.6 Hz, J_2 = 11.7 Hz, 1H), 7.72 – 7.55 (m, 4H), 7.53 – 7.42 (m, 3H), 7.42 – 7.29 (m, 4H), 7.15 (d, *J* = 15.6 Hz, 1H), 1.64 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.15, 148.92, 148.34, 145.39, 135.86, 131.76, 130.63, 129.20, 129.06, 128.95, 128.65, 128.17, 125.40, 123.92, 57.85, 28.55.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{23}ON_2$: 331.1805, found: 331.1814.

FTIR (cm^{-1}) 3733, 2975, 2358, 2177, 1986, 1986, 1589, 1486, 1205, 1106, 1019, 979, 762, 891, 700, 445.

(*Z*)-2-(*tert*-Butyl)-4-((*E*)-3-(4-methoxyphenyl)allylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (54b)



54b

Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **53b** (40.5 mg, 0.25 mmol) and 2-(*tert*-butyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-pyrazol-3-one **49a** (54 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*Z*)-2-(tert-butyl)-4-((*E*)-3-(4-methoxyphenyl)allylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **54b** as a red oil (87.0 mg, 97% yield).

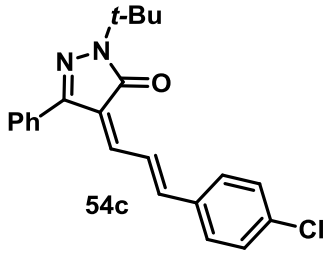
R$_f$ (Pet. ether /EtOAc = 90/10): 0.5.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.66 (dd, J_1 = 15.7 Hz, J_2 = 11.7 Hz, 1H), 7.82 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.67 – 7.57 (m, 3H), 7.53 – 7.43 (m, 3H), 7.41 – 7.32 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 1.64 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 165.29, 158.20, 148.41, 146.43, 143.66, 132.10, 131.95, 129.09, 128.90, 128.63, 128.22, 124.93, 124.71, 123.86, 121.09, 111.25, 57.77, 55.74, 28.58. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{22}H_{25}O_2N_2$: 361.1911, found: 361.1911.

FTIR (cm^{-1}) 3061, 2962, 2929, 2364, 2339, 2184, 1587, 1486, 1465, 1277, 1207, 1105, 993, 807, 701, 649, 502.

(*Z*)-2-(*tert*-Butyl)-4-((*E*)-3-(4-chlorophenyl)allylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (54c)



54c

Following the general procedure, treatment of (*E*)-3-(4-chlorophenyl)acrylaldehyde **53d** (41.6 mg, 0.25 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (54 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*Z*)-2-(*tert*-butyl)-4-((*E*)-3-(4-chlorophenyl)allylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **54c** as a red oil (90.0 mg, 99% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.66.

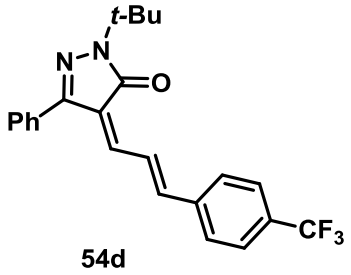
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, J_1 = 15.6 Hz, J_2 = 11.6 Hz, 1H), 7.60 – 7.54 (m, 4H), 7.50 – 7.44 (m, 3H), 7.36 – 7.29 (m, 3H), 7.08 (d, J = 15.6 Hz, 1H), 1.63 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.07, 148.27, 147.02, 144.80, 136.46, 134.35, 131.65, 129.66, 129.34, 129.25, 128.95, 128.13, 125.76, 124.33, 57.89, 28.52.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}ON_2Cl$: 365.1415, found: 365.1419.

FTIR (cm^{-1}) 3332, 3059, 2924, 2853, 2359, 1734, 1671, 1603, 1582, 1521, 1488, 1457, 1408, 1389, 1362, 1275, 1204, 1165, 1132, 1091, 1011, 977, 891, 814, 772, 761, 701, 650.

(*Z*)-2-(*tert*-Butyl)-5-phenyl-4-((*E*)-3-(4-(trifluoromethyl)phenyl)allylidene)-2,4-dihydro-3*H*-pyrazol-3-one (54d)



54d

Following the general procedure, treatment of (*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde **53e** (50.0 mg, 0.25 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (54 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether-EtOAc: 95:05) to afford (*Z*)-2-(*tert*-butyl)-5-phenyl-4-((*E*)-3-(4-(trifluoromethyl)phenyl)allylidene)-2,4-dihydro-3*H*-pyrazol -3-one **54d** as a red oil (89.0 mg, 90% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.66.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J_1 = 15.7 Hz, J_2 = 11.6 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.63 – 7.58 (m, 4H), 7.51 – 7.45 (m, 3H), 7.32 (d, J = 11.6 Hz, 1H), 7.14 (d, J = 15.7 Hz, 1H), 1.63 (s, 9H).

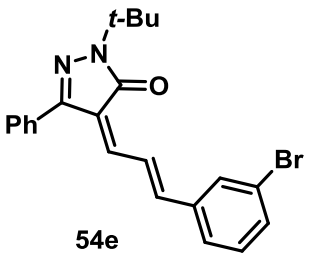
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.95, 148.25, 146.12, 144.14, 139.11, 131.89, 131.52, 129.36, 129.01, 128.55, 128.13, 126.73, 125.96, 58.00, 28.52.

HRMS (ESI) calculated $[M+H]^+$ for C23H22F_3ON_2: 399.1679, found: 399.1672.

FTIR (cm^{-1}) 3060, 2957, 2854, 2358, 1735, 1672, 1614, 1599, 1516, 1458, 1416, 1390, 1319, 1277, 1255, 1125, 1106, 1066, 976, 891, 824, 733, 679.

(*Z*)-4-((*E*)-3-(3-Bromophenyl)allylidene)-2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one (54e)

Following the general procedure, treatment of (*E*)-3-(3-bromophenyl)acrylaldehyde **53g** (52.8 mg, 0.25 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (54 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h



54e

followed by flash column chromatography (Pet. ether-EtOAc: 95:05) to afford (*Z*)-4-((*E*)-3-(3-bromophenyl)allylidene)-2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **54e** as a red oil (83.0 mg, 82% yield).

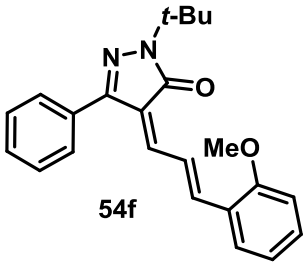
***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.66.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.65 (dd, J_1 = 15.6 Hz, J_2 = 11.6 Hz, 1H), 7.76 (s, 1H), 7.60-7.58 (m, 2H), 7.53 – 7.44 (m, 5H), 7.31 – 7.28 (m, 1H), 7.25-7.21 (m, 1H), 7.03 (d, *J* = 15.7 Hz, 1H), 1.63 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 164.97, 148.24, 146.61, 144.48, 137.90, 133.22, 131.58, 131.02, 130.48, 129.28, 128.96, 128.12, 127.09, 126.19, 125.01, 123.25, 57.92, 28.52. **HRMS (ESI)** calculated [M+H]$^+$ for $C_{22}H_{22}ON_2Br$: 409.0910, found: 409.0902.

FTIR (cm^{-1}) 3332, 3201, 3060, 2927, 1735, 1673, 1604, 1557, 1521, 1477, 1445, 1418, 1390, 1361, 1273, 1204, 1166, 1132, 1073, 1019, 978, 901, 854, 774, 680.

(*Z*)-2-(*tert*-Butyl)-4-((*E*)-3-(2-methoxyphenyl)allylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (54f)



54f

Following the general procedure, treatment of (*E*)-3-(2-methoxyphenyl)acrylaldehyde **53h** (40.5 mg, 0.25 mmol) and 2-(*tert*-Butyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-pyrazol-3-one **49a** (54 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*Z*)-2-(*tert*-Butyl)-4-((*E*)-3-(2-methoxyphenyl)allylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **54f** as a red oil (85.0 mg, 94% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.46.

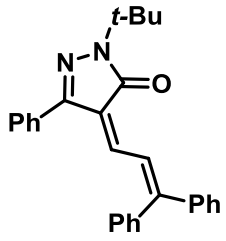
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.57 (dd, J_1 = 15.5 Hz, J_2 = 11.7 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 4H), 7.51 – 7.41 (m, 3H), 7.32 (d, *J* = 11.7 Hz, 1H), 7.10 (d, *J* = 15.5 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 1.64 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 165.35, 161.92, 149.10, 148.35, 146.05, 131.97, 130.52, 129.06, 128.88, 128.83, 128.18, 124.13, 121.97, 114.60, 57.74, 55.54, 28.56.

HRMS (ESI) calculated [M+H]$^+$ for $C_{22}H_{25}O_2N_2$: 361.1911, found: 361.1906.

FTIR (cm^{-1}) 2962, 2931, 2357, 2164, 1670, 1583, 1489, 1365, 1226, 1133, 979, 824, 807, 762, 584.

(*Z*)-2-(*tert*-Butyl)-4-(3,3-diphenylallylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (54g)



54g

Following the general procedure, treatment of 3,3-diphenylacrylaldehyde **53q** (52 mg, 0.25 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (54 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*Z*)-2-(*tert*-butyl)-4-(3,3-diphenylallylidene)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **54g** as a red oil (66.0 mg, 65% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.76.

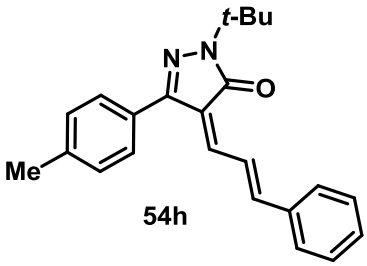
^{1}H NMR (500 MHz, CDCl$_3$) δ 8.63 (d, *J* = 12.0 Hz, 1H), 7.48 – 7.43 (m, 8H), 7.37 – 7.32 (m, 6H), 7.27-7.26 (m, 2H), 1.64 (s, 9H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 165.29, 159.29, 148.27, 143.16, 140.66, 138.07, 131.70, 130.98, 130.07, 129.32, 129.19, 128.95, 128.71, 128.60, 128.34, 127.84, 125.20, 122.67, 57.81, 28.56.

HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{27}ON_2$: 407.2118, found: 407.2106.

FTIR (cm^{-1}) 3329, 3057, 3076, 2363, 1667, 1591, 1522, 1486, 1445, 1389, 1364, 1330, 1276, 1195, 1156, 1107, 1076, 1020, 999, 935, 867, 769, 645.

(*Z*)-2-(*tert*-Butyl)-4-((*E*)-3-phenylallylidene)-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one (54h)



54h

Following the general procedure, treatment of cinnamaldehyde **53a** (40.5 mg, 0.25 mmol) and 2-(*tert*-butyl)-5-(p-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one **49b** (58 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*Z*)-2-(*tert*-butyl)-4-((*E*)-3-phenylallylidene)-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one **54h** as a red oil (82.0 mg, 95% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.7.

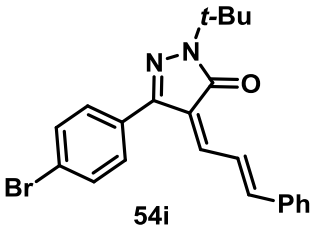
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.60 (dd, J_1 = 15.6 Hz, J_2 = 11.6 Hz, 1H), 7.56 (dd, J_1 = 6.3 Hz, J_2 = 2.5 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.36 – 7.26 (m, 3H), 7.21 (dd, J_1 = 12.9 Hz, J_2 = 4.8 Hz,, 3H), 7.06 (d, *J* = 15.6 Hz, 1H), 2.34 (s, 3H), 1.56 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 165.16, 148.70, 145.28, 139.25, 135.91, 130.58, 129.64, 129.05, 128.63, 128.07, 125.62, 123.96, 57.75, 28.56, 21.51.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{25}O_2N_2$: 345.1961, found: 345.1957.

FTIR (cm^{-1}) 3026, 2956, 2919, 2850, 2360, 2339, 2035, 1673, 1590, 1388, 1276, 1169, 1017, 978, 688, 566.

(*Z*)-5-(4-Bromophenyl)-2-(*tert*-butyl)-4-((*E*)-3-phenylallylidene)-2,4-dihydro-3*H*-pyrazol-3-one (54i)



Following the general procedure, treatment of cinnamaldehyde **53a** (33.0 mg, 32 µL 0.25 mmol) and 5-(4-bromophenyl)-2-(*tert*-butyl)-2,4-dihydro-3*H*-pyrazol-3-one **49c** (74.0 mg, 0.25 mmol) in THF (2.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*Z*)-5-(4-bromophenyl)-2-(*tert*-butyl)-4-((*E*)-3-phenylallylidene)-2,4-dihydro-3*H*-pyrazol-3-one **54i** as a red oil (70.0 mg, 69% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.73.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J_1 = 15.6 Hz, J_2 = 11.6 Hz, 1H), 7.67 – 7.62 (m, 4H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.39 (m, 3H), 7.31 (d, *J* = 11.6 Hz, 1H), 7.18 (d, *J* = 15.6 Hz, 1H), 1.65 (s, 9H).

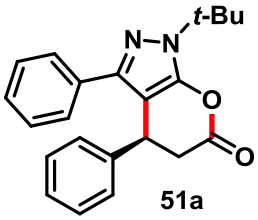
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.03, 149.31, 147.09, 145.26, 135.77, 132.13, 130.77, 130.69, 129.61, 129.08, 128.70, 124.98, 123.82, 123.45, 57.96, 28.52.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}ON_2Br$: 409.0910, found: 409.0902.

FTIR (cm^{-1}) 3062, 2976, 2930, 1668, 1602, 1587, 1510, 1480, 1450, 1383, 1315, 1282, 1203, 1169, 1133, 1105, 1069, 1009, 977, 889, 831, 781, 721, 687, 649.

4.10.7. Synthesis and Characterization of Dihydropyranopyrazoles

(*S*)- 1-(*tert*-Butyl)-3,4-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51a)



Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 µL, 0.50 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)- 1-(*tert*-butyl)-3,4-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51a** as a red oil (142.2 mg, 82% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.46.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 11.3 min, *Minor*: 13.6 min. er = 98:2; $[\alpha]_D^{25}$ = +19.36 (c 0.1, $CHCl_3$).

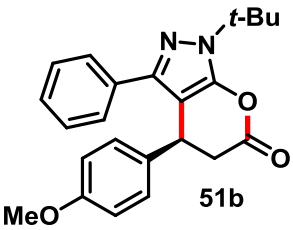
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.33-7.21 (m, 6H), 7.15 (d, *J* = 8.3 Hz, 2H), 4.43 (dd, J_1 = 2.3 Hz, J_2 = 7.4 Hz, 1H), 3.16 (dd, J_1 = 7.6 Hz, J_2 = 15.9 Hz, 1H), 2.94 (dd, J_1 = 2.3 Hz, J_2 =15.9 Hz, 1H), 1.74 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 148.3, 144.2, 141.6, 133.3, 129.3, 128.5, 127.6 (d, *J* = 5.8Hz), 126.9, 126.5, 97.7, 60.13, 38.76, 35.03, 29.16.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{23}O_2N_2$: 347.1754, found: 347.1751.

FTIR (cm^{-1}) 3228, 2978, 1791, 1496, 1367, 1258, 1116, 959, 849, 752, 665, 639, 526.

(*S*)-1-(*tert*-Butyl)-4-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51b)



Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **53b** (81.0 mg, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-Butyl)-4-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51b** as a red oil (111.0 mg, 59% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.37.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 11.3 min, *Minor*: 13.6 min. er = 98:2; $[\alpha]_D^{25}$ = -15.12 (c 0.1, $CHCl_3$).

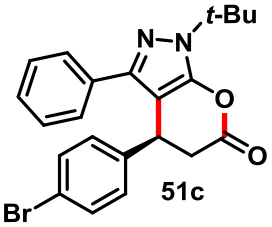
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.29-7.23 (m, 3H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H) 4.39 (dd, J_1 = 2.3 Hz, J_2 = 7.3 Hz, 1H), 3.78 (s, 3H), 3.13 (dd, J_1 = 7.3 Hz, J_2 = 15.4Hz, 1H), 2.97 (dd, J_1 = 2.3 Hz, J_2 =15.4 Hz, 1H), 1.73 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.01, 159.04, 148.32, 144.24, 133.67, 133.45, 128.62, 128.05, 127.73, 126.60, 114.70, 98.14, 60.20, 55.40, 39.08, 34.32, 29.22.

HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{25}O_3N_2$: 377.1860, found: 377.1856.

FTIR (cm^{-1}) 3063, 2838, 1788, 1578, 1463, 1247, 1095, 1051, 995, 696, 511.

(*S*)-4-(4-bromophenyl)-1-(*tert*-Butyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51c)



Following the general procedure, treatment of (*E*)-3-(4-bromophenyl)acrylaldehyde **53c** (106.0 mg, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to **(***S*)-4-(4-bromophenyl)-1-(*tert*-Butyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-on**e 51c** as a red oil (130.0 mg, 61% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.48.

HPLC (Chiralcel OD-RH, 75:25 ACN / H_2O, 0.5 mL/min) *Major*: 9.9 min, *Minor*: 16.2 min.er = 96.5:3.5; $[\alpha]_D^{25}$ = -19.72 (c 0.1, $CHCl_3$).

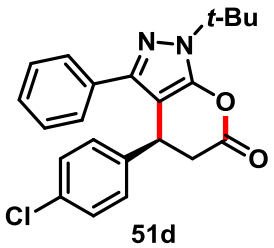
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 4H),), 7.29-7.24 (m, 3H), 7.03 (d, J = 7.8 Hz, 2H), 4.41 (dd, J_1 = 2.3 Hz, J_2 = 7.8 Hz, 1H), 3.17(dd, J_1 = 8.3 Hz, J_2 = 15.7Hz, 1H), 2.95 (dd, J_1 = 2.3 Hz, J_2 =15.7 Hz, 1H), 1.72 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.49, 148.33, 144.23, 140.68, 133.26, 132.52, 128.75, 128.69, 127.90, 126.53, 121.66, 97.16, 60.33, 38.62, 34.62, 29.21.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}O_2N_2Br$: 425.0859, found: 425.0857.

FTIR (cm^{-1}) 3064, 2934, 2359, 1791, 1572, 1074, 4050, 960, 826, 776, 634, 587, 542, 516.

(*S*)-1-(*tert*-Butyl)-4-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51d)



Following the general procedure, treatment of (*E*)-3-(4-chlorophenyl)acrylaldehyde **53d** (83.0 mg, 0.50 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-butyl)-4-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51d** as a yellow solid (118.0 mg, 62% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.56.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 9.2 min, *Minor*: 12.3 min. er = 95:5; $[\alpha]_D^{25}$ = -26.32 (c 0.1, $CHCl_3$).

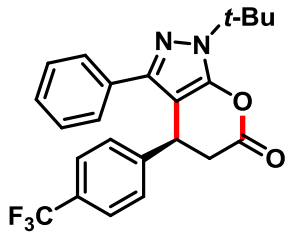
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.37 – 7.27 (m, 5H), 7.11 (d, J = 8.4 Hz, 2H), 4.52 – 4.41 (m, 1H), 3.18 (dd, J_1 = 15.6 Hz, J_2 = 7.4 Hz, 1H), 2.97 (dd, J_1= 15.7 Hz, J_2 = 2.3 Hz, 1H), 1.75 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.49, 148.31, 144.25, 140.15, 133.53, 133.26, 129.54, 128.66, 128.39, 127.87, 126.52, 97.23, 60.31, 38.67, 34.54, 29.19.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}O_2N_2Cl$: 381.1364, found: 381.1364.

FTIR (cm^{-1}) 3565, 3063, 2982, 2934, 1790, 1732, 1687, 1594, 1572, 1488, 1461, 1368, 1265, 1133, 1100, 1014, 887, 756, 696.

(*S*)-1-(*tert*-Butyl)-3-phenyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51e)



51e

Following the general procedure, treatment of (*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde **53e** (100.0 mg, 0.50 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-butyl)-3-phenyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51e** as a yellow oil (101.0 mg, 49% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.43.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 8.6 min, *Minor*: 11.7 min. er = 95:5; $[\alpha]_D^{25}$ = -6.86 (c 0.1, $CHCl_3$).

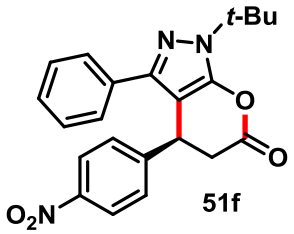
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 2H), 7.50 – 7.42 (m, 2H), 7.33 – 7.24 (m, 5H), 4.52 (dd, J_1 = 7.3Hz, J_2 = 2.0 Hz, 1H), 3.21 (dd, J_1 = 15.7Hz, J_2 = 7.4 Hz, 1H), 2.99 (dd, J_1= 15.7Hz, J_2 = 2.5 Hz, 1H), 1.75 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.28, 148.36, 145.64, 144.31, 133.21, 128.70, 127.95, 127.46, 126.52, 126.43, 126.39, 96.86, 60.41, 38.45, 34.97, 29.19.

HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{22}O_2N_2F_3$: 415.1628, found: 415.1624.

FTIR (cm^{-1}) 3566, 3064, 2983, 2936, 2358, 1790, 1694, 1617, 1595, 1572, 1486, 1461, 1369, 1323, 1266, 1246, 1165, 1109, 1068, 994, 840, 757, 696, 650.

(*S*)-1-(*tert*-Butyl)-4-(4-nitrophenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51f)



Following the general procedure, treatment of (*E*)-3-(4-nitrophenyl)acrylaldehyde **53f** (133.0 mg, 0.75 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (108.1 mg, 0.5 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-Butyl)-4-(4-nitrophenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51f** as a red oil (140.0 mg, 72% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.53.

HPLC (Chiralcel OD-RH, 75:25 ACN / H_2O, 0.5 mL/min) *Major*: 9.0min, *Minor*: 13.2 min. er = 94:6; $[\alpha]_D^{25}$ = -13.76 (c 0.1, $CHCl_3$).

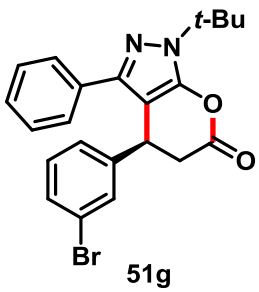
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.41-7.40 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.26-7.25 (m, 3H), 4.43 (dd, J_1 = 2.3 Hz, J_2 = 7.3 Hz, 1H), 3.25(dd, J_1 = 7.5Hz, J_2 = 16.5 Hz, 1H), 2.97 (dd, J_1 = 2.3 Hz, J_2 =16.0 Hz, 1H), 1.73(s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.91, 148.92, 148.31, 147.55, 144.33, 133.03, 28.74, 128.03, 126.49, 124.68, 96.3, 60.54, 38.20, 35.04, 29.20.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}O_4N_3$: 392.1605, found: 392.1602.

FTIR (cm^{-1}) 3111, 2871, 1790, 1600, 1519, 1447, 1369, 1212, 1109, 961, 752, 666, 526.

(*S*)-4-(3-Bromophenyl)-1-(*tert*-butyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51g)



Following the general procedure, treatment of (*E*)-3-(3-bromophenyl)acrylaldehyde **53g** (105.0 mg, 0.50 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-4-(3-bromophenyl)-1-(*tert*-butyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51g** as a yellow oil (120.0 mg, 57% yield).

R_f (Pet. ether /EtOAc = 90/10): 0.50.

HPLC (Chiralcel OD-RH, 75:25 ACN / H_2O, 0.5 mL/min) *Major*: 10.0 min, *Minor*: 16.8 min.er = 94:6; $[\alpha]_D^{25}$ = -20.13 (c 1.0, $CHCl_3$).

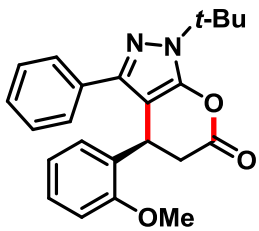
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.8 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.33-7.28 (m, 4H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 4.42 (dd, J_1 = 7.2 Hz, J_2 =2.1 Hz, 1H), 3.17 (dd, J_1 = 15.7 Hz, J_2 = 7.4 Hz, 1H), 2.98 (dd, J_1 = 15.7 Hz, *J*2 = 2.4 Hz, 1H), 1.76 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.35, 148.34, 144.27, 143.92, 133.19, 130.92, 130.19, 128.65, 127.87, 126.52, 125.60, 123.40, 96.85, 60.31, 38.59, 34.74, 29.17.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}O_2N_2Br$: 425.0859, found: 425.0857.

FTIR (cm^{-1}) 2981, 2933, 1788, 1592, 1517, 1521, 1485, 1426, 1368, 1266, 1178, 1073, 886, 752, 669.

(*S*)-1-(tert-Butyl)-4-(2-methoxyphenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51h)



51h

Following the general procedure, treatment of (*E*)-3-(2-methoxyphenyl)acrylaldehyde **53h** (81.0 mg, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(tert-Butyl)-4-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51h** as a red oil (133.0 mg, 71% yield).

R_f (Pet. ether /EtOAc = 90/10): 0.34.

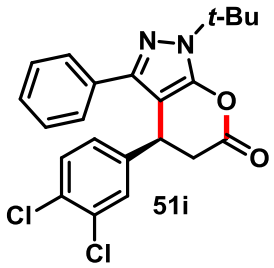
HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Minor*: 11.6 min, *Major*: 13.3 min. er = 96:4; $[\alpha]_D^{25}$ = -19.56 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.3 Hz, 2H), 7.28-7.22 (m, 4H), 6.93 (dd, J_1 = 6.9 Hz, J_2 = 15.3 Hz, 2H), 6.84 (t, *J* = 7.5 Hz, 1H), 4.67-4.65 (m, 1H), 3.84 (s, 3H), 3.06-3.03 (m, 2H), 1.73 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.46, 156.48, 148.75, 144.31, 133.56, 129.60, 128.92, 128.51, 128.44, 127.64, 127.64, 126.71, 120.94, 97.16, 60.06, 55.01, 36.27, 30.55, 29.20. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{23}H_{25}O_3N_2$: 377.1860, found: 377.1848.

FTIR (cm^{-1}) 3566, 3063, 2838, 1786, 1519, 1461, 1334, 1241, 1135, 1051, 995, 957, 888, 752, 666, 635, 510.

(*S*)-1-(*tert*-Butyl)-4-(3,4-dichlorophenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51i)



Following the general procedure, treatment of (*E*)-3-(3,4-dichlorophenyl)acrylaldehyde **53i** (66.0 mg, 64 µL, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-Butyl)-4-(3,4-dichlorophenyl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51i** as a red oil (120.0 mg, 58% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.35.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 14.5 min, *Minor*: 20.7 min. er = 96:4; $[\alpha]_D^{25}$ = -11.40 (c 0.1, $CHCl_3$).

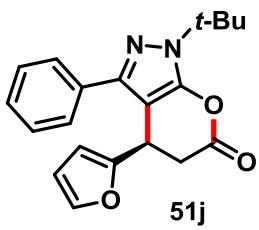
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.0 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.31 – 7.21 (m, 4H), 6.96 (dd, *J* = 8.3, 1.8 Hz, 1H), 4.39 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H), 3.15 (dd, J_1 = 15.7 Hz, J_2 = 7.4 Hz, 1H), 2.93 (dd, J_1 = 15.7 Hz, J_2 = 2.3 Hz, 1H), 1.72 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.10, 148.32, 144.28, 141.86, 133.45, 133.12, 131.93, 131.35, 129.13, 128.72, 127.99, 126.50, 126.37, 96.53, 60.43, 38.45, 34.35, 29.18.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{21}O_2N_2Cl_2$: 415.0975, found: 415.0974.

FTIR (cm^{-1}) 3194, 2549, 2414, 2360, 2197, 2094, 1978, 1507, 1396, 1210, 824, 693, 554.

(*R*)-1-(*tert*-Butyl)-4-(furan-2-yl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51j)



Following the general procedure, treatment of (*E*)-3-(furan-2-yl)acrylaldehyde **53j** (61.0 mg, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet.

ether- EtOAc: 95:05) to afford (*R*)-1-(*tert*-Butyl)-4-(furan-2-yl)-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51j** as a red oil (126.0 mg, 75% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.51.

HPLC (Chiralcel OD-RH, 85:15 ACN / H_2O, 0.5 mL/min) *Major*: 5.2 min, *Minor*: 6.8 min. er = 91:9; (the e.r. value of **6aj** was improved to >99.9:0.1 upon single crystallization in isopropanol.) $[\alpha]_D^{25}$ = +26.56 (c 0.1, $CHCl_3$).

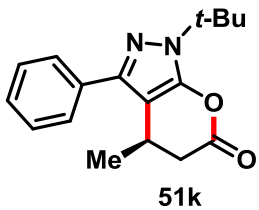
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H), 7.40 – 7.26 (m, 4H), 6.26 (dd, J_1 = 3.1, J_2 = 1.9 Hz, 1H), 6.01 (d, J = 3.2 Hz, 1H), 4.47 (dd, J_1 = 6.8 Hz, J_2 = 1.3 Hz, 1H), 3.21 (dd, J_1= 15.8 Hz, J_2 = 2.0 Hz, 1H), 3.02 (dd, J_1=15.8 Hz J_2 = 7.0 Hz, 1H), 1.70 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.66, 154.06, 148.13, 144.03, 142.82, 133.39, 128.72, 127.89, 126.59, 110.50, 106.93, 96.14, 60.25, 35.46, 29.17.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{21}O_3N_2$: 337.1547, found: 337.1544.

FTIR (cm^{-1}) 3063, 2980, 1786, 1597, 1486, 1334, 1241, 1095, 1023, 995, 696, 586, 510.

(*R*)-1-(*tert*-Butyl)-4-methyl-3-phenyl-4,5-dihydropyrano[2,3-c]pyrazol-6(1*H*)-one (51k)



51k

Following the general procedure, treatment of (*E*)-but-2-enal **53k** (35.0 mg, 41 µL, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*R*)-1-(*tert*-Butyl)-4-methyl-3-phenyl-4,5-dihydropyrano[2,3-c]pyrazol-6(1*H*)-one **51k** as a red oil (142.2 mg, 81% yield).

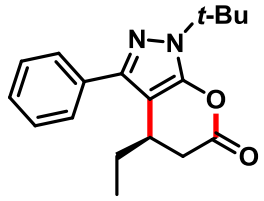
***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.45; er = 92:8; $[\alpha]_D^{25}$ = +32.60 (c 0.1, $CHCl_3$). **HPLC** (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 9.0 min, *Minor*: 10.3 min. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.3 Hz 1H), 3.47 – 3.32 (m, 1H), 2.91 (dd, J = 15.7, 6.7 Hz, 1H), 2.69 (dd, J = 15.7, 2.7 Hz, 1H), 1.67 (s, 9H), 1.30 (d, J = 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.74, 147.02, 143.28, 134.03, 128.68, 127.68, 126.42, 100.86, 59.90, 37.40, 29.12, 24.37, 21.61.

HRMS (ESI) calculated $[M+H]^+$ for $C_{27}H_{21}O_2N_2$: 285.1598, found: 285.1594.

FTIR (cm^{-1}) 3061, 2933, 2358, 1791, 1487, 1398, 1268, 1138, 1025, 858, 774, 677, 533.

(*R*)-1-(*tert*-Butyl)-4-ethyl-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51l)



51l

Following the general procedure, treatment of (*E*)-pent-2-enal **53l** (42.0 mg, 51 μL, 0.50 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*R*)-1-(*tert*-butyl)-4-ethyl-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51l** as a yellow oil (104.4 mg, 70% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.56.

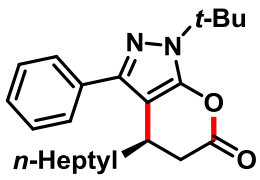
HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 10.7 min, *Minor*: 12.1 min. er = 97:3; $[\alpha]_D^{25}$ = +50.71 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.34-7.28 (m, 1H), 3.30-3.25 (m, 1H), 2.94-2.83 (m, 2H), 1.75-1.54 (m, 11H), 0.91(t, *J* = 7.5Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.03, 147.41, 143.56, 134.24, 128.67, 127.57, 126.44, 99.56, 59.89, 34.48, 30.65, 29.12, 28.70, 10.86.

HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{23}O_2N_2$: 299.1754, found: 299.1753.

FTIR (cm^{-1}) 3240, 2971, 1791, 1706, 1459, 1367, 1214, 1122, 1052, 1019, 953, 752, 692, 665, 538.

(*R*)-1-(*tert*-Butyl)-4-heptyl-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51m)



51m

Following the general procedure, treatment of (*E*)-dec-2-enal **53m** (77.0 mg, 92 μL, 0.50 mmol) and 2-(*tert*-butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h

followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*R*)-1-(*tert*-butyl)-4-heptyl-3-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51m** as a yellow oil (74.0 mg, 40% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.66.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 8.2 min, *Minor*: 8.9 min. er = 95:5; $[\alpha]_D^{25}$ = -35.19 (c 1.0, $CHCl_3$).

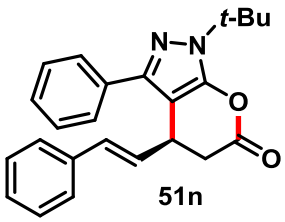
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 3.31-3.26 (m, 1H), 2.91 – 2.81 (m, 2H), 1.66 – 1.60 (m, 10H), 1.26 – 1.19 (m, 11H), 0.85 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.06, 147.33, 143.54, 134.24, 128.67, 127.69, 126.51, 100.08, 59.91, 35.72, 34.88, 31.82, 29.43, 29.24, 29.15, 26.38, 22.71, 14.19.

HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{33}O_2N_2$: 369.2537, found: 369.2534.

FTIR (cm^{-1}) 3566, 3061, 2955, 2936, 2854, 1789, 1716, 1593, 1572, 1485, 1460, 1367, 1268, 1227, 1135, 1072, 1024, 888, 813, 755, 725, 694.

(*S*,*E*)-1-(*tert*-Butyl)-3-phenyl-4-styryl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51n)



Following the general procedure, treatment of (2*E*,4*E*)-5-phenylpenta-2,4-dienal **53n** (79.0 mg, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*,*E*)-1-(*tert*-Butyl)-3-phenyl-4-styryl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51n** as a red oil (135.0 mg, 72% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.37.

HPLC (Chiralcel OD-RH, 85:15 ACN / H_2O, 0.5 mL/min) *Major*: 6.3 min, *Minor*: 11.9min. er = 88:12; $[\alpha]_D^{25}$ = -41.16 (c 0.1, $CHCl_3$).

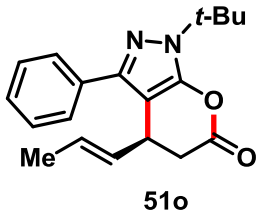
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.23 (m, 6H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.30 (dd, *J* = 15.8, 5.5 Hz, 1H), 4.03 (d, *J* = 2.9 Hz, 1H), 2.99 (t, *J* = 5.1 Hz, 1H), 1.72 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.10, 147.72, 144.27, 136.37, 133.53, 132.06, 129.26, 128.72, 128.66, 128.47, 127.95, 127.85, 126.65, 126.57, 126.41, 97.22, 77.48, 77.16, 76.84, 60.16, 36.30, 32.29, 29.16.

HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{25}O_2N_2$: 373.1911, found: 373.1910.

FTIR (cm^{-1}) 3061, 2931, 2361, 1789, 1573, 1318, 1214, 1074, 858, 750, 693, 580, 515.

(*S*,*E*)-1-(*tert*-Butyl)-3-phenyl-4-(prop-1-en-1-yl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51o)



Following the general procedure, treatment of (2*E*,4*E*)-hexa-2,4-dienal **53o** (48.0 mg, 53.4 µL, 0.50 mmol) and 2-(*tert*-Butyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*,*E*)-1-(*tert*-Butyl)-3-phenyl-4-(prop-1-en-1-yl)-4,5-dihydropyrano[2,3-c]pyrazol-6(1*H*)-one **51o** as a red oil (126.0 mg, 81% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.48.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 9.4 min, *Minor*: 10.8 min. er = 90:10; $[\alpha]_D^{25}$ = +33.16 (c 0.1, $CHCl_3$).

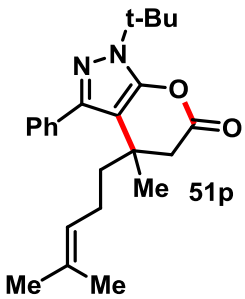
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 5.57 (dd, J_1 = 15.7 Hz, J_2 =4.8 Hz, 1H), 5.52 – 5.44 (m, 1H), 3.79 (brs, 1H), 3.01 – 2.78 (m, 1H), 1.68 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.52, 143.99, 130.66, 128.63, 127.93, 127.71, 126.52, 97.89, 77.48, 77.16, 76.84, 60.01, 36.51, 31.92, 29.16, 17.81.

HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{23}O_2N_2$: 311.1754, found: 311.1749.

FTIR (cm^{-1}) 3243, 2977, 2934, 2361, 1789, 1707, 1488, 1368, 1279, 1210, 1074, 1020, 969, 848, 757, 563.

1-(*tert*-Butyl)-4-methyl-4-(4-methylpent-3-en-1-yl)-3-phenyl-4,5-dihydropyrano[2,3- c]pyrazol-6(1*H*)-one (51p)



Following the general procedure, treatment of (*E*)-3,7-dimethylocta- 2,6-dienal **53p** (76 mg, 86 µL, 0.50 mmol) and 2-(*tert*-butyl)-5-phenyl- 2,4-dihydro-3H-pyrazol-3-one **49a** (162.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford 1-(*tert*-Butyl)-4-methyl-4-(4-methylpent-3-en-1-yl)-3-phenyl-4,5-dihydropyrano[2,3- c]pyrazol-6(1H)-one **51p** as a red oil (170 mg, 93% yield).

Rf (Pet. ether /EtOAc = 80/20): 0.61.

HPLC (kromasil 5-Amycoat, 99.8:0.2 Pet.ether / IPA, 0.5 mL/min) Major: 14.4 min, Minor: 16.8 min. er = 62:38, ; $[\alpha]_D^{25}$ = -41.16 (c 0.1, $CHCl_3$).

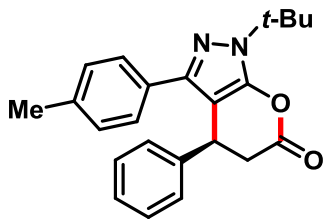
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 2H), 7.43 – 7.28 (m, 3H), 4.86 (t, *J* = 6.9 Hz, 1H), 2.72 (d, *J* = 15.6 Hz, 1H), 2.51 (d, *J* = 15.6 Hz, 1H), 1.89 – 1.83 (m, *J* 1H), 1.78 – 1.74 (m, 1H), 1.73 – 1.67 (m, 1H), 1.66 (s, 9H), 1.61 (s, 3H), 1.55 – 1.47 (m, 1H), 1.44 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.49, 146.51, 145.49, 135.31, 132.21, 129.47, 128.22, 128.02, 123.41, 103.56, 59.81, 42.70, 41.47, 34.48, 29.14, 27.74, 25.70, 23.40, 17.57.

HRMS (ESI) calculated [M+H]+ for $C_{23}H_{31}O_2N_2$: 367.2380, found: 367.2379.

FTIR (cm^{-1}) 3062, 3026, 2981, 2870, 1788, 1710, 1567, 1368, 1245, 1180, 1131, 1047, 960, 864, 824, 719.

(*S*)-1-(*tert*-Butyl)-4-phenyl-3-(*p*-tolyl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51q)



51q

Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 μL, 0.50 mmol) and 2-tert-Butyl-5-p-tolyl-2,4-dihydro-pyrazol-3-one **49b** (172.0 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-butyl)-4-phenyl-3-(*p*-tolyl)-4,5-dihydropyrano[2,3-c]pyrazol-6(1H)-one **51q** as a yellow oil (120.0 mg, 67% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.53; er = 95:5.

HPLC (kromasil 5-Amycoat, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 11.3 min, *Minor*: 21.9 min. $[\alpha]_D^{25}$ = -52.96 (c 0.1, $CHCl_3$).

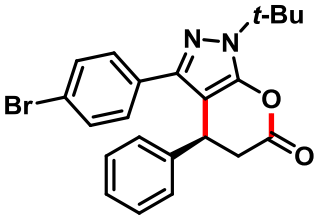
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28-7.27 (m, 1H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.43 (dd, J_1 = 7.3 Hz, J_2 = 2.0 Hz, 1H), 3.17 (dd, J_1 = 15.7 Hz, J_2 = 7.4 Hz, 1H), 2.99 (dd, J_1 = 15.6 Hz, J_2 = 2.2 Hz, 1H), 2.31 (s, 3H), 1.75 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165. 94, 144.33, 141.75, 137.47, 129.33, 129.29, 127.62, 126.96, 126.46, 97.52, 60.09, 38.81, 35.08, 29.22, 21.31.

HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{25}O_2N_2$: 361.1911, found: 361.1909.

FTIR (cm^{-1}) 3062, 3026, 2933, 1788, 1710, 1596, 1567, 1488, 1450, 1368, 1265, 1180, 1047, 1029, 960, 824, 719, 699.

(*S*)-3-(4-Bromophenyl)-1-(*tert*-butyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51r)



51r

Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 µL, 0.50 mmol) and 5-(4-bromophenyl)-2-(*tert*-butyl)-2,4-dihydro-3*H*-pyrazol-3-one **49c** (221.4 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-3-(4-bromophenyl)-1-(*tert*-butyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51r** as a yellow oil (129.7 mg, 61% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.46.

HPLC (Chiralcel OD-RH, 70:30 ACN / H_2O, 0.5 mL/min) *Major*: 10.2 min, *Minor*: 17.3 min.er = 95:5; $[\alpha]_D^{25}$ = +13.24 (c 0.1, $CHCl_3$).

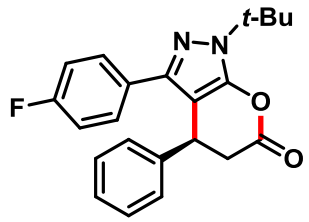
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 6H), 7.28 – 7.26 (m, 1H), 7.13 (d, J = 7.1 Hz, 2H), 4.40 (dd, J_1 = 7.4 Hz, J_2 = 2.3 Hz, 1H), 3.17 (dd, J_1 = 15.7 Hz, J_2 = 7.4 Hz, 1H), 2.99 (dd, J_1 = 15.7 Hz, J_2 = 2.5 Hz, 1H), 1.73 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.59, 148.49, 143.23, 141.39, 132.40, 131.70, 129.45, 128.11, 127.83, 126.91, 121.76, 97.79, 60.37, 38.72, 35.13, 29.18.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}O_2N_2Br$: 425.0859, found: 425.0857.

FTIR (cm^{-1}) 3258, 3063, 3029, 2935, 2836, 2358, 1791, 1735, 1710, 1691, 1517, 1488, 1456, 1368, 1177, 1128, 1105, 1041, 994, 886, 784, 699.

(*S*)-1-(*tert*-Butyl)-3-(4-fluorophenyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51s)



51s

Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 µL, 0.50 mmol) and 2-(*tert*-butyl)-5-(4-fluorophenyl)-2,4-dihydro-3H-pyrazol-3-one **49d** (175.7 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-butyl)-3-(4-

fluorophenyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51s** as a red oil (110.0 mg, 61% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.42.

HPLC (Chiralcel OD-H, 99:01 Pet.ether / IPA, 0.5 mL/min) *Major*: 13.5 min, *Minor*: 21.8 min. er = 95:5; $[\alpha]_D^{25}$ = +174.42 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.17 – 7.15 (m, 2H), 6.99 – 6.95 (m, 2H), 4.41 (dd, J_1 = 7.3 Hz, J_2 = 2.4 Hz, 1H), 3.18 (dd, J_1= 15.7 Hz, J_2 = 7.4 Hz, 1H), 3.00 (dd, J_1 = 15.7 Hz, J_2 = 2.6 Hz, 1H), 1.75 (s, 9H).

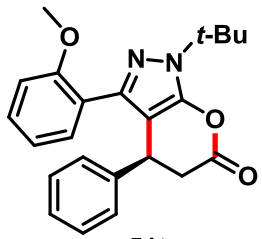
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.69, 162.52 (d, *J* = 247 Hz), 148.42, 143.52, 141.51,

129.64 (d, *J* = 3 Hz), 129.42, 128.33 (d, *J* = 8.1 Hz), 127.79, 126.95, 115.50 (d, *J* = 22 Hz), 97.57, 60.25, 38.79, 35.13, 29.20.

HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{22}O_2N_2F$: 365.1660, found: 365.1658.

FTIR (cm^{-1}) 3019, 2978, 2933, 2360, 1807, 1708, 1604, 1511, 1455, 1368, 1281, 1215, 1175, 1156, 1116, 1022, 944, 841, 748, 698.

(*S*)-1-(*tert*-Butyl)-3-(2-methoxyphenyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51t)



51t

Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 μL, 0.50 mmol) and 2-tert-Butyl-5-(2-methoxy-phenyl)-2,4-dihydro-pyrazol-3-one **49e** (184.7 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to (*S*)-1-(*tert*-butyl)-3-(2-methoxyphenyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51t** as a yellow oil (80.0 mg, 43% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.43.

HPLC (Chiralcel OD-RH, 70:30 ACN / H_2O, 0.5 mL/min) *Major*: 8.0 min, *Minor*: 9.5 min. er = 95:5; $[\alpha]_D^{25}$ = -33.76 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J_1 = 7.5 Hz, J_2 = 1.7 Hz, 1H), 7.21 – 7.10 (m, 4H), 7.03 – 7.01 (m, 2H), 6.90 (td, J_1 = 7.5 Hz, J_2 = 0.8 Hz, 1H), 6.63 (d, *J* = 8.2 Hz,

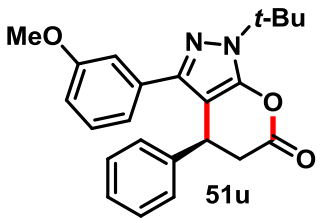
1H), 4.31 (t, J = 6.2 Hz, 1H), 3.33 (s, 3H), 3.08 (dd, J_1 = 15.7 Hz, J_2 = 6.6 Hz, 1H), 2.85 (dd, J_1 = 15.7 Hz, J_2 = 5.8 Hz, 1H), 1.72 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.60, 156.75, 142.82, 141.96, 130.69, 129.45, 128.52, 126.91, 126.84, 122.92, 120.65, 110.29, 100.02, 59.95, 54.69, 39.19, 35.88, 29.29.

HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{25}O_3N_2$: 377.1860, found: 377.1857.

FTIR (cm^{-1}) 3566**,** 3060, 3027, 2934, 2359, 1785, 1736, 1688, 1592, 1488, 1455, 1398, 1366, 1299, 1246, 1179, 1110, 1077, 1056, 1026, 987, 959, 818, 885, 796, 748, 700.

(*S*)-1-(*tert*-Butyl)-3-(3-methoxyphenyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51u)



Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 µL, 0.50 mmol) and 2-(*tert*-Butyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-pyrazol-3-one **49f** (185 mg, 0.75 mmol) with triazolium salt **4** (9.1 mg, 0.025 mmol), and the oxidant **5** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(tert-Butyl)-3-(3-methoxyphenyl)-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51u** as a red oil (152.0 mg, 81% yield).

R$_f$ (Pet. ether /EtOAc = 90/10): 0.35.

HPLC (Chiralcel OD-RH, 70:30 ACN / H_2O, 0.5 mL/min) *Major*: 17.3 min, *Minor*: 13.6 min. er = 90:10; $[\alpha]_D^{25}$ = -6.40 (c 0.1, $CHCl_3$).

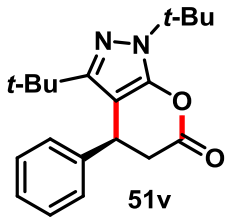
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.4 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.20-7.15 (m, 3H), 7.09 (d, J = 7.6 Hz, 1H), 6.98 (brs, 1H), 6.78 (dd, J_1 = 7.8 Hz, J_2 = 2.0 Hz, 1H), 4.43 (d, J = 5.7 Hz, 1H), 3.60 (s, 2H), 3.16 (dd, J_1 = 15.6 Hz, J_2 = 7.5 Hz, 1H), 2.98 (dd, J_1 = 15.6 Hz, J_2 = 2.0 Hz, 1H), 1.73 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.83, 159.80, 144.26, 141.72, 134.72, 129.70, 129.39, 127.74, 127.01, 119.06, 114.23, 111.48, 97.69, 60.25, 55.15, 38.83, 35.13, 29.22.

HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{25}O_3N_2$: 377.1860, found: 377.1857.

FTIR (cm^{-1}) 3260, 2935, 2362, 1791, 1711, 1601, 1517, 1318, 1287, 1128, 1041, 963, 844, 699, 518.

(*S*)-1,3-di-*tert*-Butyl-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51v)



Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 µL, 0.50 mmol) and 2,5-di-*tert*-Butyl-2,4-dihydro-3*H*-pyrazol-3-one **49g** (147.2 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1,3-di-*tert*-Butyl-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51v** as a red oil (123.0 mg, 75% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.62.

HPLC (Chiralcel OD-RH, 75:25 ACN / H_2O, 0.5 mL/min) *Major*: 5.5 min, *Minor*: 6.0 min. er = 87:13; $[\alpha]_D^{25}$ = +10.96 (c 0.1, $CHCl_3$).

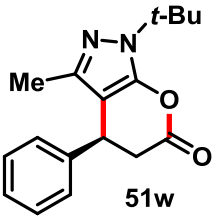
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 4.40 (d, *J* = 7.3 Hz, 1H), 3.17 (dd, J_1 = 15.5 Hz, J_2 =7.4 Hz, 1H), 2.90 (d, *J* = 15.6 Hz, 1H), 1.66 (s, 9H), 1.15 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.14, 152.70, 147.82, 142.60, 129.10, 127.39, 126.86, 96.32, 59.34, 39.14, 35.76, 33.68, 29.84, 29.17.

HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{27}O_2N_2$: 327.2067, found: 327.2067.

FTIR (cm^{-1}) 3063, 2961, 2868, 2359, 1789, 1458, 1331, 1283, 1229, 1178, 1022, 998, 817, 756, 700, 602, 572, 534.

(*S*)-1-(*tert*-Butyl)-3-methyl-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one (51w)



Following the general procedure, treatment of cinnamaldehyde **53a** (66.0 mg, 64 µL, 0.50 mmol) and 2-(*tert*-Butyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **49h** (116.0 mg, 0.75 mmol) with triazolium salt **A** (9.1 mg, 0.025 mmol), and the oxidant **B** (204.3 mg, 0.5 mmol) in toluene (5.0 mL) and stirring the reaction mixture at 25 °C for 12 h followed by flash column chromatography (Pet. ether- EtOAc: 95:05) to afford (*S*)-1-(*tert*-Butyl)-3-methyl-4-phenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one **51w** as a red oil (93.0 mg, 65% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.56; er = 93:7.

HPLC (Chiralcel OD-H, 50:50 ACN / H_2O, 0.5 mL/min) *Major*: 17.1 min, *Minor*: 18.7 min. $[\alpha]_D^{25}$ = +39.80 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 3H),7.15-7.14 (m, 2H), 4.15 (t, J = 6.4 Hz, 1H), 3.11 (dd, J_1 = 7.4 Hz, J_2 = 16.2 Hz, 1H), 2.91 (dd, J_1 = 6.0 Hz, J_2 =16.2 Hz, 1H), 1.86 (s, 3H), 1.63 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.29, 142.44, 129.15, 128.91, 127.60, 127.16, 98.60, 59.37, 38.27, 34.81, 29.26, 13.01.

HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{21}O_2N_2$: 285.1598, found: 285.1596.

FTIR (cm^{-1}) 3061, 2931, 2361, 1703, 1573, 1448, 1174, 1074, 1023, 925, 843, 580, 515.

4.11. References

1. For selected recent reviews on pyrazoles, see: (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (b) Schmidt, A.; Dreger, A. *Curr. Org. Chem*. **2011**, *15*, 1423. (c) Varvounis, G. *Adv. Heterocycl. Chem*. **2009**, *98*, 143.
2. Kuo, S.-C.; Huang, L.-J.; Nakamura, H. *J. Med. Chem.* **1984**, *27*, 539.
3. Huang, L.-J.; Hour, M.-J.; Teng, C.-M.; Kuo, S.-C. *Chem. Pharm. Bull*. **1992**, *40*, 2547.
4. Hartmut, S.; Wilhelm, B. Ger. Offen. DE 3243714A1, May 30, 1984
5. Bradley, D. M.; Chan, W. N.; Thewlis, K. M.; Ward, S. E. PCT/EP2007/061794; WO2008053031A1.
6. For a book on pyrazolone chemistry, see: (a) Varvounis, G. in *Pyrazol-3-ones*. Part IV: *Synthesis and Applications*, ed. Katritzky, A. R. *Advances in Heterocyclic Chemistry*, Academic Press, New York, **2009**, vol. *98*, p. 143. For a review, see: (b) Horton, D. A.; Bourne G. T.; Smythe, M. L. *Chem. Rev*., **2003**, *103*, 893.
7. (a) Brune, K. *Acute Pain* **1997**, *1*, 33. (b) Tainter, M. L.; *Ann. N.Y. Acad. Sci.* **1948**, *51*, 3.
8. Hadi, V.; Koh, Y.-H.; Sanchez, T. W.; Barrios, D.; Neamati, N.; Jung, K. W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6854.
9. Huang, H.; Yu, Y.; Gao, Z.; Zhang, Y.; Li, C.; Xu, X.; Jin, H.; Yan, W.; Ma, R.; Zhu, J.; Shen, X.; Jiang, H.; Chen, L.; Li, J. *J. Med. Chem.* **2012**, *55*, 7037.
10. For a recent review on asymmetric reactions of pyrazolones, see: Chauhan, P.; Mahajan. S.; Enders, D. *Chem. Commun*. **2015**, *51*, 12890.

11. (a) Companyo, X.; Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano A.; Rios, R. *Chem. Commun.* **2010**, *46*, 6953. (b) Alba, A.-N. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardia, M.; Mazzanti, A.; Moyano A.; Rios, R. *Eur. J. Org. Chem*. **2011**, 1318.
12. Enders, D.; Grossmann, A.; Gieraths, B.; Düzdemir, M.; Merkens, C. *Org. Lett*. **2012**, *14*, 4254.
13. Zhang, Y.; Wu, S.; Wang, S.; Fang, K.; Dong, G.; Liu, N.; Miao, Z.; Yao, J.; Li, J.; Zhang, W.; Sheng C.; Wang, W. *Eur. J. Org. Chem*. **2015**, 2030.
14. Wu, B.; Chen, J.; Li, M.-Q.; Zhang, J.-X.; Xu, X.-P.; Ji S.-J.; Wang, X.-W. *Eur. J. Org. Chem*. **2012**, 1318.
15. Wang, Z.; Yang, Z.; Chen, D.; Liu, X.; Lin L.; Feng, X. *Angew. Chem., Int. Ed*. **2011**, *50*, 4928.
16. Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin L.; Feng, X. *Angew. Chem., Int. Ed*. **2012**, *51*, 2776.
17. Li J.-H.; Du, D.-M. *RSC Adv*. **2014**, *4*, 14538.
18. Mazzanti, A.; Calbet, T.; Font-Bardia, M.; Moyano A.; Rios, R. *Org. Biomol. Chem*. **2012**, *10*, 1645.
19. Zhang, H.-M.; Lv, H.; Ye, S. *Org. Biomol. Chem*. **2013**, *11*, 6255.
20. Wang, L.; Li, S.; Chauhan, P.; Hack, D.; Philipps, A. R.; Puttreddy, R.; Rissanen, K.; Raabe, G.; Enders D. *Chem. Eur. J*. **2016**, *22*. DOI: 10.1002/chem.201600515.
21. (a) Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. *Adv. Synth. Catal*. **2013**, *355*, 1089. (b) Yetra, S. R.; Kaicharla, T.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. *Org. Lett*. **2013**, *15*, 5202. (c) Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A. T. *J. Org. Chem*. **2014**, *79*, 4245.
22. It is also likely that the pyrazolone **49a** could act as a base to generate the free carbene in solution
23. For reports on base-free NHC-organocatalysis, see: (a) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun*. **2011**, *47*, 8670. (b) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc*. **2010**, *132*, 8810.
24. CCDC-1029784.
25. For a report on the reaction of α,β-unsaturated acylazolium generated from related enals, see Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed*. **2012**, *51*, 9433.

26. Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.
27. (a) Samantha, R. C.; Maji, B.; De Sarkar, S.; Bergander, K.; Fröhlich, R.; Mück-Lichtenfeld, C.; Mayr, H.; Studer, A. *Angew. Chem., Int., Ed.* **2012**, *51*, 5234. (b) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266.
28. (a) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433. (b) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494. (c) Lyngvi, E.; Bode, J. W.; Schoenebeck, F. *Chem. Sci.* **2012**, *3*, 2346. (d) Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem., Int. Ed*. **2011**, *50*, 1673. (e) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378.
29. Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett*. **2015**, *17*, 1417
30. Wubea, A, A.; Hüfner, A.; Thomaschitz, C.; Blunder, M.; Kollroser, M.; Bauer, R.; Bucar F. *Bioorg. Med. Chem*. **2011**, *19*, 567.
31. Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem. Int. Ed*. **2014**, *53*, 5643.
32. Struble, J. R.; Bode, J. W. *Org. Synth.* **2010,** *87*, 362.
33. Sheldrick, G. M. SAINT 5.1 ed., Siemens Industrial Automation Inc., Madison, WI, 1995
34. SADABS, *Empirical Absorption Correction Program*, University of Göttingen, Göttingen, Germany, 1997.
35. Sheldrick, G. M. SHELXTL *Reference Manual: Version 5.1*, Bruker AXS, Madison,WI, 1997.
36. Sheldrick, G. M. SHELXL-97: *Program for Crystal Structure Refinement*, Universityof Göttingen, Göttingen, Germany, 1997.

CHAPTER 5

Enantioselective Synthesis of Spirocyclohexadienones by NHC-Catalyzed Formal [3+3] Annulation Reaction of Enals

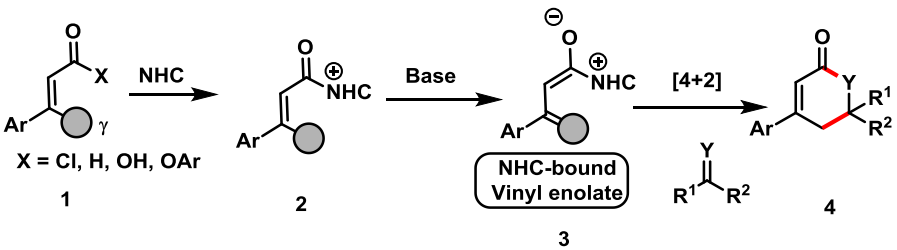
5.1. Introduction

The focal theme of the present chapter is the addition of vinylenolate (dienolate) to α,β-unsaturated acylazoliums under oxidative N-heterocyclic carbene (NHC)-catalysis. Although, the NHC-catalyzed addition of enolates to α,β-unsaturated acylazoliums are well known, the related dienolate addition in NHC-catalysis has received only scant attention. However, the generation of NHC-bound dienolates under NHC-catalysis followed by interception with electrophiles are well known. In the following sections, NHC-catalyzed reactions proceeding via the dienolate intermediates are presented.

5.1.1. Reactions involving Azolium Vinylenolates:

Recently, in NHC-organocatalysis, the NHC-bound vinyl enolates play a vital role in the construction of six-membered heterocycles and carbocycles via [4+2] cycloaddition reactions.[1] Reaction of α,β-unsaturated carbonyl compounds **1** having γ-proton with NHC could generate the α,β-unsaturated acylazolium intermediates **2**. Removal of γ-proton under basic conditions lead to the formation of key NHC-bound dienolates **3** (Scheme 5.1). Interestingly, these reactive species can undergo electrophilic additions at α- or at γ- carbons. In general, these nucleophilic NHC-bound dienolates undergoes [4+2] cycloaddition reactions.

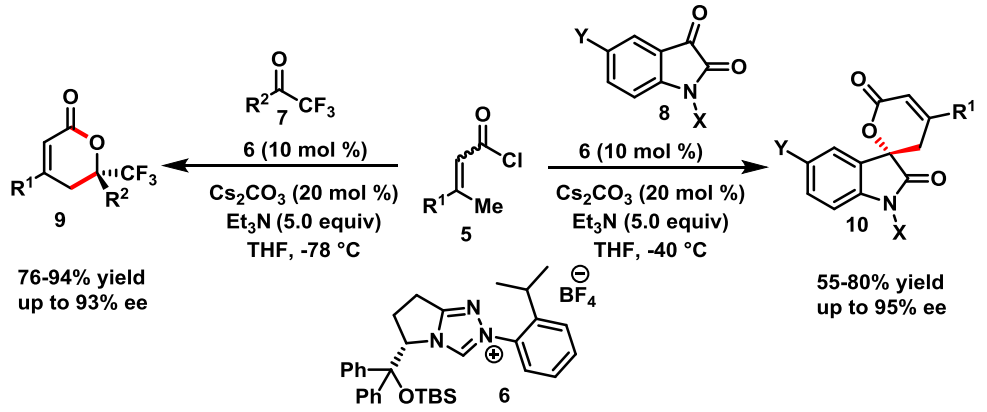
Scheme 5.1: Generation of NHC-bound Vinylenolates



In 2011, Ye and co-workers reported the catalytically generated NHC-bound dienolates from unsaturated acylchlorides **5** and NHC **6** (Scheme 5.2).[2] Interception of these intermediates with trifluoromethyl ketones **7** afforded the enantioselective

synthesis of trifluoromethyl substituted δ-lactones **9** in good yields (76-94%) with high enantioselectivity (up to 93%). Best results were obtained with NHC generated from **6** and catalytic amounts of Cs_2CO_3 in excess Et_3N. The authors also found that same optimized conditions are applicable to isatins **8** for the enantioselective synthesis of spirocyclic oxindole-δ-lactones **10**.

Scheme 5.2: Generation of NHC-bound Vinylenolates from Unsaturated Acylchlorides

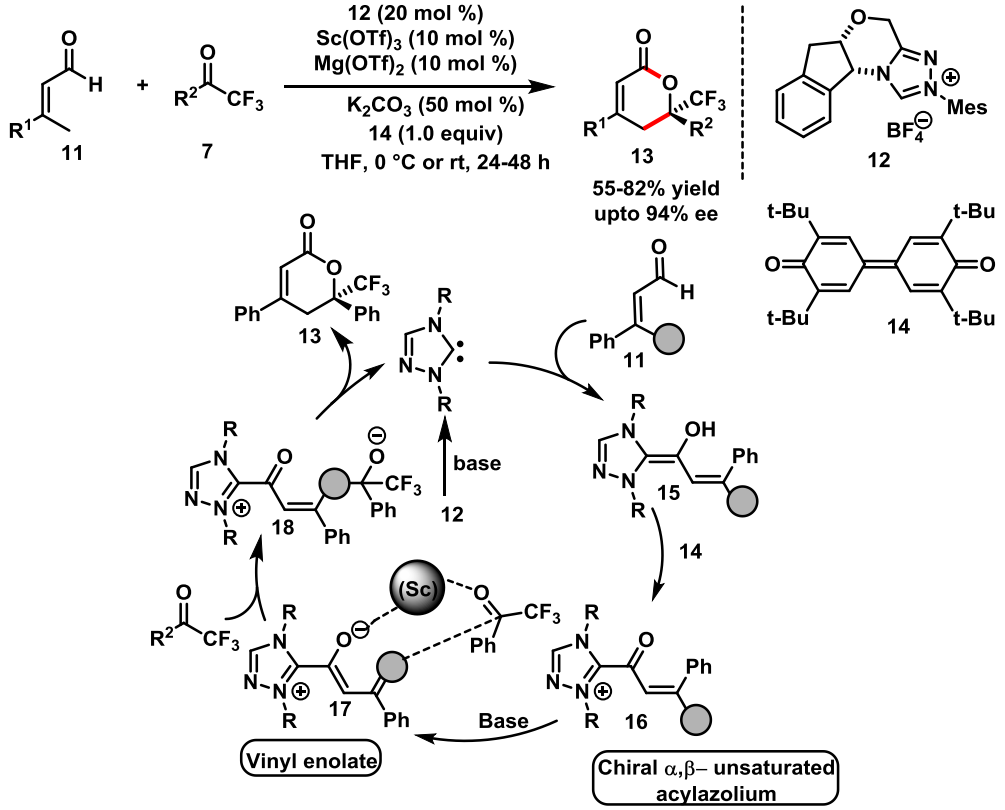


In 2012, Chi and co-workers demonstrated the oxidative NHC-catalyzed [4 + 2] cycloaddition of β,β'-disubstituted enals **11** with trifluoromethyl ketones **7** (Scheme 5.3).[3] Here, the NHC-bound dienolate intermediate was generated under oxidative NHC-catalysis. Notably, introduction of an extra substituent at β-carbon of the enal suppressed the generally observed homoenolate reactivity in NHC-mediated enal reactions. The successful oxidant (**14)** in oxidative NHC-catalysis for the oxidations of Breslow intermediates was found to be a best oxidant in this reaction as well. Substrate scope of enal includes phenyl rings with electon-withdrawing or -releasing substituents and heteroaromatic as well as alkenyl groups and furnished the desired products. In the case of trifluoromethyl ketones, aromatic and heteroaromatic ring as well as alkyl groups leads to the effective [4 + 2] annulation. In all the cases, the desired lactones are obtained in moderate to good yields (55-82%) with high enantioselectivity (up to 94% ee). The high selectivity is attained with chiral triazolium precatalyst **12** in conjunction with Sc/Mg-based Lewis acid co-catalyst.

The proposed mechanism involves the 1,2-addition of free carbene to α,β-unsaturated aldehyde **11** followed by proton transfer to afford the extended Breslow intermediate **15**. Oxidation of **15** with oxidant **14** gives the α,β-unsaturated acylazolium intermediate **16**. γ-deprotonation of α,β-unsaturated acylazolium **16** forms the key dienolate intermediate **17**. Nucleophilic addition of dienolate **17** to the trifluoromethyl ketone leads to the product dihydropyranone **13** and regenerates the NHC catalyst. The

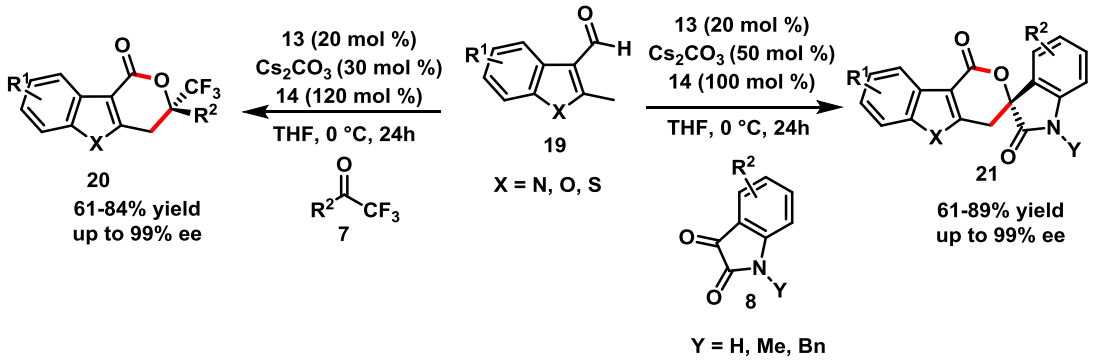
Lewis acid Sc(III) was involved in the coordination with reactants leading to the efficient [4+2] annulation.

Scheme 5.3: Generation of NHC-bound Vinylenolates from Unsaturated Aldehydes



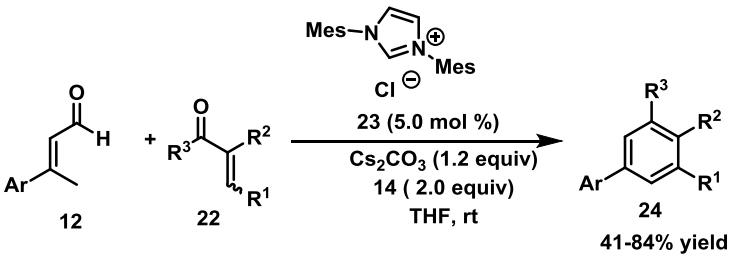
The same group later expanded the scope of enals to hetero aryl aldehydes **19** and reported the functionalization of benzylic C(sp^3)-H bonds (Scheme 5.4).[4] The reaction involves the NHC-catalyzed activation of the sp^3 carbon atom of *α*-branched indole 3-carboxaldehydes **19** to generate *ortho*-quinodimethane intermediates. The [4+2] cycloaddition reactions of **19** with trifluoromethyl ketones **7** afforded the indole fused dihydropyranones **20** in good yields (61-84%) with high ee values (up to 99%). On the other hand, with the same optimal conditions isatins **8** gave spirocyclic lactones **21**.

Scheme 5.4: Generation of NHC-bound Vinylenolates from Hetero Aryl Aldehydes



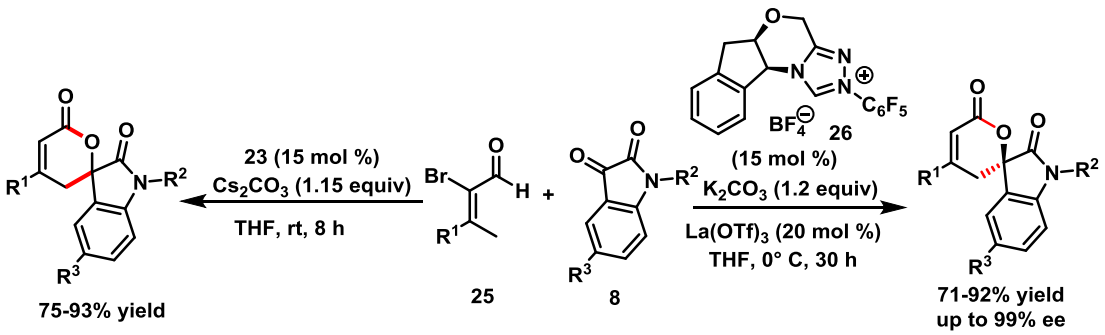
Very recently, the Chi group disclosed the construction of multi-substituted benzenes **24** via NHC-organocatalytic formal [3+3] annulation reaction (Scheme 5.5).[5] The reaction proceeds via generation of NHC-bound dienolate from enal **12** and carbene precursor **23** under oxidative conditions and its interception with enones **22** in formal [3+3] annulation. Enals **12** with aryl rings bearing both electron-withdrawing and -donating groups as well as hetero aryl groups worked well whereas in enone variation, aryl and alkyl groups were well tolerated. In all the cases, the substituted benzenes **24** were isolated in moderate to good yields (41-84%).

Scheme 5.5: Reactions of NHC-bound Vinylenolates with Enones



Alternatively, α-bromoenals **25** are employed as a NHC-bound vinyl enolate precursor by Yao and co-workers (Scheme 5.6).[6] The oxidant-free dienolate intermediates are generated by the reaction of α-bromoenal **25** and imidazolium carbene precursor **23** with excess Cs_2CO_3. Moreover, using carbene precursor **26**, the spirocyclic oxindole-dihydropyranones were obtained in good yields with excellent ee values (up to 99%). The high selectivities were accomplished using the combination of K_2CO_3 with catalytic amounts of Lewis acid $La(OTf)_3$.

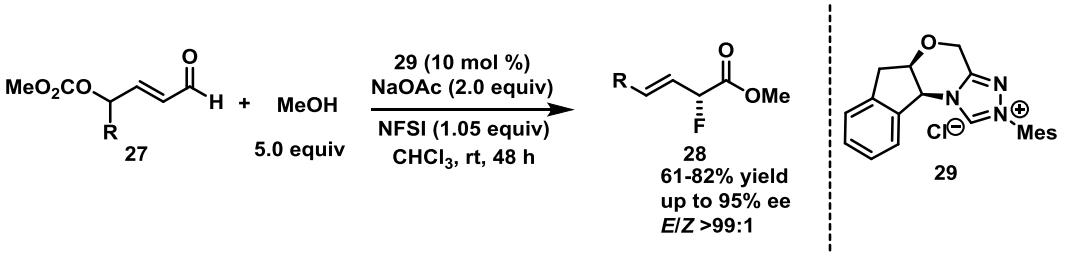
Scheme 5.6: Generation of NHC-bound Vinylenolates from α-Bromoenals



Sun and co-workers reported the generation of NHC-bound dienolates from enals **27** bearing a leaving group at the γ-carbon (Scheme 5.7).[7] This concept was utilized for the NHC-catalyzed α-fluorination of enals. Enantioselective synthesis of β,γ-unsaturated α-fluoroesters **28** were achieved by employing chiral triazolium

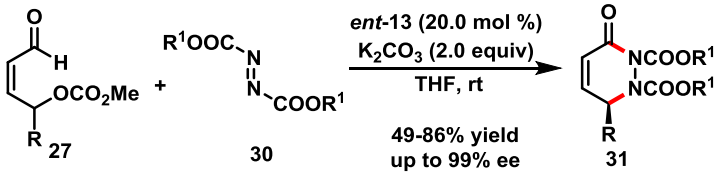
precatalyst **29** and NFSI as electrophilic fluorine source. A range of aryl-substituted enals **27** bearing a carbonate leaving group, with either electron-releasing or -withdrawing substituents on the phenyl ring are well tolerated (61-82%) to afford the product in moderate to good enantioselectivity (85-95% ee).

Scheme 5.7: NHC-Catalyzed α-Fluorination of Enals



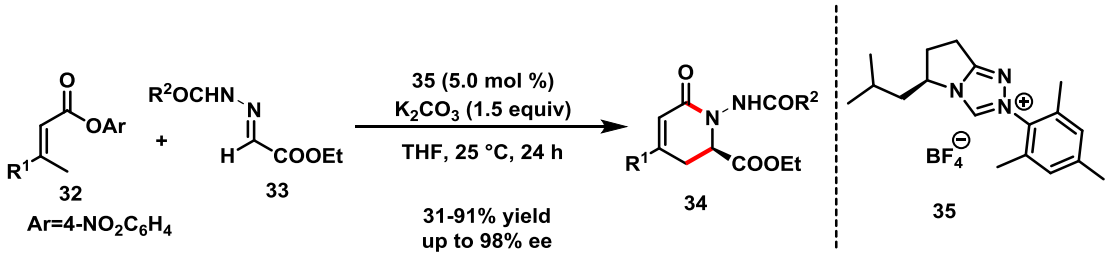
Independently, Ye and co-workers reported the generation of NHC-bound vinyl enolates from enals bearing a leaving group (**27**) and azodicarboxylates **30** as the electrophilic coupling partner. This formal NHC catalyzed [4+2] hetero Diels-Alder reaction resulted in the enantioselective synthesis of tetrahydropyridazinones **31** (Scheme 5.8).[8]

Scheme 5.8: Reactions of NHC-bound Vinylenolates with Azodicarboxylates



Recently, α,β-Unsaturated esters **32** were employed as the NHC-bound dienolate precursor for the γ-aminoalkylation reactions by Chi and co-workers (Scheme 5.9).[9] Reactions of α,β-unsaturated esters **32** with hydrazones **33** using *L*-leucine derived chiral triazolium salt **35** and K_2CO_3 afforded the enantioselective synthesis of δ-lactam products **34**.

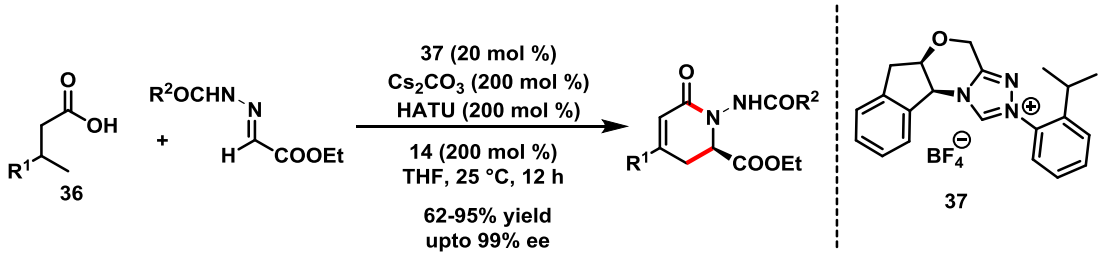
Scheme 5.9: Generation of NHC-bound Vinylenolates from α,β-Unsaturated Esters



Better results were obtained when saturated acids **36** were employed as NHC-bound dienolate precursors (Scheme 5.10).[10] Reaction of saturated acids **36** with

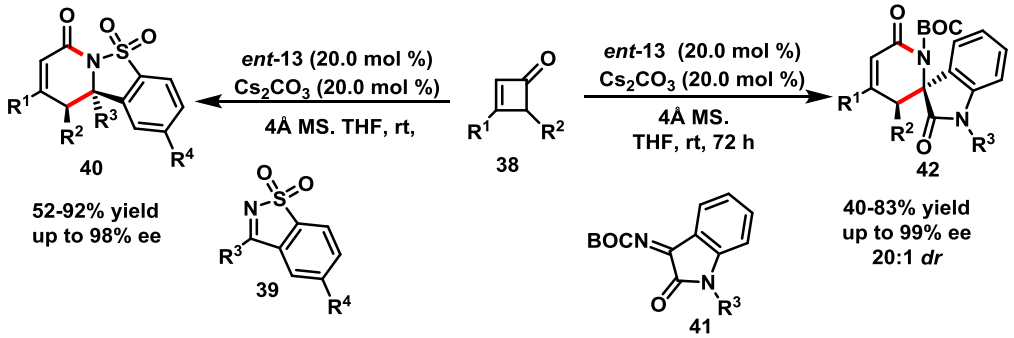
hydrazones using chiral triazolium salt **37** under oxidative conditions gave δ-lactam products **37** in good yields (65-95%) with excellent ee values (most cases 99%).

Scheme 5.10: Generation of NHC-bound Vinylenolates from Saturated Acids



Moreover, cyclobutenones **38** were demonstrated for the NHC-bound vinylenolate generation by Chi and co-workers (Scheme 5.11).[11] Here, the addition of NHC *ent*-**13** to cyclobutenones **38** initiate a C-C single bond cleavage, which is the key step to generate the NHC-bound dienolate intermediate. The interception of this intermediate with sulfonyl imines **39** afforded cyclic lactams **40** in 52-92% yield with good enantioselectivities (up to 98%). With the same optimized conditions, isatin imines gave spirolactams **42** in moderate to good yields (40-83%) with good selectivities (up to 20:1 *dr*).

Scheme 5.11: Generation of NHC-bound Vinylenolates from Cyclobutenones

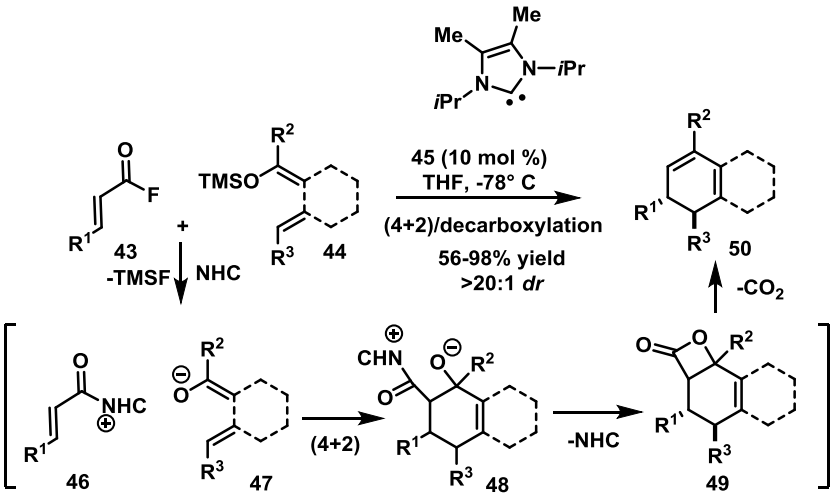


5.1.2. Reactions of Vinylenolates with α,β-Unsaturated Acylazolium Intermediates:

Lupton and co-workers disclosed the [4+2] cycloaddition reaction of silylated dienol ethers with α,β-unsaturated acylfluorides (Scheme 5.12).[12] This formal all-carbon [4 + 2] cycloaddition produced 1,3-cyclohexadienes in high yield with excellent diastereocontrol (*dr* >20:1). In this context, It is noteworthy that the previously reported NHC-bound dienolates are generated from α,β-unsaturated acylazolium intermediates whereas in this case the dienolates (generated from silyl enolethers) are intercepting with α,β-unsaturated acylazoliums. The mechanism involves the generation of α,β-unsaturated acylazoliums **46** from acylfluorides **43** and carbene **45** and its interception

with insitu formed dienolate **47** in [4+2] cyclization mode to form **48.** Subsequent lactonization affords lactone **49** and regeneration of free carbene **45**. Decarboxylation of **49** affords the final product **50.**

Scheme 5.12: NHC-catalyzed [4+2] Cycloaddition Reactions



5.2. Statement of the Problem

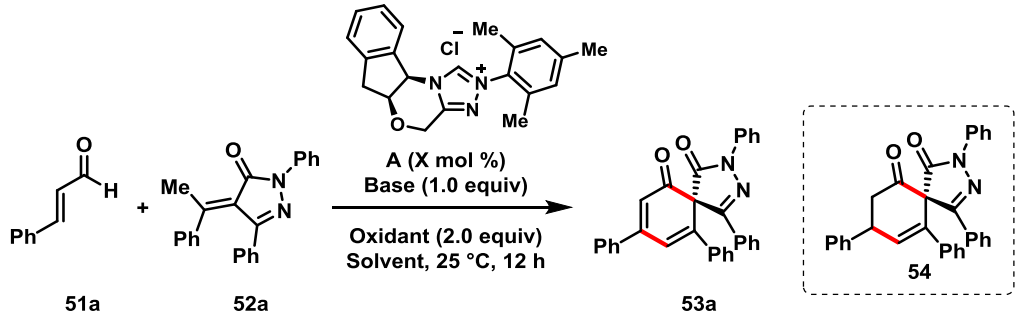
In recent times, NHC-catalysis has emerged as a powerful tool for enantioselective C-C and C-heteroatom bond-forming reactions through chiral *α,β*-unsaturated acylazolium intermediates. Interception of chiral *α,β*-unsaturated acylazolium intermediates with enolates and enamides are well explored for the enantioselective synthesis of dihydropyranones and dihydropyridinones.[13] Surprisingly, however, the reaction of dienolates[14] with *α,β*-unsaturated acylazolium has received only scant attention. Although Lupton's method[12] demonstrated the first report on dienolate addition to *α,β*-unsaturated acylazolium, prefunctionalized staring materials are needed and the reactions are not atom-economic. Moreover, the reaction failed in asymmetric transformations. Herein, we demonstrate the formal [3+3] annulation reaction of *α,β*-unsaturated aldehydes with *α*-arylidene pyrazolinones[15] under oxidative NHC-catalysis leading to the enantioselective synthesis of pyrazolone-fused spiro-1,3-cyclohexadienones.

5.3. Results and Discussion

5.3.1. Optimization Studies

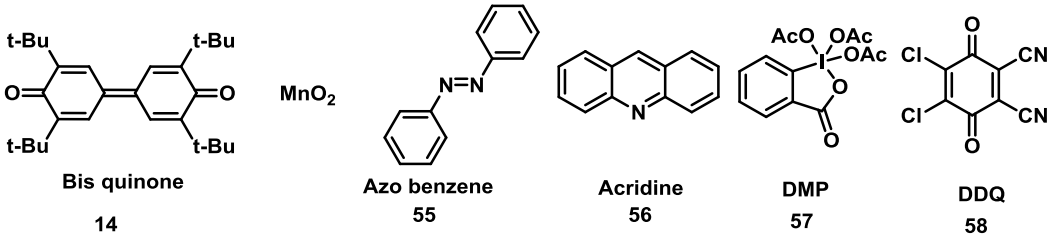
The present study commenced with the optimization of the reaction conditions for the vinylogous Michael addition/ spiroannulation cascade. In an pilot experiment, treatment of cinnamaldehyde **51a** with *α*-arylidene pyrazolinone **52a** in the presence of

Table 1. Optimization of the Reaction Conditions[a]



entry	Base	Solvent	Catalyst (mol %)	Oxidant	yield of **3** (%)[b]	ee of **3** (%)[c]
1	DBU	THF	5	**14**	50	98
2	DBU (Without A)	THF	5	**14**	-	-
3	With No base	THF	5	**14**	17	98
4	DBU (0°C to rt)	THF	5	**14**	50	98
5	DIPEA	THF	5	**14**	32	96
6	DABCO	THF	5	**14**	37	98
7	DMAP	THF	5	**14**	42	95
8	Na_2CO_3	THF	5	**14**	50	98
9	NEt_3	THF	5	**14**	55	90
10	KO^tBu	THF	5	**14**	30	90
11	DBU	toluene	5	**14**	32	99
12	DBU	DME	5	**14**	48	98
13	DBU	1,4-dioxane	5	**14**	45	98
14	DBU	DCM	5	**14**	35	98
15	DBU	THF	5 (24 h)	**14**	55	98
16	DBU	THF	10 (12 h)	**14**	60	98
17	DBU	THF	15(12 h)	**14**	75	98
18	**DBU**	**THF**	**15 (24 h)**	**14**	**84**	**98**
19	DBU	THF	15 (24 h)	**55**	40	-
20	DBU	THF	15 (24 h)	**56**	-	-
21	DBU	THF	15 (24 h)	**57**	-	-
22	DBU	THF	15 (24 h)	**58**	-	-
23[d]	DBU	THF	15 (24 h)	**59**	-	-

[a] Standard conditions: **51a** (0.375 mmol), **52a** (0.25 mmol), **A** (5 mol %), **14** (2.0 equiv), DBU (1.0 equiv), THF (6.0 mL), 25 °C and 12 h. [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC analysis on a chiral column[d] The reaction furnished the spirocyclohexenone **54** in 30% yield and 5:1 *dr*.

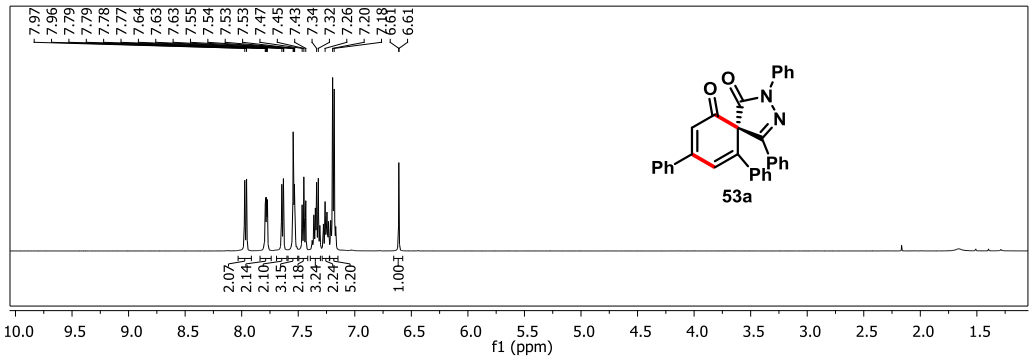


NHC generated from the chiral triazolium salt **A** under oxidative conditions using the quinone **14** and 1.0 equiv of DBU resulted in the formation of the pyrazolone-fused spiro-1,3-cyclohexadienone **53a** in 50% yield and 98%ee (Table 1, entry 1). As expected, product formation was not observed in the absence of catalyst **A** (entry 2). Interestingly, the spirocompound **53a** was formed in 12% with 98% ee when no base is used, but the reaction was very slugish with unreacted starting materials (entry 3).[16]

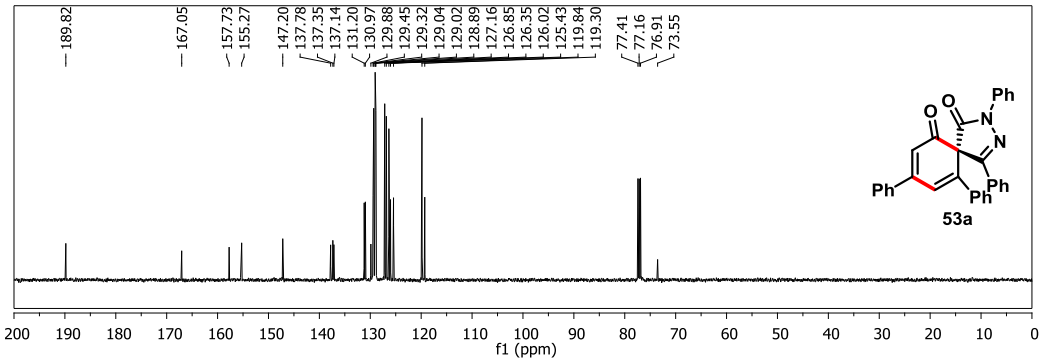
Lowering the reaction temperature did not affect the outcome of the reaction (entry 4). The reaction returned similar results when performed in Na_2CO_3 instead of DBU (entry 8) whereas the other bases such as DIPEA, DABCO, DMAP and KO*t*-Bu furnished inferior results (entries 5-7, 10). The use of Et_3N improved the yield, but reduced the ee (entry 9). A quick solvent screening revealed that solvents other than THF provided reduced yield of **53a** with comparable ee values under standard conditions (entries 11-14). The yield of **53a** was improved to 55% maintaining 98% ee when the reaction time was extended to 24 h (entry 15). Increasing the catalyst (**A**) loadings and reaction times improved the results of **53a** to 75% yield and 98% ee (entries 16-17), and finally with 15 mol % of **A**, in 24 h reaction time **53a** was isolated in 84% yield and in 98% ee (entry 18). Moreover, we evaluated various oxidants in this efficient spiro-annulation reactions and we observed that only MnO_2 afforded the corresponding spirocyclohexadienone **53a** in 40% yield whereas the other oxidants like azobenzene (**55**), acridine (**56**) and DMP (**57**) failed to afford **53a**. Interestingly DDQ (**58**) afforded the spirocyclohexenone **54** in 30% yield. The spectral data of **53a** has been provided in Section 5.3.2.

5.3.2. Spectral Data of 53a

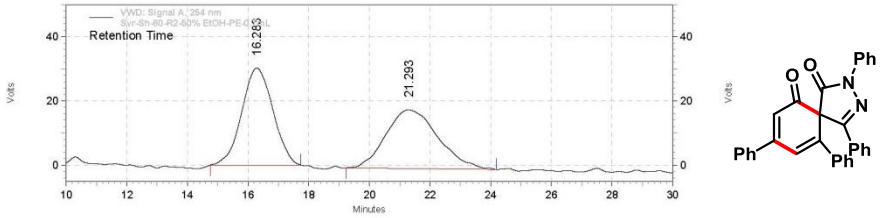
^{1}H NMR Spectrum of 53a ($CDCl_3$)



^{13}C NMR Spectrum of 53a ($CDCl_3$)



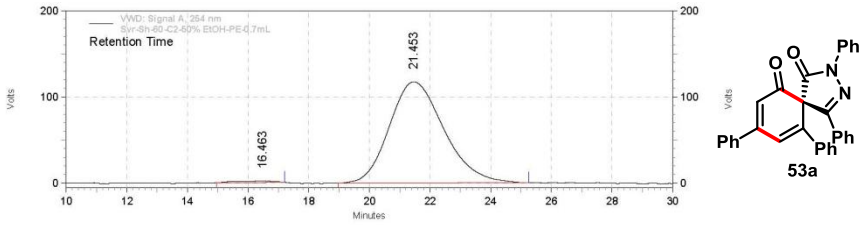
HPLC Chromatogram of Racemic-53a



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %
16.283	36230486	49.65
21.293	36747226	50.35
Totals	72977712	100.00

HPLC Chromatogram of Enantiomerically pure-53a



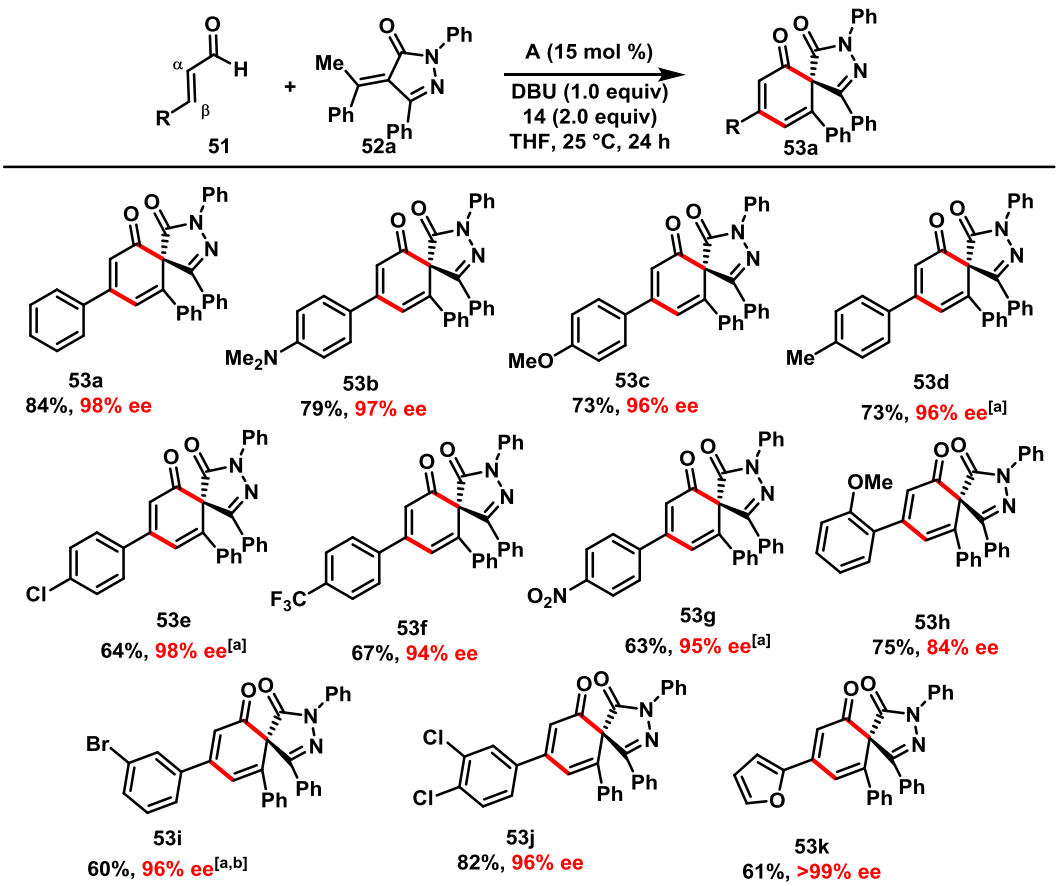
VWD: Signal A, 254 nm Results

Retention Time	Area	Area %
16.463	2608979	1.05
21.453	246777536	98.95
Totals	249386515	100.00

5.3.3. Enantioselective Synthesis of Spirocyclohexadienones:Variation of Enals

After deriving at the optimized reaction conditions, the scope of the reaction has been examined. First, we evaluated various α,β-unsaturated aldehydes (Scheme 5.13). A series of enals with electron-releasing as well as electron-withdrawing groups at the 4-position of the β-aryl ring are well-tolerated and furnished the pyrazolone-fused spirocyclohexadienones (**53a-53g**) in good yields and excellent ee values (>94% ee in all cases). Furthermore, enals having substitution at the 2-position and 3-position as well as di-substitution of β-aryl ring, were underwent efficient spiro-annulation with good yields and moderate to excellent ee values (**53h-53j**).

Scheme 5.13: Scope of the α,β-Unsaturated Aldehydes.



General conditions: **51** (0.75 mmol), **52a** (0.50 mmol), **A** (15.0 mol %), **14** (2.0 equiv), DBU (1.0 equiv), THF (12.0 mL) 25 °C and 24 h. Yields of isolated products are given and the *ee* value was determined by HPLC analysis on a chiral column. [a] Run on 0.25 mmol scale. [b] Structure and stereochemistry confirmed by X-ray analysis.

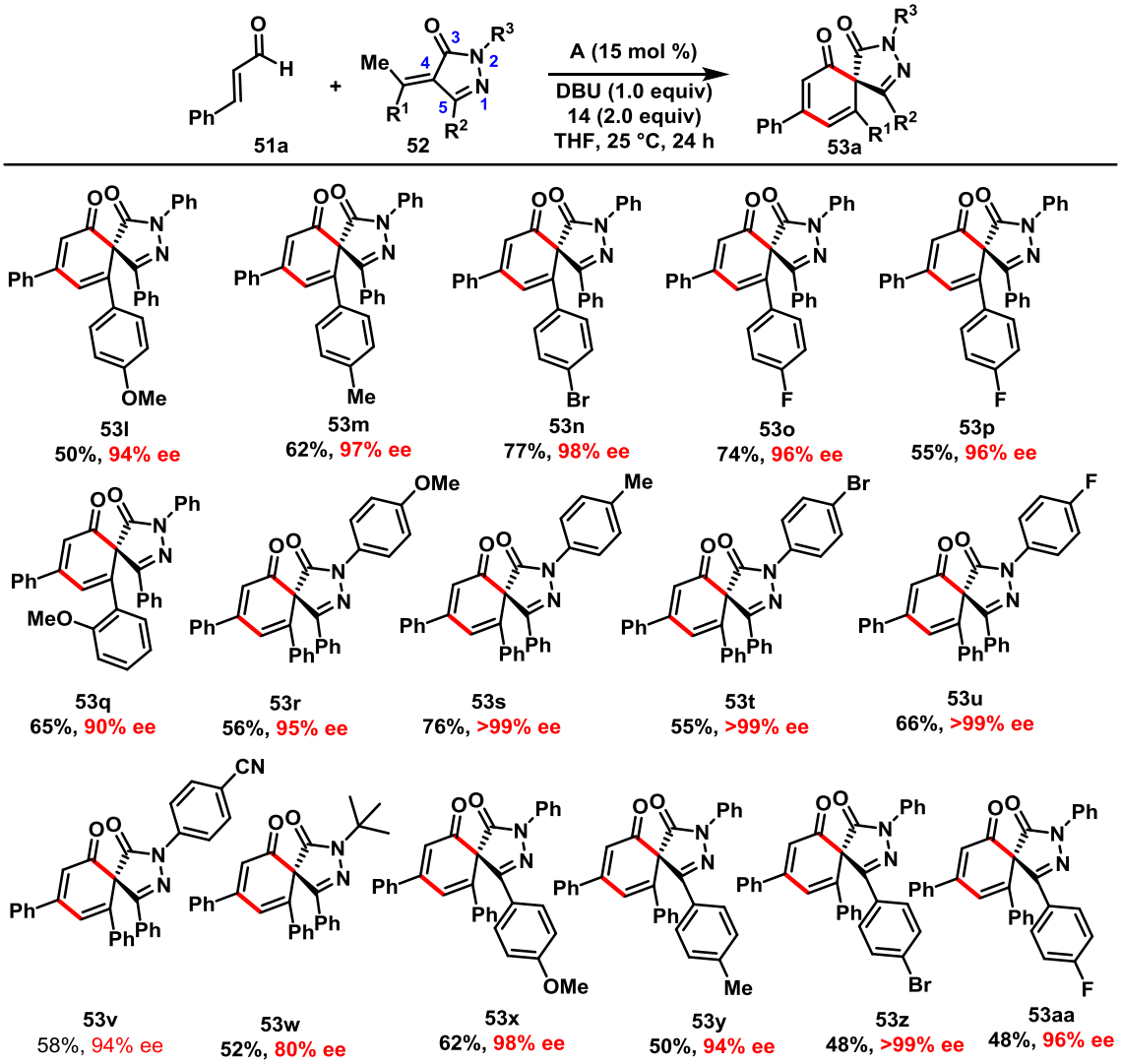
The structure and stereochemistry of the spirocentre in the bromo-derivative **53i** was confirmed by X-ray analysis (the stereochemistry of the spirocentre being *S*).[17]

Additionally, β-furyl enal also underwent smooth annulation reaction furnishing **53k** in 61% yield and >99% ee further expanding the scope of this formal [3+3] annulation.

5.3.4. Enantioselective Synthesis of Spirocyclohexadienones:Variation of α-Arylidene Pyrazolinone

Next, we evaluated the scope α-arylidene pyrazolinone moiety (Scheme 5.14). pyrazolinones having electron-releasing and -withdrawing groups on the arylidene moiety of **52** (R^1) underwent efficient annulation reaction furnishing the spirocyclic compounds in moderate to good yields and excellent ee values (**53l-53q**).

Scheme 5.14: Scope of the α-Arylidene Pyrazolinones



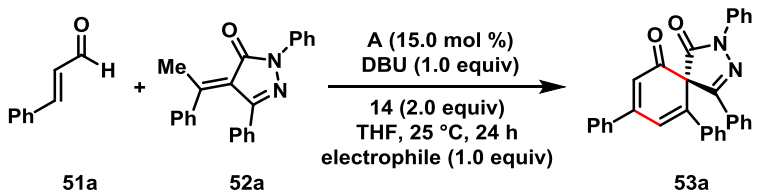
General conditions: **51** (0.75 mmol), **52a** (0.50 mmol), **A** (15.0 mol %), **14** (2.0 equiv), DBU (1.0 equiv), THF (12.0 mL) 25 °C and 24 h. Yields of isolated products are given and the *ee* value was determined by HPLC analysis on a chiral column. [a] Run on 0.25 mmol scale.

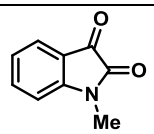
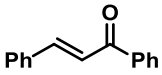
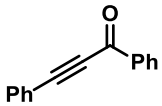
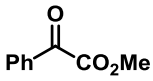
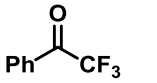
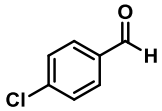
Moreover, variation on the *N*-aryl moiety (R^3) was also effective to furnish the desired product in high ee values (**53r-53v**). Notably the tolerance of functional groups

such as Br, NO_2 and CN allows further functionalization of the spirocyclohexadienones. Interestingly, *N*-Alkyl substitution like *N*-*tert*-butyl substituted pyrazolinone worked well to afford the desired product **53w** in 52% yield and 80% ee. In addition, electron releasing and -withdrawing groups at the aryl ring at the 5-position of **52** (R^2) are also well tolerated and afforded the target compounds in high ee values (**53x-53aa**).

5.3.5. Robustness with Electrophiles

Table 2. Screening of Electrophiles[a]



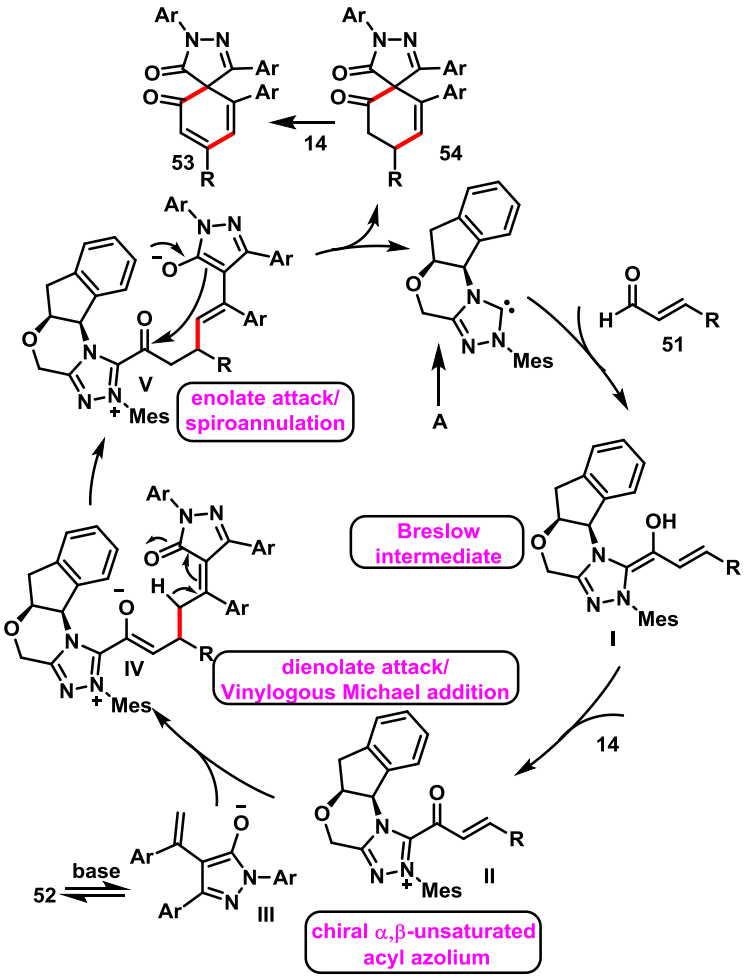
Entry	Electrophile	Yield of **3a** [%][b]	ee of **3a** [%][c]	Electrophile remaining [%][b]
1	None	84	98	---
2		82	8	99
3		70	98	83
4		84	98	90
5		80	98	95
6		65	96	63[d]
7		80	98	0

[a] Standard conditions: **51a** (0.375 mmol), **52a** (0.25 mmol), electrophile (0.25 mmol), **A** (15 mol %), **14** (2.0 equiv), DBU (1.0 equiv), THF (6.0 mL), 25 °C and 24 h. [b] Isolated yield of **3a** and additive remaining after column chromatography. [c] The *ee* value was determined by HPLC analysis on a chiral column. [d] Additive remaining determined by GC.

Next, we investigated the tolerance of this annulation reaction with commonly used electrophiles in NHC-catalysis.[18] Interestingly, the outcome of this annulation reaction did not affect with the addition of electrophiles such as *N*-methyl isatin, chalcone, ynone, and α-ketoester (Table 2, entries 2-5). In all the cases, the spirocompound **53a** was formed in good yields and ee values. Notably, the added electrophiles did not decompose under the reaction conditions indicating that the substrates having these functional groups are well tolerable under present reaction conditions. Moreover, the use of trifluoroacetophenone as the electrophile reduced the yield of **53a** to 65% and only 63% of the electrophile was recovered at the end of the reaction (entry 6). The use of 4-chlorobenzaldehyde as the electrophile did not affect the course of the reaction, but the aldehyde was decomposed under the reaction conditions demonstrating that -CHO moiety is not tolerated under the reaction conditions.

5.3.6. Plausible Mechanism

Scheme 5.15: Proposed Mechanism of the Reaction

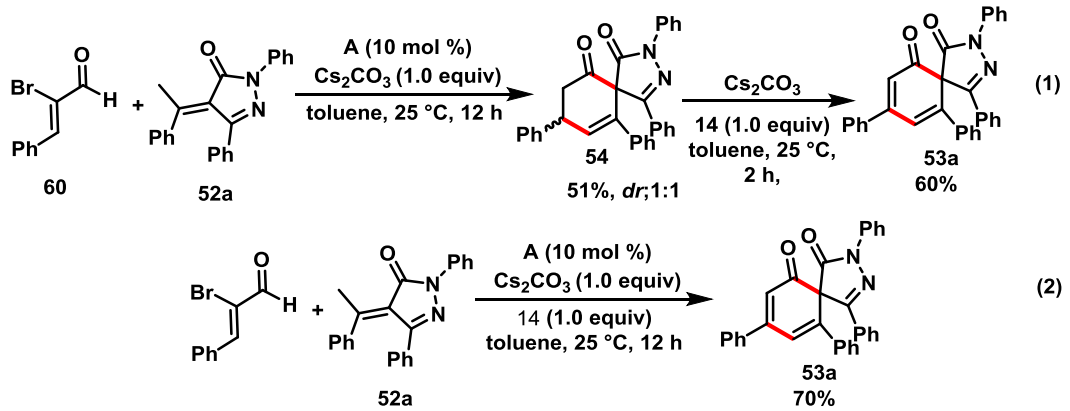


A plausible mechanism for this NHC-catalyzed spiroannulation reaction is shown in Scheme 5.15. The 1,2-addition of carbene generated from the chiral triazolium salt **A** to enal **51** followed by the proton transfer generates the nucleophilic Breslow intermediate **I**.[19] The oxidation of enaminol **I** with oxidant **14** generates the key chiral α,β-unsaturated acyl azolium intermediate **II**. at the same time, the α-arylidene pyrazolinone **52** under basic conditions generate the dienolate intermediate **III**. Vinylogous Michael addition of **III** onto the α,β-unsaturated acyl azolium **II** generates the NHC-bound enolate intermediate **IV**, which on intramolecular proton transfer generates the acyl azolium **V** having an enolate moiety separated by a carbon tether. Intramolecular enolate *C*-acylation results in the formation of the spiropyrazolone **54** with the regeneration of free carbene. The spiro compound **54** in the presence of excess oxidant **14** affords the spirocyclohexadienone product **53**.

5.3.7. Role of Oxidant

To prove the role of oxidant on the final oxidation step leading to **53**, we have performed the reaction of 2-bromoenal **60** with **52a** in the presence of **A** and Cs_2CO_3 as base in the absence of the oxidant **14**. This reaction afforded the spirocyclohexenone **54** in 51% yield and 1:1 *dr* (Scheme 5.16, eq 1). Moreover, treating **54** with the oxidant **14** under basic conditions furnished **53a** in 60% yield indicating the role of **14** in the oxidation step. In addition, when the NHC-catalyzed reaction of **60** and 5**2a** was carried out in the presence of **14**, **53a** was isolated in 70% yield showing the advantages of the domino process (eq 2).

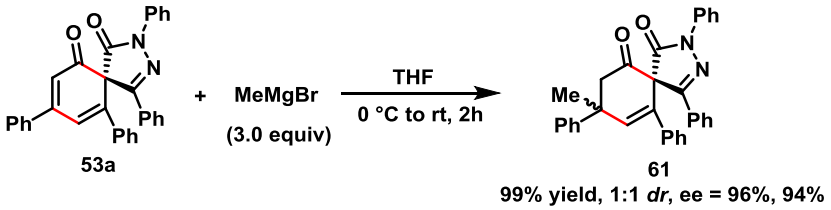
Scheme 5.16: Reactions of 2-Bromoenals with Pyrazolinones



5.3.8. Synthetic Transformation

Finally, treatment of spirocyclohexadienone **53a** with MeMgBr afforded spirocyclohexenone **61** bearing two all-carbon quaternary stereocentres in 99% yield and 1:1 *dr* and excellent ee values (Scheme 5.17).

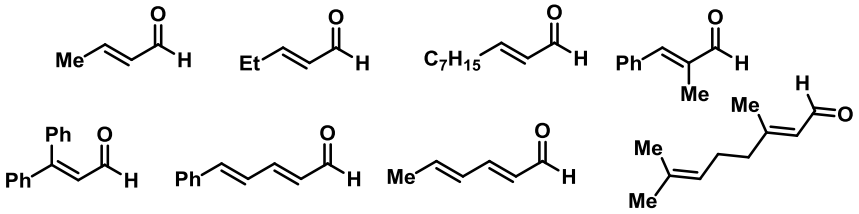
Scheme 5.17: Product Functionalization



5.3.9. Unsuccessful Substrates in this Reaction

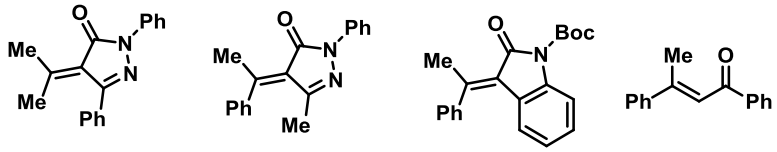
α,β-Unsaturated Aldehydes:

The following enals afforded only traces (<5%) of the desired spirocyclohexadienone product under the optimized reaction conditions.



Dienolate Precursors:

The following dienolate precursors afforded only traces (<5%) of the desired spirocyclohexadienone product under the optimized reaction conditions.



5.4. Conclusion

In conclusion, we have developed a mild and atom-economic method for enantioselective construction of pyrazolone-fused spirocyclohexadienones.[20] This NHC-organocatalyzed reaction of enals with *α*-arylidene pyrazolinones under oxidative conditions proceeds through a vinylogous Michael addition/spiroannulation/ dehydrogenation cascade to afford spirocyclic compounds with an all-carbon quaternary stereocenter in moderate to good yields and excellent ee values. Given the importance of pyrazolones in medicine, the spirocyclic compounds synthesized herein in enantiomerically pure form is expected to have interesting biological properties.

5.5. Experimental Details

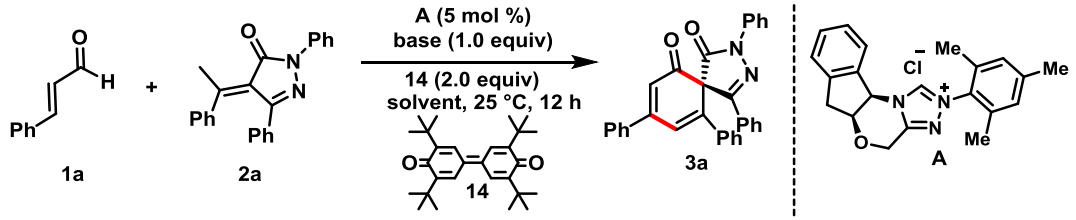
5.5.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. Dry toluene was purchased from commercial sources and stored under argon over sodium wire. THF was freshly purified by distillation over Na-benzophenone and was transferred under argon. The α,β-unsaturated aldehydes **51a-c**, **51h**, and **51k**, were purchased from commercial sources and were used without further purification, and **51d-g**, **51i**, and **51j** were synthesized following the literature procedure.[21] *α*-Arylidene pyrazolinone derivatives were synthesized by following the literature procedure.[22] The triazolium salt **A** was synthesized following the literature procedure.[23]

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 50 mm cell of 1 mL capacity. HPLC analysis was performed on Agilent Technologies 1260 Infinity with UV detector, and HPLC analysis of compound **7** was done on MERCK HITACHI with UV detector.

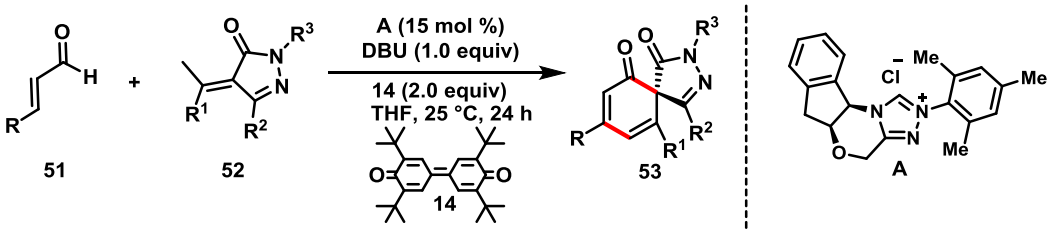
5.5.2. Procedure for the Optimization of Reaction Conditions



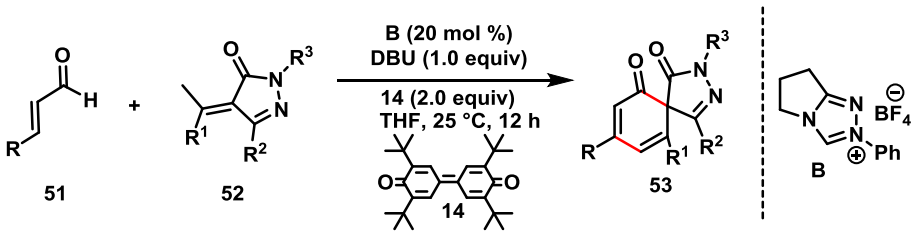
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (4.6 mg, 0.012 mmol, 5 mol%), and (*E*)-1,3-diphenyl-4-(1-

phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **52a** (0.25 mmol, 1.0 equiv), oxidant **14** (0.5 mmol, 2.0 equiv) were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added solvent (6.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C. To this mixture was added the cinnamaldehyde **51a** (0.375 mmol) followed by base (0.25 mmol, 1.0 equiv). Then the reaction mixture was stirred at 25 °C for 12 h. The solvent was evaporated and crude residue was purified by flash column chromatography on silica gel to afford the spirocyclohexadienone **53a**. The enantiomeric excess was determined by HPLC analysis on a chiral column.

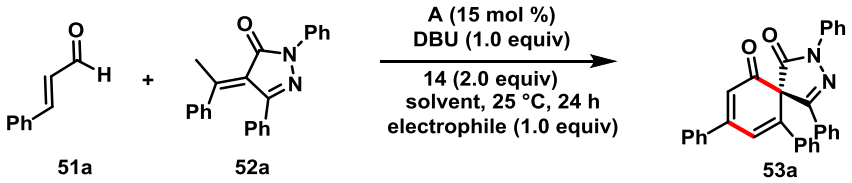
5.5.3. Procedure for the Enantioselective Synthesis of Spirocyclohexadienones



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (28.0 mg, 0.075 mmol), *α*-arylidene pyrazolinone **52** (0.50 mmol) and **14** (409.0 mg, 2.0 equiv), were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added THF (12.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C. To this mixture was added the enal **51** (0.75 mmol) followed by DBU (0.50 mmol). Then the reaction mixture was stirred at 25° C for 24 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding spirocyclohexadienones. Racemic samples were prepared by using the *N*-phenyl triazolium-derived carbenes. For compound **53z,** racemic sample was prepared by *N*-mesityl triazolium-derived carbenes.



5.5.4. Procedure for the Electrophile Additive Reactions



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken triazolium salt **A** (14 mg, 0.037 mmol, 15 mol %), α-arylidene pyrazolinone **52a** (0.25 mmol) and **5** (0.5 mmol, 2.0 equiv), were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added THF (6.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C. To this mixture was added the enal **51a** (0.375 mmol) and **electrophile** (0.25 mmol) followed by DBU (0.25 mmol). Then the reaction mixture was stirred at 25° C for 24 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford the corresponding spirocyclohexadienone **53a** and the recovered electrophile. In the case of trifluoroacetophenone as electrophile, the recovered yield of electrophile was determined using GC analysis. The enantiomeric excess was determined by HPLC analysis on a chiral column.

5.5.5. Procedure for the Scheme 5.16

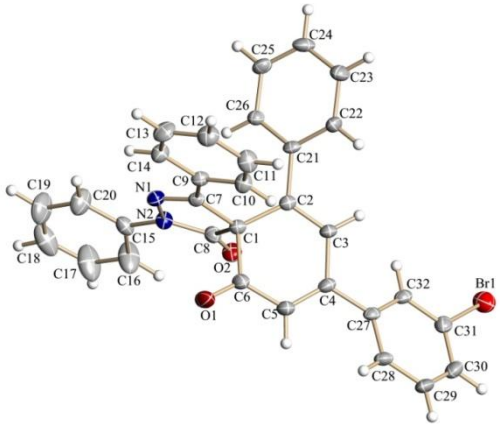
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken (*Z*)-2-bromo-3-phenylacrylaldehyde **60** (52.0 mg, 0.25 mmol), triazolium salt **A** (9.1 mg, 0.025 mmol), and *α* -arylidene pyrazolinone **52** (84.0 mg, 0.25 mmol) were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C. To this mixture was added the Cs_2CO_3 (82.0, 0.25 mmol). Then the reaction mixture was stirred at 25° C for 12 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford **54** (60 mg, 51% yield). This **54** upon treatment with Cs_2CO_3 (0.1 mmol) and oxidant **14** (1.0 equiv) in toluene (1.0 mL) for 2 h afforded the final product **53a** (36.0 mg, 60% yield). When the same reaction was performed in one-pot (without isolating **54**), **53a** was obtained in 70% yield.

5.5.6. Procedure for the Scheme 5.17

To a flame-dried screw-capped test tube equipped with a magnetic stir bar was taken (*S*)-2,4,8,10-Tetraphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53a** (58.0

mg, 0.125 mmol) in THF (2.0 mL), and the reaction mixture was cooled to 0° C. To this mixture was added methyl magnesium bromide (3M in Et_2O, 0.375 mmol, 0.13 mL) under argon atmosphere and allowed to warm to 25 °C. After being stirred at 25 °C for 2h, the solution was poured into 5 mL of saturated aqueous NH_4Cl and then diluted with 5 mL of ethyl acetate, the organic phase was separated, washed with 5 mL of saturated aqueous NH_4Cl, dried with Na_2SO_4, solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel to afford (5*S*)-8-methyl-2,4,8,10-tetraphenyl-2,3-diazaspiro[4.5]deca-3,9-diene-1,6-dione **61** as yellow solid (60.0 mg, >99% yield) in 1:1 diastereomeric ratio.

5.5.7. X-Ray Data of 53i



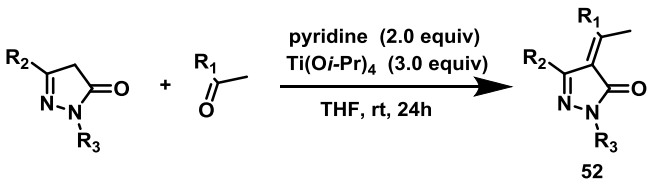
*ORTEP diagram of **53i** drawn with 30% probability displacement ellipsoids*

X-ray intensity data measurements of compound **53i** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at 200(2) K. 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 20 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[24] 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.[25] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* view of both compounds were drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary

radii. The absolute configuration established by anomalous dispersion effects in diffraction measurements on the crystal which could become possible due to the presence of heavy Br atom in the molecule. The absolute configuration of the molecule was found by using Flack parameter refinement.[26] A value of Flack parameter of 0.052(9) established that the configuration of atoms C1 is ***S***. CCDC 1417494 (**53i**) 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 **53i:** $C_{32}H_{21}BrN_2O_2$, M = 545.42, colorless block, 0.42 x 0.36 x 0.30 mm^3, orthorhombic, space group $P2_12_12_1$, a = 8.3038(8) Å, b = 11.9137(10) Å, c = 25.371(2) Å, V = 2509.9(4) Å^3, Z = 4, T = 200(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.443, $F(000)$ = 1112, μ (mm^{-1}) = 1.671, 16195 reflections collected, 4390 unique reflections (R_{int}=0.0754), 3190 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.540, T_{max} = 0.634, 334 refined parameters, S = 1.082, $R1$ = 0.0549, $wR2$ = 0.1230 (all data R = 0.0871, $wR2$ = 0.1370), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.64, $\Delta\rho_{min}$= -0.57 (eÅ^{-3}).

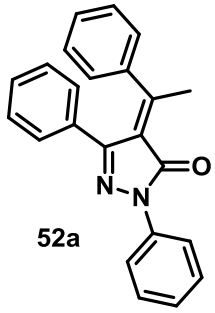
5.5.8. Synthesis and Characterization of *α*-Arylidene Pyrazolinones



Following the known procedure2[22] a mixture of pyrazolone (1.0 equiv), acetophenone (1.2 equiv) and pyridine (2.0 equiv) in THF (10.0 mL) was stirred for 10 min followed by addition of Titanium isopropoxide (3.0 equiv). The resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc and washed with 1N aqueous HCl, $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to provide *α*-arylidene pyrazolinone derivatives **52**.

(*E*)-1,3-Diphenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one (52a)

Following the known procedure, treatment of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1.5 g, 6.34 mmol) and acetophenone (0.89 ml, 7.608 mmol) with pyridine (1.02 ml, 12.68 mmol) in the presence of titanium isopropoxide (5.63ml, 19.02 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-1,3-



52a

diphenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **52a** as yellow solid (0.72 g, 34% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.5.

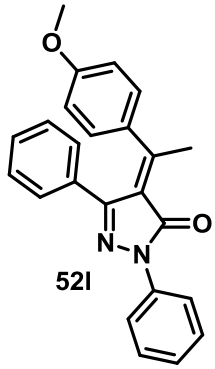
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.03 (m, 10H), 2.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.79, 164.27, 151.25, 140.24, 138.55, 133.00, 129.87, 128.93, 128.90, 128.21, 127.98, 127.81, 127.73, 125.17, 124.27, 119.43, 22.87.

FTIR (cm^{-1}) 3683, 3359, 3020, 2403, 1956, 1887, 1684, 1601, 1495, 1434, 1392, 1327, 1273, 1217, 1120, 1058, 944, 767, 679.

HRMS calculated $[M+H]^+$ for $C_{23}H_{19}ON_2$: 339.1492, found: 339.1496.

(*E*)-4-(1-(4-Methoxyphenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (52l)



52l

Following the known procedure, treatment of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1.0 g, 4.23 mmol) and 4-methoxy acetophenone (0.69 mL, 5.076 mmol) with pyridine (0.68 mL, 8.46 mmol) in the presence of titanium isopropoxide (3.75 mL, 12.69 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-4-(1-(4 methoxyphenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one **52l** as yellow solid (0.7 g, 45% yield).

***R*f** (Pet. ether /EtOAc = 90/10):0.3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.13 – 6.91 (m, 7H), 6.51 (d, *J* = 8.7 Hz, 2H), 3.69 (s, 3H), 2.98 (s, 3H).

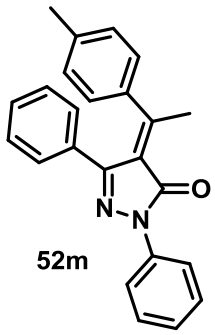
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.69, 164.47, 161.54, 151.36, 138.68, 133.29, 132.54, 131.17, 128.91, 128.29, 127.80, 125.07, 123.32, 119.45, 113.28, 55.49, 22.61.

FTIR (cm^{-1}) 3346, 3018, 1676, 1596, 1502, 1427, 1318, 1259, 1218, 1173, 1118, 1030, 954, 838, 764, 667.

HRMS calculated $[M+H]^+$ for $C_{24}H_{21}O_2N_2$: 369.1598, found: 369.1599.

(*E*)-1,3-Diphenyl-4-(1-(*p*-tolyl)ethylidene)-1*H*-pyrazol-5(4*H*)-one (52m)

Following the known procedure, treatment of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1.0 g, 4.23 mmol) and 4-methyl acetophenone (0.67 mL, 5.076 mmol) with pyridine (0.68 mL, 8.46 mmol) in the presence of titanium isopropoxide (3.75 mL,



52m

12.69 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded (*E*)-1,3-diphenyl-4-(1-(*p*-tolyl)ethylidene)-1*H*-pyrazol-5(4*H*)-one **52m** as yellow solid (1.07 g, 72% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.5.

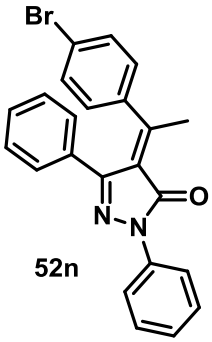
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.11 – 6.87 (m, 7H), 6.78 (d, *J* = 7.9 Hz, 2H), 2.98 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.17, 164.36, 151.38, 140.48, 138.62, 137.43, 133.15, 129.08, 128.91, 128.39, 128.25, 127.66, 125.10, 123.92, 119.43, 22.75, 21.31.

FTIR (cm^{-1}) 3355, 3020, 2403, 1682, 1597, 1496, 1394, 1328, 1217, 1120, 1034, 946, 765, 668.

HRMS calculated $[M+H]^+$ for $C_{24}H_{21}ON_2$: 353.1648, found: 353.1649.

(*E*)-4-(1-(4-Bromophenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (52n)



52n

Following the known procedure, treatment of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1 g, 4.23 mmol) and 4-bromo acetophenone (1.01g, 5.076 mmol) with pyridine (0.68ml, 8.46 mmol) in the presence of titanium isopropoxide (3.75ml, 12.69 mmol) in THF (10 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded (*E*)-4-(1-(4-bromophenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one **52n** as yellow solid (1.34 g, 76% yield)

***R*f** (Pet. ether /EtOAc = 90/10):0.4.

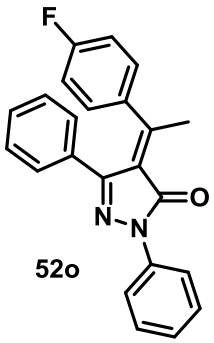
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.97 (m, 2H), 7.48 – 7.40 (m, 2H), 7.25 – 7.09 (m, 4H), 7.03 (dd, *J* = 10.5, 4.9 Hz, 2H), 6.96 (dd, *J* = 8.1, 1.1 Hz, 2H), 6.92 – 6.84 (m, 2H), 2.95 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.78, 164.00, 150.90, 138.98, 138.41, 132.74, 130.95, 130.24, 128.97, 128.31, 128.16, 127.94, 125.29, 124.75, 124.43, 119.43, 22.51.

FTIR (cm^{-1}) 3352, 3063, 2922, 1956, 1731, 1687, 1596, 1489, 1444, 1392, 1319, 1268, 1170, 1112, 1065, 1015, 948, 825, 761, 696.

HRMS calculated $[M+H]^+$ for $C_{23}H_{18}ON_2Br$: 417.0597, found: 417.0601.

(*E*)-4-(1-(4-Fluorophenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (52o)



52o

Following the known procedure, treatment of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1 g, 4.23 mmol) and 4-flouro acetophenone **2c** (0.61ml, 5.076 mmol) with pyridine (0.68ml, 8.46 mmol) in the presence of titanium isopropoxide (3.75ml, 12.69 mmol) in THF (10 ml) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded (*E*)-4-(1-(4-fluorophenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one **52o** as yellow solid (0.93 g, 61% yield).

***R*f** (Pet. ether / EtOAc = 90/10):0.4.

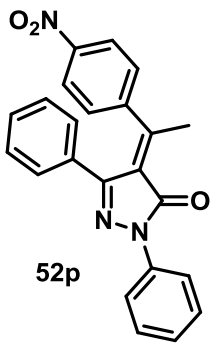
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.96 (m, 2H), 7.48 – 7.40 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.16 – 7.07 (m, 1H), 7.06 – 6.93 (m, 6H), 6.75 – 6.62 (m, 2H), 2.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.13, 134.90 (d, *J* = 248 Hz) 164.13, 150.99, 138.47, 136.27, 132.86, 131.04 (d, *J* = 8 Hz), 128.96, 128.29, 128.22, 127.89, 125.26, 119.45, 115.0513 (d, *J* = 22 Hz), 22.78.

FTIR (cm^{-1}) 3683, 3618, 3359, 302, 2403, 2353, 1890, 1685, 1598, 1499, 1394, 1327, 1219, 1170, 1119, 1057, 942, 830, 769, 673.

HRMS calculated $[M+H]^+$ for $C_{23}H_{18}ON_2F$: 357.1398, found: 357.1399.

(*E*)-4-(1-(4-Nitrophenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (52p)



52p

Following the known procedure, treatment of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1 g, 4.23 mmol) and 4-nitro acetophenone (0.83ml, 5.076 mmol) with pyridine (0.68ml, 8.46 mmol) in the presence of titanium isopropoxide (3.75ml, 12.69 mmol) in THF (10 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture using silica gel afforded (*E*)-4-(1-(4-nitrophenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one **52p** as yellow solid (0.70 g, 45% yield).

***R*f** (Pet. ether /EtOAc = 90/10):0.2.

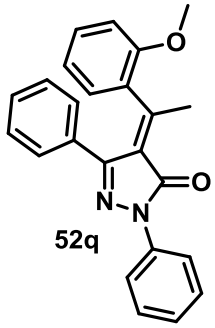
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.8 Hz, 2H), 7.85 (t, *J* = 7.7 Hz, 2H), 7.45 (dd, J_1 = 13.6, J_2 =5.9 Hz, 2H), 7.25 – 7.13 (m, 3H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.03 – 6.91 (m, 4H), 2.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.43, 147.98, 146.30, 138.20, 132.42, 129.43, 129.04, 128.65, 128.39, 128.04, 125.54, 122.92, 119.44, 22.36.

FTIR (cm^{-1}) 3347, 3023, 1686, 1601, 1519, 1444, 1392, 1340, 1218, 1111, 939, 852, 764, 664.

HRMS calculated $[M+H]^+$ for $C_{23}H_{18}O_3N_3$: 384.1343, found: 384.1343.

(*E*)-4-(1-(2-Methoxyphenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)- one (52q)



Following the known procedure, treatment of 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1.0 g, 4.23 mmol) and 2-methoxy acetophenone (0.69 mL, 5.076 mmol) with pyridine (0.68 mL, 8.46 mmol) in the presence of titanium isopropoxide (3.75 mL, 12.69 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-4-(1-(2-methoxyphenyl)ethylidene)-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one **52q** as yellow solid (0.92 g, 59% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.4.

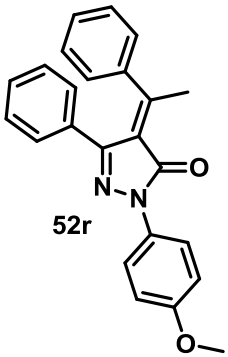
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.10 – 6.92 (m, 6H), 6.81 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 3.68 (d, *J* = 22.2 Hz, 3H), 2.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.49, 164.15, 155.40, 151.76, 138.61, 132.77, 130.73, 129.93, 129.35, 128.88, 128.04, 127.32, 124.99, 120.10, 119.31, 110.30, 55.20, 22.92.

FTIR (cm^{-1})3347, 3018, 1677, 1595, 1503, 1317, 1259, 1218, 1175, 1031, 951, 838, 761, 667.

HRMS calculated $[M+H]^+$ for $C_{24}H_{21}O_2N_2$: 369.1598, found: 369.1601.

(*E*)-1-(4-Methoxyphenyl)-3-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one (52r)



Following the known procedure, treatment of 1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (1g, 3.75mmol) and acetophenone **2a**(0.52 mL, 4.5 mmol) with pyridine (0.60 mL, 7.5 mmol) in the presence of titanium isopropoxide (3.33 mL, 11.25 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc =

98/02) of the crude reaction mixture using silica gel afforded (*E*)-1-(4-methoxyphenyl)-3-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **52r** as yellow solid (0.69 g, 50% yield).

***R*f** (Pet. ether /EtOAc = 90/10):0.3.

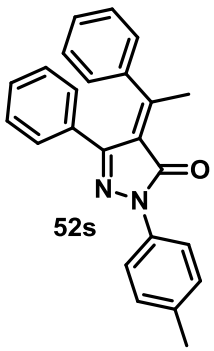
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.86 (m, 2H), 7.15 – 6.92 (m, 12H), 3.81 (d, *J* = 22.2 Hz, 3H), 2.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.61, 164.02, 157.20, 150.94, 140.27, 133.05, 131.93, 129.82, 128.91, 128.19, 127.90, 127.79, 127.71, 124.27, 121.34, 114.10, 55.63, 22.79.

FTIR (cm^{-1}) 3352, 3020, 2403, 1679, 1603, 1511, 1436, 1335, 1296, 1217, 1176, 1123, 1036, 943, 763, 669.

HRMS calculated $[M+H]^+$ for $C_{24}H_{21}O_2N_2$: 369.1598, found: 369.1600

(*E*)-3-Phenyl-4-(1-phenylethylidene)-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one (52s)



Following the known procedure, treatment of 3-phenyl-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one (1.0 g, 3.99 mmol) and acetophenone (0.55 mL, 4.78 mmol) with pyridine (0.64 mL, 7.98 mmol) in the presence of titanium isopropoxide (3.54 mL, 11.97 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-3-phenyl-4-(1-phenylethylidene)-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one **52s** as yellow solid (0.98 g, 70% yield).

***R*f** (Pet. ether /EtOAc = 90/10):0.5.

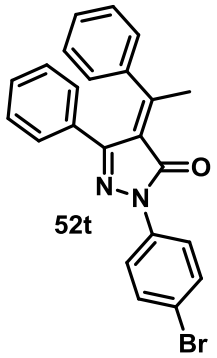
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.21 (m, 2H), 7.18 – 6.94 (m, 10H), 3.01 (s, 3H), 2.36 (d, *J* = 24.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.53, 164.15, 151.03, 140.29, 136.12, 134.82, 133.07, 129.82, 129.46, 128.90, 128.21, 127.92, 127.79, 127.71, 124.34, 119.49, 22.82, 21.14.

FTIR (cm^{-1}) 3357, 3021, 2403, 1681, 1603, 1516, 1432, 1329, 1217, 1119, 1037, 942, 764, 669.

HRMS calculated $[M+H]^+$ for $C_{24}H_{21}ON_2$: 353.1648, found: 353.1651.

(*E*)-1-(4-Bromophenyl)-3-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one (52t)



52t

Following the known procedure, treatment of 1-(4-bromophenyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (1.0 g, 3.17 mmol) and acetophenone (0.44 mL, 3.804 mmol) with pyridine (0.51mL, 6.34 mmol) in the presence of titanium isopropoxide (2.81mL, 9.51 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-1-(4-bromophenyl)-3-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **52t** as yellow solid (1.02 g, 77% yield).

***R*f** (Pet. ether /EtOAc = 90/10):0.5.

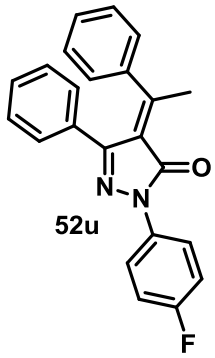
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 2H), 7.57 – 7.50 (m, 2H), 7.16 – 6.93 (m, 10H), 2.98 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.46, 164.21, 151.60, 140.09, 137.66, 132.78, 131.91, 130.02, 128.89, 128.16, 128.13, 127.84, 127.78, 124.05, 120.65, 117.94, 22.95.

FTIR (cm^{-1}) 3351, 3020, 1685, 1599, 1489, 1440, 1328, 1217, 1118, 946, 829, 762, 666.

HRMS calculated $[M+H]^+$ for $C_{23}H_{18}ON_2Br$: 417.0597, found: 417.0604.

(*E*)-1-(4-Fluorophenyl)-3-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one (52u)



52u

Following the known procedure, treatment of 1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (1.0 g, 3.93 mmol) and acetophenone (0.54 mL, 4.71mmol) with pyridine (0.63 mL, 7.86 mmol) in the presence of titanium isopropoxide (3.49 mL, 11.79 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-1-(4-fluorophenyl)-3-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **52u** as yellow solid (0.71 g, 51% yield).

***R*f** (Pet. ether /EtOAc = 90/10):0.48.

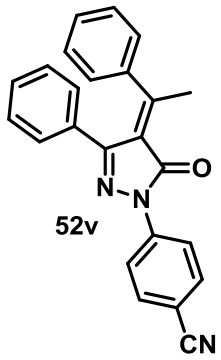
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.96 (m, 2H), 7.16 – 6.94 (m, 12H), 2.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.26, 164.13 (d, *J* = 266 Hz), 158.92, 151.34, 140.15, 134.72 (d, *J* = 3 Hz), 132.88, 129.97, 128.90, 128.17, 128.06, 127.84, 127.77, 121.20 (d, *J* = 8 Hz), 121.12, 115.72, 115.50, 22.89.

FTIR (cm^{-1}) 3349, 3020, 1683, 1603, 1508, 1437, 1332, 1220, 1120, 1031, 949, 835, 761, 704, 666.

HRMS calculated $[M+H]^+$ for $C_{23}H_{18}ON_2$ F: 357.1398, found: 357.1398.

(*E*)-4-(5-oxo-3-Phenyl-4-(1-phenylethylidene)-4,5-dihydro-1*H*-pyrazol-1-yl)benzonitrile (52v)



Following the known procedure, treatment of 4-(5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)benzonitrile (1.0 g, 3.82 mmol) and acetophenone 0.53 mL, 4.58 mmol) with pyridine (0.61 mL, 7.64 mmol) in the presence of titanium isopropoxide (3.39 mL, 11.46 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-4-(5-oxo-3-phenyl-4-(1-phenylethylidene)-4,5-dihydro-1*H*-pyrazol-1-yl)benzonitrile **52v** as yellow solid (0.9 g, 66% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10):0.3.

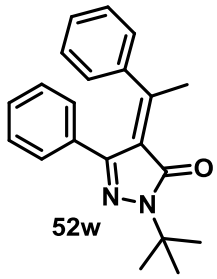
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.18 – 6.92 (m, 10H), 2.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.52, 164.58, 152.53, 142.03, 139.88, 133.18, 132.45, 130.26, 128.88, 128.39, 128.13, 127.90, 127.84, 123.69, 119.21, 118.61, 107.67, 23.15.

FTIR (cm^{-1}) 3358, 3021, 2403, 2227, 1690, 1601, 1508, 1428, 1328, 1217, 1034, 845, 767, 668.

HRMS calculated $[M+H]^+$ for $C_{24}H_{18}ON_3$: 364.1444, found: 364.1446.

(*E*)-2-(*tert*-Butyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one (52w)



Following the known procedure, treatment of 2-(tert-butyl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one (0.35 g, 1.62 mmol) and acetophenone (0.17ml, 1.45 mmol) with pyridine (0.26 ml, 3.24 mmol) in the presence of titanium isopropoxide (1.43 ml, 4.86 mmol) in THF (5 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /DCM = 60/40) of the crude reaction mixture using silica gel afforded (*E*)-2-(*tert*-butyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52w** as red oil (0.36 g, 71% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.5.

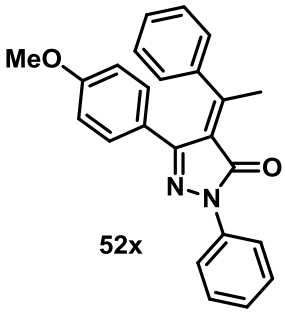
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.03 (m, 1H), 7.01-6.87 (m, 9H), 2.89 (s, 3H), 1.65 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.77, 163.81, 148.12, 140.48, 133.55, 129.26, 128.73, 128.58, 127.96, 127.53, 127.42, 127.23, 124.99, 57.64, 28.37, 22.04.

FTIR (cm^{-1}) 3350, 3019, 2406, 1966, 1902, 1728, 1681, 1596, 1218, 1083, 763, 682.

HRMS calculated $[M+H]^+$ for $C_{21}H_{23}ON_2$: 319.1805, found: 319.1805.

(*E*)-5-(4-Methoxyphenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one (52x)



52x

Following the known procedure, treatment of 5-(4-methoxyphenyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (1.0 g, 3.75 mmol) and acetophenone (0.52 ml, 4.5 mmol) with pyridine (0.60 ml, 7.51 mmol) in the presence of titanium isopropoxide (3.32 ml, 11.25 mmol) in THF (8 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-5-(4-methoxyphenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52x** as yellow solid (0.89g, 64% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.46.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.16-7.12 (m, 1H), 7.06-7.01 (m, 4H), 6.93-6.90 (m, 2H), 6.52-6.49 (m, 2H), 3.71 (s, 3H), 2.98 (s, 3H).

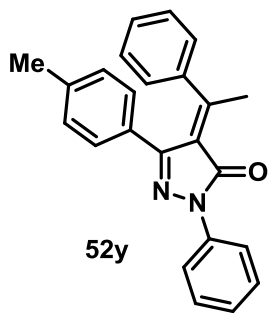
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.55, 164.30, 159.40, 150.93, 140.29, 138.58, 129.75, 129.49, 128.91, 127.83, 125.47, 125.07, 124.38, 119.39, 113.30, 55.39, 22.91.

FTIR (cm^{-1}) 3685, 3020, 2403, 1683, 1602, 1498, 1427, 1328, 1216, 1120, 1035, 940, 766, 671.

HRMS calculated $[M+H]^+$ for $C_{24}H_{21}O_2N_2$: 369.1598, found: 369.1599.

(*E*)-2-Phenyl-4-(1-phenylethylidene)-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one (52y)

Following the known procedure, treatment of 2-phenyl-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one (1.63 g, 6.51 mmol) and acetophenone (0.91ml, 7.81 mmol) with pyridine (1.04 ml, 13.02 mmol) in the presence of titanium isopropoxide (5.80ml, 19.53 mmol) in THF (10 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica



52y

gel afforded (*E*)-2-phenyl-4-(1-phenylethylidene)-5-(*p*-tolyl)-2,4-dihydro -3*H*-pyrazol-3-one **52y** as yellow solid (0.90 g, 39% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.47.

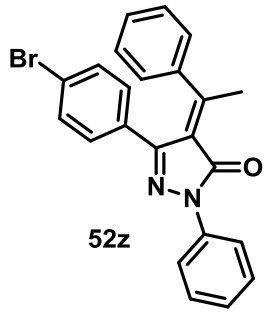
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.45-7.41 (m, 2H), 7.22-7.19 (m, 1H), 7.14-7.10 (m, 1H), 7.05-6.98 (m, 4H), 6.88-6.86 (m, 2H), 6.78-6.76 (m, 2H), 2.98 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.69, 164.32, 151.32, 140.31, 138.56, 137.84, 130.03, 129.63, 128.91, 128.37, 128.07, 127.75, 125.10, 124.36, 119.42, 22.87, 21.29.

FTIR (cm^{-1}) 3350, 3019, 2406, 1966, 1902, 1728, 1681, 1596, 1443, 1363, 1305, 1264, 1218, 1083, 1025, 959, 763, 682.

HRMS calculated $[M+H]^+$ for $C_{24}H_{21}ON_2$: 353.1648, found: 353.1643.

(*E*)-5-(4-Bromophenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one (52z)



52z

Following the known procedure, treatment of 5-(4-bromophenyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (1.0 g, 3.17 mmol) and acetophenone (0.44 ml, 3.80 mmol) with pyridine (0.54 ml, 6.34 mmol) in the presence of titanium isopropoxide (2.81 ml, 9.51 mmol) in THF (8.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-5-(4-bromophenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52z** as yellow solid (0.85g, 64% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.44.

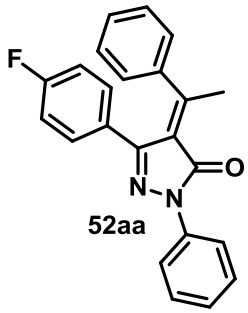
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 -8.01 (m, 2H), 7.46- 7.42(m, 2H), 7.24-7.18 (m, 2H), 7.12-7.02 (m, 6H), 6.87-6.84 (m, 2H), 2.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.03, 164.08, 150.06, 140.16, 138.41, 131.99, 130.84, 130.09, 129.68, 128.97, 128.89, 128.00, 125.32, 124.07, 122.24, 119.42, 22.85.

FTIR (cm^{-1}) 3018, 1685, 1608, 1496, 1429, 1367, 1325, 1217, 1121, 1022, 762**.**

HRMS calculated $[M+H]^+$ for $C_{23}H_{18}ON_2Br$: 417.0597, found: 417.0604.

(*E*)-3-(4-Fluorophenyl)-1-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one (52aa)



Following the known procedure, treatment of 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2.75 g, 10.8 mmol) and acetophenone (1.5 mL, 12.96 mmol) with pyridine (1.7 mL, 21.6 mmol) in the presence of titanium isopropoxide **5** (9.59 mL, 32.4 mmol) in THF (10.0 mL) at room temperature for 24 h followed by flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture using silica gel afforded (*E*)-3-(4-fluorophenyl)-1-phenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **52aa** as yellow solid (1.02 g, 27% yield).

***R*f** (Pet. ether /EtOAc = 90/10):0.44.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J_1 = 26.4 Hz, J_2 = 7.9 Hz, 2H), 7.45 (dd, J_1 = 16.7 Hz, J_2 =8.9 Hz, 2H), 7.27 – 7.12 (m, 2H), 7.09 – 6.93 (m, 6H), 6.68 (t, *J* = 8.7 Hz, 2H), 2.99 (s, 3H).

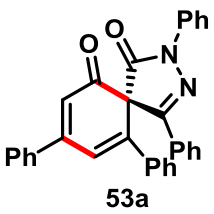
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 163.99 (d, *J* = 248 Hz), 163.53, 150.06, 140.03, 138.33, 129.91 (d, *J* = 8 Hz), 129.05, 128.84, 128.76, 127.80, 125.14, 124.10, 119.29, 114.76 (d, *J* = 26 Hz), 22.78.

HRMS calculated $[M+H]^+$ for $C_{23}H_{18}ON_2F$: 357.1398, found: 357.1401.

FTIR (cm^{-1}) 3359, 3021, 2403, 1684, 1601, 1498, 1425, 1327, 1217, 1040, 937, 763, 670.

5.5.9. Synthesis and Characterization of Spirocyclohexadienones

(*S*)-2,4,8,10-Tetraphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53a)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (169.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2,4,8,10-tetraphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53a** as a yellow solid (195.0 mg, 84% yield).

***R*f** (Pet. ether /EtOAc = 80/20): 0.62.

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 16.4 min, *Major*: 21.4 min. ee = 98%, $[\alpha]_D^{25}$ = -217.22 (c 0.1, $CHCl_3$).

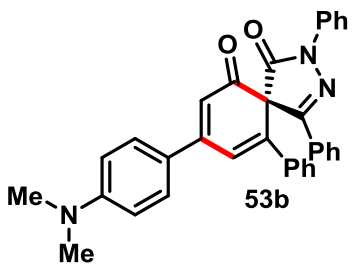
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.78 (dd, J_1 = 6.6, J_2 = 3.0 Hz, 2H), 7.69 – 7.60 (m, 2H), 7.59 – 7.50 (m, 3H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.40 – 7.29 (m, 3H), 7.29 – 7.22 (m, 2H), 7.21 – 7.15 (m, 5H), 6.61 (d, *J* = 0.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.82, 167.05, 157.73, 155.27, 147.20, 137.78, 137.35, 137.14, 131.20, 130.97, 129.88, 129.45, 129.32, 129.04, 129.02, 128.89, 127.16, 126.85, 126.35, 126.02, 125.43, 119.84, 119.30, 73.55.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{23}O_2N_2$: 467.1754, found: 467.1757.

FTIR (cm^{-1}) 3385, 3022, 2403, 1716, 1654, 1593, 1422, 1309, 1217, 1124, 1036, 928, 767, 672.

(*S*)-8-(4-(Dimethylamino)phenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53b)



Following the general procedure, treatment of (*E*)-3-(4-(dimethylamino)phenyl)acrylaldehyde **51b** (131.4 mg, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (169.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 μL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-8-(4-(dimethylamino)phenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53b** as a yellow solid (200.0 mg, 79% yield).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.62.

HPLC (Chiralpak IB, 90:00 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 17.5 min, *Major*: 21.6 min. ee = 97%, $[\alpha]_D^{25}$ = -189.20 (c 0.1, $CHCl_3$).

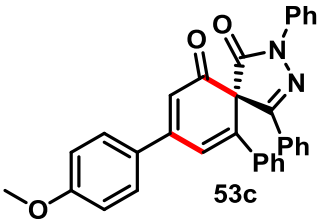
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.14 (m, 10H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.61 (s, 1H), 3.12 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.13, 167.88, 158.03, 154.24, 152.62, 146.25, 137.99, 137.90, 130.79, 130.15, 129.17, 129.00, 128.95, 128.81, 127.00, 126.43, 125.83, 125.24, 123.10, 119.85, 114.66, 112.10, 73.20, 40.24.

HRMS (ESI) calculated $[M+H]^+$ for $C_{34}H_{28}O_2N_3$: 510.2176, found: 510.2185.

FTIR (cm^{-1}) 3357, 3022, 2404, 2357, 1594, 1422, 1309, 1217, 1124, 1037, 929, 768, 671.

(*S*)-8-(4-Methoxyphenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53c)



Following the general procedure, treatment of (*E*)-3-(4-methoxyphenyl)acrylaldehyde **51c** (122.0 mg, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (169.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (S)-8-(4-methoxyphenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53c** as a yellow solid (182.0 mg, 73% yield).

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

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 26.1 min, *Major*: 35.4 min. ee = 96%, $[\alpha]_D^{25}$ = -262.38 (c 0.1, $CHCl_3$).

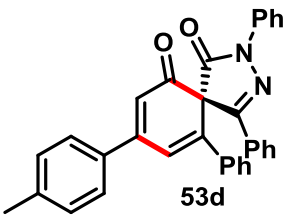
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.04 (m, 2H), 7.87 – 7.85 (m, 2H), 7.73-7.71 (m, 2H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.43 – 7.40 (m, 3H), 7.35 – 7.24 (m, 7H), 7.15 – 7.13 (m, 2H), 6.67 (s, 1H), 3.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.59, 167.27, 162.35, 157.83, 154.45, 146.93, 137.84, 137.51, 130.93, 129.94, 129.38, 129.10, 129.04, 129.01, 128.96, 128.88, 126.89, 126.38, 125.98, 125.29, 119.83, 117.48, 114.79, 73.38, 55.66.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_3N_2$: 497.1860, found: 497.1864.

FTIR (cm^{-1}) 3360, 3022, 1714, 1650, 1598, 1420, 1374, 1218, 1177, 1035, 928, 761, 671.

(*S*)-2,4,10-Triphenyl-8-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53d)



Following the general procedure, treatment of (E)-3-(*p*-tolyl)acrylaldehyde **51d** (54.0 mg, 0.375 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (84.0 mg, 0.25 mmol) with triazolium salt **A** (14.0 mg, 0.037 mmol), oxidant **14** (204.3 mg, 2.0 equiv) and DBU (38.0 mg, 37.0 µL, 0.25 mmol) in THF (6.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to

afford (S)-2,4,10-triphenyl-8-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53d** as a yellow solid (87.0 mg, 73% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.55.

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 29.1 min, *Major*: 39.7 min. ee = 96%, $[\alpha]_D^{25}$ = -172.68 (c 0.1, $CHCl_3$).

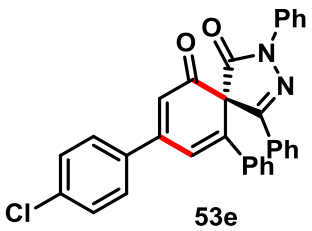
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 2H), 7.70 (d, *J* = 8.2, 2H), 7.63 (d, *J* =6.8 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.36 – 7.30 (m, 5H), 7.28 – 7.15 (m, 7H), 6.60 (S, 1H) 2.46 (S, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.81, 167.19, 157.78, 155.08, 147.04, 141.95, 137.83, 137.47, 134.20, 130.96, 130.09, 129.94, 129.42, 129.06, 129.03, 128.90, 127.18, 126.90, 126.39, 126.01, 125.47, 119.86, 118.57, 73.50, 21.63

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_2N_2$: 481.1911, found: 481.1915.

FTIR (cm^{-1}) 3685, 3022, 2403, 1717, 1654, 1608, 1542, 1498, 1426, 1374, 1305, 1216, 1030, 927, 764, 673.

(*S*)-8-(4-Chlorophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53e)



53e

Following the general procedure, treatment of (*E*)-3-(4-chlorophenyl)acrylaldehyde **51b** (62.0 mg, 0.38 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (84.6 mg, 0.25 mmol) with triazolium salt **A** (14.0 mg, 0.038 mmol), oxidant **14** (204.6 mg, 2.0 equiv) and DBU (38.0 mg, 37.5 μL, 0.25 mmol) in THF (6.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-8-(4-chlorophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (**53e**) as a yellow solid (80.0 mg, 64% yield).

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

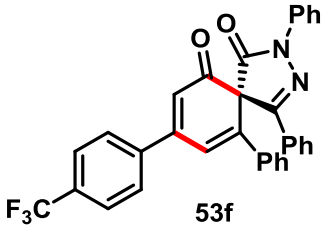
HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 25.2 min, *Major*: 32.1 min. ee = 98%, $[\alpha]_D^{25}$ = -202.18 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.94 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 6.9 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.39 – 7.12 (m, 10H), 6.57 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.69, 166.85, 157.68, 154.00, 147.62, 137.74, 137.45, 137.22, 135.59, 131.04, 129.82, 129.63, 129.59, 129.09, 129.07, 128.95, 128.49, 126.84, 126.36, 126.11, 124.90, 119.86, 119.33, 73.60.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2Cl$: 501.1364, found: 501.1372.

FTIR (cm^{-1}) 3388, 3022, 1716, 1656, 1593, 1494, 1416, 1373, 1307, 1216, 1097, 1029, 925, 761, 673.

(*S*)-2,4,10-Triphenyl-8-(4-(trifluoromethyl)phenyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53f)



53f

Following the general procedure, treatment of (*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde **51f** (150.0 mg, 95 µL, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (169.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2,4,10-Triphenyl-8-(4-(trifluoromethyl)phenyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53f** as a yellow solid (179.0 mg, 67% yield).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.51.

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 31.2 min, *Major*: 45.6 min. ee = 94%, $[\alpha]_D^{25}$ = -161.78 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.94 (m, 2H), 7.89-7.87 (m, 2H), 7.81 – 7.78 (m, 2H), 7.62 – 7.60 (m, 2H), 7.47 – 7.43 (m, 2H), 7.37 – 7.16 (m, 9H), 7.12 (s, 1H), 6.59 (s, 1H).

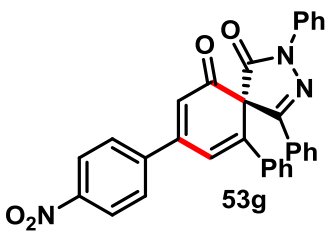
^{13}C NMR (100 MHz, $CDCl_3$) δ 189.72, 166.67, 157.61, 153.91, 147.98, 140.81, 137.70, 137.10, 131.10, 129.77, 129.69, 129.11, 129.00, 127.58, 126.82, 126.35, 126.32, 126.28, 126.18, 124.77, 120.46, 119.87, 73.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -64.37.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{22}O_2N_2F_3$: 535.1628, found: 535.1635.

FTIR (cm^{-1}) 3397, 3020, 2360, 1717, 1658, 1598, 1416, 1374, 1216, 1174, 1070, 771, 689, 669.

(*S*)-8-(4-Nitrophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53g)



53g

Following the general procedure, treatment of (*E*)-3-(4-nitrophenyl)acrylaldehyde **51g** (66.5 mg, 0.375 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (84.6 mg, 0.25 mmol) with triazolium

salt **A** (14.0 mg, 0.0375 mmol), oxidant **14** (204.6 mg, 2.0 equiv) and DBU (38.05 mg, 38 μL, 0.25 mmol) in THF (6.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-8-(4-nitrophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53g** as a yellow solid (80.0 mg, 63% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.52.

HPLC (Chiralpak IB, 95:05 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 36.0 min, *Major*: 40.4 min. ee = 95%, $[\alpha]_D^{25}$ = -137.60 (c 0.1, $CHCl_3$).

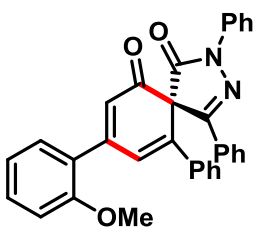
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.8 Hz, 2H), 7.93 – 7.91 (m, 4H), 7.58 (d, *J* = 6.9 Hz, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.37 – 7.25 (m, 5H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.15 – 7.13 (m, 2H), 7.09 (s, 1H), 6.59 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.58, 166.46, 157.57, 153.03, 149.14, 148.33, 143.44, 137.61, 136.93, 131.15, 129.81, 129.68, 129.13, 129.03, 128.19, 126.78, 126.35, 126.25, 124.45, 124.29, 121.06, 119.87, 73.84.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_4N_3$: 512.1605, found: 512.1615.

FTIR (cm^{-1}) 3405, 3022, 2403, 1593, 1423, 1217, 767, 671.

(*S*)-8-(2-Methoxyphenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53h)



53h

Following the general procedure, treatment of (*E*)-3-(2-methoxyphenyl)acrylaldehyde **51h** (122.0 mg, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (169.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 μL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford(*S*)-8-(2-methoxyphenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53h** as a yellow solid (185.0 mg, 75% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.45.

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min) *Major*: 14.1 min, *Minor*: 15.6 min. ee = 84%, $[\alpha]_D^{25}$ = -117.38 (c 0.1, $CHCl_3$).

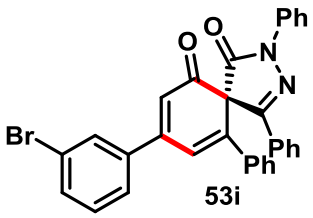
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 6.7 Hz, 2H), 7.52 – 7.41 (m, 4H), 7.37 – 7.33 (m, 3H), 7.25 – 7.14 (m, 6H), 7.11 – 7.03 (m, 3H), 6.49 (s, 1H), 3.94 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.09, 167.70, 157.68, 157.31, 155.27, 144.45, 137.83, 137.54, 131.91, 130.90, 130.01, 129.71, 129.16, 129.00, 128.94, 128.80, 127.96, 127.24, 126.91, 126.43, 125.91, 121.92, 121.21, 119.80, 111.70, 77.48, 73.28, 55.90.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{25}O_2N_2$: 497.1860, found: 497.1870.

FTIR (cm^{-1}) 3352, 3022, 2926, 1713, 1651, 1592, 1419, 1313, 1217, 1122, 1035, 930, 760, 669.

(*S*)-8-(3-Bromophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53i)



53i

Following the general procedure, treatment of (*E*)-3-(3-bromophenyl)acrylaldehyde **51i** (79.1 mg, 0.375 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (84.6 mg, 0.25 mmol) with triazolium salt **4** (14.0 mg, 0.037 mmol), oxidant **5** (204.6 mg, 2.0 equiv) and DBU (38.0 mg, 37 µL, 0.25 mmol) in THF (6.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (S)-8-(3-bromophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53i** as a yellow solid (81.0 mg, 60% yield).

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

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 24.1 min, *Major*: 36.7 min. ee = 96%, $[\alpha]_D^{25}$ = -141.72 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.94 (m, 3H), 7.71 (t, J = 9.1 Hz, 2H), 7.64 – 7.62 (m, 2H), 7.47 (dd, J_1 = 9.2, J_2 = 8.0 Hz, 3H), 7.42 – 7.31 (m, 4H), 7.30 – 7.18 (m, 5H), 7.12 (s, 1H), 6.58 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.67, 166.74, 157.64, 153.85, 147.78, 139.39, 137.75, 137.18, 133.96, 131.05, 130.86, 130.14, 129.82, 129.62, 129.09, 128.97, 126.86, 126.37, 126.12, 125.81, 124.87, 123.50, 119.93, 119.88, 73.70.

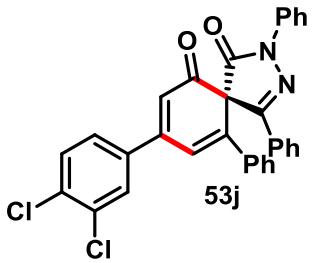
HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2Br$: 545.0859, found: 545.0861.

FTIR (cm^{-1}) 3346, 3022, 2924, 2403, 1718, 1658, 1596, 1494, 1421, 1217, 1301, 927, 762, 671.

(*S*)-8-(3,4-Dichlorophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53j)

Following the general procedure, treatment of (*E*)-3-(3,4-dichlorophenyl)acrylaldehyde **51j** (151.0 mg, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-

3*H*-pyrazol-3-one **52a** (169.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-8-(3,4-dichlorophenyl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53j** as a yellow solid (220.0 mg, 82% yield).



***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.50.

HPLC (Chiralpak IB, 95:05 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 12.8 min, *Major*: 14.4 min. ee = 96%, $[\alpha]_D^{25}$ = -196.06 (c 0.1, $CHCl_3$).

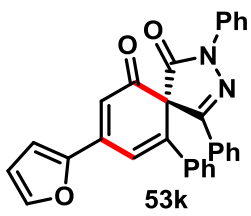
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.88 (s, 1H), 7.63 – 7.59 (m, 4H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.43 – 7.31 (m, 3H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.07 (s, 1H), 6.55 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.58, 166.61, 157.60, 152.86, 148.10, 137.71, 137.18, 137.08, 135.47, 133.87, 131.38, 131.10, 129.72, 129.12, 129.01, 126.84, 126.36, 126.18, 124.41, 119.88, 73.72.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{21}O_2N_2Cl_2$: 535.0975, found: 535.0989.

FTIR (cm^{-1}) 3383, 3022, 2403, 1717, 1658, 1594, 1547, 1490, 1383, 1306, 1217, 1133, 1036, 928, 765, 676.

(*S*)-8-(Furan-2-yl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53k)



Following the general procedure, treatment of (*E*)-3-(furan-2-yl)acrylaldehyde **51k** (91.0 mg, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52a** (169.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (S)-8-(furan-2-yl)-2,4,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53k** as a yellow solid (139.0 mg, 61% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.44.

HPLC (Chiralcel OJ-H, 80:20 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 30.4 min, *Major*: 37.1 min. ee = >99%, $[\alpha]_D^{25}$ = -441.88 (c 0.1, $CHCl_3$).

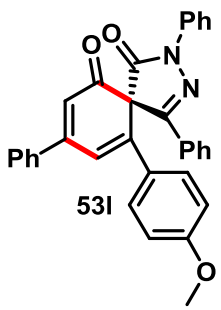
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.71 (d, *J*= 1.3 Hz, 1H), 7.62 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.30 (m, 3H), 7.29-7.24 (m, 2H), 7.22 – 7.19 (m, 2H), 7.16 – 7.12 (m, 4H), 6.71 (s, 1H), 7.66 (dd, J_1 = 3.5, J_2 = 1.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.06, 167.33, 157.76, 150.90, 147.22, 146.82, 142.62, 137.80, 137.24, 130.94, 129.90, 129.45, 129.04, 129.01, 128.87, 126.90, 126.36, 126.00, 122.20, 119.85, 115.18, 113.72, 113.39, 73.57

HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{21}O_3N_2$: 457.1547, found: 457.1548.

FTIR (cm^{-1}) 3686, 3022, 2403, 1592, 1423, 1216, 1035, 928, 764, 671.

(*S*)-10-(4-Methoxyphenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53l)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 μL, 0.75 mmol) and (*E*)-4-(1-(4-methoxyphenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one **52l** (184.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 μL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-10-(4-methoxyphenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53l** as a yellow solid (124.0 mg, 50% yield).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.42.

HPLC (Chiralpak IB, 80:20 Pet.ether / IPA, 1.0 mL/min) *Major*: 8.0 min, *Minor*: 9.1 min. ee = 94%, $[\alpha]_D^{25}$ = -76.72 (c 0.1, $CHCl_3$).

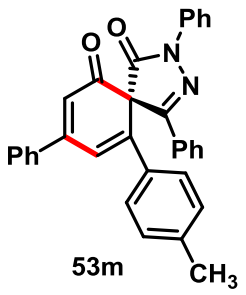
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.78 (dd, J_1 = 6.6, J_2 = 2.9 Hz, 2H), 7.64 – 7.62 (m, 2H), 7.55 – 7.54 (m, 3H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.38 – 7.24 (m, 4H), 7.15 – 7.12 (m, 3H), 6.73 – 6.70 (m, 2H), 6.55 (s, 1H), 3.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.86, 167.29, 160.57, 158.13, 155.65, 146.95, 137.87, 137.39, 131.15, 130.97, 129.90, 129.33, 129.08, 129.05, 128.14, 127.19, 126.40, 125.99, 124.24, 119.81, 118.75, 114.39, 73.57, 55.33.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_3N_2$: 497.1860, found: 497.1863.

FTIR (cm^{-1}) 3345, 320, 2961, 1717, 1652, 1604, 1543, 1503, 1452, 1372, 1299, 1247, 1227, 1176, 1128, 1029, 926, 756, 684.

(*S*)-2,4,8-Triphenyl-10-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53m)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-(*p*-tolyl)ethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52m** (176.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2,4,8-triphenyl-10-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53m** as a yellow solid (149.0 mg, 62% yield).

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.48.

HPLC (Chiralpak IB, 80:20 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 6.1 min, *Major*: 7.0 min. ee = 97%, $[\alpha]_D^{25}$ = -120.96 (c 0.1, $CHCl_3$).

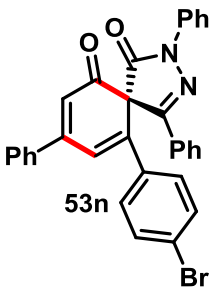
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.80-7.78 (m, 2H), 7.65-7.63 (m, 2H), 7.56-7.54 (m, 3H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.37-7.25 (m, 4H), 7.18 (s, 1H), 7.10-7.08 (m, 2H), 7.02-7.00 (m, 2H), 6.58 (s, 1H), 2.25 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.91, 167.19, 157.93, 155.46, 147.32, 139.65, 137.87, 137.32, 134.56, 131.16, 130.94, 129.94, 129.67, 129.33, 129.06, 129.02, 127.20, 126.67, 126.40, 125.99, 124.86, 119.83, 119.09, 73.55, 21.28.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_2N_2$: 481.1911, found: 481.1913.

FTIR (cm^{-1}) 3385, 3019, 1717, 1654, 1625, 1596, 1544, 1499, 1447, 1422, 1374, 1316, 1299, 1216, 1130, 1032, 930, 754, 690, 669.

(*S*)-10-(4-Bromophenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53n)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-4-(1-(4-bromophenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one **52n** (208.6 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-10-(4-bromophenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53n** as a yellow solid (210.0 mg, 77% yield).

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

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 33.4 min, *Major*: 65.0 min. ee = 98%, $[\alpha]_D^{25}$ = -215.98 (c 0.1, $CHCl_3$).

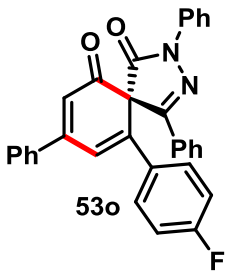
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 6.5Hz, 2H), 7.77 (dd, J_1 = 6.5 Hz, J_2 =3.1 Hz, 2H), 7.60 (d, *J* = 7.2Hz, 2H), 7.55 – 7.53 (m, 3H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.42 – 7.30 (m, 5H), 7.27 (dd, J_1 = 9.3 Hz, J_2 =5.5 Hz, 1H), 7.16 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.61 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.45, 166.85, 157.51, 155.03, 145.89, 137.68, 137.01, 136.25, 132.15, 131.33, 131.18, 129.72, 129.41, 129.16, 129.14, 128.46, 127.18, 126.32, 126.18, 125.86, 123.90, 119.80, 119.62, 73.31.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2Br$: 545.0859, found: 545.0866.

FTIR (cm^{-1}) 3685, 3406, 3020, 2401, 1717, 1656, 1597, 1488, 1447, 1423, 1216, 1127, 1077, 929, 772, 669.

(*S*)-10-(4-Fluorophenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53o)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-2,5-diphenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52o** (168.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2,4,8,10-tetraphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53o** as a yellow solid (180.0 mg, 74% yield).

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

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 20.6 min, *Major*: 57.0 min. ee = 96%, $[\alpha]_D^{25}$ = -197.28 (c 0.1, $CHCl_3$).

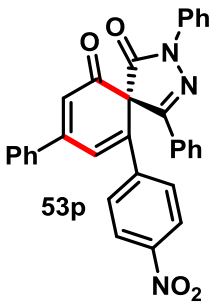
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.79 – 7.76 (m, 2H), 7.62 – 7.60 (m, 2H), 7.55 – 7.54 (m, 3H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.38 – 7.32 (m, 3H), 7.27 (t, *J* = 6.5 Hz, 1H), 7.15 – 7.11 (m, 3H), 6.89 (t, *J* = 8.6 Hz, 2H), 6.61 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.57, 166.95, 163.21 (d, *J* = 249 Hz), 157.57, 155.12, 145.97, 137.64, 136.96, 133.42 (d, *J* = 3 Hz), 131.25, 131.10, 129.71, 129.33, 129.10, 129.07, 128.87, 128.79, 127.12, 126.26, 126.10, 125.61, 119.73, 119.34, 115.97

(d, J = 22 Hz), 73.48. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2F$: 485.1660, found: 485.1664.

FTIR (cm^{-1}) 3401, 3022, 2403, 1715, 1655, 1594, 1508, 1421, 1309, 1217, 1123, 1036, 927, 766, 672.

(*S*)-10-(4-Nitrophenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53p)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-4-(1-(4-nitrophenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one **52p** (191.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-10-(4-nitrophenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53p** as a yellow solid (140.0 mg, 55% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.45.

HPLC (Chiralpak IB, 95:05 Pet.ether / IPA, 1.0 mL/min) *Major*: 12.4 min, *Minor*: 13.7 min. ee = 96%, $[\alpha]_D^{25}$ = -121.76 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.77 (dd, J_1 = 6.5, J_2 = 3.1 Hz, 2H), 7.61 – 7.58 (m, 2H), 7.56 – 7.53 (m, 3H), 7.45 (t, J = 8.0 Hz, 2H), 7.40 – 7.25 (m, 6H), 7.16 (s, 1H), 7.01 (d, J = 8.6 Hz, 2H), 6.61 (s. 1H).

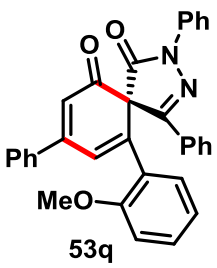
^{13}C NMR (100 MHz, $CDCl_3$) δ 189.46, 166.85, 157.52, 155.05, 145.87, 137.66, 136.99, 136.23, 132.15, 131.33, 131.18, 129.69, 129.41, 129.16, 129.13, 128.45, 127.18, 126.31, 126.18, 125.86, 123.90, 119.80, 119.60, 73.29.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_4N_3$: 512.1605, found: 512.1596.

FTIR (cm^{-1}) 3686, 3626, 3022, 2969, 2403, 1717, 1657, 1595, 1540, 1493, 1375, 1305, 1217, 1077, 1019, 927, 768, 674.

(*S*)-10-(2-Methoxyphenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53q)

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-4-(1-(2-methoxyphenyl)ethylidene)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one **52q** (184.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column



53q

chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-10-(2-methoxyphenyl)-2,4,8-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53q** as a yellow solid (161.0 mg, 65% yield).

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

HPLC (Chiralcel OJ-H, 60:40 Pet.ether / EtOH, 0.5 mL/min) *Minor*: 27.9 min, *Major*: 36.7 min. ee = 90%, $[\alpha]_D^{25}$ = -124.56 (c 0.1, $CHCl_3$).

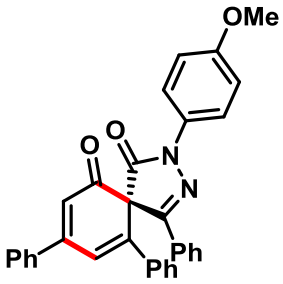
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (d, *J* = 8.4 Hz, 2H), 7.79 (dd, J_1 = 6.6 Hz, J_2 =2.8 Hz, 2H), 7.53 – 7.48 (m, 5H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.29 – 7.19 (m, 4H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.11 (m, 1H), 7.07 (s, 1H), 6.98 (dd, *J* = 15.8, 8.0 Hz, 2H), 6.95 (s, 1H), 3.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.19, 166.58, 157.63, 156.60, 155.56, 144.73, 138.36, 137.20, 131.03, 130.78, 130.50, 130.35, 129.91, 129.21, 128.99, 128.47, 127.16, 127.01, 126.71, 126.65, 125.37, 120.49, 119.10, 118.75, 110.44, 74.74, 55.00.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_3N_2$: 497.1860, found: 497.1864.

FTIR (cm^{-1}) 3367, 3022, 2403, 1716, 1654, 1592, 1490, 1312, 1216, 1123, 1035, 928, 762, 670.

(*S*)-2-(4-Methoxyphenyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53r)



53r

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-2-(4-methoxyphenyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52r** (184.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2-(4-methoxyphenyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53r** as a yellow solid (140.0 mg, 56% yield).

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

HPLC (Chiralpak IB, 70:30 Pet.ether / IPA, 1.0 mL/min) *Major*: 7.1 min, *Minor*: 7.9 min.ee = 95%, $[\alpha]_D^{25}$ = -172.72 (c 0.1, $CHCl_3$).

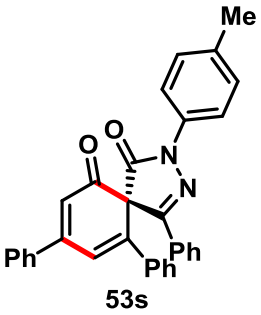
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J_1 = 10.4 Hz, J_2 = 6.5 Hz, 4H), 7.69 (d, J = 6.9 Hz, 2H), 7.67 – 7.59 (m, 3H), 7.44 – 7.40 (m, 3H), 7.37 – 7.21 (m, 6H), 7.05 (d, J = 9.0 Hz, 2H), 6.69 (s, 1H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.01, 166.92, 157.82, 157.58, 155.25, 147.34, 137.42, 137.23, 131.19, 130.99, 130.89, 129.95, 129.45, 129.34, 129.03, 128.88, 127.20, 126.92, 126.31, 125.40, 121.83, 119.42, 114.23, 73.37, 55.65.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_3N_2$: 497.1860, found: 497.1862.

FTIR (cm^{-1}) 3391, 3022, 2404, 1713, 1655, 1593, 1435, 1306, 1217, 1126, 1035, 927, 767, 673.

(*S*)-4,8,10-Triphenyl-2-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53s)



53s

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 μL, 0.75 mmol) and (*E*)-5-phenyl-4-(1-phenylethylidene)-2-(p-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one **52s** (176.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 μL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-4,8,10-triphenyl-2-(p-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53s** as a yellow solid (183.0 mg, 76% yield).

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

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 18.0 min, *Major*: 27.8 min. ee = >99%, $[\alpha]_D^{25}$ = -100.02 (c 0.1, $CHCl_3$).

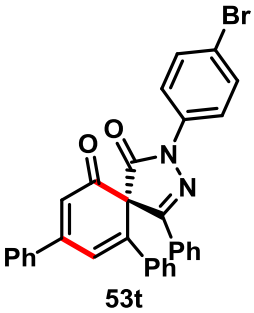
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J_1 = 11.2 Hz, J_2 = 6.0 Hz, 4H), 7.77 – 7.67 (m, 2H), 7.67 – 7.58 (m, 3H), 7.50 – 7.37 (m, 3H), 7.37 – 7.20 (m, 8H), 6.68 (s, 1H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.96, 166.94, 157.61, 155.26, 147.33, 137.43, 137.26, 135.89, 135.37, 131.19, 130.91, 129.98, 129.59, 129.45, 129.35, 129.03, 128.90, 127.21, 126.90, 126.36, 125.41, 119.97, 119.41, 73.52, 21.16.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_2N_2$: 481.1911, found: 481.1914.

FTIR (cm^{-1}) 3395, 3022, 2403, 1592, 1423, 1309, 1217, 1122, 1037, 928, 767, 671.

(*S*)-2-(4-Bromophenyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53t)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-2-(4-bromophenyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52t** (209.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2-(4-bromophenyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53t** as a yellow solid (150.0 mg, 55% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.62.

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.5 mL/min) *Minor*: 21.8 min, *Major*: 26.6 min. ee = >99%, $[\alpha]_D^{25}$ = -191.22 (c 0.1, $CHCl_3$).

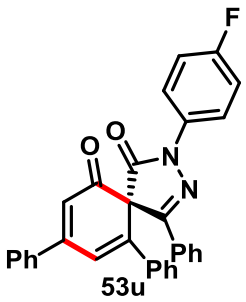
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.78 (dd, J_1 = 6.5 Hz, J_2 = 3.1 Hz, 2H), 7.67 – 7.58 (m, 2H), 7.56 – 7.53 (m, 5H), 7.39 – 7.29 (m, 3H), 7.26 – 7.17 (m, 4H), 7.16 – 7.09 (m, 2H), 6.59 (d, *J* = 0.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.70, 167.03, 158.03, 155.40, 147.07, 137.29, 137.14, 136.87, 132.11, 131.32, 131.21, 129.72, 129.57, 129.40, 129.12, 128.97, 127.23, 126.87, 126.45, 125.59, 121.13, 119.31, 119.00, 73.52.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2Br$: 545.0859, found: 545.0871.

FTIR (cm^{-1}) 3408, 3022, 2403, 1718, 1655, 1591, 1490, 1434, 1375, 1308, 1217, 1128, 1030, 928, 768, 673.

(*S*)-2-(4-Fluorophenyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53u)



Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-2-(4-fluorophenyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52u** (178.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction

mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2-(4-fluorophenyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53u** as a yellow solid (160.0 mg, 66% yield).

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

HPLC (Chiralcel OJ-H, 95:05 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 40.9 min, *Major*: 63.6 min. ee = >99%, $[\alpha]_D^{25}$ = -197.28 (c 0.1, $CHCl_3$).

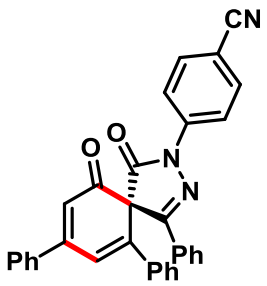
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J_1 = 8.9 Hz, J_2 = 4.7 Hz, 2H), 7.80 – 7.78 (m, 2H), 7.63 (d, *J* = 7.7 Hz, 2H), 7.56 – 7.55 (m, 3H), 7.38 – 7.33 (m, 3H), 7.27 – 7.12 (m, 8H), 6.62 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.80, 167.03, 160.57 (d, 248 Hz), 157.89, 155.36, 147.14, 137.34, 137.16, 133.89 (d, 3Hz) 131.28, 131.11, 129.79, 129.53, 129.38, 129.10, 128.94, 127.22, 126.89, 126.38, 125.54, 121.71, 121.63, 119.34, 115.84 (d, 22 Hz), 73.42.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2$: 485.1660, found: 485.1664.

FTIR (cm^{-1}) 3408, 3022, 2403, 1715, 1654, 1592, 1427, 1309, 1217, 1124, 1036, 927, 767, 672.

(*S*)-4-(1,10-dioxo-4,6,8-Triphenyl-2,3-diazaspiro[4.5]deca-3,6,8-trien-2-yl)benzonitrile (3v)



53v

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-4-(5-oxo-3-phenyl-4-(1-phenylethylidene)-4,5-dihydro-1*H*-pyrazol-1-yl)benzonitrile **52v** (182.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-4-(1,10-dioxo-4,6,8-triphenyl-2,3-diazaspiro[4.5]deca-3,6,8-trien-2-yl)benzonitrile **53v** as a yellow solid (142.0 mg, 58% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.45.

HPLC (Chiralpak IB, 95:05 n-hexane / IPA, 1.0 mL/min) *Minor*: 42.0 min, *Major*: 44.6 min. ee = 94%, $[\alpha]_D^{25}$ = -124.26 (c 0.1, $CHCl_3$).

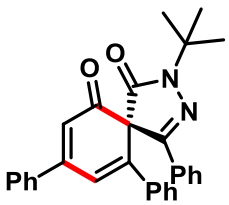
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.79 – 7.77 (m, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.56 – 7.55 (m, 3H), 7.40 – 7.34 (m, 3H), 7.26 – 7.18 (m, 4H), 7.12 (d, *J* = 7.4 Hz, 2H), 6.61 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.30, 167.37, 158.58, 155.55, 146.68, 141.18, 137.08, 136.91, 133.27, 131.55, 131.44, 129.66, 129.41, 129.36, 129.19, 129.02, 127.20, 126.77, 126.52, 125.76, 119.20, 119.06, 118.81, 108.74, 73.49.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{22}O_2N_3$: 492.1707, found: 492.1696.

FTIR (cm^{-1}) 3365, 3022, 2403, 1725, 1653, 1595, 1422, 1309, 1216, 1036, 928, 766, 671.

(*S*)-2-(*tert*-Butyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53w)



53w

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 μL, 0.75 mmol) and (*E*)-2-(*tert*-butyl)-5-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52w** (159.0 mg, 0.50 mmol) with triazolium salt **4** (28.0 mg, 0.075 mmol), oxidant **5** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 μL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2-(*tert*-butyl)-4,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53w** as a yellow solid (115.0 mg, 52% yield).

R$_f$ (Pet. ether /EtOAc = 80/20): 0.46.

HPLC (Chiralpak IB, 95:05 Pet.ether / IPA, 1.0 mL/min) *Minor*: 8.4 min, *Major*: 9.7 min. ee = 80%, $[\alpha]_D^{25}$ = -200.62 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J_1 = 6.6 Hz, J_2 = 2.8 Hz, 2H), 7.76 – 7.61 (m, 5H), 7.47 – 7.37 (m, 7H), 7.33 (d, J = 7.0 Hz, 2H), 6.71 (s, 1H), 1.70 (s, 9H).

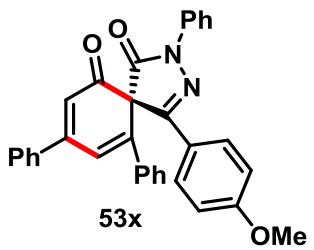
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.39, 155.21, 155.01, 147.77, 137.61, 137.46, 130.96, 130.64, 130.18, 129.27, 129.20, 128.89, 128.55, 127.19, 127.15, 125.92, 124.99, 119.74, 74.10, 59.01, 28.19.

HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{27}O_2N_2$: 447.2067, found: 447.2069.

FTIR (cm^{-1}) 3358, 3022, 2403, 1715, 1654, 1593, 1492, 1417, 1375, 1217, 1124, 1036, 928, 767, 671.

(*S*)-4-(4-Methoxyphenyl)-2,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53x)

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 μL, 0.75 mmol) and (*E*)-5-(4-methoxyphenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52x** (184.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 μL, 0.5 mmol)



53x

in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-4-(4-methoxyphenyl)-2,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53x** as a yellow solid (153.9 mg, 62% yield).

***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.42.

HPLC (Chiralcel OJ-H, 90:10 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 59.1 min, *Major*: 73.1 min. ee = 98%, $[\alpha]_D^{25}$ = -165.14 (c 0.1, $CHCl_3$).

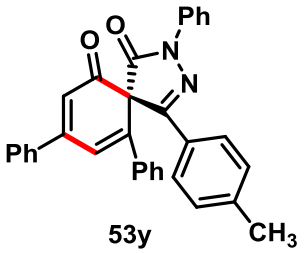
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.80-7.78 (m, 2H), 7.60-7.54 (m, 5H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.27-7.19 (m, 7H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.61 (s, 1H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.08, 167.05, 161.79, 157.43, 155.16, 147.45, 137.88, 137.44, 137.21, 131.18, 129.42, 129.33, 129.01, 128.89, 128.02, 127.18, 126.92, 125.87, 125.33, 122.61, 119.80, 119.34, 114.53, 73.63, 55.44.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_3N_2$: 497.1860, found: 497.1861.

FTIR (cm^{-1}) 3391, 3022, 2403, 1713, 1654, 1599, 1506, 1424, 1375, 1310, 1217, 1126, 1033, 926, 764, 671.

(*S*)-2,8,10-Triphenyl-4-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53y)



53y

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 µL, 0.75 mmol) and (*E*)-2-phenyl-4-(1-phenylethylidene)-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one **52y** (176.0 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-2,8,10-triphenyl-4-(*p*-tolyl)-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53y** as a yellow solid (200.0 mg, 50% yield).

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

HPLC (Chiralpak AD, 50:50 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 7.9 min, *Major*: 16.7 min. ee = 94%, $[\alpha]_D^{25}$ = -201.18 (c 0.1, $CHCl_3$).

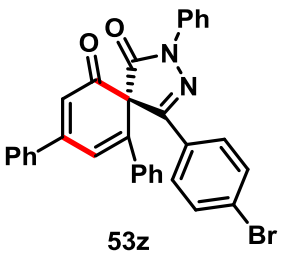
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.9 Hz, 2H), 7.79-7.78 (m, 2H), 7.55 – 7.51 (m, 5H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.26-7.11 (m, 9H), 6.59 (s, 1H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.00, 167.10, 157.78, 155.22, 147.37, 141.45, 137.85, 137.43, 137.27, 131.18, 129.81, 129.44, 129.35, 129.05, 128.91, 127.20, 126.94, 126.34, 125.96, 125.40, 119.87, 119.40, 73.60, 21.64.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{25}O_2N_2$: 481.1911, found: 481.1901.

FTIR (cm^{-1}) 3397, 3020, 2400, 2360, 1717, 1658, 1598, 1548, 1416, 1301, 1216, 1174, 1134, 1070, 771, 669.

(*S*)-4-(4-Bromophenyl)-2,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53z)



53z

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 μL, 0.75 mmol) and (*E*)-5-(4-bromophenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52z** (208.6 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075 mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 μL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-4-(4-bromophenyl)-2,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53z** as a yellow solid (130.0 mg, 48% yield).

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

ee = >99%, $[\alpha]_D^{25}$ = -192.20 (c 0.1, $CHCl_3$).

HPLC (Chiralcel OJ-H, 50:50 Pet.ether / EtOH, 0.7 mL/min) *Minor*: 23.3 min, *Major*: 31.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.79 (s, 2H), 7.56-7.48 (s, 9H), 7.28-7.17 (m, 7H), 6.61 (s, 1H).

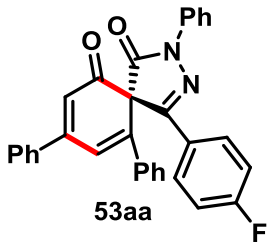
^{13}C NMR (100 MHz, $CDCl_3$) δ 189.56, 166.75, 156.80, 155.41, 146.85, 137.64, 137.18, 137.00, 132.32, 131.32, 129.62, 129.37, 129.11, 129.03, 128.80, 127.69, 127.17, 126.70, 126.19, 125.57, 125.45, 119.85, 119.20, 73.36.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2Br$: 545.0859, found: 545.0865.

FTIR (cm^{-1}) 3384, 3022, 2403, 1719, 1655, 1593, 1493, 1307, 1217, 1126, 1038, 926, 767, 673.

(*S*)-4-(4-Fluorophenyl)-2,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione (53aa)

Following the general procedure, treatment of cinnamaldehyde **51a** (99.1 mg, 95 μL, 0.75 mmol) and (*E*)-5-(4-fluorophenyl)-2-phenyl-4-(1-phenylethylidene)-2,4-dihydro-3*H*-pyrazol-3-one **52aa** (178.2 mg, 0.50 mmol) with triazolium salt **A** (28.0 mg, 0.075



53aa

mmol), oxidant **14** (409.0 mg, 2.0 equiv) and DBU (76.1 mg, 75 µL, 0.5 mmol) in THF (12.0 mL) and stirring the reaction mixture at 25 °C for 24 h followed by flash column chromatography (Pet. ether- EtOAc: 90:10) to afford (*S*)-4-(4-fluorophenyl)-2,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7,9-triene-1,6-dione **53aa** as a yellow solid (116.0 mg, 48% yield).

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

HPLC (Chiralpak AD, 50:50 Pet.ether / EtOH, 1.0 mL/min) *Minor*: 11.5 min, *Major*: 15.2 min. ee = 96%, $[\alpha]_D^{25}$ = -196.52 (c 0.1, $CHCl_3$).

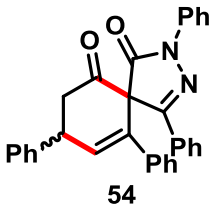
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.81-7.78 (m, 2H), 7.64 – 7.54 (m, 5H), 7.48-7.44 (m, 2H), 7.30-7.16 (m, 7H), 7.03 (t, *J* = 8.6 Hz, 2H), 6.61 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.73, 166.81, 164.26 (d, J = 252.9 Hz), 156.76, 155.41, 146.98, 137.71, 137.25, 137.03, 131.32, 129.58, 129.37, 129.00 (J = 10.67 Hz), 128.39 (J = 8.65 Hz), 127.19, 126.73, 126.11, 125.53, 119.82, 119.21, 116.31(J = 22.2 Hz), 73.54

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{22}O_2N_2F$: 485.1660, found: 485.1651.

FTIR (cm^{-1}) 3391, 3022, 2403, 1713, 1654, 1506, 1375, 1126, 926, 764.

2,4,8,10-Tetraphenyl-2,3-diazaspiro[4.5]deca-3,9-diene-1,6-dione (54)



54

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

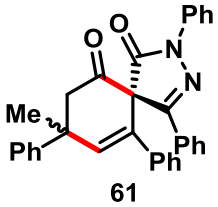
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.51 – 7.26 (m, 10H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.16 – 7.07 (m, 2H), 6.99 (d, *J* = 7.0 Hz, 2H), 6.61 (d, *J* = 4.6 Hz, 1H), 4.62 – 4.46 (m, 1H), 3.76 (dd, J_1 = 14.8 Hz, J_2= 7.8 Hz, 1H), 2.96 (dd, J_1 = 14.8 Hz, J_2= 4.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.30, 168.20, 157.81, 142.02, 138.19, 137.86, 135.85, 134.46, 130.67, 130.24, 129.26, 129.13, 128.65, 128.53, 128.43, 127.45, 127.38, 126.93, 126.86, 126.08, 119.73, 73.43, 42.18, 41.72.

HRMS (ESI) calculated $[M+H]^+$ for $C_{32}H_{25}O_2N_2$: 469.1911, found: 469.1900.

FTIR (cm^{-1}) 3391, 3022, 2403, 1713, 1506, 1310, 1217, 1126, 1033, 926, 764, 671.

(5*S*)-8-Methyl-2,4,8,10-tetraphenyl-2,3-diazaspiro[4.5]deca-3,9-diene-1,6-dione (61)



***R*$_f$** (Pet. ether /EtOAc = 80/20): 0.42.

HPLC (Chiralcel OD-RH, 80:20 ACN / H_2O, 0.5 mL/min) d.r.1- *Minor*: 11.11 min, *Major*: 12.07 min, d.r.2 - *Minor*: 11.16 min, *Major*: 12.11 min. d.r.1- 96% ee, d.r.2- 94% ee, $[\alpha]_D^{25}$ = -142.32 (c 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 7.9, 2H), 7.71 (d, *J* = 7. 3 Hz, 2H), 7.51 (t, *J* = 6.5 Hz, 2H), 7.49 – 7.42 (m, 8H), 7.39 – 7.33 (m, 5H), 7.30 – 7.23 (m, 5H), 7.15 –7.09 (m, 6H), 7.01 (m, 6H), 6.67 (s, 1H), 6.42 (s, 1H), 3.96 (d, *J* = 13.3 Hz, 1H), 3.66 (d, *J* = 13.6 Hz, 1H), 3.33 (d, *J* = 13.6 Hz, 1H), 2.69 (d, *J* = 13.2 Hz, 1H), 1.80 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.78, 167.62, 158.07, 157.73, 146.65, 145.60, 140.03, 139.91, 138.06, 137.99, 137.89, 137.80, 134.29, 133.72, 130.75, 130.67, 130.45, 129.78, 129.14, 129.06, 128.97, 128.67, 128.56, 128.41, 128.35, 127.21, 127.12, 126.76, 126.67, 126.33, 126.08, 126.05, 126.00, 119.67, 76.84, 73.30, 50.47, 48.38, 44.96, 44.00, 32.96, 25.99.

HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{27}O_2N_2$: 483.2067, found: 483.257.

FTIR (cm^{-1}) 3391, 3022, 2403, 1713, 1654, 1599, 1506, 1424, 1310, 1217, 1126, 1033, 926, 164, 671.

5.6. References

1. Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A. Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.
2. Shen, L.-T.; Shao, P.-L.; Ye, S. *Adv. Synth. Catal*. **2011**, *353*, 1943.
3. Mo, J.; Shen, L.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810.
4. Chen, X.; Yang, S.; Song, B. A.; Chi, Y. R. *Angew. Chem., Int., Ed.* **2013**, *52*, 11134.
5. Zhu, T.; Zheng, P.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. *Nat. Commun*. **2014,** *5*, 5027.
6. (a) Yao, C.; Xiao, Z.; Liu, R.; Li, T.; Jiao, W.; Yu, C. *Chem. Eur. J*. **2013**, 19, 456. (b) Xiao, Z.; Yu, C.; Li, T.; Wang, X.-S.; Yao, C. *Org. Lett.* **2014,** *16*, 3632.
7. Zhao, T.-M.; Cheung, M. S.; Lin, Z.; Sun, J. *Angew. Chem., Int. Ed*. **2012**, *51*, 10359.
8. Chen, X.-Y.; Xia, F.; Cheng, J.-T.; Ye, S. *Angew. Chem., Int. Ed*. **2013**, *52*, 10644.

9. Xu, J.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2013,** *15*, 5028.
10. Que, Y.; Xie, Y.; Li, T.; Yu, C.; Tu, S.; Yao, C.; *Org. Lett.* **2015**, *17*, 6234.
11. Li, B.-S.; Wang, Y.; Jin, Z.; Zheng, P.; Ganguly, R.; Chi, Y. R. *Nat. Commun*. **2015,** *6*, 6207.
12. (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 4694; for related [4+2] annulations, see: (b) Candish, L.; Levens, A.; Lupton, D. W. *J. Am. Chem. Soc.* **2014**, 136, 14397.
13. (a) Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. *Adv. Synth. Catal*. **2013**, *355*, 1089. (b) Yetra, S. R.; Kaicharla, T.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. *Org. Lett*. **2013**, *15*, 5202. (c) Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A. T. *J. Org. Chem*. **2014**, *79*, 4245. (d) Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett*. **2015**, *17*, 1417.
14. For a review on vinylogous Michael reaction, see: Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531.
15. Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal*. **2014,** *356*, 2330.
16. For reports on base-free NHC-organocatalysis, see: a) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun*. **2011**, *47*, 8670. b) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810.
17. CCDC 1417494.
18. (a) Collins, K. D.; Glorius, F. *Nat. Chem*. **2013**, *5*, 597; (b) Collins, K. D.; Rühling, A.; Glorius, F. *Nat. Protoc*. **2014**, *9*, 1348.
19. Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.
20. Yetra, S. R.; Mondal, S.; Mukherjee, S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2016,** *55*, 268.
21. Wubea, A. A.; Hüfner, A.; Thomaschitz, C.; Blunder, M.; Kollroser, M.; Bauer, R.; Bucar, F. *Bioorg. Med. Chem*. **2011**, *19*, 567.
22. (a) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem. Int. Ed*. **2014**, *53*, 5643. (b) Liu, Y.; Yang, Y.; Huang, Y.; Xu, X.-H.; Qing, F.-L. *Synlett.* **2015**, *26*, 67.
23. Struble, J. R.; Bode, J. W. *Org. Synth.* **2010,** *87*, 362.
24. Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

25. Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112.

26. Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143.

List of Publications:

1. Mukherjee, S.; Joseph, S.; Bhunia, A.; Gonnade, R. G.; **Yetra, S. R**.; Biju, A. T ., Enantioselective Synthesis of Spiro γ-Butyrolactones by NHC-Catalyzed Formal [3+2] Annulation of Enals with Dioxindoles. (*Manuscript Submitted*)
2. Bhunia, A.; **Yetra, S. R**.; Gonnade, R. G.; Biju, A. T., Synthesis of 4H-chromenes by an unexpected, K_3PO_4-mediated intramolecular Rauhut-Currier type reaction. *Org. Biomol. Chem*. **2016**, *15*, 5612.
3. Enantioselective Synthesis of Spirocyclohexadienones by NHC-Catalyzed Formal [3+3] Annulation Reaction of Enals.
   Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T.
   Angew. Chem., Int. Ed. **2016**, *55*, 268.
4. Diastereoselective Synthesis of Cyclopentanone-Fused Spirooxindoles by N-Heterocyclic Carbene-Catalyzed Homoenolate Annulation with Isatilidenes.
   Patra, A.; Bhunia, A.; **Yetra, S. R**.; Gonnade, R. G.; Biju, A. T.
   Org. Chem. Front. **2015**, *02*, 1584.
5. Enantioselective Synthesis of Functionalized Pyrazoles by NHC-Catalyzed Reaction of Pyrazolones with Alpha,Beta-Unsaturated Aldehydes.
   Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T.
   Org. Lett. **2015**, *17*, 1417.
6. Recent Advances in the N-Heterocyclic Carbene (NHC)-Organocatalyzed Stetter Reaction and Related Chemistry.
   Yetra, S. R.; Patra, A.; Biju, A. T.
   Synthesis. **2015**, *47*, 1357.
7. N-Heterocyclic Carbene-Catalyzed Enantioselective Synthesis of Functionalized Cyclopentenes via α,β-Unsaturated Acylazoliums.
   Mondal, S.; **Yetra, S. R**.; Patra, A.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T.
   Chem. Commun. **2014**, *50*, 14539.
8. Synthesis of Functionalized Coumarins and Quinolinones by NHC-Catalyzed Annulation of Modified Enals with Heterocyclic C-H Acids.
   Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A. T.
   J. Org. Chem. **2014**, *79*, 4245.
9. Asymmetric N-Heterocyclic Carbene-Catalyzed Annulation of Modified Enals with Enolizable Aldehydes.

Yetra, S. R.; Trinadh, K.; Kunte, S. S.; Gonade, R. G.; Biju, A. T.
Org. Lett. **2013**, *15*, 5202.

10. Engaging Isatins in Solvent- Free, Sterically Congested Passerini Reaction.
Trinadh, K.; **Yetra, S. R.**; Roy, T.; Biju, A. T.
Green Chem. **2013**, *15*, 1608.

11. Enantioselective N-Heterocyclic Carbene-Catalyzed Annulations of 2-Bromoenals with 1,3-Dicarbonyl Compounds and Enamines via Chiral α,β-Unsaturated Acylazoliums.
Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T.
Adv. Synth. Catal. **2013**, *355*, 1089.

12. Efficient Synthesis of γ-Keto Sulfones by NHC-Catalyzed Intermolecular Stetter Reaction.
Bhunia, A.; **Yetra, S. R.**; Bhojgude, S. S.; Biju, A. T.
Org. Lett. **2012**, *14*, 2830.

13. Recent Advances in Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions Using Arynes.
Bhunia, A.; **Yetra, S. R.**; Biju, A. T.
Chem. Soc. Rev. **2012**, *41*, 3140.

Patents:

1. Enantioselective Synthesis of Spirocyclohexadienones by NHC-Catalyzed Formal [3+3] Annulation Reaction of Enals.
Biju, A. T.; Yetra, S. R.; Mondal, S.; Mukherjee, S.
PCT Int. Appl. (Application date. 10/9/2015)

2. Novel Oxindole Derivatives and their Solvent Free Synthesis.
Biju, A. T.; Kaicharla, T.; **Yetra, S. R.**; Roy, T.
PCT Int. Appl. (Application No. 0992- DEL -2013).

3. A Process for the Enantioselective NHC-Catalyzed Synthesis of 4, 5-Disubstituted Dihydropyranones.
Biju, A. T.; **Yetra, S. R.**; Kaicharla, T.
PCT Int. Appl. (Application No. 1385/ DEL/ 2013).