"ORGANOCATALYTIC CASCADE REACTION FOR THE SYNYHESIS OF POLYCYLIC COMPOUNDS UTILIZING TRIENAMINE ACTIVATION"

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Abbreviation

Ar	Aromatic
ApDOS	Aminocatalytic Privileged Diversity-Oriented Synthesis
Boc	*tert*-Butoxycarbonyl protecting group
C-C	Carbon carbon bond
C-X	Carbon heteroatom bond
DMF	*N.N*-Dimethyl formamide
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
d	Doublet
dd	Doublet of doublet
DMAP	4-Dimethylaminopyridine
DIBAL	Diisobutylaluminium hydride
DA	Diels–Alder reaction
DOS	Diversity-Oriented Synthesis
dr	Diasteromeric ratio
E	Electrophile
AcOEt	Ethyl acetate
ee	Enantiomeric excess
NEt_3	Triethylamine
Equiv.	Equivalents
Et	Ethyl
g	Gram

h	Hours
IBX	2-Iodo benzoic acid
J	Coupling constant
LUMO	Lowest Unoccupied Molecular Orbital
mg	Miligram
MHz	Megahertz
Me	Methyl
min	Minutes
MeOH	Methanol
mmol	Milimole
MsCl	Mesyl chloride
m	Multiplet
ml	Mililitre
µl	Microlitre
mmol	Milimole
NaOAc	Sodium acetate
***n*-BuLi**	*n*-Butyllithium
$NaBH_4$	Sodium borohydride
Nu	Nucleophile
AcO	Acetoxy group
pDOS	Privileged Diversity-Oriented Synthesis
Ph	Phenyl
ppm	Parts per million

pKa	The negative decadic logarithm of the ionization constant (K_a) of an acid
r.t.	Room Temperature
s	Singlet
TsO	Tosyloxy group
THF	Tetrahydrofuran
TMS	Trimethylsilyl group
td	Triplet of doublet
t	Triplet
TOS	Target-Oriented Synthesis

Content Pg. No.

CH-1 Introduction

1.1 Molecular Diversity 13

1.1.1 Chemical Genetics 13

1.2 Target Oriented Synthesis 14

1.3 Diversity Oriented Synthesis 15

1.4 Background of Organocatalysis 17

1.5 Aminocatalysis 17

1.5.1 The concept of modes of activation (enamine and iminum ion) 18

1.5.2 Aminocatalytic remote fuctionalization 21

1.5.2.1 Dienamine Activation 23

1.5.2.2 Trienamine Activation 23

1.5.2.3 Cross trienamine Activation 24

1.5.2.4 Tetraenamine Activation 24

1.5.2.5 Vinylogous iminium ion Activation 24

1.5.3 Catalytic System in aminocatalysis 24

1.6 The ApDOS concept 26

1.7 Organocatalytic cascade reaction 27

1.8 Summary 30

CHAPTER 2

31

2.1 Organocatalytic Cascade Reactions via Trienamine Activation 33

2.2 Introduction and design plan 35

2.2.1. Isatin Moiety as a dienophile in organocatlysis: Some new pathways to access enantioenriched privileged scaffolds 36

2.2.1.1. Conceptualization of the project**:** 37

2.2.1.2 Hypothesis 39

2.2.1.3 Objective 39

2.2.1.4 Result and Discussion 40

A) Nitro-oxindole as dienophile via trienamine catalysis 46

B) 1, 6-Oxa-Michael cycloaddition of iminium ion with ester-olefinic oxindole 48

	2.2.1.5 Perspective	52
	2.2.1.6 Conclusion	53
	Project	
2.3	Dithioamides as a hetero-dienophile in organocatlysis: Some new pathways to access enantioenriched privileged scaffolds.:	55
	2.3.1.1 Conceptualization of the project	56
	2.3.1.2 Hypothesis	57
	2.3.1.3 Objective	57
	2.3.1.4 Result and Discussion	58
	2.3.1.5 Asymmetric one pot reaction: Synthesis of the thiopyrano-piperidone-tetrahydrocarboline via trienamine catalysis	63
	2.3.1.6 Asymmetric bis-cascade reaction:	68
	2.3.1.7 Perspective	69
	2.3.1.8 Conclusion	70
	CHAPTER 3	
CH3-	**Experimental Section**	73
3.1	Synthesis of aldehydes used for aminocatalysis	73
	4.1.1 Synthesis of 2,4-dienal	77
	4.1.2 Synthesis of 2-methyl indole acryldehyde	79
	4.1.3 Synthesis of hydroxy aldehyde	79
3.2	Synthesis of aminocatalysis	
	4.2.1 Synthesis of (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine	
3.3	General procedure for synthesis of Cyano-ester oxindole	80
3.4	General procedure for the synthesis of nitro-oxindole olefin	81
3.5	General procedure for the synthesis of ester oxindole olefin	
3.6	Synthesis of thiopyrano-piperidone cycloadducts and derivatization.	
	4.6.1 Synthesis of chloro-amides	81
	4.6.2 Synthesis of dithioamides	
	4.6.3 Synthesis of bis-dithioamides	84
3.7	Synthesis of thiopyrano-piperidone cycloadducts	86
3.8	Synthesis of thiopyarano-piperidone indole adduct	93
3.9	Synthesis of bis-thiopyrano-piperidone adduct	96

CHAPTER 4

Appendix-I 97

Appendix II 120

Chapter 1

1.1 Molecular Diversity

Currently, one of the most interesting topics of research in chemistry and biology is the discovery of small molecule, which may act as perturbing agents in biological systems and these agents activate specific gene product by direct interaction. Therefore, there is huge demand to find or create diverse and complex molecules, which can serve as modulators of different biological processes. In this context, the extraordinarily vast set of organized chemical structures distributed over the whole of chemical space that a cover a wide range of molecular diversity, has defined development of new arising area in biology and chemistry such as chemical genetics and medicinal chemistry.

1.1.1 Chemical genetics

A biological system composed of small molecules is known as chemical genetics. In chemical genetics, the study of gene function carried out by altering the activity of the cognate protein, using small molecule inhibitors analogous to the genetic knockout. The working style of chemical genetics is divided into two ways: forwards and reverse chemical genetics. In forward chemical genetics, small molecules are incorporated to inflect gene production function, compounds that activate a phenotype of interest are selected and then the protein, which they target are screened. On the other hand, reverse chemical genetics similarly involves a specific protein (or gene product) that is screened with libraries of small molecules to identify ligands that perturb its function. Once an appropriate protein binding partner is identified, it is introduced into a cell or organism and the resulting phenotypic changes are studied; the ligand is used to mimic the effects of a genetic mutation. The employment of small molecules provides extensive advantages compared to traditional genetics techniques. The study of the systems which can not be investigated using a classical genetics way, chemical genetics provide the greatest impact on that field, chemical genetics can be readily applied in either cellular or organismal contexts, etc. Chemical genetics is a subsection of chemical biology and as such it operates at the interface of several research fields. Despite all the other advantages, this area is closely related to the Diversity-Oriented Synthesis and can be used with the combination of traditional genetic techniques to discover novel targets for various therapies, drug

discovery, etc. For such reason, nowadays the field of chemical biology is expanding rapidly.

1.2 Target oriented synthesis

The greatest supplier of a great variety of molecular entities within the chemical space has been nurtured through natural products. The first libraries of compounds directed to molecular diversity were designed through combinatorial chemistry to generate similar or analogous compounds to each other, which are later systematically analyzed to determine their interactions with biological systems and in activities related to the natural product of origin. This type of small molecular collection is part of the target Oriented Synthesis (TOS) strategy, which is widely used to search for small compounds. With the help of target-oriented synthesis, find the appropriate pathway to synthesize the target molecule. (Fig. 1) The main aim of the TOS is most often a natural product, complex molecules discovered by nature through many processes of diversity generation and selection. Pharmaceutical industries are attracted for the targets are drugs or library of a drug candidate to discover solutions to otherwise intractably complex problems in chemistry and medicine. In 1960 a method, which helps to develop an appropriate synthetic strategy was introduced.[1] This technique called retrosynthesis is effective and involves the recognition of crucial structural elements in the target molecule, rather than substrate, which code for synthetic transformation. The application of this process allows a synthetic chemist to start with a structurally complex target and structurally simple compound that can be used to start from a synthesis. This strategy won't be able to leads frequently to new discoveries that have a profound impact on this area, due to the fact that they only modulate functional factors of the same biological activity instead of seeking responses to totally different processes. As a result, the development of new drugs that can treat diseases for which there are not yet showing any considerable slowed down.

[1] Corey, E.J.; Cheng, X, M.; *The Logic of Chemical Synthesis*, **1989**, *52*, 4527.

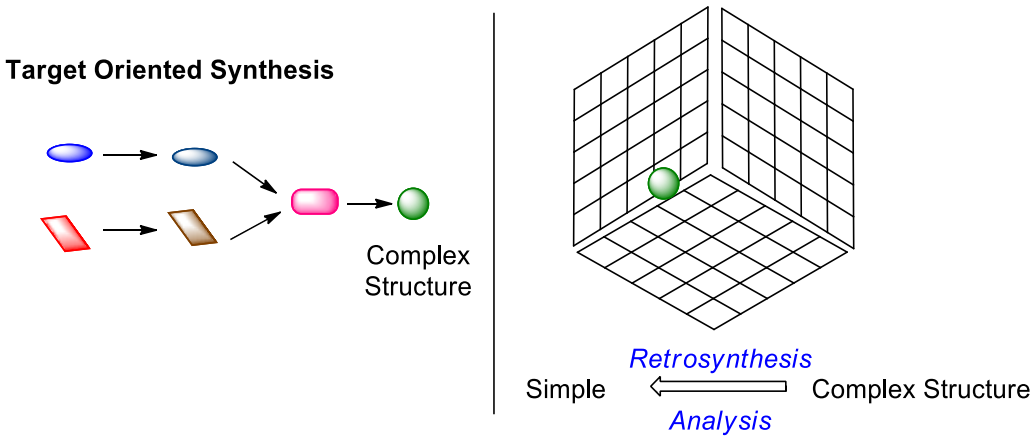


Fig.1 Target Oriented Synthesis concept.

1.3 Diversity-Oriented Synthesis

In order to solve the problems associated with the generation of molecular libraries with the maximum of structural and stereochemical diversity, In 2020, Schreiber et al. a proposed a new strategy called Diversity-Oriented Synthesis (DOS).[1] In recent years, library sizes in both industry and academia have increased dramatically, though now the emphasis is set on the quality of the library as well as the quantity. It has been recognized that different target types require different compound selection. For example, compounds that will target kinases may not be appropriate for proteases. With the expansion of the druggable genome, more diverse libraries appropriate for different sets of targets are required. The diversity-oriented synthesis was borne out of these requirements, which aim to populate new chemical spaces randomly with molecules of high complexity and added value. The libraries generated by DOS are composed of highly diverse compounds, some of them with new stereocenters and which are an essential part of the set of parameters necessary for the identification of a particular phenotype. In order to make the most of this technique, a third strategy called privileged Diversity-Oriented Synthesis (pDOS) was introduced after the DOS conceptualization. This strategy uses important base skeletons from the biological point of view. Therefore, there is a higher probability of finding molecules with biological activity. The strategies typically employed in synthetic chemistry

can be broadly classified into three approaches that are distinguished by chronology, philosophy, and coverage of chemical space (Figure 2).[2]

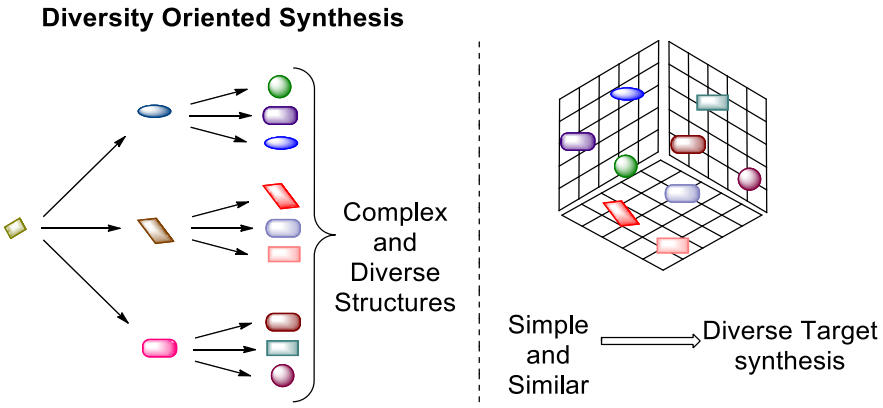


Fig.2: The Diversity Oriented Synthesis concept.

The main goal of the pDOS strategy is to explore and discover small bioactive molecules. In 1988 Evans and co-workers demonstrated as a single molecular framework could provide high-affinity ligands for more than one type of receptor.[3]. Privileges structure moieties found in a wide range of diverse bioactive molecules, natural products, and therapeutic reagents. Therefore, a small molecule library is involved with privileged structures maximizing the potential for the discovery of bioactive compounds. Therefore, pDOS represent an efficient and rational strategy for creating libraries of relevant architectures that can populate bioactive regions in chemical space.

[2] Schreiber S. L: *Target-oriented and diversity-oriented organic synthesis in drug discovery.* Science **2000**, 287: 1964-1969

[3]. Evans, B. E; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M,; Whitter, W. L.; Lundell, G. F.; Veber, G. F. Anderson, ; P. S.; Chang, R. S. L ; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.;. Kunkel, K. A.;. Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235-2246.

1.4 Background of Organocatalysis

While the DOS conceptualization, the evolution of asymmetric catalysis facilitated by small-molecule organic compounds also took place.[4] At the same time, the concept of organocatalysis was effectively demonstrated. The use of small organic molecule to catalyze organic transformations in smooth and profitable manner is known as organocatalysis. [5,6] MacMillan[7] and List,[8] who reported two ingenious methodologies. From then, organocatlysis has become the third pillar of asymmetric catalysis. Between 2000 and 2020, thousand of publications have been reported in this field and new developments will continue to appear in the future. Nowadays, different organocatlytic activation modes have been developed. Specifically, aminocatalysis have been played vital role due to its ability to functionalize carbonyl compound in a stereoselective manner. This type of catalysis has led to the development of a great variety of enantioselective transformations and the construction of a wide range of enantioenriched compounds. Moreover, the investigation of this Ph.D thesis mainly was focused on these strategies. In the next chapter will be disclosed in detail.

1.5 Aminocatalysis

Asymmetric aminocatalysis has been of great interest due to the ability to functionalize stereoselectively carbonyl compounds. The knowledge that chiral amines can be used to activate carbonyl compounds through fundamental concepts of reactivity has been crucial in the evolution of this field.

Activation by increasing the HOMO, enolizable carbonyl compounds **1** are activated because of the formation of an intermediate enamine **3**, which increases the HOMO energy. Thus, α carbons have a high nucleophilic degree (Scheme 1).

---

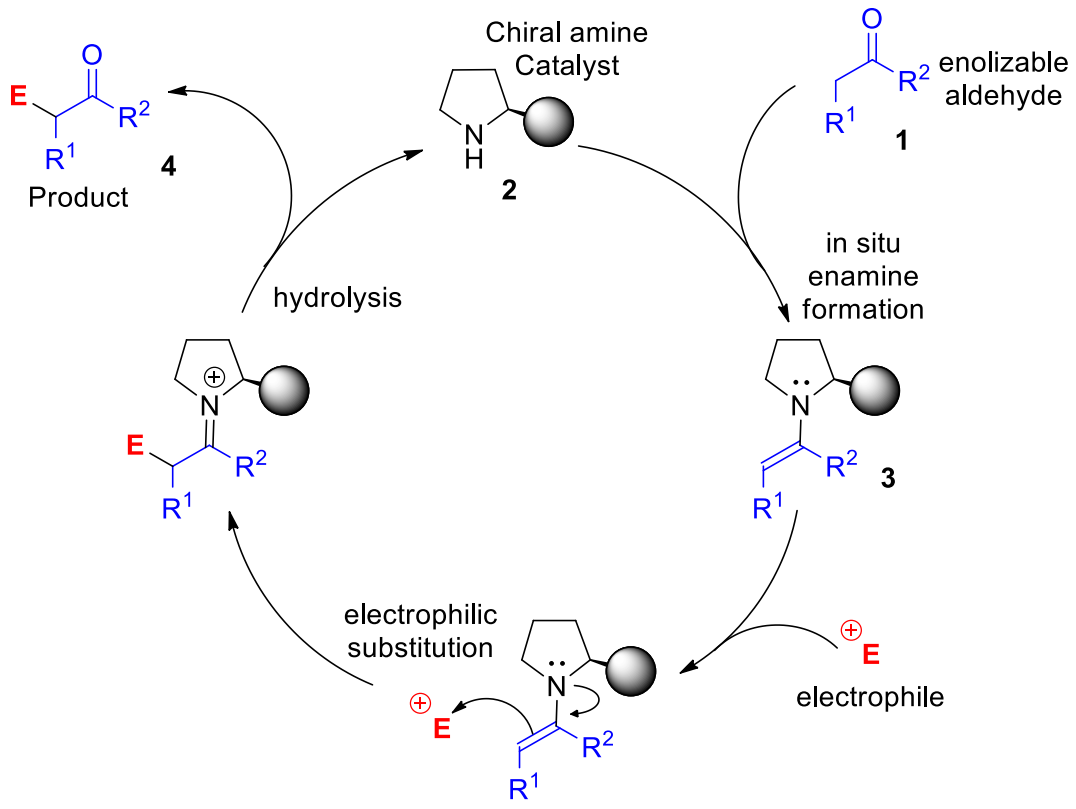
4. MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308.

5 Berkessel, A.; Groeger, H. *Asymmetric Organocatalysis*, **2005**, Wiley-VCH, 409-435.

6 Reetz, M.T.; List, B.; Jaroch, S.; Weinmann, H. *Ernst Schering Foundation Symposium Proceedings* **2007**-2 Organocatalysis.

7 Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am Chem. Soc.* **2000**, *122*, 9874-9875

8. List, B.;. Lerner, R. A.;. Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

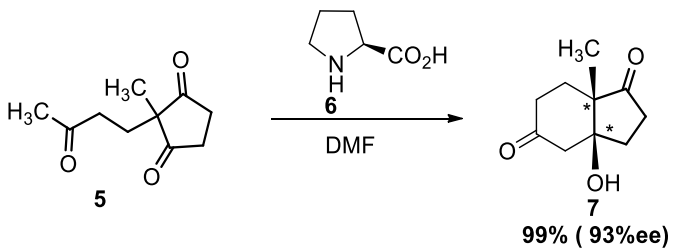


Scheme 1: Catalytic cycle of the enamine activation.

Many important intramolecular reactions, such as aldol reaction, Michael addition, transannular reactions, *α*-alkylations among others undergoes by enamine catalysis. A pioneering reaction was reported in the 1971 and is called the Hajos–Parrish reaction (Scheme 2). Zoltan Hajos & David Parrish[9] and Rudolf Weichert, Gerhard Sauer & Ulrich Eder[10] were independently reported an enantioselective intramolecular aldol reaction which was catalyzed by proline. **6** After this tremendous invention, up to 1997, there were very few reports about the use organic catalysts for asymmetric synthesis, but these chemical studies were viewed more as unique chemical reactions than as integral parts of a larger, interconnected field.

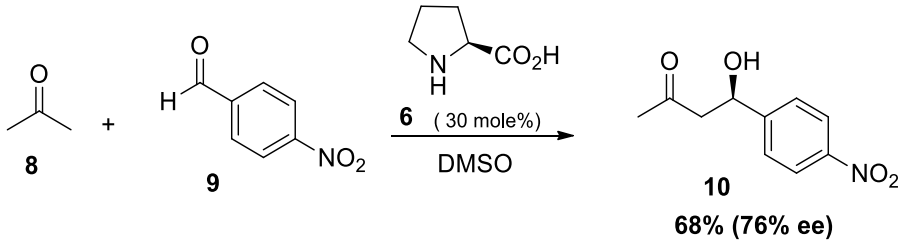
[9] Hajos, Z. G.; Parrish, D. R. *German patent,* **1971**, DE 2102623.

[10] Eder, U.; Sauer, G. R.; Wiechert, R. *German patent,* **1971**, DE 2014757.



Scheme 2: First enantioselective intramolecular aldol condensation.

In 2000, Barbas, Lerner and List used enamine catalyst to functionalize carbonyl compounds at the α-carbon.[11] **8** This result is quite remarkable since it is known that proline **6** can undergo a variety of reactions with aldehydes **9** (Scheme 3). After that, tremendous work has been carried out towards identifying new types of chiral enamine catalysts.



Scheme 3: Proline-catalyzed direct asymmetric aldol reaction

On the other hand, the effect of LUMO lowering is considered the principle of the activation via iminium ion catalysis. This activation mode is based on the ability aminocatalyst **2** to condense reversibly with α,β-unsaturated carbonyl compounds **11** to form an iminium intermediate **12**, which means their β carbon atoms are susceptible to nucleophilic attack due to the LUMO energy decrease **13** (Scheme 4).

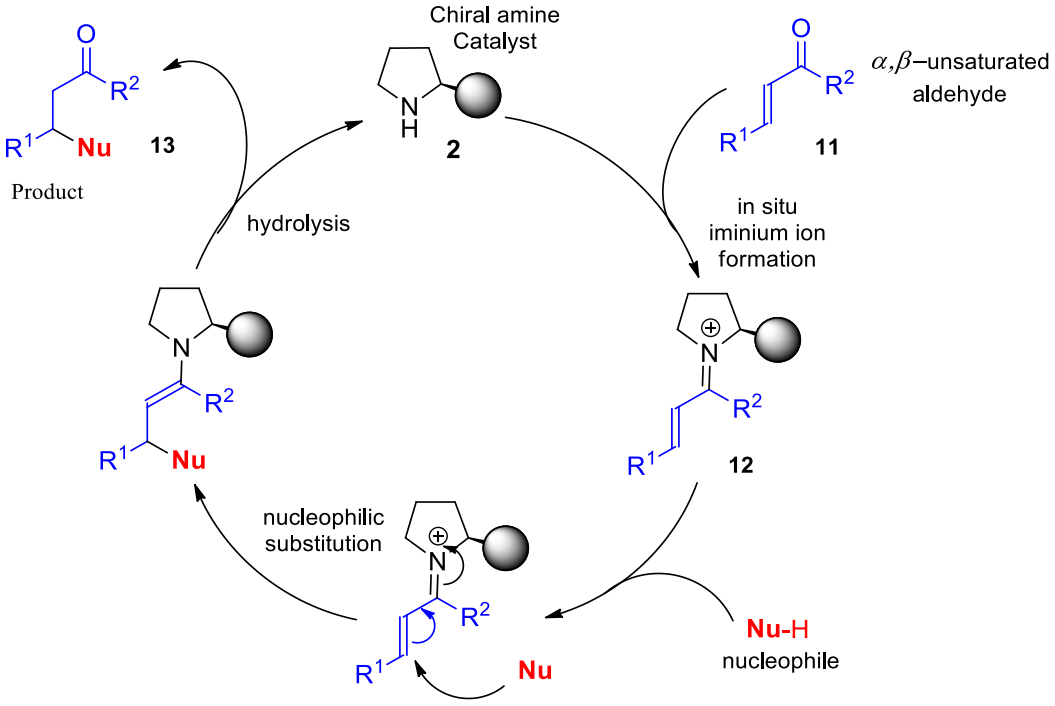
The LUMO-lowering effect is the underlying activation principle of iminium ion catalysis.[12,13] This aminocatalytic mode is based on the ability of a aminocatalyst to reversibly condense with α, β-unsaturated carbonyls **11**, rendering their β-carbon atoms more susceptible to nucleophilic attack by lowering the energy of the LUMO **13.**

---

[11] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396

[12] Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.***2007**,*107*,5416−5470

[13] Tietze, L. F.; Beifuss, U. Trost, B. M.; Fleming, I. *Eds.; Pergamon: Oxford, U.K.*, **1991**; *2*, 341.



Scheme 4: Catalytic cycle of the iminium ion activation.

The key feature of iminium ion activation is the lowering of the LUMO energy, whereby an increased reactivity of the unsaturated system towards nucleophilic addition is obtained. The generic approved mechanism for these reactions undertakes with the acid promoted condensation of the carbonyl moiety with the amine to form unsaturated iminium ion. This reactive intermediate then undergoes the addition of the nucleophile at the β position, leading to the β-functionalized enamine that could provide, after protonation, a saturated iminium ion, or could undergo a cascade reaction with a convenient electrophile. Hydrolysis of these saturated iminium ions releases both the product and the catalyst (Scheme 4).

Since the first report from Macmillan in 2000[14], the research community has concerned many efforts to the development of new techniques based on the iminium activation of enals for the enantioselective construction of C-hetero-atom bonds. Activation of the β-position of the enal allows the attack of distinct nucleophiles. During the last decade

[14] Ahrendt, K.A.; Borths, C. J.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122*, 4243.

carbon, nitrogen, oxygen, sulphur, or phosphorous nucleophiles have been used to form new stereogenic bonds with high level of rate and selectivity.

The iminium-activated reaction will be catalytic only if the amine catalyst is released in the final hydrolysis or elimination step. As an example, nucleophilic addition of hydride ion to the C-N double bond is the basis of reductive amination processes. These reactions proceed via iminium intermediates and are properly called iminium-activated reactions. However, they are not iminium-catalyzed since the amine becomes trapped in the reduction step. Perhaps the earliest recorded example of an iminium catalyzed process is the Knoevenagel condensation[15,16] mediated by primary or secondary amines. The idea that the Knoevenagel reaction might proceed via iminium catalysis emerged slowly. Knoevenagel himself suggested a possible role for the aldehyde-derived imines or aminals in this reaction. It is known, however, that the Knoevenagel-type reactions can also be catalyzed by tertiary amine bases. The iminium mechanism is, thus, only one of the mechanistic possibilities.

1.5.1 Aminocatalytic Remote Fuctionalization.

Since the early work in the field of aminocatalysis,[17] activations via iminium ion and enamine have achieved a high degree of maturity. Because of this, they are currently considered as two of the most used methodologies for the enantioselective functionalization of carbonyl compounds in positions β and α respectively. Through these two classical methods of activation, aminocatalysis has found a new direction in the new modes of activation called dienamine,[18] trienamine,[19] cross trienamine[20] tetraenamine and vinylogous iminium ion (Scheme 5).

---

[15] Knoevenagel, E. *Chem. Ber*. **1894**, *27,* 2345.

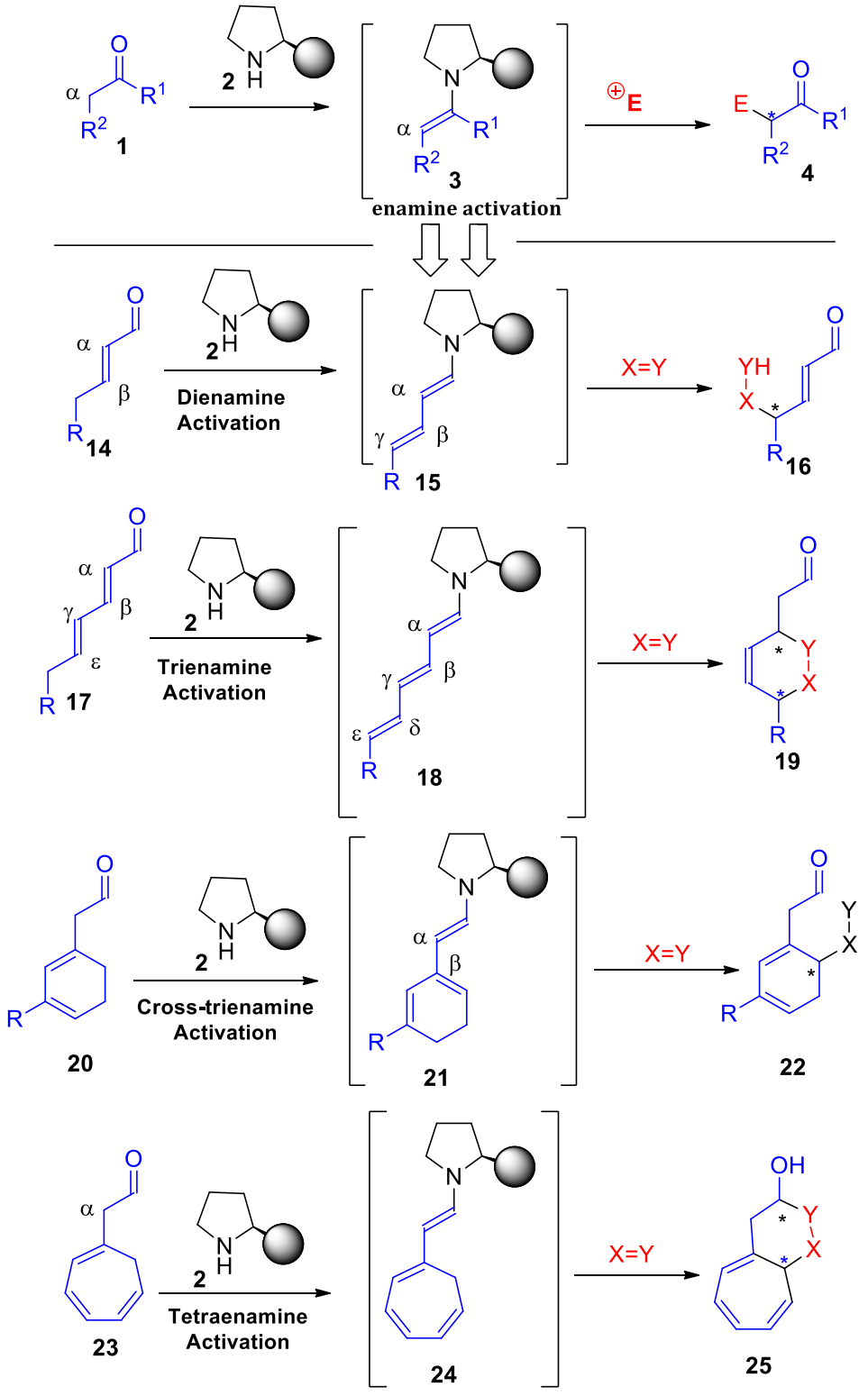
[16] Knoevenagel, E. *Chem. Ber.* **1898**, *31*, 2596.

[17] List B.; Lerner R. A.; Barbas C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

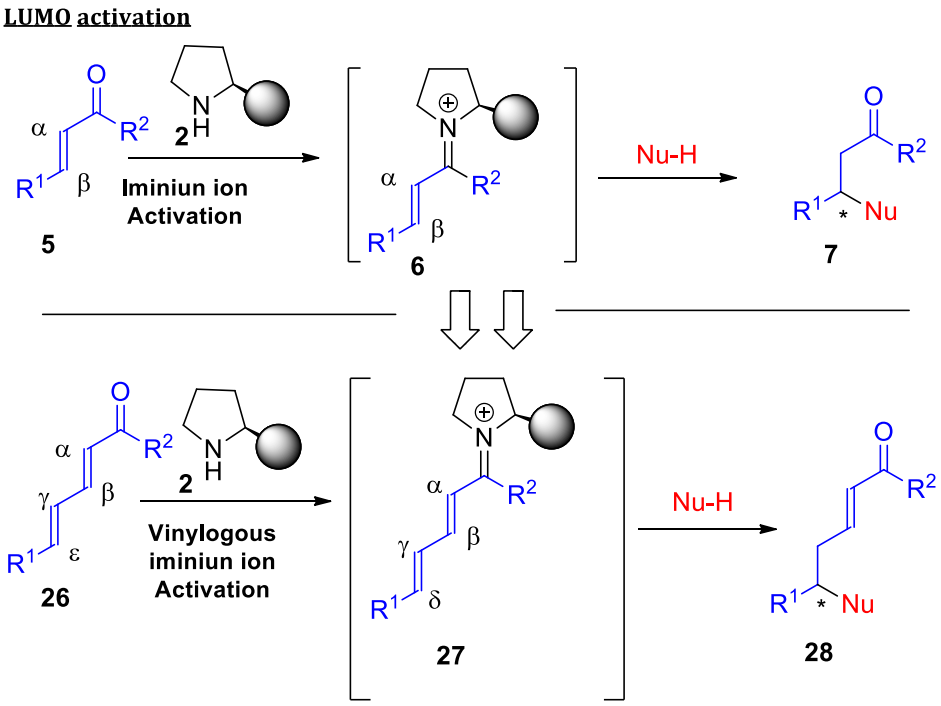
[18] Ramachary D. B.; Reddy Y. V. *Eur. J. Org. Chem*. **2012**, 865-887.

[19] (a) Arceo, E.; Melchiorre, P.; *Angew. Chem. Int. Ed*. **2012**, *51*, 5290-5292; (b) Jia, Z.-J., Jiang, H.; Li ,J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2011**, *113*, 5053-5061; (c). Jia, Z.-J.; Zhou, Q.; Zhou Q.-Q.; Chen P.-Q.; Chen Y.-C.; *Angew. Chem. Int. Ed*. **2011**, *50*, 8638-8641: (d) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc*. **2011**, *133*, 15212-15218; (e) Albrecht, Ł.; Cruz-Acosta, F.; Fraile, A.; Albrecht, A.; Christensen, J.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2012**, *51*, 9088-9092.

HOMO activation



[20] Halskov, K. S.; Johansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A.; J. *Am. Chem. Soc.* **2012,** *134*, 12943-1246



Scheme 5: Remote functionalization in aminocatalysis.

1.5.1.1 Dienamine Activation.

Amino substituted dienes are electron-rich conjugated systems and therefore appropriate for Diels-Alder type reaction with dienophiles or for vinylogous addition reactions to electrophiles. It was realized that the HOMO-raising principle applied in enamine intermediate **3** reaction generate from saturated carbonyl compound such as **7** to *α,β*-unsaturated system. The enal can be employed as starting material, leading to the formation of dienamine intermediate **15**, from which the reaction dienophile/electrophile may occur. For example, enatioselective γ-functionalization of enal substrate **16** has been obtained via dienamine intermediate asymmetric reactions.

1.5.1.2Trienamine Activation.

Later. the concept of dienamines could be further expanded to incorporate the use of poly-conjugated enals, such as the 2,4-dienal **17**, condensation with aminocatalyst **2** can produce trienamine intermediate **18** which can participate in [4+2]Diels-Alder cycloaddition reaction as an activated diene with various electron deficient dienophiles and

also reaction of remote functionalization 2,4-dienal with reactive dienophile could deliver highly enantioenriched cyclohexane products **19** with gaining up to four stereocenters . The development of linear triamine intermediate reaction will be discussed in chapter 2 of this thesis.

1.5.1.3Cross-trienamine Activation

In 2012, Cross-conjugated trienamines which is one of the new concepts in asymmetric organocatalysis revealed. In this concept, cyclic-polyconjugated enals **20** condensation with aminocatalyst **2** can produce cyclic trienamine intermediate **21** which can participate Diels-Alder cycloaddition reaction as an activated diene with various electron deficient dienophiles deliver highly enantioenriched complex structure **22**.

1.5.1.4 Tetraenamine Activation.

Once the HOMO activation was demonstrated through the dienamine and trienamine pathways by using *α,β*-unsaturated carbonyl compounds and diene carbonyls compounds respectively, in 2014 the first reaction of tetraenamine activation **24** was revealed by using cylic trienal **23** which was reacted with a dienophile, leading to the enantioenriched complex structure **25**.

1.5.1.5 Vinylogous iminium ion Activation

The LUMO-lowering effects achieve iminium ion by condensation of dienals with an enantiopure aminocatalyst **2**. The vinylogous iminium ions are electrophilic intermediates, which are reactive towards multiple reactions. The LUMO-lowering effect formed by condensation of aminocatalyst **2** with unsaturated 2,4-dienal **26** generates a vinylogous iminium ion **27**, which contains electrophilic positions whereas, the terminal carbon (δ-carbon) is more electrophilic than that of *β*-carbon. Hence the nucleoplilic attack is more susceptible at δ-carbon to deliver δ-substituted chiral skeleton **28**.

1.5.2 Catalytic System in aminocatalysis

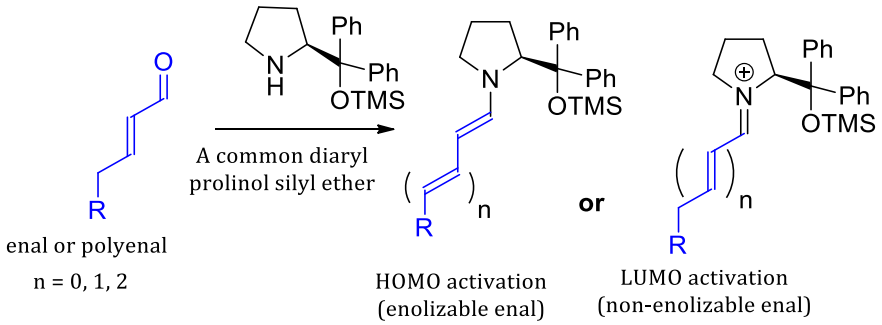
The past few decades have witnessed some of the most important and revolutionizing advances in the field of asymmetric catalysis. Chemists no longer rely solely

on natural sources as the starting point of their synthetic strategy, as in chiral pool or auxiliary-based synthesis. Instead, naturally occurring chiral motifs are selected and, either unchanged or after modification, used in substoichiometric amounts as chiral catalysts or ligands. In this way, they effectively transfer their chirality to prochiral substrates, thereby rapidly amplifying and diversifying the arsenal of useful chiral building blocks available to the synthetic community. A long-standing goal in the pursuit of new catalytic systems is the discovery of general catalysts. Ideally, such catalytic systems should be capable of promoting many enantioselective reactions, via multiple modes of activation, with good substrate tolerance and high stereoselectivity. In this Account, the synthetic usefulness, efficiency, selectivity, and robustness of different types of aminocatalysts are described below.

Based on the prolinol derived aminocatalyst,[21] several studies on enamine-mediated transformations of saturated aldehydes have resulted in the introduction of different functionalities into the ρ-position of aldehydes in a highly stereoselective manner. This HOMO-activation concept was later extended to include α,β-unsaturated aldehydes, which after condensation with the aminocatalyst generate a dienamine species capable of undergoing stereoselective cycloaddition reactions.[22] As a result, the effective functionalization of the γ-position of the aldehyde is achieved. Recently, the activation principle was further developed to include 2,4-dienals, which form trienamine intermediates upon condensation with the aminocatalyst. The trienamines effectively react with carbon-centered dienophiles, forming aldehyde products having up to four contiguous stereocenters. Because of the concerted nature of the reaction and the efficient catalyst shielding of the β-position, the stereo-induction is achieved at the remote ε-position of the original aldehyde.

[21] Jensen, K. L.; Dickmeiss, G.; Jiang, H., Albrecht, Ł.; Jørgensen, K. A., *Accounts of Chemical Research*, **2012**, *45*, 248–264.

[22] Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, *J. Acc. Chem. Res*. **1999**, *32*, 605–613.



Scheme 6 Prolinol derived aminocatalysis.

Complementary to the enamine-mediated activations, *α,β*-unsaturated aldehydes can also be efficiently functionalized by applying the diaryl prolinol silyl ether system via conjugate addition through iminium-ion-mediated processes, i.e. LUMO activation. In such reactions, the aminocatalyst not only effectively shields one of the enantiotopic faces of the enal, but it also ensures excellent chemoselectivity, affording 1,4-adducts as the only products. Several different carbon and heteroatom nucleophiles can be added in a highly stereoselective fashion. The ability of the catalysts to participate in various enamine- and iminium-ion mediated processes also makes them ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner. These cascade reactions thereby afford access to products having at least two stereocenters (Scheme 6. and 4, trienamine activation section).

In the years to come, the diaryl prolinol silyl ether catalysts will probably maintain their prominent position as general catalysts in the field of aminocatalysis. Moreover, recent efforts devoted to mechanistic studies might soon engender further advances with this versatile catalytic system, particularly in the areas of activation modes, catalyst loadings, and industrial applications.

1.6 The ApDOS concept.

The aminocatalysis has a dynamic role in synthesis of complex privileged structures. It is argue that pDOS and aminocatalysis are closely associated with each other. As stated into their central aim, in 2018 my research group envisioned the aminocatalytic privileged diversity-oriented synthesis (ApDOS) concept as a set of

processes from which a great variety of diverse privileged structures can be prepared from simple molecular building blocks, through an aminocatalytic strategy. Aminocatalytic process generates a common intermediate scaffold from simple molecules, which in turn serve as a platform for the synthesis of complex and diverse frameworks. In the presence of a catalyst, they can react with a wide range of substrates to generate collections of different and diverse privileged structures. As a result, libraries of important molecules are prepared in simple and efficient pathways (Figure 3).

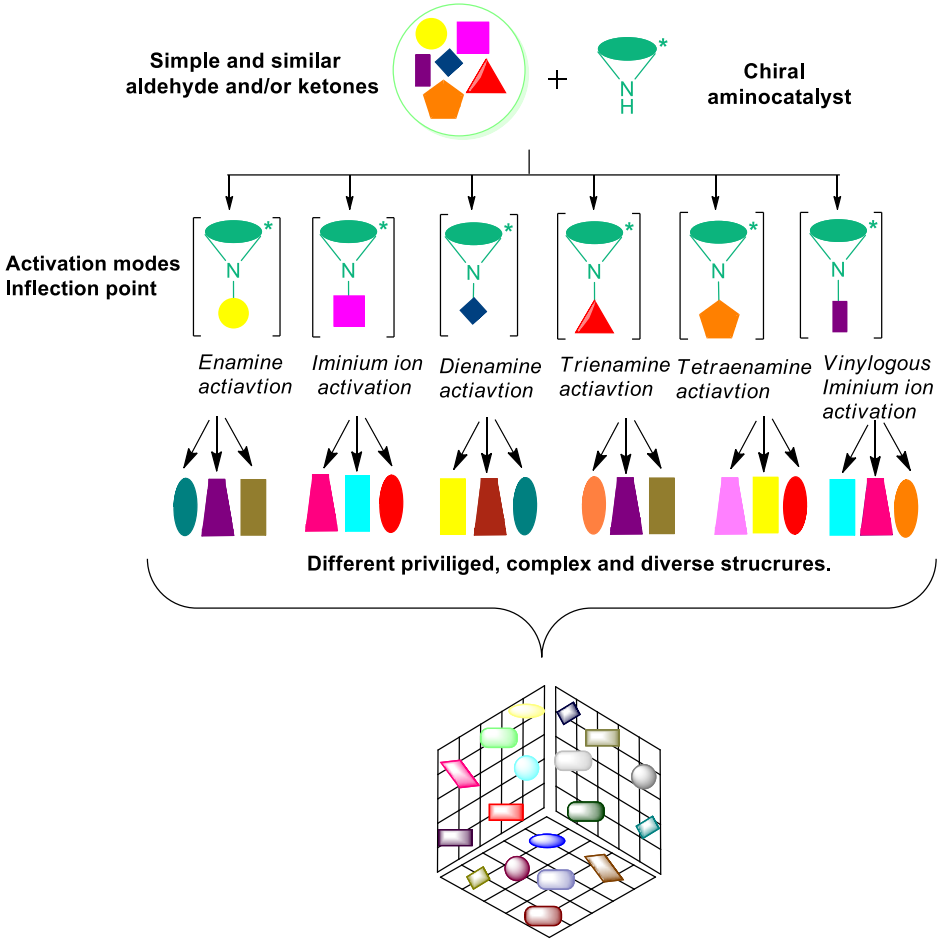


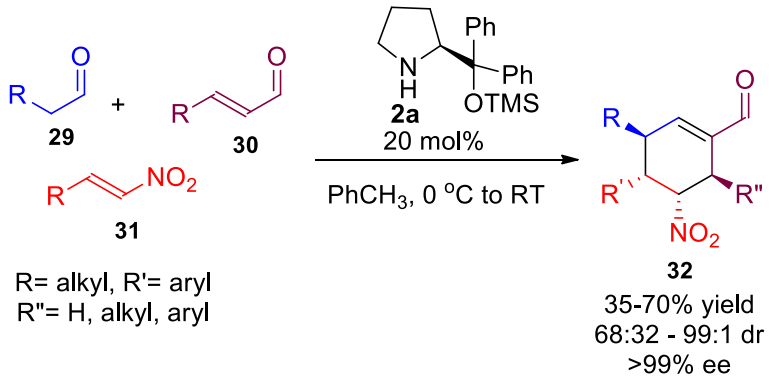
Fig.3: The ApDOS concept.

1.7 Organocatalytic cascade reactions.

Organocatalytic cascade reactions, in which multiple chemical bonds are formed in the same reaction conditions with great structural complexity have received great

attention. These methods increase the efficiency of overall process by minimizing manual efforts (work-up and purification procedure) and chemical, solvents and avoids the time and isolation of intermediates. In this pathway, structural complexity is achieved easily with high stereoselectivity. A main topic of current research is the expansion of catalyzed cascade reactions by incorporating a single catalyst capable of promoting every step. Organocatalyst are successful when used in catalytic cascade reactions because they allow distinct modes of activation, which can often to be easily combined. Furthermore, organocatalysts are tolerant for various functional groups and can be employed under mild reaction conditions. This enables a single organocatalyst to be used in a wide variety of possible cascade reactions. It is not surprising that the field of asymmetric organocatalytic cascade reactions has attracted much attention and various novel cascade reactions for the construction of structural complexity from the simple starting material.

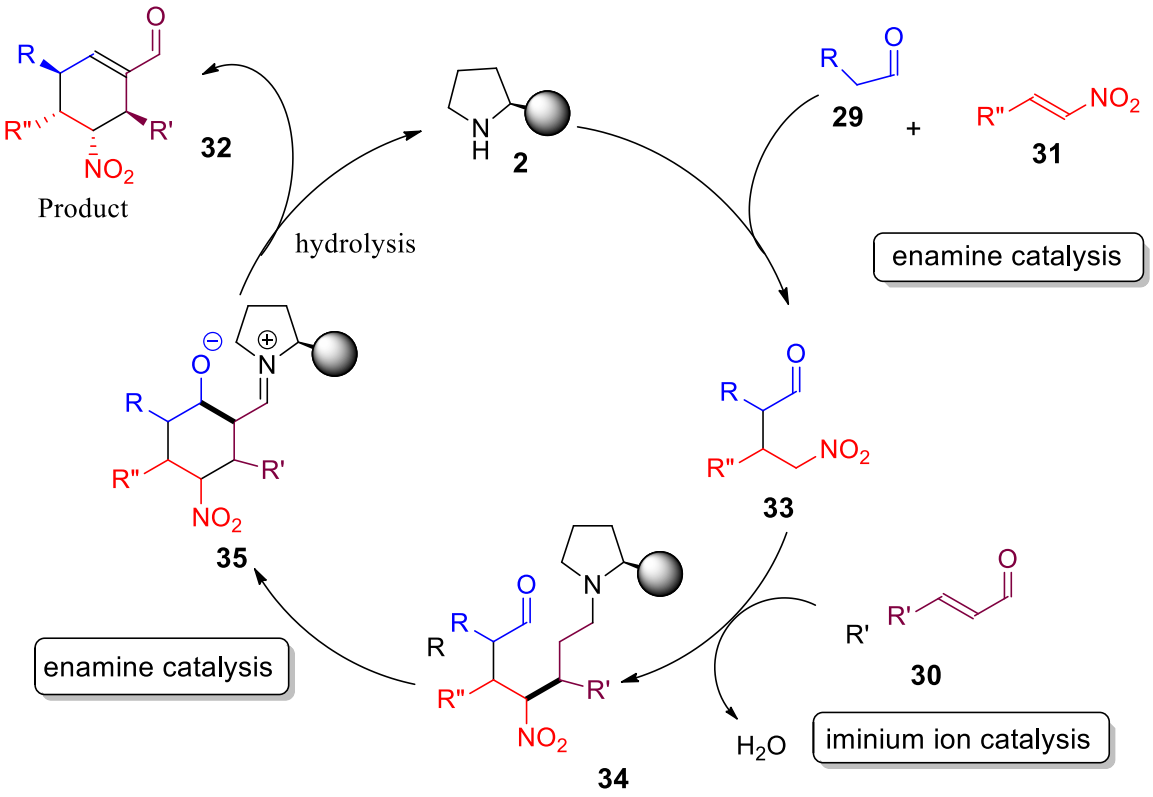
An excellent triple organocatalytic cascade (or multi-component) reaction was reported by Raabe et al. in 2006. In this study, linear aldehydes **29**, nitroalkenes **31** and *α,β*-unsaturated aldehydes **30** could be condensed together organocatalytically to afford *tetra*-substituted cyclohexane carbaldehydes **32** with moderate to excellent diastereoselectivity and complete enantiocontrol (Scheme 7). The transformation is mediated by the readily available proline-derived aminocatalyst **2a**[23]



Scheme 7: Asymmetric synthesis of tetra-substituted cyclohexane carbaldehyde via triple cascade reaction.

[23] Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature,* **2006**, *441*, 861–863.

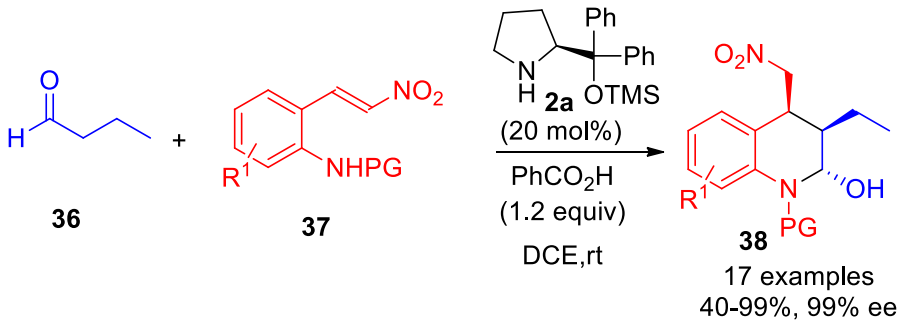
The transformation was proposed to proceed via the first step, aldehyde **29** reacted with nitroalkene **31** occurs through enamine catalysis, yielding nitroalkane **33** The condensation of *α,β*-unsaturated aldehyde **30** with the organocatalyst then facilitates the conjugate addition of **30** to give intermediate enamine **34**, which is prone to undergo an intramolecular aldol condensation to iminium species **35**. Finally, the organocatalyst **2** is regenerated by hydrolysis, along with the product **32**, thus closing the triple cascade cycle (Scheme 8).



Scheme 8: Mechanism of triple cascade reaction

In 2014, the Kim Sung group reported a Michael addition/aza-cyclization organocatalytic cascade reaction between the 2-amino *β*-styrene **37** and the linear aldehyde **29** in presence of chiral secondary aminocatalyst **2a** to obtain the corresponding

4-substituted tetrahydroqunolines **38** with moderate to excellent yield and excellent enantiomeric excess (Scheme 9). [24]



Scheme 9: Asymmetric Michael addition/aza-cyclization cascade reaction.

1.8 Summary and Goals

This Chapter explained asymmetric synthesis, organocatalysis cascade reactions and strategies, and all activation modes to better understand further chapters towards my investigation work during this Ph.D study. Finally, to obtain a higher level of scholar presentation, the underlying importance of the current research topic has been put into a greater perspective incorporating subjects, such as the evolutionary processes and current scientific demands.

In chapter 2, three different dienophiles were related to 3-oxindole compounds will be discussed. Herein, in this project investigation, isatin contained spirooxindole enantioenriched complex framework concerning, Diels-Alder cycloaddition/ nucleophilic ring-closing cascade reaction via trienamine catalysis, and 1,6-oxa-Michael-Michael addition via iminium catalysis will be uncovered. Unfortunately, we did not obtain the desired product yet. Still, the investigation is going on this project. In project 2, three different hetero-dienophiles were related to dithioamides compounds will be discussed. Herein, in this project investigation, hetero atom contained thio-pyrano-piperidone fused complex framework concerning thia-Diels-Alder cycloaddition/ nucleophilic ring-closing cascade reaction and Pictet Spengler type reaction via trienamine catalysis to access complex structures.

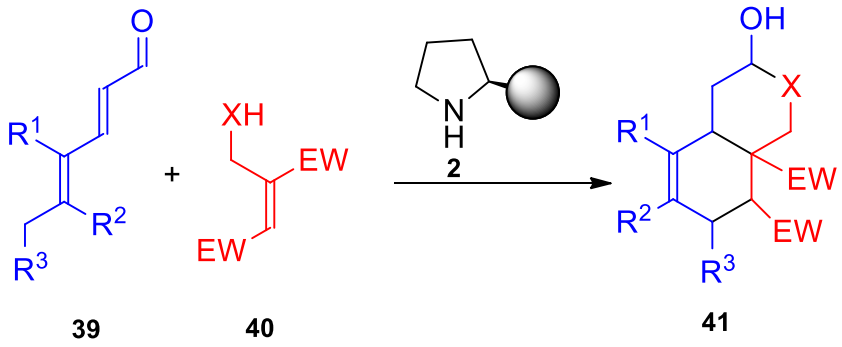
[24] Lee, Y.; Kim. S. *J. Org. Chem*. **2014**, *79*, 8234–8243.

This final chapter has been discussed synthetic procedures of all chemical reactions, chemical measurement, and spectral data. Organocatalytic cycloadducts and their product development and broadly explained scope and their expansion of the project. And mentioned their chiral HPLC details and their purification data.

Chapter 2

2.1 Organocatalytic Cascade Reactions via Trienamine Activation

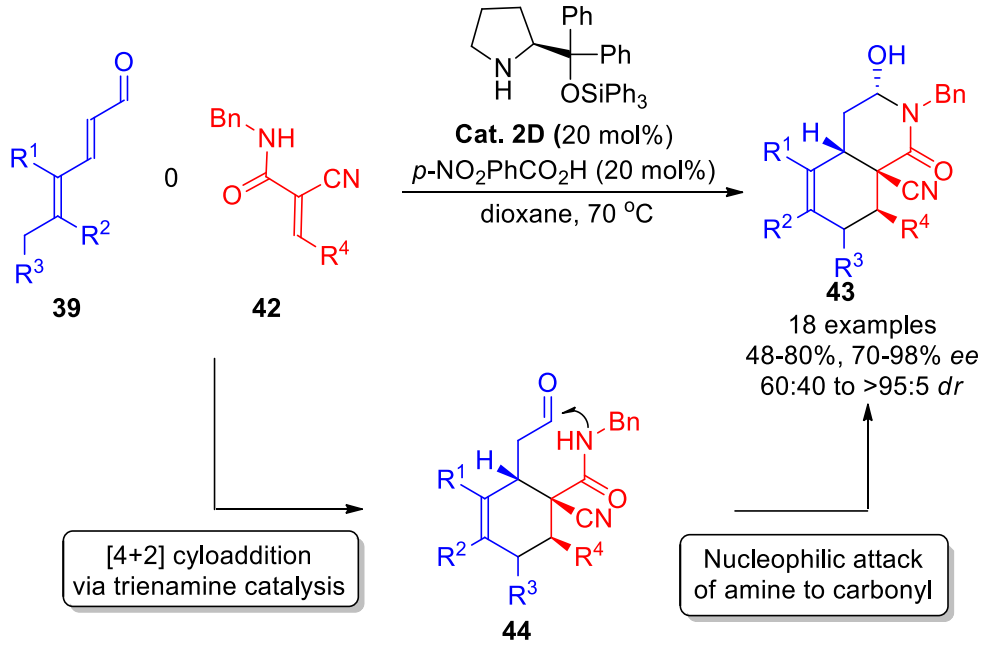
In this section, trienamine intermediate reactions were shown as a useful tool for the cascade reaction to access polycyclic complex structure. In the following scheme, it will disclose that trienamine catalysis could also be incorporated in amino catalytic cascade rection. Multiple activation modes of an aminocatalyst act tandemly to access privileged chemical scaffolds within a single manual operation. The proposed design strategy exploits the simple fact that the cycloadducts generated via trienamine activation are the 2,4-dienal aldehydes **39** which can construct complex structures **41.** The trienamine intermediate treated with an appropriate dienophile **40**, should contain an activated olefinic bond and a nucleophilic moiety (like amine or alcohol) to access to the polycyclic complex structure **41** (Scheme 10). It was hypothesized that trienamine catalyzed [4+2] Diels-Alder cycloaddition/nucleophilic ring-closing cascade reaction with different kind of dienals and appropriate dienophiles would reveal a variety of new enantioenriched compounds. This kind of complex enantioenriched structures are synthetically useful compounds and can be further modified.



Scheme 10: Strategy for the synthesis of enantioenriched polycylic complex structures via trienamine catalysis.

Considering this strategy, in 2014 Jørgensen and coworkers reported an organocatalytic cascade sequence to synthesize privileged hydroisoquinoline scaffolds. In this study, the reaction of substituted 2,4-dienals **39** with cycnoacrylamides **42** in presence of chiral secondary amionocatalyst **2D** delivered the [4+2] cycloadduct **44**, which through

an intramolecular ring-closing reaction leads to the hydroisoquinolines **43** with excellent stereocontrol (Scheme 11)..[25]

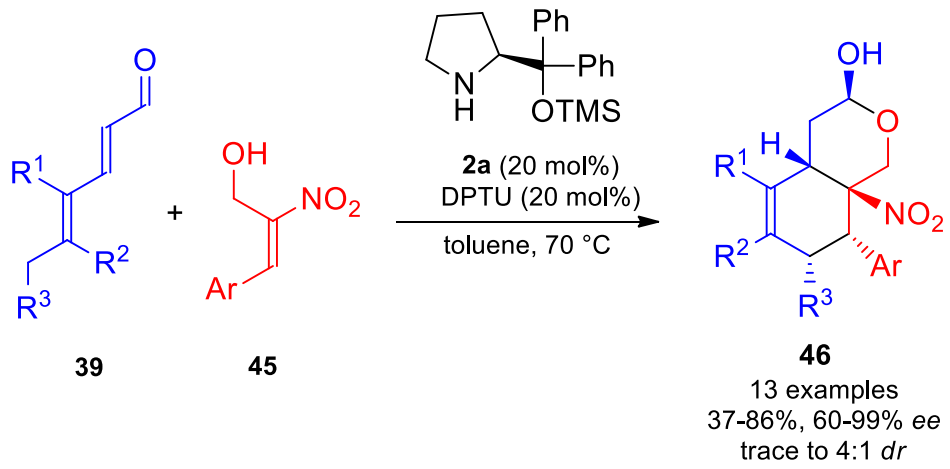


Scheme11: Organocatalytic cascade reaction via trienmine activation.

Later, under the same strategy, the same group demonstrated another organocatalytic enantioselective domino sequence for the diversification of hydroisochromenes **46** from 2,4-dienals **39** and 2-nitroallylic alcohols **45** through a [4 + 2] cycloaddition followed by nucleophilic ring-closing process. Under these conditions one or two extra fused cycles can be attached to the hydroisochromene **46** framework depending on the aldehyde. The reaction proceeds with fair to high yields and high stereoselectivities (Scheme 12).[26]

[25] Gómez, C. V.; Cruz, D. C.; Mose, R.; Jørgensen, K. A., *Chem. commun.*, **2014**, *50*, 6035-6038.

[26] Cruz, D. C.; Mose, R.;, Gómez, C. V.; Torbensen, S. V. ; Larsen, M. S.; Jørgensen, K. A. *Chem. Eur. J.*, **2014**, *20*, 11331-11335



Scheme 12. Asymmetric [4+2] cycloaddition/nucleophilic ring-closing reaction cascade sequence.

In the last 9 years, around 27 aminocatalytic cascade reaction with several biologically and naturally important moieties has been reported and still, chemists are focusing more to outlining new methodologies to contribute to this field.

2.2 Introduction and design plan

The trienamine catalysis has played a vital role in the synthesis of enantioenriched privileged structures such as spiroxindole motif in the biologically active compound and important biosynthetic intermediates (Fig. 4). For example, the spiroxindole contained compound horsfiline, spirotryprotatins A, B, and others have shown excellent antitumor activity.

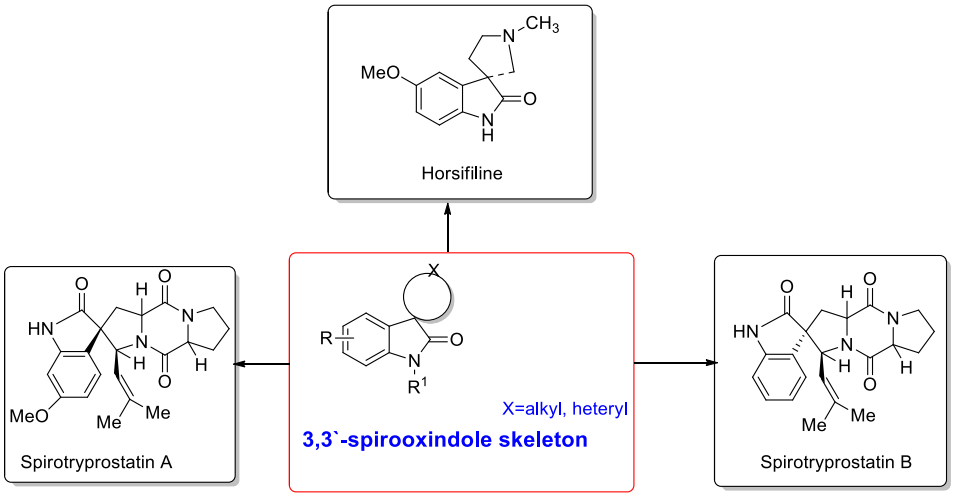


Fig. 4 Spiroxindole bioactive moiety.

Also, from the point of view of a scientific community, enantioenriched spiroxindole features useful and highly versatile building block with broad applications in organic synthesis. In this context, chemists are actively involved in the design, development, and application of catalytic cascade reactions to construct privileged scaffolds with multiple stereocenters collectively. These bioactive natural products and drug molecules synthesized through asymmetric catalytic cascade reaction. During this investigation, catalyst and reagent provide a new cascade reaction. Furthermore, a considerable number of natural products exist as diastereomers. We also show examples of catalyst- or reagent-controlled diastereomer selection in the synthesis of target molecules with multiple stereocenters. Meanwhile, successful applications of cascade reactions in the synthesis of natural products concerning aminocatalysis will also be discussed.

2.2.1 Isatin moiety as dienophile in organocatlysis: Some new pathways to access enantioenriched privileged scaffolds.

Indoline-2,3-dione or indole-1*H*-2,3-dione is important class of heterocylic compound that can be used in drug synthesis and it is commonly known as isatin. It is a well-known natural product found in plants of genus Isatis and in Couropita

guianancis aubl. [27,28] It has also been isolated as a metabolic derivative of adrenaline in humans.[29] It was first time synthesized as an oxidation product of indigo in the early 19th century, and its structure was projected by Kekule.[30] Currently, isatin itself and many substituted isatins are commercially available at easily cost-effective prices. An extensive investigation on the synthesis and reactivity of isatins, possessing an indole motif with a ketone and a *γ*-lactam moiety, has unfolded many interesting aspects of organic reactions and mechanisms. It undergoes electrophilic aromatic substitution at positions C-5 and C-7 of the phenyl ring, *N*-substitutions, nucleophilic additions on to the C-3 carbonyl group, chemoselective reductions, oxidations, ring-expansions, spiro-annulation etc (Fig.5).

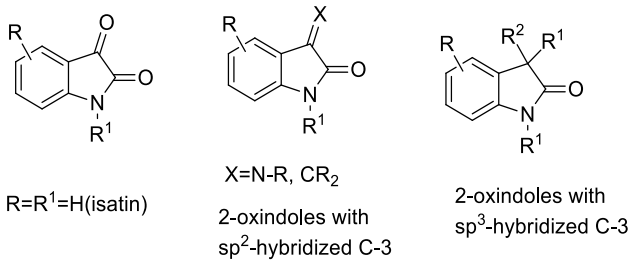


Fig. 5: Some bioactive isatin structures.

The Isatin has an unique potential to be used for both as an electrophile and nucleophile. Its easy availability has made it a valuable building block in organic synthesis. The synthesis of several heterocyclic frameworks of biological significance such as pyrrolidines, quinolines, indoles, β-lactams, and 2-oxindoles, etc. have been formed by using isatins as substrates.

2.2.1.1 Conceptualization of the project

Nowadays, organocatalysis is considered the third pillar of asymmetric catalysis, due to the way in which both small and complex molecules are prepared with high level of

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[27] da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J. *Braz*. *Chem. Soc.* **2001**, 12, 273

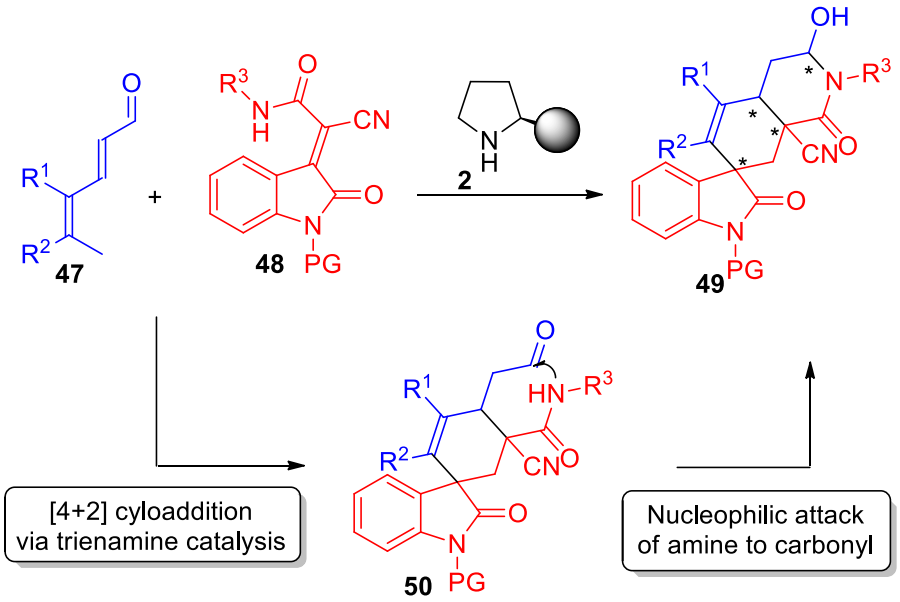
[28] Bergman, J.; Lindstrom, J, O.; Tilstam, *U. Tetrahedron* **1988**, 41, 2879

[29] Chiyanzu, I.; Hansell, E.; Gut, J.; Rosenthal, P. J.; McKerrowb, J. H.; Chibale, K. Bioorg. *Med. Chem. Lett.* **2003**, 13, 3527

[30] Kekule, *A. Chem. Ber*. **1869**, 2, 748.

stereocontrol. In recent years, organocatalytic remote functionalization strategies have attracted great attention due to the ability to functionalize far away reactive centers without loss of stereoselectivity. In this sense, activations involving trienamines have played an important role. The recent development of this new organocatalytic activation mode, offers new tools for the diversity-oriented synthesis (DOS). In previous literature, there is so much wonderful, predicted work about trienamine activation. Trienamine activation is an efficient HOMO-raising strategy in organocatalysis for both simple and cascade asymmetric transformations. The enlargement of novel developed activation mode such as trienamine activation is one of the most significant themes of this project. In the following it would be tremendous to apply the trienamine activation to provide an efficient methodology to access the privileged hydroisoquinoline-spirooxindole structures. It will be an important contribution because of the application of the organocatalysis in the synthesis and diversification of natural products. This will give an amazing pragmatic application in the field of organocatalysis. This strategy for the asymmetric synthesis of highly functionalized hydroisoquinolines-spirooxindole will be based on an organocatalytic [4+2] cycloaddition/nucleophilic ring-closing cascade sequence.

Previous reports on trienamine activation showed promising results with 2,4-dienal with some appropriate dienophiles for tandem reactions (Scheme 10). During a recent study of isatin derivatives, it was conceptualized that these substrates should also be useful for the synthesis of spirocyclohexane oxindole derivatives **49**. Herein we decided to investigate a highly stereoselective synthesis of spirocyclohexane oxindole derivatives by using different substituted dienals **47** and isatin dienophiles **48** via an organocatalyzed [4+2] cycloaddition/nucleophilic ring-closing cascade sequence (Scheme 13).



Scheme 13: Conceptualization of the project, trienamine activation through [4+2] cycloaddition with cyano-oxoindoline-ylidine acetamide.

2.2.1.2 Hypothesis:

The cyano-oxoindolin-ylidine acetamide might be good dienophiles to react with an activated trienamine system. The two electron-withdrawing groups attached to the double bond in the cyano-oxoindolin-ylidine acetamide will ensure a good reactivity toward the [4+2] cycloaddition, while it is expected that the planarity of the molecule will provide a correct *endo–exo* selection. Finally, once the catalytic cycloaddition proceeds, a nucleophilic ring closing reaction can take place between the nitrogen atom of the amide and the aldehyde to obtain the corresponding hydroisoquinolines spirooxindole **42** in a cascade fashion (Scheme 13).

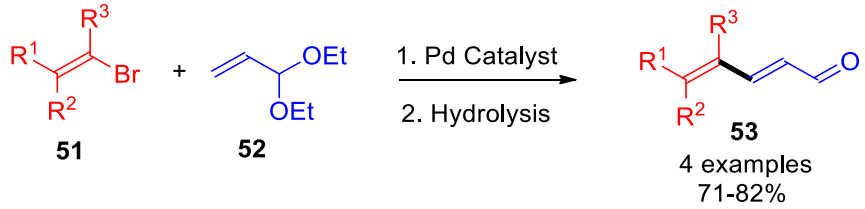
2.2.1.3 Objectives:

- To synthesize the starting material of different derivatives of dienals and dienophiles.
- To optimize organocatalytic cascade reaction.
- To synthesize different derivatives of organocatalytic cascade adducts.
- To characterize all the obtained products.
- To do adduct transformation.

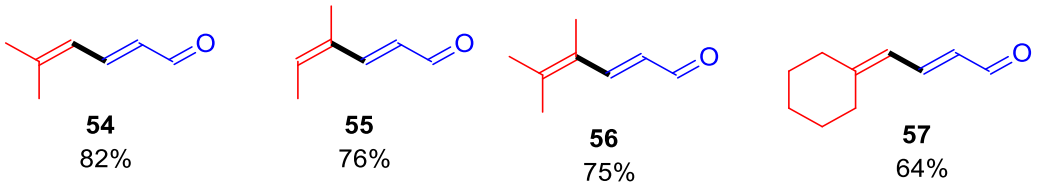
2.2.1.4 Result and discussion:

Synthesis of starting materials:

For the trienamine activation, are required some applicable and different substituted acyclic and cyclic aldehyde derivatives, which easily can undergo a Diels-Alder reaction. The chain aldehydes can be prepared by a Heck reaction by using vinyl bromides **51** and acrolein diethyl acetal **52** to deliver the corresponding 2,4-dienals **53** (Scheme 14).



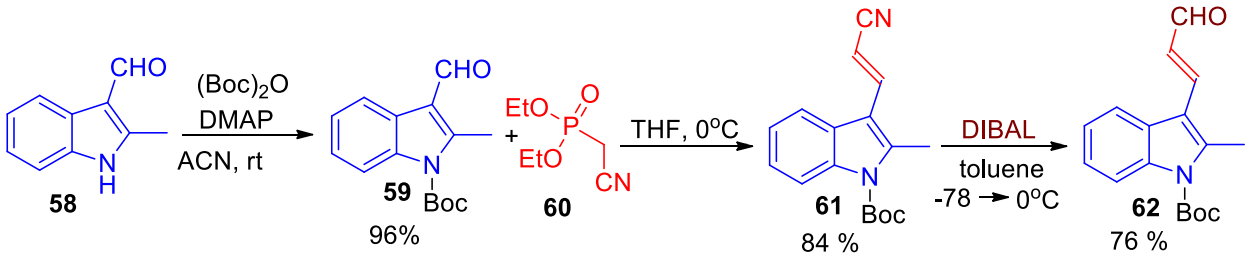
Derivatives:



Scheme 14: General procedure for the synthesis of 2,4-dienals.

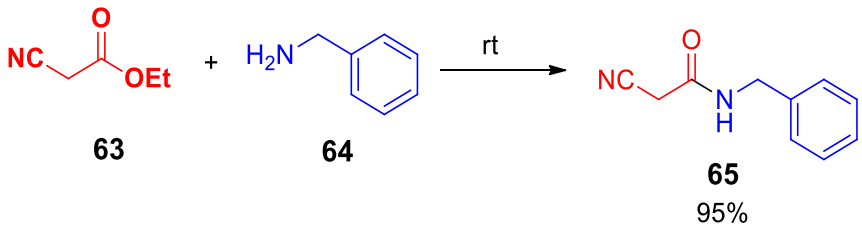
The 2-methyl indole acryldehyde **62** was prepared according to the literature[31] by the following strategy: In the first step, the indole carbaldhyde **58** reacted $(Boc)_2O$ in presence of DMAP and CH_3CN as a solvent to form corresponding *N*-protected indole carboxyl aldehyde **59**, it treated with cyano-Wittig reagent **60** then underwent reduction of cyano-vinyl carboxylate **61** delivered 2-methyl indole acryldehyde **62** with good yield (Scheme 15).

[31] Liu, Y. K.; Nappi, M.; Arceo, E.; Vera, S.;. Melchiorre, S. *J. Am. Chem. Soc.* **2011**, *133*, 15212.



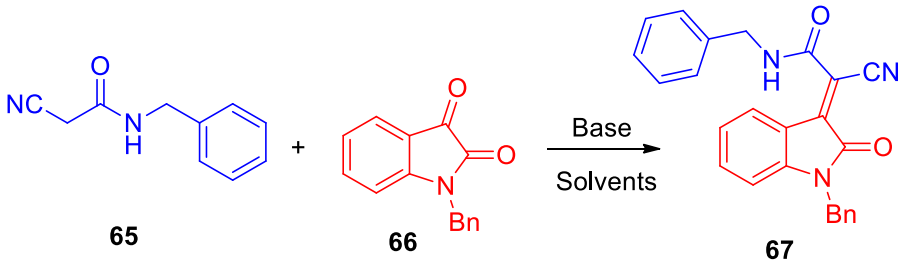
Scheme 15: General procedure for the synthesis of 2-methyl indole acryldehyde.

A mixture of ethyl cyanoacetate **63** and benzyl amine **64** was stirred at room temp. After 24 h, the precipitate of cyano-acetamide **65** obtained with excellent yield. It required for the synthesis cyano-oxoindolin-ylidine acetamide **60** (Scheme 16).



Scheme 16: General procedure for synthesis of cyano-acetamide.

The cyno-acetamide **65** treated with protected isatin **66** in presence of a base, unfortunately, did not obtain the desired product. Then we attempted with different solvents, and some other strong bases with differ time but disappointingly, not obtained the desired product (Scheme17)

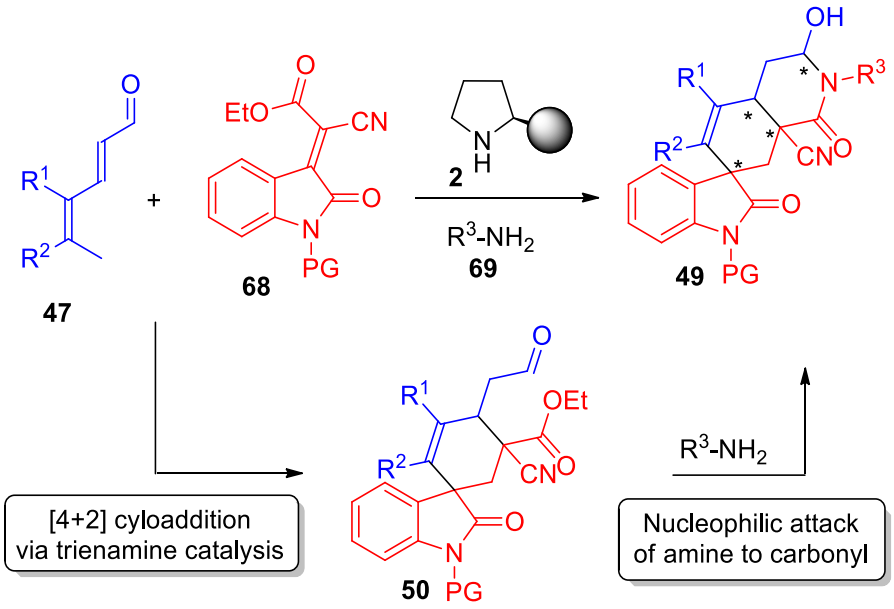


Entry	Base	Equiv. **65**	Sovents	t (h)	Conv. (%)	Yield (%)
1	Pyrrolidine	1	EtOH	60	n.r	---

2	Pyrrolidine	1.2	ACN	96	n.r	----
3	Pyrrolidine	1.2	DMF	96	n.r	-----
4	Pyrrolidine	1.2	DCM	96	n.r	---
5	Pyrrolidine	1.2	THF	96	n.r	---
6	Pyrrolidine	1.2	Toluene	96	n.r	---
7	Piperidine	1.2	EtOH	96	n.r	---
8	Piperidine	1.2	ACN	96	n.r	---
9	Piperidine	1.2	Toluene	96	n.r	---
10	Piperidine	1.2	DMF	96	n.r	---
11	Et_3N	1.2	EtOH	96	n.r	---
12	NaOH	1.2	EtOH	96	n.r	---

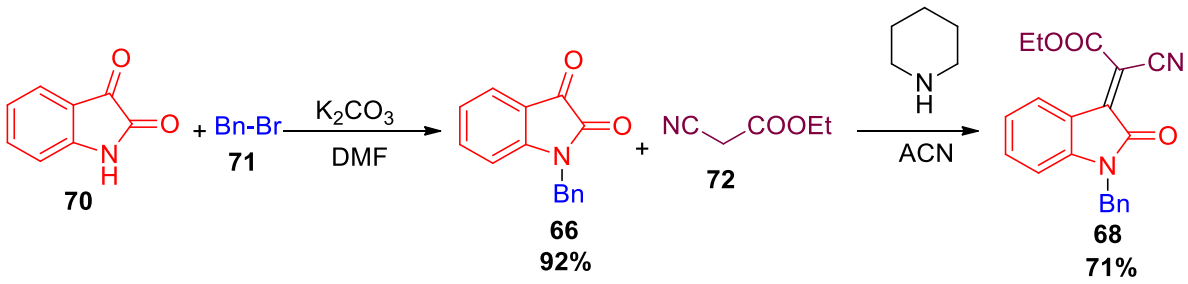
Scheme 17: General procedure for the synthesis of cyano-oxoindolin-ylidine acetamide.

Disappointingly, we failed to synthesize cyano-oxoindolin-ylidine acetamide **67**; after several attempts. Due these results we proposed another strategy to obtain the corresponding hydroisoquinoline-spirooxindole compound **49**. In this first reaction cyano-ester-oxindole olefin **68** and 2,4-dienal **47** in presence of aminocatalyst **2** deliver [4+2] cycloadduct and then the addition of primary amine **69** will provide enantioenriched hydroisoquinoline-spirooxindole **49** (Scheme 18).



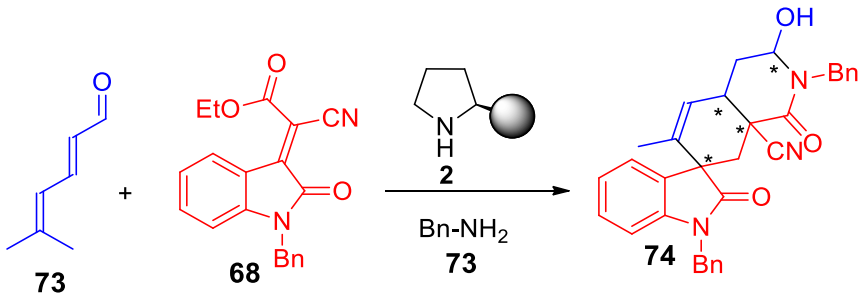
Scheme 18: Trienamine activation through [4+2] cycloaddition with cyano-oxoindoline-ylidine ester.

To synthesize cyano-ester olefinic oxindole **68** in this first process, the commercially available isatin **70** was treated with benzyl bromide **71** in the presence of K_2CO_3 to deliver the *N*-protected isatin **66**. Then, it was reacted with cyano-ethyl ester **72** in presence of piperidine to provide the expected cyano-ester olefinic oxindole **68** with good yield (Scheme 24).



Scheme 24: General procedure for the synthesis of cyano-ester olefinic oxindole.

With the cyano-ester dienophile **68** in hand, the reaction was carried out with 2,4-dienal **73** in the presence of the Jørgensen–Hayashi catalyst **2A** in chloroform without any additive at room temperature (entry 1). Under these conditions, we did not observe the desired product **74** or not even a very low conversion (entry 1). In order to obtain desired product **74**, we tested the addition of additives as a benzoic acid with different solvents at room temperature to 55 ^{0}C (entries 2-7). Various Acidic and basic additives were tested with chloroform solvent under 2A catalyst were not obtain the desired product (entry 8-12). Latter we tested different substituted proline derived catalysts in chloroform and acidic additive at room temperature to 55 ^{0}C without any good result. In future we expect to do some changes in oxindole and some different bifunction catalyst will be applied to obtain desire product **74**(Table 1).



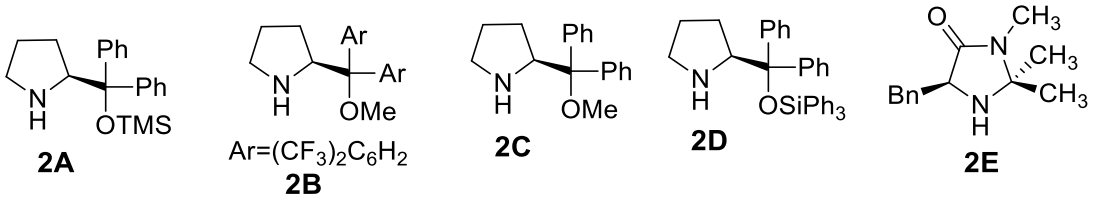


Table 1: Optimization table of Oxindole and 2,4-dienal

Entry	Cat.	Equiv. of Ald.	Solvent	Addt.	Temp. (^{o}C)	Time (h)	Conv.[a] (%)	dr[b]

1	**2A**	1.2	$CHCl_3$	--	rt	72	n.r	n.d
2	**2A**	1.2	$CHCl_3$	BA	rt-40	96	n.r	n.d
3	**2A**	1.2	THF	BA	rt-40	96	n.r	n.d
4	**2A**	1.2	CH_3CN	BA	rt-40	96	n.r	n.d
5	**2A**	1.2	PhMe	BA	rt-55	96	n.r	n.d
6	**2A**	1.2	DCM	BA	rt-40	96	n.r	n.d
7	**2A**	1.2	dioxane	BA	rt-40	48	n.r	n.d
8	**2A**	1.2	$CHCl_3$	NaOAc	rt-40	48	n.r	n.d
9	**2A**	1.2	$CHCl_3$	DPTU	rt-40	48	n.r	n.d
10	**2A**	1.2	$CHCl_3$	p-NBA	rt-40	48	n.r	n.d
11	**2A**	1.2	$CHCl_3$	DABCO	rt-40	48	n.r	n.d
12	**2A**	1.2	$CHCl_3$	OFBA	rt-40	48	n.r	n.d
13	**2B**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d
14	**2C**	1.2	$CHCl_3$	BA	rt-40	72	n.r	n.d
15	**2D**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d
16	**2E**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d

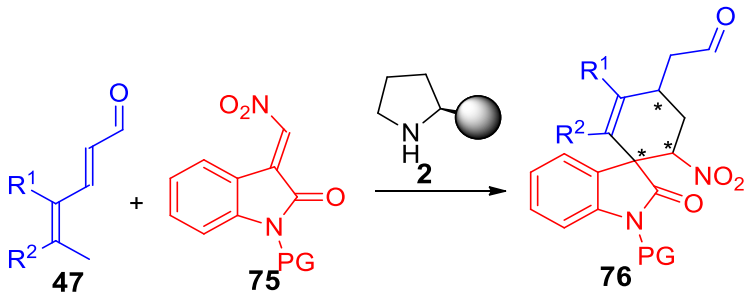
The reactions were performed with 0.12 mmol of **73**, 0.1 mmol of **68** 20 mol% of catalyst, additive in 0.5 ml of solvent at different. The yield is for both diastereoisomers of **74** after chromatographic purification on silica gel. The dr was determined by ^1H NMR of crude product.

Due to the incomplete optimization table (ee is not performed), we hadn't synthesized any derivative. But in future, we will use a bifunctional catalyst it may help to obtain the desired product. And also, we are applying a stronger electron-withdrawing group on olefin to synthesize organocatalytic cycloadduct. After completing the optimization condition, we will synthesize all derivative corresponding to the starting material. Already prepared starting material (Denials and Dienophiles) will be used to synthesize planned products.

A) Oxindole (Nitro oxindole) as dienophile in trienamine catalysis:

After the failure result from last scheme 18, we turned our attention towards another dienophile which was nitro-oxindole olefin, which might offer new enantioenriched complex structures. Inspired by the previous project, we have cyano-ester oxindole **68** replaced by nitro -oxindole. A variety of nitro-dienophile substituted proved to electron-withdrawing group delivered high yield and diastereoselective were obtained.

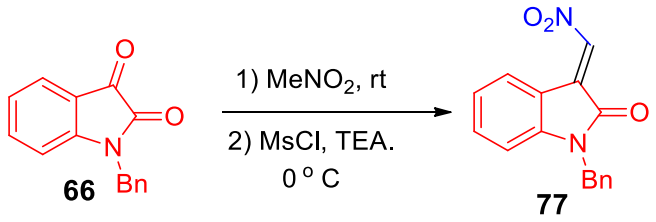
In particular, trienamine catalysis is efficient catalysts for a wide range of asymmetric reactions. Therefore, it was interesting to develop an efficient and practical organocatalytic approach to access chiral nitro-substituted spirooxindole via trienamine catalysis. Herein, it has been disclosed that trienamine aminocatalysis can promote the cycloaddition of 2,4-dienals **47** and nitro-substituted spirooxindole **76** with high enantioselectivity. The [4 + 2] cycloaddition via trienamine catalysis can provide a library of chiral multifunctional nitro-substituted spirooxindole complex structure **76** which, further useful for different organic transformations (Scheme 19).



Scheme 19: Diels-Alder reaction of trienamine with nitro-olefinic oxindole.

Synthesis of starting material

The synthesis of 3-oxindole as a dienophile developed according to the previously reported reaction. Nitromethane was treated with *N*-protected isatin **66** in presence of triethylamine and MsCl delivered nitro oxindole **77**. We are also working on the synthesis of different protecting group isatin and C-5 position substituted isatin for obtaining nitro oxindole (Scheme 20).



Scheme 20: General procedure for synthesis of nitro-olefinic isatin.

Synthesis of organocatalytic adduct

The reaction was started with the reaction between the 2,4-dienal **47** and the dienophile **77** in the presence of the Jørgensen–Hayashi catalyst **2A** in chloroform without any additive at room temperature (entry 1). We did not observe the desired product **78** or not even a very low conversion (entry 1). In order to obtain desired product **78**, we tested the addition of additives as a benzoic acid with different solvents at room temperature to 55 ^{0}C (entries 2-7), Different basic and acidic additives were tested with chloroform solvents under **2A** catalysis were examine not delivered desired product (entries 8–12). Latter we tested different substituted proline derived catalyst in chloroform and in acidic additive at room temperature to 55 ^{0} C with no results. In future that we are going to do some changes in oxindole and some different bifunction catalyst will be applied to obtain desire product **78**.

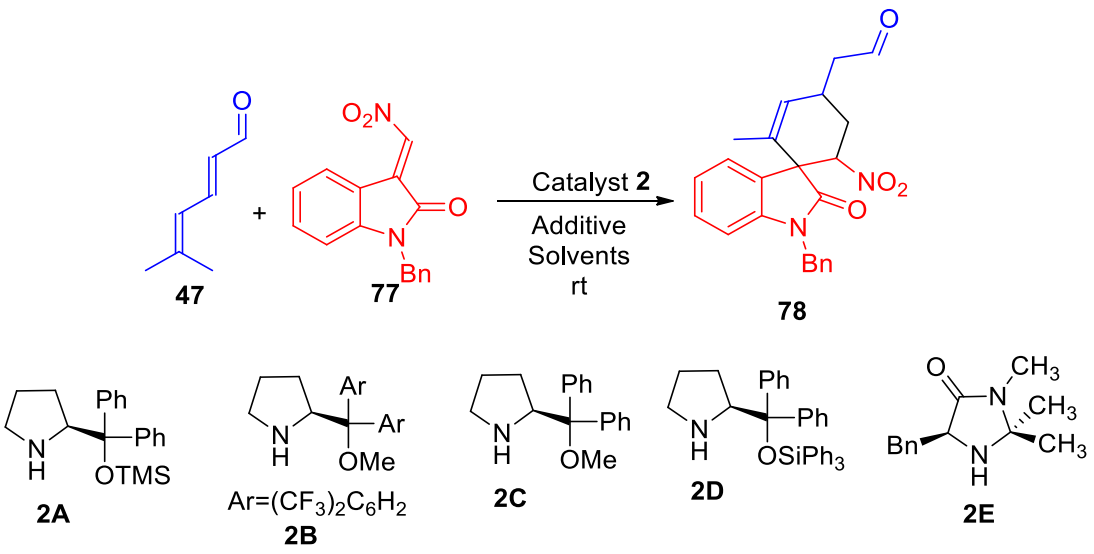


Table 2: Optimization table of Oxindole and 2,4-dienal

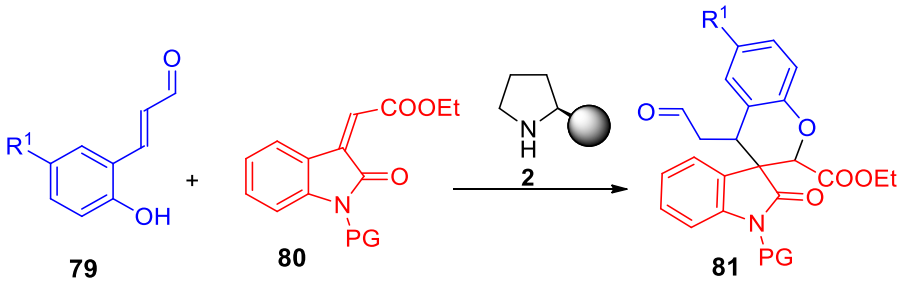
Entry	Cat.	Equiv. of Ald.	Solvent	Addt.	Temp. (°C)	Time (h)	Conv.[a] (%)	dr[b]
1	**2A**	1.2	$CHCl_3$	--	rt	72	n.r	n.d
2	**2A**	1.2	$CHCl_3$	BA	rt-40	96	n.r	n.d
3	**2A**	1.2	THF	BA	rt-40	96	n.r	n.d
4	**2A**	1.2	CH_3CN	BA	rt-40	96	n.r	n.d
5	**2A**	1.2	PhMe	BA	rt-55	96	n.r	n.d
6	**2A**	1.2	DCM	BA	rt-40	96	n.r	n.d
7	**2A**	1.2	dioxane	BA	rt-40	48	n.r	n.d
8	**2A**	1.2	$CHCl_3$	NaOAc	rt-40	48	n.r	n.d
9	**2A**	1.2	$CHCl_3$	DPTU	rt-40	48	n.r	n.d
10	**2A**	1.2	$CHCl_3$	p-NBA	rt-40	48	n.r	n.d
11	**2A**	1.2	$CHCl_3$	DABCO	rt-40	48	n.r	n.d
12	**2A**	1.2	$CHCl_3$	OFBA	rt-40	48	n.r	n.d
13	**2B**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d
14	**2C**	1.2	$CHCl_3$	BA	rt-40	72	n.r	n.d
15	**2D**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d
16	**2E**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d

The reactions were performed with 0.12 mmol of **73**, 0.1 mmol of **77** 20 mol% of catalyst, additive in 0.5 ml of solvent at different. The yield is for both diastereoisomers of **78** after chromatographic purification on silica gel. The dr was determined by ^1H NMR of crude product.

B) 1, 6-Oxa-Michael cycloaddition of iminium ion with ester-olefinic oxindole

Disappointingly, After the failure result from the last scheme **19** of trienamine catalysis, we moved to another dienophile which was ester-oxindole olefin, which shows excellent work in trienamine catalysis, here in applying another activation mode with ester oxindole **75**. It

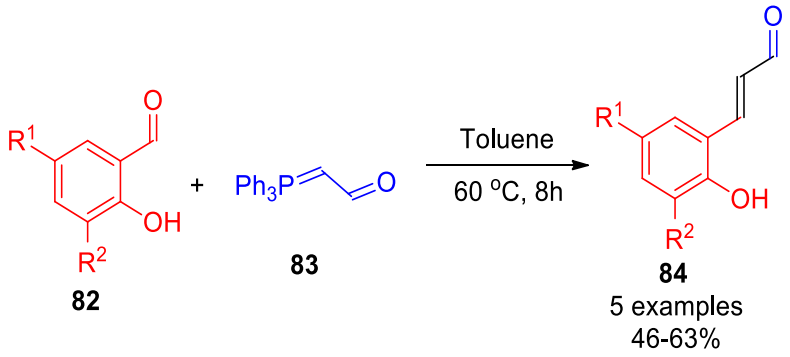
will deliver an enantioenriched complex structure. One obvious pathway for the future advance is the broadening of the scope of applicable dienophile in reaction with 2-hydroxy acryaldehyde **79**. The gained experience from trienamine activation that proved ester-oxindole **80** can deliver a highly complex structure. An interestingly, we were planning to synthesis hetero atom contained spiroxy oxindole via iminium ion. Therefore, it was interesting to develop an efficient and practical organocatalytic approach to access chiral hetero atom spirooxindole via iminium ion. Herein, it has been disclosed that iminium ion aminocatalysis can promote the cycloaddition of 2-hydroxy acryaldehyde **79** to hetero atom contained spirooxindole **81** with high enantioselectivity. The 1,6-Oxa-Michael cycloaddition via iminium ion catalysis can provide a library of a chiral multifunctional hetero atom contained spirooxindole complex structure which further useful for different organic transformations (Scheme 21).



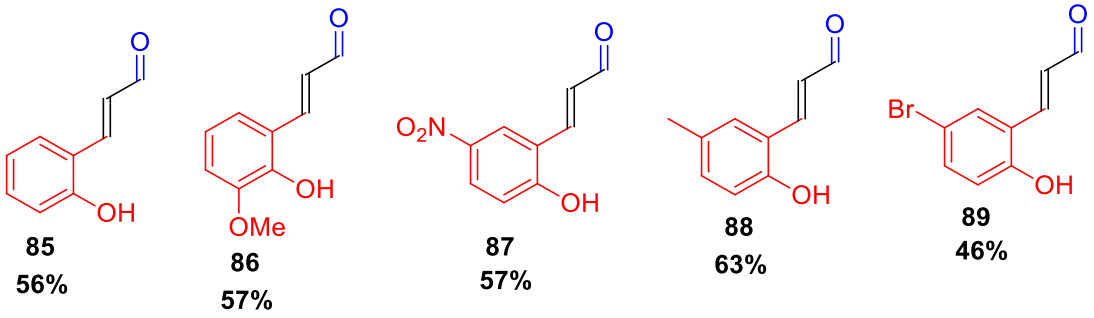
Scheme 21: 1, 6-Oxa-Michael cycloaddition of iminium ion with ester-olefinic oxindole.

Synthesis of starting material

A mixture of a corresponding aldehyde **82** with Wittig reagent **83** in toluene was stirred at 60 ^{o}C for 8 h under nitrogen. The reaction mixture delivered desired 2-hydroxyphenyl aldehyde **84** with moderate to good yield (Scheme 22).

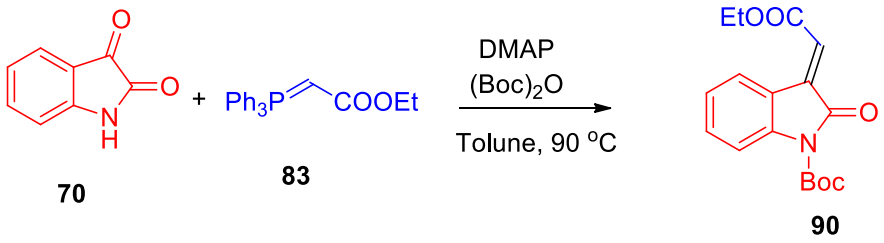


Derivatives:



Scheme 22: General procedure for the synthesis of 2-hydroxyphenyl aldehyde.

The commercially available isatin **70** was treated with Wittig reagent **83** in toluene, and the reaction mixture was heated up to 90 ^{0} C. Then, the reaction mixture was treated with. 4-(dimethylamino)pyridine (20 mol%)., and di-tert-butyl-dicarbonate (1.1 equiv.) was added to the reaction mixture. The reaction mixture delivered desired 3-olefinic oxindole product **90** with a high yield. (Scheme 23)



Scheme 23: General procedure for the synthesis of ester olefinic oxindole.

The reaction was started with the reaction between the 2-hydroxyphenyl aldehyde **85** and the ester olefincndole **90** in the presence of the Jørgensen–Hayashi catalyst **2A** in

chloroform without any additive at room temperature (entry 1). Under these conditions, we did not observe the desired product **91** or not even a very low conversion (entry 1). In order to obtain desired product **91**, we tested the addition of additives as a benzoic acid with different solvents at room temperature to 55 ^{0}C (entries 2-7), Different basic and acidic additives were tested with chloroform solvents under **2A** catalysis were examine not delivered desired product (entries 8–12). Latter we tested different substituted proline derived catalyst in chloroform and in acidic additive at room temperature to 55 ^{0} C with no results. In future that we are going to do some changes in oxindole and some different bifunction catalyst will be applied to obtain desire product **91** (Table 3).

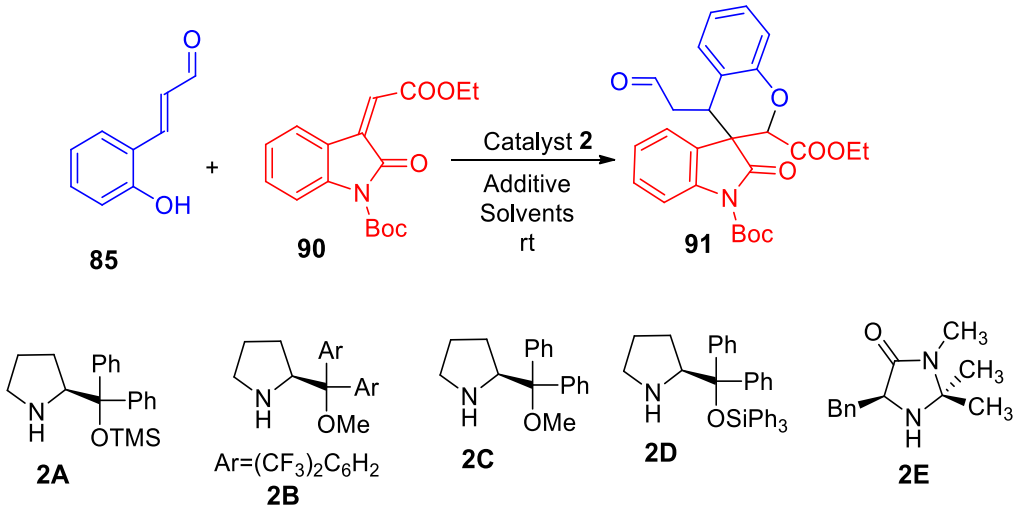


Table 3: Optimization table of Oxindole and 2-hydroxy acryldehyde,

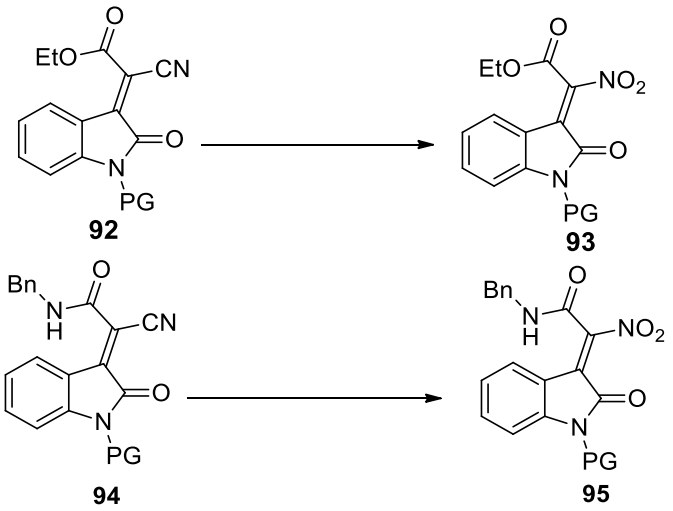
Entry	Cat.	Equiv. of Ald.	Solvent	Addt.	Temp. (^{o}C)	Time (h)	Conv.[a] (%)	dr[b]
1	**2A**	1.2	$CHCl_3$	--	rt	72	n.r	n.d
2	**2A**	1.2	$CHCl_3$	BA	rt-40	96	n.r	n.d
3	**2A**	1.2	THF	BA	rt-40	96	n.r	n.d
4	**2A**	1.2	CH_3CN	BA	rt-40	96	n.r	n.d
5	**2A**	1.2	PhMe	BA	rt-55	96	n.r	n.d
6	**2A**	1.2	DCM	BA	rt-40	96	n.r	n.d
7	**2A**	1.2	dioxane	BA	rt-40	48	n.r	n.d

8	**2A**	1.2	$CHCl_3$	NaOAc	rt-40	48	n.r	n.d
9	**2A**	1.2	$CHCl_3$	DPTU	rt-40	48	n.r	n.d
10	**2A**	1.2	$CHCl_3$	p-NBA	rt-40	48	n.r	n.d
11	**2A**	1.2	$CHCl_3$	DABCO	rt-40	48	n.r	n.d
12	**2A**	1.2	$CHCl_3$	OFBA	rt-40	48	n.r	n.d
13	**2B**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d
14	**2C**	1.2	$CHCl_3$	BA	rt-40	72	n.r	n.d
15	**2D**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d
16	**2E**	1.2	$CHCl_3$	BA	rt-40	48	n.r	n.d

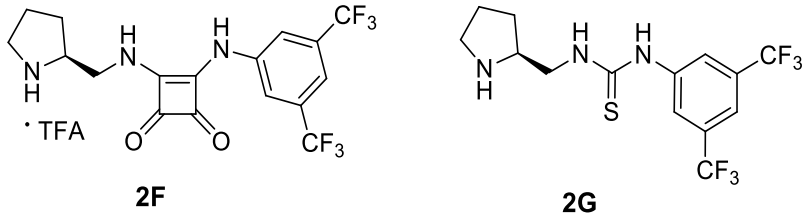
The reactions were performed with 0.12 mmol of **85**, 0.1 mmol of **90** 20 mol% of catalyst, additive in 0.5 ml of solvent at different. The yield is for both diastereoisomers of **91** after chromatographic purification on silica gel. The dr was determined by ^1H NMR of crude product.

2.3.1.5 Perspective

- To optimize the cascade reaction and synthesized a series of [4+2] cycloadducts/ nucleophilic ring closing reaction via aminocatalysis with maximum derivatives from corresponding starting material.
- To Synthesize starting material such as cyano-oxoindolin-ylidine acetamide and for better result by changing substituent like nitro group instead of cyano as mention below.



- To synthesize bifunctional catalyst to obtain desire product.



- To complete the scope of the reaction as mentioned in above scope table.
- To do adduct transformation.

- To study the stereochemistry of desired product and exact structural will be studied by X-ray**.**

2.2.1.6 Conclusion:

In conclusion, we are developing the reaction of isatin derivatives and 2,4-dienal in presence of aminocatalyst leads enantioenriched framework from the basic starting material. Disappointingly, the reaction had not proceeded efficiently to obtain desired the product. Additionally, by using nitro-olefinic oxindole with trienamine catalysis also not shown results then we moved to another activation modes such as iminium ion; in this reaction, ester oxindole treated with 2-hydroxy acryldehyde via 1, 6-Oxa-Michael

cycloaddition of iminium ion had not delivered desired product. In the future, work will continue to optimize all three-reaction scheme to find the optimal condition to access complex enantioenriched structures and plans for biological activity and X-structures.

Project-2

2.3 Dithioamides as a hetero-dienophile in organocatlysis: Some new pathways to access enantioenriched privileged scaffolds.

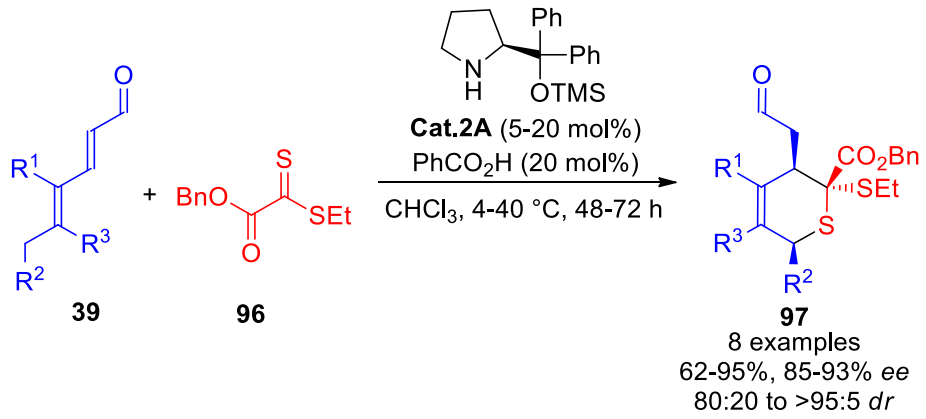
2.3.1 Introduction:

Over the past decade chemists are focusing more towards different new methodologies to synthesize known or novel thio-pyrano and piperidone derivatives.[32] At the same time, newly developed trienamine catalysis strategy grips a great consideration in the synthesis of enantioenriched privileged structures. In fact, a new methodology was developed to synthesize chiral thio-pyrano by using thiocarbonyl compounds and 2,4-dienal in trienamine catalysis. Another way to utilize the fact that the formal [4+2]

[32]) (a) Eicher, T.; Hauptmann, S: *The Chemistry of Heterocycles: Structure, Reactions, Syntheses and Applications*; 2nd ed., Wiley-VCH, Weinheim, **2003**. (b) Nolan, S. P. *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley-VCH, Weinheim, **2006**.

cycloadducts of trienamine-mediated reactions contain aldehyde moieties, which can undergo further cyclizations.[33]

Thiocarbonyls such as dithioesters, thioamides and thioketones, constitute a select group of sulfur-containing compounds, which have been employed efficiently as heterodienophiles for thio-Diels–Alder cycloadditions.[34][35] In 2013, the organocatalytic version of this reaction was first reported by Jørgensen *et al.*[36] through trienamine catalysis, which is an important factor for the development of Diels-Alder reactions. Catalyst-bounded dienes and thiocarbonyl derivatives **96** lead to dihydro-thiopyrane derivatives **97** with high to excellent enantioselectivities and high to excellent diastereoselectivities (Scheme 24).



Scheme 24: Thio-Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and dithioesters.

Later, Albrecht and co-workers reported the first asymmetric thio-Diels–Alder reaction by taming thioketones. Highly activated thioketones **98** were shown to undergo enantioselective trienamine catalyzed [4+2] cycloaddition with 2,4-dienals **39** to form dihydro-thiopyrane scaffolds **99**, which is found in some bioactive natural and unnatural

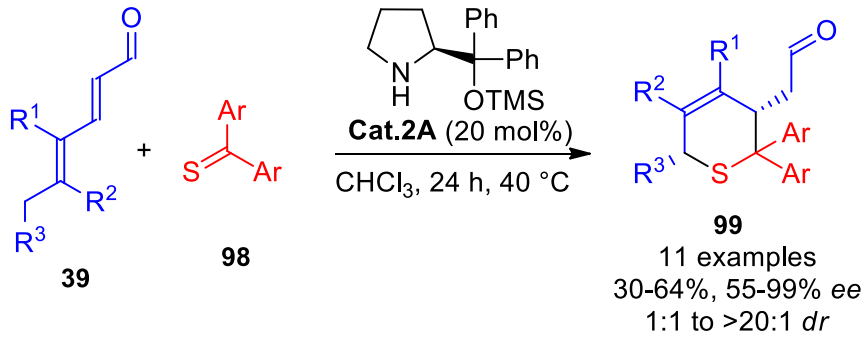
[33] (a) Villegas Gómez, C.; Cruz Cruz, D.; Mose, R.; Jørgensen, K. A. *Chem. Commun*. **2014**, *50*, 6035-6038. (b) Cruz Cruz, D.; Mose, R.; Villegas Gómez, C.; Torbensen, S. V.; Larsen, M. S. *Chem. Eur. J.* **2014**, *20*, 11331-11335. (c) Li, Y.; Barløse, C.; Yang Li, Jørgensen, J.; Carlsen, B. D.; Jørgensen, K. A. *Chem. Eur. J.* **2017**, *23*, 38-41.

[34] Blond, G.; Gulea, M.; Mamane, V. *Curr. Org. Chem.* **2016**, *20*, 2161-2210.

[35] Jaiswal, V.; Mondal, B.; Saha, J. *Asian J. Org. Chem.* 10.1002/ajoc.202000238.

[36] Jiang, H.; Cruz Cruz, D.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am.Chem. Soc*. **2013**, 135, 5200-5207.

compounds. The reaction provides fair to moderate yields with fair to moderate stereoselectivities (Scheme 25)[37].

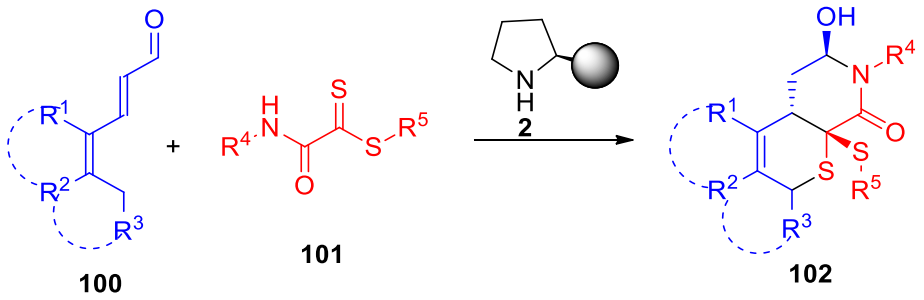


Scheme 25: Thio-Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and thioketones.

2.3.1.1 Conceptualization of the project:

The expansion of the one of the tremendous activation modes, which is trienamine activation brings a great interest to this project. In the present research we have been initiated a program to explore the diversification of substituted dithiomide **101** through cascade catalytic reactions. It is known that such structure form enantioenriched fused hetero product, it contains two different bioactive moieties, such as thio-pyrano and piperidone. The proposed strategy combines the synthesis of variety of dithioamides and subsequent thio-Diels-Alder/nucleophilic cycloaddition reaction via trienamine activation. The key to carrying out this process is to initially form the trienamine intermediate using dienal and an aminocatalyst **2**, whose raction with dithioamide deliver fused thio-prano piperidone **102** in stereoselective form. Through this process, it is possible to access the corresponding enantioenriched fused thio-pyrano-piperidone complex structure **102** with up to four stereogenic centres(Scheme 26).

[37] Hejmanowska, J.; Jasiński, M.; Mlostoń, G; Albrecht, Ł. *Eur. J. Org. Chem.* **2017**, 950-954.



Scheme 26: Synthesis of fused thio-pyrano-piperidone complex structures.

2.3.1.2Hypothesis:

The dithioamide act as dienophiles to react with an activated trienamine system. The electron-withdrawing groups attached to the thiocarbonyl will ensure a good reactivity toward the thio[4+2] cycloaddition, while it is expected that the planarity of the molecule will provide a correct *endo–exo* selection. Finally, once the catalytic cycloaddition proceeds, a nucleophilic ring closing reaction can take place between the nitrogen atom of the amide and the aldehyde to obtain the corresponding thio-pyrano-piperidone in a cascade and bis-cascade fashion.

2.3.1.3 Objectives:

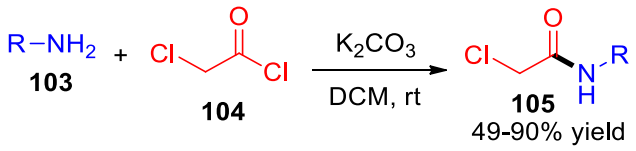
- To synthesize starting materials such as different derivatives of dithiomide of tryptamine for one pot reaction and bis-cascade reaction.
- To optimize the one pot reaction, and bis-cascade reactions in order to obtain the corresponding bis-[4+2] cycloadducts via aminocatalysis with maximum derivatives from corresponding starting material.
- To develop derivatives scope table.
- To characterize all the obtained products.
- To do adduct transformations.

2.3.1.4 Result and discussion:

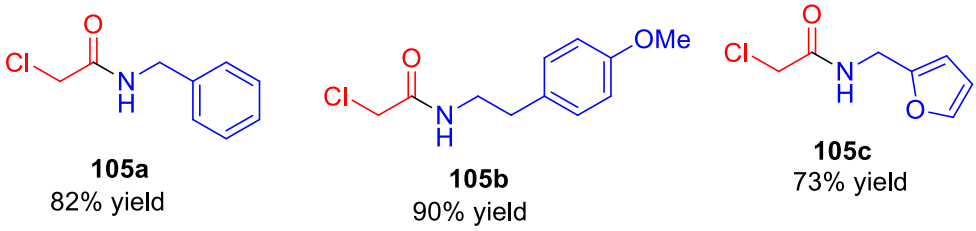
Synthesis of starting material:

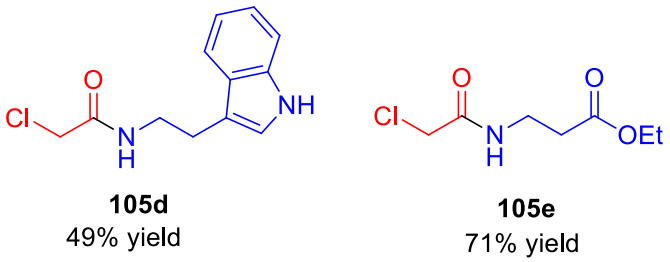
The primary amines **103** were treated with chloroacetyl chloride **104** in presence of K2CO3 and DCM as a solvent to form the corresponding chloroacetyl amides **105** (Scheme 27a). Later, the reaction with sulphur in presence of triethyl amine and then alkyl halide delivered desired products **106** in moderate to good yield Scheme 27b).

a)

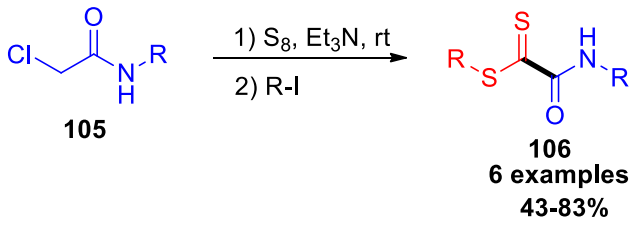


Derivatives:

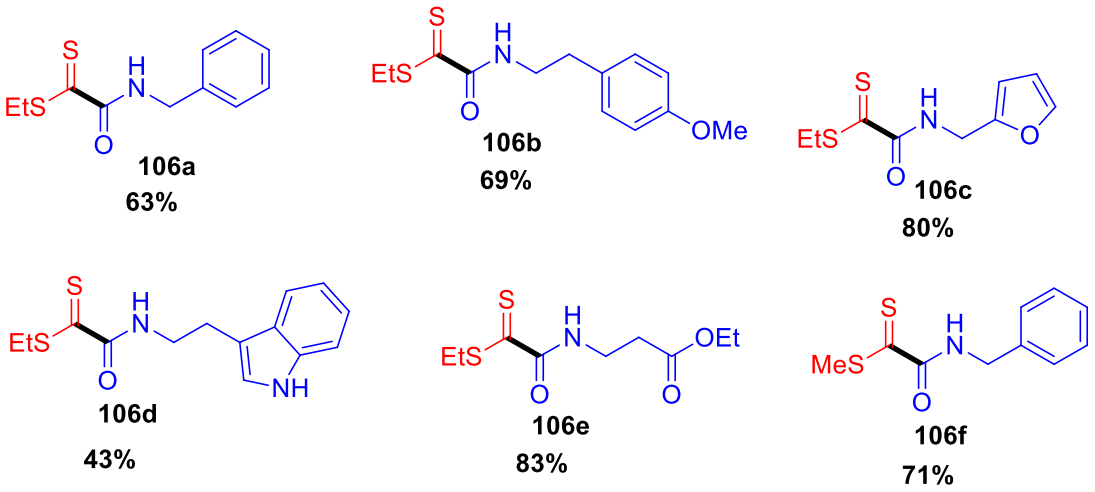




b)



Derivatives:



Scheme 33: General procedure for the synthesis of dithioamide.

Optimization of reaction

The optimization was started with the reaction between the 2,4-dienal **47** and the dithioamide **106a** as model substrates for the cascade sequence thio-Diels–Alder/nucleophilic ring-closing. Gratifyingly, when the reaction was carried out in presence of 20 mol% of Jørgensen-Hayashi catalyst **2A** and benzoic acid as additive in $CHCl_3$, the desired product **107a** was obtained after 24 h at room temperature with excellent yield (93%) and stereocontrol (93:7 dr, 92% ee) (Table 4, entry 1). In order to improve the stereoselectivity, we tested different catalysts. When the reaction was performed with the catalysts **2B**-**C**, the diastereoselectivity was slightly improved but the enantioselectivity and the yield were not satisfying (entries 2 and 3). By using the more sterically demanding *O*-$Si(Ph)_3$ catalyst **2D**, a better enantioselectivity was observed (96% ee) along with the same diasteromeric ratio. However, the isolated yield decreased less than 80% (entry 4). Therefore, we decided to work with the readily available catalyst **2A**. Finally, no further improvement was observed by changing solvents such as CH_3CN, THF and CH_2Cl_2 (entries 5, 6 and 7). And, with low loading of catalyst (entry 8).

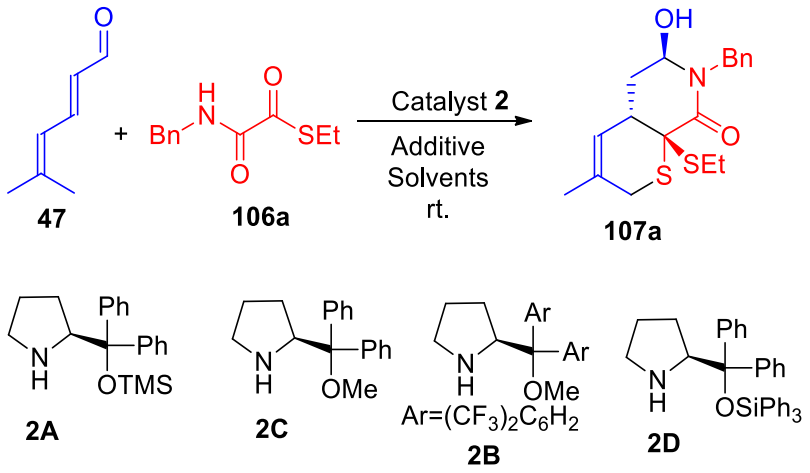


Table 4: Optimization of 2,4-dienal and dithiamide

Entry	Cat.	Solvent	t (h)	Conv. (%)	Yield (%)[a]	dr[b]	ee[c] (%)
1	**2A**	$CHCl_3$	24	100	93	93:7	92
2	**2C**	$CHCl_3$	48	64	62	97:3	68
3	**2B**	$CHCl_3$	48	74	70	94:6	76
4	**2D**	$CHCl_3$	48	100	78	93:7	96
5	**2A**	CH_2Cl_2	48	61	57	71:26	n.d.
6	**2A**	CH_3CN	48	63.	61	74:26	82
7	**2A**	THF	48	dec	--	--	--
8	**2A**	$CHCl_3$	48	64	61	72:28	--

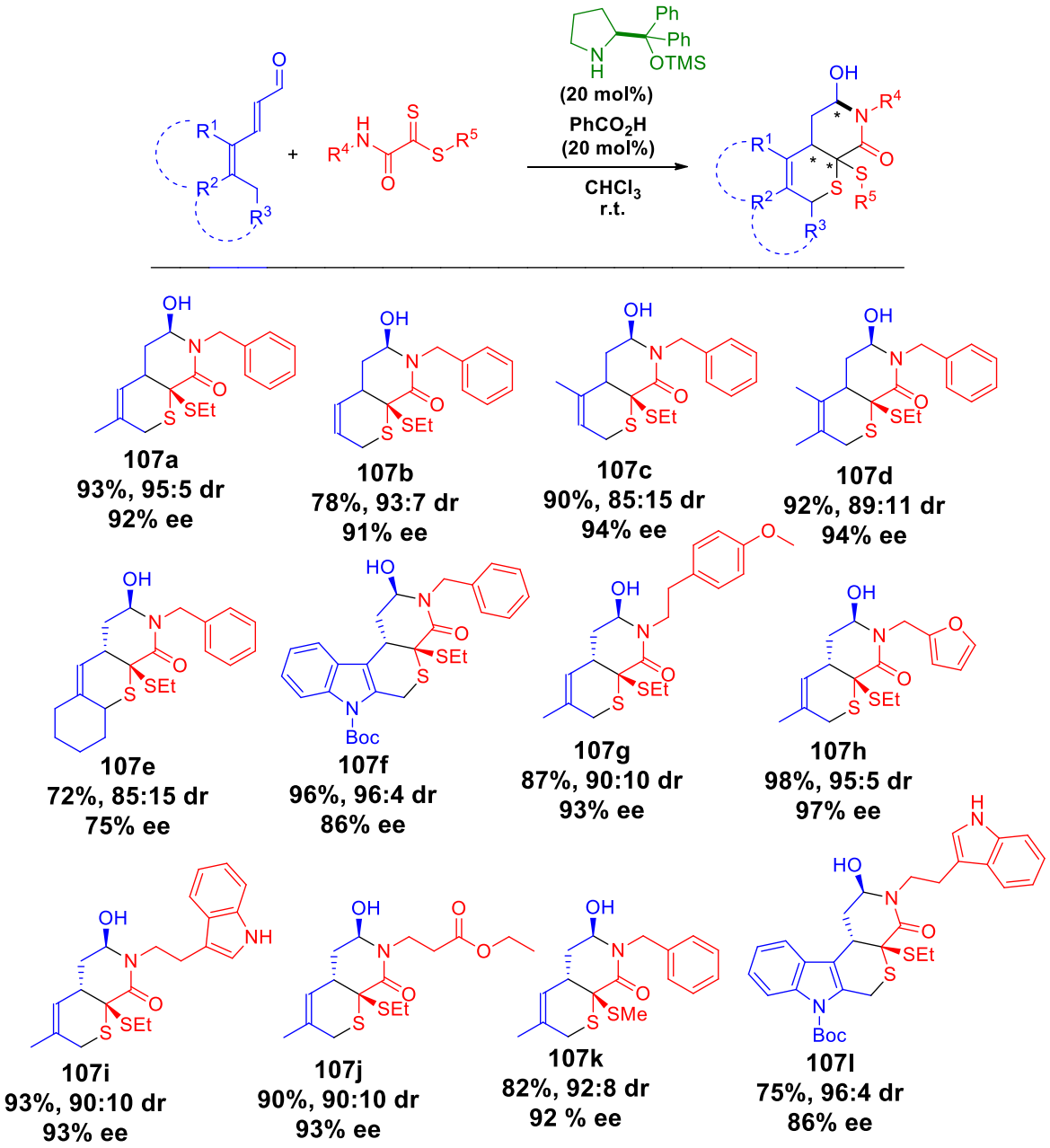
The reactions were performed with 0.15 mmol of **47** 0.1 mmol of **106a** 20 mol% of catalyst and benzoic acid as additive in 0.5 ml of solvent at room temperature. [a]Yield of both diastereoisomers of **107a** after chromatographic purification on silica gel. [b]Determined by ^1H NMR of crude product. [c]Measured by chiral HPLC

Scope of the reaction

Once the best conditions were determined, the scope of the reaction was carried out using different substituted dienals **47** and dithioamides **106a**. As shown in Table 5, alkyl groups at *γ*- and *δ*-positions were well tolerated, maintaining good yields and stereoselectivities. An extra cyclohexane fused ring was also generated by using the

derivative **106e** and gain one more extra stereocentre with good yield (72%) and high enantioselectivities (86%). Interestingly, an indole moiety could be incorporated when the 2-methylindole acrylaldehyde **106f** was employed as masked 2,4-dienal, leading to the corresponding tetracyclic adduct **106f** in excellent yield (96%) and stereoselectivity (96:4 dr, 98% ee). Next, we investigated the protocol using different dithioamides. To our delight, the reaction was also effective for dithioamides carrying with hetero-aromatic or ester substituents resulting in good to excellent yields (87-98%) and stereoselectivities (90:10-95:5 dr, 93-97% ee). Only a small difference was observed by changing the alkyl group at the sulfur atom with with high yield (82%) and excellent stereoselectivities (92:8 dr, 90% ee). Notably, an interesting polycyclic derivative with two indole cores **106l** was able to prepare through the reaction between **106f** and **106i**.

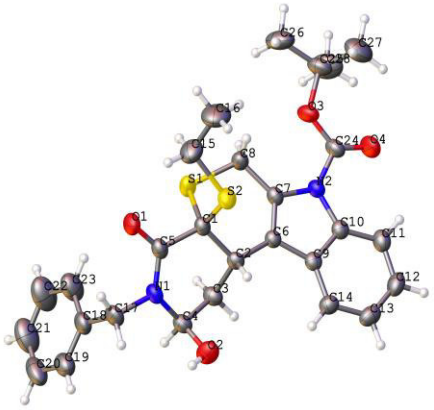
Table 5: Scope of the reaction.

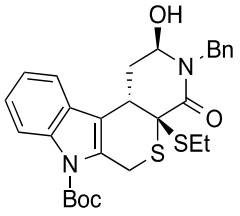


The reactions were performed with 0.15 mmol of **47**, 0.1 mmol of **106**, 20 mol% of catalyst, and benzoic acid as additive in 0.5 ml of solvent at room temperature. The yield is for both diastereoisomers of **107** after chromatographic purification on silica gel. The dr was determined by ^{1}H NMR of crude product. The ee was measured by chiral HPLC.

X-ray structure

The absolute stereochemistry of the enantioenriched thiopyrano-piperidone (2*R*, 4a*R*, 11c*S*) was obtained through x-ray analysis of the reaction product derived from the reaction between 2,4-dienal and dithioamide. For the remaining product, the configurations were assumed by analogy (Figure 5).





4f

Fig. 5: X-ray structure **107f**. Colour coding yellow Sulphur; blue Nitrogen; red oxygen.

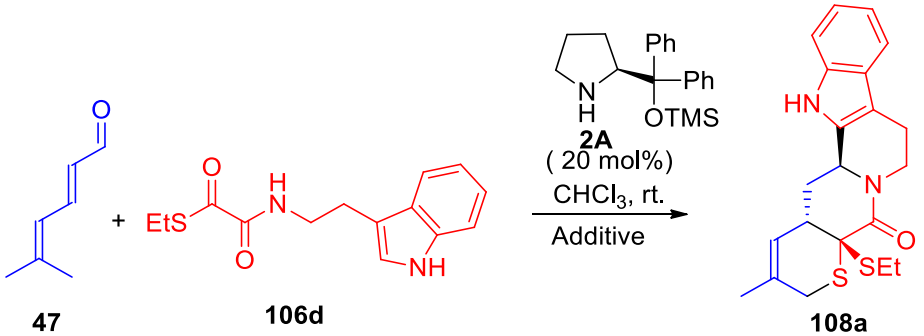
2.3.1.5 Asymmetric one pot reaction: Synthesis of the thiopyrano-piperidone-tetrahydrocarboline via trienamine catalysis

Organocatalytic one-pot reaction which can construct multiple bonds and delivered complex molecule in a single vessel, are great interest to the scientific community. These reactions have many advantages, as they are atom-economical and have reduced synthetic step, minimizing practical aspects like purification and removing the need for protecting group strategies. Highly enantioenriched thiopyrano-piperidone-tetrahydrocarboline molecule. The Pictet-Spengler type rection and lactamization was achieved by introducing tryptamine moety in dithioamide **106a**, a Pictet-Spengler type reaction proceeds after [4+2] thio-Diels-Alder/nucleophilic ring -closing cascade sequence, led to complex framework in a one pot process. Whose synthesis has benefited from this cascade

sequence. These systems are ubiquitous in nature and, as such, are important medicinal and pharmaceutical probe.,of particular note in recent times is the use of asymmetric organocatalysis in cascade chemistry, which has contributed toward the synthesis of an impressive diversity of complex structures. Inspired from previous reports, it was envisioned the cascade cycloadduct **107i**, which can undergo an intramolecular Pictet-Spengler type reaction once an iminium ion intermediate is formed via hydroxyl group elimination. The reaction was promoted under acidic conditions. This reaction delivered the thiopyrano-piperidone-tetrahydrocarboline fused rings compound.

Optimization of reaction

The optimization was started with the reaction between the dienal and tryptamine dithioamide in presence of Jørgensen–Hayashi catalyst in chloroform at room temperature. It was not delivering the desired product (entry 1). To find the desired product, it was tested different acidic additive but unfortunately the desired product was not obtained (entry 2,3). Interestingly, when we used TFA, the desired product was obtained with modest yield, with low loading of acidic additive 20 mol% the obtained product with high yield (entry 6).



47 106d 108a

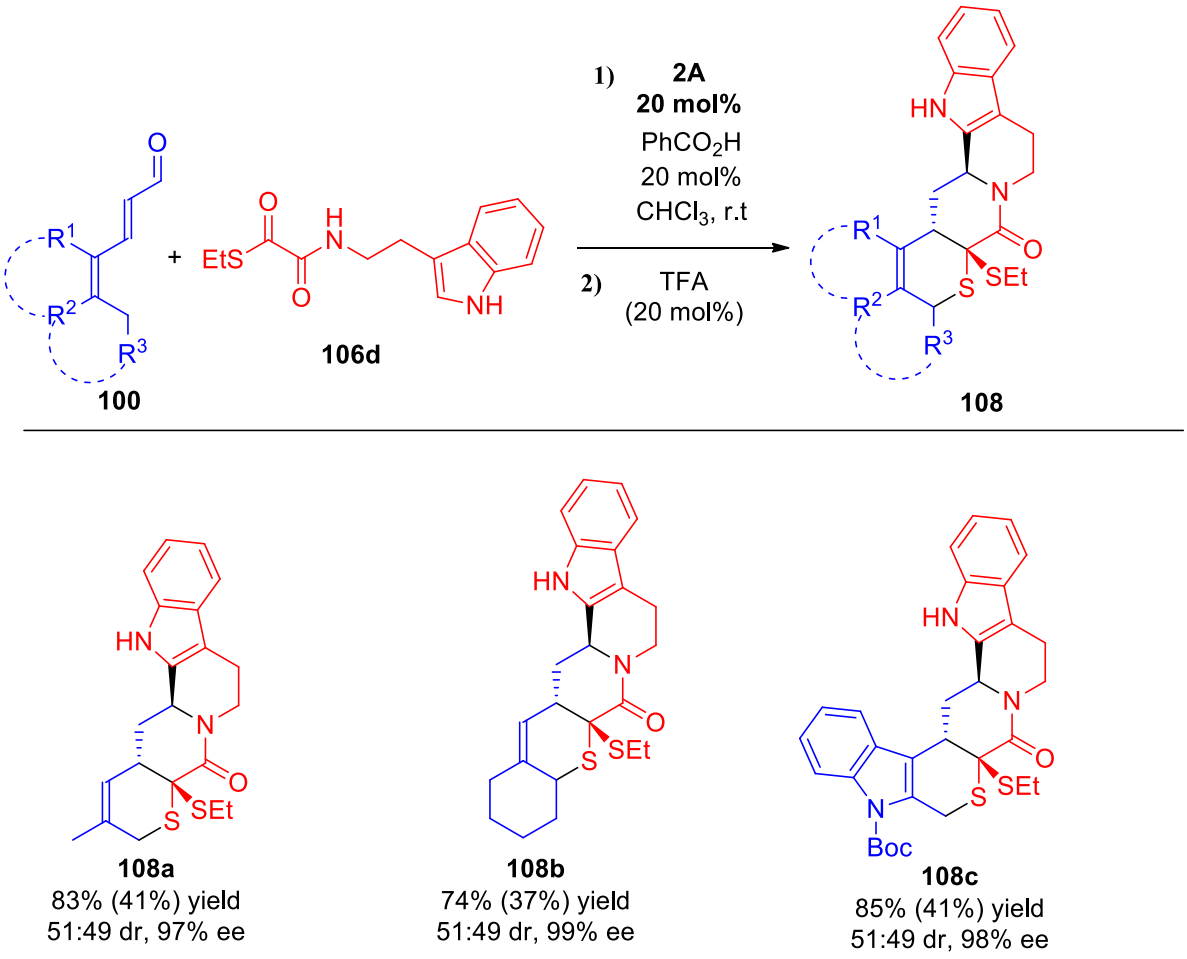
Entry	Additive	Equiv.	t (h)	Conv. (%)	Yield (%)[a]	dr[b]
1	$PhCO_2H$	1	96	100	---	---
2	$p\text{-}NO_2CO_2H$	1	96	100	---	----

3	$PhCHOHCO_2H$	1	96	100	---	-----
4	CF_3CO_2H	1	1	100	36	54:46
5	CF_3CO_2H	50 mole%	1.5	100	47	52:48
6	CF_3CO_2H	20 mole%	2	100	83	51:49

The reactions were performed with 0.15 mmol of **47**, 0.1 mmol of **106d**, 20 mol% of catalyst and benzoic acid as additive in 0.5 ml of solvent at room temperature. [a]Yield of both diastereoisomers of **108a** after chromatographic purification on silica gel. [b]Determined by ^1H NMR of crude product. [c]Measured by chiral HPLC.

Scope of the reaction

Once the best conditions had been determined, the scope of the reaction was carried out using different substituted dienal **47** and aromatic dithioamides **102d** . The thio-Diels–Alder/nucleophilic ring closing and Pictet-Spengler reactions were performed in a one-pot fashion using catalytic amounts of TFA, the desired product **108a** was furnished in 83% overall yield and 97% ee. In order to prove the strategy, . An extra cyclohexane fused ring was also generated by using the derivative **108b** and gain one more extra stereocentre with good yield (74%) and high enantioselectivities (99% ee). By using indole aldehyde obtained heptacylic compound **108c** good yields (85 %) and excellent enantioselectivities (98%). Rest of the devrivatives will be synthesize in future with better improvement of optimization.



The reactions were performed with 0.15 mmol of **96**, 0.1 mmol of **102d**, 20 mol% of catalyst, and benzoic acid as additive in 0.5 ml of solvent at room temperature. Then TFA (20 mol%) was added. The yield is for both diastereoisomers, the yield in parenthesis is for single major diatereoisomer. The dr was determined by ^{1}H NMR of crude product. The ee was measured by chiral HPLC.

X-ray structure

The absolute stereochemistry of the enantioenriched thiopyrano-piperidone-tetrahydrocarboline (7a*R*, 16b*R*, 17a*S*) **108c** was obtained through x-ray analysis of the reaction product derived from the reaction between 2,4-dienal and tryptamine dithioamide. For the remaining product, the configurations were assumed by analogy (Figure 6).

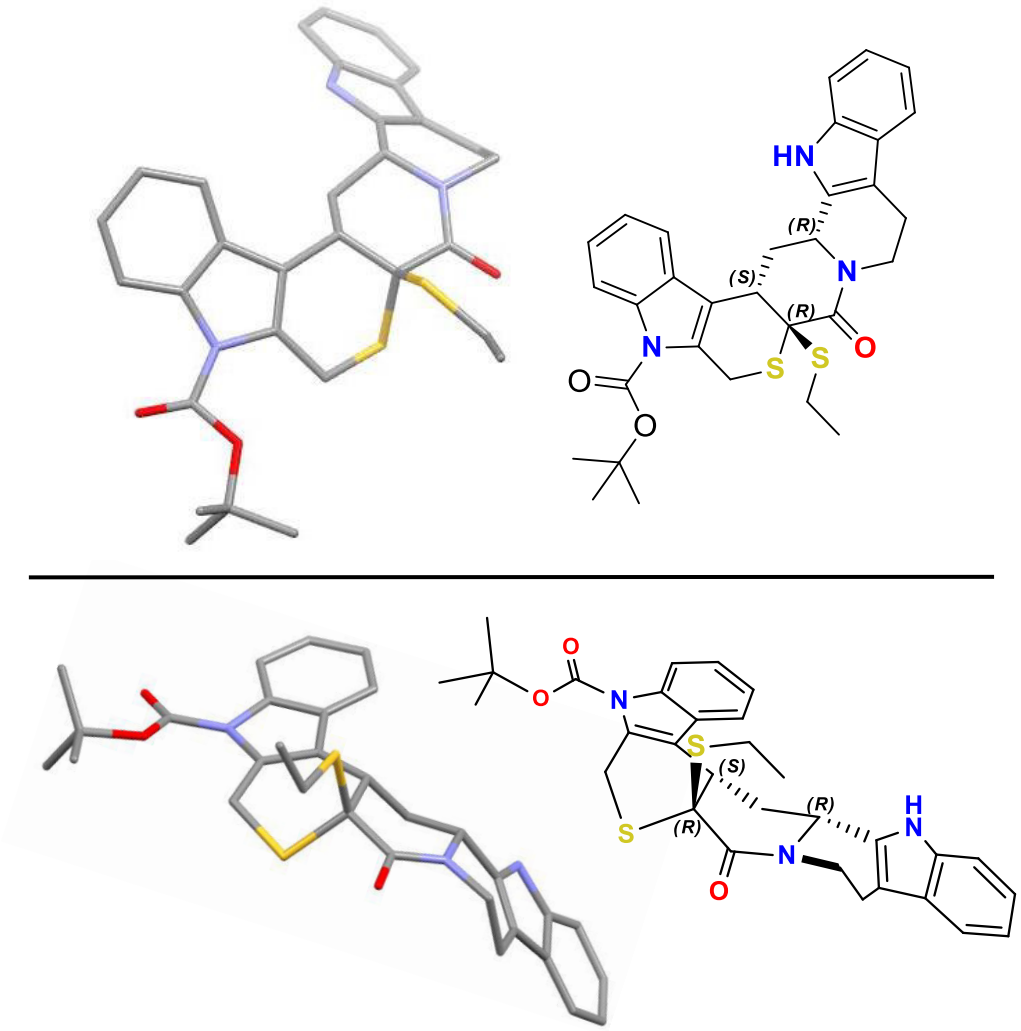
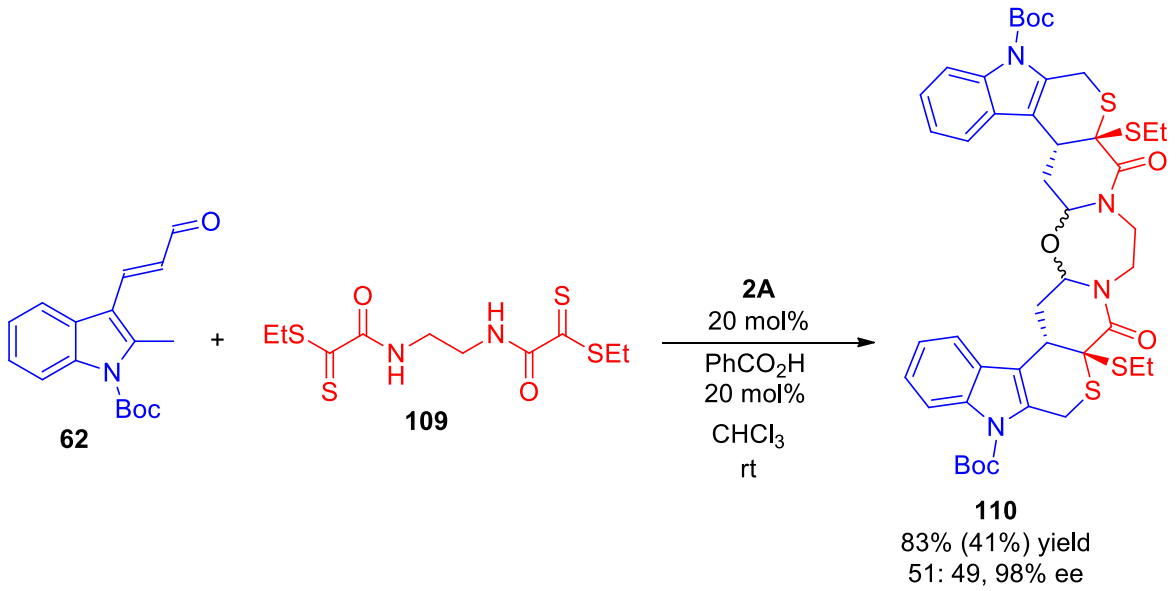


Fig. 6: X-ray structure **108c**. Colour coding yellow Sulphur; blue Nitrogen; red oxygen.

2.3.1.6 Asymmetric bis-cascade reaction:

Replacing by dithioamide by bis-dithioamide deliver to more diverse and complex molecules containing these attractive scaffolds we were wondering if a double aminocatalytic cascade process would be possible through the reaction with the bis-dithioamide **109** and construct two cycloadducts connected by the amide moiety in one process. Surprisingly, when the bis-dithioamide **109** was reacted with three equivalent of the aldehyde **62** under the standard conditions, the nine fused ring compound **110** was directly obtained in a double-(thio-Diels–Alder/*N*-nucleophilic ring closing)/elimination/*O*-nucleophilic ring closing sequence (Scheme 34). Notably, through this reaction, a separable mixture of two diastereoisomers with six new stereocenters were smoothly furnished in 41 and 39% of yield and 98% of ee for the major diastereoisomer .

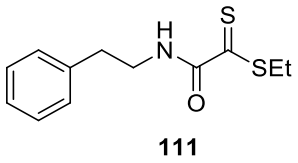


Scheme 34. Aminocatalytic double-(thio-Diels–Alder/*N*-nucleophilic ring closing)/elimination/*O*-nucleophilic ring closing cascade reaction.

The reaction was performed with 0.3 mmol of **62**, 0.1 mmol of **109**, 20 mol% of catalyst **2A** and benzoic acid as additive in 0.5 ml of solvent at room temperature. The yield is for both diastereoisomers. [a]The yield is for a single major diastereoisomer. The dr was determined by ^{1}H NMR of crude product. The ee was measured by

2.3.1.7. Perspective;

- To optimize the one pot reaction reaction and synthesized a series of thio-[4+2] cycloadducts/ nucleophilic ring closing and Pictet-Spengler reactions via aminocatalysis with maximum derivatives from corresponding starting material.
- To Synthesize starting material such as different substituted dithioamides .



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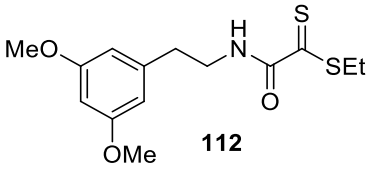

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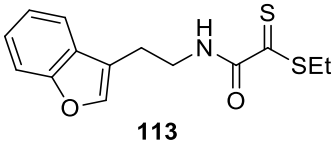
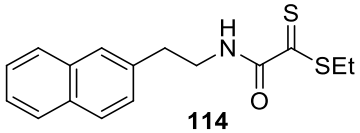
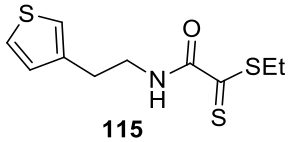


113

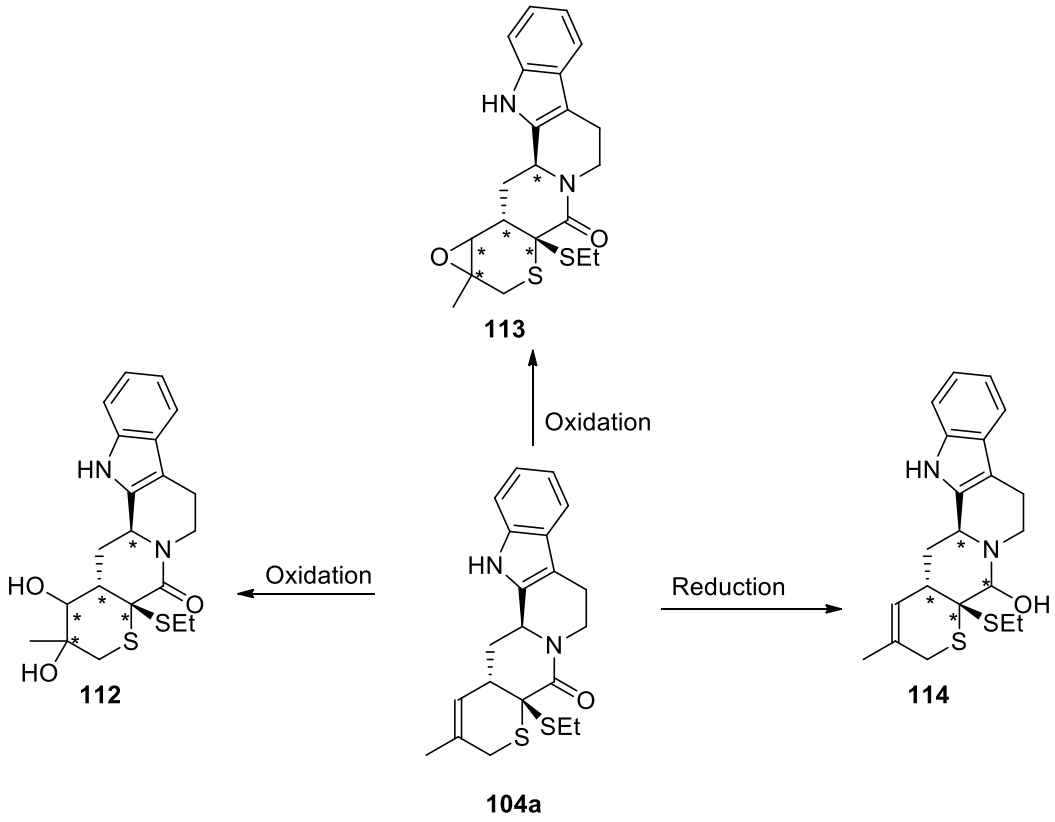


114



115

- To complete the scope of the reaction as mentioned in above scope table.
- To do adduct transformation as mention in below.



- To publish article on one pot reaction

2.3.1.8 Conclusion:

In conclusion, we have developed a new thia-Diels–Alder/nucleophilic ring-closing cascade sequence for the enantioselective synthesis of thio-pyrano-piperidone fused ring compounds through trienamine catalysis. The reaction proceeds efficiently with high levels of stereocontrol. Additionally, by promoting an intramolecular Pictet-Spengler reaction after the cascade sequence, different thiopyrano-piperidone-carboline fused ring compounds were constructed in a one-pot with good yield and excellent enantiocontrol. Interestingly, by using a bis-dithioamide as hetero-dienophile, a double-(thio-Diels–Alder/*N*-nucleophilic ring closing)/elimination/*O*-nucleophilic ring closing super cascade reaction was achieved, leading to a new type of nine fused ring derivative with six new stereocenters. These aminocatalytic cascade methodologies, open new perspectives for the

synthesis of a new class of complex and diverse thiopyranes, which contribute to populate new relevant regions in the chemical space.

Chapter 3

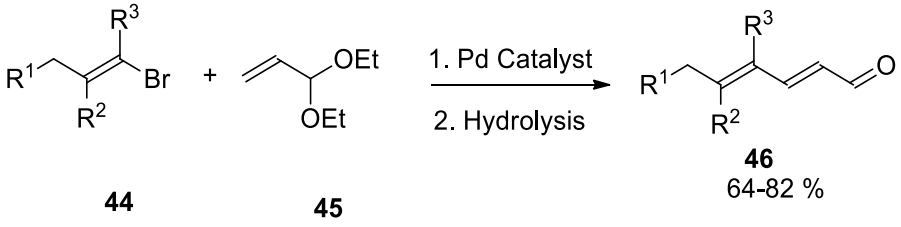
Chapter 3- Experimental section

Synthesis of Aldehydes:

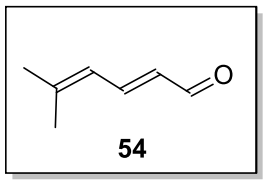
3.1 Synthesis of aldehydes used for aminocatalysis

3.1.1 Synthesis of 2,4-dienal

A) General procedure to synthesize substituted 2,4-dienals using Pd-catalyst: To a stirred solution of vinyl bromides **51** in DMF were added acrolein diethyl acetal **52,** $Pd(OAc)_2$, nBu_4NOAc, K_2CO_3, and KCl. The mixture was stirred for overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 minutes and then diluted with ether and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography. (Scheme 35).[38]



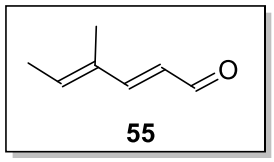
Scheme 35: Synthesis of dienals.



(*E*)-5-methylhexa-2,4-dienal (54): To a stirred solution of 1-bromo-2-methylprop-1-ene (7.41 mmol) in DMF (50.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.22 mmol), nBu_4NOAc (14.8 mmol), K_2CO_3 (11.1 mmol), and KCl (7.41 mmol). The mixture was stirred for overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 minutres and then diluted with ether and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

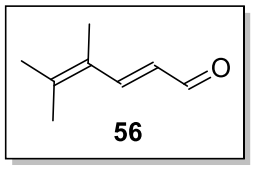
[38] Battistuzzi, G.; Cacchi, S.; Fabrizi, G., *Org. Lett.,* **2003**, *55*, 777-780

The residue was purified by column chromatography (pentane/diethyl ether 19:1). Yellow oil; 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.32 (dd, *J* = 15.1, 11.5 Hz, 1H), 6.06 (dd, *J* = 11.5, 0.5 Hz, 1H), 5.96 (dd, *J* = 15.1, 8.4 Hz, 1H), 1.86 (d, *J* = 8.4 Hz, 6H).



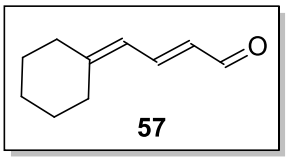
55

(2*E*,4*E*)-4-methylhexa-2,4-dienal (55): To a stirred solution of 1-bromo-2-methylprop-1-ene (5.5 mmol) in DMF (30.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.17 mmol), nBu_4NOAc (11.0 mmol), K_2CO_3 (8.26 mmol), and KCl (5.5 mmol). The mixture was stirred for overnight at 90 °C. After coolong 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 minutres and then diluted with ether and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (pentane/diethyl ether 19:1). Yellow oil; 76% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 15.6 Hz, 1H), 6.16 – 6.04 (m, 2H), 1.86 (d, *J* = 7.2 Hz, 3H), 1.80 (s, 3H).



56

(*E*)-4,5-dimethylhexa-2,4-dienal (56): To a stirred solution of 1-bromo-2-methylprop-1-ene (5.5 mmol, 0.64 mL) in DMF (30.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.17 mmol, 37.0 mg), nBu_4NOAc (11.0 mmol), K_2CO_3 (8.26 mmol), and KCl (5.5 mmol). The mixture was stirred for overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 minutres and then diluted with ether and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (pentane/diethyl ether 19:1). Yellow oil; 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 15.4 Hz, 1H), 6.17 – 6.05 (m, 1H), 2.02 – 1.99 (m, 3H), 1.92 (s, 3H), 1.83 – 1.81 (m, 3H).



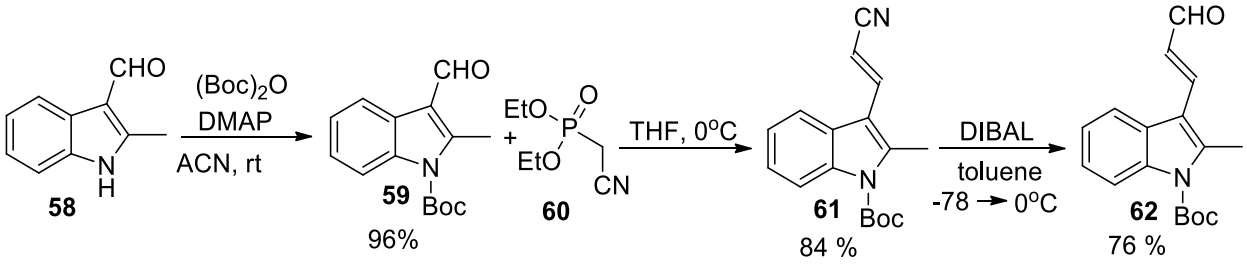
57

(*E*)-4-cyclohexylidenebut-2-enal (57): To a stirred solution of 1-bromo-2-methylprop-1-ene (5.5 mmol) in DMF (30.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.17 mmol, 37.0 mg), nBu_4NOAc (11.0 mmol, 3.32 g), K_2CO_3 (8.26 mmol, 1.13 g), and KCl (5.5 mmol, 410 mg). The mixture was stirred for

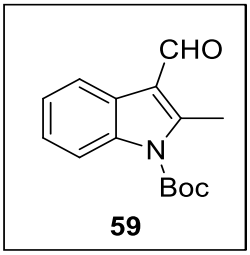
overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 minutres and then diluted with ether and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (pentane/diethyl ether 19:1). Yellow oil; 64% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (t, *J* = 9.8 Hz, 1H), 7.45 (dd, *J* = 15.0, 11.6 Hz, 1H), 6.18 – 5.90 (m, 2H), 2.42 (d, *J* = 6.0 Hz, 2H), 2.28 – 2.23 (m, 2H), 1.67 – 1.59 (m, 6H).

3.1.2 Synthesis of 2-methyl indole acryldehyde

The 2-methyl indole acryldehyde **62** was prepared according to the literature by the following strategy: In the first step, the indole carbaldhyde **58** reacted $(Boc)_2O$ in presence of DMAP and CH_3CN as a solvent to form corresponding *N*-protected indole carboxyl aldehyde **59**, it treated with cyano-Wittig reagent **60** then underwent reduction of cyano-vinyl carboxylate **61** delivered 2-methyl indole acryldehyde **62** with good yield (Scheme 36).

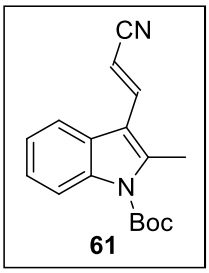


Scheme 36: Synthesis of (*E*)-tert-butyl 2-methyl-3-(3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxyate.



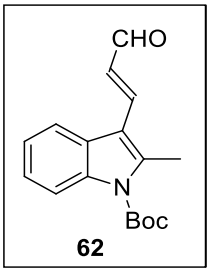
tert-butyl 3-formyl-2-methyl-1*H*-indole-1-carboxylate(59): To a solution of 2-methyl-1H-indole-3-carbaldehyde **13** (25.1 mmol,) in CH_3CN (65 mL), DMAP (2.5 mmol) and di-tert-butyl dicarbonate (30 mmol) were added and stirred at room temperature for 4 h. The solvent was removed and then extracted with $CHCl_3$ (2 x 30 mL). The organic layer was washed with $NaHCO_3$ solution (2 x 30 mL) and then dried ($NaSO_4$). Removal of the solvent followed by crystallization from methanol afforded product **14**. Pale

yellow solid; compound was isolated by flash-chromatography (20% EtOAc/hexanes). Yield = 96 %; M.p. 110 °C.;^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.31 (m, 1H), 8.06 (m, 1H), 7.33 (m, 2H), 2.93 (s, 3H), 1.72 (s, 9H).



61

tert-butyl (*E*)-3-(2-cyanovinyl)-2-methyl-1*H*-indole-1-carboxylate(61): To a solution of diethylcyanomethyl phosphonate **60** (20.6 mmol, 3.2 mL) in anhydrous THF (30 mL) at 0°C, BuLi (2.5M in hexanes, 7.4 mL) was added dropwise and the mixture was stirred for 1h at the same temperature. A solution of the aldehyde (15.4 mmol, 4 g) in anhydrous THF (15 mL) was prepared and the solution of the Wittig reagent was added dropwise via cannula. After the addition, the reaction mixture was stirred at 0°C for 4h. The reaction was then concentrated, and the product was recrystallized from hexane/ethyl acetate to give 1.8 g of the corresponding nitrile **61**(84%). White solid; compound was isolated by flash-chromatography (20% EtOAc/hexanes). Yield = 84 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, 1H), 7.53 (d, 1H), 7.45 (d, *J* = 16.6 Hz, 1H), 7.21 (d, 2H), 5.78 (d, *J* = 16.6 Hz, 1H), 2.55 (d, 3H), 1.61 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.93, 142.26, 141.07, 136.26, 126.28, 124.65, 123.82, 118.94, 115.76, 114.28, 94.63, 85.24, 28.20, 14.30.



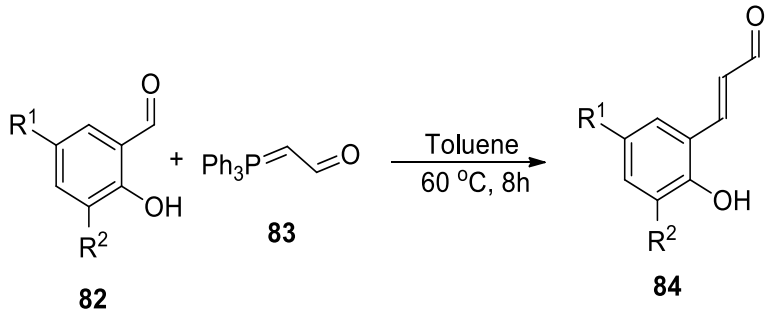
62

tert-butyl (*E*)-2-methyl-3-(3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate(62): A solution of the nitrile **15** (7 mmol, 2 g) in anhydrous toluene (30 mL) was cooled down to -78 °C and at that temperature, a solution of diisobutylaluminium hydride DIBAL in heptane (1M, 8.5 mL) was added dropwise for about 10 minutes. The reaction mixture was stirred at -78°C for 4 hours. Then, the reaction was quenched with methanol (2.3 mL) at -78 °C. The reaction flask could warm to room temperature then stirred with 1M HCl (12 mL) for two minutes. The solution was diluted with 25 mL of EtOAc and the organic phase was separated. The aqueous layer was extracted twice with 12 mL of EtOAc. The combined organics were washed with brine and dried over Na_2SO_4. After concentration, the material was purified by column chromatography to give the desired product. Orange brown solid; Yield = 76 %; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (d, 1H, *J* = 7.65 Hz), 8.14 (m, 1H), 7.81 (m, 1H), 7.70 (d, 1H, *J* = 15.80 Hz), 7.33 (m, 2H), 6.86

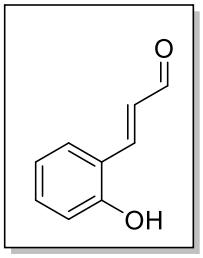
(dd, 1H, *J* = 15.80, J = 7.65 Hz), 2.76 (s, 3H), 1.71 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.38, 150.12, 144.58, 142.27, 136.46, 128.02, 126.79, 124.75, 123.98, 119.69, 115.73, 114.89, 85.36, 28.34, 14.54 ppm.

3.1.3 Synthesis of hydroxyphenyl Aldehyde:

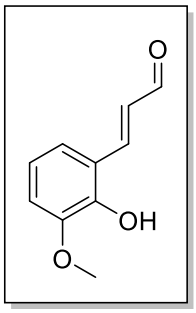
General procedure to synthesize 2-hydroxyphenyl acrylaldehyde: A mixture of a corresponding aldehyde (1.0 mmol) with Ph_3P=CHCHO (1.2 mmol) in toluene (1.0 mL) was stirred at 60 ºC for 8 h under nitrogen. The crude product was directly purified by silica gel column directly eluting with hexane/EtOAc=10:1 to 5:1 and the designed product can be isolated.



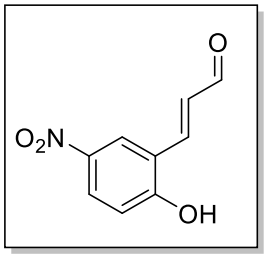
Scheme 37: Synthesis of 2-hydroxyphenyl aldehyde.



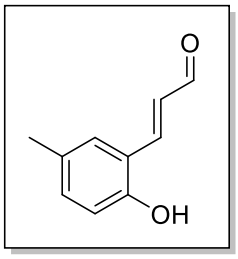
(*E*)-3-(2-hydroxyphenyl)acrylaldehyde (85): A mixture of a 2-hydroxy-5-benzaldehyde (24.6 mmol) with Ph_3P=CHCHO (29.5 mmol) in toluene (25.0 mL) was stirred at 60 ºC for 8 h under nitrogen. The crude product was directly purified by silica gel column directly eluting with hexane/EtOAc=10:1 to 5:1. Yellow solid; Yield 56%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 16.0 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.08 – 7.00 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.09, 156.00, 150.13, 132.92, 130.33, 129.29, 121.46, 121.09, 116.71, 77.16.



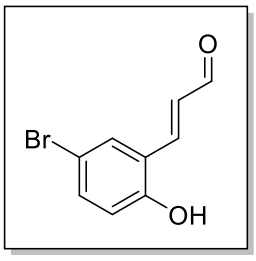
(*E*)-3-(2-hydroxy-3-methoxyphenyl)acrylaldehyde(86): A mixture of a 2-hydroxy-3-methoxybenzaldehyde (6.6 mmol) with Ph_3P=CHCHO (7.9 mmol) in toluene (10.0 mL) was stirred at 60 ºC for 8 h under nitrogen. The crude product was directly purified by silica gel column directly eluting with hexane/EtOAc=10:1 to 5:1. Yellow solid; Yield 57%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 16.1 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.86 – 6.80 (m, 1H), 6.30 – 6.24 (m, 1H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.72, 147.76, 147.03, 145.62, 129.48, 120.60, 120.54, 120.06, 112.78, 77.16, 56.37.



(*E*)-3-(2-hydroxy-5-nitrophenyl)acrylaldehyde(88): A mixture of a 2-hydroxy-5-nitrobenzaldehyde (6.0 mmol) with Ph_3P=CHCHO (7.9 mmol) in toluene (10.0 mL) was stirred at 60 ºC for 8 h under nitrogen. The crude product was directly purified by silica gel column directly eluting with hexane/EtOAc=10:1 to 5:1. Yellow solid; Yield 57%; ^{1}H NMR (500 MHz, DMSO) δ 9.68 (d, *J* = 7.7 Hz, 1H), 8.54 (d, *J* = 2.8 Hz, 1H), 8.19 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.88 (d, *J* = 16.1 Hz, 1H), 7.11 (d, *J* = 9.1 Hz, 1H), 7.03 (dd, *J* = 16.1, 7.7 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 194.99, 183.92, 162.66, 153.53, 146.60, 145.99, 139.91, 137.26, 130.55, 129.27, 127.67, 127.62, 125.60, 123.34, 121.32, 120.26, 116.85, 39.52.



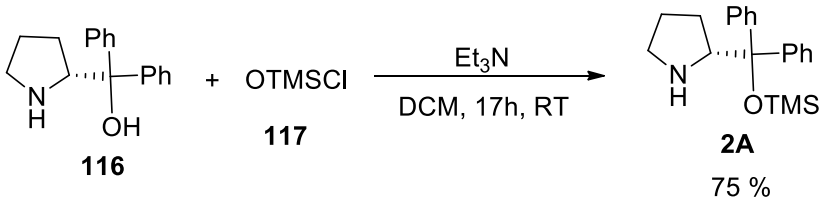
(*E*)-3-(2-hydroxy-5-methylphenyl)acrylaldehyde(89): A mixture of a 2-hydroxy-5-methylbenzaldehyde (7.3 mmol) with Ph_3P=CHCHO (7.9 mmol) in toluene (10.0 mL) was stirred at 60 ºC for 8 h under nitrogen. The crude product was directly purified by silica gel column directly eluting with hexane/EtOAc=10:1 to 5:1. Yellow solid; Yield 63%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 16.0 Hz, 1H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.11 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.91 (dd, *J* = 16.0, 7.9 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.96 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.34, 153.29, 149.12, 133.51, 130.55, 129.90, 129.15, 121.21, 116.46, 77.16, 20.55.



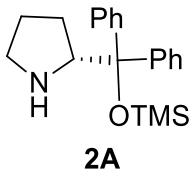
(*E*)-3-(5-bromo-2-hydroxyphenyl)acrylaldehyde(90): A mixture of a 2-hydroxy-5-bromobenzaldehyde (5.0 mmol) with Ph_3P=CHCHO

(7.9 mmol) in toluene (10.0 mL) was stirred at 60 ºC for 8 h under nitrogen. The crude product was directly purified by silica gel column directly eluting with hexane/EtOAc=10:1 to 5:1. Yellow solid; Yield 46%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 16.1 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.90 (dd, *J* = 16.1, 7.8 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.32 – 6.26 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.85, 154.32, 147.01, 135.03, 132.12, 130.26, 123.50, 118.25, 113.34, 77.16.

3.1.4. Synthesis of aminocatalysis



Scheme38: Synthesis of (S)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine



2A

(R)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine:

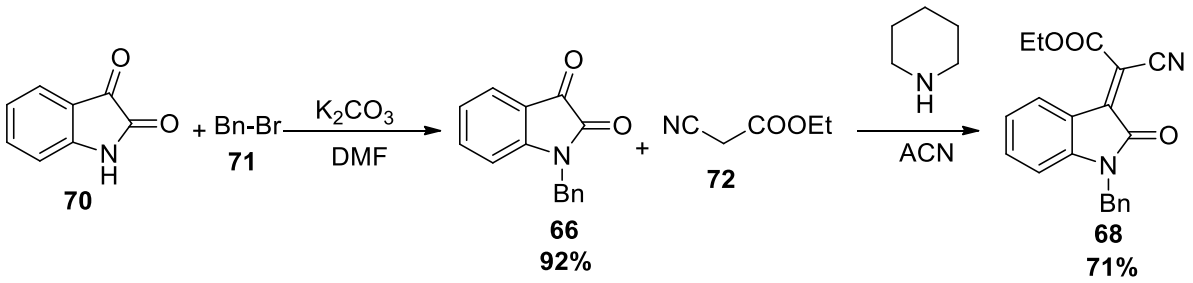
The commercially available α,α-diphenyl-2-pyrrolidinemethanol **116** (100 mg, 0.39 mmol) was readily protected with TMSOCl **117** (5.1 mmol) in the presence of TEA (5.1 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C. The reaction was stirred at room temperature for 17 h and quenched with water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3x1.5 mL). The combined organic extracts were stirred with $NaHCO_3$ for 15 minutes, dried over anhydrous Na_2SO_4 and concentrated in vacuo after filtration. Purification with silica gel column chromatography (ethyl acetate/pentane-1.7→1.3) furnished as a thick oil (78% yield). (Scheme 38). ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.00 (s, 9H), 1.6 (m, 4H), 2.8 (m, 2H), 3.51 (t, *J* = 7.0 Hz, 1H), 7.46 (m, 1H), 7.2-7.5 (m, 10H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ: 2.4, 25.1, 28.0, 47.3, 65.5, 83.3, 126.8, 127.0, 128.0, 129.0, 146.0, 147.0. (ppm)

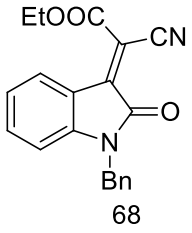
3.2 General procedure for the synthesis of cyno-olefenic-oxindole

To a solution of the appropriate isatin (10 mol)**70** in DMF (25.0 ml) and then K_2CO_3 was added. Then the mixture was stirred for 15 min after that added benzyl bromide **71** at room temperature for 1 h. The reaction mixture was extracted three times with DCM. The

organic layer was dried over sodium sulphate. Then organic layer extracted with diethyl ether and dried over again sodium sulphate and recrystallization in Pentane: DCM.

A mixture of protected isatin **66** with cyanoethyl ester **72** in presence of piperidine in acetonitriles was stirred at room temp. for overnight. The crude product was directly eluting with hexane/EtOAc=90:10 to 70:30, and the expected product **68** can be isolated with 71% yield**.**





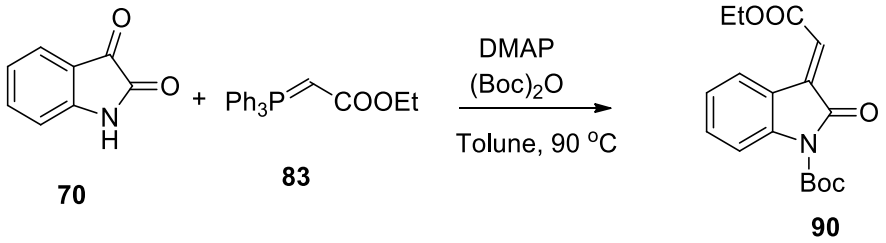
68

(*E*)-ethyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-2-cyanoacetate (68)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.20 (m, 6H), 6.94 (t, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 4.86 (s, 2H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.47, 161.55, 145.76, 144.50, 135.59, 134.78, 129.92, 129.01 (2C), 128.06, 127.50 (2C), 123.18, 118.88, 114.08, 109.77, 106.69, 63.45, 44.04, 14.0.

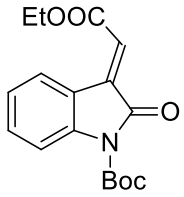
3.3 General procedure for the synthesis of ester oxindole olefin

The commercially available isatin **70** was treated with Wittig reagent (1.1 equiv.) **83** in toluene and the reaction mixture was heated up to 90 ^{0} C for 30 min. After cooling, the mixture was filtered, and then solvent was evaporated to have crude Wittig product. The crude product was dissolved in DCM and mixed with 4-(dimethylamino)pyridine (20 mol%). The reaction mixture was cooled down to 0 ^{0} C, and di-tert-butyl-dicarbonate (1.1 equiv.) was added to the reaction mixture. The reaction was monitored by TLC. The solvent was removed under reduced pressure and the crude reaction mixture was purified by FC to 72 %yield the 3-olefinic oxindole. **90**.



70 **83** **90**

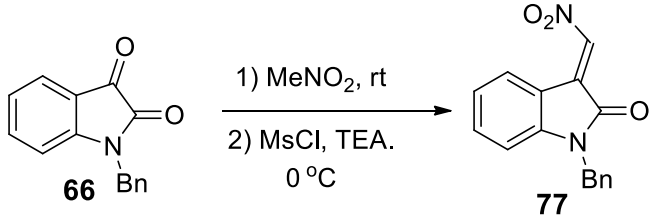
(*E*)-tert-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (90)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.22 (td, *J* = 7.7, 1.8 Hz, 1H), 6.94 (d, *J* = 3.2 Hz, 1H), 4.38 – 4.32 (m, 2H), 1.67 (s, 9H), 1.40 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.47, 161.55, 145.76, 144.50, 135.59, 134.78, 129.92, 129.01 (2C), 128.06, 127.50 (2C), 123.18, 118.88, 114.08, 109.77, 106.69, 63.45, 44.04, 14.0.

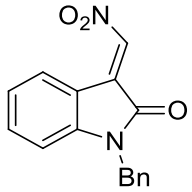
3.4 General procedure for the synthesis of nitro-oxindole olefin

N-substituted isatin (2 mmol) **66** was dissolved in nitromethane (10 mL). Two drops of diethylamine were added stirred at room temperature for a few minutes until the orange coloured solution turned light orange. The solvent was removed under pressure to give the nitroaldol adduct as a light orange powder. To the stirred solution of the obtained nitro alcohol and MsCl (1.2 equiv.) in dry THF (7.0 ml) was added TEA (2.1 equiv.) dropwise 0 ^{0} C. After 3 h, saturated ammonium chloride was added to the reaction mixture and aqueous phase was extracted with AcOEt. The extract was washed with 1N HCl (two times), saturated $NaHCO_3$ and brine, dried sodium sulphate, filtrated and concentrated in vacuo. The residual solid was purified by column chromatography using $CHCl_3$ as eluent. The expected product obtained **77** with 65% yield.



66 **77**

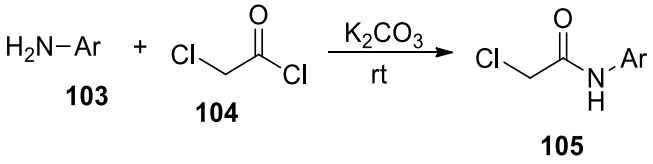
(*E*)-1-benzyl-3-(nitromethylene)indolin-2-one (77)



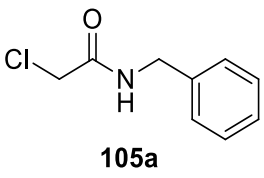
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.41 (d, *J* = 5.4 Hz, 1H), 7.23 (d, *J* = 41.1 Hz, 6H), 7.02 (d, *J* = 4.7 Hz, 1H), 6.71 (s, 1H), 4.86 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.98, 146.38, 138.3, 134.77, 134.68, 130.85, 130.09, 129.98, 128.98, 128.78, 128.04, 127.24, 123.48, 117.31, 109.91, 44.06.

3.5 Synthesis of chloro-amides

A mixture of primary amine (10 mmol, 1 equiv.) **99** and anhydrous potassium carbonate (10 mmol, 1 equiv.) in dichloromethane (20 mL) was stirred for 30 min at room temperature. The reaction mixture was cooled on an ice bath. Then, chloro-acetyl chloride **100** was added drop wise over 30 min. The ice bath was removed, and the reaction mixture was stirred overnight followed by reflux for additional 30 min. The solvent was evaporated under reduced pressure, the residue was neutralized with an aqueous 5% sodium bicarbonate solution. The obtained product **101** was filtered and washed with cold water for three times and dried. The crude product was enough pure and used for next step directly.



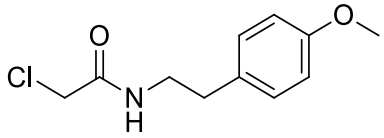
***N*-Benzyl-2-chloroacetamide 105a.**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 6.88 (s, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 4.12 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.81, 137.28, 128.86 (2C), 127.82 (3C), 43.87, 42.63. **HRMS** (ESI+) *m/z*

calcd. for $C_9H_{10}ClNO^+$ 184.0523 found 184.0527.

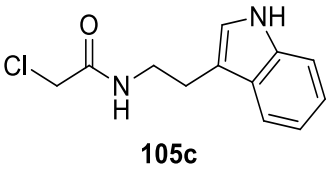
2-Chloro-*N*-(4-methoxyphenylethyl) acetamide 105b.



105b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.86 (t, *J* = 5.7 Hz, 2H), 6.61 (s, 1H), 4.01 (s, 2H), 3.79 (s, 3H), 3.52 (dd, *J* = 13.1, 6.8 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.80, 158.42, 130.30, 129.70 (2C), 114.15 (2C), 55.27, 42.67, 41.14, 34.57 **HRMS** (ESI+) *m/z* calcd. for $C_{11}H_{14}ClNO_2^+$ 228.0785 found 228.0789. m.p. 94^0 – $98\ ^0$C.

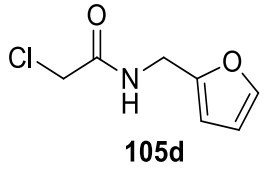
***N*-(2-(1*H*-indol-3-*yl*) ethyl)-2-chloroacetamide 105c.**



105c

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.19 – 7.15 (m, 1H), 7.09 (t, *J* = 3.9 Hz, 1H), 6.69 (s, 1H), 4.04 (s, 2H), 3.67 (dd, *J* = 12.8, 6.6 Hz, 2H), 3.05 (t, *J* = 6.8 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.82, 136.44, 127.16, 122.35 (2C), 122.07, 119.61, 118.67, 111.30, 42.71, 39.98, 25.12. **HRMS** (ESI+) *m/z* calcd. for $C_{12}H_{13}ClN_2O^+$ 237.0789 found 237.0795.

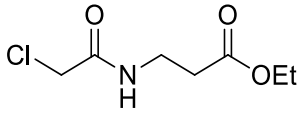
2-Chloro-*N*-(furan-2-ylmethyl) acetamide 105d.



105d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.90 (s, 1H), 6.36 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.30 (dd, *J* = 3.2, 0.6 Hz, 1H), 4.52 (d, *J* = 5.6 Hz, 2H), 4.11 (s, 2H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.68, 150.28, 142.57, 110.51, 107.95, 42.53 , 36.75 **HRMS** (ESI+) *m/z* calcd. for $C_7H_8ClNO_2^+$ 174.0316 found 174.0322.

Ethyl 3-(2-chloroacetamido) propanoate 105e

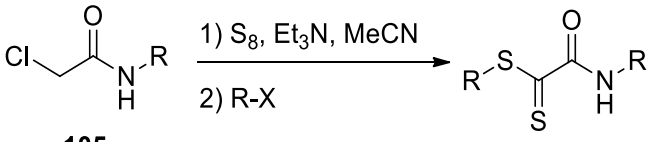


105e

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 4.18 (qd, *J* = 7.1, 2.2 Hz, 2H), 4.04 (d, *J* = 1.8 Hz, 2H), 3.59 (qd, *J* = 6.1, 2.2 Hz, 2H), 2.60 – 2.55 (m, 2H), 1.31 – 1.26 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.28, 166.01, 60.95, 42.58, 35.18, 33.73, 14.18. **HRMS** (ESI+) *m/z* calcd. for $C_7H_{12}ClNO_3^+$ 194.0578 found 194.0577.

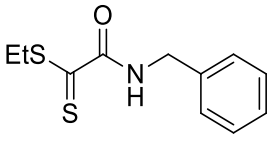
3.6 General procedure for the synthesis of dithioamides.

A mixture of chloro-acetamide **105** (10 mmol, 1 equiv.), sulphur (30 mmol, 3 equiv.) and triethylamine (30 mmol, 3 equiv.) was stirred in acetonitrile (15 mL) for 3h at room temperature. After 3h, the corresponding alky halide (30 mmol, 3 equiv.) was added and the reaction was stirred for 15h. The formed salts were removed by filtration and washed with a small amount of acetonitrile. To the organic layer was added water and extracted three times with dichloromethane. The combined organic layers were washed with saturated sodium bicarbonate, aqueous 10% sodium thiosulfate and dried over sodium sulfate. Finally, the crude product was purified by FC on silica gel (gradient: Hexane/EtOAc 70:30).



105 106

Ethyl 2-(benzylamino)-2-oxoethanedithioate 106a.

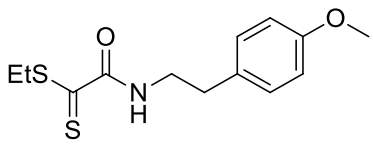


106a

Following the general procedure, the compound **106a** was obtained after FC on silica gel in 63% yield as a pink solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.77 (s, 1H), 7.37 – 7.25 (m, 5H), 4.55 (d, *J* = 6.0 Hz, 2H), 3.13 (q, *J* = 7.4 Hz, 2H), 1.31 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz,**

$CDCl_3$) δ 158.80, 137.08, 128.84 (3C), 127.84 (3C), 44.49, 31.08, 11.44. **HRMS** (ESI+) *m/z* calcd. for $C_{11}H_{13}NOS_2^+$ 240.0511 found 240.0513.

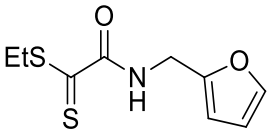
Ethyl 2-((2-(4-methoxyphenethyl) amino)-2-oxoethanedithioate 106b.



106b

Following the general procedure, the compound **106b** was obtained after FC on silica gel in 69% yield as a pink oil.**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 45.1 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 3.79 (s, 3H), 3.55 (q, *J* = 6.6 Hz, 2H), 3.18 (q, *J* = 7.4 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.88, 158.39, 130.38 (3C), 129.73 (2C), 114.13, 55.27, 41.92, 34.46, 31.01, 11.44. **HRMS** (ESI+) *m/z* calcd. for $C_{13}H_{17}NO_2S_2^+$ 284.0773 found 284.0782.

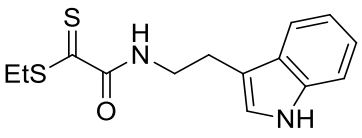
Ethyl 2-((furan-2-ylmethyl) amino)-2-oxoethanedithioate 106c.



106c

Following the general procedure, the compound **106c** was obtained after FC on silica gel in 80% yield as a pink oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.67 (s, 1H), 7.30 (dd, *J* = 1.8, 0.7 Hz, 1H), , 6.26 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.21 (dd, *J* = 3.2, 0.6 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 3.12 (q, *J* = 7.5 Hz, 2H), 1.31 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.57, 150.05, 142.57, 110.51 (2C), 108.09, 37.39, 31.03, 11.42. **HRMS** (ESI+) *m/z* calcd. for $C_9H_{11}NO_2S_2^+$ 230.0303 found 230.0314.

Ethyl 2-((2-(1*H*-indol-3-yl) ethyl) amino)-2-oxoethanedithioate 106d.

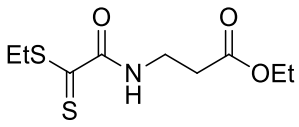


106d

Following the general procedure, the compound **106d** was obtained after FC on silica gel in 43% yield as a pink solid.**^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.58 (s, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 1.3 Hz, 1H), 3.68 (q, *J* = 6.6 Hz, 2H), 3.18 (q, *J* = 7.5 Hz, 2H), 3.06 (t, *J* = 6.9 Hz, 2H), 1.37 (t, *J* = 7.5 Hz, 3H) **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.9, 136.4, 127.2, 122.2 (2C), 119.6, 118.7,

112.6, 111.2 (2C),40.7, 31.0, 25.1, 11.4 **HRMS** (ESI+) *m/z* calcd. for $C_{14}H_{16}N_2OS_2^+$ 293.0776 found 293.0777.

Ethyl 3-(2-(ethylthio)-2-thioxoacetamido) propanoate 106e.

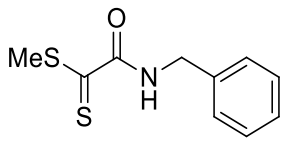


106e

Following the general procedure, the compound **106e** was obtained after FC on silica gel in 83% yield as a pink oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.84 (m, 1H), 4.21 – 4.10 (m, 2H), 3.63 – 3.56 (m, 2H), 3.16 (q, *J* = 7.5 Hz, 2H), 2.61 – 2.53 (m, 2H), 1.35 (q, *J* = 7.5 Hz, 3H), 1.27 – 1.22 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 191.3, 172.1, 158.9, 60.9, 35.9, 33.7, 30.9, 14.2, 11.4 **HRMS** (ESI+) *m/z* calcd. for $C_9H_{15}NO_3S_2^+$ 250.0566 found 250.0570.

Methyl 2-(benzylamino)-2-oxoethanedithioate 106f.



106f

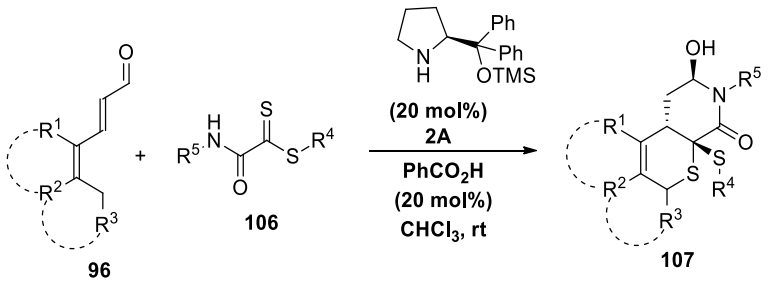
Following the general procedure, the compound **106f** was obtained after FC on silica gel in 71% yield as a light pink solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.70 (s, 1H), 7.29 – 7.22 (m, 5H), 4.47 (d, *J* = 6.1 Hz, 2H), 2.58 (s, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.7, 137.1, 128.8 (3C), 127.9 (2C), 127.8, 44.5, 20.3 **HRMS** (ESI+) *m/z* calcd. for $C_{10}H_{11}NOS_2^+$ 226.0354 found 226.0356.

3.7 Synthesis of thiopyrano-piperidone cycloadducts

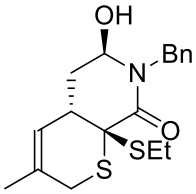
3.7.1 General procedure for the organocatalytic thio-Diels-Alder/nucleophilic ring closing reaction of dithioamides with 2,4-dienals.

In a simple screw cap glass vial equipped with a magnetic stirring bar, the 2,4-dienal **96** (0.15 mmol, 1.5 equiv.), benzoic acid (0.02 mmol, 0.2 equiv.) and catalyst **3** (0.02 mmol, 0.2 equiv.) in 0.5 mL of chloroform were stirred for 10 min. Then, dithioamide **106** was added (0.1mmol, 1 equiv.) and the mixture was stirred for the indicated time. Once the reaction finished, the mixture was directly purified by FC on silica gel to afford the desired

product **107**. The racemic mixture for HPLC analysis was obtained by using 20 mol% of a 1:1 mixture of S and R catalyst of **3a.**



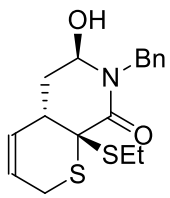
(4a*S*,6*R*,8a*R*)-7-benzyl-8a-(ethylthio)-6-hydroxy-3-methyl-4a,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-c]pyridin-8(8a*H*)-one 4a.



107a

Following the general procedure (reaction time 24 h), the compound **107a** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 93% yield and 95:5 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{25.5}$= +96.82 ($CHCl_3$, *c* 0.79). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.26 – 7.17 (m, 5H), 5.22 (dd, *J* = 5.1, 3.8 Hz, 1H), 4.87 (d, *J* = 14.9 Hz, 1H), 4.77 (t, *J* = 3.8 Hz, 1H), 4.39 (d, *J* = 14.9 Hz, 1H), 3.16 (dd, *J* = 17.0, 0.8 Hz, 1H), 3.06 – 2.98 (m, 2H), 2.86 (dt, *J* = 16.9, 7.4 Hz, 1H), 2.68 (dd, *J* = 18.2, 12.1 Hz, 1H), 2.59 – 2.31 (m, 1H), 2.06 – 1.93 (m, 2H), 1.69 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.7, 137.1, 131.8, 128.7 (2C), 128.1 (2C), 127.6, 123.5, 78.3, 58.1, 48.5, 36.5, 35.2, 28.9, 25.3, 24.1, 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{18}H_{23}NO_2S_2^+$ 350.1242 found 350.1241. **HPLC** OD-H, 90:10 Hex/IPA, 1 mL/min, t_{major}=10.4 min; t_{minor}=9.3 min (92% ee).

(4a*S*,6*R*,8a*R*)-7-benzyl-8a-(ethylthio)-6-hydroxy-4a,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-c] pyridin-8(8a*H*)-one 4b.

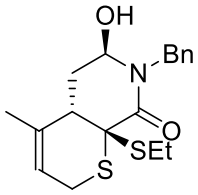


107b

Following the general procedure (reaction time 24 h), the compound **107b** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 78%

yield and 93:7 dr (determined by ^{1}H NMR analysis; major isomer) as a light yellow solid. $[\alpha]^{26.9}$= +186.72 ($CHCl_3$, *c* 1.5). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.36 (dt, *J* = 13.0, 7.6 Hz, 5H), 6.03 – 5.97 (m, 1H), 5.72 – 5.64 (m, 1H), 5.00 (d, *J* = 15.0 Hz, 1H), 4.95 (t, *J* = 3.4 Hz, 1H), 4.51 (d, *J* = 15.0 Hz, 1H), 3.45 (ddd, *J* = 17.3, 5.1, 2.5 Hz, 1H), 3.21 – 3.12 (m, 2H), 3.08 – 3.02 (m, 1H), 2.98 (dd, *J* = 17.3, 5.7 Hz, 1H), 2.20 (ddd, *J* = 14.4, 11.3, 3.4 Hz, 1H), 2.09 (dt, *J* = 14.0, 3.3 Hz, 1H), 1.37 – 1.31 (m, 4H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.9, 136.9, 129.1, 128.7 (2C), 127.9 (2C), 127.6, 123.9, 78.2, 58.8, 48.8, 35.4, 34.9, 25.4, 24.9, 14.0. **HRMS** (ESI+) *m/z* calcd. for $C_{17}H_{21}NO_2S_2^+$ 336.1086 found 336.1086. **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=11.3 min; t_{minor}=10.2 min (91% ee).

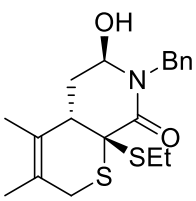
(4a*S*,6*R*,8a*R*)-7-benzyl-8a-(ethylthio)-6-hydroxy-4-methyl-4a,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-c]pyridin-8(8a*H*)-one 4c.



107c

Following the general procedure (reaction time 24 h), the compound **107c** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 90% yield and 85:15 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{27.9}$= +83.6 ($CHCl_3$, *c* 2.5). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.26 – 7.17 (m, 5H), 5.63 – 5.56 (m, 1H), 4.87 – 4.80 (m, 2H), 4.35 (dd, *J* = 14.1, 11.6 Hz, 1H), 3.39 – 3.31 (m, 1H), 3.12 – 2.98 (m, 2H), 2.92 – 2.85 (m, 1H), 2.83 – 2.76 (m, 1H), 2.69 (t, *J* = 9.6 Hz, 1H), 2.14 – 2.06 (m, 1H), 2.01 (dt, *J* = 14.0, 2.8 Hz, 1H), 1.70 – 1.68 (m, 3H), 1.20 – 1.17 (m, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.5, 137.0, 134.1, 128.8 (2C), 127.8 (2C), 127.6, 118.4, 78.0, 59.7, 49.0, 38.8, 33.6, 25.8, 24.7, 23.1, 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{18}H_{23}NO_2S_2^+$ 350.1242 found 350.1237. **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=17.5 min; t_{minor}=14.6 min (94 % ee).

(4a*S*,6*R*,8a*R*)-7-benzyl-8a-(ethylthio)-6-hydroxy-3,4-dimethyl-4a,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*c*]pyridin-8(8a*H*)-one 4d.

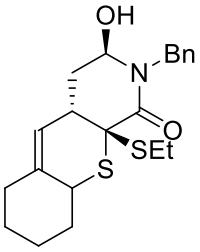


107d

Following the general procedure (reaction time 24 h), the compound **107d** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 92%

yield and 89:11 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{27.5}$= +211.33 ($CHCl_3$, *c* 1.5). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.26 – 7.17 (m, 5H), 4.84 – 4.78 (m, 2H), 4.37 (dd, *J* = 15.1, 4.7 Hz, 1H), 3.32 (d, *J* = 16.9 Hz, 1H), 3.12 – 2.96 (m, 2H), 2.73 (dd, *J* = 38.3, 11.9 Hz, 1H), 2.64 (t, *J* = 15.5 Hz, 2H), 2.13 – 2.05 (m, 1H), 1.99 (dt, *J* = 14.0, 2.6 Hz, 1H), 1.67 (s, 3H), 1.63 (s, 3H), 1.21 – 1.17 (m, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.7, 137.1, 128.8, 127.8 (2C), 127.6, 126.1, 123.6, 78.1 (2C), 59.5, 48.9, 40.2, 33.7, 29.6, 25.8, 19.8, 19.1, 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{19}H_{25}NO_2S_2^+$ 364.1399 found 364.1393. **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=16.3 min; t_{minor}=14.7 min (94% ee).

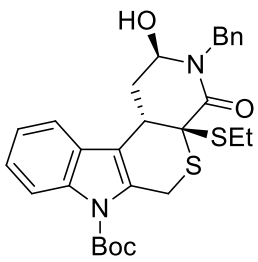
(3*R*,4a*S*,10a*R*)-2-benzyl-10a-(ethylthio)-3-hydroxy-2,3,4,4a,6,7,8,9,9a,10a-decahydro-1*H*-thiochromeno[2,3-*c*]pyridin-1-one 4e.



107e

Following the general procedure (reaction time 24 h), the compound **107e** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 72% yield and 85:15 dr (determined by ^{1}H NMR analysis; major isomer) as a light yellow solid. $[\alpha]^{26.8}$= +185.61 ($CHCl_3$, *c* 1.5). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.55 – 7.45 (m, 5H), 5.51 (d, *J* = 5.6 Hz, 1H), 5.16 (d, *J* = 15.0 Hz, 1H), 5.10 (t, *J* = 2.8 Hz, 1H), 4.61 (d, *J* = 15.0 Hz, 1H), 3.71 – 3.60 (m, 1H), 3.41 – 3.27 (m, 2H), 3.24 – 3.14 (m, 1H), 2.50 (d, *J* = 14.4 Hz, 1H), 2.45 – 2.28 (m, 2H), 2.25 – 2.13 (m, 2H), 2.09 – 1.95 (m, 2H), 1.71 – 1.50 (m, 4H), 1.48 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.3, 137.3, 137.1, 128.8 (2C), 128.0 (2C), 127.5, 121.6, 77.9, 59.4, 48.8, 39.1, 35.5, 35.3, 35.2, 32.1, 26.8, 25.9 (2C), 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{21}H_{27}NO_2S_2^+$ 390.1556 found 390.1550. **HPLC** OD-H, 90:10 Hex/IPA, 1 mL/min, t_{major}=18.4 min; t_{minor}=14.8 min (86% ee).

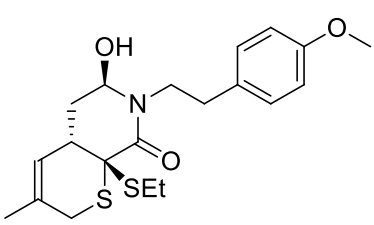
(2*R*,4a*R*,11c*S*)-*tert*-butyl 3-benzyl-4a-(ethylthio)-2-hydroxy-4-oxo-1,2,3,4,4a,11c-hexahydropyrido[4',3':5,6]thiopyrano[3,4-b]indole-7(6*H*)-carboxylate 4f.



107f

Following the general procedure (reaction time 72 h), the compound **107f** was obtained after FC on silica gel (gradient: Hexane/EtOAc 70:30) in 96% yield and 96:04 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{27.7}$= +82.33 ($CHCl_3$, *c* 0.6). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.30 (m, 6H), 7.24 (t, *J* = 7.4 Hz, 1H), 5.05 (s, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.68 (d, *J* = 15.0 Hz, 1H), 4.22 (q, *J* = 17.4 Hz, 2H), 3.99 (dd, *J* = 15.4, 7.5 Hz, 1H), 3.32 – 3.17 (m, 2H), 2.62 (d, *J* = 3.8 Hz, 1H), 2.42 (d, *J* = 6.7 Hz, 2H), 1.71 (s, 9H), 1.29 (t, *J* = 7.5 Hz, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.1, 150.4, 136.9, 135.5, 128.9 (2C), 127.9 (2C), 127.7, 124.4, 122.8, 117.4, 117.3, 115.9, 84.4, 59.4, 49.3, 35.1, 33.8, 28.3 (4C), 26.1, 24.9, 22.3, 14.1, 13.8. **HRMS** (ESI+) *m/z* calcd. for $C_{28}H_{32}N_2O_4S_2^+$ 525.1876 found 525.1870. **HPLC** OD-H, 90:10 Hex/IPA, 1 mL/min, t_{major}=11.7 min; t_{minor} = 9.8 min (98% ee).

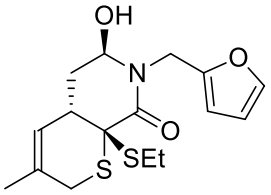
(4a*S*,6*R*,8a*R*)-8a-(ethylthio)-6-hydroxy-7-(4-methoxyphenethyl)-3-methyl-4a,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-c]pyridin-8(8a*H*)-one 4g.



107g

Following the general procedure (reaction time 24 h), the compound **107g** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 87% yield and 90:10 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{25}$= +107.63 ($CHCl_3$, *c* 1.59). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.16 (d, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 7.7 Hz, 2H), 5.28 (s, 1H), 4.53 (s, 1H), 3.80 (s, 3H), 3.65 (dt, *J* = 13.2, 6.6 Hz, 1H), 3.57 – 3.51 (m, 1H), 3.31 (d, *J* = 16.8 Hz, 1H), 3.19 – 3.06 (m, 2H), 2.87 (t, *J* = 6.8 Hz, 2H), 2.82 (d, *J* = 11.2 Hz, 1H), 2.72 (d, *J* = 16.9 Hz, 1H), 2.42 (s, 1H), 2.00 (t, *J* = 12.7 Hz, 1H), 1.84 (d, *J* = 13.9 Hz, 1H), 1.80 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.8, 158.3, 131.2, 131.2, 130.1 (2C), 123.5, 114.1 (2C), 79.9, 58.4, 55.3, 49.8, 35.7, 35.0, 32.9, 28.5, 25.4, 24.1, 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{20}H_{27}NO_3S_2^+$ 394.1505 found 394.1501. **HPLC** AS-H, 90:10 Hex/IPA, 1 mL/min, t_{major}=20.3 min; t_{minor}=13.0 min (93% ee).

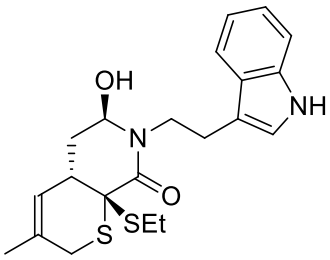
(4a*S*,6*R*,8a*R*)-8a-(ethylthio)-7-(furan-2-ylmethyl)-6-hydroxy-3-methyl-4a,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-c]pyridin-8(8a*H*)-one 107h..



107h

Following the general procedure (reaction time 24 h), the compound **103h** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 98% yield and -98:02: dr (determined by ^{1}H NMR analysis; major isomer) as a colorless oil. $[\alpha]^{25.9}$= -90.44 ($CHCl_3$, *c* 2.0). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.51 (dt, *J* = 8.1, 2.3 Hz, 2H), 5.50 – 5.48 (m, 1H), 5.18 (d, *J* = 3.4 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 2H), 3.41 (dd, *J* = 16.9, 0.8 Hz, 1H), 3.24 – 3.19 (m, 3H), 3.13 (dt, *J* = 19.6, 8.9 Hz, 1H), 2.92 (d, *J* = 17.0 Hz, 1H), 2.31 – 2.27 (m, 2H), 1.94 (s, 3H), 1.43 (t, *J* = 7.6 Hz, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.4, 150.5, 142.3, 131.9, 123.4, 110.7, 108.9, 78.9, 58.0, 42.1, 36.3, 34.9, 28.9, 25.2, 24.1, 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{16}H_{21}NO_3S_2^+$340.1035 found 340.1037. **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=12.5; t_{minor}= (97% ee)

(3*R*,4a*S*,8a*S*)-2-(2-(1*H*-indol-3-yl)ethyl)-8a-(ethylthio)-3-hydroxy-6-methyl-2,3,4,4a,8,8a-hexahydroisoquinolin-1(7*H*)-one 107i.

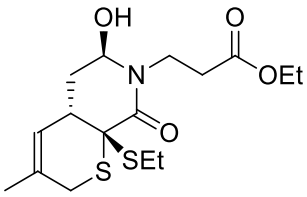


107i

Following the general procedure (reaction time 24 h), the compound **107i** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 93% yield and 90:10 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{25.8}$= +88.48 ($CHCl_3$, *c* 1.6). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.08 – 8.03 (m, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.16 – 7.12 (m, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 5.28 – 5.22 (m, 1H), 4.54 (s, 1H), 3.79 – 3.62 (m, 2H), 3.31 (dd, *J* = 16.8, 0.8 Hz, 1H), 3.17 (tt, *J* = 17.7, 6.5 Hz, 1H), 3.12 – 3.07 (m, 3H), 2.79 (t, *J* = 10.1 Hz, 1H), 2.69 (d, *J* = 16.9 Hz, 1H), 2.06 (d, *J* = 13.3 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.79 (t, *J* = 3.1 Hz, 1H), 1.77 (s, 3H), 1.30 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.79, 136.32, 131.22, 126.94, 123.50, 122.79, 122.34, 119.72, 118.87, 113.06, 111.32, 80.07, 58.52, 48.66, 35.77, 34.91, 28.53, 25.43, 24.08, 23.42, 13.98.

HRMS (ESI+) *m/z* calcd. for $C_{21}H_{26}N_2O_2S_2^+$ 403.1508 found 403.1515. **HPLC** OD-H, 90:10 Hex/IPA, 1 mL/min, t_{major}=17.5 min; t_{minor}=15.0 min (93% ee).

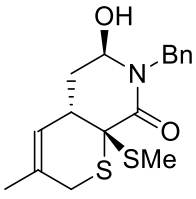
Ethyl 3-((4a*S*,6*R*,8a*R*)-8a-(ethylthio)-6-hydroxy-3-methyl-8-oxo-5,6,8,8a-tetrahydro-2*H*-thiopyrano[2,3-c]pyridin-7(4a*H*)-yl)propanoate 107j.



107j

Following the general procedure (reaction time 24 h), the compound **107j** was obtained after FC on silica gel (gradient: Hexane/EtOAc 80:20) in 90% yield and 90:10 dr (determined by ^{1}H NMR analysis; major isomer) as a yellow oil. $[\alpha]^{23.7}$= +28.21 ($CHCl_3$, *c* 1.05). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.26 (d, *J* = 4.8 Hz, 1H), 4.93 (t, *J* = 2.9 Hz, 1H), 4.12 (qd, *J* = 7.2, 2.1 Hz, 2H), 3.91 (ddd, *J* = 13.9, 5.4, 3.7 Hz, 1H), 3.25 (dd, *J* = 16.8, 1.0 Hz, 1H), 3.21 – 3.14 (m, 1H), 3.01 – 2.83 (m, 4H), 2.58 (d, *J* = 16.9 Hz, 1H), 2.50 (ddd, *J* = 18.2, 5.4, 3.2 Hz, 1H), 1.99 (ddd, *J* = 14.7, 11.7, 3.1 Hz, 1H), 1.90 (dt, *J* = 13.9, 2.9 Hz, 1H), 1.72 (s, 3H), 1.21 – 1.17 (m, 7H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.14, 169.47, 130.87, 123.66, 81.38, 61.42, 58.78, 44.69, 35.45, 34.91, 32.51, 28.36, 25.20, 24.09, 14.11, 13.95. **HRMS** (ESI+) *m/z* calcd. for $C_{16}H_{25}NO_4S_2^+$ 360.1297 found 360.1302 **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=16.5 min; t_{minor}=19.1 min (94% ee).

(4a*S*,6*R*,8a*R*)-7-benzyl-6-hydroxy-3-methyl-8a-(methylthio)-4a,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-c] pyridin-8(8a*H*)-one 107k.

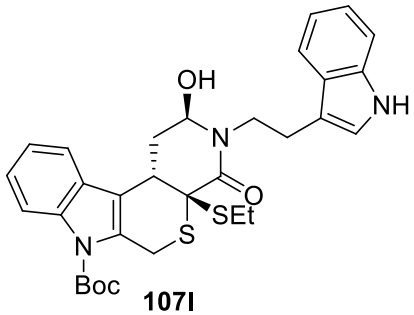


107k

Following the general procedure (reaction time 24 h), the compound **103k** was obtained after FC silica gel (gradient: Hexane/EtOAc 80:20) in 82% yield and 92:8 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{27.8}$= +76.57 ($CHCl_3$, *c* 2.0). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.35 – 7.26 (m, 5H), 5.32 – 5.29 (m, 1H), 4.94 (d, *J* = 15.0 Hz, 1H), 4.89 (dd, *J* = 6.0, 3.1 Hz, 1H), 4.49 (d, *J* = 15.0 Hz, 1H), 3.25 (d, *J* = 17.0 Hz, 1H), 2.95 (d, *J* = 10.1 Hz, 1H), 2.74 (d, *J* = 17.0 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.47 (s, 3H), 2.13 (ddd, *J* = 14.4, 11.1, 3.5 Hz, 1H), 2.02 (dt, *J* = 14.0, 3.4 Hz, 1H), 1.78 (s, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.6, 137.0,

131.5, 128.8 (2C), 128.0 (2C), 127.6, 123.4, 78.3, 57.7, 48.6, 36.1, 35.2, 28.6, 24.1, 14.4. **HRMS** (ESI+) *m/z* calcd. for $C_{17}H_{21}NO_2S_2^+$ 336.1086 found 336.1081 **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=13.1 min; t_{minor}=12.3 min (90% ee).

(2*R*,4a*R*,11c*S*)-*tert*-butyl 3-(2-(1H-indol-3-yl)ethyl)-4a-(ethylthio)-2-hydroxy-4-oxo-1,2,3,4,4a,11c-hexahydropyrido[4',3':5,6]thiopyrano[3,4-*b*]indole-7(6*H*)-carboxylate 107l.

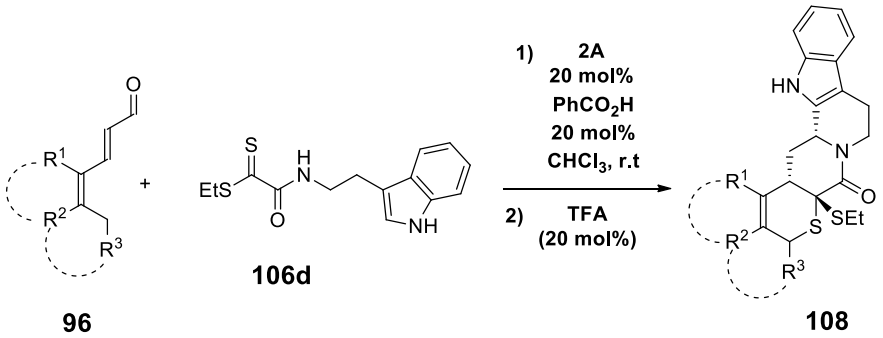


107l

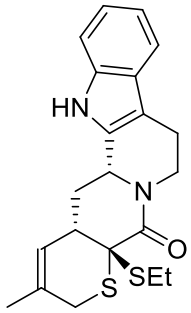
Following the general procedure (reaction time 72 h), the compound **107l** was obtained after FC on silica gel (gradient: Hexane/EtOAc 70:30) in 78% yield and 96:04 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{28}$= +79.33 ($CHCl_3$, *c* 1.0). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.21 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.38 – 7.21 (m, 5H), 4.69 (s, 1H), 4.27 (t, *J* = 12.3 Hz, 2H), 3.95 (dd, *J* = 14.7, 7.2 Hz, 1H), 3.85 (ddt, *J* = 19.8, 13.3, 6.6 Hz, 2H), 3.38 (dq, *J* = 14.7, 7.4 Hz, 1H), 3.30 – 3.21 (m, 3H), 2.38 (s, 1H), 2.28 (d, *J* = 7.5 Hz, 2H), 1.78 (s, 9H), 1.37 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.8, 150.4, 136.3, 135.5, 129.9, 128.3, 126.9, 124.4, 122.9, 122.7, 122.4, 119.7, 118.8, 117.4 (2C), 115.8, 112.9, 111.4, 84.4, 80.1, 59.6, 49.1, 34.8, 33.7, 28.3 (3C), 26.0, 24.8, 23.4, 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{31}H_{35}N_3O_4S_2^+$ 578.2141 found 578.2143 **HPLC** OD-H, 90:10 Hex/IPA, 1 mL/min, t_{major}= 42.4 min; t_{minor}= 31.5 min. (97% ee).

3.8 Synthesis of thiopyarano-piperidone indole adduct.

Following the general procedure for the cascade reaction, once the corresponding adduct was formed, 20 mol% of TFA was added to the reaction mixture and stirred at r.t. for 2h. When the reaction was complete, the solvent was removed in vacuo and the crude was directly purified by FC on silica gel (gradient: Hexane/EtOAc 90:10). The racemic mixture for HPLC analysis was obtained by using 20 mol% of a 1:1 mixture of S and R catalyst of 2A.

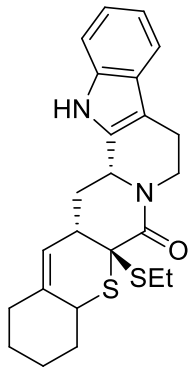


(4a*R*,13b*R*,14a*S*)-4a-(ethylthio)-2-methyl-7,8,13,13b,14,14a-hexahydro-3*H*-indolo[2,3-a]thiopyrano[2,3-g]quinolizin-5(4a*H*)-one 108a.



Following the general procedure, the product **108a** was obtained after FC silica gel in 83% yield and 51:49 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{25.5}$= +254.88 ($CHCl_3$, *c* 0.1) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.82 (s, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 5.42 (s, 1H), 5.08 – 5.01 (m, 1H), 4.63 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.17 (d, *J* = 17.5 Hz, 1H), 3.01 (s, 1H), 2.95 – 2.88 (m, 1H), 2.82 – 2.66 (m, 6H), 2.13 (dt, *J* = 13.4, 4.5 Hz, 1H), 1.75 (s, 3H), 1.11 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.1, 136.3, 135.6, 132.9, 126.9, 123.2, 122.2, 119.9, 118.3, 111.0, 109.7, 51.7, 41.3, 40.3, 31.3, 31.1, 29.7, 24.7, 24.4, 21.3, 14.3. **HRMS** (ESI+) *m/z* calcd. for $C_{21}H_{24}N_2OS_2^+$ 385.1403 found 385.1414 **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=56.7 min; t_{minor}=52.1 min. (97% ee).

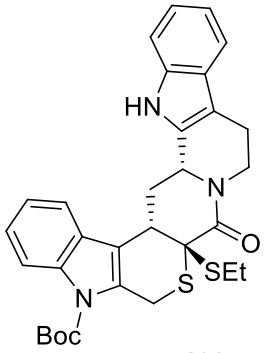
(8a*R*,14a*S*,15a*R*)-8a-(ethylthio)-8a,9a,10,11,12,13,14a,15,15a,16-decahydro-5*H*-indolo[2,3-a]thiochromeno[2,3-g]quinolizin-8(6*H*)-one 108b.



108b

Following the general procedure, the product **108b** was obtained after FC silica gel in 74% yield and 51:49 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{25.5}$= +254.88 ($CHCl_3$, *c* 0.1). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.82 (s, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.14 – 7.09 (m, 1H), 5.39 (d, *J* = 5.7 Hz, 1H), 4.98 – 4.93 (m, 1H), 4.89 – 4.83 (m, 1H), 3.39 (d, *J* = 8.4 Hz, 1H), 3.30 – 3.09 (m, 2H), 2.94 – 2.83 (m, 2H), 2.75 (dd, *J* = 14.1, 2.6 Hz, 1H), 2.67 – 2.61 (m, 1H), 2.38 (ddd, *J* = 13.4, 4.2, 2.4 Hz, 1H), 2.24 (d, *J* = 11.9 Hz, 1H), 2.13 (t, *J* = 12.7 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.79 (d, *J* = 10.3 Hz, 2H), 1.59 (dd, *J* = 17.9, 4.7 Hz, 3H), 1.45 – 1.40 (m, 1H), 1.29 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.7, 137.6, 132.7, 126.8, 122.3, 121.0, 119.9 (2C), 118.5, 110.9, 109.7, 59.6, 53.6, 41.4, 40.0, 38.9, 35.5, 34.2, 32.0, 26.9, 26.1, 25.9, 20.8, 13.8. **HRMS** (ESI+) *m/z* calcd. for $C_{24}H_{28}N_2OS_2^+$ 425.1716 found 425.1720. **HPLC** OD-H, 90:10 Hex/IPA, 1 mL/min, t_{major}=19.7 min; t_{minor}=16.1 min. (99% ee).

(7a*R*,16b*R*,17a*S*)-tert-butyl 7a-(ethylthio)-8-oxo-7a,8,10,11,16,16b,17,17a-octahydroindolo[2,3-a]indolo[3',2':4,5]thiopyrano[2,3-g]quinolizine-5(6*H*)-carboxylate 108c.



108c

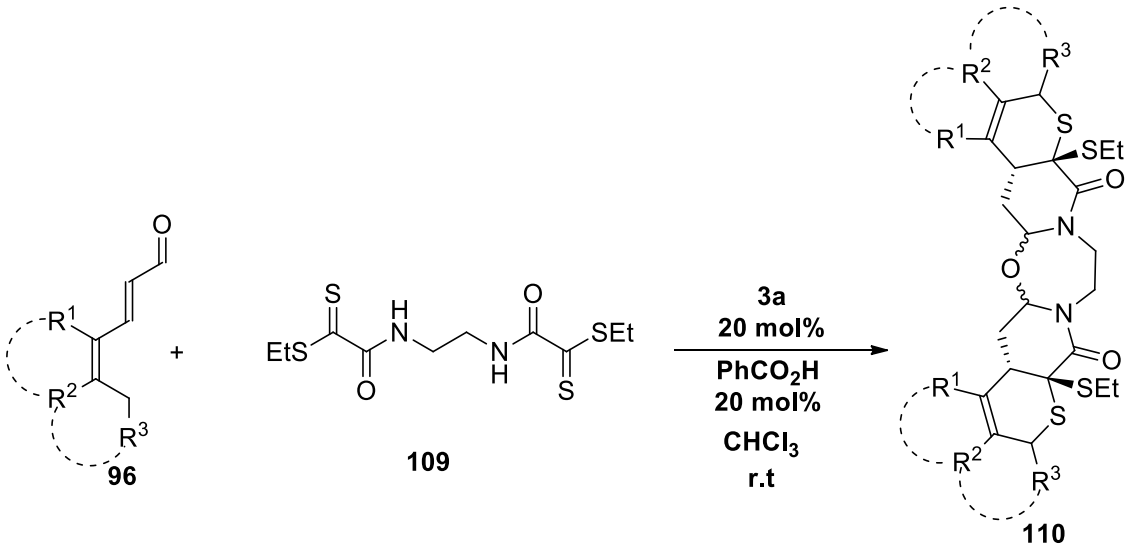
Following the general procedure, the product **108c** was obtained after FC on silica gel in 85% yield and 51:49 dr (determined by ^{1}H NMR analysis; major isomer) as a white solid. $[\alpha]^{25.5}$= -42.43 ($CHCl_3$, *c* 0.1)

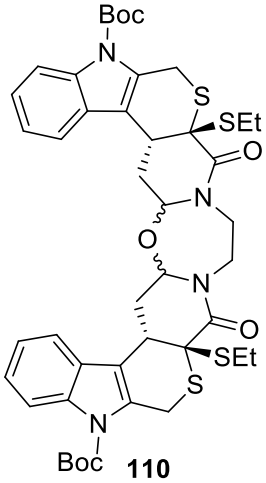
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.09 (m, 1H), 8.05 (s, 1H), 7.55 – 7.51 (m, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.18 – 7.09 (m, 2H), 5.30 (s, 1H), 5.14 (dd, *J* = 9.8, 1.8 Hz, 1H), 5.02 (dd, *J* = 12.7, 4.1 Hz, 1H), 4.19 – 4.08 (m, 2H), 3.56 (d, *J* = 11.9 Hz, 1H), 3.37 – 3.31 (m, 1H), 3.21 (dq, *J* = 12.0, 7.7 Hz, 1H), 3.03 (td, *J* = 12.3, 4.1 Hz, 1H), 2.88 – 2.78 (m, 2H), 2.39 (dd, *J* = 25.7, 12.2 Hz, 1H), 1.69 (s, 9H), 1.26 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.4, 150.4, 136.3, 135.6, 132.3, 130.2, 128.3, 126.7, 124.6, 122.8, 122.4, 120.0, 118.5, 116.9 (2C), 116.2,

111.0, 109.8, 84.6, 59.5, 53.9, 41.7, 38.6, 33.9, 28.3 (3C), 26.3, 24.8, 20.8, 13.7 **HRMS** (ESI+) *m/z* calcd. for $C_{31}H_{33}N_3O_3S_2^+$ 560.2036 found 560.2044 **HPLC** OD-H, 95:5 Hex/IPA, 1 mL/min, t_{major}=33.5 min; t_{minor}=42.4 min. (99% ee).

3.9 Organocatalytic bis-cascade reaction.

In a screw cap glass vial equipped with a magnetic stirring bar, a mixture of 2,4-dienal **96** (0.2 mmol, 2.0 equiv.), benzoic acid (0.02 mmol, 0.2 equiv.) and catalyst **2A** (0.02 mmol, 0.2 equiv.) in 0.5 mL of chloroform was stirred for 10 min. Then, bis-dithioamide **109** was added (0.1mmol, 1 equiv.) and the mixture was stirred for the indicated time. The crude reaction was directly purified by FC on silica gel to afford the desired product **110**. The racemic mixture for HPLC analysis was obtained by using 20 mol% of a 1:1 mixture of S and R catalyst of 2A.





Following the general procedure (reaction time 72h), the product **110** was obtained as a mixture of two separable diastereoisomers

(51:49) after FC on silica gel in 41 % and 39 % and dr as a white solid. $[\alpha]^{26.0}$= +32.11($CHCl_3$, *c* 0.1). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 5.11 (s, 2H), 4.78 – 4.70 (m, 2H), 4.16 – 4.12 (m, 4H), 3.99 (d, *J* = 10.8 Hz, 2H), 3.21 – 3.09 (m, 4H), 2.83 – 2.75 (m, 2H), 2.65 – 2.59 (m, 2H), 2.53 – 2.41 (m, 2H), 1.63 (d, *J* = 6.6 Hz, 18H), 1.19 (t, *J* = 7.6 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.8 (2C), 150.4 (2C), 135.7 (2C), 130.0 (2C), 128.4 (2C), 124.6 (2C), 122.9 (2C), 117.2 (2C), 117.0 (2C) 116.2 (2C), 84.5 (2C), 84.3 (2C), 59.4 (2C), 47.0 (2C), 34.9 (2C), 33.8 (2C), 28.3 (6C), 26.1 (2C), 24.9 (2C), 13.7(2C). **HRMS** (ESI+) *m/z* calcd. for $C_{44}H_{52}N_4O_7S_4^+$ 877.2792 found 877.2787 **HPLC:** OD-H, 90:10 Hex/IPA, 1 mL/min, t_{major}=5.00 min; t_{minor}=4.33 min. (98% ee).

Appendix I

Appendix A.

Polyenals and Polyenones in Aminocatalysis: A Decade Building Complex Frameworks from Simple Blocks

Tushar J. Pawar, **Suhas Balasaheb Mitkari**, Eduardo Peña-Cabrera, Clarisa Villegas Gomez* and David Cruz Cruz.*

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Polyenals and Polyenones in Aminocatalysis: A Decade Building Complex Frameworks from Simple Blocks

Tushar Janardan Pawar,[a] Suhas Balasaheb Mitkari,[a] Eduardo Peña-Cabrera,[a] Clarisa Villegas Gómez,*[a] and David Cruz Cruz*[a]

Abstract: Polyenals and polyenones are simple chemical compounds which can be constructed into large and complex structures by virtue of aminocatalysis. In the past eight years, new aminocatalytic activation modes based on trienamine, cross-trienamine, tetraenamine, iminium ion, and vinylogous iminium ion intermediates have attracted great attention in the field of asymmetric synthesis. Key to the increasing focus is their inherent ability to allow functionalization of remote sites with excellent stereoselectivities. Moreover, methodologies involving one-pot, cascade or multicomponent strategies have been developed through the combination of these new activation modes with classical activation modes. In the course of expanding the applicability of organocatalysis, polyenals and polyenones have been introduced as simple and novel substrates, which have enabled discovery of new concepts for the synthesis of many diverse and complex privileged structures.

1. Introduction

Diversity and complexity constitute two of the central topics in current organic chemistry. During the last decades, great efforts have been devoted to the development of new synthetic methodologies to efficiently construct compounds with high structural, functional and stereochemical diversity. Herein, asymmetric catalysis has demonstrated to be a powerful tool, due to its ability to promote reactions leading to C-C and C-X bonds formations in a regio-, diastereo- and enantioselective fashion[1] Traditionally, these types of transformations are governed by metal- and biocatalysis. However, at the beginning of this century, the interest in the use of chiral metal-free molecules as asymmetric catalysts led to the rediscovery and conceptualization of organocatalysis.[2] Since then, this research area has experienced an impressive growth and rapidly has become a promising synthetic platform to access new and know optically active compounds. In particular, aminocatalysis has demonstrated to be one of the most prominent strategies. The use of primary or secondary amines to activate carbonyl compounds such as aldehydes and ketones through the fundamental concepts of HOMO-raising and LUMO-lowering is a central theme in this field. This complementary catalyst-substrate pair of amines and carbonyl compounds has promoted countless stereoselective transformations governed by several efficient and predictable activation modes.[3] Initially, HOMO and LUMO activation was limited to enamine and iminium ion activation. By extension to the vinylogy principle, aminocatalysis has found new perspectives for challenging transformations. The ability of aminocatalysts to enhance reactivity and induce selectivity at distant centers along to π-systems of the substrate have led to the development of new activation modes such dienamine,[4a-b] trienamine,[4c-d] tetraenamine[4e-f] and vinylogous iminium ion.[4g-h] Intriguingly, the stereoselective functionalization of remote positions may be facilitated and controlled by a stereocenter in the catalyst located up to 8 bonds away.[4]

Polyunsaturated carbonyls and their synthesis have been known for more than a century.[5a-b] They constitute an important type of molecules involved in countless biological and synthetic transformations. Particularly, conjugated or non-conjugated polyenals and polyenones have attracted great attention because of their synthetic applications.[5c] These simple and easily available building blocks have played a fundamental role in the field of remote functionalization via aminocatalysis. The condensation between primary or secondary chiral amines and polyenals or polyenones rapidly affords to the corresponding polyenamines or vinylogous iminium ions. Polyenamines are nucleophilic intermediates, which can react with an extensive range of electrophiles with different manners like Michael additions, [4+2] cycloadditions, etc. On the contrary, vinylogous iminium ions are electrophilic intermediates, which are highly reactive towards nucleophilic additions or ring-closing reactions. Moreover, very creative methodologies using aromatic aldehydes and ketones as masked polyenals and polyenones have also developed, either through the corresponding vinylogous iminium ion or by breaking the aromaticity to form the polyenamine intermediate. (Figure 1).[6]

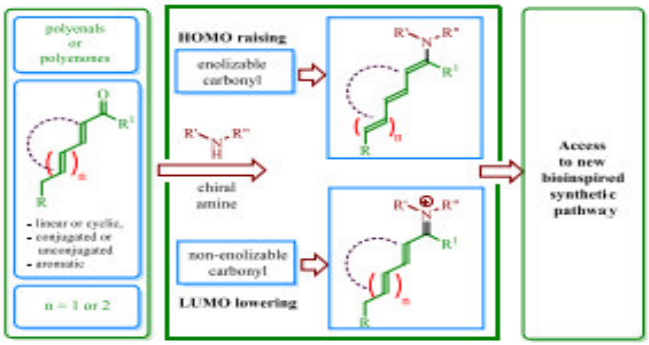

Figure 1. Strategy of polyenals and polyenones in aminocatalysis

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In this contribution, we present a review of recent developments and applications of polyenals and polyenones in aminocatalysis. Strategies involving the use of aromatic aldehydes and ketones as masked polyenamines through transient dearomatization are also discussed.

Tushar Janardan Pawar was born in 1992 in Maharashtra, India. He obtained his Ph.D. in April 2020 at Universidad de Guanajuato, Mexico under the supervision of Dr. David Cruz Cruz. He also worked under the supervision of Dr. José Alemán for a year in Universidad Autónoma de Madrid, Spain in 2018-2019. His research interests include new modes of activation for remote functionalization by organocatalysis, as well as asymmetric synthesis and application of natural compounds, bioactiveactive compounds and fluorescent compounds and development of cascade reactions with use of aminocatalysis.

Suhas Balasaheb Mitkari was born in 1991 in Maharashtra, India. He received his bachelor's degree in 2012 from Modern A.C.S. college ganeshkhind pune-53, India and he completed his master degree in 2015 from Pad. Dr. D. Y. patil A.C.S. college pimpri-18, India. Currently he is a Ph.d student under the guidance of Dr. David Cruz Cruz at the universidad de Guanajuto, Mexico. His research interest development of cascade , triple cascade and bis-cascade via trienamine catalysis.

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Clarisa Villegas Gómez was born in Puebla, México, after her studies in Chemistry, she received her Ph.D degree in 2009 under the supervision of Prof. Mariano Martínez at Universidad Nacional Autónoma de México, working in the isolation and synthesis of Bioactive Natural Products. Then in 2012, she worked as a postdoctoral researcher with Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University in Denmark. In 2016, she moved to the Department of Chemistry at Universidad de Guanajuato as Associate Professor. Her research is focused on the isolation of bioactive natural products as well as the synthesis of natural products scaffolds by new methodologies in organocatalysis inspired in the concept of Diversity-Oriented Synthesis.

David Cruz Cruz was born in Puebla, México where he studied Chemistry. In 2010 he got his Ph.D in Chemical Sciences at Universidad Nacional Autónoma de México (UNAM) working in the field of asymmetric synthesis via chiral sulfoxides, by the guidance of Prof. Francisco Yuste López. From 2006 to 2007, he was visiting Ph.D student at Department of Organic Chemistry at Universidad Autónoma de Madrid (UAM), Spain, in the group of Prof. José Luis García Ruano. From 2011 to 2014, he joined to the group of Prof. Karl Anker Jørgensen as postdoctoral researcher at Center for Catalysis, Aarhus University, Denmark. Since 2015, he works at Department of Chemistry, Universidad de Guanajuato, México as Associated Professor. His main research interest is the structural diversification of bioactive molecules, through different methodologies in organocatalysis.

2. Dienals and dienones in trienamine catalysis.

In its simplicity, the condensation of dienals or dienones **1** with chiral amines can produce trienamine intermediates **2** (Scheme 1), which can participate in electrophilic addition or Diels–Alder reactions as an activated chiral diene with various electron-deficient dienophiles **3**. These simple processes allow the construction of complex frameworks **4** with high level of stereocontrol.

Scheme 1. Reactivity transmission via trienamine activation of enolizable di-conjugated carbonyls.

2.1. Dienals

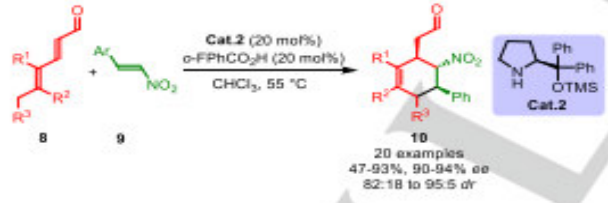
In 2011 Jørgensen and Chen reported the first organocatalytic Diels–Alder reaction via trienamine activation.[7] In this study, it was demonstrated that optically pure amine **Cat.1** and prochiral 2,4-dienals **5** can form trienamines effectively and react with dienophiles such as 3-olefinic oxindoles **6** and olefinic cyanoacetates, leading to several enantioenriched cyclohexene frameworks **7** in moderate to excellent yields and good to excellent stereoselectivities. Notably, the excellent

enantioselectivities demonstrated the ability of the catalyst to transfer chirality up to seven bonds of distance (Scheme 2). A mechanistic survey showed a stepwise reaction where the terminal double bond of the *in situ* formed *s*-cis diene adds to the dienophile forming high-energy zwitterionic species, which undergoes a rapid 1,4-addition to complete the annulation.

Scheme 2. First trienamine strategy in asymmetric organocatalysis.

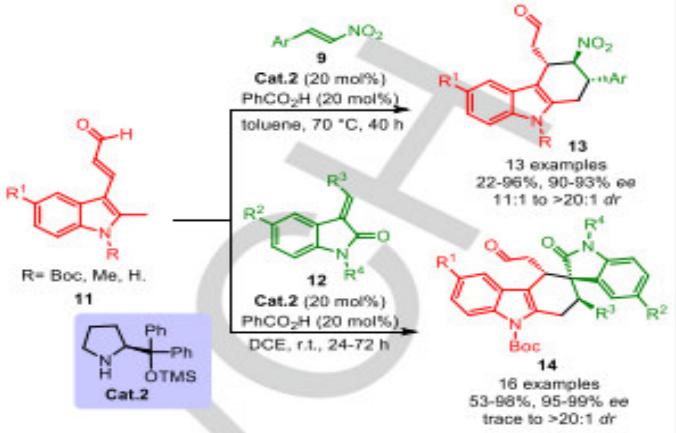
Although dienals constitute a key piece to create libraries of cyclic and polycyclic frameworks under trienamine catalysis, the success of this strategy also comes from the dienophiles that can be applied. In this context, after the first report, a great variety of electron-deficient olefins have been used for this strategy.

The second report of trienamine catalysis by Chen et al. utilized nitroalkenes **9** and 2,4-dienals **8** to furnish densely substituted cyclohexenes **10** in moderate to excellent yields and high to excellent stereoselectivities (Scheme 3).[8] In this study, it was also demonstrated that by the introduction of appropriate substituents on the dienals, the reactivity through the HOMO raising is considerably improved.



Scheme 3. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and nitroalkenes.

The same year, Melchiorre reported another trienamine strategy by using 3-(2-methyl-indolyl)acrylaldehyde derivatives **11** as masked 2,4-dienals, which in the presence of chiral secondary amine **Cat.2** leads to the *in situ* generation of heterocyclic *ortho*-quinodimethanes by dearomatization of the indole ring. Then, once it reacts the aromaticity is recovered. In this study, nitroalkenes **9** and 3-olefinic oxindoles **12** were shown to be suitable dienophiles for the formal Diels–Alder reaction, leading to the formation of highly enantioenriched fused indole **13** and spiro-indole motif **14** (Scheme 4).[9b]

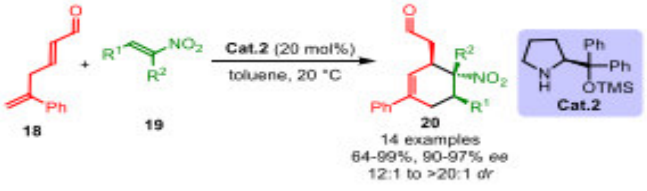


Scheme 4. Diels–Alder cycloaddition via dearomative trienamine catalysis of 2-methylindole acrylaldehydes with nitroalkanes and 3-olefinic oxindoles.

In 2018, another masked 2,4-dienal was reported by Chen and co-workers. Herein, benzofulvenes **15** as 2,4-dienals were shown to react with dienophile **16** via trienamine intermediates. Through this strategy, a library of polyhydrofluorenes **17** was generated with high level of regio- and enantioselectivities in moderate to high yields (Scheme 5).[9i]

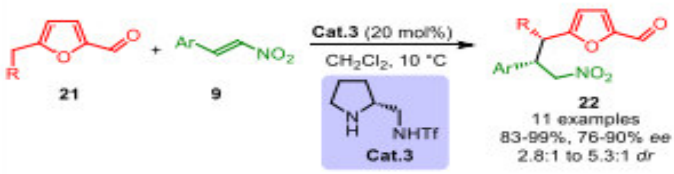
Scheme 5. Diels–Alder cycloaddition via trienamine catalysis of benzofulvenes and 3-olefinic oxindoles.

Reyes and Vicario have demonstrated a Diels–Alder cycloaddition strategy by using diverse nitroalkenes **19** with unconjugated 2,5-dienals **18**, which were found to be more reactive compared to regular 2,4-dienals **8**. The reaction delivers cyclohexene adducts **20** with moderate to excellent yields and high stereoselectivities (Scheme 6).[10]



Scheme 6. Diels–Alder cycloaddition via trienamine catalysis of unconjugated dienals and nitroalkenes.

In 2015, Albrecht and co-workers reported an organocatalytic approach thrcugh a nonclassical trienamine activation for the remote functionalization of furan derivatives **21** using nitroalkenes **9** as reaction partner. The methodology justified the use of furfurals, a masked dienal for trienamine catalysis. The reaction was carried out in the presence of H-bonding aminocatalyst **Cat.3** which underwent alkylation at ε-position with nitroalkenes **9** to produce **22** with high to excellent yields and moderate to high stereoselectivities (Scheme 7).[11]



Scheme 7. Remote alkylation via nonclassical trienamine catalysis of furfural derivatives and nitroalkenes.

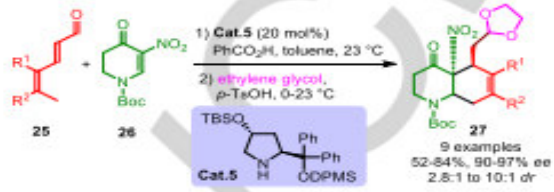
Five years later, a slightly improvement to this strategy was developed by Miura and co-workers by using the bifunctional catalyst **Cat.6** (Scheme 8).[12]

Scheme 8. Catalyst survey fort he remote alkylation via nonclassical trienamine catalysis.

Jørgensen and co-workers reported a different approach by using 3-nitroirdoles **23** as indolyne equivalents, through Diels–Alder reaction with 2,4-dienals **8** via *in situ* generated trienamine intermediates, to form the corresponding cycloadducts, which promptly eliminates and re-aromatizes to construct carbazolyl acetaldehyde derivatives **24** with high to excellent enantioselectivities and moderate to high yields (Scheme 9).[13]

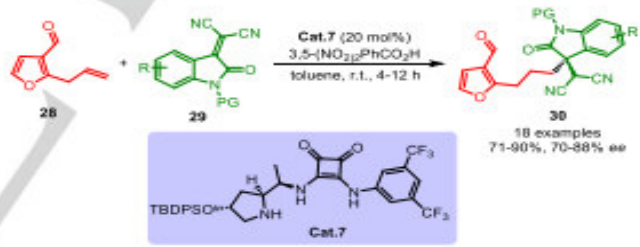
Scheme 9. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and 3-nitroindoles.

In 2019, Ishikawa et al. used the 5-nitro-2,3-dihydropyridone **26** as dienophile to react with 2,4-dienals **25** by applying trienamine catalyzed *endo* selective [4+2] cycloaddition reaction to construct octahydroquinoline derivatives **27** with moderate to high yields and excellent enantioselectivities (Scheme 10).[14]



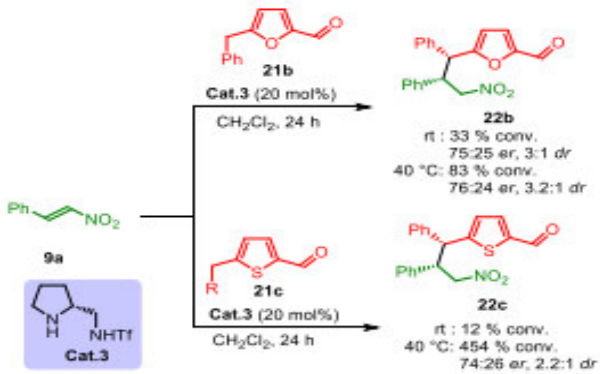
Scheme 10. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and the 2,3-nitro-2,3-dihydropyridone.

After the revelation of trienamine reactivity of furfural, the group of Chen reported a ε-functionalization of 2-allyl-3-furfural **28** via Michael addition of isatine-derived dicyanoalkenes **29** using squaramide bounded chiral secondary amine **Cat.7**. The reaction delivers the product **30** in good to high yields and enantioselectivities (Scheme 11).[15]



Scheme 11. ε-functionalization via dearomative trienamine catalysis of furfurals and isatine-derived dicyanoalkenes.

More recently, inspired by the trienamine activation of 2-furfral derivatives, Albrecht and co-workers reported a theoretical study on the mechanism of the organocatalytic remote alkylation of 5-alkylfurfurals **21b**, which involves the dearomatization of the heteroaromatic core in the presence of **Cat. 3** to form the corresponding trienamine intermediate. Through the study of the density functional theory (DFT) calculations and the symmetry-adapted perturbation theory (SAPT) method, the authors revealed important insights about the mechanism according to the influence and contribution of several molecular interactions. This investigation was also extended theoretical and experimentally to the thiophene analogue (Scheme 12).[16]



Scmeme 12: Theoretical study of the reactivity of furan- and thiophene-derived system in the aminocatalytic remote functionalization.

In 2016 Anderson et al. disclosed an organocatalyzed cycloaddition strategy of pyrrolidinyl dienals **31** with various electron-deficient dienophiles **32a-32c** via trienamine catalysis using **Cat.2**. This novel pyrrolidine dienals were synthesized by palladium-catalyzed cycloisomerization of enynamides. The reaction delivers highly functionalized hexahydroindole complex **33** with fair to excellent stereoselectivities and yields (Scheme 13).[17]

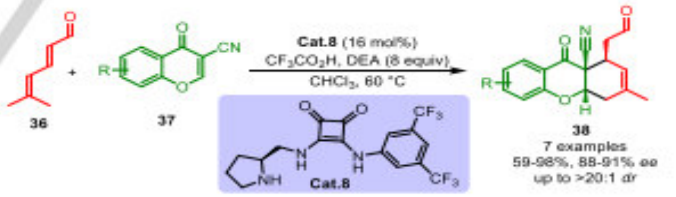
Scheme 13. Diels–Alder cycloaddition via trienamine catalysis of pyrrolidinyl dienals with diverse dienophiles.

Formation of fused polycyclic or spirocyclic structures from dienals via trienamine catalysis is an important strategy in aminocatalysis, beyond this methodology, the formation of chiral bridged bicyclic framework can also be constructed by specially designed cyclic dienals **34** through the *in situ* generation of cross-trienamines. In 2012, Jørgensen and co-workers demonstrated this strategy by using cyclic dienals **34** and a range of dienophiles **16** to construct highly enantioenriched bridged bicyclic frameworks **35** in fair to good yields and excellent enantioselectivities (Scheme 14).[18a]

Scheme 14. Diels–Alder cycloaddition via cross-trienamine catalysis of cyclic 2,4-dienals and 3-olefinic oxindoles.

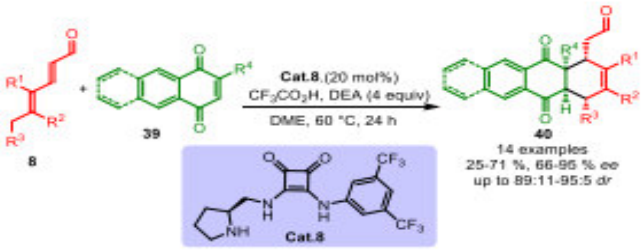
Later, Houk and co-workers reported a theoretical DFT study about the Diels–Alder reactions involving cyclic linear and cross-conjugated trienamines with 3-olefinic oxindoles (Scheme 14). In this investigation, was demonstrated a stepwise mechanism, which are involved several intermediates such as zwitterionic species, unstable [2+2] and hetero-Diels-Alder cycloadducts. On the other hand, a combination of kinetic and thermodynamic control explains the regio- and stereoselectivity.[18b]

In the evolution of trienamine catalysis, many electron-deficient cyclic olefins have been implemented as dienophiles, which have led to the asymmetric synthesis and diversification of bi- and polycyclic compounds. In 2012, a H-bond directing methodology in asymmetric synthesis via trienamine catalysis was reported. In this study, the 5-methyl-2,4-dienal **36** was treated with a H-bonding aminocatalyst **Cat.8** for the *in situ* generation of trienamine intermediate which undergoes a [4+2] cycloaddition with 3-cyanochromones **37** to furnish naturally occurring tetrahydroxanthone framework **38** with high enantioselectivities and moderate to good yields (Scheme 15).[19]



Scheme 15. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienal **36** and cyanochromones.

Later, a methodology was disclosed to combine 2,4-dienals **8** with1,4-naphthoquinones **39** to construct carboannulated dihydronaphthoquinones derivatives **40** with three to four chiral centers using H-bonding aminocatalyst **Cat.8** in fair to good yields and high to excellent stereoselectivities (Scheme 16).[20]



Scheme 16. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and 1,4-naphthoquinones.

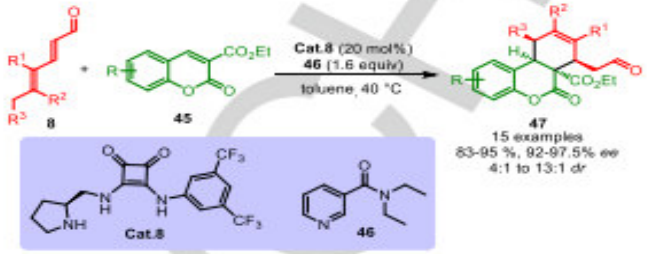
In 2013, Greck et al. demonstrated that oxidative dearomatization of the hydroquinone **41** to the corresponding quinone was compatible with the trienamine catalysis. The reaction was catalyzed by the chiral amine **Cat.9** to construct structurally diverse bridged tricyclic framework **42** in fair to moderate yields and excellent enantio- and diastereoselectivities (Scheme 17).[21]

Scheme 17. Cascade cycloaddition reaction via trienamine catalysis of 2,4-dienals and hydroquinone **41**.

In 2015, the same group extended the previous methodology towards the construction of enantioenriched polycyclic compounds **44a** and **44b** through the *in situ* formation of the 1,4-naphtoquinone as dienophile via dearomatization of 1,4-dihydroxynaphthalene **43**. Using this strategy, enantioenriched polycyclic compounds **44a** and **44b** were obtained in fair to moderate yields and excellent stereoselectivities (Scheme 18).[22]

Scheme 18. Cycloaddition reactions via trienamine catalysis of 2,4-dienals and 1,4-dihydroxynaphthalene.

Albrecht and co-workers established another methodology in 2016 towards the synthesis of polycyclic compounds. By using dual mode aminocatalyst **Cat.8** with 2,4-dienals **8** the *in situ* generated trienamine intermediates undergo cycloaddition reaction with ethyl coumarin carboxylates **45** in presence of DEP **46**, leading to the formation of 3,4-dihydrocoumarin derivatives **47** with high enantioselectivities and high to excellent yields (Scheme 19).[23]



Scheme 19. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and coumarin carboxilates.

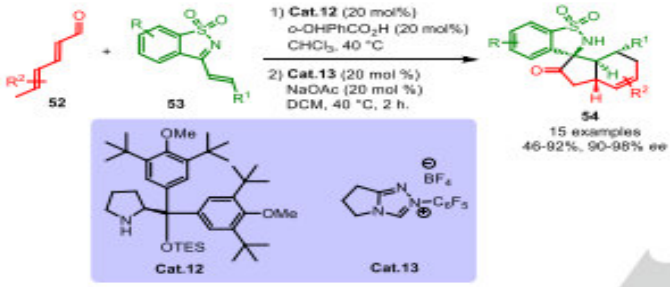
In 2019, the same group also used coumarin carboxylic acids **48** with 2,4-dienals **8** to furnish biologically important dihydrocoumarines **49** (Scheme 20).[24]

Scheme 20. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and coumarin carboxylic acids.

In 2016, Waldmann and co-workers developed another pathway for access to heterobicyclic compounds by using maleimides. In this study, alkyl substituted 2,4-dienals **8**, *in situ* generates active trienamine species by using aminocatalyst **Cat.11**, which undergo a cycloaddition reaction with maleimide derivatives **50** followed by a Wittig reaction to avoid the isolation of unstable products, leading to the formation of hexahydroisoindole unsaturated ester compounds **51** in fair to good yields and good to excellent stereoselectivities. The study also demonstrated that hexahydroisoindole moiety is present in naturally occurring *Cytochalasin B* (Scheme 21).[25]

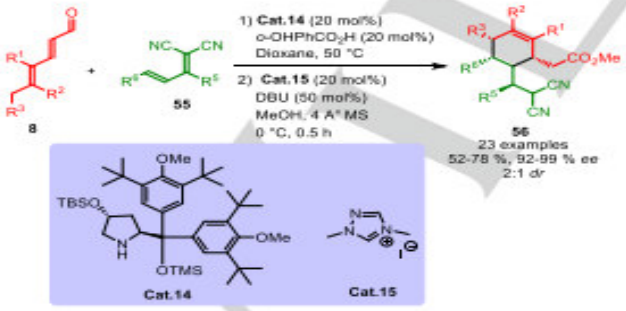
Scheme 21. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and maleimides.

Organocatalytic cascade reactions via trienamine activation, constitute well-planned strategies to assemble bi- or polycyclic frameworks. The combination of different processes after the first cycloaddition reaction has allowed the access to complex structures from simple molecules. In this regard, in 2013, Chen and co-workers, reported a cascade methodology to construct spirocyclic frameworks effectively. In this investigation, the treatment of heterodienes **53** with 2,4-dienals **52** in presence of aminocatalyst **Cat.12** delivers the corresponding cycloadduct, which through the condensation with a suitable carbene catalyst precursor **Cat.13** leads to the construction of spirocyclic framework **54** with four stereogenic centers. The reaction proceeds with fair to excellent yields and excellent enantioselectivities (Scheme 22).[26]



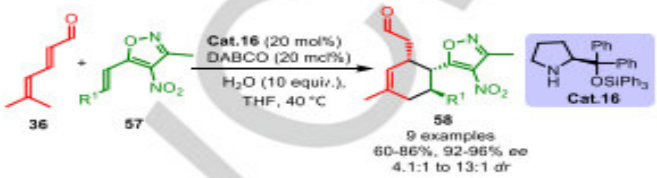
Scheme 22. Cycloaddition cascade reaction via trienamine and carbene catalysis of 2,4-dienals and aza-dienes.

Chen et al. also reported a Diels–Alder reaction between 2,4-dienals **8** and 2,4-dienes **55**, derived from malononitrile, which act as electron-deficient dienophiles. The reaction was catalyzed by chiral secondary amine **Cat.14** and Scheidt's triazolium salt **Cat.15** as carbene precursor, to form the densely substituted cyclohexenes **56** with good to high yields and excellent stereoselectivities (Scheme 23).[27]



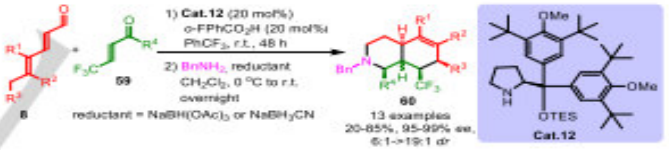
Scheme 23. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and 2,4-dienes.

Isoxazole motif shows a fundamental appearance in development of aminocatalysis, which is worthy due to its medicinal application. In 2014, Jørgensen and co-workers used isoxazol containing electron-deficient olefin **57** as a dienophile for the trienamine mediated Diels–Alder cycloaddition with the 2,4-dienal **36**, to access cyclohexene hooked up with isoxazole framework **58** under excellent enantioselectivities and good yields (Scheme 24).[28]



Scheme 24. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienal **36** and 4-nitro-5-styrylisoxazole derivatives.

In 2016, Chen and co-workers investigated an excellent stereocontrolled organocatalytic pathway by reaction of highly electron-deficient trifluoromethylated olefin **59** with prochiral 2,4-dienals **8** via *in situ* generated trienamine intermediate, leading to the Diels–Alder cycloadduct. A subsequent reductive amination with $BnNH_2$ and $Na3H(OAc)_3$ or $NaBH_3CN$ furnished bicyclic frameworks **60** with up to four stereogenic centers in fair to high yields and excellent enantioselectivities. (Scheme 25).[29]



Scheme 25. One-pot three component reaction via trienamine catalysis.

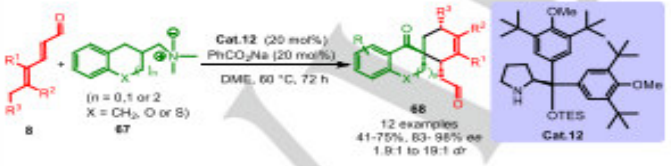
It is known that carbo- and heterocyclic spiro-compounds are distributed all over nature. An important feature of this type of compounds is the stereochemistry associated to its structure, which robustly determines its pharmacological and biological activity. In this context, Jørgensen et al. have established a scope of trienamine catalyzed asymmetric Diels–Alder reaction between different azalactone derivatives **62** as dienophiles and the 2,4-dienal **61** in presence of chiral aminocatalyst **Cat.17** to furnish the desired spirocyclic amino acids derivatives **63**. The reaction provides moderate to high yields and good to excellent stereoselectivities (Scheme 26).[30]

Scheme 26. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and azalactones.

Later, in 2013 Ye and co-workers revealed an asymmetric Diels–Alder reaction to furnish enantioenriched aza-spiro compounds by using olefinic rhodanines or hydantoins **65** and 2,4-dienals via trienamine intermediate. In this reaction, various substituents on **64** and both, rhodanine and hydantoin derivatives can be included to obtain the desired enantioriched adducts **66** in moderate to excellent yields and stereoselectivities (Scheme 27).[31]

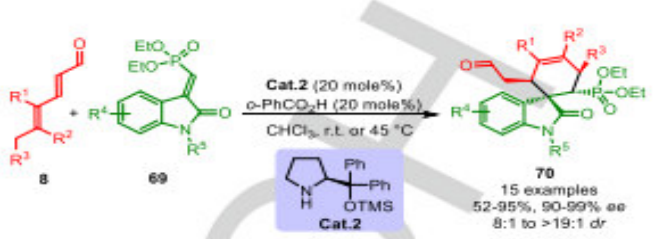
Scheme 27. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and rhodanines or hydantoins.

In the same year, Chen and co-workers disclosed a protocol to construct spirocyclic scaffolds by using stable methiodide salts of Mannich bases **67** and 2,4-dienals **8** via trienamine catalysis. The reaction tolerated various substituents on methiodide derivatives and 2,4-dienals to form the desired adducts **68** in moderate to good yields and with high to excellent enantioselectivities (Scheme 28).[32]



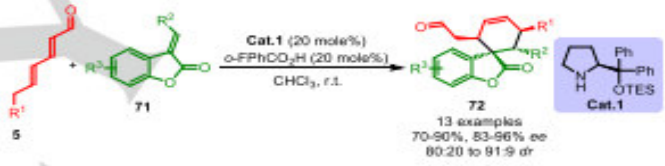
Scheme 28. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and methiodide salts.

The same group revealed in 2013 the asymmetric Diels–Alder reaction of 3-(phosphorylmethylene) oxindole olefins **69** and 2,4-hexadienals **8** to construct enantioenriched spiro compounds **70** through trienamine intermediate in moderate to excellent yields and excellent enantioselectivities (Scheme 29).[33]



Scheme 29. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and olefinic 3-(phosphorylmethylene) oxindoles.

In 2014, Chen´s group reported another similar asymmetric Diels–Alder reaction of 3-olefinic benzofuran-2-one **71** and 2,4-dienals **5** catalyzed by chiral secondary amine **Cat.1**, which delivers optically active spirocyclic benzofuran derivatives **72** via trienamine intermediate. Also, various substituted 3-olefinic benzofuran and dienals being a key piece to access a series of highly enantioenriched benzofuran spiro compounds with moderate to high yields and excellent enantioselectivities (Scheme 30).[34]

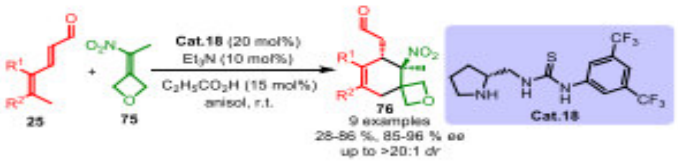


Scheme 30. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and 3-benzofuran-2-one.

In the same year, Albrecht and co-workers established a methodology for accessing spirocyclic $\Delta^{\beta,\gamma}$-butenolides **74**. This framework is a biological relevant and dispersed in nature, as well as an important building block for synthesis. The asymmetric Diels–Alder reaction of (*E*)-3-alkylidine-5-arylfuran-2(3*H*)-ones **73** with 2,4-dienals **25** via trienamine catalysis **Cat.1** furnished desired spirocyclic compounds **74** with three chiral centers with high to excellent enantioselectivities and fair to moderate yields (Scheme 31).[35]

Scheme 31. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and 3-olefinic furanones.

In 2016, Jørgensen co-workers demonstrated that trienamine catalysis could be extended to trisubstituted nitroolefins **75** as dienophiles. In this case the reaction furnished highly enantioenriched spirocyclohexene adducts oxetanes **76** in fair to high yields and excellent stereoselectivities (Scheme 32).[36]

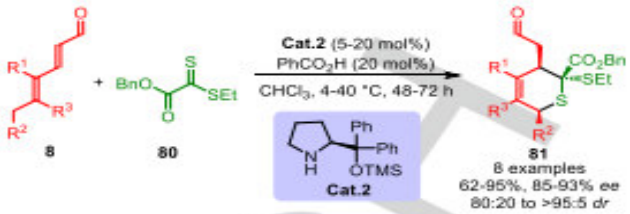


Scheme 32. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and oxetane derivatives.

Considering the importance of spirocyclic compounds, the same group established an approach to construct enantioenriched spiroindenes through catalyst-bound trienamines. In this reaction, a series of different benzofulvenes derivatives such nitrile- and ester **78** were reacted with 2,4-dienals **77** and catalyzed by chiral secondary amine **Cat.2** to furnish optically active spiroindenes **79** in moderate to excellent yields and moderate to excellent stereoselectivities (Scheme 33).[37]

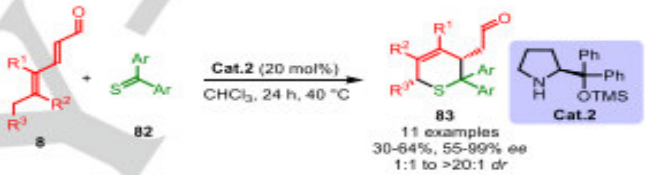
Scheme 33. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and benzofulvenes.

The asymmetric organocatalytic hetero-Diels–Alder reaction is one of the most important methodologies to obtain optically active six-membered heterocyclic scaffolds with high regio- and stereoselectivity. These heterocycles have many synthetic applications in natural product synthesis and assembly of biologically active moieties. The synthetic demand of these type of compounds in synthetic chemistry has subjected to the development of this field. In 2013, Jørgensen and co-workers demonstrated the first thio-Diels–Alder reaction via trienamine catalysis, which is an important factor for the development of DA reactions. Catalyst-bounded dienes from **8** and thiocarbonyl derivatives **80** lead to dihydro-thiopyrane derivatives **81** with high to excellent enantioselectivities and high to excellent diastereoselectivities (Scheme 34).[38]



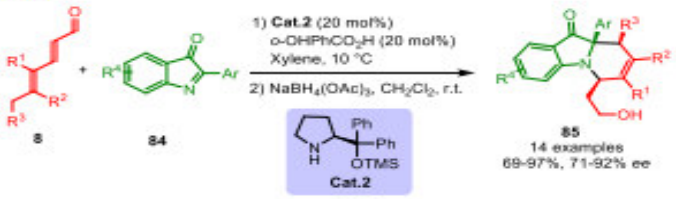
Scheme 34. Thio-Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and dithioesters.

Inspired by this, Albrecht and co-workers reported the first asymmetric thio-Diels–Alder reaction by taming thioketones. Highly activated thioketones **82** were shown to undergo enantioselective trienamine catalyzed [4+2] cycloaddition with 2,4-dienals **8** to form dihydro-thiopyrane scaffolds **83**, which is found in some bioactive natural and unnatural compounds. The reaction provides fair to moderate yields with fair to moderate stereoselectivities (Scheme 35).[39]



Scheme 35. Thio-Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and thioketones.

Similarly, an excellent contribution of a hetero-Diels–Alder reaction has been reported in trienamine catalysis. In 2013, the first trienamine catalyzed asymmetric normal-electron-demand aza-Diels–Alder reaction was reported by Chen and co-workers. In this study, it was demonstrated that the [4+2] cycloaddition between 2,4-dienals **8** and 2-aryl-3*H*-indol-3-ones **84** via trienamine catalysis **Cat.2** efficiently form multifunctional tricyclic polyhydropyrido[1,2-a]indoles **85** with good to excellent yields and good to excellent stereoselectivities (Scheme 36).[40]



Scheme 36. Aza-Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienals and indolones.

Another strategy on aza-Diels–Alder reaction was reported by Jørgensen and co-workers in 2017. In this methodology, acylhydrazones **86** were strategically employed as

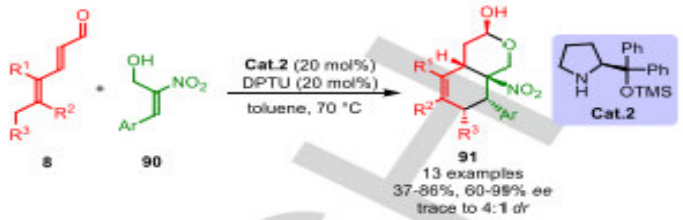
heterodienophiles in order to construct optically active azaheterobicycles **87**, through a [4+2] cycloaddition/ring-closing cascade sequence. The **Cat.2**-bounded trienamine in the presence of DABCO provides the cascade reaction with fair to excellent stereoselectivities and fair to good yields (Scheme 37).[41]

Scheme 37. Aza-Diels–Alder/ring-closing cascade reaction via trienamine catalysis of 2,4-dienals and acylhydrazones.

In 2014, Jørgensen and co-workers reported an enantioselective cascade sequence to synthesize privileged hydroisoquinoline scaffolds, which occurs in several bioactive products such as reserpine, deserpidine, yohimbine, etc. In this investigation, the reaction of substituted 2,4-dienals **8** with cyanoacrylamides **88** in presence of protected prolinol catalyst **Cat.16** generated the [4+2] cycloadduct, which through an intramolecular ring-closing reaction led to the construction of hydroisoquinolines **89** in moderate to high yields and good to excellent stereoselectivities (Scheme 38).[42]

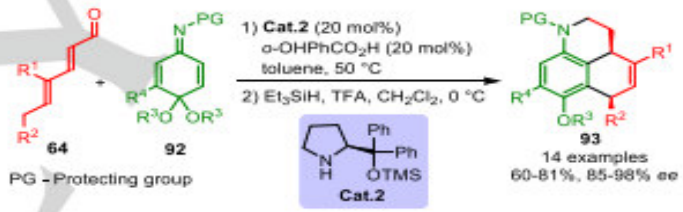
Scheme 38. Diels–Alder/ring-closing cascade reaction via trienamine catalysis of 2,4-dienals and cyanoacrylamides.

In 2014, the Jørgensen´s group demonstrated another organocatalytic enantioselective domino sequence obtained structuraly diverse hydroisochromenes **91** from 2,4-dienals **8** and 2-nitroallylic alcohols **90** through a [4+2] cycloaddition followed by nucleophilic ring-closing process. Under these conditions one or two extra fused cycles can be attached to the hydroisochromene framework depending on the aldehyde. The reaction proceeds with fair to high yields and high stereoselectivities (Scheme 39).[43].



Scheme 39. Diels–Alder/ring-closing cascade reaction via trienamine catalysis of 2,4-dienals and 2-nitroallylic alcohols.

A one-pot reaction for the construction of tricyclic compounds **93** was developed by Chen et al. in 2016. This strategy, involves a [4+2] cycloaddition/aromatization/nucleophilic ring closing sequence by using *N*-Boc-quinone imine ketals **92** and 2,4-dienals **64**. After the reduction of the formed hemiaminal the tricyclic derivatives **93** were obtained in moderate to high yields and high to excellent stereoselectivities via trienamine catalysis **Cat.2** (Scheme 40). This methodology may be interest to medicinal chemistry, due to the ability to produce scaffolds which are found in bioactive natural products such as *cycloprotoberberine* and *pseudopteroxazole*.[44]

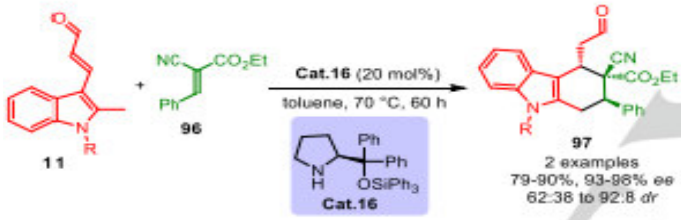


Scheme 40. Diels–Alder/aromatization/ring-closing cascade reaction via trienamine catalysis of 2,4-dienals and N-protected quinone imine ketals..

Recently, the exploration of novel dienophiles in trienamine catalysis has led to the disclosure of another strategy by our group. In this new strategy, it was demonstratec the ability of the BODIPY core, an important fluorescent framework, to act as a strong electron withdrawing group and activate double bonds for asymmetric catalysis. In this sense, 2,4-dienals **8**, were reacted with alkenyl-BODIPY derivatives **94** in presence of **Cat. 17**, to furnish the cycloahexane derivatives containing the BODIPY unit, which after the treatment with the corresponding triphenylphosphorane leads to **95** in good to excellent yields and high to excellent enantioselectivities (Scheme 41).[45]

Scheme 41. Diels-Alder cycloaddition via trienamine catalysis of 2,4-dienals and alkenyl-BODIPYs.

Following the first trienamine report and intrigued for the biological activity of the privileged tetrahydrocarbazoles (THC's), we recently demonstrated the enantioselective synthesis of two new chiral THC's via trienamine catalysis and their anxiolytic-like activity. The reaction proceeds with good to high yields and excellent stereoselectivities. The anxiolytic-like activity was also demonstrated, opening new perspectives for this type of chiral compounds (Scheme 42).[46]



Scheme 42. Diels–Alder cycloaddition via dearomative trienamine catalysis of 2-methylindole acrylaldehydes and cyanoacrylate **96**.

The ability of the 2-methylindole acrylaldehyde derivatives **11a** to act as masked dienals was further utilized by Chen and co-workers, which reported an interesting dearomative strategy for the remote functionalization of this type of aldehydes by electrophilic addition to 1-azadienes **6a**. Through this strategy, only the ε-regioisomer of **98** was observed. Thus, a series of different alcohol derivatives were prepared after the reduction of the corresponding aldehyde in moderate to high yields and high to excellent enantioselectivities (Scheme 43).[47]

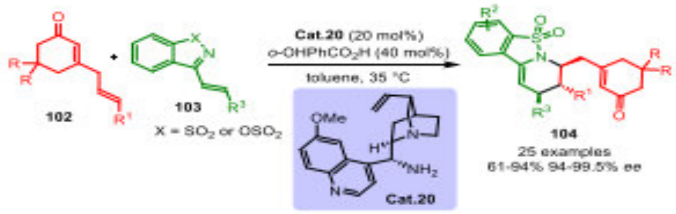
Scheme 43. Remote functionalization via dearomative trienamine catalysis of 2-methylindole acrylaldehyde **11a** and 1-azadienes.

2.2. Dienones

After the introduction of trienamine catalysis via dienals in aminocatalysis, it was reasonable for the development of trienamine catalysis would extend with dienones as substrates. Despite the similarities between the two substrate classes, a different set of challenges are present for the ketone counterpart requiring efforts in design of catalyst, selection of substrates and understanding of reactivity. The first asymmetric Diels–Alder cycloaddition reaction of 2,4-dienones by trienamine catalysis was reported in 2012. The reaction of 2,4-dienones with dienophiles seemed closely related with that of aliphatic 2,4-dienals, however, an important difference is the inherent lower reactivity of ketones when engaged with secondary amines as catalyst. As such, in order to activate dienones via the trienamine pathway, chiral primary amines were found to be more suitable as catalysts. Cinchona based amine **Cat.19** was shown to catalyze the Diels–Alder reaction between 2,4-dienones **99** with *N*-substituted maleimide **100** in presence of trifluoroacetic acid. The resulting cycloadduct **101** with four stereogenic centers showed high to excellent enantioselectivities (Scheme 44).[48]. The generally used dienophiles such as 3-olefinic oxindoles **16**, benzylidene malanonitriles **109** and nitroalkenes **9** used in chiral primary amine-based trienamine catalysis were examined in the same report. The resulting cycloadducts were highly stereoselective with good yields.

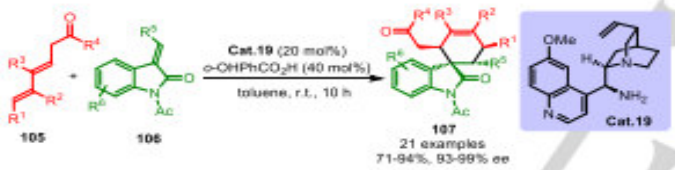
Scheme 44. Diels–Alder cycloaddition via trienamine catalysis of 2,4-dienones and maleimides.

In 2013, the same group demonstrated an asymmetric inverse-electron demand aza-Diels-Alder reaction by using unconjugated cyclic 2,5-dienones **102**. The condensation with chiral amine **Cat.20** generated an activated trienamine, which further reacted with electron-deficient 1-azadienes **103** in presence of salicylic acid as additive to obtain the corresponding [4+2] cycloadducts **104** with up to three chiral centers. The reaction was highly enantioselective furnishing products in moderate to excellent yields. Hence, it was shown that this catalytic mode is applicable to the specifically designed 2,5-dienone **102** substrates, which activates the convenient positioned the δ,ε-C=C bond by HOMO raising principle through the *in situ* generated linear trienamine intermediates (Scheme 45).[49]



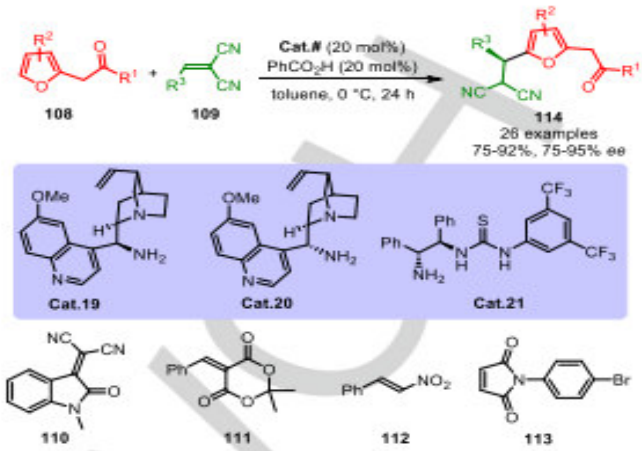
Scheme 45. Inverse-electron demand Diels–Alder cycloaddition via trienamine catalysis of unconjugated dienones and aza-dienes.

The next report from Chen group was in 2014. In this study, they demonstrated a novel catalytic strategy by using linear unconjugated 3,5-dienone **105**. Previously, this strategy further evolved from the use of linear 2,4- and 2,5-dienones **99** and **102** demonstrating that 3,5-dienones **105** can be used as substrates in trienamine catalysis. Highly substituted 3,5-dienone **105** were successfully condensed with cinchona based chiral primary amine **Cat.19** to form activated trienamine species which underwent [4+2] cycloaddition with commonly used 3-olefinic oxindole **106** in presence of salicylic acid. The reaction affords spirooxindoles **107** with four stereogenic centers (Scheme 46).[50]



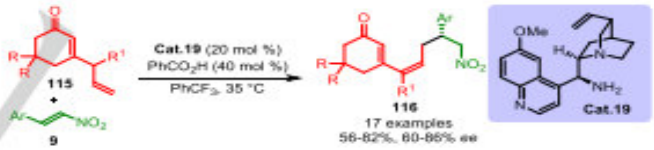
Scheme 46. Diels–Alder cycloaddition via trienamine catalysis of unconjugated dienones and 3-olefinic oxindoles.

Later, the same research laboratory reported an enantioselective Friedel-Crafts alkylation of furans via HOMO-activation. It was demonstrated that aromatic π-system of 2-furfuryl carbonyl species **108** can generate *in situ* trienamine substrate by using chiral amines. The strategy of Friedel-Crafts alkylation with 2-furfuryl ketone was expanded by using several activated alkenes. The reaction of 2-oxoindolin-3-ylidene malononitrile **109** with **108** in the presence of **Cat.21** furnished **114** with good to excellent stereoselectivity whereas, substrate **111** derived from Meldrum's acid showed higher reactivity with **Cat.19**. Also, the use of **108** as substrate was broadened to include α-regioselective Michael addition to β-nitrostyrene **112** as well as asymmetric Diels–Alder cycloaddition with maleimide **113** using **Cat.21** albeit under different reaction conditions. It was also demonstrated that substrate **110** shows good reactivity in presence of **Cat.20** (Scheme 47).[51]



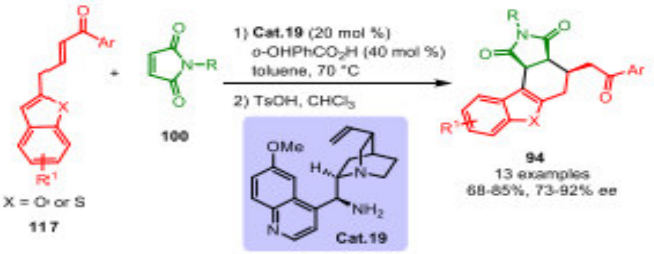
Scheme 47. Friedel-Crafts alkylation via trienamine catalysis of 2-furfurylketones and diverse electron deficient olefins.

In the same year, Chen´s group demonstrated one more strategy in which showed that cyclic 2,5-dienones can be used as vinylogous precursors in presence of the cinchona based primary amine **Cat.19** to *in situ* generate linear trienamine species. The reaction promoted a remote ε-regioselective 1,4-addition of 2,5-dienone **115** with nitroalkanes **9** and efficiently delivered enantioenriched compounds **116** with moderate to high stereoselectivities (Scheme 48).[52]



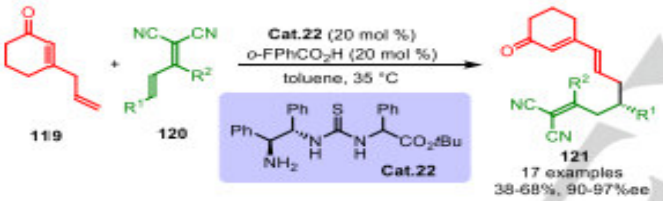
Scheme 48. 1,4-addition via trienamine catalysis of unconjugated dienones and nitroalkenes.

Inspired by the trienamine activation of π-system of 2-furfuryl ketone, Chen group reported a stereoselective dearomatic Diels–Alder cycloaddition reaction through the activation of the π-system of heteroaromatic moiety with the *in situ* generation of a trienamine equivalent. In this case, 2,5-dienone type substrate **117** condense with the chiral primary amine **Cat.19** to form the trienamine species, which further react in a Diels–Alder cycloaddition with maleimide derivatives **100** to form the tetracyclic fused compounds **94** with high molecular complexity and diversity in good to high yields and good to excellent stereoselectivities (Scheme 49).[53]



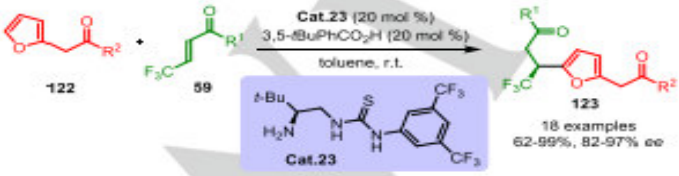
Scheme 49. Diels–Alder cycloaddition via trienamine catalysis of masked dienones and maleimides.

In continuation of their efforts in this field, Chen and co-workers, later reported an asymmetric methodology to furnish **121** via a direct bisvinylogous 1,6-addition reaction between previously reported β-allyl-2-cyclohexenone **119** and β-substituted α,α-dicyanodienes **120** catalyzed by bifunctional chiral primary amine-thiourea substrate **Cat.22** in presence of *o*-flurobenzoic acid. This reaction exhibited a remote ε-regio-selectivity, and high chemoselectivity with exellent enantioselectivities (Scheme 50).[54]



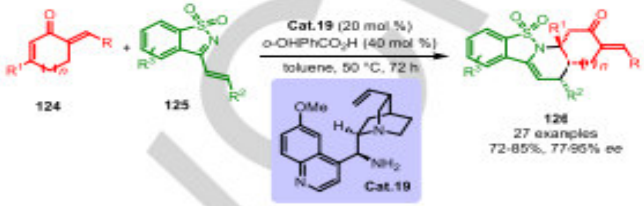
Scheme 50. 1,6-addition via trienamine catalysis of unconjugated dienones and dicyanodienes.

In 2016, the same group reported another enantioselective Friedel-Crafts alkylation reaction of 2-furfuryl ketones **122** with β-trifluoromethyl enones **62** as activated alkene in presence of bifunctional primary amine-thiourea **Cat.24**. The reaction showed moderate to excellent yields with high to excellent enantioselectivities for the asymmetric synthesis of **123** (Scheme 51).[55]



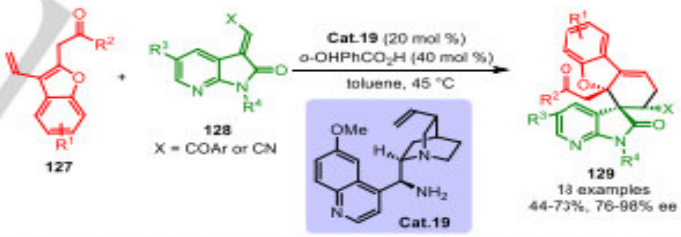
Scheme 51. Friedel-Crafts alkylation via trienamine catalysis of 2-furfuryl ketones and *β*-trifluoromethylenones.

In 2017, an *endo*-type cross conjugated trienamine catalysis by using dienones was reported by Chen et al. α′-Alkylidene 2-cyclohexenone substrates **124** proceeded in an inverse electron-demand aza-Diels–Alder cycloaddition with 3-styryl-1,2-benzoisothiozole-1,1-dioxide **125** in the presence of cinchona-based primary amine **Cat.19**, leading to the fused heterocyclic frameworks **126** with a β,γ-regioselectivity, *endo*-diastereoselectivity and good to excellent enantioselectivity (Scheme 52).[56]



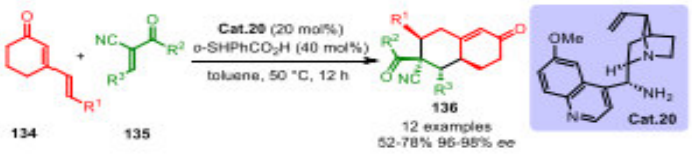
Scheme 52. Inverse-electron demand Diels–Alder cycloaddition via cross trienamine catalysis of cyclohexenones and aza-dienes.

Another asymmetric dearomatizative Diels–Alder reaction aimed to construct hydrodibenzo[*b,d*]furan skeleton **129** via trienamine catalysis. This strategy involves the reaction of 2-(3-vinylbenzofuran-2-yl)ethan-1-ones **127** and 3-olefinic 7-azaoxindoles **128**. The 3,5-dienone type substrate easily condensed with Cinchona alkaloid-derived primary amine catalyst **Cat.19** and *in situ* formed trienamine intermediate by transient dearomatization. Thereafter, a [4+2] cycloaddition to construct spirocyclic frameworks **129** with fair to good yields and good to excellent enantioselectivities (Scheme 53).[57]



Scheme 53. Diels–Alder cycloaddition via trienamine catalysis of 3-vinylbenzofuranones and 3-olefinic 7-azaoxindoles.

In 2018, the same group established a regio- and stereoselective [4+2] cycloadditions of cyclic 2,4-dienones **134** and α-cyano-α,β-unsaturated ketone **135**, to deliver the corresponding γ′,δ-cycloadducts **136** in a regicselectively manner. The reaction was catalyzed by cinchona-derived primary amine **Cat.20** in presence of thiosalicylic acid (Scheme 54).[58]

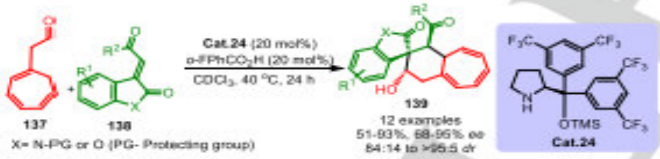


Scheme 54. Diels–Alder cycloaddition via trienamine catalysis of cyclic 2,4-dienones and α-cyanoenones.

3. Trienals in tetraenamine catalysis

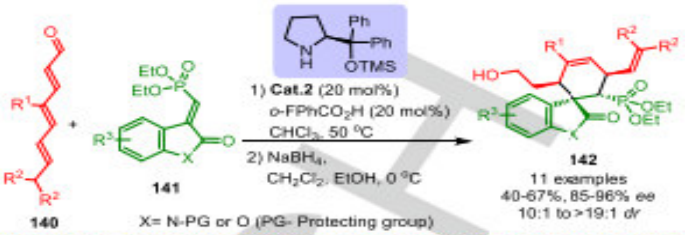
Previous sections have demonstrated that the HOMO activation can be extended to dienamine and trienamine pathways by using α,β-unsaturated carbonyl compounds and diene carbonyls compounds respectively. By virtue of extending the conjugation of the carbonyl substrate further tetraenamine activation mode has been developed, which offers new opportunities for asymmetric transformations. Previously, inherent problems occurred in the reactivity and regioselectivity of this type of species. However, recently several successful methodologies have been developed within tetraenamine catalysis.

In 2014, Jørgensen et al. reported the first reaction through a tetraenamine process, by using the cyclic trienal **137**, which was specifically designed to react with 3-olefinic oxindoles **138**, leading to the formation of three chiral centered spirocyclic oxindoles **139** with good stereoselectivities and moderate to excellent yields. Although this strategy is limited for the cyclic trienal **137**, the reaction is quite general; in fact, it can be extended to olefinic bezofuranones (Scheme 55).[46]



Scheme 55. [4+2] cycloaddition via tetraenamine catalysis of cyclic trienals and 3-olefinic oxindoles/benzofuranones.

In the same year, a methodology was reported by Chen group, using the linear 2,4,6-trienals **140** as substrate. In the presence of the chiral secondary amine **Cat.2** *in situ* generated tetraenamine species showed 3,6-regioslectivity when paired with a commonly used dienophile **141** leading to the spirocyclic compounds **142** with four stereogenic centers and high stereoselectivities (Scheme 56)[47]

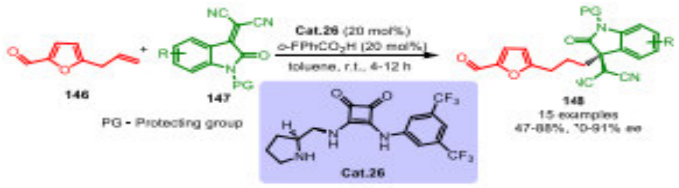


Scheme 56. [4+2] cycloaddition via tetraenamine catalysis of 2,4,6-trienals and 3-olefinic oxindoles/benzofuranones.

In 2018, Chen and group reported a third strategy on tetraenamine catalysis. This report has proven that specifically designed trienals can be useful in the aminocatalysis. The reaction was designed by using 5-allylic furfural substrates **143**, which *in situ* generates a tetraenamine equivalent species in the presence of chiral bifunctional amine-thiourea **Cat.25**. Then, an oxa-Diels–Alder cycloaddition reaction with **144** delivers multifunctional spirocyclic frameworks **145** in moderate to excellent yields and good to excellent stereoselectivities (Scheme 57).[59]

Scheme 57. Oxa-Diels–Alder cycloaddition via dearomative tetraenamine catalysis of 5-allylic furfurals and oxa-dienes.

More recently, in 2019 another remote η-regioselective Michael addition on similar substrates **147** via tetraenamine intermediate was reported (Scheme 58).[15]

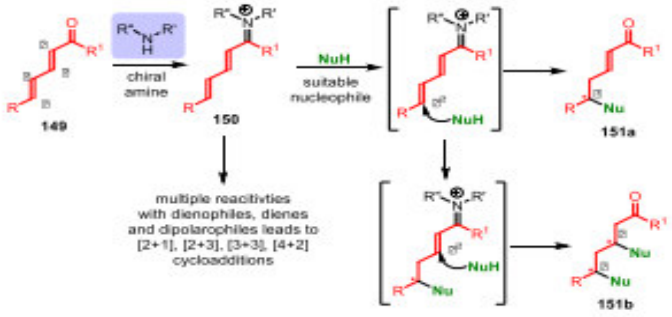


Scheme 58. η-functionalization via dearomative tetraenamine catalysis of furfurals and isatine-derived dicyanoalkenes.

4. Dienones, dienals and trienanls in vinylogous iminium ion catalysis

The LUMO-lowering and HOMO-raising effects achieve iminium ion and additionally di- or trienamines by condensation of dienals or dienones with an enantiopure aminocatalyst. The

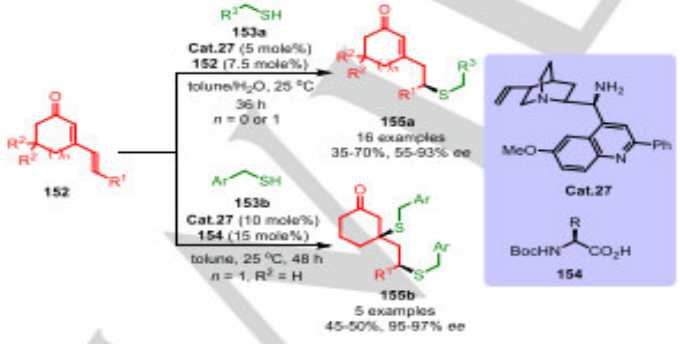
vinylogous iminium ions are electrophilic intermediates, which are reactive towards multiple reactions. The LUMO-lowering effect formed by condensation of chiral aminocatalyst with unsaturated 2,4-dienal **149** generates a vinylogous iminium ion **150**, which contains three electrophilic positions (carbonyl carbon, β-carbon and δ-carbon) whereas, the terminal carbon (δ-carbon) is more electrophilic than the of β-carbon. Hence the nucleoplilic attack is more susceptible at δ-carbon to deliver δ-substituted chiral skeleton **151** (Scheme 59).



Scheme 59. Vinylogous iminium ion activation.

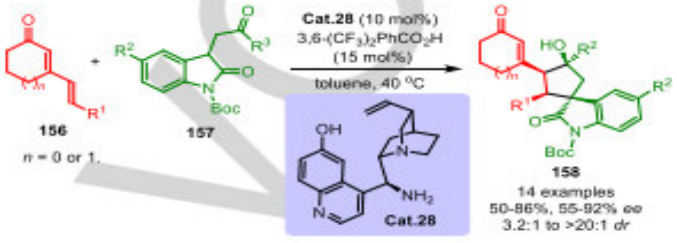
4.1. Dienones

In 2012, Melchiorre et al. reported the first aminocatalyzed reaction via vinylogous iminium ion activation mode. 2,4-Dienones were activated by LUMO-lowering activation and a 1,6-addition on the catalyst-bound vinylogous iminium ion species with alkyl thiols **153a** formed the adducts **155a**, in fair to good yields and moderate to good enantioselectivities with a good regioselectivity. Moreover, cascade reaction covering both 1,6-addition and 1,4-addition of a aromatic thiol **153b** to 2,4-cyclic dienones **152** proceeded well to provide the double addition adducts **155b** with moderate diastereoselectivity and excellent enantioselectivity by using an excess of alkyl thiol (Scheme 60).[60]



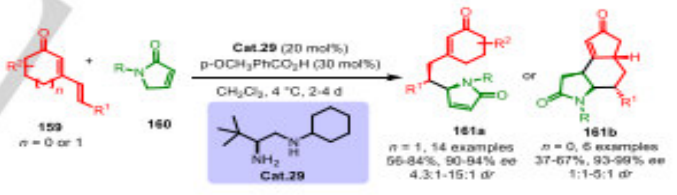
Scheme 60. 1,6 and 1,6-1,4 additions via vinylogous iminium ion catalysis of cyclic dienones and thiols.

In 2013, the same group reported an aminocatalytic cascade reaction taking advantage of the nucleophilicity of γ-position of dienamine species formed after the first 1,6-addition by vinylogous iminium ion activation. Thus, the 1,6-addition/aldolization sequence of 2,4-dienones **156** with 3-substituted oxindoles **157** proceeded through a vinylogous iminium ion and dienamine catalysis using a chiral cinchona-derived primary amine catalyst **Cat.28**. Following this strategy, highly enantioriched spiro derivatives **158** were obtained (Scheme 61).[61]



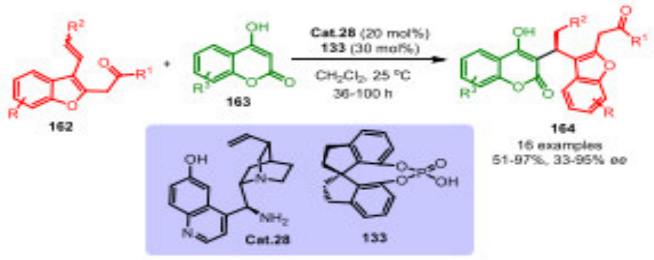
Scheme 61. 1,6-addition/aldolization cascade reaction via vinylogous iminium ion catalysis of cyclic dienones and 3-substituted oxindoles.

In 2015 Ye and co-workers reported a doubly vinylogous Michael addition reaction between sterically congested 2,4-cyclic dienone **159** and *N*-protected α,β-unsaturated γ-butyrolactam **160** in presence of primary amine catalyst **Cat.29** leading to the desired products **161** with high to excellent enantio- and diastereoselectivity (Scheme 62).[62]



Scheme 62. Vinylogous iminium ion catalysis of 3-alkenyl cycloalkenones and *N*-protected α,β-unsaturated γ-butyrolactams.

In 2017, Chen group revealed an asymmetric dearomatizative Diels–Alder reaction of masked 3,5-dienone **162**, which generates trienamine intermediate by the condensation with chiral primary amine. The trienamine intermediate was transformed to the vinylogous iminium ion by ε-protonation, which allows nucleophilic attack with 4-hydroxycoumarins **163** to furnish the corresponding 1,1-disubstituted ethane benzofuranes **164**. The reaction proceeded with moderate to excellent yields and fair to excellent enantoselectivities (Scheme 63).[63]



Scheme 63. Nucleophilic addition via vinylogous iminium ion of masked 3,5-dienones and 4-hydroxycoumarins.

4.2. Dienals and trienals

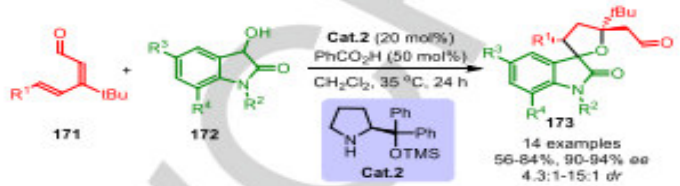
In 2013 Jørgensen and co-worker reported a vinylogous Michael addition between olefinic azalactones **166** and unsubstituted dienals **165**. The secondary amine catalyst **Cat.9** promotes the enantioselective vinylogous 1,6-addition of this olefinic substrate to the 2,4-linear dienals to affords to the corresponding products **167** with moderate to high yields and high enantioselectivities (Scheme 64). [64]

Scheme 64. 1,6-adition via vinylogous iminium ion catalysis of 2,4-dienals and azalactones.

In the same year, Jørgensen developed one more vinylogous iminium ion/dienamine cascade reaction by reacting cyclic 2,4-dienals **168** with TsONHBoc. The extended cyclic 2,4-dienals **168** forms the vinylogous iminium ion by using chiral secondary amine. Through a 1,6-addition with the TsONHBoc as nucleophile results in the formation of a dienamine intermediate, which conveniently react again with the TsONBoc moiety in the presence of basic additive to furnish the aziridines **170** in moderate to high yields and fair to excellent stereoselectivities (Scheme 65). [65]

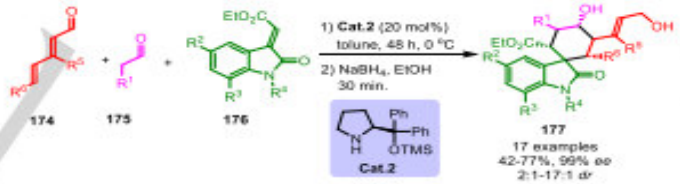
Scheme 65. Remote aziridination via vinylogous iminium ion catalysis of cyclic dienals and TsONHBoc.

In the same year, the group of Melchiorre reported an amino catalytic enantioselective 1,6-addition/oxa-Michael cascade reaction vinylogous iminium ion activation, furnishing enantioenriched tetrahydrofuran spirooxindoles **173** in good distereoselectivites, excellent enantioselectivities and moderate to good yields (Scheme 66).[66]



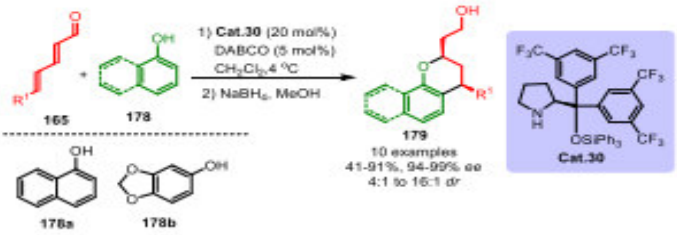
Scheme 66. 1,6-Addition/oxa-Michael cascade reaction via vinylogous iminium ion catalysis of 2,4-dienals and 3-hydroxyoxindoles.

Later, the same catalyst was used in the synthesis of spiro-oxindolic cyclohexane derivatives by reacting three different components via vinylogous iminium ion in a triple cascade reaction. The three-component reaction proceeded by a catalyzed Michael/1,6-addition/vinylogous aldol sequence with aldehydes **175**, linear 2,4-dienals **174** and olefinic oxindoles **176** to form the enantioenriched methylene indolinones **177** with six stereogenic centers in fair to good yields and very high control of the stereochemistry (Scheme 67).[67]



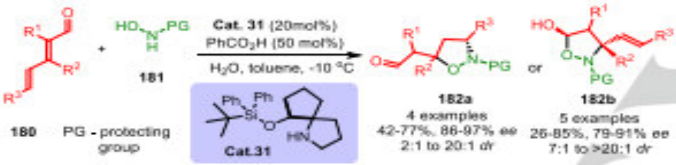
Scheme 67. Three component cascade reaction via vinylogous iminium ion catalysis of 2,4-dienals, aldehyde and 3-olefinic oxindoles.

In 2015 Jørgensen and co-workers, reported a 1,6-Friedel-Crafts/1,4-oxa-Michael addition cascade sequence with 2,4-dienals **165** and a variety of phenols **178**, through the vinylogous iminium ion intermediates to afford exclusively to the chromane derivatives **179** in moderate to excellent yields and good to excellent stereoselectivities (Scheme 68).[68]



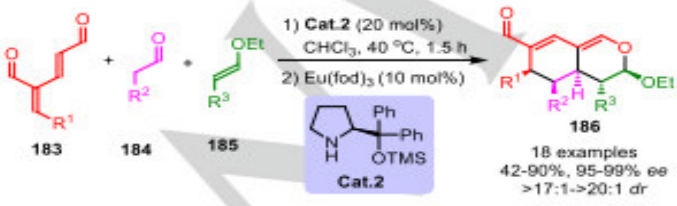
Scheme 68. 1,6-Friedel-Crafts/1,4-oxa-Michael cascade reaction via vinylogous iminium ion catalysis of 2,4-dienals and phenols.

In 2016, Wang and co-workers reported a highly enantioselective domino aza-1,4-addition/hemi-acetalization reaction with enals and *N*-hydroxycarbamates catalyzed by a spiro-pyrrolidine **Cat.31**. This domino aza-1,6-/1,4-conjugate addition reaction via generation of vinylogous iminium ion leads to the formation of enantioenriched hydroxyisozolidines derivatives **182** with fair to high yields and good to excellent stereoselectivities (Scheme 69).[69]



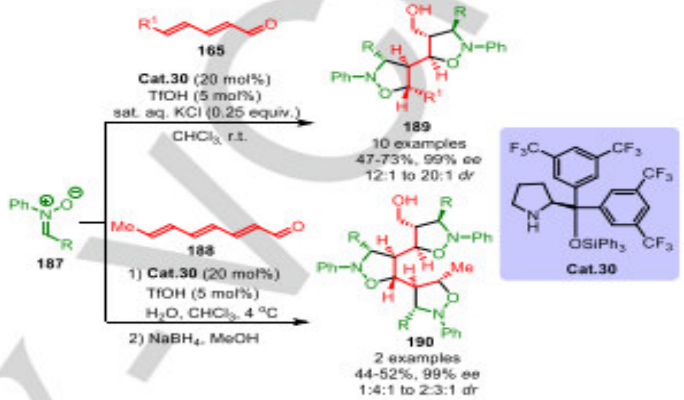
Scheme 69. Aza-1,6-/1,4-conjugate additions via vinylogous iminium ion catalysis of 2,4-dienals and *N*-hydroxycarbamates..

In 2016, Jørgensen et al. established a one-pot cascade hetero-Diels–Alder reaction for the diversification of complex bicyclic heterocyclic moieties. This strategy involves the oxadendralenic dienals **183** and aldehydes **184** in presence of chiral secondary aminocatalyst **(Cat. 2)** to lead to oxadendralenic intermediate via vinylogous iminium ion. Then, the resulting intermediate and the vinyl ether **185** affords to the corresponding tetrahydroisochromenes **186** with moderate to high yields and excellent enantioselectivites (Scheme 70).[70]



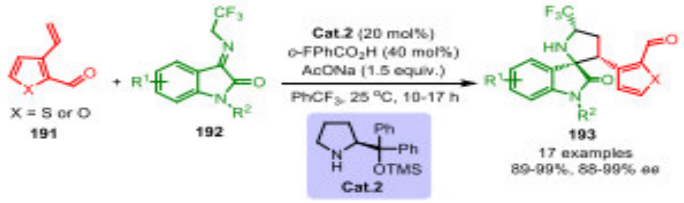
Scheme 70. One-pot three component reaction via vinylogous iminium ion catalysis of oxadendralenic dienals with aldehydes and vinyl ethers.

The same group also demonstrated the first report on vinylogous and bis-vinylogous iminium ion with nitrones. The extended 2,4-dienals **165** and 2,4,6-trienals **188** were proceeded through double and triple 1,3-dipolar cycloaddition cascades affording to bi- and tri-isoxazolidine compounds **189** and **192** with gaining up to six and nine stereocenters with fair to good yields and remarkable stereoselectivities (Scheme 71).[71]



Scheme 71. Double and triple cascade 1,3 dipolar cycloaddition via vinylogous and bis-vinylogous iminium ion catalysis of 2,4-di- and 2,4,6-trienals and nitrones.

Later, a [3+2] cycloaddition strategy for the functionalization of vinyl substituted heteroaryl and aryl aldehydes with *N*-trifluoroethyl-substituted isatin imines via vinylogous iminium ion came from Chen and co-workers in 2019. Under this methodology, diverse spirooxindoles incorporating a 3,2′-pyrrolidine framework **193** was efficiently prepared by using secondary amines **Cat.2** with high to excellent stereoselectivities (Scheme 72).[72]

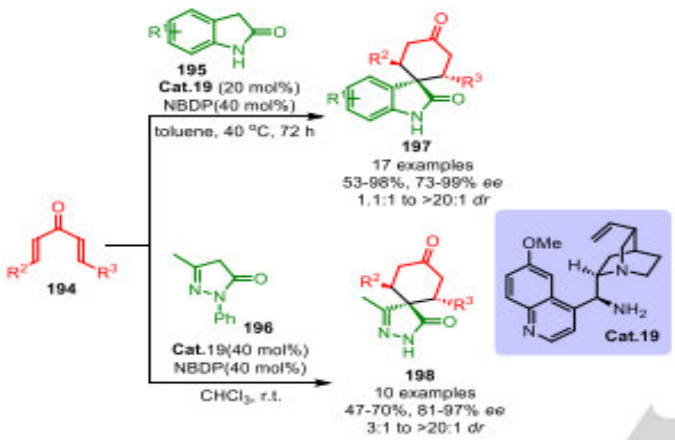


Scheme 72. [3+2] cycloaddition via vinylogous iminium ion catalysis of vinyl substituted heteroary aldehydes and isatin imines.

5. Miscellaneous

5.1 Divinyl ketones for double iminium ion catalysis

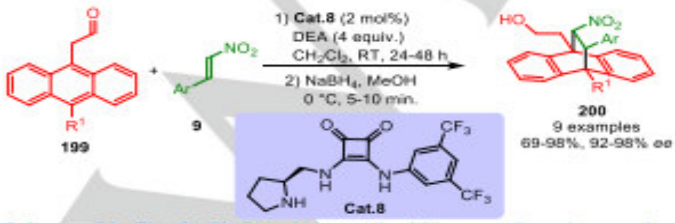
Considering the divinyl ketones as 2,2′-dienones for a double iminium ion activation, in 2012 wang and co-workers, reported a [5+1] double Michael addition cascade reaction between dienones **194** and oxindoles **195** in presence of primary amine catalyst **Cat.19** to achieve the chiral spirocyclohexanone **197**. Reaplacing oxindoles **195** with pyrazolones **196** the reaction affords to the corresponding spirocyclohexanone adduct **198** with moderate to excellent yields, diastereoselectivities and excellent enantioselectivities (Scheme 73).[73]



Scheme 73. Double Michael reaction via vinylogous iminium ion catalysis of 2,2′-dienones with oxindoles and pyrazolones.

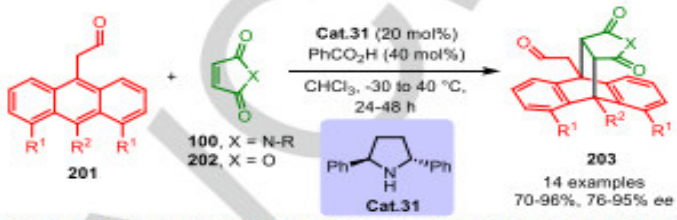
5.2. Polycyclic aromatic compounds in aminocatalytic Diels-Alder reactions.

The HOMO-raising ability of aminocatalyst helps to activate polycyclic π-system, which leads to a Diels-Alder reaction to the central ring by aromaticity breaking process to build bridged structure efficiently. As a proof, in 2012, Jørgensen and co-workers reported a first Diels-Alder reaction of anthracene **199** by using nitrostyrene **9** as a dienophile. The reaction was catalyzed by dual-activation approach using bifunctional aminocatalyst **Cat.8** whereas, a steric shielding approach ended with poor stereoselectivity due to the two available enantiotopic faces. The cycloadduct **200** was obtained with excellent enantioselectivities (Scheme 74).[74]



Scheme 74: The [4+2] Diels-Alder cycloaddition reaction via enamine catalysis of anthracene derivatives with nitrostyrenes.

Same group later reported a similar approach by using *N*-methylmaleimide **100** and furan-2,5-dione **202** as dienophiles. The reaction was carried out using C_2-symmetric aminocatalyst **Cat.31** which takes the advantage of the symmetry of anthracene ring to direct two faces approach of dienophile to achieve expected chirality. The desired cycloadduct **203** was obtained in good to excellent yields and enantioselectivities (Scheme 75).[75]



Scheme 75: Asymmertric Diels-Alder cycloaddition reaction of anthracene aldehyde and malemide.

6. Conclusions

In conclusion, we presented how simple polyenals and polyenones have contributed to the enantioselective synthesis of a great variety of more complex frameworks through different activation modes. These examples, demonstrate the extraordinary progress of the organocatalysis in the field of asymmetric synthesis during last decade. Currently, efforts are focused in the construction of more challenging architectures as well as for the remote functionalizations to more distal centers through well-designed cascades or by breaking aromaticity, which reveals the importance of these simple blocks for new expected transformations. In addition, we envision that this contribution may attract more interest in this area.

Acknowledgements

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Keywords: polyenals • polyenones • aminocatalysis • trienamine • vinylogous iminium ion

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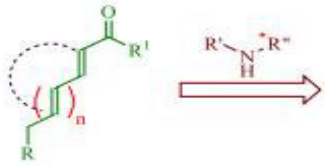
Appendix II

Layout 2:

MINIREVIEW

polyenals or polyenones
n = 1 or 2
- linear or cyclic,
- conjugated or unconjugated
- aromatic
- enolizable or non-enolizable



Access to new biosynthetic pathway

Tushar Janardan Pawar, Suhas B. Mitkari, Eduardo Peña-Cabrera, Clarisa Villegas Gómez, and David Cruz Cruz**

Page No. – Page No.

Polyenals and Polyenones in Aminocatalysis: A Decade Building Complex Frameworks from Simple Blocks

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Organocatalytic Cascade Reactions for the Diversification of Thiopyrano-Piperidone Fused Rings *via* Trienamine Activation.

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Abstract: We report an Aminocatalytic privileged Diversity-Oriented Synthesis (ApDOS) strategy via trienamine catalysis for the construction of diverse and complex thiopyrans-piperidone fused rings through a thia-Diels–Alder/nucleophilic ring closing sequence by using dithioamides as activated heterodienophiles. Following this strategy, a super cascade reaction to assemble nine fused rings can be achieved by employing a bis-dithioamide. Additionally, by linking an indole moiety on the dithioamide, a Pictet-Spengler type reaction can be promoted once the cascade sequence has been achieved, leading to more complex penta- hexa- and heptacyclic fused ring derivatives in a one-pot process. This investigation, open new perspectives for the synthesis of a new class of complex and diverse thiopyrans, which contribute to populate new relevant regions in the chemical space.

The construction of chiral privileged structures of sulfur- and nitrogen-based heterocycles constitutes a highly attractive research topic in contemporary synthesis.[1] These relevant frameworks are present in diverse natural and unnatural biologically active molecules. Particularly, thiopyrans have shown important biological properties such as analgesic,[2] anti-cancer,[3] anti-hyperplasia,[4] antibacterial,[5] among others[6] (Figure 1a). Meanwhile, piperidones have demonstrated to be important therapeutic agents against different diseases such as Alzheimer disease[7] anti-cancer[8] and inflammatory bowel disease (IBD)[9] (Figure 1b). The constant demand of these significant scaffolds has driven the development of new synthetic methods, which have contributed to the diversification of these skeletons.[10] However, the elaboration of effective stereocontrolled protocols while maximizing atom economy is still a challenge. In this context, aminocatalytic cascade reactions have provided important protocols for the enantioselective synthesis of simple and complex molecules with high levels of structural diversity and atom economy.[11] Particularly, trienamine catalysis has demonstrated the ability to promote consecutive transformations to provide diverse polycyclic frameworks.[12] One approach is to utilize the fact that the formal [4+2] cycloadducts of trienamine-mediated reactions contain aldehyde moieties, which can undergo further cyclizations.[13]

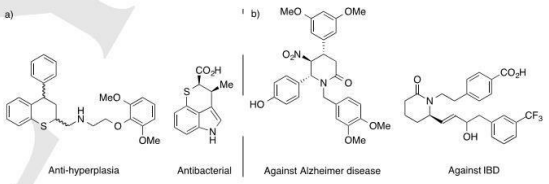


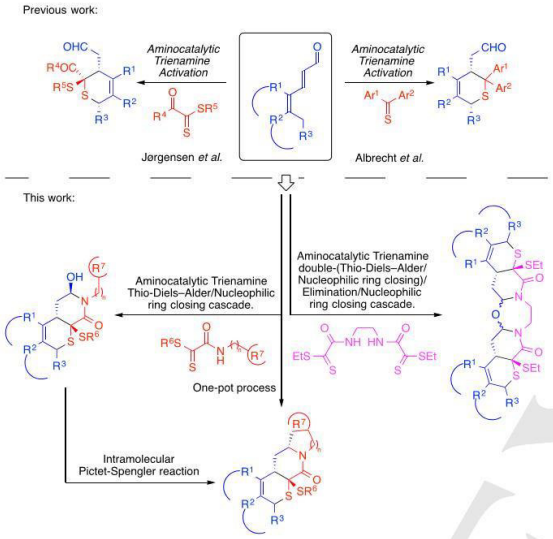
Figure 1. Some examples of biological active thiopyrans and piperidones.

Thiocarbonyls such as dithioesters, thioamides and thioketones, constitute a select group of sulfur-containing compounds, which have been employed efficiently as heterodienophiles for thia-Diels–Alder cycloadditions.[10a-b] In 2013, the organocatalytic version of this reaction was first reported by Jørgensen *et al.* through a trienamine-mediated cycloaddition using dithioesters as dienophiles.[14] Later, under the same catalytic strategy, Albrecht and co-workers demonstrated the dienophilic ability of aryl and hetaryl thioketones.[15] In both cases, the reactions proceeded smoothly and efficiently for the construction of diverse optically active dihydro-2*H*-thiopyrans.

In order to explore this relevant chemical design space and contribute with reliable and efficient methodologies for the Aminocatalytic privileged Diversity-Oriented Synthesis (ApDOS)[16] via trienamine catalysis, we envisioned an organocatalytic cascade strategy through a thia-Diels–Alder/nucleophilic ring-closing sequence by using dithioamides as activated heterodienophiles for the assembly of diverse thiopyran-piperidone fused rings. Additionally, by linking an indole moiety on the dithioamide, a Pictet-Spengler type reaction can be performed once the first cascade sequence has been achieved. Thus, high order polycyclic frameworks of greater

complexity can be prepared in a one-pot process. Finally, by considering a bis-dithioamide as hetero-dienophile, we hypothesized a double cascade reaction for the construction of two thiopyrano-piperidone cycloadducts at the same molecule, in a simple process (Scheme 1).

Herein we present the results of this investigation, which open new perspectives for the diversification of thiopyrans and piperidones. To best of our knowledge, there are no reports about the synthesis or natural occurrence of these fused cores. Therefore, this strategy aims to populate relevant regions in the chemical space.

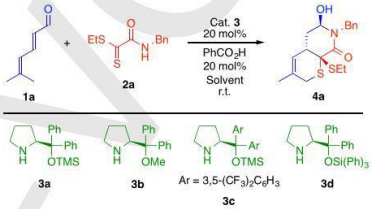


Scheme 1. Thiocarbonyl compounds in aminocatalysis and our present synthetic strategy.

To proof the concept, we initiated our work by choosing the 2,4-dienal **1a** and the dithioamide **2a** as model substrates for the cascade sequence thia-Diels–Alder/nucleophilic ring-closing. Gratifyingly, when the reaction was carried out in presence of 20 mol% of Jørgensen-Hayashi catalyst **3a** and benzoic acid as additive in $CHCl_3$, the desired product **4a** was obtained after 24 h at room temperature with excellent yield (93%) and stereocontrol (93:7 dr, 92% ee) (Table 1, entry 1). In order to improve the stereoselectivity, we tested different catalysts. When the reaction was performed with the catalysts **3b-c**, the diastereoselectivity was slightly improved but the enantioselectivity and the yield were not satisfying (entries 2 and 3). By using the more sterically demanding *O*-Si(Ph)$_3$ catalyst **3d**, a better enantioselectivity was observed (96% ee) along with the same diasteromeric ratio. However, the isolated yield decreased less than 80% (entry 4). Therefore, we decided to work with the readily available catalyst **3a**. No further improvement was observed by changing solvents such as CH_2Cl_2, CH_3CN and THF (entries 5, 6 and 7). Finally, the results were not satisfying when the reaction was carried out with less catalyst loading (entry 8).

With the optimal conditions in hand, we explored the scope of the cascade reaction with different 2,4-dienals as trienamine precursors. As shown in Table 2, alkyl groups at γ- and δ-positions were well tolerated, maintaining good yields and stereoselectivities. An extra cyclohexane fused ring was also generated by using the derivative **1e**. Interestingly, an indole moiety could be incorporated when the 2-methylindole acrylaldehyde **1f** was employed as masked 2,4-dienal, leading to the corresponding tetracyclic adduct **4f** in excellent yield (96%) and stereoselectivity (96:4 dr, 98% ee). Next, we investigated the protocol using different dithioamides.

Table 1. Screening of the thia-Diels–Alder/nucleophilic ring closing cascade reaction.



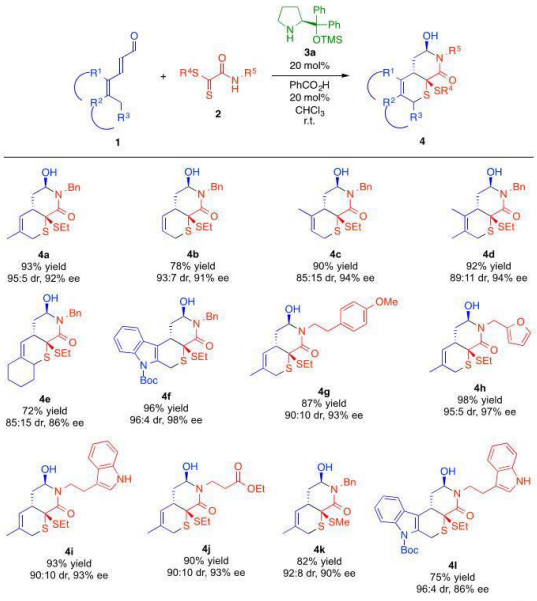
Entry	Cat.	Solvent	t (h)	Conv. (%)	Yield (%)[a]	dr[b]	ee[c] (%)
1	**3a**	$CHCl_3$	24	100	93	93:7	92
2	**3b**	$CHCl_3$	48	64	62	97:3	68
3	**3c**	$CHCl_3$	48	74	70	94:6	76
4	**3d**	$CHCl_3$	48	100	78	93:7	96
5	**3a**	CH_2Cl_2	48	61	57	71:29	n.d.
6	**3a**	CH_3CN	48	63	61	74:26	82
7	**3a**	THF	48	dec.	---	---	---
8[d]	**3a**	$CHCl_3$	48	64	61	72:28	---

The reactions were performed with 0.15 mmol of **1a**, 0.1 mmol of **2a**, 20 mol% of catalyst and benzoic acid as additive in 0.5 ml of solvent at room temperature. [a]Yield of both diastereoisomers of **4a** after chromatographic purification on silica gel. [b]Determined by ^{1}H NMR of crude product. [c]Measured by chiral HPLC. [d]The reaction was performed with 10% of the catalyst.

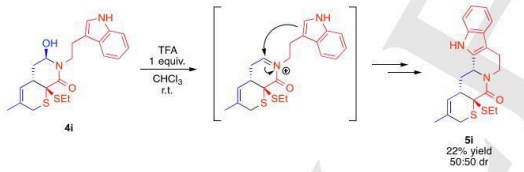
To our delight, the reaction was also effective for dithioamides carrying with aromatic or ester substituents resulting in good to excellent yields (87-98%) and stereoselectivities (90:10-95:5 dr, 93-97% ee). Only a small difference was observed by changing the alkyl group at the sulfur atom. Notably, an interesting polycyclic derivative with two indole cores **4l** was able to prepare through the reaction between **1f** and **2i**.

Once we demonstrated the scope of the developed methodology, we considered to extend the methodology towards the construction of more complex frameworks. In this sense, we focused our attention on the reactivity of the cycloadduct **4i**, which can undergo an intramolecular Pictet-Spengler type reaction once an iminium ion intermediate is formed via hydroxyl group elimination. To validate this hypothesis, the reaction was promoted under acidic conditions. To our glad, when **4i** was treated with 1 equiv of TFA at room temperature, the thiopyrano-piperidone-tetrahydrocarboline fused ring derivative **5i** was obtained as a mixture of two diastereoisomers in 22% of yield (Scheme 2).

Table 2. Scope of the thia-Diels–Alder/nucleophilic ring closing cascade reaction.



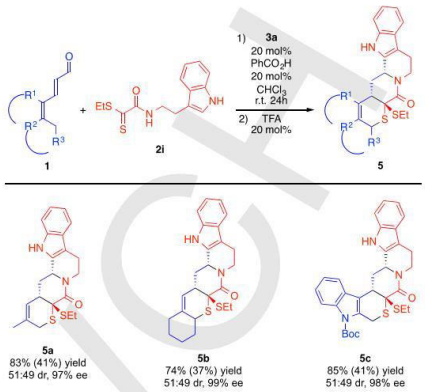
The reactions were performed with 0.15 mmol of **1**, 0.1 mmol of **2**, 20 mol% of catalyst, and benzoic acid as additive in 0.5 ml of solvent at room temperature. The yield is for both diastereoisomers of **4** after chromatographic purification on silica gel. The dr was determined by ^{1}H NMR of crude product. The ee was measured by chiral HPLC.



Scheme 2. Intramolecular Pictet-Spengler reaction to furnish **5i**.

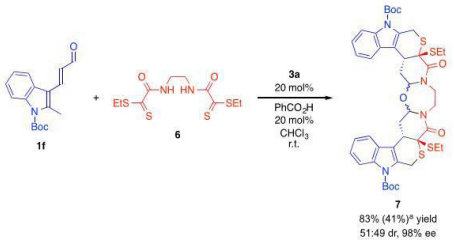
More importantly, when both, thia-Diels–Alder/nucleophilic ring closing and Pictet-Spengler reactions were performed in a one-pot fashion using catalytic amounts of TFA, the desired product **5i** was furnished in 83% overall yield and 97% ee.[17] In order to prove the strategy, more complex hexa- and heptacyclic compounds were successfully prepared following the same conditions with good yields and excellent enantioselectivities (Table 3).

Table 3. Scope of the thia-Diels–Alder/nucleophilic ring closing Pictet-Spengler one-pot reaction.



The reactions were performed with 0.15 mmol of **1**, 0.1 mmol of **2i**, 20 mol% of catalyst, and benzoic acid as additive in 0.5 ml of solvent at room temperature. Then TFA (20 mol%) was added. The yield is for both diastereoisomers, the yield in parenthesis is for single major diatereoisomer. The dr was determined by ^{1}H NMR of crude product. The ee was measured by chiral HPLC.

Finally, driven by the access to more diverse and complex molecules containing these attractive scaffolds we were wondering if a double aminocatalytic cascade process would be possible through the reaction with the bis-dithioamide **6** and construct two cycloadducts connected by the amide moiety in one process. Surprisingly, when the bis-dithioamide **6** was reacted with three equiv of the aldehyde **1f** under the standard conditions, the nine fused ring compound **7** was directly obtained in a double-(thia-Diels–Alder/*N*-nucleophilic ring closing)/elimination/*O*-nucleophilic ring closing sequence (Scheme 3). Notably, through this reaction, a separable mixture of two diastereoisomers with six new stereocenters were smoothly furnished in 41 and 39% of yield and 98% of ee for the major diastereoisomer.



Scheme 3. Aminocatalytic double-(thia-Diels–Alder/*N*-nucleophilic ring closing)/elimination/*O*-nucleophilic ring closing cascade reaction. The reaction was performed with 0.3 mmol of **1f**, 0.1 mmol of **6**, 20 mol% of catalyst **3a** and benzoic acid as additive in 0.5 ml of solvent at room temperature. The yield is for both diastereoisomers. [a]The yield is for a single major diastereoisomer. The dr was determined by ^{1}H NMR of crude product. The ee was measured by chiral HPLC.

The absolute configuration of the compounds **4f** and **5c**, were unequivocally established as (2*R*, 4a*R*, 11c*S*) and (7a*R*, 16b*R*, 17a*S*) respectively by X-ray analysis. For the remaining products the configurations were assumed by analogy (Figure 2).

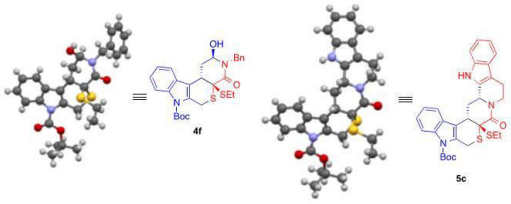


Figure 2. X-ray structure of compounds **4f** and **5c**.

In conclusion, we have developed a new thia-Diels–Alder/nucleophilic ring-closing cascade sequence for the enantioselective synthesis of thiopyrano-piperidone fused ring compounds through trienamine catalysis. The reaction proceeds efficiently with high levels of stereocontrol. Additionally, by promoting an intramolecular Pictet-Spengler reaction after the cascade sequence, different thiopyrano-piperidone-carboline fused ring compounds were constructed in a one-pot with good yield and excellent enantiocontrol. Interestingly, by using a bis-dithioamide as hetero-dienophile, a double-(thia-Diels–Alder/*N*-nucleophilic ring closing)/elimination/*O*-nucleophilic ring closing super cascade reaction was achieved, leading to a new type of nine fused ring derivative with six new stereocenters. These aminocatalytic cascade methodologies, open new perspectives for the synthesis of a new class of complex and diverse thiopyrans, which contribute to populate new relevant regions in the chemical space.

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[17] For more screening conditions, see Supplementary Information.