NEW MODES OF ACTIVATION FOR THE REMOTE FUNCTIONALIZATION BY ORGANOCATALYSIS

by

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To Mom and Karla

Preface

The aim of this thesis is to summarise my work within the field of organocatalysis during the four years of my Ph.D. This work was carried out under the supervision of Dr. David Cruz Cruz at "laboratory of organocatalysis and natural products" in the Universidad de Guanajuato, Mexico. During my four years of Ph.D., the field of organocatalysis has witnessed a gradual transition from being "hot topic" to become a mature field research. While a researcher's curiosity usually dictates developments in "hot topic" chemistry, applicative aspects are in general the key driving force of progress in more mature research field. To have work in the field of organocatalysis during this transition period has truly been as exciting and highly educative experience, which rendered a good mixture of curiosity and application driven research.

Nevertheless, a great collaboration with the group of Dr. Eduardo Peña Cabrera provided me a great knowledge about BODIPY chemistry and fluorescent compounds. A collaboration with Dr. Clarisa Villegas Gómez became a deep source of knowledge in the field of natural products and bioactive compounds. Also, a period of one year of stay and collaboration with Dr. José Aléman and Dr. Alberto Fraile in Universidad Aútonoma de Madrid, Spain gives me some additional skills to my practical hand as well as a knowledge of current "hot topics" such as photocatalysis and computational chemistry.

The main objective of my Ph.D. has always been to demonstrate the versatility and applicability of organocatalysis – a path that I have trustfully followed throughout a series of projects conducted during the last four years. These research projects have been divided into five main topics, each covered by an individual chapter in the thesis. However, prior to these, an introductory chapter, which includes background information and personal perspectives of the field is presented. An individual chapter for the experimental work gives a simplicity to the thesis to understand smoothly. Complementarily, a summary chapter can be found in the end of the thesis and herein, the author's contribution to each project will be discussed. It is noteworthy that strong emphasis has been devoted to scholarly presentational aspects of the thesis, which aims to provide an interesting read for insiders as well as outsiders of the field of research.

I would like to acknowledge the tremendous support and help I have received during the past four years, both inside and outside of the walls of our laboratory. First, I would like to thank David for taking me to his group (so called, a first organocatalysis group in Mexico) and the efforts that he made to create the most pleasant and inspiring working atmosphere that made it possible a long journey of my Ph.D. career. Secondly, I thank to my codirector Dr. César for his support. Thirdly, I would like to thank my colleagues in the group, Charlie, Beto and Suhas for their help and support. Also, I gratefully acknowledge a group of Dr. Eduardo, especially Wicho and Siddhant for consistent help throughout this journey.

At last, I must thank my family for all the support and trust I have been given during all these years, without which I would never have reached so far. With these words, I would like to end this long preface and let the flow of this thesis begin.

Tushar Janardan Pawar

January 2019, Guanajuato.


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Abstract

During past two decades, enormous efforts have been devoted to the exploration of small molecule as catalytic mimics for nature's enzymatic system. This has enabled researchers to use the inspiration found in various biosynthetic pathways and project these into useful laboratorial or industrial synthetic methods. In comparison to other conventional methods and catalyst, the organocatalyst have the advantage of being less toxic and more easily degradable, which may lead to 'greener' chemical synthesis. One of the main objectives for this Ph.D. project is to develop new and useful catalytic reactions using organic molecules as "open site" enzymes. Especially, in the synthesis of chiral non-racemic compounds, or compound libraries, which have great importance for life sciences, organocatalyst have shown to be useful. During this Ph.D. study, eight new asymmetric catalytic reactions or reaction sequence have in collaboration with others, been developed. Using these new methodologies, the synthesis of natural products, bioactive moieties and privileged synthetic building blocks can be accomplished from readily available reagents and non-toxic catalyst in a simple and benign way.

In this thesis, ten individual research projects have been categorized into five different chapters, entitled: *i*) "Theoretical survey in aminocatalysis"; *ii*) "Trienamines in aminocatalysis: the diarylprolinol system action beyond enamine and iminium-ion chemistry"; *iii*) "Enantioselective synthesis of chiral tetrahydrocarbazole: a trienamine strategy to access bioactive molecules"; *iv*) "BODIPY compounds as a dienophiles in aminocatalysis: some new efficient pathways to construct chiral fluorescent scaffolds"; *v*) "Cooperative catalysis: The strategy of amino- and gold catalysis". In addition to the five chapters dedicated to the original research, fundamental catalysis, asymmetric catalysis and organocatalysis have been summarised in an introductory chapter, which sets the foundation for the better understandings of the remaining text for non-specialist. Also, for the proper presentation, experimental section has been provided separately as an individual chapter.

Overall, the aim of this Ph.D. project is to develop methods that could simplify future chemical synthesis. Hopefully, this thesis and underlying work may demonstrate that organocatalysis could serve as a useful tool in chemistry.

Resumen

Durante las últimas dos décadas, se han dedicado enormes esfuerzos a la exploración de moléculas pequeñas como imitadores catalíticos para el sistema enzimático de la naturaleza. Esto ha permitido a los investigadores utilizar la inspiración que se encuentra en varias vías biosintéticas y proyectarlas en métodos sintéticos útiles de laboratorio e industriales. En comparación con otros métodos y catalizadores convencionales, el organocatalizador tiene la ventaja de ser menos tóxico y más fácilmente degradable, lo que puede conducir a una síntesis química "más verde". Uno de los objetivos principales para este proyecto de doctorado es desarrollar reacciones catalíticas nuevas y útiles utilizando moléculas orgánicas como enzimas de "sitio abierto". Especialmente, en la síntesis de compuestos quirales no racémicos, o bibliotecas de compuestos, que tienen gran importancia para las ciencias de la vida, los organocatalizadores han demostrado ser útiles. Durante este doctorado se estudió, ocho nuevas reacciones catalíticas asimétricas o secuencia de reacción se han desarrollado en colaboración con otros grupos. Usando estas nuevas metodologías, la síntesis de productos naturales, restos bioactivos y bloques sintéticos privilegiados se puede lograr a partir de reactivos disponibles y catalizadores no tóxicos de una manera simple y benigna.

En esta tesis, diez proyectos de investigación individuales se han catalogado en cinco capítulos diferentes, titulados: i) "Encuesta teórica en aminocatálisis"; ii) "Trienaminas en la aminocatálisis: la acción del sistema diarilprolinol más allá de la química de la enamina y el ion iminio"; iii) "Síntesis enantioselectiva de tetrahidrocarbazol quiral: una estrategia de trienamina para acceder a moléculas bioactivas"; iv) "Compuestos BODIPY como dienófilos en la aminocatálisis: algunas nuevas vías eficientes para construir andamios fluorescentes quirales"; v) "Catálisis cooperativa: la estrategia de la catálisis de amino y oro". Además de los cinco capítulos dedicados a la investigación original, la catálisis fundamental, la catálisis asimétrica y la organocatálisis se han resumido en un capítulo introductorio, que establece las bases para una mejor comprensión del texto restante para los no especialistas. Además, para la presentación adecuada, la sección experimental se ha proporcionado por separado como un capítulo individual.

En general, el objetivo de este proyecto de doctorado consiste en desarrollar métodos que puedan simplificar la síntesis química futura. Con suerte, esta tesis y el trabajo subyacente pueden demostrar que la organocatálisis podría servir como una herramienta útil en química.

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List of Acronyms

Ar	aryl
BA	benzoic acid
Boc	*tert*-butyloxycarbonyl
BP or BODIPY	Boron Dipyrromethane
t-Bu	*tert*-butyl
CyH	cyclohexane
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminium hydride
DMF	dimethyformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
Equiv.	equivalents
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
FC	flash chromatography
H-acceptor	hydrogen bond acceptor
H-bonding	hydrogen bonding
H-donor	hydrogen bond acceptor
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
LG	leaving group
LUMO	lowest unoccupied molecular orbital
NaOAc	sodium acetate
Nu-H	generic nucleophile
OAc	acetate
OFBA	ortho-flurobenzoic acid
OTES	triethylsilyl ether
OSiPh3	triphenylsilyl ether
OTMS	trimethylsilyl ether
OTBDMS	*tert*-butyldimethylsilyl ether
PG	protecting group
Ph	phenyl
Pr	propyl
iPr	*iso*-propyl
Py	pyrazole
SM	starting material
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THC	tetrahydrocarbazole
tol	toluene
Ts	tosyl

Chapter 1.

Introduction and Background

"As natural selection acts solely by accumulating slight, successive, favorable variations, it can produce no great or sudden modification; it can act only by very short and slow steps" – Charles Darwin.[1]

1.1 Evolution of Asymmetric synthesis.

1.1.1. How the "chemical evolution" meets an asymmetric synthesis in synthetic advancement.

Chemistry is a foundation of human life; a composition of random chemicals created a single cell, which brings life on the earth. We are an amazing chemical creation of nature whereas all our activities are controlled by chemicals as well as we are surrounded by chemical reactions and materials made up of chemical compounds. By 3000BC, civilization started to use technologies based on numerous branches of chemistry such as extraction of metals from ores, manufacturing of pottery, glazes and glass, fermentation of wine and beer, extraction of medicines from plants, preparation of soap, perfumes, the

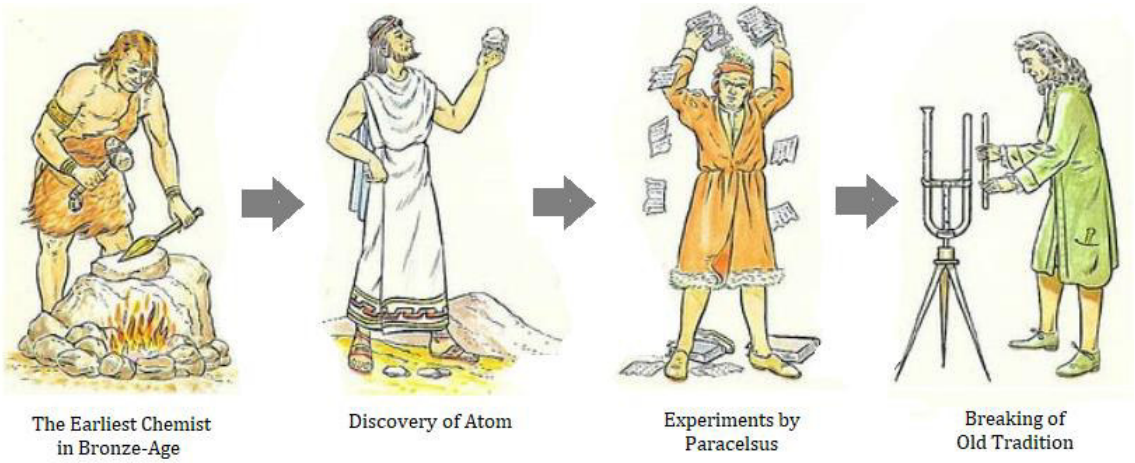


Figure 1: *History of chemistry*

[1] Darwin, **1859**, 510

composition of an alloy such as bronze and so on (**Figure 1**). In this time, the chemistry was an art more than science. With time, chemists started to analyze the composition of various substances, their physical and chemical properties, the specific conditions under which they combine with other substances, along with all practical applications of chemistry affecting every aspect of civilization. Later, by performing experiments and recording the results, chemists set the stage for modern chemistry. Both alchemy and chemistry were concerned with matter and its transformation, chemists started applying scientific methods to their work. The history of chemistry is intertwined with the history of thermodynamics, especially through the work of Willard Gibbs. The idea of a drug appears from the ancient Indian Vedas from before 1000BC and it started growing without knowing the chemical composition of the drugs. In 1789 a French chemist Antoine-Laurent de Lavoisier established the Law of Conservation of Mass, which is also called "Lavoisier's Law" and himself called father of modern chemistry. John Dalton in 1803 proposed that matter is composed of indivisible smallest particle called atom.[2] In nineteenth-century, at the time of the first world war, the preparation of enantiomerically enriched compounds became a fundamental aspect to categories into the resolution of a racemic mixture and asymmetric synthesis which are well-known methods today. The result of more than one hundred years of research in the chemistry field brings an asymmetric synthesis to modern chemistry.[3]

1.1.2. Asymmetric synthesis.

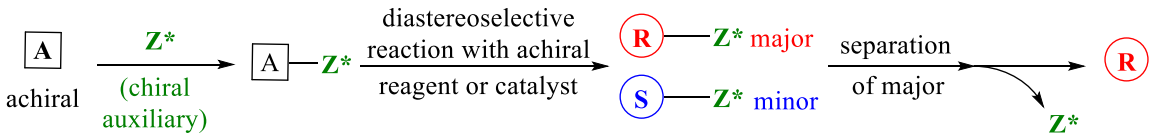
Asymmetric synthesis has become a major aspect of modern organic chemistry. The stereochemical properties of an organic compound are often essential to its bioactivity, and the need for stereochemically pure pharmaceutical products is a key example of the fundamental importance of stereochemical control in organic synthesis. However, achieving high levels of stereoselectivity in the synthesis of complex natural products represents a considerable intellectual and practical challenge for chemists.

Asymmetric synthesis needs the use of a chiral auxiliary, which will be temporarily introduced in the substrate or is part of the reagent or the catalyst (Figure **2**). Izumi proposed

[2] Nath, B. K.; *International Journal of Development Research*, **2016**, *6*, 8810-8812.
[3] Kagan, H. B.; Gopalaiah, K.; *New J. Chem*., **2011**, *35*, 1933–1937.

in 1971 to divide the asymmetric synthesis into two classes: the diastereoselective reactions and the enantioselective reactions.[4] Soon after Izumi and Tai, introduced another classification of stereoselective reactions which is not considered here.[5]

Diastereoselective reactions



Enantioselective reactions

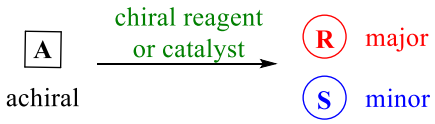


Figure 2: *Synthesis of chiral products*

In the diastereoselective synthesis, a chiral auxiliary is bound to a substrate which contains, for example, a keto group. The two faces of the carbonyl become diastereotopic and may react at different rates with an achiral reagent. The mixture of diastereomers that are formed becomes a mixture of enantiomers after removal of the chiral auxiliary. On the other hand, the substrate in enantioselective synthesis is achiral and contains at least one pro-stereogenic unit. A chiral reagent or a chiral catalyst may well differentiate the two enantiotopic faces or groups of an achiral molecule, providing the preferred formation of one enantiomer of the product.

The commonly used statement ‘‘asymmetric synthesis’’ is an expression which should refer to the chiral products constructed by non-racemic compounds and not to the process or the mechanism of the reaction. It has been pointed out by various authors that some stereochemical expressions acquired meaning in each context and cannot always be strictly defined.[6]

[4] Glorius, F.; Gnas, Y., *Synthesis*, **2006,** *12*, 1899-1930
[5] Izumi, Y.; Tai, A., *Kodansha*, *Academic Press, Tokyo and New York*, **1977**, ISBN 0-12-377850-6
[6] Pasteur, L; Hebd. C. R., *Séances Acad. Sci.*, **1848**, *26*, 538.

1.1.3. What is Catalysis?

Catalysis is the process of increasing the rate of a chemical reaction by adding a substance known as a catalyst[7], which is not consumed in the catalyzed reaction and can continue to act repeatedly. Because of this, only very small amounts of catalyst are required to alter the reaction rate in principle.[8] In general, chemical reactions occur faster in the presence of a catalyst because the catalyst provides an alternative reaction pathway with lower activation energy than the non-catalyzed mechanism. In catalyzed mechanisms, the catalyst usually reacts to form a temporary intermediate, which then regenerates the original catalyst in a cyclic process. A substance which provides a mechanism with higher activation energy does not decrease the rate because the reaction can still occur by the non-catalyzed route.[9] An added substance which does reduce the reaction rate is not considered a catalyst but a reaction inhibitor.

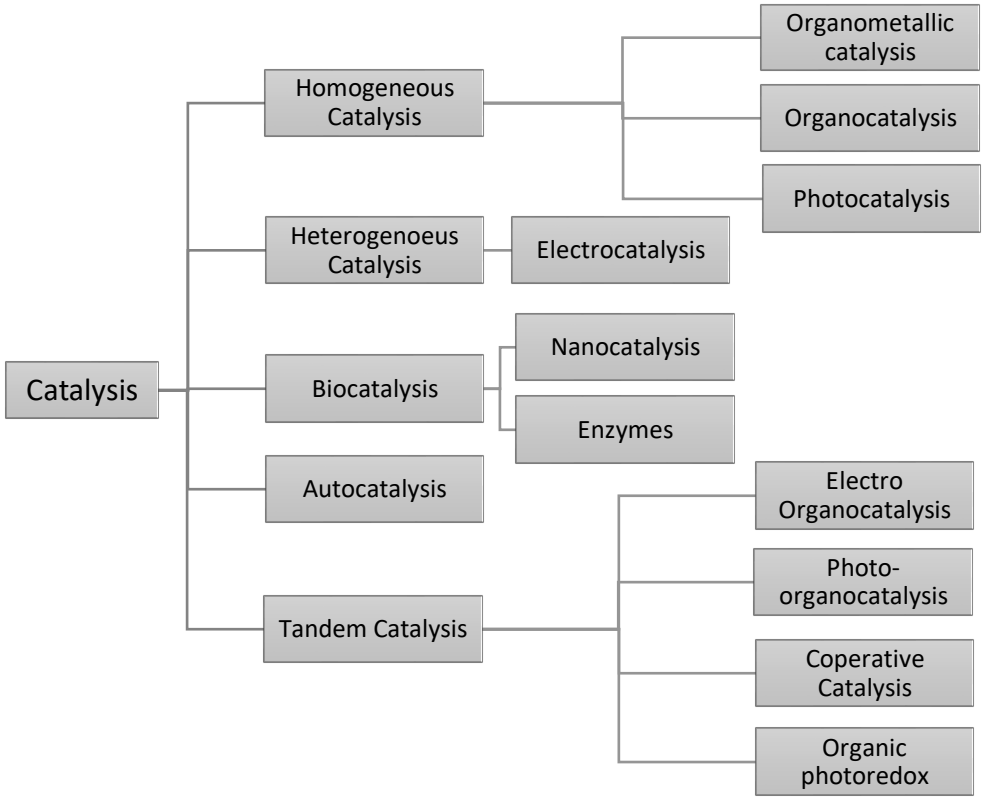


Figure 3: *Classification of Catalysis*

[7] "*Catalyst" IUPAC Compendium of Chemical Terminology.* **2009.** ISBN 978-0-9678550-9-7.
[8] Lerner, L., "7 things you may not know about catalysis" *Argonne National Laboratory*, **2011**.
[9] Laidler, K.J.; Meiser, J. H., *Physical Chemistry*, **1982**, 425. ISBN 0-618-12341-5.

Catalysts may be classified as either homogeneous or heterogeneous. A homogeneous catalyst is one whose molecules are dispersed in the same phase (usually gaseous or liquid) as the reactant's molecules. A heterogeneous catalyst such as electrocatalysis is one whose molecules are not in the same phase as the reactant's, which are typically gases or liquids that are adsorbed onto the surface of the solid catalyst. Enzymes, nanocatalysts and other biocatalysts are often considered as a third category.[10] Autocatalysis is another category can be considered.[11] Also, a combination of two different catalysis called tandem catalysis[12] is one of the important categories has been developed these days (Figure **3**).

In the presence of a catalyst, less free energy is required to reach the transition state or intermediate, but the total free energy from reactants to products does not change. A catalyst may participate in multiple chemical transformations. The effect of a catalyst may vary due to the presence of other substances known as inhibitors or poisons (which reduce the catalytic activity) or promoters (which increase the activity and affect the temperature of the reaction).

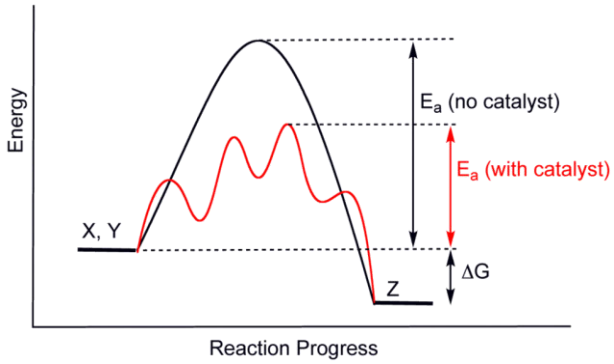


Figure 4: *Energy diagram for the reaction progress with and without catalyst.*

Catalyzed reactions have lower activation energy (rate-limiting free energy of activation) than the corresponding uncatalyzed reaction, resulting in a higher reaction rate at the same temperature and for the same reactant concentrations (Figure **4**). However, the detailed mechanics of catalysis is complex. Catalysts may bind to the reagents to polarize

[10] Jayasinghe, L. Y.; Smallridge, A. J.; Trewhella, M. A., *Tetrahedron Letters.* **1993,** *34,* 3949–3950

[11] Steinfeld, J. I.; Francisco, J. S.; Hase, W. L., *Chemical Kinetics and Dynamics* (2nd ed.), **1999**, 151-152. ISBN 0-13-737123-3

[12] Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C., *Chemical Reviews*, **2005,** *105*, 1001–1020.

bonds, e.g. acid catalysts for reactions of carbonyl compounds, or form specific intermediates that are not produced naturally, such as osmate esters in osmium tetroxide-catalyzed dihydroxylation of alkenes, or cause dissociation of reagents to reactive forms, such as chemisorbed hydrogen in catalytic hydrogenation.

1.1.4. Introduction of Organocatalysis in Asymmetric Synthesis

Organocatalysis is the use of small organic molecules to catalyze many organic transformations simply and efficiently.[13,14]

In the past two decades, the success of organocatalysis has been the invention or identification of generic modes of catalytic activation, induction, and reactivity (Figure 5). A generic activation mode describes a reactive species that can participate in many reaction types with consistently high enantioselectivity (as opposed to one or two unique transformations). Such reactive species arise from the interaction of a single chiral catalyst with a basic functional group (such as a ketone, aldehyde, alkene or imine) in a highly organized and predictable manner.

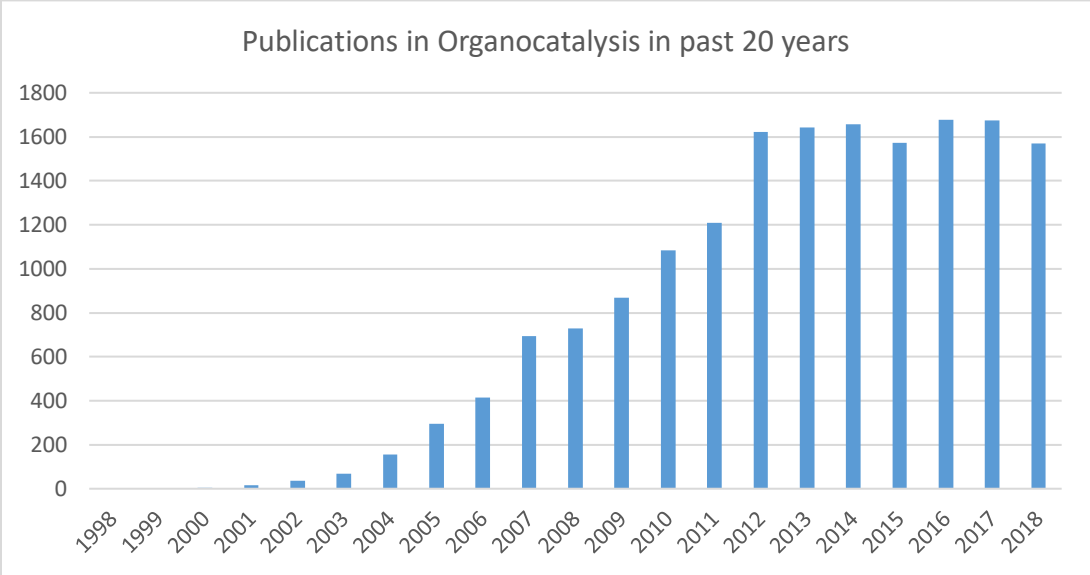


Figure 5: *Publications in Organocatalysis in last 20 years (Source: Sci-finder)*

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

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

The value of generic activation modes is that, after they have been established, it is relatively straightforward to use them as a platform for design new enantioselective reactions. Indeed, most of the organocatalytic reactions that have been reported since 1998 are founded directly on only seven or eight activation modes. The small number of activation modes in organocatalysis (and in catalysis in general) is not surprising - when devising a new enantioselective reaction, it is far easier to make use of a known activation mode than to invent a new one (together with a new catalyst). Hence, the number of enantioselective catalytic reactions will always be much larger than the number of activation modes that underpin them. The work in this field is growing constantly, as the scope and the exploration is still an open-ended challenge (Figure 3).

1.1.5. When asymmetric synthesis meets aminocatalysis

It has been two decades, asymmetric organocatalysis is recognized as an efficient and reliable strategy for the stereoselective preparation of valuable chiral compounds. The use of purely organic molecules as chiral catalysts complements the traditional organometallic and biological approaches to asymmetric catalysis, thus enabling synthetic chemists to move closer to being able to construct any chiral scaffold in an efficient, rapid, and stereoselective manner. Asymmetric organocatalysis offers alternatives to the activation of substrates and can deliver unique, orthogonal, or complementary selectivities compared to metal-catalyzed processes. Besides, it offers some attractive benefits: The metal-free organic catalysts are generally non-toxic, readily available, and stable. These properties allow most reactions to be performed in a wet solvent and in air, which increases the reproducibility and operational simplicity.

Asymmetric organocatalysis is impressive because of its synthetic utility and because it gained its prominent role in such a short period; from 2000 to now! Although it was known for a long time that chiral small organic molecules were able to promote different transformations in a stereoselective fashion, it was not until two seminal reports by few chemists on catalysis by chiral secondary amines that the potential of this approach was realized. Till now, numerous high-quality studies on catalysis by chiral primary and secondary amines (asymmetric aminocatalysis) were reported. This was quickly extended

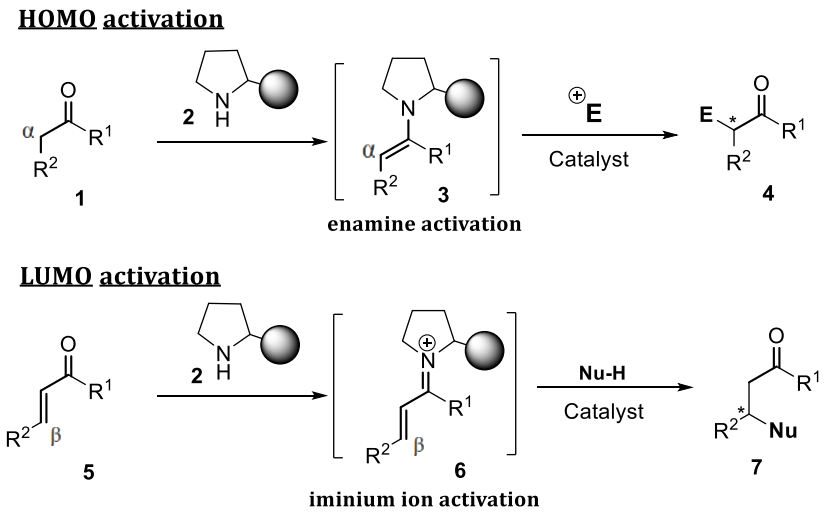
to different organocatalytic activation concepts and still, the scope of this field is on fastest train.

1.2. Development of 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.

1.2.1. The concept of activation mode

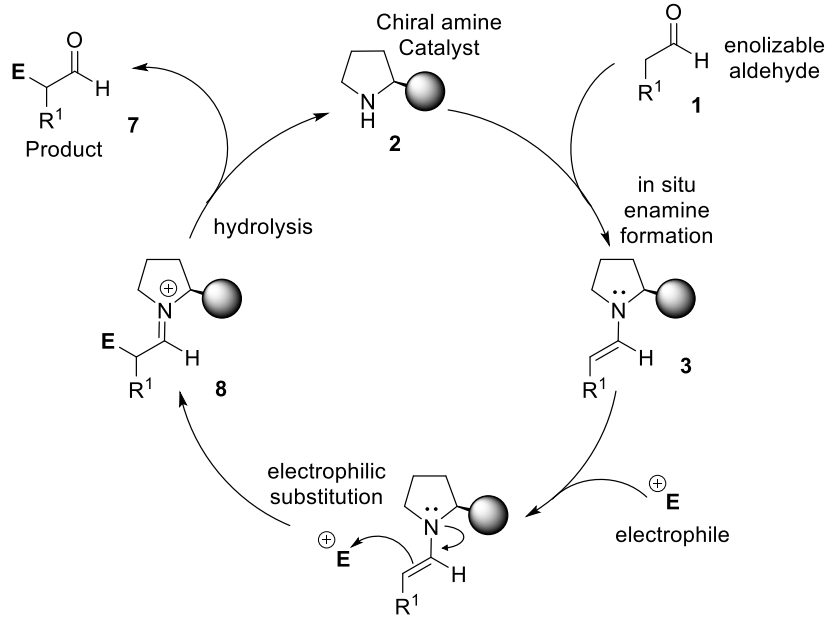
Activation by increasing the HOMO, enolizable carbonyl compounds are activated because of the formation of an intermediate enamine **3**, which increases the HOMO energy thus; α-carbons have a high nucleophilic degree. On the other hand, the effect of LUMO lowering is considered the principle of the underlying activation via iminium ion catalysis. This activation mode is based on the ability of secondary amines to condense reversibly with α,β-unsaturated carbonyl compounds to form an iminium intermediate, which means their β carbon atoms are susceptible to nucleophilic attack due to the LUMO energy decrease (Scheme 1).



Scheme 1: *The concept of activation mode*

1.2.2. Enamine Activation

The condensation between a chiral secondary amine **2** and an enolizable carbonyl compound **1** rapidly affords reactive enamines **3** as nucleophilic intermediates, which can react with an extensive range of electrophiles, representing the corresponding α-functionalization of those carbonyl compound. The enamine has more reactivity as compared to the corresponding enol due to higher energy HOMO. Furthermore, equilibrium favours to the enamine and not iminium ion. This chiral enamine intermediate may attack electrophile from the opposite side to the bulky substituent on the catalyst. Finally, hydrolysis releases the catalyst and delivers an enantioenriched product (Scheme 2).

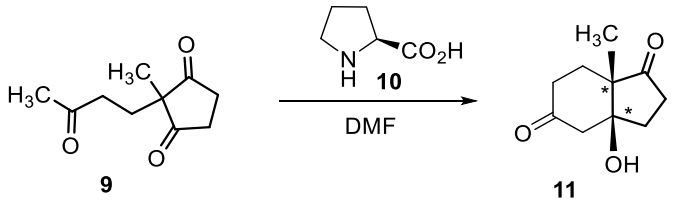


***Scheme 2**: Enamine activation mechanism*

Many important intramolecular reactions, such as aldol reaction, Michael addition, transannular reactions, α-alkylations among others undergo by enamine catalysis. A pioneering reaction was reported in 1971 and is called the Hajos–Parrish reaction (Scheme 3). Zoltan Hajos & David Parrish[15] and Rudolf Weichert, Gerhard Sauer & Ulrich Eder[16] were independently reported an enantioselective intramolecular aldol reaction which

[15] Hajos, Z. G.; Parrish, D. R. *German patent,* **1971**, DE 2102623
[16] Eder, U.; Sauer, G. R.; Wiechert, R. *German patent,* **1971**, DE 2014757

was catalyzed by proline. After this tremendous invention, up to 1997, there were very few reports of 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.



***Scheme 3**: First enantioselective intramolecular aldol reaction*

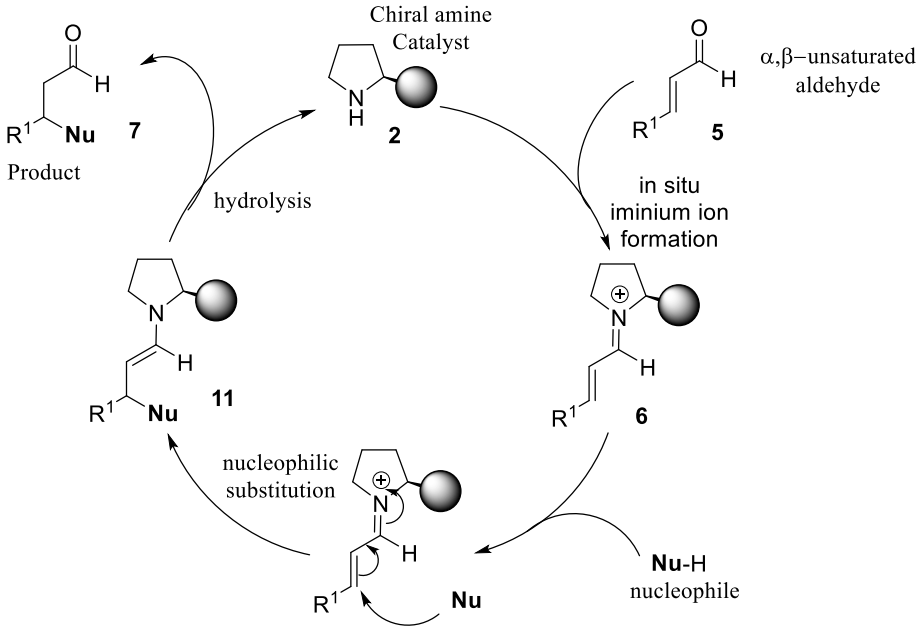
Mechanistically, proline enamine catalysis might be better described as bifunctional catalysis because the amine-containing catalyst typically interacts with a ketone substrate to form an enamine intermediate but simultaneously engages with an electrophilic reaction partner through either hydrogen bonding or electrostatic attraction. This mode of activation has now been used in a wide range of enantioselective carbonyl α-functionalization processes.

1.2.3. Iminium Ion Activation

The LUMO-lowering effect is the underlying activation principle of iminium ion catalysis. [17,18] This aminocatalytic mode is based on the ability of a chiral amine **2** to reversibly condense with α,β-unsaturated carbonyls **5**, rendering their β-carbon atoms more susceptible to nucleophilic attack by lowering the energy of the LUMO 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

[17] Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev*.**2007**,107,5416−5470
[18] Tietze, L. F.; Beifuss, U. Trost, B. M.; Fleming, I. *Eds.; Pergamon: Oxford, U.K.*, **1991**; 2, 341.

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). In the case of enals, the most common catalysts are secondary chiral amines, which can be divided into two large groups: (1) amines substituted with bulky groups and (2) amines with hydrogen bond directing groups.



Scheme 4: *Iminium ion mechanism*

Since the first report from Macmillan in 2000[19], 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-X bonds. Activation of the β-position of the enal allows the attack of distinct nucleophiles. During the last decade carbon, nitrogen, oxygen, sulphur, or phosphorous nucleophiles have been used to form new stereogenic bonds with a 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

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

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[20,21] 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

1.2.4. Remote functionalization in aminocatalysis

Since the early work in the field of amine catalysis,[22] activations via iminium and enamine ion have achieved a high degree of maturity, because of this, they are currently considered as the most used methodologies for the enantioselective functionalization of carbonyl compounds in positions β and α respectively. Through these two classical methods of activation, amine catalysis has found a new direction in the new modes of activation called dienamine,[23] linear trienamine,[24] cross trienamine[25], tetraenamine, and vinylogous iminium ion [26] (Scheme 5,6)

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

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

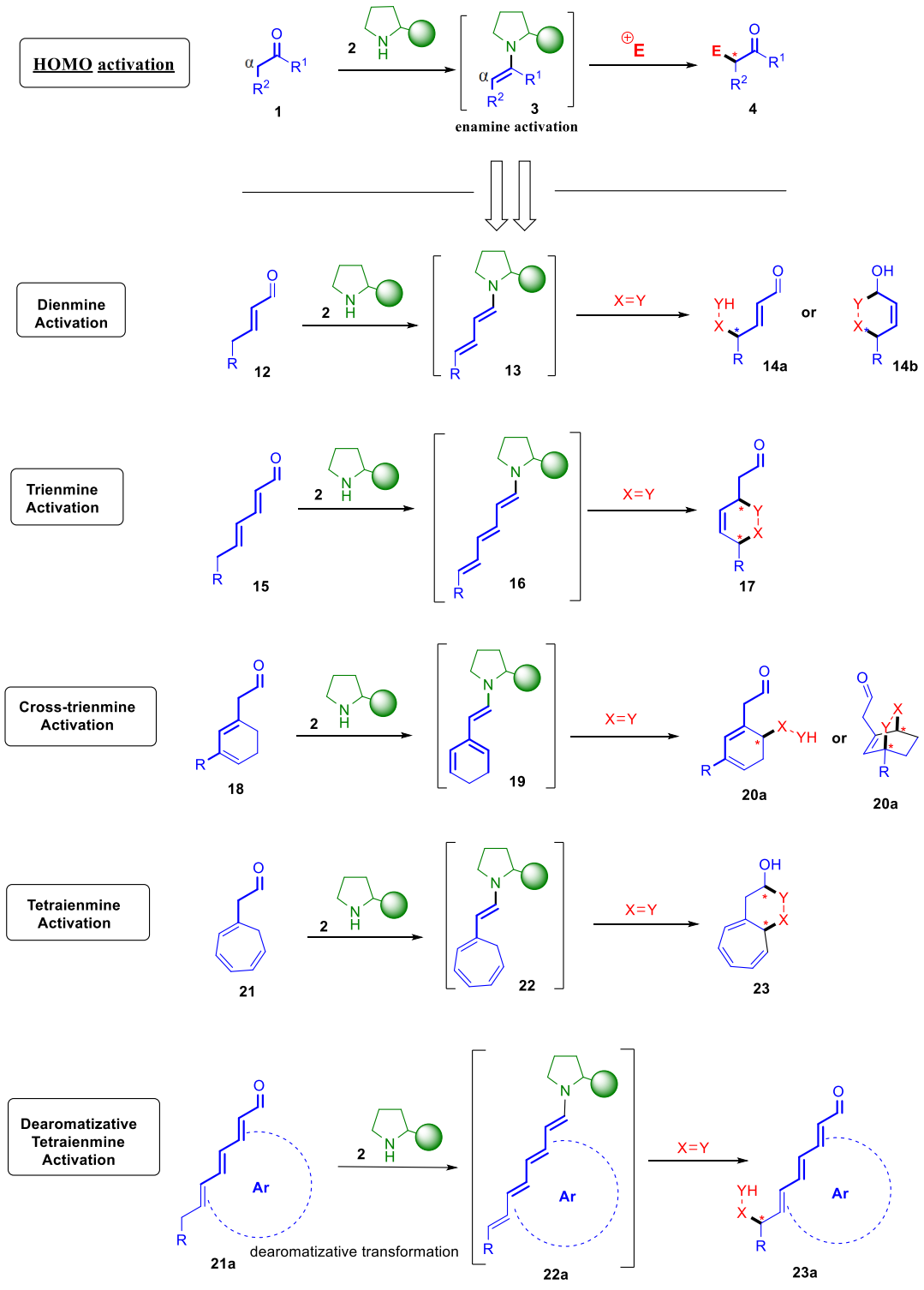
[22] List B.; Lerner R. A.; Barbas C. F. *J. Am. Chem. Soc.* **2000**, 122, 2395.

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

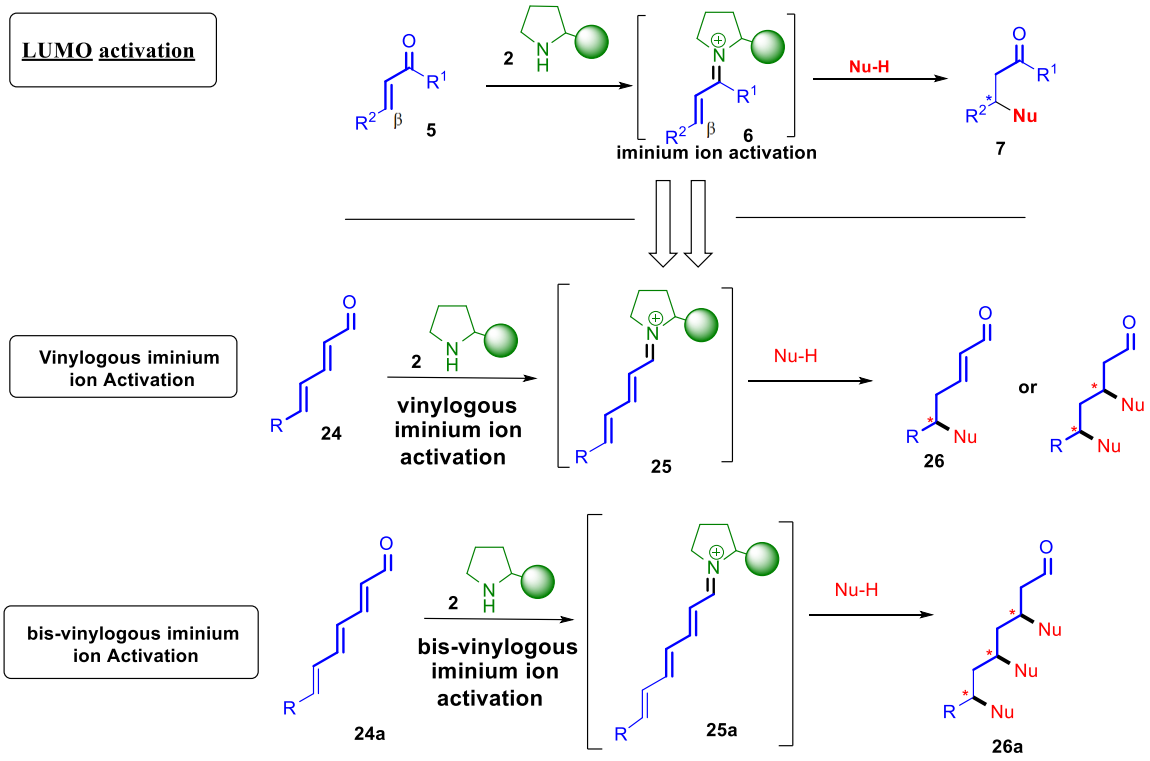
[24] (a) Arceo, E.; Melchiorre, P.; *Angew. Chem. Int. Ed*. **2012**, 51, 5290-5292; (b) Jia, Z.-J., Jiang, H.; Li ,J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2011**, 113, 5053-5061; (c). Jia, Z.-J.; Zhou, Q.; Zhou Q.-Q.; Chen P.-Q.; Chen 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.

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

[26] (a) Tian, X.; Liu, Y.; Melchiorre, P. Angew. *Chem. Int Ed*. **2012**, 51, 6439-6442; (b) Hayashi, Y.; Okumara, D.; Umemiya, S.; Uchimaru, T. *ChemCatChem,* **2012**, 4, 959-962; (c) Tian, X.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2013**, 52, 5360-5363; (d) Dell´Amico, L.; Albrecht, Ł.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2013**, 135, 8063-8070; (e) Halskov, K. S.; Naicker, T.; Jensen, M. E.; Jørgensen, K. A. *Chem. Commun*, **2013**, 49, 6382-6384; f) Lear, M. J.; Hayashi, Y. *ChemCatChem*, 2013, **5**, 3499-3501.



Scheme 5: *Remote functionalization of HOMO activation in aminocatalysis*



Scheme 6: *Remote functionalization of LUMO activation in aminocatalysis*

1.3. The 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.

1.3.1. The Diaryl prolinol ethers

Based on the diaryl prolinol silyl ether system,[27] several studies on enamine-mediated transformations of saturated aldehydes have resulted in the introduction of different functionalities into the α-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.[28] 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

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

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

shielding of the β-position, the stereo-induction is achieved at the remote ε-position of the original aldehyde (Figure **6**).

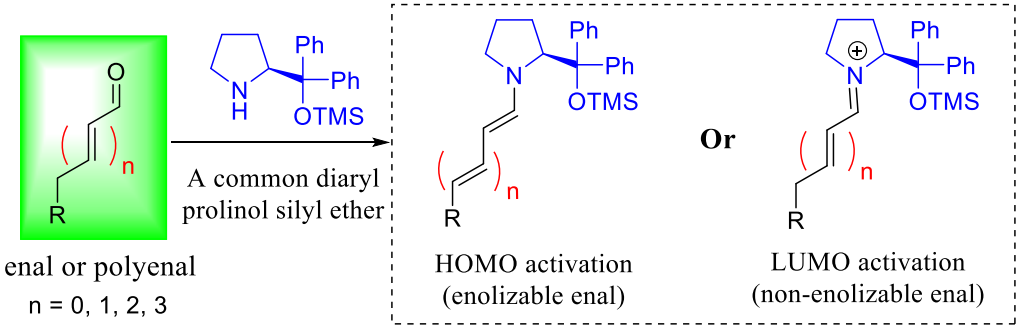


Figure 6: *Diaryl prolinol silyl ether in aminocatalysis*

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 [Figure 6, 4 (trienamine activation)].

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.

1.3.2. Cinchona based alkaloids

Cinchona alkaloids[29] are simple organic molecules generously provided by nature, have historically played a privileged role in asymmetric catalytic synthesis.[30] The first organocatalytic enantioselective reaction was carried out exactly one century ago by Georg Bredig and Paul S. Fiske using quinine and quinidine as chiral inducers.[31] About 50 years later, Horst Pracejus demonstrated the possibility of reaching high levels of enantioselectivity in the asymmetric catalytic preparation of chiral molecules, again using a cinchona derivative as the catalyst.[32] The pioneering studies by Hans Wynberg in the 1970s began a new era for asymmetric catalysis using cinchona derivatives. He demonstrated how the basic bridge-head nitrogen atom in the quinuclidine core can be used in general Brønsted base catalysis.[33] This privileged molecular scaffold has also had an impact on the field of asymmetric aminocatalysis. This influence is because the introduction of a primary amine moiety recently led to the identification of 9-epi-amino cinchona derivatives as effective covalent-based activators of hindered carbonyl compounds.

Asymmetric aminocatalysis exploits the potential of chiral primary and secondary amines to catalyse asymmetric reactions. It has greatly simplified the functionalization of carbonyl compounds while ensuring high enantioselectivity. Recent advances in cinchona-based primary amine catalysis have provided new synthetic opportunities and conceptual perspectives for successfully attacking major challenges in carbonyl compound chemistry, which traditional approaches have not been able to address (Figure 7).

The reliability and impressive versatility of the cinchona amines have motivated researchers toward more ambitious objectives, providing a general and solid catalytic platform from where successfully attacking those major challenges connected with the preparation of chiral molecules that cannot be addressed by traditional approaches. It is

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[29] Melchiorre, P., *Angew. Chem. Int. Ed.* **2012**, *51*, 9748-9770

[30] a) Song, C. E., *Wiley-VCH, Weinheim*, **2009**; b) Marcelli, T.; Hiemstra, H., *Synthesis*, **2010**, 1229-1279; c) T. P. Yoon, T. P.; Jacobsen, E. N., *Science*, **2003**, *299*, 1691-1693

[31] Bredig, G.; Fiske, P. S., *Biochem. Z,.* **1912**, *46*, 7-23.

[32] Pracejus, H.; Liebigs J., *Ann. Chem.***1960**,*634*, 9-22.

[33] a) Hiemstra, H.; Wynberg, H., *J. Am. Chem. Soc*. **1981**, *103*, 417-430; b) Wynberg, H., *Top. Stereochem.*, **1986**, *16*, 87-129.

clear, however, that, to sustain future methodological innovation, a deeper understanding of the complex mechanisms associated with the multistep processes inherent to primary aminocatalysis is required. This is particularly true for the cinchona-based primary amine catalysts. The lack of information about the active conformer of this catalyst class stands in sharp contrast to the extensive experimental studies that have delineated its reactivity. It is anticipated that the "tools of the trade" of traditional physical organic chemistry will play a decisive role shortly to elucidate reaction mechanisms and elements of stereocontrol.[34] To fully exploit the potential of this nature-inspired catalyst class, it will thus be crucial to combine computational methods, spectroscopic measurements and X-ray crystallography to detect, analyse, and characterize the reactive intermediates involved in cinchona-based primary amine catalysis.

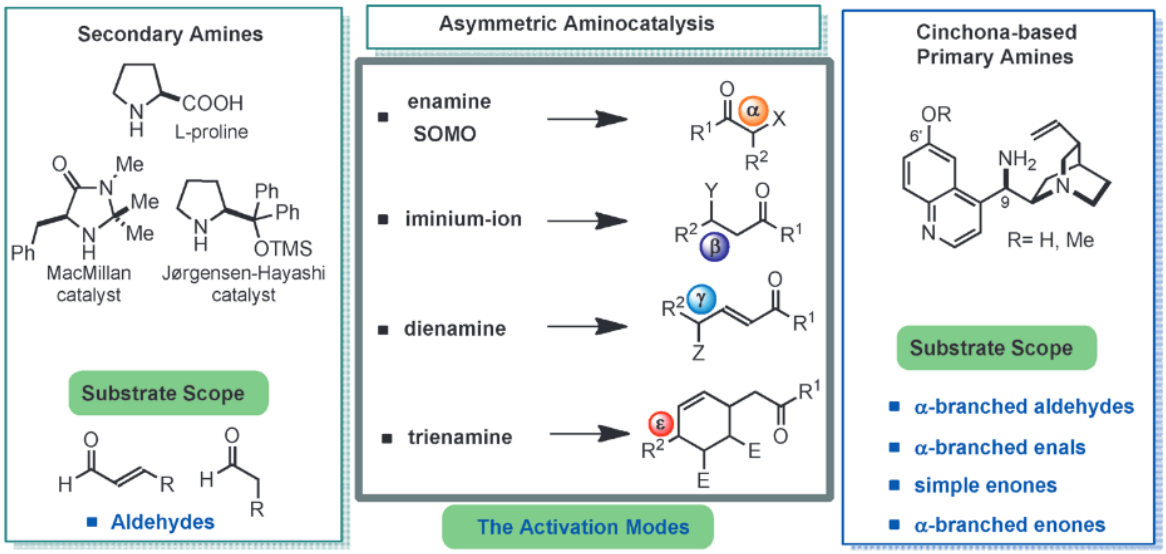


Figure 7: *Cinchona based alkaloids in aminocatalysis*

1.3.3. Bifunctional Aminocatalysts.

The catalyst that operates aminocatalyst as well as single hydrogen bond interaction with the electrophile is term as bifunctional catalyst.[35] In the field of organic chemistry proline is one of the most important amino acids and it plays a vital role in asymmetric synthesis. In 1971, Hajos-Parrish-Eder-Sauer-Wiechert reaction launched the discovery of

[34] Knowles, R. R.; Jacobsen, E. N., *Proc. Natl. Acad. Sci. USA,* **2010**, *107*, 20678-20685.
[35] Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2014,** 20, 358-368.

proline. After 2000, the intramolecular aldol reaction reported by List, Lerner, and Barbas explain the potential of proline and its derivatives (Figure **8**).

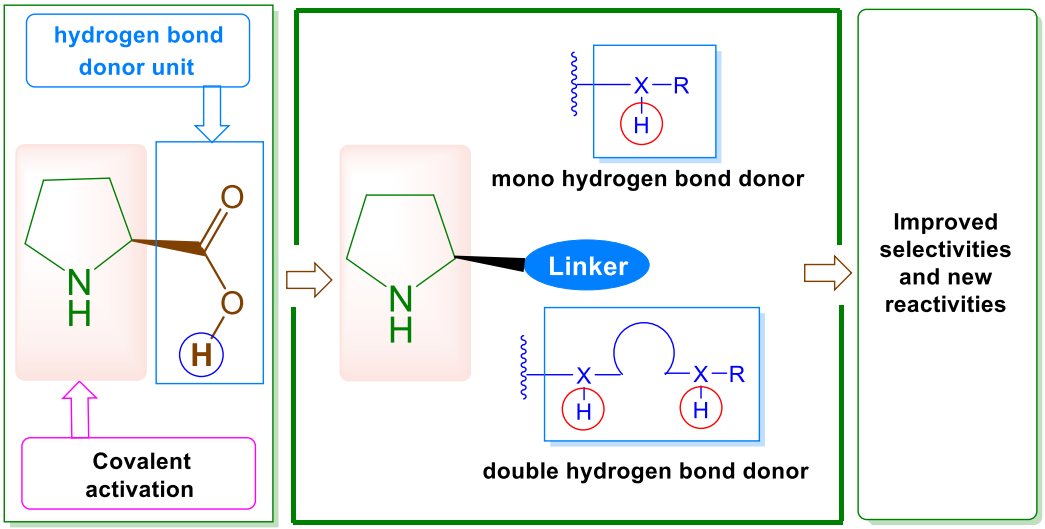


Figure 8: *From proline to new proline-derived hydrogen-bond-donating aminocatalysts.*

In the past decade, the work on hydrogen bond donor aminocatalysts has been started; which shows that this bifunctional aminocatalysis is widely used in asymmetric synthesis. These proline derived moieties (Figure 8) are designed by considering the factors, which are (1) the length and flexibility of the linker, (2) the acidity of the Brønsted acid (X-H) and (3) complementarity between the molecular recognition moiety and recognized substrate. These catalysts are categorized into two groups. mono hydrogen bond donors and double hydrogen bond donors.

From the literature study, it is concluded that the area of research is consistently growing and has tremendous scope in future work.

A. Mono Hydrogen Bond Donors

Proline derived aminocatalysts with the additional ability of hydrogen bonding catalyst achieved great success in the field of organocatalysis. Consequently, a series of mono hydrogen donating catalysts were synthesized by *N*-protected proline and evaluated in a short period. All these catalysts have different activation properties concerning the change in the corresponding structure (Figure **9**).

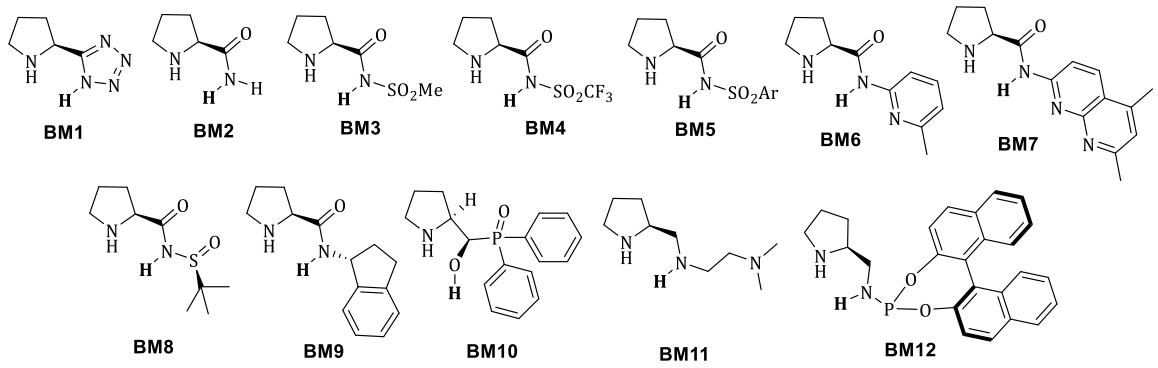


Figure 9: *Mono hydrogen-bond-donating aminocatalysts.*

Catalyst	Role
BM1	Suitable for both enamine & iminium ion activation[36]
BM2	Improving enantioselectivity[37]
BM3	Increases the acidity of N-H & are suitable for both aldehyde and ketone substrates[38,39]
BM4	
BM5	
BM6	Dual hydrogen-bond donor–acceptor aminocatalysts[38]
BM7	
BM8	Catalysts for additional stereocenters[39]
BM9	
BM10	For Benchmark reaction[40]
BM11	
BM12	

Table 1: *Bifunctional aminocatalysts and their roles*

[36] Cobb, J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004,** 558; b) A. Cobb, A. J.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun*. **2004,** 1808; c) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem*. **2005**, 3, 84;

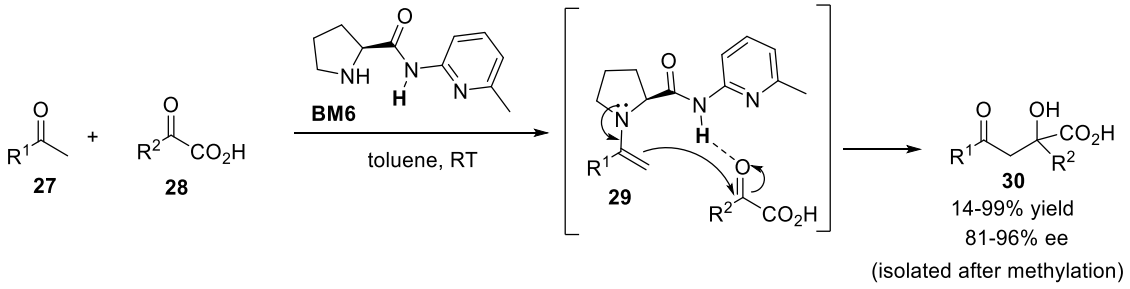
[37] a) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004,** 126, 4790; b) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006,** 128, 7442; c) Zhang, X.-M.; Wang, M.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Zhang, S.-Y.; Zhang, F.-M. *Synlett* **2008,** 2831.

[38] a) Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, Org. Lett. 2006, 8, 1263; b) X.-Y. Xu, Z. Tang, Y.-Z. Wang, S.-W. Luo, L.-F. Cun, L.-Z. Gong, J. Org. Chem. 2007, 72, 9905; c) M. L. Clarke, J. Fuentes, Angew. Chem. 2007, 119, 948; Angew. Chem. Int. Ed. 2007, 46, 930.

[39] a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Tetrahedron* **2011,** 67, 4412; b) Almasi, D.; Alonso, D. A.; Balaguer, A.-N.; Njera, C. *Adv. Synth. Catal*. **2009,** 351, 1123; c) Chen, J.-R.; An, X.-L.; Zhu, X.-Y.; Wang, X.-F.; Xiao, W.-J. *J. Org. Chem*. **2008**, 73, 6006.

[40] a) Dahlin, N.; Bøgevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004,** 346, 1101; b) Wang, W.; Wang, J.; Li, H. *Angew. Chem.* **2005,** 117, 1393; c) Wang, J.; Li, H.; Lou, B.; Zu, L.-S.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, 12, 4321.

Some proline-derived catalysts with heteroaromatic rings, (Figure 9) generates aminocatalysts with unique dual hydrogen-bond donor-acceptor properties (Scheme 7).[41] These catalysts are especially advantageous in reactions involving substrates with a similar dual hydrogen-bond donor-acceptor capability. The possibility of creating multiple hydrogen bonds between catalyst and substrate can be beneficial for the reaction stereoselectivity since stronger molecular recognition often leads to superior enantiodifferentiation in asymmetric catalysis. [42]



Scheme 7: *Dual hydrogen-bond donor-acceptor aminocatalysts.*

B. Double Hydrogen Bond Donors

Double hydrogen bonding catalysts (Figure **10**) play an important role in the evolution of bifunctional organocatalysis. These catalysts can be categorized by two important features- (1) the type of double hydrogen bonding frames, which determines the acidity of the hydrogen bond donors. And (2) the distance between the two hydrogen bonding units, which is responsible for the geometry of the transition state and proper contiguous positioning of the two reactants.

Since the discovery of the ability of proline to catalyze stereodifferentiating transformations, many other aminocatalysts capable of fascinating in hydrogen-bonding interactions with the substrate have been designed and synthesized. The development in this field of research in recent few years is tremendous, and the number of different

[41] Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z; *Org. Lett.* **2006**, 8, 1263; (b) Xu, X.-Y.; Tang, Z.; Wang, Y.-Z.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Org. Chem.* **2007,** 72, 9905; (c) Clarke, M. L. Fuentes, J. *Angew. Chem.* **2007,** 119, 948;

[42] Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006,** 128, 9624; b) Lu, A.-D.; Wu, R.-H.; Wang, Y.-M.; Zhou, Z.-H.; Wu, G.-P.; Fang, J.-X.; Tang, C.-C. *Eur. J. Org. Chem*. **2010,** 2057; c) Zeng, Z.-P.; Luo, P.; Jiang, Y.; Liu, Y.; Tang, G.; Xu, P.-X.; Zhao, Y.-F.; Blackburn, G. M. *Org. Biomol. Chem.* **2011,** 9, 6973;

hydrogen-bonding moieties incorporated in the structure of secondary aminocatalysts is constantly growing.[43,44]

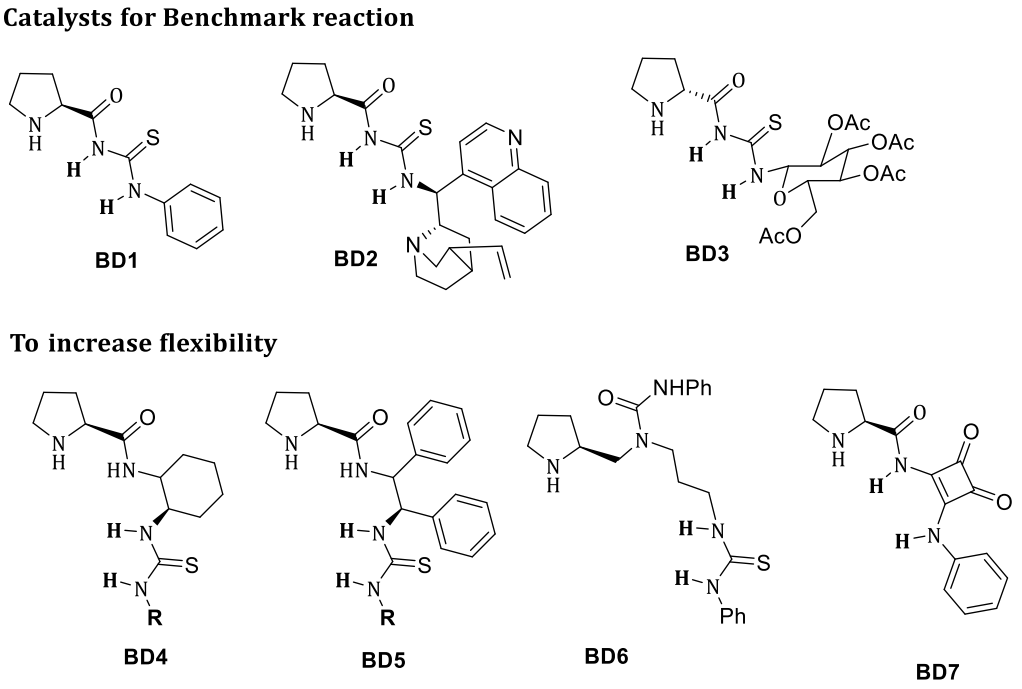


Figure 10: *Some examples of (thio)urea containing double hydrogen-bond-donating aminocatalysts.*

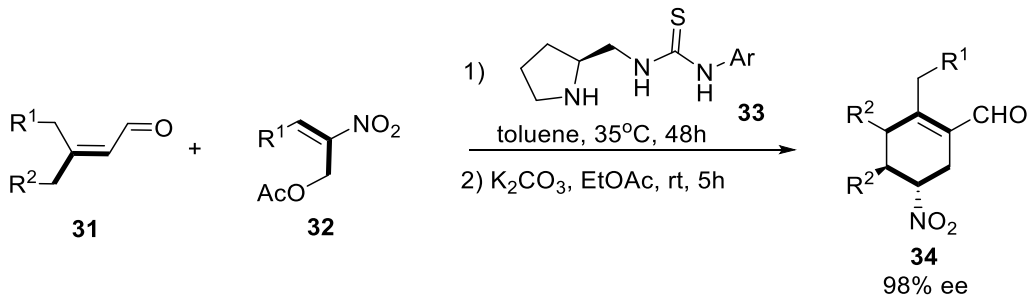
The rapid progress in this field and continuous resolution of different research groups around the world have made the Michael addition of carbonyl compounds to nitroolefins one of the most studied reactions in the field of asymmetric catalysis. Furthermore, the direct aldol reaction between ketones and aromatic aldehydes has also attracted much consideration. Mostly, such a heightened research activity also give rise to the evolution of new reaction profiles and the passport of innovative stereocontrolled

[43] (a) Ban, S.; Zhu, X.; Zhang, Z.; Xie, H.; Li, Q. *Eur. J. Org. Chem.* **2013,** 2977; (b) Chen, J.-R.; Cao, Y.-J.; Zou, Y.-Q.; Tan, F.; Fu, L.; Zhu, X.-Y.; Xiao, W.-J. *Org. Biomol. Chem.* **2010,** 8, 1275; c) Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C.; *Org. Biomol. Chem*. **2009,** 7, 3141.

[44] (a) Bai, J.-F.; Xu, X.-Y.; Huang, Q.-C.; Peng, L.; Wang, L.-X. *Tetrahedron Lett.* **2010,** 51, 2803; b) Wang, Q.; Peng, L.; Fu, J.; Huang, Q.; Wang, L.; Xu, X. *Arkivoc* **2010,** 340; c) Fu, J.-Y.; Xu, X.-Y.; Li, Y.-C.; Huanga, Q.-C.; Wang, L.-X. *Org. Biomol. Chem.* **2010,** 8, 4524; d) Fu, J.-Y.; Huang, Q.-C.; Wang, Q.-W.; Wang, L.-X.; Xu, X.-Y. *Tetrahedron Lett.* **2010,** 51, 4870; e) Fotaras, S.; Kokotos, C. G.; Tsandi, E.; Kokotos, G. *Eur. J. Org. Chem.* **2011,** 1310; f) Carley, A. P.; Dixon, S.; Kilburn, J. D. *Synthesis* **2009**, 2509; for a related study, see: g) Fotaras, S.; Kokotos, C. G.; Kokotos, G.; *Org. Biomol. Chem.* **2012,** 10, 5613.

transformations. It is doubtless that, in the years to come, this direction will become more noticeable in the literature. Aftereffect, new bifunctional catalysts introduced will treasure trove new inspiring applications showing their true unrealized potential in asymmetric synthesis.

In the recent work on the bifunctional catalyst, Ying-Chun Chen *et al.* did asymmetric α,γ-regioselective [3+3] formal cycloadditions of α,β- unsaturated aldehydes. (Scheme 8) This cycloaddition is reported first time in the literature. These reactions proceeded through a cloak Michael addition−Michael addition sequence via a significant cascade dienamine−dienamine catalysis of a chiral secondary amine, and multifunctional cyclohexene derivatives were generally designed in moderate yields with magnificent stereoselectivity after simple treatment with K_2CO_3.[45]



Scheme 8: *Double hydrogen-bond aminocatalysts.*

1.4. Future Challenges in Organocatalysis

Organic chemists have been attracted by the seminal reports on secondary amine catalysis by List, Lerner, Barbas, MacMillan, Chen, and Jørgensen. The rediscovery of enamine chemistry and its application in catalytic enantioselective reactions had greater consequences than expected. The initial results of a few leading research groups prompted the explosion of organocatalysis, a fast-growing research field with a scope that now goes beyond amino-catalyzed reactions. However, chiral amine catalysts play a key role in this unstoppable stream of discovery, and the combined efforts of many highly skilled individuals have turned asymmetric aminocatalysis into a well-established and reliable synthetic strategy. This approach has great potential since organocatalysts are generally

[45] Xiao, W.; Yin, X.; Zhou, Z.; Du, W.; Chen, Y.-C. *Org. Lett.* **2016**, *18*, 116−119

readily available, very robust, and less toxic than organometallic complexes. It is important to stress the operational simplicity of these reactions: Limited specialist equipment is required since reactions usually take place under very mild conditions, do not need inert atmospheres and might be carried out under neat conditions or in environmentally friendly solvents. Furthermore, several examples have demonstrated how aminocatalyzed reactions may be readily scaled-up without detrimental effects on the yield or enantiomeric excess.

As is true of any field that has reached a certain stage of maturity, new developments will focus on more ambitious objectives, thus increasing the high standards of innovation and practicality. There is now a deep understanding of the complex mechanisms associated with the multistep processes inherent to aminocatalysis. This knowledge is beginning to form a reliable platform for the rational design of new catalysts and new reactions. Recent studies have demonstrated that it is now possible to engineer and prepare specific catalysts to efficiently address important issues relating to the synthesis of challenging and previously inaccessible target molecules. Moreover, asymmetric aminocatalysis is becoming an invaluable tool for the direct preparation of enantiopure complex molecules through domino and multicomponent reactions. Such regulated catalytic cascade sequences, which are typical of biological systems, do not require time-consuming and costly operations, such as isolation or purification of intermediates. In this context, this strategy may be a key element in the design of sustainable processes for the synthesis of drugs and relevant biologically active compounds.[46]

Finally, a critical goal for the continued expansion of aminocatalysis will be the design and implementation of new activation concepts to enable previously unknown transformations to be carried out. Thousands of amazing results are reported in aminocatalysis and yet a lot to come as the investigation is still going on.[47]

[46] Marcia de Figueiredo, R..; Christmann, M., *Eur. J. Org. Chem*. **2007**, 2575-2600
[47] Melchiorre. P., Marigo, M., Carlone, A., Bartoli, G., *Angew. Chem. Int. Ed*. **2008**, 47, 6138-6171

1.5. Asymmetric Catalytic Cascade Reactions: A shortcut for the diversification of Privileged structures

With the increasing concerns about chemical pollution and sustainability of resources, among the significant challenges facing synthetic chemists are the development and application of elegant and efficient methods that enable the concise synthesis of natural products, drugs, and related compounds in a step-, atom- and redox-economic manner. One of the most effective ways to reach this goal is to implement reaction cascades that allow multiple bond-forming events to occur in a single vessel. This thesis included our progress on the rational design and strategic application of asymmetric catalytic cascade reactions in constructing diverse scaffolds and synthesizing complex chiral molecules. This type of research is aimed at developing robust cascade reactions for the systematic synthesis of a range of interesting molecules that contain structural motifs prevalent in natural products, pharmaceuticals, and biological probes. The strategies employed to achieve this goal can be classified into three categories: bifunctional base/Brønsted acid catalysis, covalent aminocatalysis/*N*-heterocyclic carbene catalysis, and asymmetric organocatalytic relay cascades. Using rationally designed substrates with properly reactive sites, chiral oxindole, chroman, tetrahydroquinoline, tetrahydrothiophene, and cyclohexane scaffolds were successfully assembled under bifunctional base/Brønsted acid catalysis from simple and readily available substances such as imines and nitroolefins. It is also demonstrated that some of these reactions are highly efficient since catalyst loadings as low as 1 mol% can promote the multistep sequences affording complex architectures with high stereoselectivities and yields. Furthermore, one of the bifunctional base/Brønsted acid-catalyzed cascade reactions for the synthesis of chiral cyclohexenes has been used as a key step in the construction of the tetracyclic core of lycorine-type alkaloids and the formal synthesis of α-lycorane. Guided by the principles of covalent aminocatalysis and *N*-heterocyclic carbene catalysis, many chemists synthesized chiral piperidine, indole and spirooxyindoles, coumarins, cyclohexane, bicyclic scaffolds, cyclobutane derivatives, etc. The synthesis of chiral cyclobutanes and pyrroloindolones showed unprecedented reactivity of substrates and catalysts. The development of the strategy of asymmetric organocatalytic relay cascades has provided a useful tool for the controlled synthesis of specific diastereomers in complex molecules.

1.5.1. Structural importance in a cascade reaction

Some structural motifs, such as indole, spirooxindole, chroman, piperidine, pyrazole etc. are widely distributed in pharmaceutical compounds and complex natural products. To this end, chemists are actively involved in the design, development, and application of catalytic cascade reactions to collectively construct those privileged scaffolds with multiple stereocenters. This bioactive natural products and drug molecules serve as starting points for the exploration of asymmetric catalytic cascade reactions.[48] During this process, the comprehensive investigation of known and specially tailored reagents and catalysts provides valuable insights into understanding reaction mechanisms and designing new cascade reactions. Furthermore, a considerable number of natural products exist as diastereomers, and 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.

1.5.2. The combination of one-pot strategy with aminocatalysis

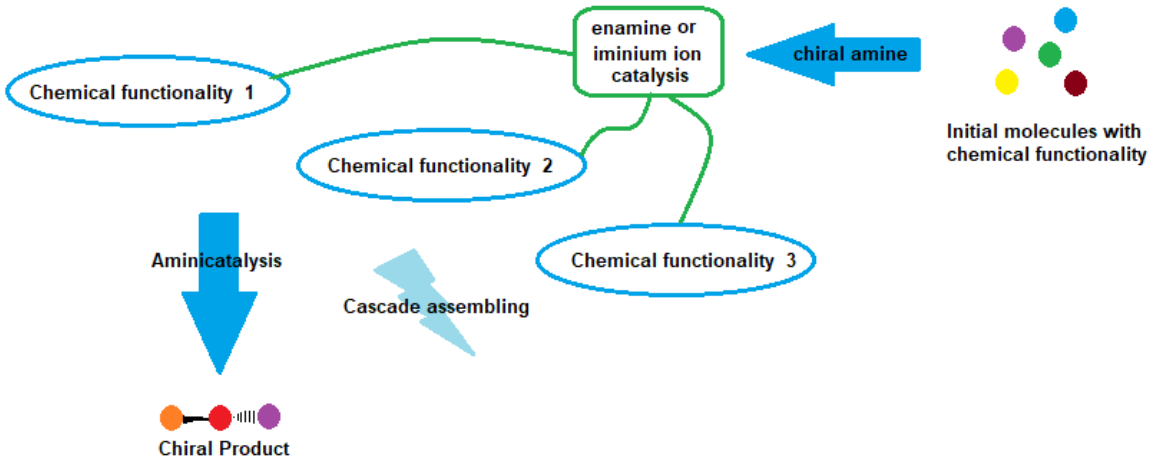


Figure 11: *Cascade assembly in aminocatalysis*

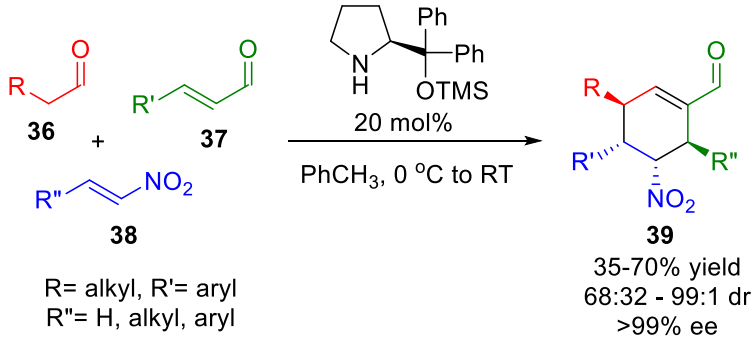
[48] Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Last 25 Years. J. Nat. Prod. 2007, 70, 461−477.

Chiral amine-mediated organocatalytic cascade reactions have become a benchmark in contemporary organic synthesis, as witnessed by several cascade processes developed in the past two decades. The great success is attributed to two unique interconvertible activation modes, enamine, and iminium ion activations. Enamine catalysis has been widely applied for the α-functionalization of aldehydes and ketones (Scheme 2). Mechanistically, dehydration between a chiral amine and the carbonyl of an aldehyde or ketone generates an intermediate, which undergoes an enantioselective α-substitution or nucleophilic addition reaction to produce respective iminium intermediate (Scheme 3). Hydrolysis affords the products and meanwhile, releases the chiral amine catalyst (Figure **11**).

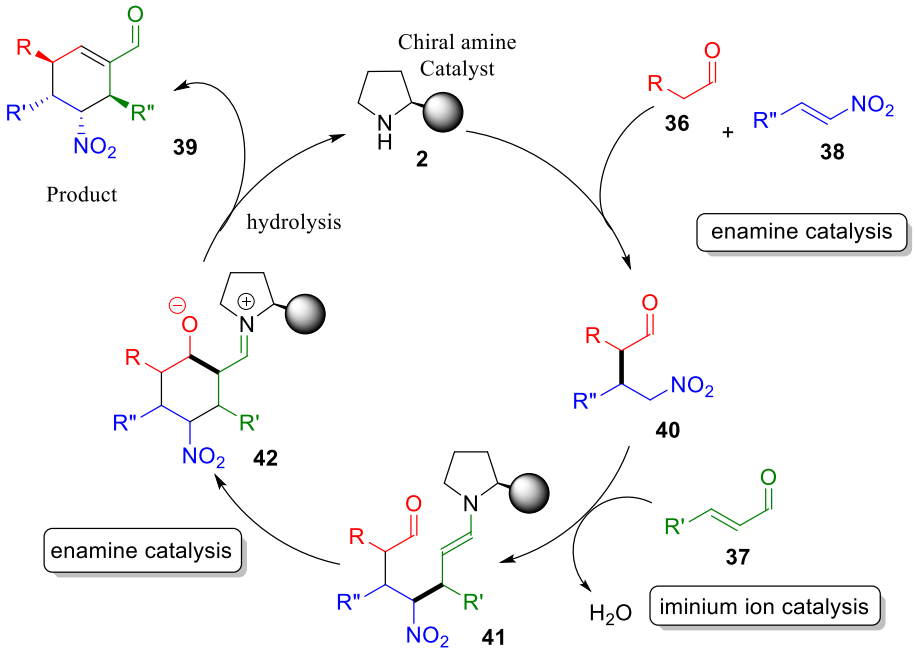
Beyond the organic chemist's initial imagination, two unique interconvertible enamine and iminium ion activation modes have produced several unprecedented powerful cascade processes in the formation of diverse complex structures with high efficiency and excellent stereoselectivities. This not only expands the scope of amino catalysis significantly but more important, affords new and efficient synthetic methods in organic synthesis. It is expected that new cascade reactions with activation modes will continue to be developed to meet the synthetic demand. Also, beyond the original domain of organocatalysis, powerful cycle-specific catalyzes, in which cycle-specific catalysts are employed discretely in iminium and enamine steps, have been established as effective strategies to achieve new organic transformations. Furthermore, chiral amino catalysts have been employed in cascade reactions mediated by new SOMO catalysis. However, the scope of the cascade reactions mediated by cycle-specific and SOMO catalysis is still limited. More important, further efforts also need to be made in larger-scale synthesis and possible applications in the total synthesis of natural products. Among existing problems, it is also realized that, for example, in general, high catalyst loadings are required for effective transformations. Therefore, the development of new and more efficient catalysts and new activation modes to overcome the obstacles is a fundamentally important but challenging task for organic chemists.

An outstanding triple organocatalytic cascade (or multi-component) reaction was reported by Raabe et al. in 2006. Linear aldehydes **36**, nitroalkenes **37** and *α*,*β*-unsaturated aldehydes **38** could be condensed together organocatalytically to afford *tetra*-substituted

cyclohexane carbaldehydes **39** with moderate to excellent diastereoselectivity and complete enantiocontrol (Scheme 9). The transformation is mediated by the readily available proline-derived organocatalyst.[49]



Scheme 9: *A triple cascade reaction*



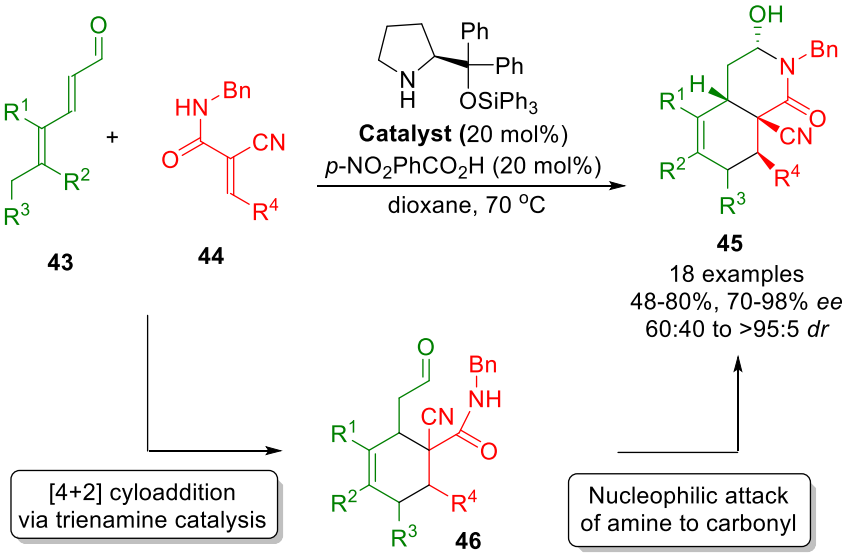
Scheme 10: *Mechanism of triple cascade reaction*

The transformation was proposed to proceed via a Michael addition/Michael addition/aldol condensation sequence (Scheme 10). In the first step, Michael addition of aldehyde **36** to nitroalkene **38** occurs through enamine catalysis, yielding nitroalkane **40**. Condensation of *α,β*-unsaturated aldehyde **37** with the organocatalyst then facilitates the

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

conjugate addition of **40** to give intermediate enamine **41**, which is prone to undergo an intramolecular aldol condensation to iminium species **42**. Organocatalyst **2** is regenerated by hydrolysis, along with the product **39**, thus closing the triple cascade cycle.

Also, in 2014, Jørgensen and coworkers 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 **43** with cyacnoacrylamides **44** in presence of protected prolinol catalyst generates the [4+2] cycloadduct **46**, which through an intramolecular ring-closing reaction leads to the hydroisoquinolines **45** with excellent stereocontrol (Scheme 11).[50]



Scheme 11: *Cascade reaction*

In the last 8 years, around 25 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 in this field.

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

1.5.3. Cooperative Catalysis

The term "Cooperative Catalysis" is used when two catalysts and two catalytic cycles work in concert to create a single new bond. In another way; "when the nucleophile and electrophile are simultaneously activated by two separate catalysts to afford a single chemical transformation" this type of reaction is called cooperative catalysis.

Organocatalysis and metal catalysis have deepened the scientific knowledge about their activation modes and synthetic utility. However, this development has also urged researchers to objectively examine both the pros and cons of either form of catalysis, thus searching for novel solutions to tap into the strengths of each catalysis system to access novel molecular structures with high diastereo- and enantiocontrol (Figure **12**).

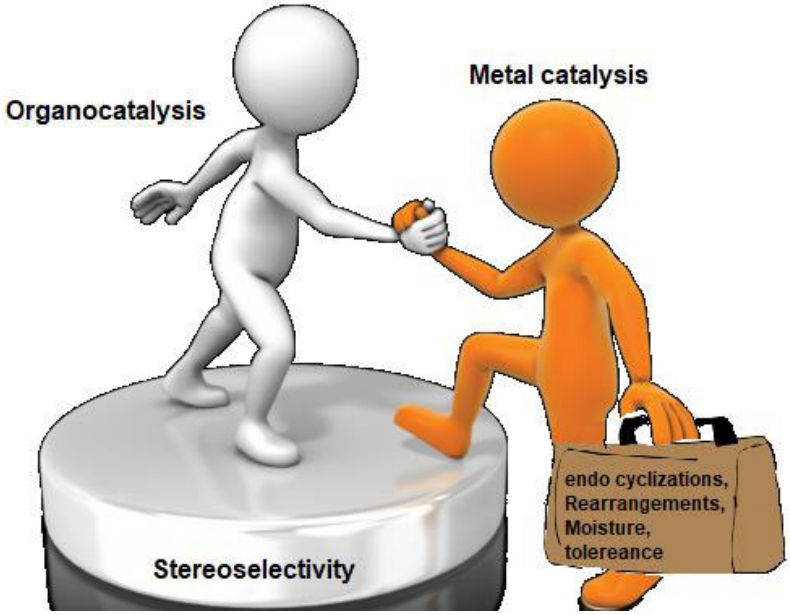


Figure 12: *Cooperative catalysis*

Organocatalysis on one hand, has witnessed a stunning growth especially in the main subareas of chiral amine catalysis including secondary amine catalysis based on proline and oxazolidinone scaffolds, and more recently also primary amine catalysis to activate both saturated and unsaturated aldehydes and ketones through various activation modes such as enamine and iminium ion intermediates.[51]

[51] a) List, B. *Acc. Chem. Res*. **2004**, 37, 548–557; b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B.; *Chem. Rev*. **2007**, 107, 5471–5569; c) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, 107, 5416–5470.

Gold catalysis

Gold catalysis[52] has seen tremendous growth in accessing highly challenging molecular structures based on its alkynophilicity as a carbophilic Lewis acid.[53] This intrinsic π-activation property of gold catalysis, either in Au[I] or Au[III] species, has shown remarkable progress in various cyclization reactions, such as single or multiple C-C bond formations and C–heteroatom bond-forming reactions in the same reaction flask. Moreover, gold catalysis confers nonclassical cationic type intermediates, which in many cases allow access to cationic rearrangement cascades of the Wagner–Meerwein type,[54] 1,2-alkyl shifts, for example,[55] to form interesting molecular frameworks. Another key property, especially in Au[I] catalysis, is the general tolerance of the catalytic system towards moisture and air, which makes a combination with an organocatalytic system highly feasible under open flask conditions.

There are indeed certain shortcomings in both organo- and gold catalysis that can be resolved in a binary system utilizing both forms of catalysis. While organocatalysis is highly useful in accessing molecular structures with excellent enantiocontrol, in many cases the reactions will require the strict presence of certain functional groups such as aldehydes, α,β-unsaturated aldehydes or a nitro moiety to allow organocatalytic activation. Moreover, alkyne activation is extremely rare in organocatalysis apart from hydroacylation reactions catalyzed by *N*-heterocyclic carbenes, which are also highly substrate-dependent.[56] Gold catalysis, in contrast, does provide good solutions for activating alkyne-containing substrates and most importantly, access to cyclization modes unseen in organocatalysis, such as macrocycle formation. While recent reports are utilizing either chiral ligands,[57] or an asymmetric counterion directing strategy to allow asymmetric

[52] a) Hashmi, A. S. K.; Hutchings, G. J.; *Angew. Chem.* **2006,** 118, 8064–8105; *Angew. Chem. Int.* Ed. 2006, 45, 7896–7936; b). Hashmi, A. S. K.; *Chem. Rev*. **2007,** 107, 3180–3211

[53] Furstner, A.; Davies, P. W.; *Angew. Chem.* **2007**, 119, 3478–3519; Angew. Chem. Int. Ed. 2007, 46, 3410–3449;

[54] Kirsch, S. F.; *Synthesis* **2008**, 3183–3204.

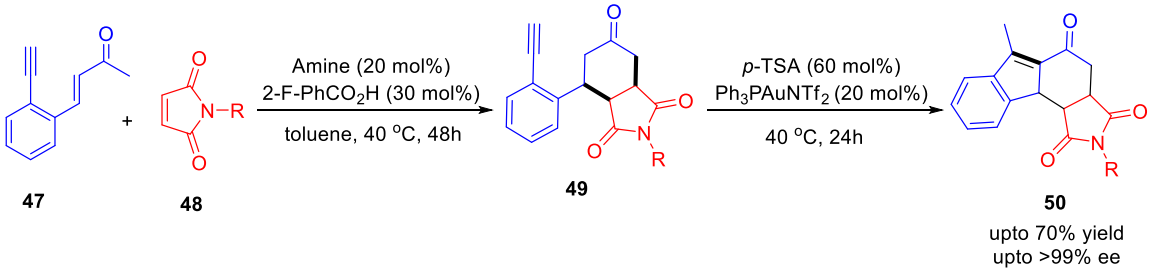
[55] Crone, B.; Kirsch, S. F.; *Chem. Eur. J.* **2008**, 14, 3514–3522.

[56] a) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F.; *J. Am. Chem. Soc.* **2009**, 131, 14190–14191; b Biju, A. T.; Glorius, F.; *Angew. Chem.* **2010**,122, 9955–9958; *Angew. Chem. Int. Ed.* **2010**, 49, 9761–9764; c) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, 132, 5970–5971.

[57] a) Widenhoefer, R. A.; *Chem*. Eur. J. **2008**, 14, 5382–5391; b) Bongers, N.; Krause, N.; *Angew. Chem*. **2008**, 120, 2208–2211; *Angew. Chem. Int. Ed*. **2008**, 47, 2178–2181.

catalysis in gold chemistry,[58] the scope and variations achievable are still in their infancy as compared to organocatalysis. Moreover, cationic rearrangement reactions are certainly more versatile in gold-catalyzed systems, which are rather challenging if a pure organocatalytic strategy is utilized.

In 2014, Chen et al. reported an efficient strategy for the enantioselective construction of [6,5,6]-carbocyclic compounds. A highly stereoselective one-pot sequential cyclization reaction of (*E*)-4-(2-ethynylphenyl)-but-3-en-2-ones **47** with maleimides **48** sequentially catalyzed by the cinchona alkaloid-based primary amine and gold complex, providing a facile approach to access the [6,5,6]-tricyclic **50** skeleton with perfect enantioselectivities. Importantly, the combination of dienamine catalysis and enamine/gold cooperative catalysis would allow the design of new sequential reactions for the efficient construction of structurally complicated polycyclic compounds.



Scheme 12: *The combination of dienamine catalysis and enamine/gold cooperative catalysis*

Similarly, hundreds of strategies with cooperative catalysis have been reported with the parallel research in aminocatalysis.

[58] a) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, 317, 496–499; b) Hashmi, A. S. K.; *Nature* **2007**, 449, 292–293; c) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D.;*Angew. Chem.* **2010**, 122, 608–611; *Angew. Chem. Int. Ed.* **2010,** 49, 598–601.

1.6. Summary and Outlook

In this Chapter, a deep knowledge of the beginning of asymmetric synthesis, organocatalysis (specifically aminocatalysis), cascade reactions and strategies as well as the overall scope in the field has been provided, thereby setting the requisite basis for a better understanding of upcoming chapters dedicated to original research conducted in this Ph.D. study. Finally, in order to achieve a higher level of scholar presentation, the underlying importance of the current topic of research has been put into a greater perspective incorporating subjects, such as the evolutionary processes and current scientific demands.

In the next part of the thesis (chapter 2-6), some projects have been carried out during the Ph.D. study will be disclosed. However, instead of describing these as individual topics, a grouping of work has been made, hence summing up into four chapters covering a small concept of organocatalytic strategies. In this way, a more comprehensive picture of each topic should be provided, which hopefully could convince the reader about the high versatility and usefulness of organocatalysis.

In chapter 2, a backstage preparation of a new concept in organocatalysis will be disclosed. The central theme of this project is to conceptualize a classified work done regarding Diversity-Oriented-Synthesis in the field of aminocatalysis. Also, a review on the current scope of the aminocatalysis will be discussed in short notes.

In chapter 3, the infusion of new types of modified dienophiles in trienamine chemistry has been provided. In the first project, pyrazole containing dienophiles which more susceptible for the naturally occurring moieties have been used in trienamine catalysis to synthesize chiral pyrazole skeleton. However, in the second project sulfone containing dienophiles have been used. The central theme of this project is to use sulfone for trienamine catalyzed cycloaddition and then use the corresponding desulfonated product for further cyclization processes.

In chapter 4, a biological approach of trienamine chemistry has been demonstrated. 2-methylindole acryl aldehyde (masked dienal) can condensed with aminocatalyst to generate trienamine species which can undergo [4+2] cycloaddition reaction to form biologically important chiral tetrahydrocarbazole moiety. Two different dienophiles are

used under this strategy and the resulting THC's have shown tremendous biological activities which contribute in the medicinal chemistry.

In chapter 5, four different projects related to Alkenyl BODIPY compounds will be discussed. Herein, the scope of BODIPY containing fluorescent chiral compounds with respect to Diels-Alder cycloaddition via trienamine catalysis, one-pot strategy of trienamine-BODIPY combinate reaction, 1,6-oxa-Michael-Michael addition via iminium catalysis will be uncovered.

In chapter 6, new ongoing research about cooperative catalysis will be disclosed. Mainly, the participation of gold catalyst in aminocatalysis as well as underlying synthetic potential of one-pot strategy is provided.

For better understandings, experimental section has shown as a separated in chapter 7 as, most of the starting material has been used in different projects and was synthesized multiple times. In the end, a final summary of all this work has been provided to conclude this thesis.

Chapter 2.

Theoretical Survey in Aminocatalysis

During the progress of this Ph.D. study, a realization about how aminocatalysis has been involved in asymmetric synthesis to construct privileged structures with an efficient manner which brings a categorized concept called ApDOS have been demonstrated in this chapter. Also, a potential of polyenals and polyenones that support a field of aminocatalysis to achieve a great success of populating chemical space gives an inspiration to write a review, a backstage preparation has been discussed in this chapter.

2.1. The ApDOS Concept: An efficient strategy to populate relevant chemical space

The synthetic work by chemists in all over the world has proven that diversity-oriented synthesis (DOS) and aminocatalysis constitute two important tools for access to extensive range of compounds to populate the chemical space. Thereupon, new libraries of complex and diverse frameworks are becoming available for drug discovery. By considering all this work in the literature, it seems worthy to conceptualize this new field separately to understand its importance and progress, so a new opportunity can be created for the development of aminocatalysis. Consequently, ApDOS has been presented as a new concept that shows the scope of aminocatalysis for the synthesis and diversification of privileged structures.

2.1.1. Molecular Diversity

Despite hundreds of years of development, the basic strategy of synthetic organic chemistry convergent generation of a target molecule from simpler starting materials has remained largely unchanged. In the modern age of systems biology and high-throughput genomics/proteomics, the pace of such a strategy is insufficient to meet the growing demand for biologically active compounds. Building upon the goals of combinatorial chemistry (a largely failed attempt to address this issue), the emerging method of diversity-

oriented synthesis (DOS) is poised to revolutionize the discovery and development of new pharmaceuticals. Arising from the intersection of chemistry and biology, DOS combines the structural diversity of natural products with the transformative power of synthetic chemistry to rapidly interrogate larger expanses of biologically-active chemical space than ever before possible (**Error! Reference source not found.**).[59]

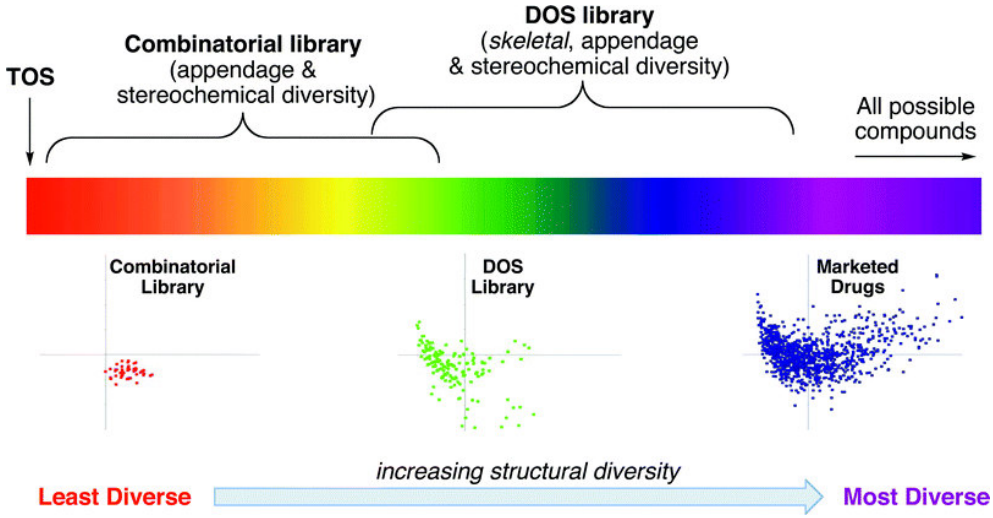


Figure 13: *Molecular diversity spectrum*

In terms of diversity, nature has provided a vast supply of diverse and complex molecular architectures, which represent molecules distributed in all directions throughout chemical space. For years, these natural products have played an important role, because of their ability to modulate a variety of biological functions. However, their use as drugs has been limited due to the problems associated with their natural abundance, isolation, and characterization.[60] Nevertheless, their structures have inspired the development of new drugs through chemical synthesis.[61] Traditionally, the search for synthetic bioactive compounds has been pursued by the synthesis and/or modification of target molecules (Target-Oriented Synthesis, TOS);[62] however, the inherent low diversity of this methodology limits the probability of finding a lead compound. To address this issue,

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[59] R. J. Spandl, M. Diaz-Gavilan, K. M. G. O'Connell, G. I. Thomas, D. R. Spring, *Chem. Rec*. **2008**, *8*, 129-142.

[60] J. W.-H. Li, J. C. Vederas, *Science* **2009**, *325*, 161-165.

[61] a) C. Cordier, D. Morton, S. Murrishon, A. Nelson, C. O´Leary-Steele, *Nat. Prod. Rep.* **2008**, *25*, 719-737; b) A. L. Harvey, *Drug Discov. Today* **2008**, *13*, 894-901.

[62] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis,* Wiley, New York, **1989**.

Diversity-Oriented Synthesis (DOS) has emerged as a powerful tool for maximizing molecular diversity through the creation of compound libraries.[63] In a DOS methodology, simple and similar compounds are transformed efficiently into several complex and diverse structures. In contrast to TOS, in which target compounds are prepared by retrosynthetic analysis and total synthesis (convergent synthesis), DOS follows a divergent process, a branched pathway, by which libraries with broad diversity are generated through a forward synthetic analysis.

2.1.2. Diversity Oriented Synthesis (DOS)

Diversity-Oriented Synthesis aims to produce chemical libraries that are representative of a large portion of chemical space by applying a variety of reaction conditions to starting materials with multiple different functional groups. Multiple rounds of such reactions result in rapid access to structurally diverse products suitable for screening. The most significant contribution from the field of synthetic organic chemistry is the improvement of human health through the generation of biologically active compounds and pharmaceuticals. The development of a host of powerful reactions, reagents, and techniques has permitted the efficient synthesis of an ever-increasing number of such molecules. As our capabilities have grown, so has our ambition, particularly about the synthesis of complex natural products. The therapeutic value of such products has been known since ancient times (in the guise of medicinal herbs), but only through the tools of modern chemistry has the identification and artificial production of the active compounds been a possibility. The synthesis of such compounds is complicated by a variety of structural features, most notably a large number of heteroatoms (which often necessitate protecting groups) and stereocenters (which often require difficult stereoselective reactions or separations). Therefore, the discovery of new techniques for the synthesis of such compounds is one of the most active areas of research at the frontier of chemical biology.

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[63] a) S. L. Schreiber, *Science* **2000**, *287*, 1964-1969; b) M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.***2004**, *43*, 46-58; c) R. J. Spandl, M. Díaz-Gavilán, K. M. G. O´Connell, G. L. Thomas, D. R. Spring, *Chem. Rec.* **2008**, *8*, 129-142; d) R. J. Spandl, A. Bender, D. R. Spring, *Org. Biomol. Chem.* **2008**, *6*, 1149-1158; e) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 80-93; C. J. O´Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444-4456.

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 **14**).[64]

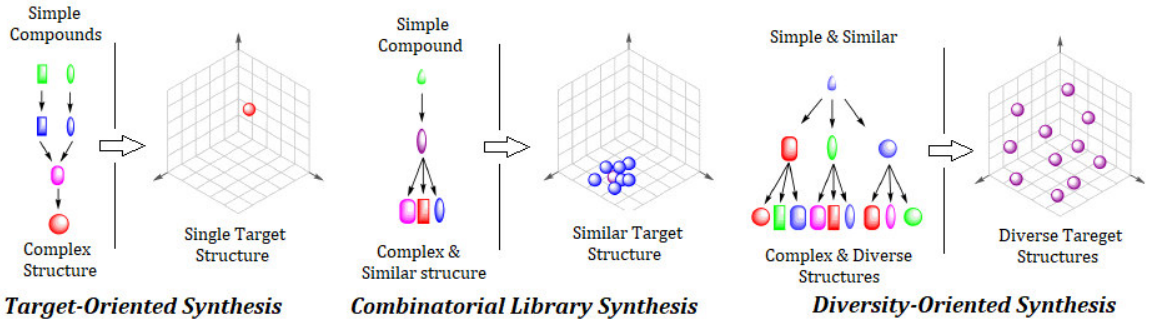

Figure 14: *Comparison of Target-oriented, Combinatorial, and Diversity-oriented synthesis*

Since the conceptualization of DOS by Schreiber in 2000, several original strategies have been developed for the generation of libraries containing complex compounds with different elements of diversity, such as appendage, functional group, stereochemistry, and chemical skeleton.[65] These structurally diverse collections populate new regions in chemical space, which in turn opens up new possibilities for the discovery of new therapeutic agents.

2.1.3. When DOS represents an efficient strategy to create a library of the biological region of chemical space

In order to maximize the potential of library synthesis and hit rate in drug design, privileged diversity-oriented synthesis has been introduced as a strategy for creating

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

[65] a) S. Kotha, A. S. Chavan, D. Goyal, *ACS Comb. Sci.* **2015**, *17*, 253-302; b) M. García-Castro, S. Zimmermann, M. G. Sankar, K. Kumar, *Angew. Chem. Int. Ed.* **2016**, *55*, 7586-7605; c) A. H. Bansode, P. Chimala, N. T. Patil, *ChemCatChem* **2017**, *9*, 30-40. d) O. Kwon, S. B. Park, S. L. Schreiber, *J. Am. Chem. Soc.* **2002**, *124*, 13402-13404; For selected examples see: e) S. Caputo, L. Banfi, A. Basso, A. Galatini, L. Moni, R. Riva, C. Lambruschini, *Eur. J. Org. Chem.* **2017**, 6619-6628; f) S. Dubbu, Y. D. Vankar, *Eur. J. Org. Chem.* **2017**, 5986-6002; g) D. M. Kuznetsov, A. G. Kutateladze, *J. Am. Chem. Soc.* **2017**, *139*, 16584-16590; h) S. R. Kandimalla, G. Sabitha, *Adv. Synth. Catal.* **2017**, *359*, 3444-3453; i) J. J. Ciardiello, H. L. Stewart, H. F. Sore, W. R. J. D. Galloway, D. R. Spring, *Bioorganic Med. Chem.* **2017**, *25*, 2825-2843.

collections of small-molecule compounds based on privileged cores.[66] A privileged structure is defined as a single molecular framework capable of providing high-affinity ligands for more than one type of receptor.[67] Therefore, pDOS represent an efficient and rational strategy for creating libraries of relevant architectures that can populate bioactive regions in chemical space.

Coincidentally, during the DOS conceptualization, the renaissance of asymmetric catalysis facilitated by small-molecule organic compounds also took place.[68] In the same year, the concept of organocatalysis was effectively demonstrated by the groups of MacMillan[69] and List,[70] who reported two ingenious synthetic methodologies simultaneously. Since then, the field of organocatalysis has experienced tremendous progress and has now come to be considered the third pillar of asymmetric catalysis.[71] In particular, aminocatalysis has played an important role, due to its ability to functionalize carbonyl compounds in a stereoselective manner. This type of catalysis has led to the development of a great variety of enantioselective transformations and constitutes a powerful tool for accessing a wide range of enantioenriched compounds.

2.1.4. Activation modes in aminocatalysis and the ApDOS concept.

The success of aminocatalysis lies in the ability of chiral primary or secondary amines to condense effectively but also reversibly with aldehydes and ketones. This complementary amine/carbonyl pairing can promote different enantioselective transformations through a variety of activation processes in which organized, and highly reactive intermediates are involved. Depending on the features of the aldehyde or ketone, a predictable activation mode can be formed, and as a result, a rational methodology for

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[66] a) S. Oh, S. B. Park, *Chem. Commun.* **2011**, *47*, 12754-12761; b) J. Kim, H. Kim, S. B. Park, *J. Am. Chem. Soc.* **2014**, *136*, 14629-14638.

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

[68] D. W. C. MacMillan, *Nature* **2008**, *455*, 304-308.

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

[70] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

[71] *Comprehensive Enantioselective Organocatalysis: Catalysis, Reactions, and Applications* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**.

desired products can be achieved. Currently, approximately seven activation modes have been successfully developed and have served as platforms for many asymmetric transformations. The essence of activation modes in aminocatalysis is in the fundamental reactivity-enhancing concepts of raising the HOMO and lowering the LUMO. The archetypal HOMO-raising process is *enamine activation*. In this strategy, enolizable carbonyl compounds are activated with catalytic amounts of chiral primary or secondary amines, which induces the formation of enamine intermediates. These nucleophilic enolate equivalents can then react with electrophilic reagents, and as a consequence, new C–C or C–heteroatom bonds α to carbonyl groups can be effectively formed in an enantioselective fashion.[72]

On the other hand, lowering the energy of the LUMO is the underlying principle of iminium ion activation. In this activation mode α,b-unsaturated aldehydes and ketones condense with chiral amines to generate iminium ion intermediates, and this facilitates both asymmetric nucleophilic additions at the α,β-position and also pericyclic reactions.[73] Additionally, once HOMO and LUMO activation were established, MacMillan and co-workers introduced SOMO activation. This term refers to one-electron oxidation of the enamine intermediate to generate a 3π-radical cation intermediate. This new species is then able to participate in a variety of asymmetric radical transformations.[74] Moreover, the development of this SOMO activation invention has influenced the combination of photoredox catalysis with aminocatalysis, to extend possibilities in this area.[75]

Thanks to both enamine and iminium ion activation modes, a great variety of methodologies for the enantioselective functionalization of carbonyl compounds at the α and β positions have been successfully developed. Moreover, these two classical activation strategies have been extended, leading to the discovery of new activation modes. Through

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[72] a) B. List, *Synlett*, **2001**, 1675-1686; d) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580-591; b) B. List, *Acc. Chem. Res.* **2004**, *37*, 548-557; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471-5569; d) G. Guillena, C. Nájera, D. J. Ramón,

[73] a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79-87; b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416-5470;

[74] a) T. D. Beeson, A. Mastracchio, J. Hong, K. Ashton, D. W. C. MacMillan, *Science*, **2007**, *316*, 582-585; b) S. Bertelsen, M. Nielsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 7356-7359; c) M. Mečiarová, P. Tisovsky, R. Šebesta, *New J. Chem.* **2016**, *40*, 4855-4864.

[75] a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77-80; b) P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 1360-1363.

the above reactivity concepts, aminocatalysis has been transformed with the development of the so-called dienamine,[76] linear trienamine,[77] cross trienamine,[78] tetraenamine,[79] and vinylogous iminium ion patterns,[80] by extension of π-conjugated systems in carbonyl compounds. These new activation modes have allowed the functionalization of remote centers (i.e., reactive sites located five to seven bonds distant from the catalyst).[81]

Together with the discovery of new activation modes, the development of new catalysts is also crucial. Aminocatalysts based on pyrrolidine-, imidazolidinone-, and cinchona-alkaloid derived scaffolds has been designed and prepared not only to promote different activation modes but also to provide efficient chirality transfer. In these senses, both steric-shielding and hydrogen-bond bifunctional operational modes can be involved, depending on the features of the groups attached to the main core of the catalyst.

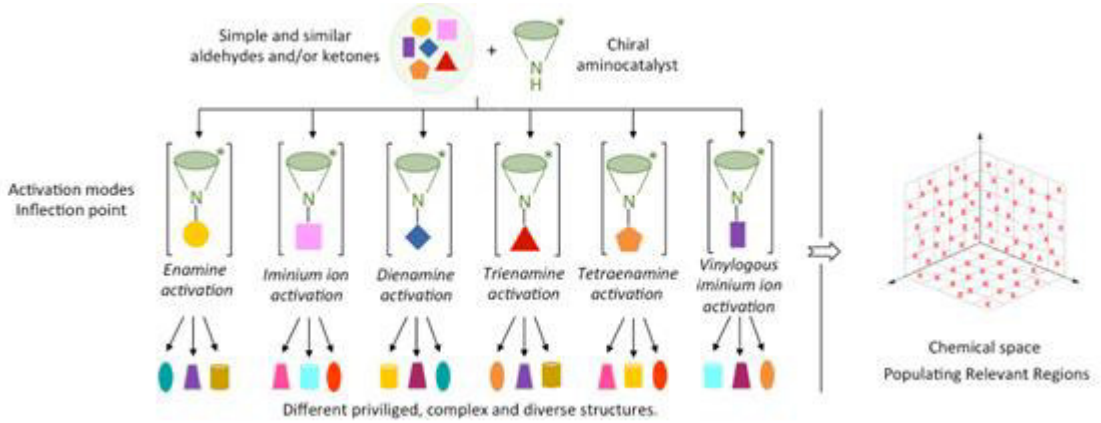


***Figure 15**: The ApDOS concept*

The success of aminocatalysis has been driven both by the development of new activation modes and by the design of new catalysts enabling the efficient transfer of asymmetry and high rate enhancement. In terms of diversity, molecular architectures

[76] a) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865-887; b) V. Marcos, J. Alemán, *Chem. Soc. Rev*. **2016**, *45,* 6812-6832.

[77] a) I. Kumar, P. Ramaraju, N. A. Mir, *Org. Biomol. Chem.* **2013**, *11*, 709-716; b) S. Reboredo, A. Parra, J. Alemán, *Asymmetric Catal.* **2013**, *1*, 24-31;

[78] K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 12943-12946.

[79] a) J. Stiller, P. H. Poulsen, D. Cruz Cruz, J. Dourado, R. L. Davis, K. A. Jørgensen, *Chem. Sci.* **2014**, *5*, 2052-2056; b) Q.-Q. Zhou, Y.-C. Xiao, X. Yuan, Y.-C. Chen, *Asian J. Org. Chem.* **2014**, *3*, 545-549;

[80] a) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869-4883; b) H. B. Hepburn, L. Dell´Amico, P. Melchiorre, *Chem. Rec.* **2016**, *16*, 1787-1806.

[81] H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Chem. Sci.* **2013**, *4*, 2287-2300.

produced by aminocatalysis have allowed the population of new regions of chemical space. More importantly, biologically relevant regions have been targeted, with a wide variety of methodologies having been directed towards the synthesis and diversification of privileged structures.

In general, pDOS and aminocatalysis are closely related. According to their main goals, we envision 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 pathways typically involve a process that generates a common intermediate scaffold from simple molecules, which in turn serve as a platform for the synthesis of complex and diverse frameworks. These key intermediates represent the inflection point at which extensive molecular diversity arises. Therefore, in ApDOS, aldehydes and ketones are the simple, common molecular building blocks, able to participate in different activation modes. 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 **15**).

2.1.5. Summary

This can be conceptualizing by considering the scope and covering diversification of privileged structures with the aid of aminocatalytic processes, either through the utilization of a single activation mode or by combining multiple modes in a single process (cascade reactions). The aim of this concept was to demonstrate the broad utilization of aminocatalysis in asymmetric synthesis since it serves as a genuine tool to amplify and diversify the chiral pool, and to create diverse chiral frameworks in relevant regions of chemical space. This contribution shows representative examples of rapid assemblies of diverse product classes enabled by this strategy. (See Appendix I)

2.2. Polyenals and Polyenones in Aminocatalysis

Polyenals and polyenones are simple chemical compounds with the ability to construct giant structures with the help of aminocatalysis. In the past eight years, new aminocatalytic activation modes like trienamine, cross-trienamine, tetraenamine, iminium ion, and vinylogous iminium ion have attracted great attention in the field of asymmetric synthesis, because of the ability to functionalize remote sites with high stereoselectivities, even more, methodologies such as one-pot, cascade or multicomponent have been developed through the combination of these new activation modes with classical activation modes. During the expanding of organocatalysis, polyenals and polyenones have introduced novel methodologies and concepts and they have contributed to the synthesis of privileged structures. The work using these important compounds prove that they are simple blocks for access to complex frameworks.

2.2.1. Introduction

Diversity and complexity constitute two of the central topics in current organic chemistry. During the last decades, efforts have been focused on the development of new synthetic methodologies to construct compounds efficiently with high levels of structural, functional and stereochemical diversity. During the progress for reach diversity, asymmetric catalysis has demonstrated to be a powerful tool, because of the ability to promote reactions in which new C-C and C-X bonds are formed in a regio-, diastereo- and enantioselective fashion[82] Traditionally, these types of transformations were 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 lead to the rediscovery and conceptualization of organocatalysis.[83] Since then, this extraordinary area has experienced an impressive growth and rapidly has become a promising synthetic platform to access to new optically active compounds. Particularly, aminocatalysis has demonstrated to be one

[82] a) S. Afewerki, A. Córdova, *Chem. Rev*. **2016**, *116*, 13512−13570; b) H. Yoon, X. Ho, J. Jang, H. Lee, S. K. Jang, *Org. Lett*. **2012**, *14*, No. 3272-3275. C) M. Gruttadauria, L. A. Bivona, P. L. Meo, S. Riela, R. Noto, *Eur.J. Org. Chem*. **2012**, *2012*, 2635− 2642.

[83] C. M. Marson, *Chem. Soc. Rev.* **2012**, *41*, 7712-7722.

of the most prominent strategies. The knowledge that chiral primary or secondary amines can be used to activate efficiently carbonyl compounds such as aldehydes and ketones through the fundamental concepts of reactivity HOMO-rising and LUMO-lowering, has been a central theme in this field. This type of catalysts (extraordinary complementary catalyst-substrate pair) has promoted countless stereoselective transformations under several efficient and predictable activation modes. Initially, HOMO and LUMO activation was limited to enamine and iminium ion activation. However, by considering the vinylogy principle, aminocatalysis has found new perspectives for challenging transformations. The ability of this types of catalysts to transfer reactivity to distant centers along to π-systems in the substrate, lead to the development of new activation modes such dienamine,[84] trienamine,[85] tetraenamine[86] and vinylogous iminium ion,[87] which allow the functionalization of remote positions located up to 8 bonds of distance from the catalyst without loss of stereoselectivity (Figure **16**).

Polyunsaturated carbonyl are well-known compounds from a century[88] and represent 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.[89] 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 enolizable 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

[84] a) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem*. **2012**, 865–887; b) V. Marcos, J. Alemán, *Chem. Soc. Rev*. **2016**, *45*, 6812–6832.

[85] a) I. Kumar, P. Ramaraju, N. A. Mir, *Org. Biomol. Chem*. **2013**, *11*, 709–716; b) S. Reboredo, A. Parra, J. Alemán, *Asymmetric Catal*. **2013**, *1*, 24–31.

[86] a) J. Stiller, P. H. Poulsen, D. Cruz Cruz, J. Dourado, R. L. Davis, K. A. Jørgensen, *Chem. Sci.* **2014**, *5*, 2052–2056; b) Q.-Q. Zhou, Y.-C. Xiao, X. Yuan, Y.-C. Chen, *Asian J. Org. Chem*. **2014**, *3*, 545–549.

[87] a) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun*. **2013**, *49*, 4869–4883; b) H. B. Hepburn, L. Dell'Amico, P. Melchiorre, *Chem. Rec*. **2016**, *16*, 1787–1806.

[88] (a) T. Zincke, G. Heuser, W. Möller, *Liebigs Ann.* **1904**, *333*, 361-374. (b) T. Zincke, W. Würker, *Liebigs Ann.* **1904**, *338*, 107-141.

[89] Jens M. J. Nolsøe,* Marius Aursnes, Jørn E. Tungen, and Trond V. Hansen, *J. Org. Chem.* **2015**, 80, 5377−5385.

Michael additions, [4 + 2] cycloadditions or Diels–Alder type reactions, etc. while vinylogous iminium ions are electrophilic intermediates, which are highly reactive towards nucleophilic additions or ring-closing reactions. On the other hand, during the exploration of strategies for remote functionalization involving polyenamines, very creative methodologies using aromatic aldehydes and ketones (carbonyl compounds) have also developed. Thorough the condensation with an aminocatalyst, these masked polyenals and polyenones are able to form efficiently polyenamines by breaking the aromaticity. Then, once it reacts the aromaticity is recovered (see, section 4.1).[90]

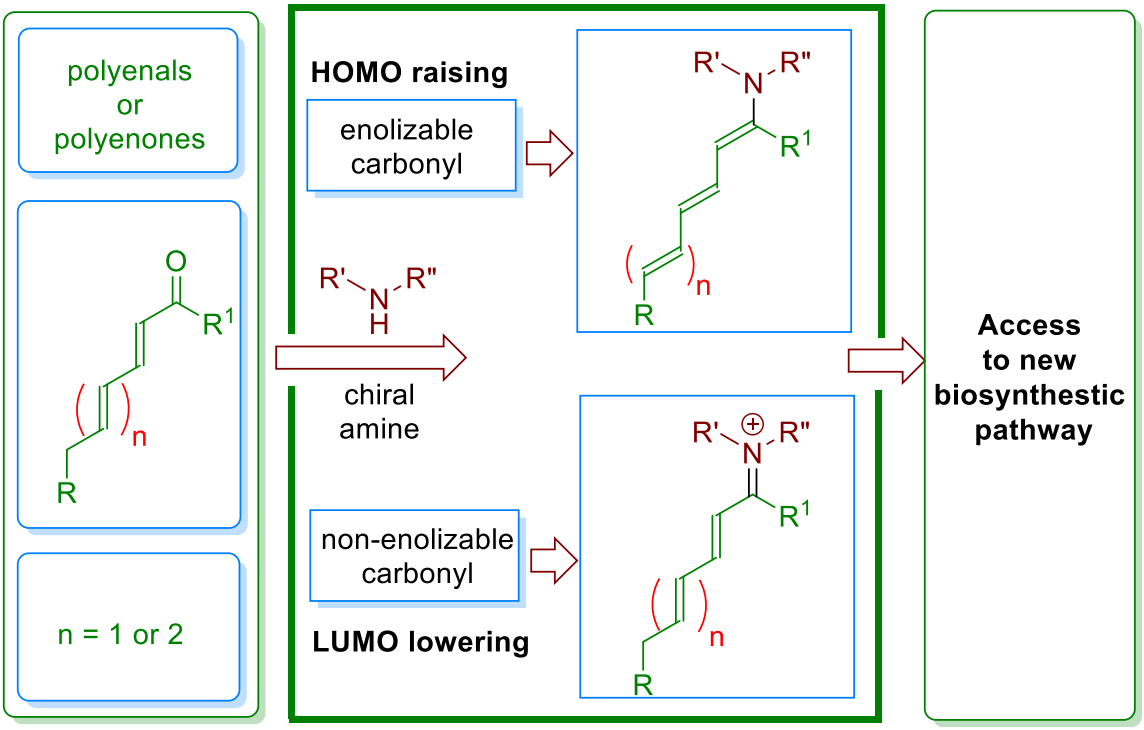


Figure 16: *strategy of polyenals and polyenones in aminocatalysis.*

2.2.2. Summary

In conclusion, a review presented is about how polyenals and polyenones have contributed during the last decade to the extraordinary progress of aminocatalysis. Strategies involving aromatic aldehydes and ketones, which can form polyenamines through breaking the aromaticity are also discussed (See Appendix II).

[90] Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.*, **2011**, *133*, 15212-15218.

Chapter 3.

Trienamines in aminocatalysis: the diarylprolinol system action beyond enamine and iminium ion chemistry.

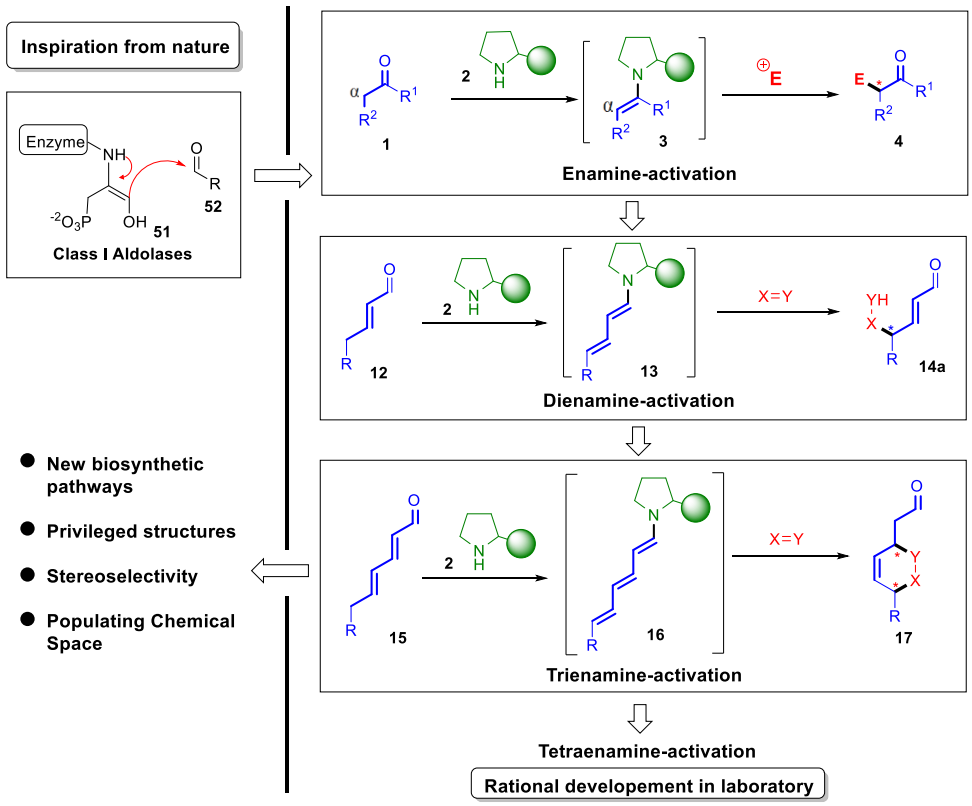
In previous chapter, it has been discussed theoretically that how trienamine strategy perform outstandingly to construct privileged structures. In this chapter, the concept of trienamine chemistry will be disclose. Also, two different projects that contributes in trienamine methodology and are carried out during the Ph.D. study are presented. Moreover, this Ph.D. study has focused on the discovery of new dienophiles in trienamine chemistry for the stereoselective [4+2] cycloaddition of this dienophile with the 2,4-dienals to generate a library of enantiopure cyclohexene systems. To achieve this goal, a several new dienophiles were planned and were perform multiple experiments with a variety of 2,4-dienals.

3.1. Introduction and design plan

One of the most successful approaches to quest new synthetic methods and activation modes is via the union of natural inspiration and rational design, which in a "joint venture" fashion have led to many important discoveries within contemporary organic synthesis. The invention and extensive exploration of aminocatalysis is, for example, a direct result of combining knowledge from molecular biology with rational design (see chapter 2). Also, Rutter's clarification of the underlying mechanism of the activity of aldolases has indisputably acted as a vital source of inspiration for today's well-appreciated enamine mediated reactions.[91] By rational developments, this amino-mediated HOMO-raising principle was later successfully extended to α,β-unsaturated carbonyl system **12**. This mode of activation, trivially known as dienamine activation, proceed via the intermediary of dienamine species **13**, which readily undergoes reaction with appropriate electrophiles or dienophiles (Scheme 13, only with dienophile is shown). In the continuation of this path of rational design, the possibility to further extrapolate such a

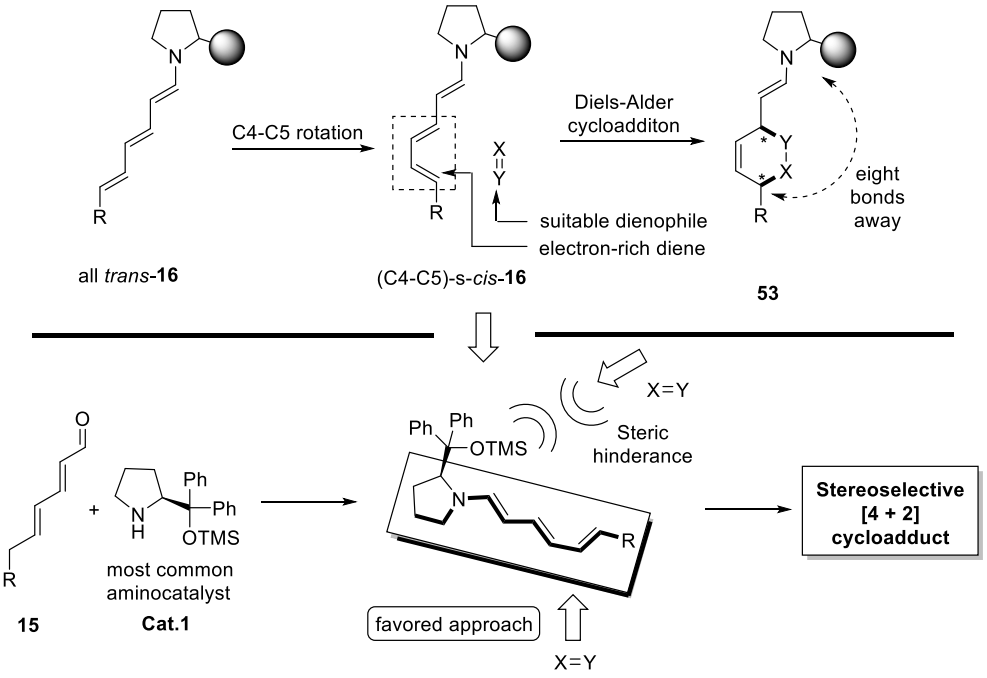
[91] Rutter, W. J.; *Fed. Proc.* **1964***, 23,* 1248-1257.

HOMO-raising concept to more conjugated carbonyl system was questioned. One of the simplest members in such a series would be 2,4-dienals **15**, which in combination with aminocatalyst **2** may form trienamine **16** as a versatile reaction intermediate (Scheme 13, bottom).



Scheme 13: *Rational design in the development of activation modes in amino catalysis*

A brief look at the proposed trienamine species **16** would suggest that the desire HOMO-raising can be anticipated in three distinct positions, namely at the α-, γ- and ε-position of the original aldehyde moiety (Scheme 13). Thus, whether selectivity can be achieved in the course of any potential new reaction became a decisive question that required urgent answer. Since, α- and γ-activation pathways via enamine and dienamine mediated reactions have been well-explored, the most interesting outcome is, obviously, a selective activation of the most remote reactive center.



Scheme 14: *Design Plan: trienamines in Diels-Alder reactions.*

As illustrated above (Scheme 14, top), the distant olefins (in C4-C5-s-cis-**16**) are likely to form an electron-rich *cis*-diene system, which may become good reaction partners in asymmetric Diels-Alder type reaction with excellent stereoselectivity (Scheme 14, bottom). After the first proof, which was an extraordinary invention and introduced a new future to the asymmetric synthesis by Chen and Jorgensen [ref], many dienophiles participated in a reaction with polyenamines (See section 2.2.) and introduced new methodologies, which is a remarkable jump in the research of organocatalysis. For instance, the capacity of the catalyst to offer enough stereo-induction at the center eight bonds away from the stereo-controlling motif (Scheme 14, R-group) can be listed as one of the major concerns. In the following, investigations on the use of trienamines in asymmetric synthesis will be presented. (For the full study, see Appendix I and II).

For further contribution to this field, six new types of dienophiles were discovered during the progress of this investigation. It was decided to explore the use of BODIPY's, pyrazole, chromene, benzoquinone, cyanosulfones as an electron deficient groups on dienophile. It was hypothesized that trienamine catalyzed [4+2] cycloaddition of this dienophiles with different kinds of dienals (masked or regular) would reveal a variety of new chiral cyclohexenes with an expected factor such as biological importance,

fluorescence, natural moieties etc. Also, it was hypothesized that, this kind of cycloadducts can be used for further cascade reactions or derivatization to expand the molecular skeleton, as the resulting chiral cyclohexenes are synthetically useful compounds and can be further modified in several ways[92] (Figure 17).

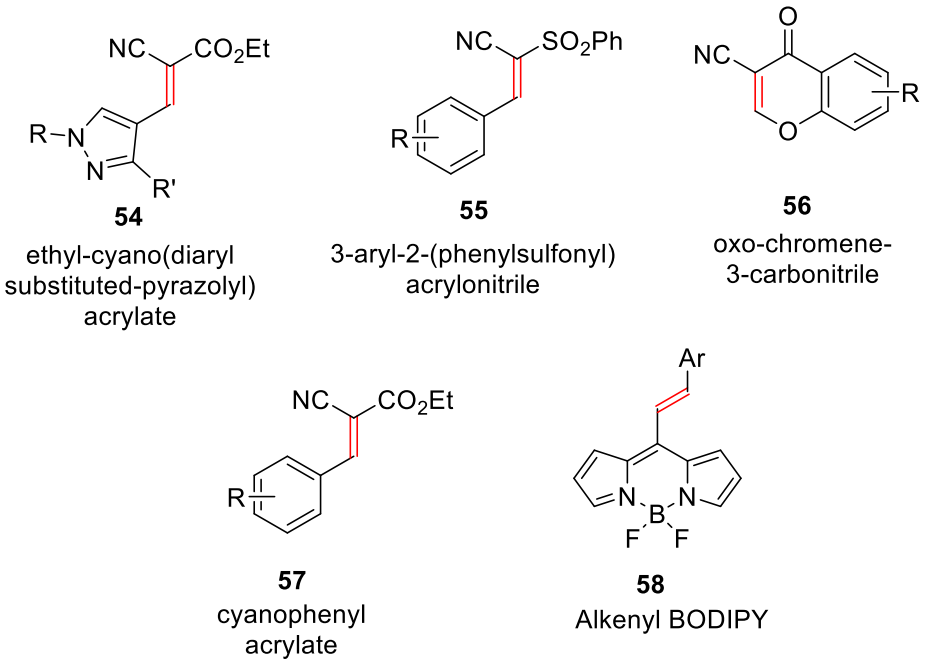


Figure 17: *New dienophiles and new reactivities of previously used dienophiles in trienamine chemistry*

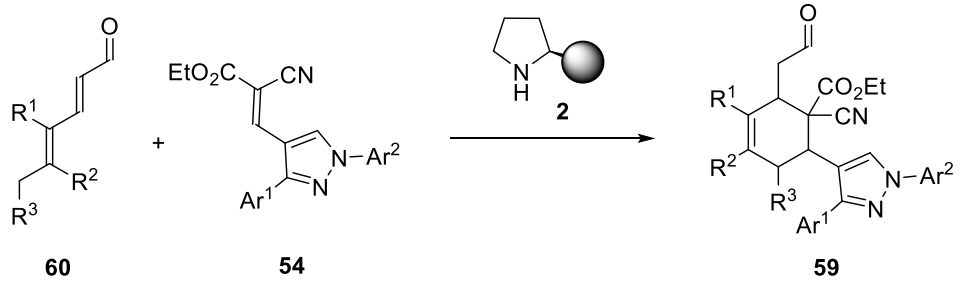
In this chapter, only two dienophiles (**54** and **55**) will be discussed, previously used dienophiles (**56** and **57**) will be elaborated in chapter 4, whereas BODIPY dienophile **59** is presented in a separate (5th) chapter due to the ability to producing novel chiral fluorescent compounds.

[92] Simpkins, *N. S. In Sulphones in Organic Synthesis (Tetrahedron Organic Chemistry Series); Pergamon* Press: Oxford, **1993**; *Vol. 10*. (b) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paix~ao, M. W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2668. (c) Alba, A.-N. R.; Company_o, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018.

3.2. Olefinic pyrazoles as dienophiles in trienamine catalysis

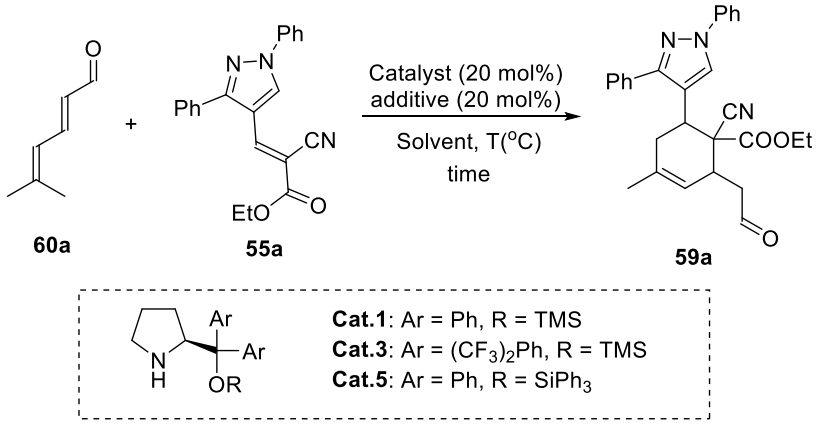
3.2.1. Conceptualization and importance of project

Synthesis of new biologically active compounds is an open challenge to the scientific community, while the number of asymmetric pathways to construct privileged framework are already reported. Also, 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 have been initiated a program to explore the diversification of substituted pyrazol through cascade catalytic reactions. It is known that such structures form part of a series of biologically active products, as a product contains two biological moieties, such as pyrazol and cyclohexene. The proposed strategy combines the synthesis of a substituted pyrazol methylene cyanoester **54** and subsequent cycloaddition [4 + 2] via organocatalytic trienamine activation. The key to carrying out this process is to initially form the trienamine species using dienals **60** and aminocatalyst **2**, whose reaction with the olefinic pyrazole **54** can generate a multifunctional cyclohexene adduct **59** in stereoselective form. Through this process, it is possible to access the corresponding functionalized pyrazol and cyclohexene framework with up to four stereogenic centers (Scheme 15).



Scheme 15: *conceptualization of the project*

3.2.2. Optimization of Reaction:



Scheme 16: *Optimization of reaction.*

Entry	Cat.	Equiv. of Ald.	Solvent	Addt.	Temp. (°C)	Time (h)	Conv.[a] (%)	dr[b]
1	Cat.1	1.2	$CHCl_3$	--	rt	36	23.9	n.d
2	Cat.1	1.2	$CHCl_3$	--	40	48	34.1	n.d
3	Cat.3	1.2	$CHCl_3$	--	40	48	7.9	n.d
4	Cat.1	1.2	$CHCl_3$	BA	40	48	39.1	n.d
5	Cat.1	1.2	$CHCl_3$	DPTU	rt	48	46.8	2:1
6	Cat.1	1.2	$CHCl_3$	p-NBA	rt	48	36.7	n.d
7	Cat.1	1.2	$CHCl_3$	o-FBA	rt	48	44.6	n.d
8	Cat.1	1.2	$CHCl_3$	NaOAc	rt	48	41.2	n.d
9	Cat.1	1.2	CH_3CN	DPTU	rt	48	n.r	n.r
10	Cat.1	1.2	PhMe	DPTU	rt	48	51.6	2:1
11	Cat.1	1.2	THF	DPTU	rt	48	29.8	2:1
12	Cat.1	1.2	dioxane	DPTU	rt	48	31.8	2:1
13	Cat.1	1.2	PhMe	DPTU	45	48	72.6	3:1
14	Cat.1	1.2	PhMe	DPTU	0	72	88.5	4:1
15	Cat.1	2	PhMe	DPTU	45	48	92.6	4:1
16	Cat.1	3	PhMe	DPTU	45	48	100	4:1
17	Cat.5	3	PhMe	DPTU	45	48	100	9:1
18	Cat.5	2	PhMe	DPTU	45	48	100	9:1
19	Cat.5	**1.5**	**PhMe**	**DPTU**	**45**	**48**	**100**	**9:1**
20	Cat.5	1.2	PhMe	DPTU	45	48	90.3	n.d

Table 2: *Optimization table for the reaction between olefinic pyrazole and 2,4-dienals. ([a],[b]*All the values of conversion[a] and dr[b] are determined from ^{1}H NMR spectra.)*

The optimization of the reaction was started with the reaction between the dienal **60a** and the dienophile **54a** in the presence of the Jørgensen–Hayashi catalyst **Cat.1** in chloroform at room temperature (Scheme 16). We found that the reaction gave the desired product **59a** with a very low conversion (entry 1, Table 2). In order to improve this preliminary result, we tested the addition of different additives (entries 4-8), increasing the conversion to 46.8% with addition of DPTU. Different solvents under **Cat.1** catalysis were then examined (entries 9–12). Toluene gave an impressive yield with 51.6% of conversion. Latterly, when the temperature was increased to 45 ºC (entry 13), a conversion was increased to 72.6% whereas at 0 ºC it was around 88.5% conversion but with 72 hours of time (entry 14). By changing the equivalents of aldehyde to 3 equiv. gave a full conversion (entry 16). Following this, different aminocatalysts **Cat.1, Cat.3** and **Cat.5** were tried. Interestingly, **Cat.5** gave an impressive dr and ee. The the equivalents of aldehyde were decreased to 1.5 equiv., achieving the product **59a** with full conversion, and 74% isolated yield (entry 19). However, when the aldehyde loading was 1.2 equiv., conversion was found 90% (entry 20).

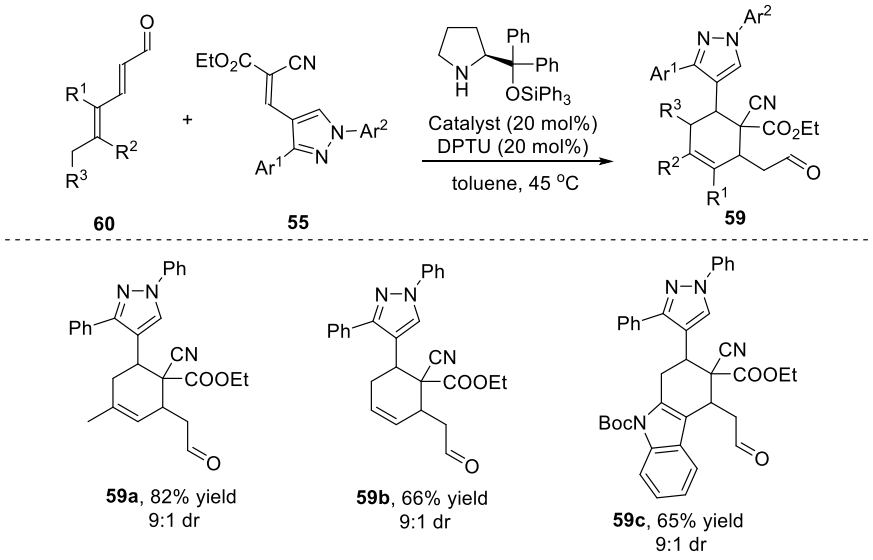
3.2.3. Scope of Reaction

After determination of the best condition, the work begins with the scope of the reaction using different aldehydes **60** and dienophiles **54** (Table 2). Aldehydes were synthesized as per procedure mentioned in section 7.1.1 and 7.1.2 and dienophiles were synthesized by using the simple method mentioned in section 7.2.1 and 0.

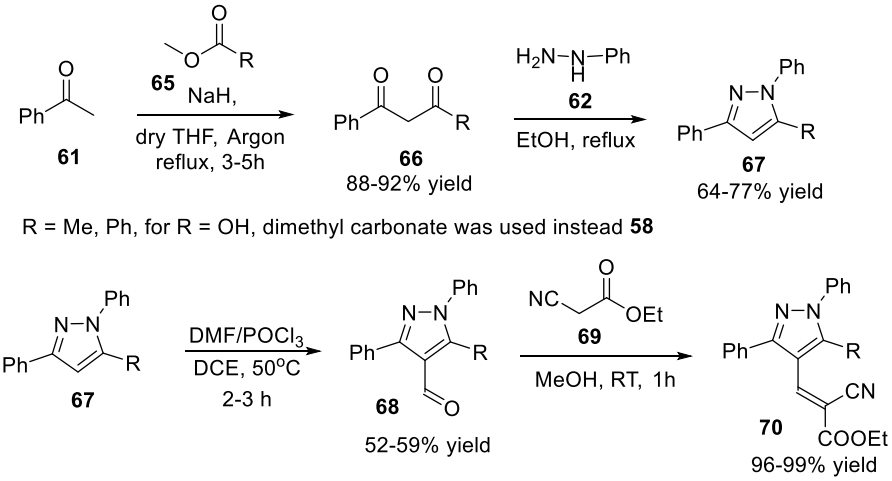
Due to the partial optimization (ee is not performed) only few derivatives **59a-c** have been synthesized to evaluate the reactivity of optimized reaction (Scheme 17). After the confirmation of ee of optimized product, already prepared starting material (Dienals and Dienophiles) will be used to synthesize previously planned products (see, section 3.2.5).

During the synthesis of new dienophiles, a novel procedure for the C-5 substituted pyrazole compounds has been developed. Condensation of β-ketoester and substituted 2,4-dione **65** with phenyl hydrazine **62** generates C-5 substituted (hydroxy and phenyl or methyl respectively) which on Vilsmere Haack formylation followed by knovengel

condensation with cyanoethylester **69** gives corresponding dienophile **54** with C-5 substitution (Scheme 18).



Scheme 17: *Synthesized derivatives.*

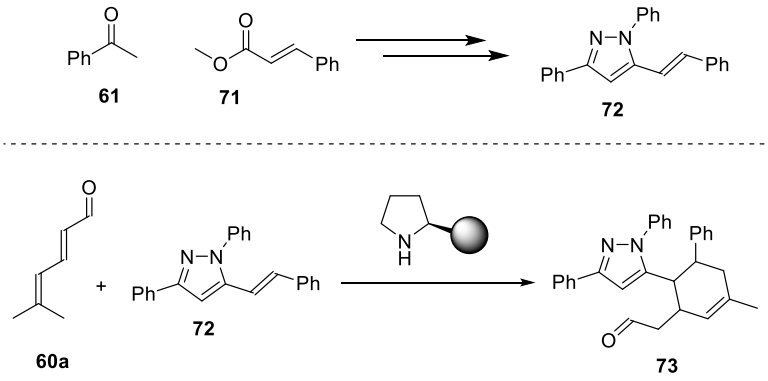


Scheme 18: *Synthesis of C-5 substituted pyrazoles*

3.2.4. An extension to the project:

The strategy (Scheme 18) also allowed to synthesize pyrazole with alkenyl substitution at C-5 (Scheme 19, top) which leads to a suitable dienophile **72** for asymmetric transformation. By extending this project, it has been planned that this dienophile will be used in trienamine chemistry to unlock a new reactivity of pyrazole (very less reports at C-

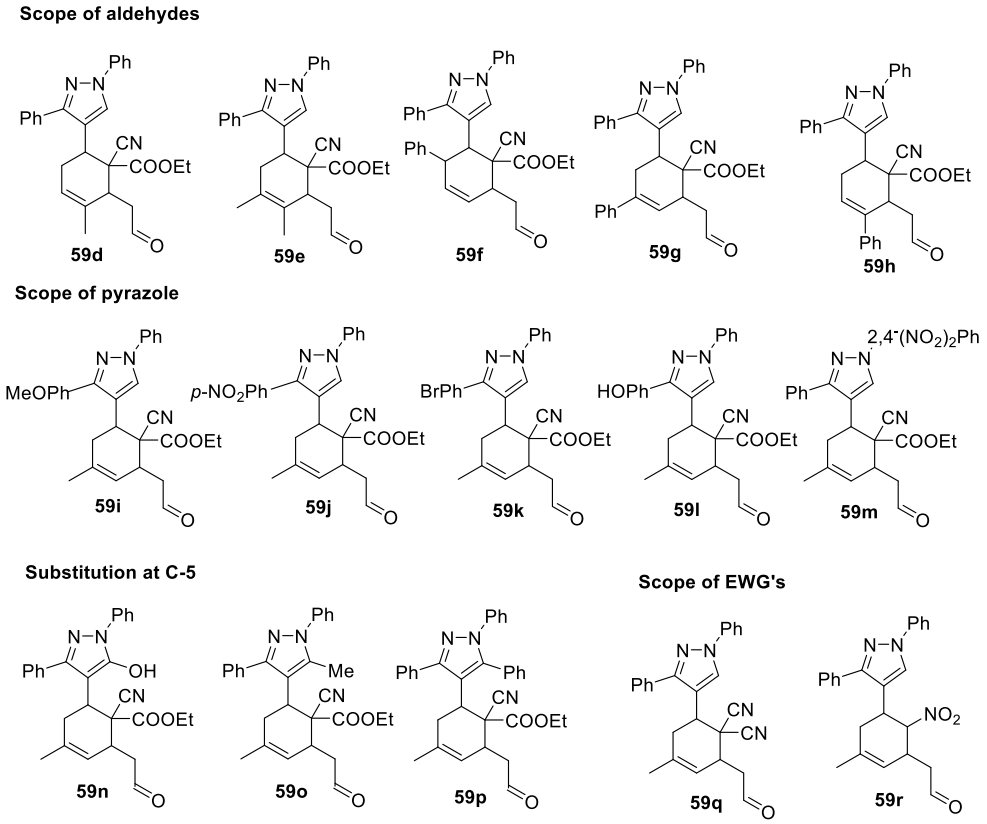
5 substitution of pyrazole, source: scifinder) in the addition of chiral moiety attached. (Scheme 19, bottom).



Scheme 19: *Another aminocatalytic reactivity at C-5 of pyrazole*

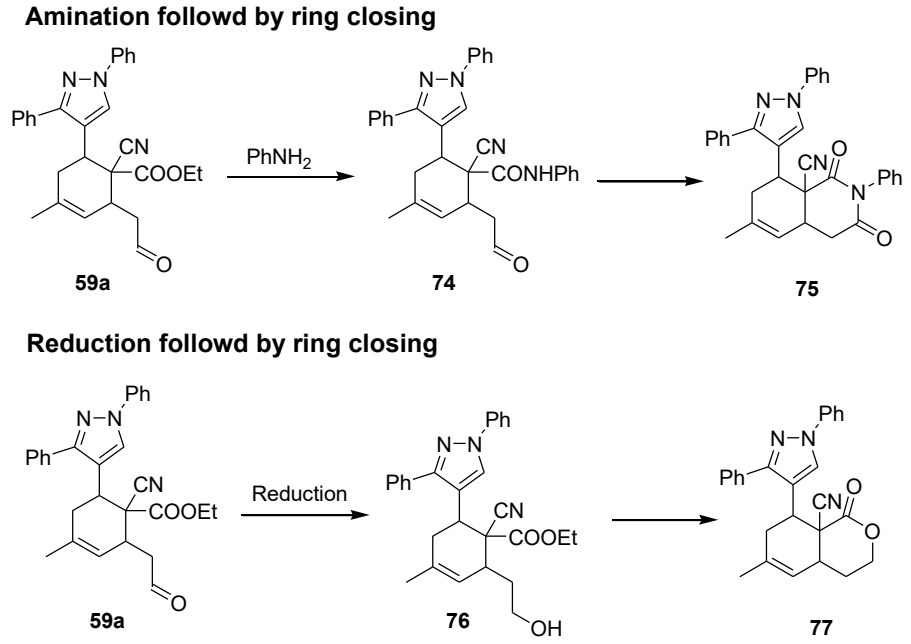
3.2.5. Perspectives

- To measure the ee for the optimization of reaction
- To complete the scope of the reaction: In current status, some of the derivatives has been synthesized and the following derivatives are planned to complete the scope (Scheme 20).



Scheme 20: *Scope of reaction*

- To derivatize the corresponding adduct: In the pre-planned derivatization, some of the reaction on the cycloadduct **59a** will be perform as below. Amination of **59a** can generate **74** which can undergo ring closing leads to **75**. whereas, reduction of **59a** can deliver chromene **77** scaffold (Scheme 21).



Scheme 21: *Derivatization of cycloadduct.*

- To study the absolute configuration of the cycloadduct: Compound **59k** (Scheme 20) has been chosen for the x-ray study, and the absolute configuration of compound will be obtained.
- To study biological activity: As, the resulting pyrazole contains pyrazole with multiple substitutions, it is worthy to study biological activities. Also tetrahydrocarbazole and pyrazole, two most bioactive compounds are present in same compound, can probably show tremendous activities (Figure **18**).

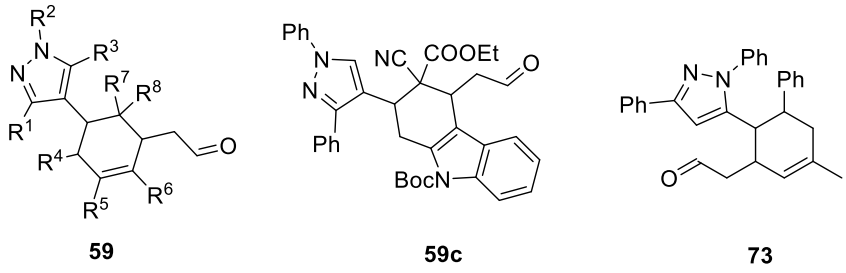


Figure 18: *Resulting compounds probably possess biological activities.*

- To study the electrophilic reactivity of pyrazole moiety: The computational study will be done by comparing the reactivity of C-4 and C-5 in the sense of trienamine catalysis (Scheme 19).

3.2.6. Conclusion

In conclusion, the reaction of pyrazol derivatives and 2,4-dienals in presence of an organocatalyst leads to giant framework from basic starting material. The first time ever a pyrazole moiety is used in aminocatalytic cycloaddition reactions. A substitution on C-5 of pyrazole will probably show an interesting reactivity on corresponding trienamine mediated [4+2] cycloaddition. A new type of chiral cyclohexene attached with pyrazole can possibly show some interesting biological activities.

3.3. Sulfone containing dienophiles

*(*The project has been carried out during the research stay at Universidad Aútonoma de Madrid, Spain under the Ph.D. program. Due to the lack of time, the project did not finish, and the rest of the work will be done in the future)*

3.3.1. Introduction

Sulfones are widely employed as valuable intermediates in organic synthesis.1[93] Asymmetric Michael addition of carbon nucleophiles to vinyl sulfones represents an important carbon-carbon bond-forming reaction and provides an easy access to various optically pure sulfones. In several reports,[94] enamines preformed from ketones were successfully added to vinyl sulfones; however, the additions were nonstereoselective. D'Angelo and co-workers later developed enantioselective additions of imines derived from cyclic ketones and chiral 1-phenyethylamine to vinyl sulfones.[95] Deng et al. reported elegant cinchona alkaloidmediated enantioselective conjugate additions to vinyl sulfones for the construction of all-carbon quaternary stereocenters.[96] Also, Alexakis and his co-workers described an asymmetric organocatalytic Michael addition of aldehydes to vinyl sulfones.[97] These reactions were promoted by their well-designed N-iPr-2,2′-bipyrrolidine catalysts, and the adducts were obtained with modest to good enantioselectivity. After many of reports, Cobb reported a cycloaddition of ε-nitro-ρ,β-unsaturated esters with vinyl sulfones via bifunctional thiourea catalyst.[98] Despite all the excellent advances, highly enantioselective catalytic Michael addition of carbonyl substrates to vinyl sulfones remains a challenging task, particularly with aldehyde substrates.

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[93] (a) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. (b) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, **1993**.

[94] (a) Risaliti, A.; Fatutta, S.; Forchiassin, M. *Tetrahedron* **1967**, *23*, 1451. (b) Benedetti, F.; Fabrissin, S.; Risaliti, A. *Tetrahedron* **1984**, *40*, 977. (c) Lucchi, O. D.; Pasquato, L.; Modena, G. *Tetrahedron Lett.* **1984**, *25*, 3643.

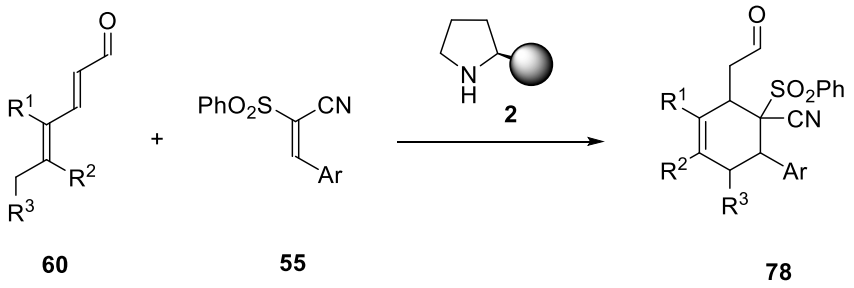
[95] (a) Pinheiro, S.; Guingant, A.; Desmae¨le, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003. (b) Desmae¨le, D.; Delarue-Cochin, S.; Cave, C.; d'Angelo, J.; Morgant, G. *Org. Lett.* **2004**, *6*, 2421.

[96] Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.

[97] (a) Mosse, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. (b) Sulzer-Mosse, S.; Tissot, M.; Alexakis, A. *Org. Lett.* **2007**, *9*, 3749.

[98] Rajkumar, S.; Shankland, K.; Goodman, J. M.; Cobb, A. J. A., Org. Lett., 2013, 15, 1386-1389.

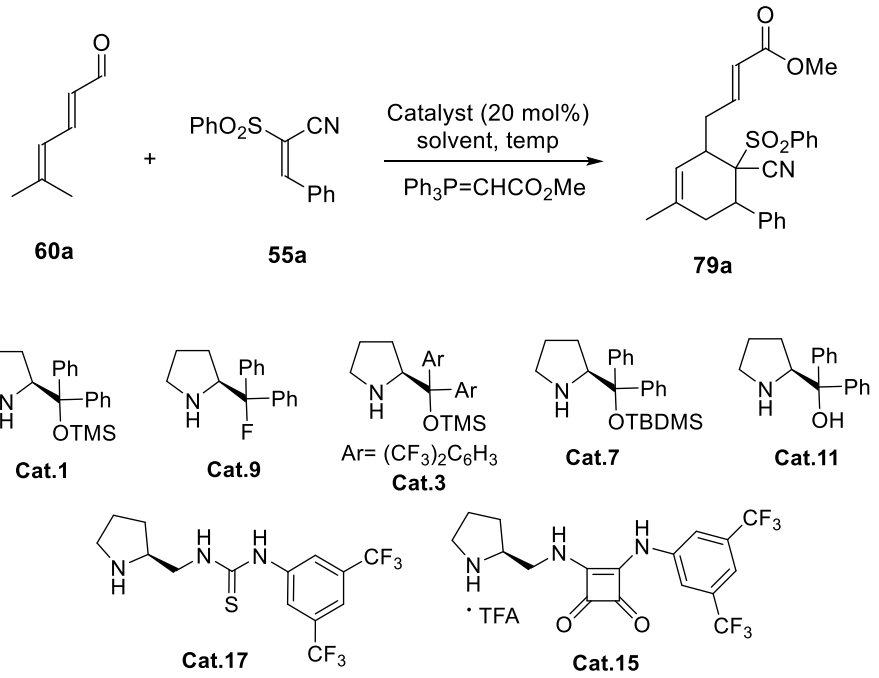
Asymmetric organocatalysis has attracted much attention in recent years. In particular, trienamine catalysis have been shown to be efficient catalysts for a wide range of asymmetric reactions. Therefore, it was interesting to develop an efficient and practical organocatalytic approach to access chiral sulfones via trienamine catalysis. Herein, it has been disclosed that trienamine aminocatalysis can promote the cycloaddition of 2,4-dienals to various vinyl sulfones with exceptional enantioselectivity. The [4 + 2] cycloaddition via trienamine catalysis can provide a library of chiral multifunctional sulfone adducts which further useful for different organic transformations (Scheme 22).



Scheme 22: *Conceptualization of the project*

3.3.2. Optimization of Reaction:

The optimization of the reaction was started with the reaction between the dienal **60a** and the dienophile **55a** in the presence of the Jørgensen–Hayashi catalyst **Cat.1** in DCM at room temperature. As, the corresponding aliphatic aldehyde **78a** was not stable enough to run in the HPLC, Wittig reagent was used to transform the compound to ester. It was found that the reaction gave the desired product **79a** with full conversion with 54% ee (entry 1, Table 3). In order to improve this preliminary result, we tested the addition of different solvents under **Cat.1** catalysis and then examined (entries 2–7). Chloroform also gave a full conversion with 72% of ee. Following this, different aminocatalysts **Cat.1, Cat.3-8** were tried (entries 8-14). Interestingly, **Cat.1** still found as best catalyst for this reaction. Latterly, when the temperature was reduced to 0 ^{o}C (entry 15), the reaction time was increase to 72 hours (entry 16). Hence the best conditions were obtained (Scheme 23).



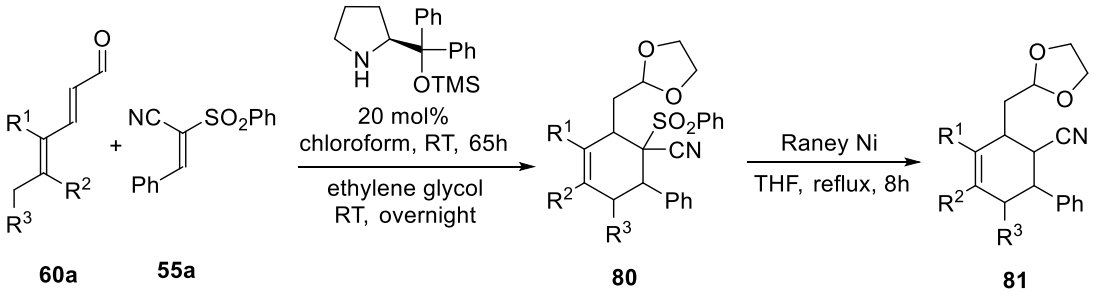
Scheme 23: *Optimization of reaction.*

Entry	Cat.	mol %	Equiv. of alde.	Time (hours)	Solvent	Temp. (°C)	Conv. (%)	Yield (%)	dr	ee (%)
1	Cat.1	20	1.5	60	DCM	rt	100	76	1:2	54
2	Cat.1	20	1.5	60	Chloroform	rt	68	--	1:2	**72**
3	Cat.1	20	1.5	60	toluene	rt	20.6	--	--	8
4	Cat.1	20	1.5	60	p-xylene	rt	19.3	--	--	9
5	Cat.1	20	1.5	60	THF	rt	31	--	1:3	nd[1]
6	Cat.1	20	1.5	60	dioxane	rt	37.5	--	1:5	nd[1]
7	Cat.1	20	1.5	60	acetonitrile	rt	65.4	--	4:9	nd[1]
8	Cat.1	20	2	65	Chloroform	rt	84.6	--	1:2	nd[1]
9	Cat.9	20	2	65	Chloroform	rt	47.6	--	1:2	72
10	Cat.3	20	2	65	Chloroform	rt	22.5	--	--	nd[1]
11	Cat.7	20	2	65	Chloroform	rt	88	--	1:2	35
12	Cat.15	20	2	65	Chloroform	rt	18	--	1:3	nd[1]
13	Cat.11	20	2	65	Chloroform	rt	nr[2]	--	--	--
14	Cat.17	20	2	65	Chloroform	rt	nr[2]	--	--	--
15	Cat.1	20	2	65	Chloroform	0	86.2	--	2:3	78
16	**Cat.1**	**20**	**2**	**72**	**Chloroform**	**0**	**100**	**80**	**2:3**	**78**

Table 3: *Optimization Table ([1] n.d – not determine, [2]nr – no reaction, [3]conversion and dr is calculated by [1]H NMR, [4]ee is calculated by CO_2 gas HPLC)*

3.3.3. Derivatization of reaction

After optimization of reaction, a different approach was performed by desulfonating the cycloadduct by using Raney Ni. The cycloadduct was protected by using ethylene glycol, later on, resulting compound **80** were treated with Raney Ni in THF under reflux condition to achieve **81** in good yields. The resulting type of compounds are difficult to synthesize and has synthetic applications.



Scheme 24: *Desulfonation by Raney Nickel*

3.3.4. Perspectives

- To complete the scope of the reaction: In current status, some of the derivatives has been synthesized and some of derivatives are planned to complete the scope. The starting material for each planned derivative, are already synthesized.
- To study the absolute configuration of the cycloadduct.

3.3.5. Conclusion

In conclusion, we have demonstrated that aminocatalysts could control the asymmetric reactivity of sulfone substituted dienophiles to generate highly enantioenriched products with up to four contiguous stereocenters, one of which is quaternary in nature. Future work will involve both the theoretical study of the mechanism of reaction, as well as the use of this new amino acid precursor within peptide chemistry.

3.4. Summary and Outlook

In this chapter, a contribution of our group in trienamine catalysis has been disclosed and another four different dienophiles treated with trienamine catalysis will be presented in the next two chapters with different aspects. As a closing remark, it is tempting to look back at the opening words of the chapter, in which it was stated that, most of the rational chemical designs were initially trigger by natural inspirations (Scheme 14), however, one might wonder if rationally designed activation modes, such as trienamine activation also might serve as potential lead in the quest for more unknown biosynthetic pathways. The polyenal chromophores found in many life essential compounds (e.g. retinal), and as such, the following question could be asked: could it be possible that polyenamines mediated reactions actually presented in biosynthesis? To the best of our knowledge, such examples are up-to-date unknown or else, can we just prepare some bioactive compounds? Well, let's find out in the next chapter.

Chapter 4.

Enantioselective synthesis of chiral tetrahydrocarbazole: A trienamine strategy to access bioactive molecules.

In previous chapter, trienamine strategy with specifically designed dienophiles was discussed. Herein, modification of previous reports as well as it has been discussed, how previously used dienophiles can be useful to synthesize bioactive compounds.

4.1. Concept and design plan

The chiral tetrahydrocarbazoles (THCs) are an important class of heterocyclic compounds with wide existence in numerous natural indole alkaloids as well as synthetic pharmaceuticals.[99] They have been reported to display a broad spectrum of bioactivities (Fig. 1). To name a few, (-)-alloaristoteline **82** and (+)-aristoteline **83** are used in Chilean folk medicine to reduce pain and inflammation.[100] Fischambiguine B **84** exhibits strong inhibitory activity against *Mycobacterium tuberculosis*.[101] Moreover, frovatriptan **85** is a novel triptan drug for the treatment of migraine headaches[102] and (R)-ramatroban **86** shows great potential for treating coronary artery disease and asthma (Figure **19**).[103]

Driven by their high significance and important bioactivities, the synthesis of chiral THCs continues to be a highly active research area in organic synthesis. Over the past decades, the rapid development of asymmetric catalysis enables a plethora of catalytic asymmetric methodologies involving diverse disconnection strategies toward the construction of the THC architecture. These mainly include intramolecular Friedel–Crafts-type alkylations, [4+2] cycloadditions, domino Michael–Henry reaction, Michael addition/Ciamician–Plancher rearrangement, [3+3] annulation, Fischer indolization and intramolecular hydroamination/ Michael addition cascade.

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[99] (a) J. Bonjoch and D. Sole´, Chem. Rev., 2000, 100, 3455; (b) J. Steele, N. Veitch, G. Kite, M. Simmonds and D. Warhurst, J. Nat. Prod., 2002, 65, 85.

[100] D. Stoermer and C. H. Heathcock, J. Org. Chem., 1993, 58, 564

[101] S. Mo, A. Krunic, B. D. Santarsiero, S. G. Franzblau and J. Orjala, Phytochemistry, 2010, 71, 2116.

[102] S. E. Easthope and K. L. Goa, CNS Drugs, 2001, 15, 969.

[103] T. Ishizuka, T. Matsui, Y. Okamoto, A. Ohta and M. Shichijo, Cardiovasc. Drug Rev., 2004, 22, 71.

Conjointly, in the development of trienamine catalysis, several reports to synthesize chiral THCs have been observed, by continuing this streak, our group was more interested to synthesize THCs by using indole carboxylate (masked 2,4-dienal) with chromenes, benzoquinones and naphthoquinones as dienophiles via trienamine catalysis. Not impossibly, these types of moieties can show new biological activities or can improve previous generation to synthesize THCs efficiently (Scheme 25).

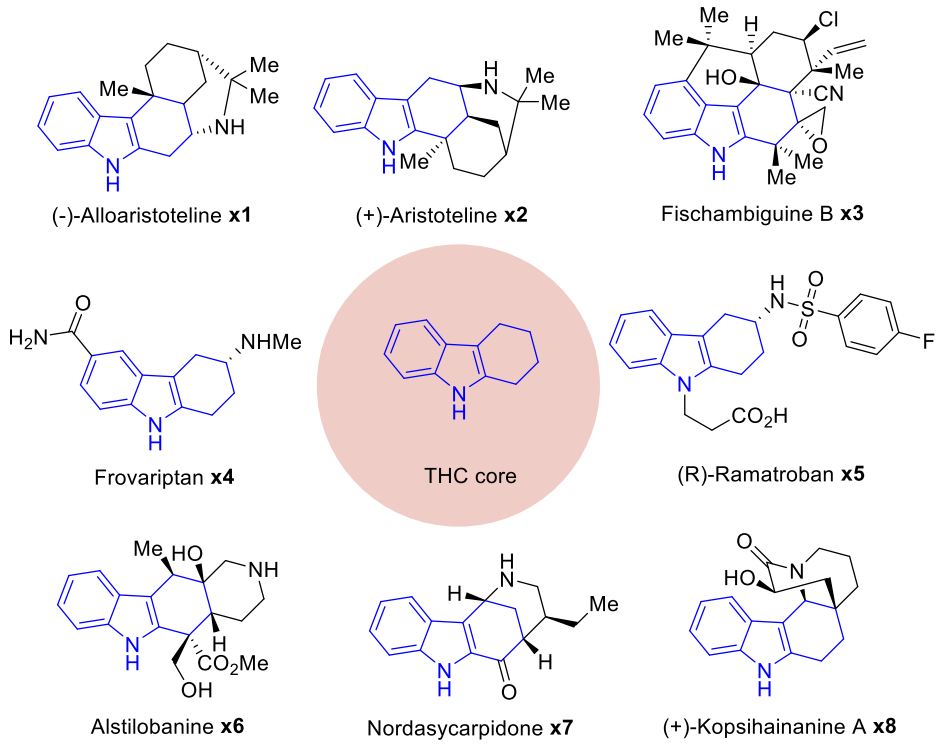


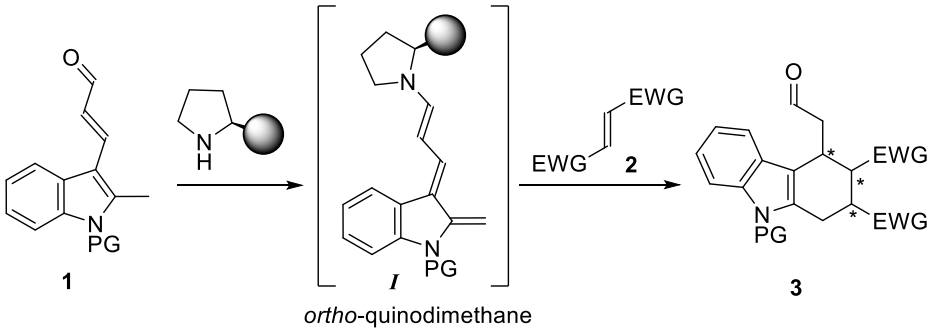
Figure 19: *Representative chiral THCs in natural products and bioactive molecules.*

over the past decades, chemists are focusing more towards new methodologies to synthesize known or novel chiral THC frameworks. At the same time, the newly developed trienamine catalysis strategy has attracted considerable attention for the synthesis of chiral privileged structures.[104] In fact, during its conceptualization, a new methodology was developed to synthesize chiral THC´s by using 2-methylindole acrylaldehyde **87** as a masked 2,4-dienal.[105] In this strategy, the condensation of a chiral secondary amine with

[104] Pawar, T. J.; Jiang, H.; Vazquez, M. A.; Villegas-Gomez, C.; Cruz-Cruz, D. *Eur. J. Org. Chem.* **2018**, 1835–1851.

[105] Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212–15218. B) Liu, Y.; Nappi, M.; Escudero-Adán, C. E.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310-1313.

the acrylaldehyde **87** lead to the formation of a *ortho*-quinodimethane intermediate **88**, which is an active trienamine species with the ability to react with a variety of dienophiles **89** and construct different chiral THC derivatives **90** (Scheme 25). Recently, many asymmetric transformations have been reported using this strategy along with the modification of previous reports but none of the chiral THC were studied before.[106]



Scheme 25: *A trienamine strategy to synthesize THC core.*

The purpose of this study is to synthesize novel THC's which can be biologically and pharmacologically important and can be considered as a member of alkaloids. Also, the trienamine methodology for the synthesis of THC will set a new base for the organic chemists to contribute to the medicinal field as it is necessary to uncover this kind of chiral THC compounds and their biological activities.

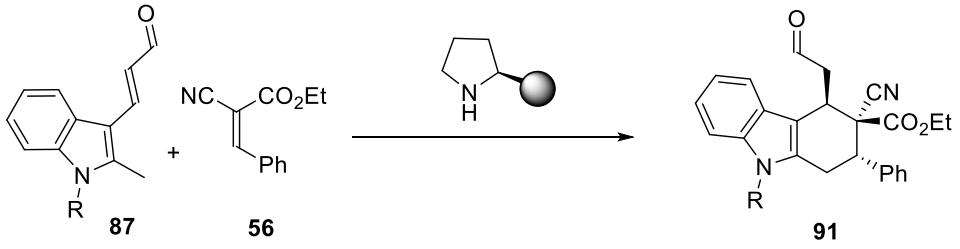
[106] a) Jiang, H.; Cruz-Cruz, D.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 5200-5207. b) Portalier, F.; Bourdreux, F.; Marrot, J.; Moreau, X.; Coeffard, V.; Greck, C. *Org. Lett.* **2013**, *15*, 5642-5645. c) Villegas-Gómez, C.; Cruz-Cruz, D.; Mose, R.; Jørgensen, K. A. *Chem. commun.* **2014**, *50,* 6035-6038. d) Cruz-Cruz, D.; Mose, R.; Villegas-Gómez, C.; Torbensen, S. V.; Larsen, M. S.; Jørgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 11331-11335. e) Pantaine, L.; Coeffard, V.; Moreau, X.; Greck, C., *Eur. J. Org. Chem.* **2015**, *2015*, 2005-2011. f) Guerrero-Corella, A.; Asenjo-Pascual, J.; Pawar, T. J.; Díaz-Tendero, S.; Martín-Sómer, A.; Villegas-Gómez, C.; Belmonte-Vázquez, J. L.; Ramírez-Ornelas, D. E.; Peña-Cabrera, E.; Fraile, A.; Cruz-Cruz, D.; Alemán, J. *Chem. Sci.* **2019**, *10*, 4346–4351.

4.2. Asymmetric synthesis of tetrahydrocarbazole using cyanophenyl acrylate as dienophile in trienamine catalysis

4.2.1. Conceptualization of project

From the past 20 years, it has been observed that depression, anxiety and mood disorder are the cause of morbidity in the developed nations. Hence, the circumstance call for research for the discovery of new drugs or medicines that possess anxiolytic activity with no toxicity and withdrawal effect.[107] In this era, a number of drugs has been reported with this type of activity, whereas chiral THC alkaloids are pharmacologically important compounds that make worthy to synthesize it and perform biological tests to disclose forbidden activities of these structures.

From previously reported reaction, dienophile **56** can be treated with 2-methylindole acrylaldehyde **87** can deliver novel THC's efficiently via Diels-Alder cycloaddition reaction. In addition, the resulting THC's can turn up with outstanding biological activities, that can contribute to the medicinal field (Scheme 26).



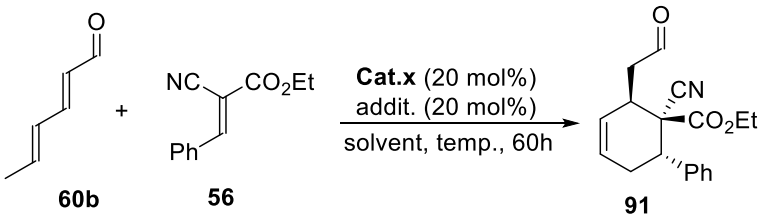
Scheme 26: *Conceptualization of project*

4.2.2. Optimization of reaction

We started this work by analysing the first report of trienamine strategy by Jorgensen,[8] in this study, the 2,4-dienal **60** condense with chiral amine **Cat.18, Cat.20, Cat.1 and Cat.5** to form corresponding trienamine intermediate which through a Diels-Alder cycloaddition with ethyl cyanophenyl acrylate **87** lead to the expected cyclohexene **92** (Table 4, entries 1 and 2). We initiate our work by improving the previous condition.

[107] edláčková, N.; Ponechalová, V.; Ujházy, E.; Dubovický, M.; Mach, M. *Interdiscip Toxicol*. **2011**, *4,* 211-215.

Initially, we check the reaction with different solvents with or without additives and by varying the temperature (rt to 70 ºC). by using toluene as solvent and without additive, the reaction response was satisfied at 70 ºC. In the trial of Jorgensen-Hayashi catalysts, **Cat.1** the stereoselectivity was improved (entry 3) However, to our glad the best results (98% ee and 96:4 dr were obtained in presence of more sterically hindered catalyst **Cat.5** (entry 4). Thus, we improve the stereoselectivity of reaction far better than the previous report. Although, best conditions were obtained, subsequently same conditions were tried with *N*-protected 2-methyl indole acrylaldehyde **87** along with individual optimization for compound **87** were performed, and earlier condition found to be best as well (Scheme 27).



Scheme 27: *Optimization of reaction*

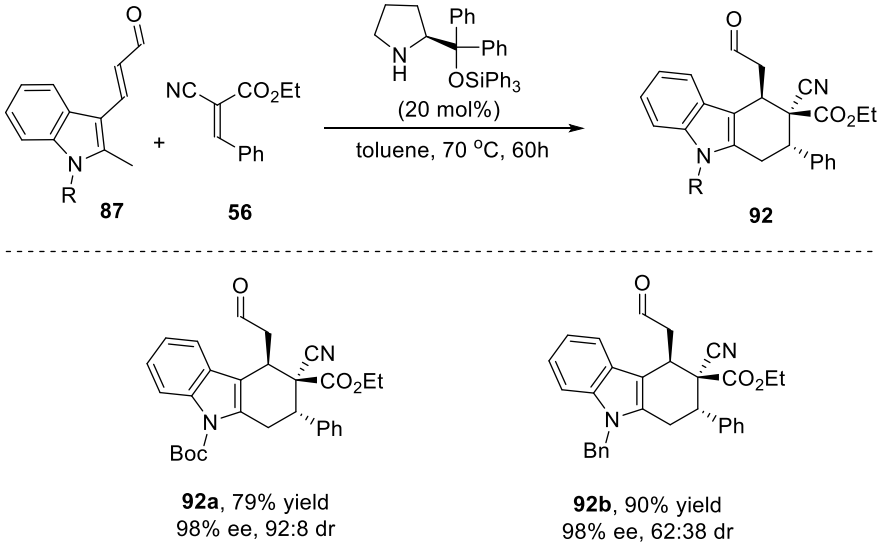
Entry	Cat.	T (°C)	Solvent	Addit.	Yield (%)[d]	dr [c]	ee (%)
1[b]	Cat.18	50	$CHCl_3$	*o*FBA	81	86:14	89
2[b]	Cat.20	50	$CHCl_3$	*o*FBA	87	80:20	86
3	Cat.1	70	toluene	-	75	82:18	93
4	Cat.5	70	toluene	-	73	96:4	98

Table 4: *Optimization of reaction: All the reactions were carried out in the scale of 0.1 mmol of dienophile, 0.2 mmol of aldehyde, and 0.02 mmol of catalyst for 60 h. [b]condition of previous report, [c]all values are calculated by ^{1}H NMR analysis, [d]calculated after isolation of the product.*

4.2.3. Scope of reaction

The reaction handovers outstanding response with **92a** and **92b** due to bulky protection (Boc and benzyl respectively) of nitrogen on indole. On the basis of this result

as well as by considering the THC motif, we started performing different biological activity tests on **92a** and **92b** (Scheme 28).



Scheme 28: *Scope of reaction*

4.2.4. Biological activities.

After performing multiple tests, it was found that these THC molecules reduced the anxiety-like behavior in a dose-dependent fashion (Figure 20, A and B). The Emax were shown by these compounds were: 72% (25 mg/kg, **92a** (**THC-1**)) and 83.4% (25 mg/kg, **92b** (**THC-1**)). These effects were almost similar compared to those found with 1.5 mg/kg CNZ. (Fig. 2 A and B). The values for the effective dose 50 were: 3.3 mg/kg (**92a**) and 7.7 mg/kg (**92b**). Molecules **92a** and **92b** slightly reduced the time on the rotarod in a dose-dependent impairment. However, this effect was not significant compared to the vehicle group (Figure 20, C). Only molecule **92b** (100 mg/kg) significantly ($p<0.05$) reduced the time on rotarod at 60 min-post-treatment. However, this was a partial effect since mice recover their motor coordination 60 min later (Figure 20, D).

Although the anxiolytic-like actions of these two molecules were not comparable to those found with CNZ, these two molecules did not significantly affect motor coordination in mice at doses lower than 25 mg/kg (Figure 20).

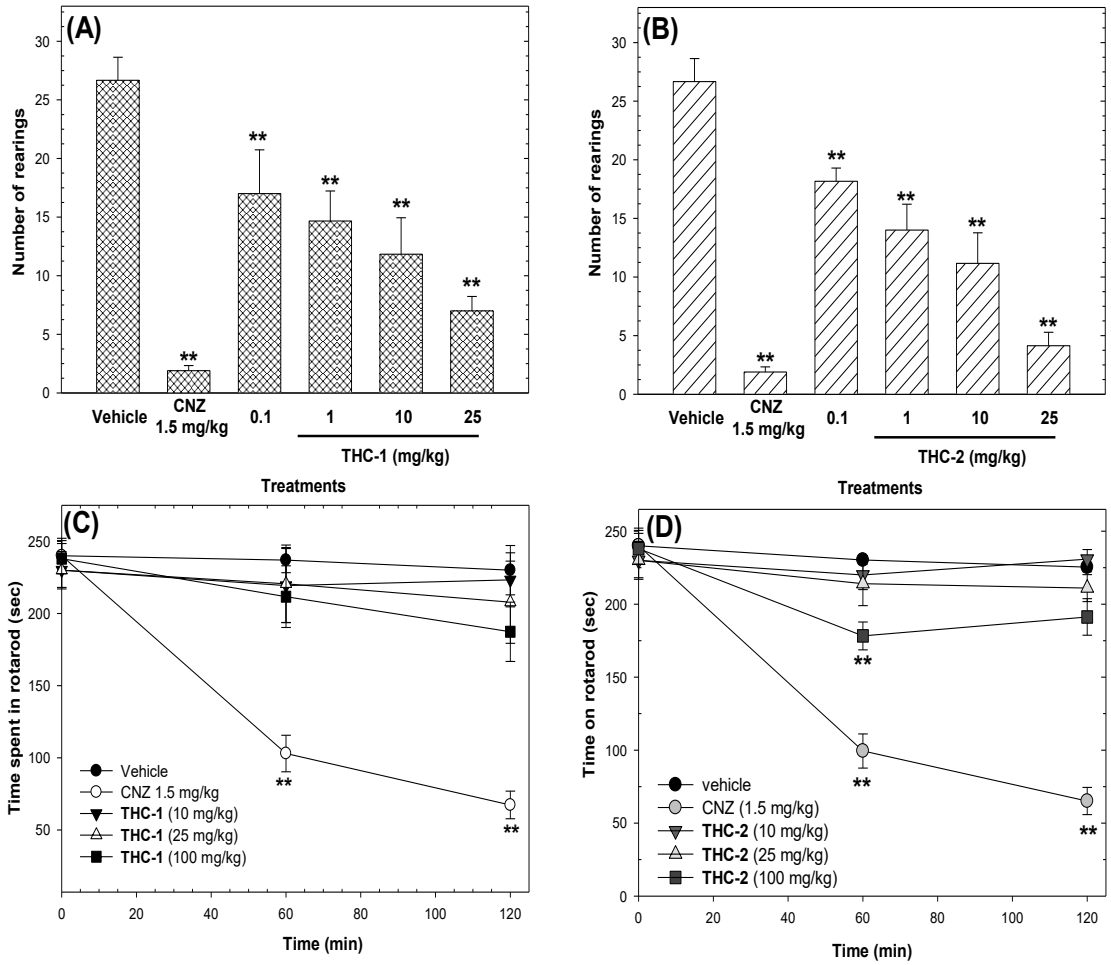


Figure 20: *Anxiolytic-like and locomotor effects of molecules **92a (THC-1)** and **92b (THC-2)**. The anxiolytic effects of **92a** and **92b** (0.1–25 mg/kg p.o.) were evaluated using the cylinder exploratory test, recording the number of readings (A and B). The effects of **92a** and **92b** (10-100 mg/kg) on locomotion in mice were evaluated with the rotarod test (C and D). Additional groups were administered with 1.5 mg/kg clonazepam (CNZ) as the positive control or the vehicle (saline solution). Data are demonstrative of two parallel experiments (n = 8). Results represent the mean ± standard error media (SEM). ** represents $p \leq 0.05$ in comparison to the vehicle group, using ANOVA and Dunnett´s post hoc test.*

4.2.5. Conclusion.

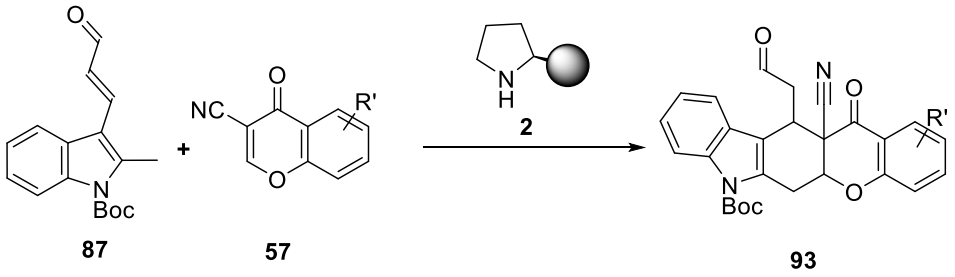
The results showed that, these THC molecules possess potent anxiolytic activity, and can be used as lead compounds in the drug discovery area. Also, the trienamine methodology for the synthesis of THC will set a new base for the organic chemists to contribute to the medicinal field as it is necessary to uncover this kind of chiral THC compounds and their biological activities (See Appendix III).

4.3. Asymmetric synthesis of tetrahydrocarbazole using chromenes, benzoquinones and naphthoquinones as dienophile in trienamine catalysis

4.3.1. Conceptualization of project

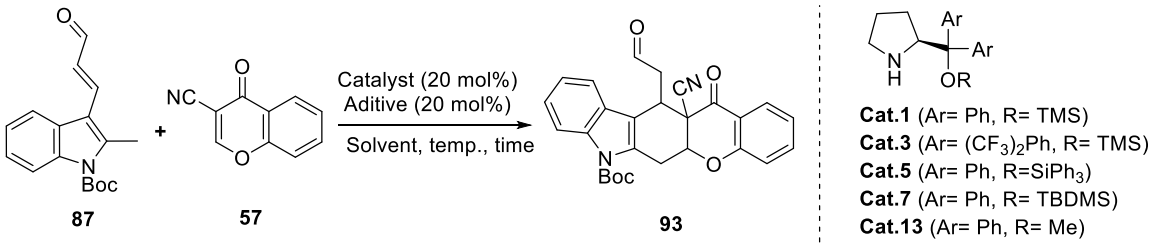
Over the past decades, chemists are focusing more towards different new methodologies to synthesize known or novel chiral THC cores. At the same time, newly developed trienamine catalysis strategy grips a great consideration in the synthesis of chiral privileged structures.[4] In fact, a new methodology was developed to synthesize chiral THC by using 2-methylindole acrylaldehyde as a masked 2,4-dienal in trienamine catalysis.[5] In this strategy, Indole (Scheme 1, down) get dearomatize to form ortho-quinodimethane which is an active trienamine species with ability to react with a variety of dienophiles and can construct chiral THC core.[6] Recently, many asymmetric transformations have been reported using this strategy along with the modification of previous reports.

The purpose of this study is to synthesize novel THC's which can be biologically and pharmacologically important and can be consider as a member of alkaloids. And they can be synthesized by using different types of previously used or novel dienophiles (Scheme 29).



Scheme 29: *Conceptualization of project*

4.3.2. Preliminary tests



Scheme 30: *Optimization of reaction*

Entry	Cat.	Solvent	Additive	Conditions	conv.[b] (%)	dr[b]	ee %
1	Cat.1	$CHCl_3$	--	rt, 72h	24	--	n.d.[f]
2	Cat.1	$CHCl_3$	--	55°C, 72h	44	--	n.d.
3	Cat.1	$CHCl_4$	--	70°C, 72h	56	--	n.d.
4	Cat.1	$CHCl_3$	BA	70°C, 72h	85 (48)	03:01	n.d.
5	Cat.1	$CHCl_3$	*p*NBA	70°C, 72h	84 (54)	03:01	n.d.
6	Cat.1	$CHCl_3$	AcONa	70°C, 72h	29	05:01	n.d.
7	Cat.1	$CHCl_3$	DPTU	70°C, 72h	28	03:01	n.d.
8	Cat.1	THF	BA	70°C, 72h	37	03:01	n.d.
9	Cat.1	MeCN	BA	70°C, 72h	44	03:01	n.d.
10	Cat.1	DCE	BA	70°C, 72h	68	03:01	n.d.
11	Cat.1	toluene	BA	70°C, 24h	93 (67)	03:01	n.d.
12	Cat.1	dioxane	BA	70°C, 48h	73 (69)	08:01:01	n.d.
13	Cat.1	toluene	BA	70°C, 24h	92 (67)	03:01	81
14	Cat.3	toluene	BA	70°C, 96h	62	05:02:01	26
15	**Cat.5**	**toluene**	BA	70°C, 46h	**96 (51)[c]**	**<3:1**	**83**
16	Cat.7	toluene	BA	70°C, 96h	63	06:01:01	2
17	Cat.13	toluene	BA	70°C, 60h	85	02:01	5
18	Cat.5	toluene	BA	110°C[h], 10h	71	03:01	55
19	Cat.5	toluene	BA	130°C[h], 7h	D[i]	--	--

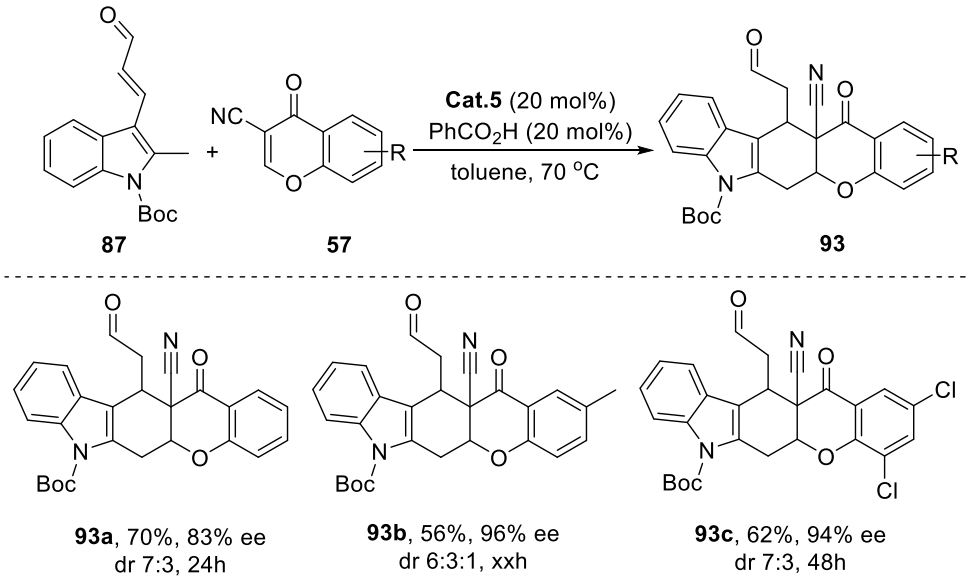
Table 5: *Optimization of reaction: [a] 0.1 mmol of **57a**, 0.15 mmol of **87** in 0.5 mL of the indicated solvent and the same amount of additive as catalyst [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield after flash-chromatography in brackets. [d] Determined by SFC. [e] Complex mixture. [f]Not determined. [g] No reaction. [h] Reactions were done in microwave. [i] Distortion.*

The optimization of the reaction was started with the reaction between the indole carboxylate **87** and the dienophile **57** in the presence of the Jørgensen–Hayashi catalyst **Cat.1** in chloroform at room temperature. We found that the reaction gave the desired

product **93a** with a very low conversion (entry 1, Table 5). Latterly, when the temperature was increased to 70 °C (entry 13), a conversion was increased to 56% .In order to improve this preliminary result, we tested the addition of different additives (entries 4-7), increasing the conversion to 85% with addition of benzoic acid. Different solvents under **Cat.1** catalysis was then examined (entries 8–13). Toluene gave an impressive yield with 24% of conversion (81% ee). Following this, different aminocatalysts **Cat.3, Cat.5, Cat.7** and **Cat.13** were tried. Interestingly, **Cat.5** gave an impressive dr and ee. The results were not satisfied in the microwave.

4.3.3. Scope of Reaction

After getting best conditions, reaction was performed with two different substituted cyanochromenes. It was found that, the reaction works better with **93b** and **93c**. On the basis of this result as well as by considering the THC motif, we started performing different biological activity tests on following compounds **93a-c** (Scheme 31).



Scheme 31: *Scope of the reaction*

4.3.4. Biological activities.

After performing multiple tests, it was found that these THC molecules reduced the anxiety-like behavior and low antidepressant-like actions in mice (Figure 21, A and B). **93a** showed anxiolytic-like actions in a dose-dependent manner (Figure 21A). The E_{max}

and the value for the effective dose 50 were 61.1% (25 mg/kg**)** and 4.1 mg/kg, respectively. **93a** exerted antidepressant-like effects with Emax=16% (Figure 21B). The enantiomer of **93a** showed ED_{50}> 50 mg/kg in the cylinder exploratory test and the tail suspension test (results not shown). The positive controls CNZ (1.5 mg/kg) and FLX (20 mg/kg) induced anxiolytic-like and antidepressant-like actions by 90% and 49%, respectively. The findings showed that **93a** induced anxiolytic-like behavior.

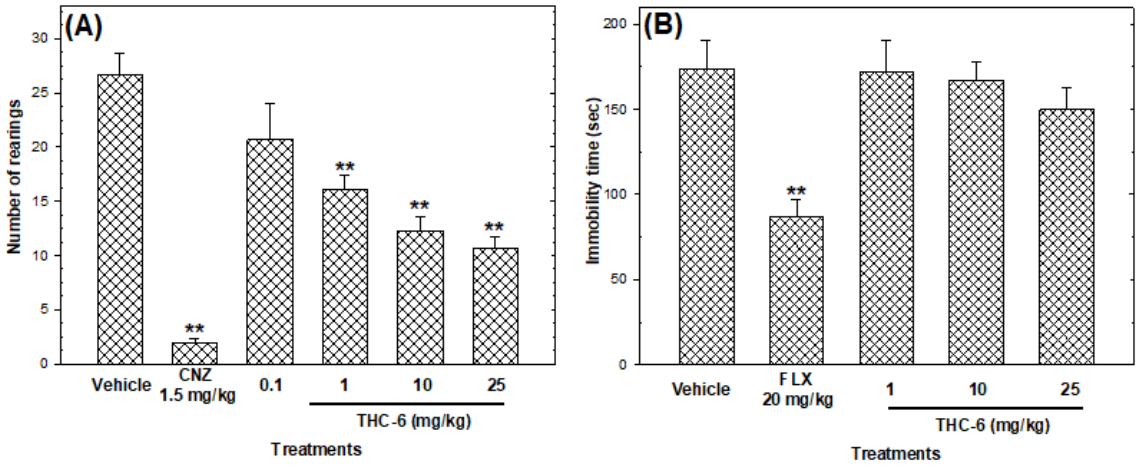


Figure 21: *Anxiolytic-like and anti-depressant effects of* ***93a*** *(**THC-6**). The anxiolytic-like and antidepressant-like effects of* ***93a*** *(0.1–25 mg/kg p.o.) were evaluated using the cylinder exploratory test, recording the number of readings (A) and the tail suspension test recording the immobility time (B). Additional groups were administered with 1.5 mg/kg clonazepam (CNZ) or fluoxetine (FLX) as the positive controls or the vehicle (saline solution). Data are demonstrative of two parallel experiments (n = 8). Results represent the mean ± standard error media (SEM). ** represents p ≤ 0.05 in comparison to the vehicle group, using ANOVA and Dunnett's* post hoc *test.*

4.3.5. Perspective

- To study the absolute configuration of the cycloadduct

4.3.6. Conclusion

In conclusion, it was found that these THC molecules possess potent anxiolytic activity and can be used as lead compounds in the drug discovery area.

4.4. Summary and Outlook

In this chapter, a contribution of our group in medicinal chemistry has been disclosed which was perform under trienamine catalysis. As a closing remark, it is tempting to look back at the opening words of the chapter, in which it was stated that, both projects will be carried out under the perspective of contribution in the drug discovery and luckily we end up with success. Also, we used previously used dienophiles used in trienamine catalysis, which proves the never-ending extension of trienamine methodology as well as different approach towards medicinal chemistry via trienamine chemistry acted as buildings blocks for the construction of THC's efficiently. Overall, this chapters explains the applications of trienamine catalysis and in the next chapter, another BODIPY dienophile treated with trienamine catalysis as well as iminium-ion catalysis will be presented.

Chapter 5.

BODIPY compounds as dienophiles in aminocatalysis: new efficient pathways to construct chiral fluorescent scaffolds.

Until now, it has been shown that, this thesis work is mainly focusing on trienamine catalysis, which explains new approach to the known dienophiles or exploration of new dienophiles. This never-ending research uncovered a new BODIPY dienophile or in other words, BODIPY as electron withdrawing group, that can make a suitable dienophile for the trienamine catalysis. In this chapter, it has been demonstrated that, new BODIPY dienophiles can be used for asymmetric transformations, such as trienamine activation and 1,6-oxaMichael-Michael addition, in short "new dog with old tricks" to synthesize novel chiral fluorescent compounds has been discussed.

5.1. BODIPY and Importance of the Scaffold.

BODIPY dyes (BOron DIPYrromethene) was first discovered in 1968 by Treibs and Kreuzer.[108] Since then, there has been a remarkable work in the chemistry and properties of BODIPY; but still the work on BODIPY is an open-ended challenge BODIPY is a small planar intensely fluorescent system with partial aromatic character. The IUPAC numbering system for BODIPY is offbeat than dipyrromethenes which can cause disorientation.[109] Delocalization of BODIPY may lead to partial aromaticity. (Figure 22)

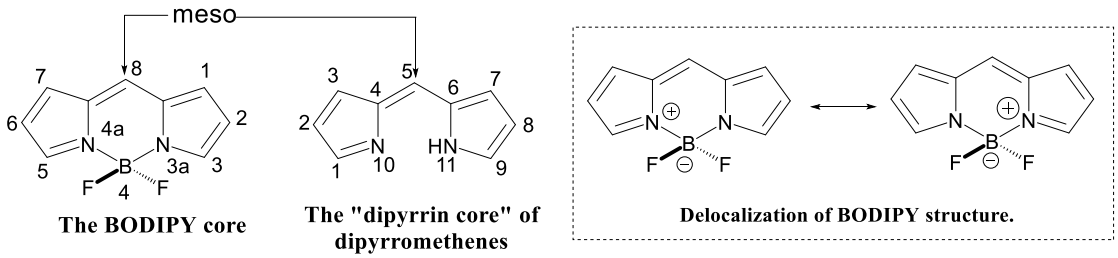


Figure 22: *The BODIPY core and IUPAC nomenclature system and delocalization of BODIPY.*

[108] Treibs, A.; Kreuzer, F. H. Justus Liebigs *Ann. Chem.* **1968**, *718*, 208.
[109] Loudet, A.; Burgess, K. *Chem. Rev*., **2007**, 107, 4891.

BODIPY scaffold is used as a fluorophore in the design, synthesis and application of fluorescent indicators for pH, metal ions, anions, biomolecules, reactive oxygen species, reactive nitrogen species, redox potential, chemical reactions and various physical phenomena[110] due to their excellent robustness, and chemical- and photo-stability.[111] The structure of the BODIPY derivatives is formed by two pyrrole units linked by a carbon and complexed with a disubstituted boron atom, mainly a BF_2 motif, which forms the core scaffold. BODIPY dyes are notable for their uniquely small Stokes shift, high, environment-independent fluorescence quantum yields, often approaching 100% even in water, sharp excitation and emission peaks contributing to overall brightness, and high solubility in many organic solvents. The combination of these qualities makes the BODIPY fluorophore an important tool in a variety of imaging applications. The position of the absorption and emission bands remain almost unchanged in solvents of different polarity as the dipole moment and transition dipole are orthogonal to each other. Applications include the use of cadmium-selective probes, based on BODIPY, to image and sense cadmium in cells[112] and labelling oligonucleotides for sequencing.

BODIPY shows impressive spectroscopic properties such as narrow absorption and emission bands in the visible wavelength range, high fluorescence quantum yields and large molar absorption coefficients among others.[113] As a result of these interesting characteristics, this class of fluorophores has attracted a lot of attention due to their numerous applications, for instance, as labelling reagents, in the bioimaging of living

[110] Boens, N.; Leen V.; Dehaen, W. *Chem Soc Rev.* **2012**, *41*, 1130-1172.

[111] (a) Boens, N.; Verbelen, B.; Dehaen, W., *Eur. J. Org. Chem*., **2015**, 6577; (b) Ulrich, G.; Ziessel, R.; Harriman, A., *Angew. Chem., Int. Ed*., **2008**, *47*, 1184.

[112] Taki, M. *Springer*. **2013,** 11, 99115.

[113] (a) Boens, N.; Leen, V.; Dehaen, W., *Chem. Soc. Rev*., **2012**, *41*, 1130; (b) Loudet, A.; Burgess, K., *Chem. Rev*., **2007**, *107*, 4891.

cells,[114] as radiotracers for positron emission tomography,[115] photocatalysts[116] or photodynamic therapy (PDT).[117] In addition, the introduction of stereogenic centres in these types of structures is of great importance as it is possible to modulate the BODIPY photophysics. Therefore, chiroptical applications based on circular dichroism (CD) and circularly polarized luminescence (CPL) can be used in devices for optical storage, enantioselective CPL sensors, Optical Processing system, 3D optical display, biological probes and signatures, future development of CPL microscopes, spintronic-based devices, security tags and also light-emission system for asymmetric photosynthesis.[118]

[114] (a) Kolemen, S.; Akkaya, E. U., *Coord. Chem. Rev.*, **2018**, *354*, 121; (b) Krajcovicova, S.; Stankova, J.; Dzubak, P.; Hajduch, M.; Soural, M.; Urban, M., *Chem. Eur. J.*, **2018**, *24*, 4957; (c) Lincoln, R.; Greene, L. E.; Zhang, W.; Louisia, S.; Cosa, G., *J. Am. Chem. Soc*., **2017**, *139*, 16273; (d) Kowada, T.; Maeda, H.; Kikuchi, K., *Chem. Soc. Rev.*, **2015**, *44*, 4953; (e) Rivera-Fuentes, P.; Lippard, S. J., *Acc. Chem. Res*., **2015**, *48*, 2927; (f) Ni, Y.; Wu, J., *Org. Biomol. Chem*., **2014**, *12*, 3774.

[115] (a) Chansaenpak, K.; Vabre, B.; Gabbaı, F. P., *Chem. Soc. Rev*., **2016**, *45*, 954; (b) Chansaenpak, K.; Wang, H.; Wang, M.; Giglio, B.; Ma, X.; Yuan, H.; Hu, S.; Wu, Z.; Li, Z., *Chem. Eur. J.*, **2016**, *22*, 12122; (c) Nigam, S.; Burke, B. P.; Davies, L. H.; Domarkas, J.; Wallis, J. F.; Waddell, P. J.; Waby, J. S.; Benoit, D. M.; Seymour, A.-M.; Cawthorne, C.; Higham, L. J.; Archibald, S. J., *Chem. Commun.*, **2016**, *52*, 7114; (d) Liu, S.; Li, D.; Shan, H.; Gabbaı, F. P.; Li, Z.; Conti, P. S., *Nucl. Med. Biol.*, **2014**, *41*, 120; (e) Adam Hendricks, J.; Keliher, E. J.; Wan, D.; Hilderbrand, S. A.; Weissleder, R.; Mazitschek, R., *Angew. Chem., Int. Ed.*, **2012**, *51*, 4603.

[116] (a) Turksoy, A.; Yildiz, D.; Akkaya, E. U., *Coord. Chem. Rev.,* **2019**, *379*, 47; (b) Magagnano, G.; Gualandi, A.; Marchini, M.; Mengozzi, L.; Ceroni, P.; Cozzi, P. G., *Chem. Commun.,* **2017**, *53*, 1591; (c) Bandyopadhyay, S.; Anil, A. G.; James A.; Patra, A., *ACS Appl. Mater. Interfaces*, **2016**, *8*, 27669; (d) Liras, M.; Iglesias, M.; Sanchez, F., *Macromolecules*, **2016**, *49*, 1666.

[117] (a) Guo, X.; Li, X.; Liu, X.-C.; Li, P.; Yao, Z.; Li, J.; Zhang, W.; Zhang, J.-P.; Xue, D.; Cao, R., *Chem. Commun.*, **2018**, *54* , 845; (b) Kamkaew, A.; Lim, S. H.; Lee, H. B.; Kiew, L. V.; Chung, L. Y.; Burgess, K., *Chem. Soc. Rev.*, **2013**, *42*, 77; (c) Awuahab, S. G.; You, Y., *RSC Adv.*, **2012**, *2*, 11169.

[118] Sanchez-Carnerero, E. M.; Agarrabeitia, A. R.; Moreno, F.; Maroto, B. L.; Muller, G.; Ortiz, M. J.; de la Moya, S., *Chem. Eur. J*., **2015**, *21*, 13488.

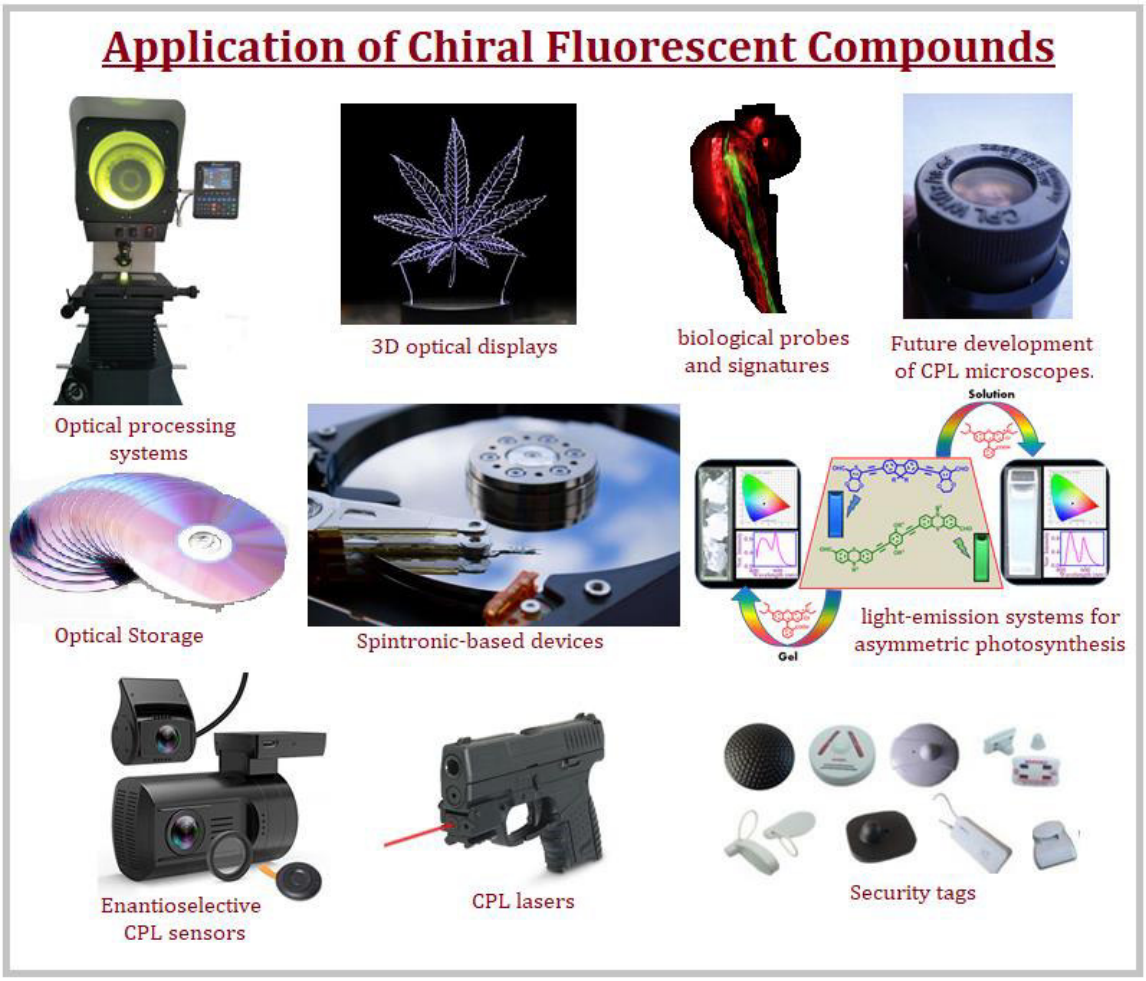


Figure 23: *Application of chiral fluorescent compounds*

BODIPY is a highly reactive species, almost all positions of BODIPY are reactive (Figure 18). There has been remarkable work on BODIPY's by palladium catalyzed C-C couplings, nucleophilic substitutions and electrophilic substitution are reported. In general, the BODIPY core is susceptible to a variety of changes, due to the high reactivity presented, allowing the different types of reactions in all positions of the nucleus depending on the type of substituents that are present. Different modes of functionalization of BODIPY dyes have been described in the literature. They present eight different positions that can be modulated, causing changes and modifications of the spectral and photochemical properties.[119] Initial studies into the reactivity and derivatization of these important

[119] Ziessel, R.; Ulrich, G.; Harriman, A., *New J. Chem.*, **2007**, *31*, 496.

building blocks have been carried out by Peña,[120] Werz,[121] Ziessel,[122] Shinokubo,[123] Burgess,[124] Liras,[125] Broring,[126] and de la Moya[127] (Figure 18).

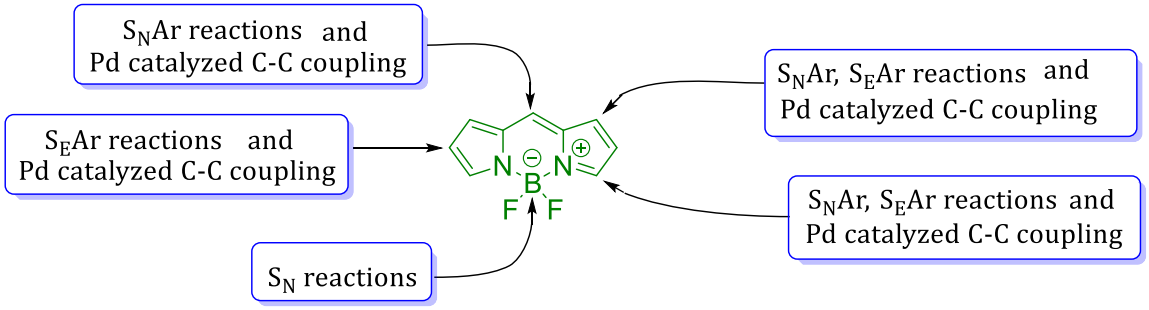


Figure 24: *Reactivity of BODIPY.*

However, despite these efforts, very little is known about the catalytic asymmetric synthesis of BODIPY derivatives. Two main reactivities can be found: aromatic type reactivities, which are related to the direct regioselective halogenations that can be performed at different positions,[128] aromatic substitutions,[129] as well as cross coupling reactions; [130] and reactivity at the methyl of the methylene bridge, the most acidic position, although the number of these examples is scarce. This latter position can be deprotonated and can react with diethyl ketomalonate, or aldehydes. Moreover, de la Moya group have

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[120] Arroyo, I.; Hu, R.; Tang, B. Z.; Lopez, F.; Peña-Cabrera, E. *Tetrahedron,* **2011**, *67*, 7244.

[121] (a) Patalag, L. J.; Ulrichs, J. A.; Jones, P. G.; Werz, D. B.; *Org. Lett*., **2017**, *19*, 2090. 2090; (b) Patalag, L. J.; Ho, L. P.; Jones, P. G.; Werz, D. B., *J. Am. Chem. Soc.,* **2017**, *139*, 15104

[122] Bura, T.; Retailleau, P.; Ulrich, G.; Ziessel, R., *J. Org. Chem.*, **2011**, *76*, 1109.

[123] Chen, J.; Mizumura, M.; Shinokubo, H.; Osuka, A., *Chem. Eur. J*., **2009**, *15*, 5942.

[124] Li, L.; Nguyen, B.; Burgess, K., Bioorg. Med. *Chem. Lett*., **2008**, *18*, 3112

[125] Liras, M.; Iglesias, M.; Sanchez, F., *Macromolecules*, **2016**, *49*, 1666

[126] Ahrens, J.; Boker, B.; Brandhorst, K.; Funk, M.; Broring, M., *Chem.–Eur. J*., **2013**, *19*, 11382

[127] (a) Sanchez-Carnerero, E. M.; Moreno, F.; Maroto, B. L.; Agarrabeitia, A. R.; Ortiz, M. J.; Vo, B. J.; Muller, G.; de la Moya, S., *J. Am. Chem. Soc*., **2018**, *136*, 3346; (b) Ray, C.; Dıaz-Casado, L.; Avellanal-Zaballa, A.; Banuelos, J.; Cerdan, L.; Garcıa-Moreno, I.; Moreno, F.; Maroto, B. L.; Lopez-Arbeloa, I.; de la Moya, S., *Chem.. Eur. J*., **2017**, *23*, 9383

[128] (a) Gutsche, C. S.; Hohlfeld, B. F.; Flanagan, K. J.; Senge, M. O.; Kulak, N.; Wiehe, A., *Eur. J. Org. Chem.,* **2017**, 3187; (b) Leen, V.; Van der Auweraer, M.; Boens, N.; Dehaen, W., *Org. Lett*., **2011**, *13*, 1470; (c) Leen, V.; Zaragozı Gonzalvo, V.; Deborggraeve, W. M.; Boens, N.; Dehaen, W., *Chem. Commun*., **2010**, *46*, 4908.

[129] Zhou, X.; Yu, C.; Feng, Z.; Yu, Y.; Wang, J.; Hao, E.; Wei, Y.; Mu, X.; Jiao, L., *Org. Lett*., **2015**, *17*, 4632

[130] (a) Leen, V.; Yuan, P.; Wang, L.; Boens, N.; Dehaen, W., *Org. Lett.,* **2012**, *14*, 6150; (b) Arroyo, I. J.; Hub, R.; Zhong Tang, B.; Lopez, F. I.; Peña-Cabrera, E., *Tetrahedron*, **2011**, *67*, 7244.

shown that boron functionalization can be easily achieved as well, introducing different alcohol or amine derivatives.

Chiral fluorescent BODIPY:

Circularly polarized luminescence (CPL) in simple (small, nonaggregate, nonpolymeric) BODIPYs is one of the important inventions from past decade. There are very few reports on chiral fluorescent compounds in the literature. In this context, Santiago de la Moya *et al.* have been reported a kind chiral BODIPY dyes in 2014; They described CPL in simple BODIPYs by irradiation with visible light. It is first detected as proof of the ability of a new structural design to achieve CPL from inherently achiral monochromophore systems in simple organic molecules (Figure 25).[131]

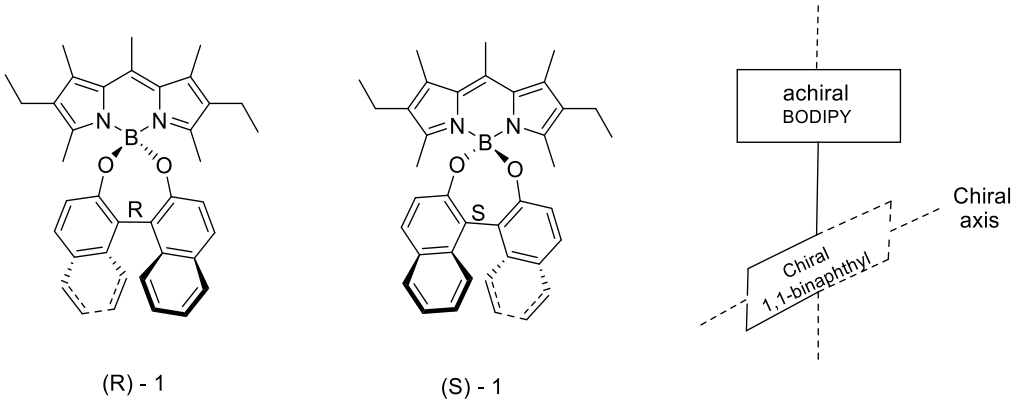

Figure 25: *chiral spiroBODIPYs.*

[131] Sánchez-Carnerero, E. M.; Moreno, F.; Maroto, B. L.; Agarrabeitia, A. R.; Ortiz, M. J.; Vo, B. G.; Muller, G.; de la Moya, S. *J. Am. Chem. Soc.* **2014**, *136*, 3346−3349.

5.2. A Trienamine strategy with a dienophile in which BODIPY as one of the electron-withdrawing groups.

As discussed in previous chapters, trienamine catalysis, being one of the most used strategies to polarize double bonds in asymmetric catalysis, is the employment of Electron Withdrawing Groups (EWG's), which decrease the energy of the LUMO, thus favouring the interaction with the HOMO of the nucleophile. This strategy has been widely used for Michael-type nucleophilic additions or stepwise [4+2] cycloadditions. For this latter reaction, trienamine catalysis has shown to be one of the most prominent strategies, using double bonds activated with nitro,[132] azlactones[133] or cyanoacetate groups[134] as dienophiles (see appendix 2). These reports have described this [4+2] addition reaction as an asynchronous cycloaddition,[135] via a Michael addition followed by an intramolecular iminium ion reaction. In all these examples, very strong EWG's, e.g. nitro group, or two nitriles, at the double bond were used in order to achieve the desired reactivity.

Therefore, based on electron-withdrawing character of the BODIPY core,[136] makes worthy if it would be possible to use this interesting fluorescent moiety as an EWG of a double bond located at one of the position of BODIPY to perform an asymmetric [4 + 2] cycloaddition. In brief, BODIPY at position 8, 1 and 3 shows more electron deficiency, whereas, position 2 can be well stabilized by resonance which tends to less reactivity (Scheme 32).

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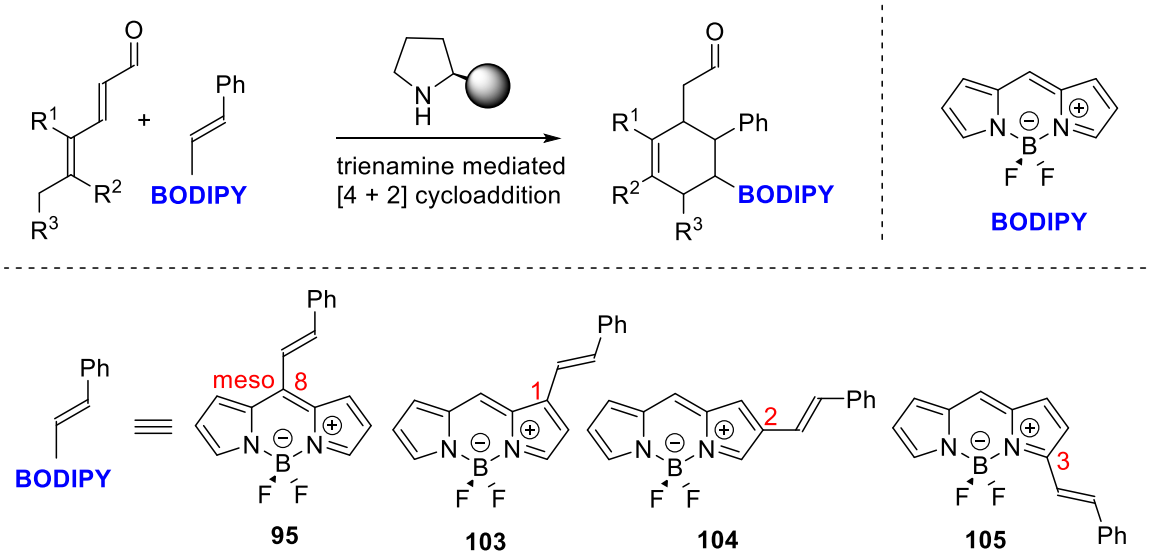
[132] (a) Li, Y.; Tur, F.; Nielsen, R. P.; Jiang, H.; Jensen, F.; Jørgensen, K. A., *Angew. Chem., Int. Ed*., **2016**, *55*, 1020; (b) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q. Chen, Y.-C., *Angew. Chem., Int. Ed*., **2011**, *50*, 8638.

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

[134] 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**, 133, 5053.

[135] Dieckmann, A.; Breugst, M.; Houk, K. N., *J. Am. Chem. Soc*., **2013**, *135*, 3237.

[136] a) Arroyo, I. J.; Hub, R.; Zhong Tang, B.; Lopez, F. I.; Peña-Cabrera, E., *Tetrahedron*, **2011**, *67*, 7244. b) Liu, Y.; Lv, X.; Hou, M.; Shi, Y.; Guo, W.; *Anal. Chem.*, **2015**, *87*, 11475.



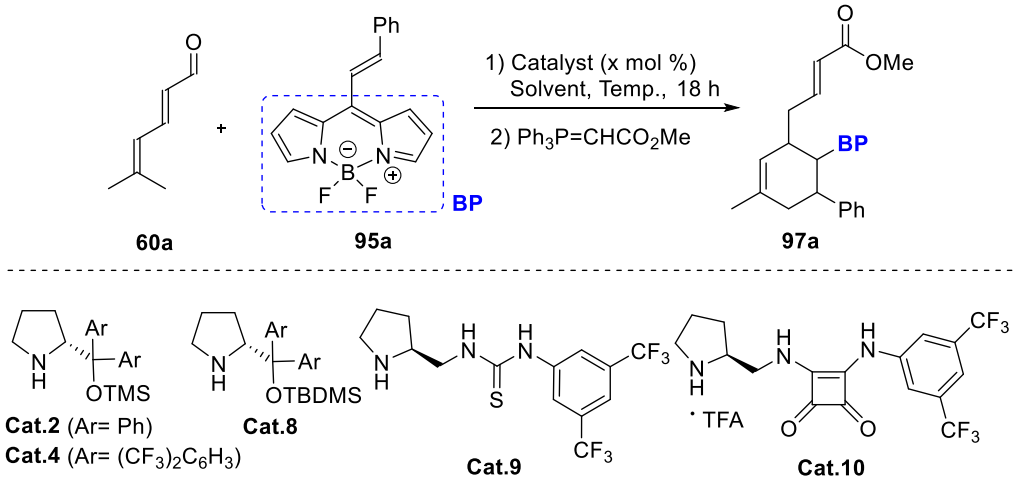
Scheme 32: *Trienamine strategy with BODIPY as one of the EWG on dienophile*

To achieve this goal, we started the work with meso-alkenyl BODIPY **95**. In the next part of this chapter, how this dienophile showed an interesting reactivity has been discussed. Furthermore, the dienophile was involved in one-pot reaction, additionally, this dienophile also showed an outstanding reactivity in 1,6-oxaMichael-Michael cycloaddition reaction via iminium ion catalysis, which also create new interesting projects for another dienophiles **103-105** with plenty of questions: Would all these dienophiles show the same reactivity? Does a computational study will be enough to explain electron deficiency of each position of BODIPY? Or is it really possible to synthesize such type of dienophiles to check their reactivity? Well, time will answer all this questions or maybe there is no answer for this. That's how chemistry works.

5.3. Alkenyl BODIPY as dienophile in trienamine reactivity.

5.3.1. Optimization of reaction.

The optimization was started with the reaction between the dienal **60a** and the BODIPY **95** in the presence of the Jørgensen–Hayashi catalyst **Cat.2** in chloroform at room temperature. It was found that the reaction gave the desired product **97a** with a very low conversion (entry 1, Table 6). In order to improve this preliminary result, it was tested the addition of benzoic acid as an additive (entry 2), increasing the conversion to 32%. Latterly, when the temperature was increased to 45 ºC, full conversion was achieved (entry 3). Following this, different aminocatalysts **Cat.4, Cat.8, Cat.9, Cat.10** were evaluated (entries 4-7). Interestingly, the bulkiest catalyst **Cat.4** or the hydrogen bond type catalysts **Cat.9** and **Cat.10** did not provide any conversion to the product **97a**. Different solvents under **Cat.2** catalysis were then examined. Chlorinated solvents and THF gave only modest results, but very apolar solvents such as toluene and p-xylene provided full conversions and very high enantioselectivities (94 and 96% ee). The catalytic loading was decreased to 10 mol%, achieving the product **97a** with 96% ee, full conversion, and 82% isolated yield (entry 12). However, when the catalyst loading was 5 mol%, only 10% conversion was found (entry 13).



Scheme 33: *Optimization of reaction.*

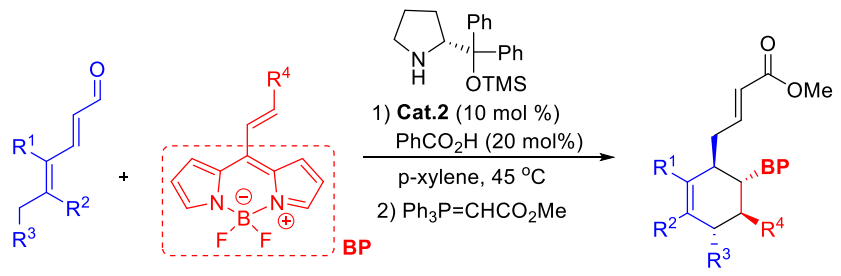
Entry	Catalyst	Solvent	T (°C)	Conv.%[b]	ee (%)
1	**Cat.2** (20)	Chloroform	rt	9	n.d.[f]
2	**Cat.2** (20)	Chloroform	rt	32	92
3	**Cat.2** (20)	Chloroform	45	100	84
4	**Cat.4** (20)	Chloroform	45	n.r.[g]	-
5	**Cat.8** (20)	Chloroform	45	n.r.[g]	-
6	**Cat.9** (20)	Chloroform	45	44	n.d.[f]
7	**Cat.10** (20)	Chloroform	45	n.r.[g]	-
8	**Cat.2** (20)	DCM	45	15	n.d.[f]
9	**Cat.2** (20)	THF	45	c.m.[e]	-
10	**Cat.2** (20)	Toluene	45	100	-
11	**Cat.2** (20)	*p*-xylene	45	100	-
12	**Cat.2** (10)	***p*-xylene**	**45**	**100 (82)**[c]	**96**
13	**Cat.2** (5)	*p*-xylene	45	10	n.d.[f]

Table 6: *Optimization of reaction: [a]All the reactions were performed in 0.05 mmol scale of 2 and 0.5 mL of solvent for 18 h. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Isolated yield after flash-chromatography in brackets. [d] Determined by SFC. [e] Complex mixture. [f]Not determined. [g]No reaction.*

5.3.2. Scope and limitations.

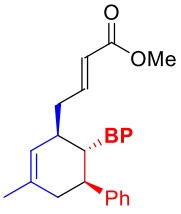
Once the best conditions were determined, the scope of the reaction was carried out using different aldehydes **60** and BODIPYs **95** (Scheme 34). The reaction worked even when all substituents were hydrogen ($R^1 = R^2 = R^3 = H$), giving **60b** with a 92% ee and a 72% yield. The cyclohexenes **97c** and **97d**, with different substitutions at R^1 or R^3 (Ph), were also obtained with excellent yields and enantioselectivities after 18 h. An additional stereogenic centre can be also obtained using **97e** (R^1 = Ph, $R^2 = R^3$ = Me) and **97f** ($R^1 = R^2 = R^3$ = Me), that allows access to the products **97e** and **97f** with complete stereocontrol at the four stereogenic centres. An interesting indole derivative **87** was obtained with a very good ee and a good yield. The use of different EDGs (*p*-MeO) and EWG's (*p*-CF3 or *p*-Cl) at the aromatic ring of the double bond, gave dienal products **97h–j** with good results. Aliphatic derivatives were also tolerated. We also measured the absorption and emission spectra of these new BODIPYs (**97a–k**), which are comparable with other previously related derivatives, described in the literature.[137]

[137] (a) Boens, N.; Verbelen, B.; Dehaen, W., *Eur. J. Org. Chem*., **2015**, 6577; (b) Sanchez-Carnerero, E. M.; Agarrabeitia, A. R.; Moreno, F.; Maroto, B. L.; Muller, G.; Ortiz, M. J.; de la Moya, S., *Chem. Eur. J.*, **2015**, *21*, 13488; (c) Sanchez-Carnerero, E. M.; Moreno, M.; Maroto, B. L.; Agarrabeitia, A. R.; Banuelos, J.; Arbeloa, T.; Lopez-Arbeloa, I.; Ortiz, M. J.; de la Moya, S., *Chem. Commun*., **2013**, *49*, 11641.

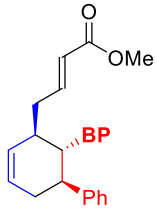


60 **95** **96**

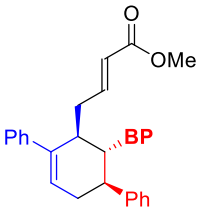
Scope of aldehydes:



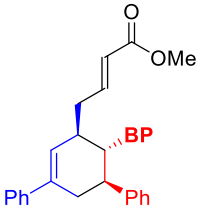
96a, 82% yield, 96% ee, 18 h



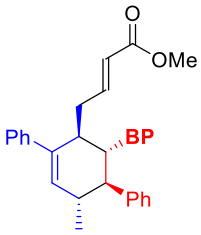
96b, 72% yield, 92% ee, 48 h



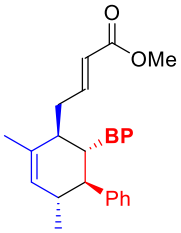
96c, 78% yield, 95% ee, 18 h



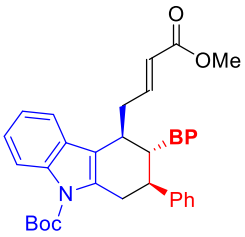
96d, 80% yield, 95% ee, 18 h



96e, 92% yield, 98% ee, 48 h

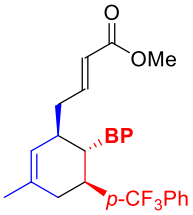


96f, 78% yield, 93% ee, 48 h

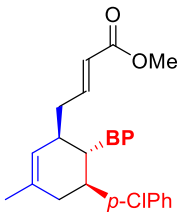


96g, 67% yield, 82% ee, 18 h

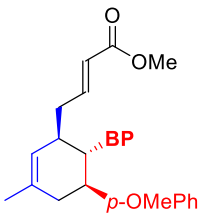
Scope of BODIPY's:



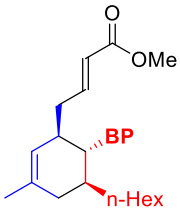
96h, 76% yield, 94% ee, 18 h



96i, 62% yield, 95% ee, 18 h



96j, 80% yield, 95% ee, 18 h

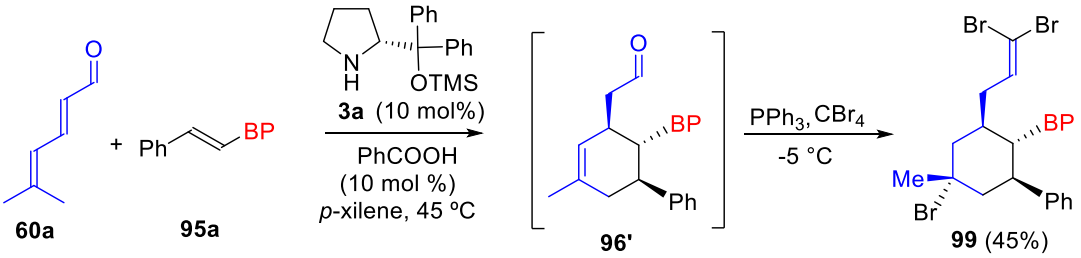


96k, 75% yield, 88% ee, 15 h

Scheme 34: *Scope of reaction*

5.3.3. Derivatization and x-ray study.

The absolute configuration was determined by derivatization of the intermediate **96'**, yielding the olefin **99** with concomitant bromination of the cyclohexene double bond (Scheme 35). Therefore, we assigned the configuration of compounds **99** as 1*S*, 2*S*, 3*R* using X-Ray analysis (Figure 26).[138]



Scheme 35: *Derivatization of the product*

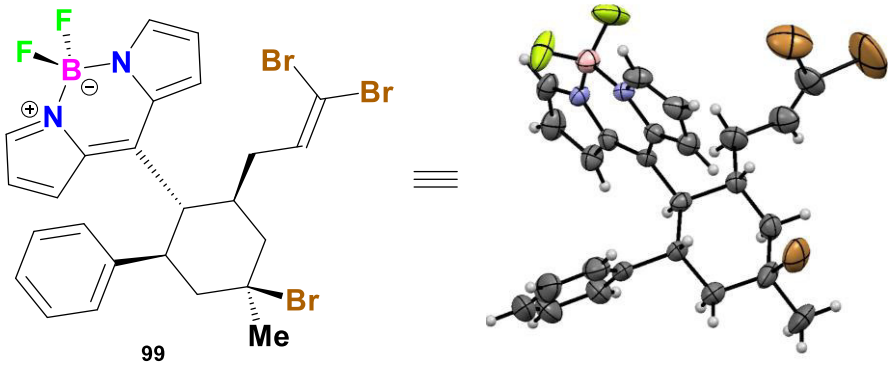


Figure 26: *X-ray structure of* ***99.***

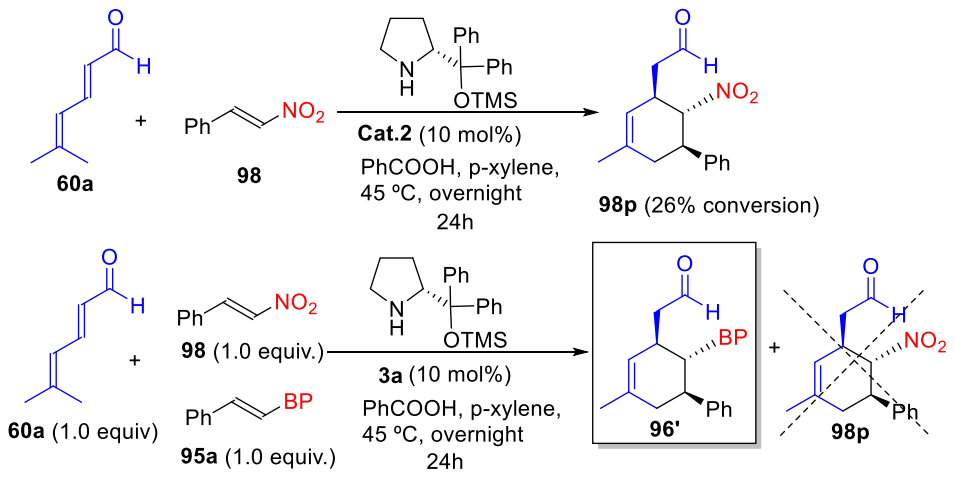
5.3.4. Reactivity Comparison with nitroalkanes.

Finally, to study the relative reactivity of BODIPY **95a**, we compared its reaction with other known dienophiles in trienamine chemistry such as the nitrostyrene.[139] The reaction of dienal **60a** with nitroalkene **98** yielded **99** with a 26% conversion after 24 h under the same reaction conditions (Scheme 35, top). We then carried out a competitive

[138] CCDC 1880124 contains crystallographic data of compound **99**. These data can be obtained free of charge at www.ccdc.cam.ac.uk.

[139] Z. –J. Jia, H. Jiang, J. –L. Li, B. Gschwend, Q. –Z. Li, X. Yin, J. Grouleff, Y. –C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053

reaction between **95a** and **98,** and found that only the BODIPY derivative reacted, without any traces of product **98p**, and highlighting the higher reactivity of **95a**. The origin of this notable difference in the reactivity was analyzed with the frontier orbitals of diene **A**, and dienophiles **95a** and **98** (Scheme 35, bottom). The HOMO orbital of trienamine **A** is delocalized over the two central double bonds, between the nitrogen and the terminal nucleophilic carbon atom that will attack the β position of the BODIPY double bond. The LUMO orbital of **97a** is delocalized over the BODIPY with an important contribution at the β position of the double bond and without any contribution at the α position. This explains the regioselectivity, as the β carbon of **95a** is the first to react. However, in the case of nitroalkene **9**, the LUMO orbital is fully delocalized through the molecule with contributions from α and β carbon atoms. In addition, the HOMO-LUMO gap is much lower for **95a (**3.19 eV) than for **98** (3.58 eV). This means that the BODIPY is a better EWG than the NO_2 and explains the higher reactivity of the BODIPY derivatives **95** when compared with nitrostyrene **98** (Scheme 36).



Scheme 36: *Reaction and reactivity comparison of BODIPY* ***95a*** *with nitroalkene* ***98***

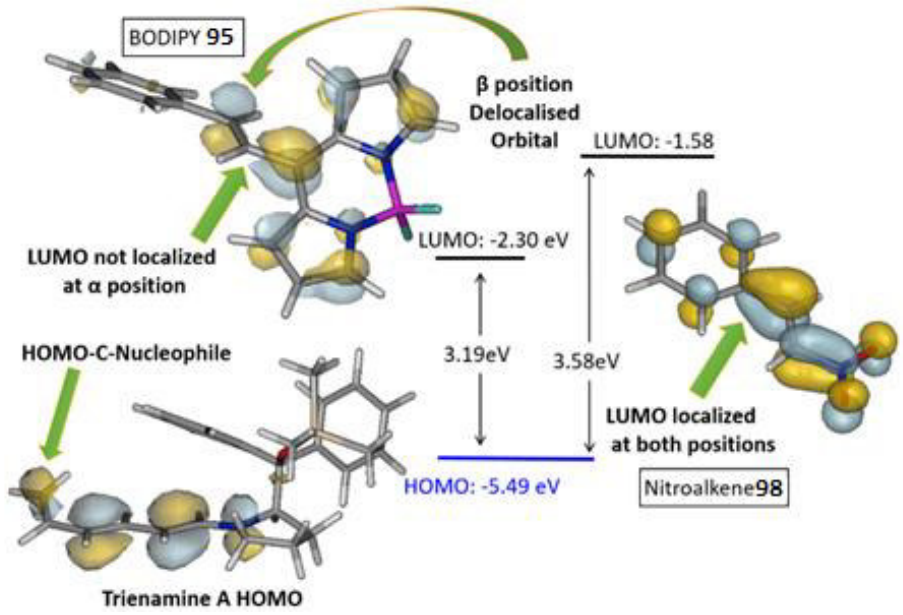


Figure 27: *Orbital analysis of* ***95a, 98*** *and trienamine A.*

5.3.5. Gibbs free energy profile

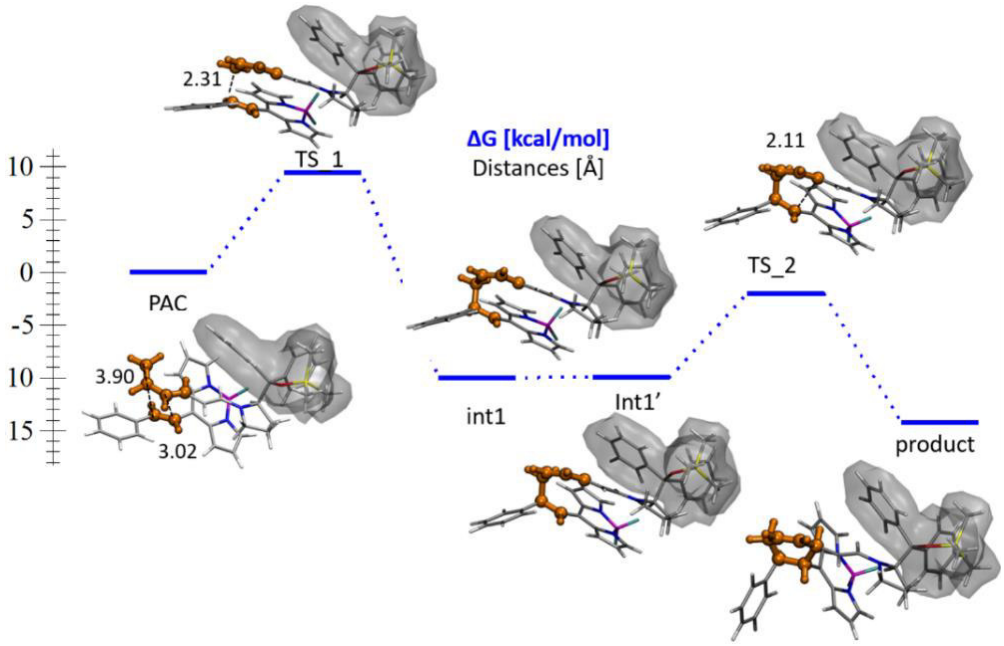


Figure 28: *Gibbs free energy profile of the endo-[4+2] cycloaddition of the trienamine formed from 60b and catalyst Cat.2 to the double bond 95a. The reactive part is highlighted in orange and the shadow wraps the catalyst. Energies in kcal mol-1. Geometry optimization was carried out at the M06-2X/6-31G(d,p) level of theory and single point energies including solvent at the SMD$_{(p\text{-}xylene)}$/M06-2X/6-31+G(d,p) level of theory.*

5.3.6. UV-VIS absorption and fluorescence emission spectra of cycloadducts.

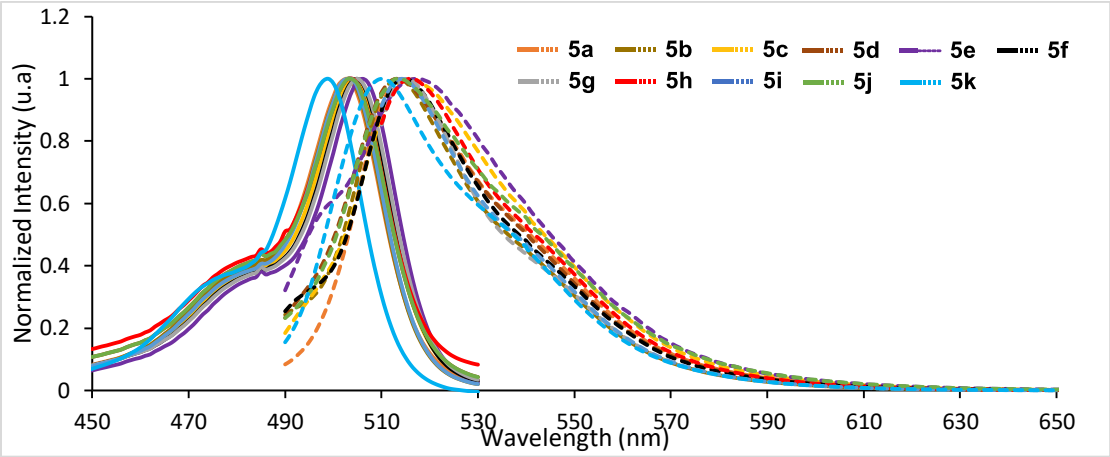


Figure 29: *UV-vis absorption and fluorescence emission spectra of final products* ***96*** *(here,* ***5a-5k****) dissolved in acetonitrile.*

5.3.7. Intrinsic reaction coordinate plots.

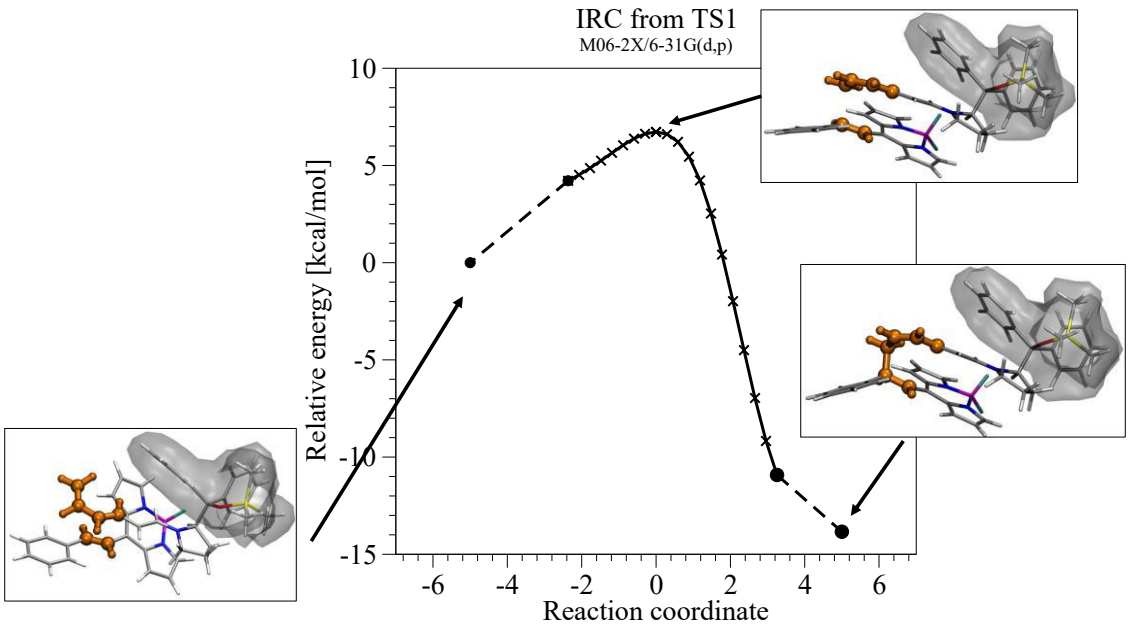


Figure 30: *Intrinsic reaction coordinate curve starting from TS_1: first C-C bond formation. The crosses are the IRC pints and the black dots correspond to the energy of the last point of the IRC (forward and reverse) and the energy of the optimized structure of this point, that corresponds to the PAC (left hand side) and int1 (right hand side).*

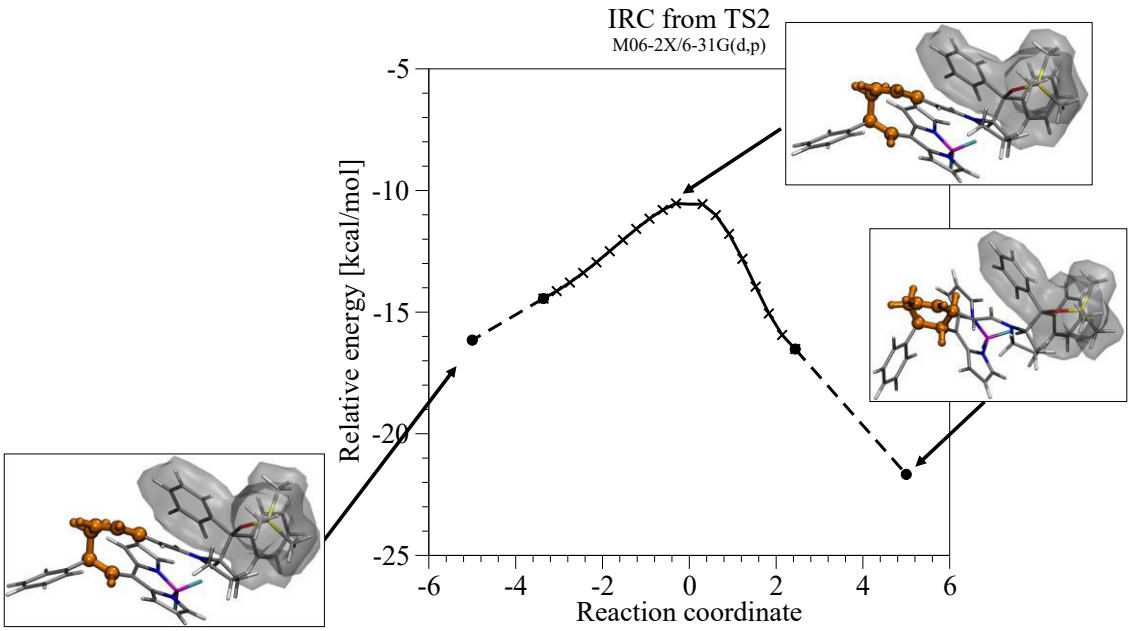


Figure 31: *Intrinsic reaction coordinate curve starting from TS_2: second C-C bond formation. The crosses are the IRC pints and the black dots correspond to the energy of the last point of the IRC (forward and reverse) and the energy of the optimized structure of this point, that corresponds to the int1 (left hand side) and product (right hand side).*

5.3.8. Frontier molecular orbitals.

The frontier molecular orbital (FMO) theory is a widely used model to describe chemical reactivity, especially for pericyclic reactions.[16] The frontier molecular orbitals are the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) respectively. The electrons coming from or moving to these orbitals are the most prone to participate in a reaction. Therefore, analyzing the energies, shapes and localizations of these orbitals it is possible to explain and predict reactivity and selectivity.

For this reaction the relevant orbitals are the HOMO of the nucleophile (trienamine **60b**), and the LUMO of the electrophile, the double bond with the BODIPY as EWG (**95**), that is the orbital receiving electron density from the nucleophile. Trienamines are good as nucleophiles since the energy of their HOMOs is relatively high, however, simple alkenes have relatively high-energy LUMOs and therefore they are not good reactants on these kinds of reactions. By conjugating the double bond with an electron-withdrawing group (the BODIPY) the LUMO energy is lowered favoring the interaction with the trienamine HOMO. This HOMO-LUMO interaction results in an energetically favorable bond

formation. Thus, the closest the LUMO energy to the trienamine HOMO energy the more favorable the reaction.

Reactant	Frontier Orbitals Energies [eV]		GAP
	HOMO	**LUMO**	
Trienamine	-5.49		
BODIPY **95**		-2.3	3.19
Nitrostyrene **98**		-1.58	3.91
Styrene		0.15	5.64
Alkene		**1.7**	**7.19**

***Table** 7: HOMO energy for trienamine 1b and BODIPYs 2a. The energies for LUMO orbitals of nitrostyrene 9, styrene, and alkene are also shown for comparison.*

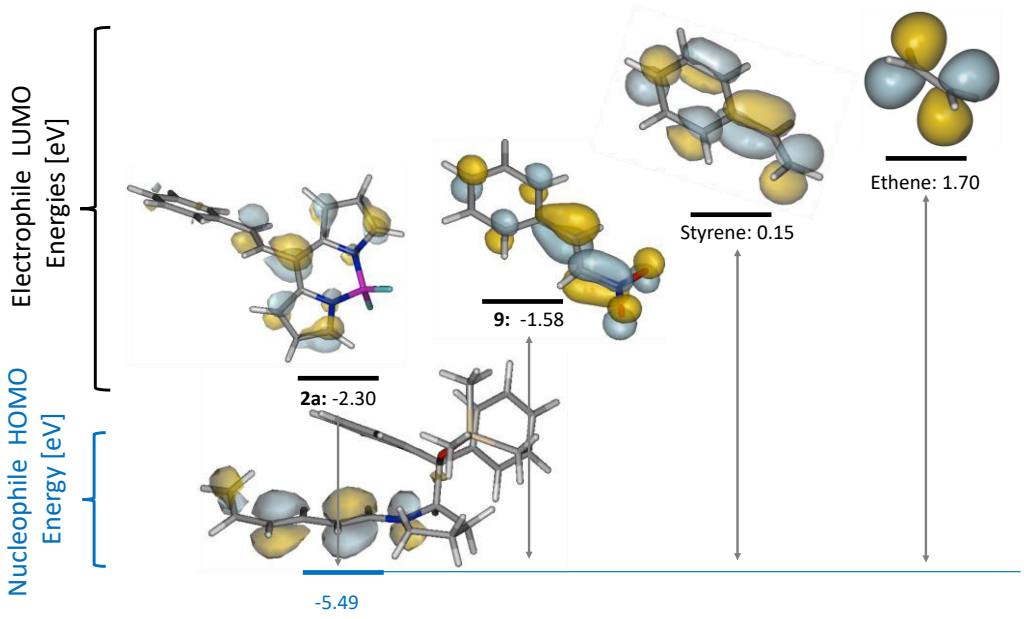


***Figure 32:** Orbitals and orbital energies for trienamine **60b** HOMO and BODIPYs **95a** LUMO. The energies for LUMO orbitals of nitrostyrene **98**, styrene, and alkene are also shown for comparison.*

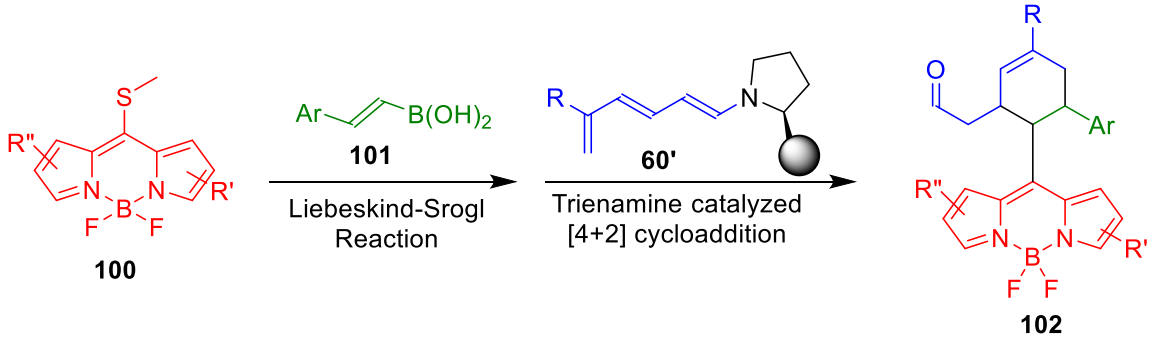
5.3.9. Conclusion.

In conclusion, it has been shown that the BODIPY can be used as an electron withdrawing group for the activation of double bonds in asymmetric catalysis. Indeed, the BODIPY acts as a stronger EWG than the nitro group. In this work, this characteristic has been applied for the synthesis of asymmetric cyclohexyl derivatives via trienamine catalysis, that contain a BODIPY unit in their structure, allowing a new functionalization of these fluorophores. In addition, it has been able to explain the observed reactivity with Quantum Chemistry calculations, confirming the role of the BODIPY as an EWG in the double bond. The new reactivity here presented can be used in the future for further asymmetric transformations (see appendix IV).

5.4. One-pot reaction: Synthesis of alkenyl BODIPY followed by trienamine mediated [4 + 2] cycloaddition.

5.4.1. Introduction and design plan

One-pot reactions, which can construct multiple bonds and lead to complex molecules in a single step, are of great interest to the synthetic community.[140] Such reactions can have many advantages, as they are atom-economical[141] and have reduced synthetic steps, minimizing the amount of purification required and removing the need for protecting group strategies. Highly functionalized cyclohexane rings are a class of molecules whose synthesis has benefited from this cascade approach.[142] These systems are ubiquitous in nature and, as such, are important medicinal and agrochemical targets. 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.[143] Being inspired on this theory, after the previous project was reported, it was envisioned the cascade reaction directly from 8-thiomethyl BODIPY, that is, one pot reaction of Liebeskind-Srogl cross coupling reaction followed by aminocatalytic [4 + 2] cycloaddition reaction (Scheme 25).



Scheme 37: *Idea and design plan*

[140] (a) Pellissier, H., *Adv. Syn. Catal.* **2012**, *354*, 237. (b) Tietze, L. F.; Brasche, G.; Gericke, K. M. In Domino Reactions in Organic Synthesis; *Wiley-VCH: Weinheim*, **2006**.

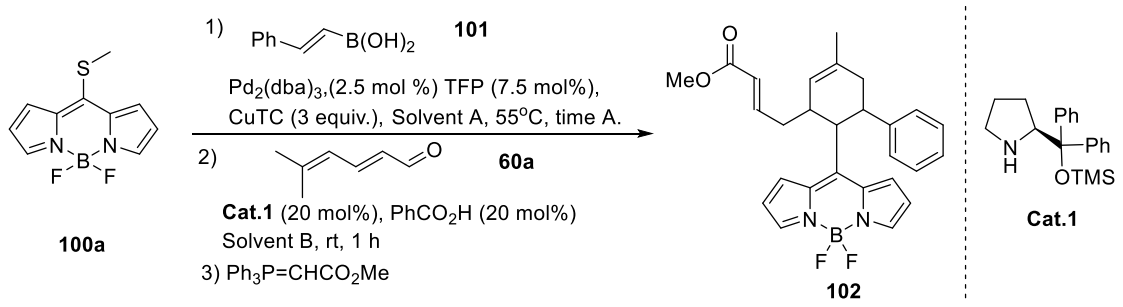
[141] a) Trost, B. M. *Science*, **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed.,* **1995**, *107*, 258.

[142] (a) Mao, Z. F.; Jia, Y. M.; Xu, Z. Q.; Wang, R. *Adv. Synth. Catal.* **2012**, *354*, 1401. (b) Shi, D. J.; Xie, Y. J.; Zhou, H.; Xia, C. G.; Huang, H. M. *Angew. Chem., Int. Ed*. **2012**, *51*, 1248. (c) Shen, H.; Yang, K. F.; Shi, Z. H.; Jiang, J. X.; Lai, G. Q.; Xu, L. W. *Eur. J. Org. Chem.* **2011**, 5031.

[143] (a) Walji, A. M.; MacMillan, D. W. C. Synlett, **2007**, 1477. (b) Enders, D.; Grondal, C.;H€uttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (c) Dondoni, A.; Massi, A. Angew. *Chem., Int. Ed.* **2008**, *47*, 4638. (d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

5.4.2. Optimization of the reaction:

Optimization was started by considering the results obtained from previous project and the conditions of Liebeskind-Srogl cross coupling reaction. As, Liebeskind-Srogl cross coupling reaction was performed and optimized with THF as solvent, we tried to optimize next aminocatalytic step in one pot with the same solvent, but the aminocatalytic reaction does not respond and ended up with 29% of conversion (Table 8, Entry 1). By trying chloroform for the first step, ended up with complex mixture because, the reaction of trienamine and unreacted thiomethyl BODIPY gives multiple compounds formation (Entry 2). By performing the 1st step for 4 hours in chloroform delivers a better amount of alkenyl BODIPY that gives about 88% overall conversion (Entry 3). After the 1st step in THF, the aminocatalytic reaction was perform with the addition of chloroform gives a full conversion and with 95% of ee (entry 4) whereas the use of *p*-xylene did not help the reaction (entries 5 and 6).



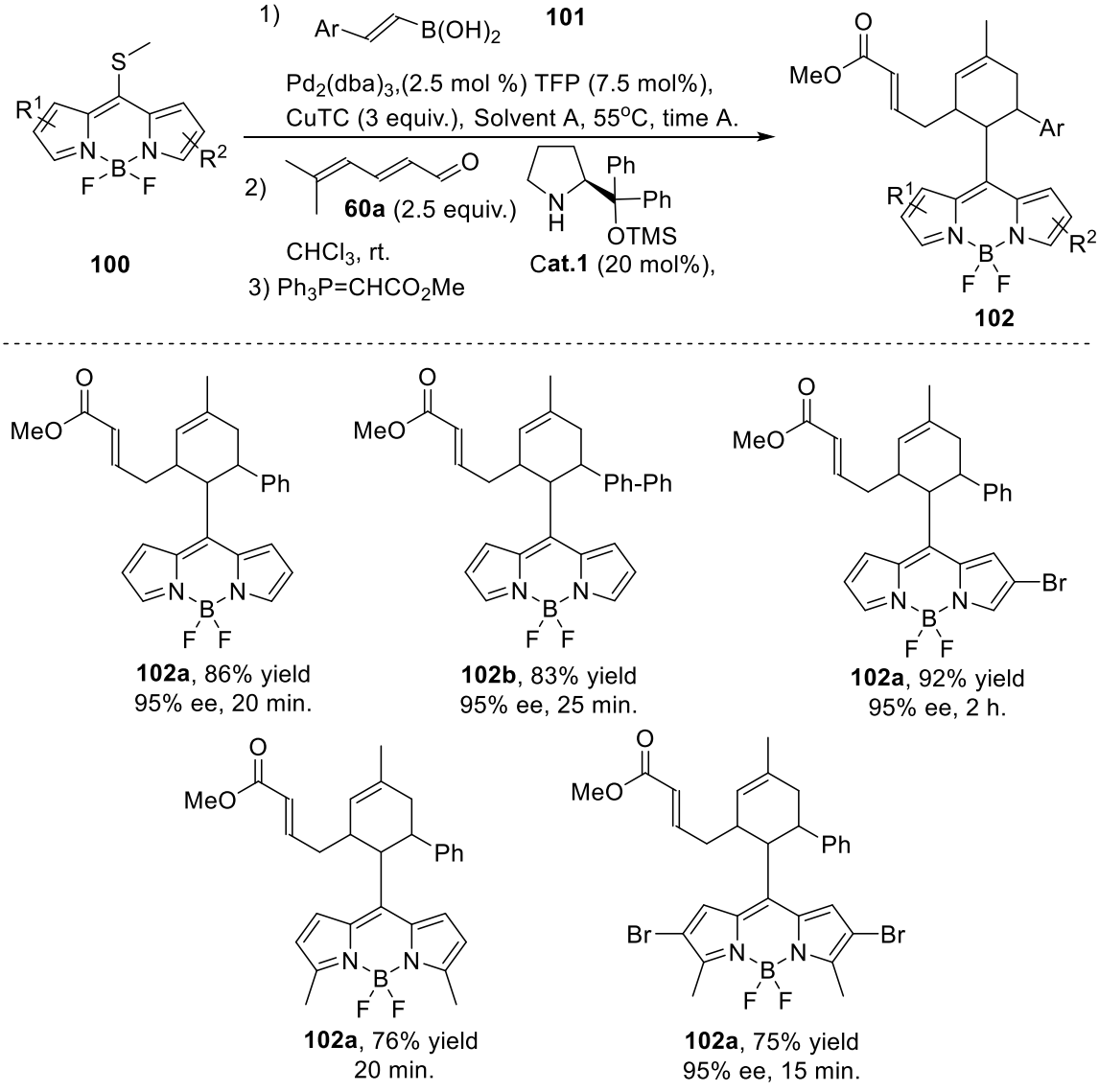
Scheme 38: *Optimization of reaction*

Entry	Solvent 1	Solvent 2	Time 1 (h)	Time 2 (h)	Conv.(%)[b]	ee (%)[d]
1	THF	THF	1	1	29%	n.d.[f]
2	$CHCl_3$	$CHCl_3$	1	1	c.m[e]	n.d.[f]
3	$CHCl_3$	$CHCl_3$	4	1	88	n.d.[f]
4	THF	$CHCl_3$	1	1	100 (86)[c]	95
5	p-xylene	p-xylene	5	-	n.r.[g]	-
6	THF	p-xylene	1	8	92	95

Table 8: *Optimization of reaction: [a]The first step of the reaction were followed as reported Liembkind-Srogl reaction in the scale of 0.05 mmol, and the second step were performed by the one-pot by changing the solvents. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Isolated yield after flash-chromatography in brackets. [d]Determined by SFC. [e]Complex mixture. [f]Not determined. [g]No reaction.*

5.4.3. Scope of the reaction

After optimization, we started scope of the reaction, in which, we consider different substituents on the BODIPY core as well as on the Phenyl group of boronic acid. The reaction performs well with all the derivatives **102a-e** Also, it is found that, reaction time for all of these derivatives was reduced with massive difference. (Scheme 39).



Scheme 39: *Scope of the reaction*

5.4.4. Conclusion

In conclusion, it has been shown that the BODIPY is not only a better electron withdrawing group for asymmetric cycloaddition reactions but also, one-pot reactions can be performed on the BODIPY to achieve enantioselective compounds. Substitution on BODIPY core will demonstrate new reactivity of alkenyl BODIPY's with the possibility to deliver a cycloadduct with different stereocontrol. Also, reactivity of each carbon of BODIPY will be studied, which can elaborate the importance of BODIPY in asymmetric cycloaddition reactions.

5.5. 1,6-oxamichael-machael addition of alkenyl BODIPY with hydroxyphenyl acrylaldehyde via iminium ion activation

5.5.1. Introduction and design plan

An important goal of asymmetric catalysis is the development of novel activation modes that enable us to promote unprecedented transformations. In the recent past, organocatalysis has significantly advanced the field as a result of the novelty of concept and unique activation modes.[144] Furthermore, the scope of organocatalyzed asymmetric reactions has been dramatically expanded by their ability for catalyzing highly powerful cascade processes that generate complex molecular architectures.[145] In the last decade, many groups have reported organocatalyzed oxa-Michael-aldol reactions for forming chromenes.[146] In the cascade process, only one stereogenic center in the products was created due to the spontaneous dehydration of the -hydroxy aldimine. Mechanistically, these reactions share the same pathway, involving the direct conjugate addition of the free phenol -OH group to the activated enal derived iminium.

It is noteworthy that chiral chromenes and chromans are important "privileged" structures found in a myriad of biologically intriguing molecules.[147] In our continuing effort on the construction of the synthetically useful scaffold with stereochemical and

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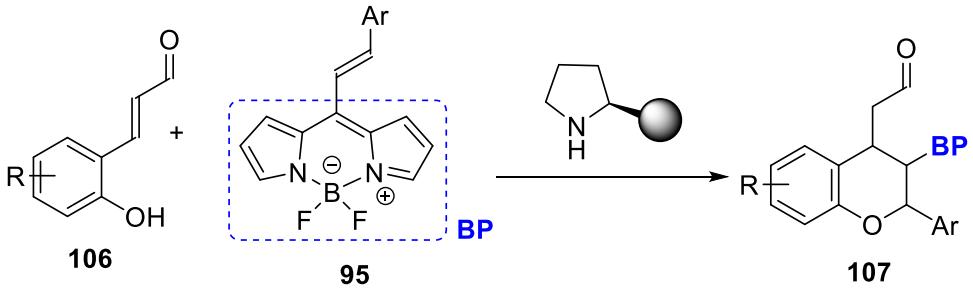
[144] (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Re*V. **2007**, *107*, 5471. (c) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Re*V. **2007**, *107*, 5416. (d) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005.

[145] (a) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Yu, X.-H.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2036. And recent selected examples, see: (c) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539. (d) Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585. (e) Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, E. R. T. *Ad*V. *Synth. Catal.* **2008**, *350*, 537. (f) Dodda, R.; Mandal, T.; Zhao, C.-G. *Tetrahedron Lett.* **2008**, *49*, 1899.

[146] (a) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507. (b) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (c) Li, H.; Zu, L.-S.; Xie, H.-X.; Wang, J.; Jiang, W.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (d) Sunde´n, H.; Ibrahem, I.; Zhao, G. L.; Eriksson, L.; Co´rdova, A. *Chem.-Eur. J.* **2007**, *13*, 574.

[147] (a) Zeni, G.; Larock, R. C. *Chem. Re*V. **2004**, *104*, 2285. (b) Keay, B. A. In *Comprehensi*V*e Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 395. (c) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C *J. Am. Chem. Soc.* **2004**, *126*, 11966, and references cited therein. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939, and references cited therein.

functional diversity, herein we wish to disclose an unprecedented organocatalyzed asymmetric cascade oxa-Michael-Michael reaction, which affords chiral highly functionalized chromans with the creation of three new stereogenic centers (Scheme 41).[148] The cascade process is efficiently catalyzed by a commercial diphenylprolinol silyl ether from simple achiral substances and provides one-pot access to enantioenriched chromans. Significantly, a novel activation mode of the chiral amine-catalyzed cascade process involving formation of aminal, which serves as a nucleophile, rather than a free phenol -OH group for the Michael addition, has been identified for the first time. In our exploratory study, we decided to choose 2-hydroxy cinnamaldehyde **106** and alkenyl BODIPY **95** as substrates for the proposed cascade oxa-Michael-Michael reaction in the presence of a chiral amine since the aldehyde and BODIPY core are highly versatile functionalities in organic transformations.



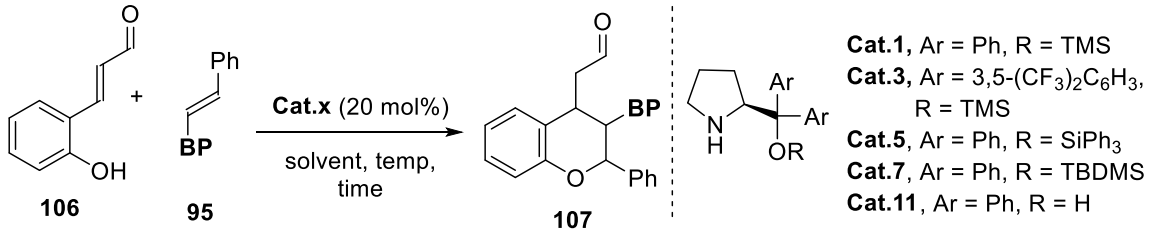
Scheme 40: *Idea and design plan*

5.5.2. Optimization of the reaction

We started optimization of reaction of **106a** with **95a** by using chiral amine and we observed 78% of conversion (Table 9, Entry 1), by increasing the equivalents of **2a** from 1 to 1.2 gave 100% conversion (Entry 2) with more than 99% of ee. In the trial of various solvents, toluene was with impressive conversion, whereas, dioxane and THF ended up without any reaction. Later on, we tried different catalyst **Cat.3**, **Cat.5**, **Cat.7**, and **Cat.11** (Entry 9-12), we were not able to improve previous result as we found with 3a. surprisingly,

[148](a) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (b) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928. (c) Sun, X.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X.-D. *Org. Lett.* **2007**, *9*, 4495. (d) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (e) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177.

a bulky catalyst 3c delivers the product with just 8% of ee (Entry 9). By changing the temperature to 0 °C gave more than 99% of ee with 82% of yield (Entry 13).



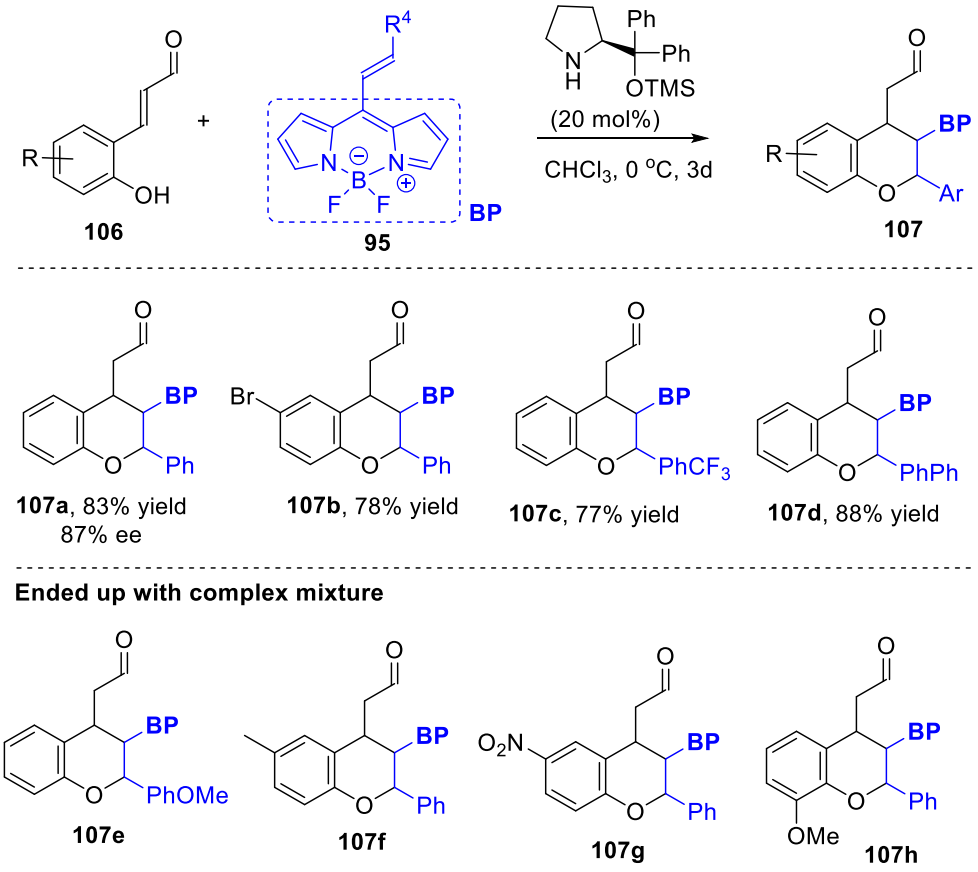
Scheme 41: *Optimization of reaction.*

Entry[a]	Catalyst	Solvent	Conversion[b]	ee[e]
1[c]	**Cat.1**	$CHCl_3$	78	n.d.[f]
2	**Cat.1**	$CHCl_3$	100	>99
3	**Cat.1**	toluene	100	>99
4	**Cat.1**	DCM	72	>99
5	**Cat.1**	p-xylene	28	-
6	**Cat.1**	dioxane	n.r.[g]	-
7	**Cat.1**	Acetonitrile	22	-
8	**Cat.1**	THF	n.r.[g]	-
9	**Cat.3**	$CHCl_3$	73	8
10	**Cat.5**	$CHCl_3$	54	68
11	**Cat.7**	$CHCl_3$	63	52
12	**Cat.11**	$CHCl_3$	42	12
13	**Cat.1**	$CHCl_3$	100 (82)[d]	>99

Table 9: *Optimization of reaction: [a]All the reactions were performed in 0.05 mmol scale of 2 and 0.5 mL of solvent for 65 h. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Reaction carried out at aldehyde = 1 equiv. [d]Isolated yield after flash-chromatography in brackets. [e]Determined by SFC. [f]Not determined. [g]No reaction.*

5.5.3. Scope of the reaction

After optimization, we headed up with the scope of reaction, in which, we consider different substituents on the phenyl ring present in alkenyl BODIPY and some substituents on 2-hydroxy acrylaldehydes. The reaction performs well with **107b-d** whereas **107e-h** ended up with complex mixture (Scheme 43).



Scheme 42: *Scope of reaction*

5.5.4. Perspectives

- To complete the scope of the reaction: In current status, some of the derivatives have been synthesized and the following derivatives are planned to complete the scope.

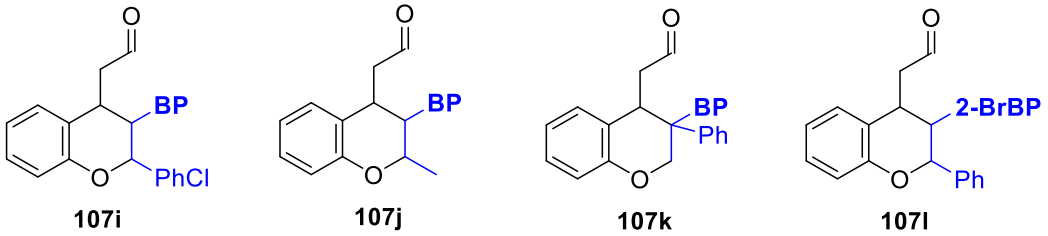


Figure 33: *Compounds remained to synthesize to complete the scope.*

- To study the absolute configuration of the cycloadduct: Compound **107b** has been chosen for the x-ray study, and the absolute configuration will be studied.

5.5.5. Conclusion

In summary, we have developed a new powerful catalytic cascade oxa-Michael-Michael strategy for the facile construction of biologically significant, heavily functionalized chiral chromans containing multiple stereogenic centers. The study significantly expands the scope of organocatalyzed reactions with the new activation mode. Further application of this organocatalytic activation mode in new organic transformations, the elaboration of the highly versatile chiral chromans in organic synthesis, and the detailed mechanistic aspects will be reported in due course.

5.6. Summary and Outlook.

Organocatalytic cascade reactions represent an important methodology to access to new enantiomeric complex structures. In this chapter, the ability of BODIPY dienophiles to participate in asymmetric cycloaddition reaction is demonstrated. In the other hand, the one pot reaction from 8-thiomethyl BODIPY shows the great value of this methodology, which can be applied to get complexity from simple starting materials. Also, this strategy represents a very important methodology for the diversification of privileged structures. These all strategies are able to unlock a new asymmetric pathway to access novel chiral fluorescent compounds efficiently. As a closing note, it has proven that, BODIPY can be used as an electron withdrawing group for the activation of double bonds in asymmetric catalysis which leads to the synthesis of asymmetric cyclohexyl and chromene derivatives via trienamine and iminium ion catalysis respectively. In the next chapter, new ongoing research about cooperative catalysis will be disclosed. Mainly, the participation of gold catalyst in aminocatalysis as well as underlying synthetic potential of one-pot strategy is provided.

Chapter 6.

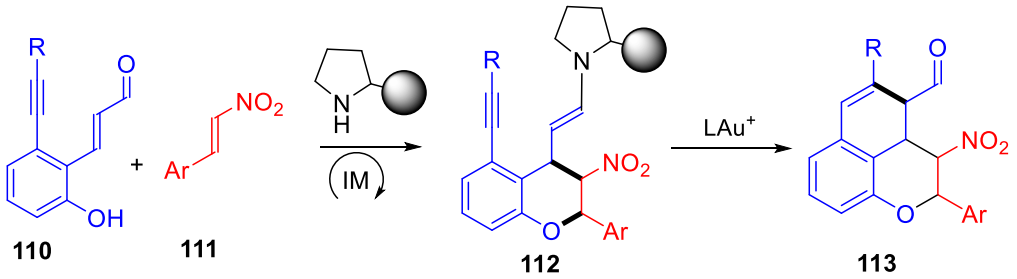
Cooperative Catalysis: The strategy of Amino- and Gold catalysis.

(The project has been carried out during the research stay in Universidad Aútonoma de Madrid, Spain under the Ph.D. program. Due to the lack of time, the project did not finish, and the rest of the work will be done in the future.)

6.1. Introduction and design plan

In recent years, cooperative catalysis strategies have attracted great attention due to the ability to activate two different functional groups with compatible catalysts without loss of stereoselectivity. In this sense, gold and aminocatalysis have played an influential role. Organocatalysis and Au catalysis have demonstrated to be powerful strategies for the construction of enantioenriched compounds. In this sense, cascade reactions using both amino catalysis activation will be possible to have access to new complex organic frameworks through simple starting materials. Both are chemoselective and compatible each other.

Recently, we started another new project, in which we are going to use combination of aminocatalysis with gold catalysis i.e. cooperative catalysis. In that, we are going to use specifically designed compound **93** and then aminocatalytic 1,6-oxa-Michael-Michael cycloaddition followed by gold catalytic ring closing reaction (Scheme 44)



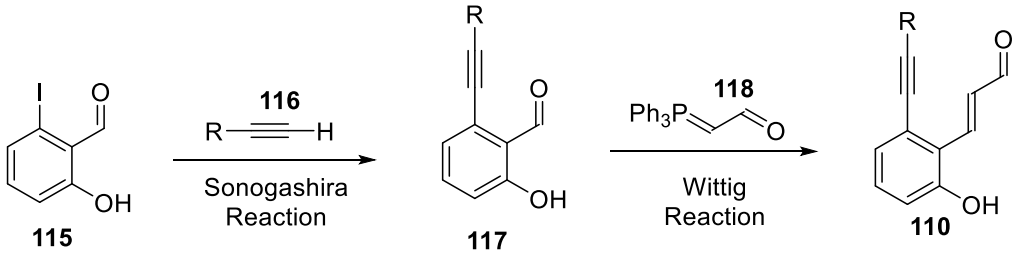
Scheme 43: *Reaction Plan*

The proposed strategy for the enantioenriched construction of chromene is depicted in the scheme 1. Initially the corresponding 2-hydroxy-6-alkynylphenyl acrylaldehyde **15** in the presence of an O-protected prolinol **3** derivative as a catalyst generates the corresponding iminium ion intermediate **16**, which then reacts with a nitro styrene **17** to form the first cycle via an oxa-Michael/Michael sequence. Then, under an enamine and π-activation in the aldehyde and alkyne respectively form the second cyclisation **20** with four new stereocenters (Scheme 43).

Organocatalysis and Au^{I} catalysis have demonstrated to be powerful strategies for the construction of enantioenriched compounds. In this sense, cascade reactions using both amino catalysis activation will be possible to have access to new complex organic frameworks through simple starting materials. Both are chemoselective and compatible each other

6.2. Methodology and design plan for the starting material

To ensure good reactivities in the cooperative methodology, the 2-hydroxy-6-alkynylphenyl acrylaldehyde **110** has been chosen. In this sense, it will be prepared as follow: A Sonogashira coupling with the 2-hydroxy-6-iodobenzaldehyde **115** and an alkyne **116** will produce the corresponding the 2-hydroxy-6-alkyny-benzaldehyde **117**. Then a Wittig reaction with **118** on the aldehyde generate the corresponding aldehyde **110** (Scheme 45).



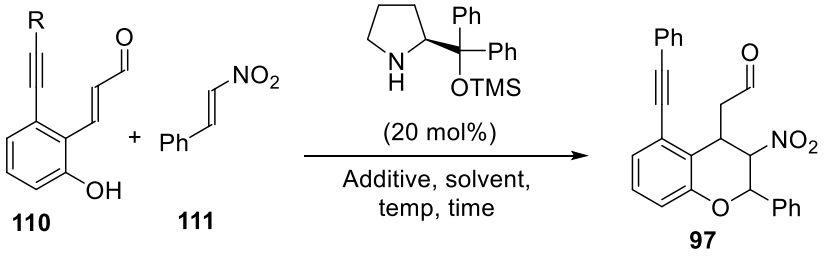
Scheme 44: *Methodology to synthesize starting material*

Then asymmetric organocatalytic functionalization of 2-hydroxy-6-alkynylphenyl acrylaldehyde **110** with nitrostyrene **111** will produce corresponding enantioenriched compound **112**. Thereafter cascade reaction continuous by using gold catalyst, in which ring closing reaction takes place via enamine activation. This organocatalytic oxa-

Michael/Michael cascade reaction will be investigated with different O-protected prolinol derivative organocatalyst to get the highest diastereo and enantioselectivities. Once established the best conditions for the organocatalytic pathway, the second cyclization through π-and enamine activation will be analyzed. Finally, the entire process in a one-pot fashion will be achieved. (Scheme 3)

6.3. Optimization of reaction (Step-1)

As per previous report of 1,6-oxaMichael-Michael cycloaddition, we started with the same conditions (Table 10, Entries 1 and 2) that gives desired product. By increasing the equiv. of aldehyde from 1 to 1.2 gave full conversion with 99% ee and 1:4 dr with 82% of yield (Entry 3). Changing of solvents doesn't help much to improve these results (Entries 5 and 6).



Scheme 45: *Optimization of reaction.*

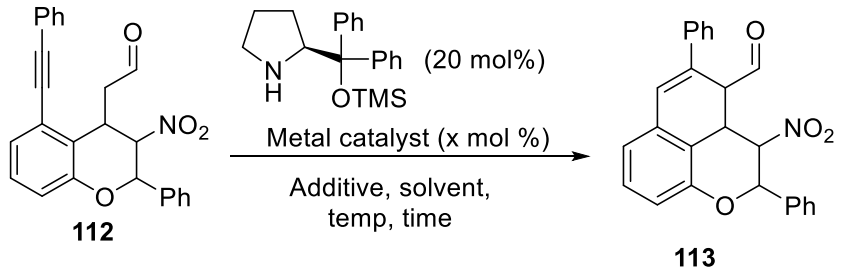
Entry	Equiv. of alde.	Solvent	Conv. (%)	dr	Yield (%)	ee (%)
1	1	DCM	78	1:4	--	nd[1]
2	1	chloroform	76	1:3	--	nd[1]
3	1.2	DCM	100	1:4	82	99
4	1.2	toluene	82	1:2	--	--
5	1.2	Chloroform	96	1:3	--	96

Table 10: *First step - Optimization table ([1]nd – not determined, [2]conversion is calculated by [1]H NMR, [3]ee is measured by CO_2 HPLC, dr is calculated by [1]H NMR)*

6.4. Optimization of reaction (Step-2)

Once we got best conditions for the first step, we moved to optimize second step, in which we initiate with some conditions from literature, but the desired product was not

observed (Table 11, Entries 1 to 13). Use of Cu Metal was also not suitable for this transformation (entries 6 and 7). After using $Au(PPh_3)Nf_2$ as catalyst, in toluene at 80 °C, in 24 hours, a desired product was observed with 42% of conversion and was confirmed by NMR (entry 14). By keeping the reaction for another 24 hours, reaction handover 61% of conversion.



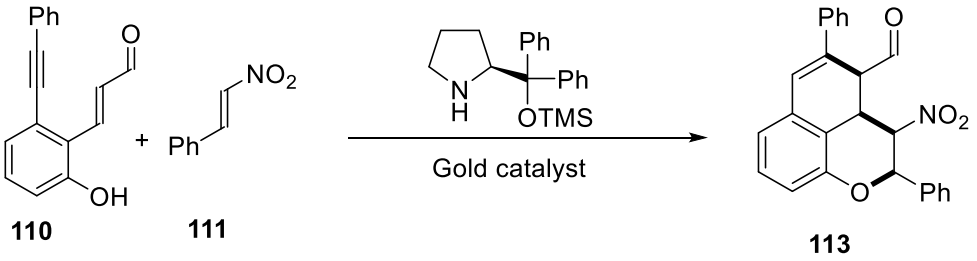
Scheme 46: *Second step - Ring closing with metal catalysis.*

Entry	Metal Catalyst	mol %	Addt. (mol%)	Time (hours)	Solvent	Temp. (°C)	Conv. (%)
1	$Au(PPh_3)Cl_2$	5	--	24	DCM	rt	n.r. [b]
2	$Au(PPh_3)Cl_2$	10	--	24	DCM	rt	n.r. [b]
3	$Au(PPh_3)Cl_2$	20	*p*-TSA (60)	24	DCM	rt	n.r.[b]
4	$Au(PPh_3)Cl_2$	20	*p*-TSA (60)	24	toluene	rt	n.r. [b]
5	$Au(PPh_3)Cl_2$	20	*p*-TSA (60)	24	toluene	45	n.r. [b]
6	$Cu(OTf)_2$	20	PPh_3 (20)	24	toluene	45	n.r. [b]
7	$Cu(OTf)_2$	20	PPh_3 (20)	24	Ethanol	rt	n.r.[b]
8	$Au(PPh_3)Nf_2$	20	--	24	toluene	rt	n.r. [b]
9	$Au(PPh_3)Nf_2$	20	--	24	toluene	45	n.r. [b]
10	$Au(PPh_3)Nf_2$	20	*p*-TSA (60)	24	toluene	rt	n.r. [b]
11	$Au(PPh_3)Nf_2$	20	*p*-TSA (60)	24	ethanol	rt	n.r. [b]
12	$Au(PPh_3)Nf_2$	20	*p*-TSA (60)	24	$CHCl_3$	rt	n.r. [b]
13	$Au(PPh_3)Nf_2$	20	*p*-TSA (60)	24	toluene	45	n.r. [b]
14	$Au(PPh_3)Nf_2$	20	*p*-TSA (60)	24	toluene	80	42
15	$Au(PPh_3)Nf_2$	20	*p*-TSA (60)	48	toluene	80	61

Table 11: *Second step - Optimization table (Reaction is carried out only with one diastereomer; a* conversion is calculated by ^1H NMR; b* nr – no reaction,)*

6.5. Perspectives

- To optimize the second step and then a cascade reaction: In the present status, a final desired product is observed, soon a both steps will be performed in one pot to get the best optimized conditions (Scheme 48).



Scheme 47: *Target reaction.*

- To plan and perform scope of the reaction
- To find out absolute configuration of final product.

6.6. Conclusion

Organocatalysis and Gold Catalysis have demonstrated to be powerful strategies for the construction of enantioenriched compounds. In this sense, cascade reactions using both amino catalysis activation will be possible to have access to new complex organic frameworks through simple starting materials. Both are chemoselective and compatible each other.

Chapter 7.

Experimental section

General reactions: Reactions were carried out at room temperature, at minimum -78 °C and up to 180 °C in magnetically stirred unless otherwise stated. Anhydrous solvents were supplied as Sureseal® bottles by Aldrich and KARAL. All reagents and solvents were supplied by Sigma-Aldrich, Fluorochem, TCI, Alfa-Aesar, Fisher and VWR and were used as supplied unless otherwise stated. Racemic mixture was prepared by the 1:1 combination of R and S of corresponding catalyst

Chromatography: Thin layer chromatography (TLC) was performed on Merck aluminium backed plates coated with 0.2 mm silica gel 60F254. The spots were visualised using UV light (254 nm). Column chromatography was performed on Sigma-Aldrich silica gel 60Å (230-400 mesh) using cyclohexane and ethyl acetate as eluent.

NMR data: ^{1}H NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or deuterated DMSO using a Bruker DPX 500 (500 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million using the abbreviations: s, singlet; bs, broad singlet; d, doublet; dd, double doublet; qd, quartet doublet; t, triplet; tt, triplet triplet; q, quartet; m, multiplet and the coupling constants J are quoted in Hz. ^{13}C NMR spectra were recorded at 126 MHz on a DPX 400 in deuterated chloroform ($CDCl_3$).

(Universidad Aútonoma de Madrid) ^{1}H NMR spectra were recorded in deuterated chloroform ($CDCl_3$) using a Bruker DPX 300 (300 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million using the abbreviations: s, singlet; bs, broad singlet; d, doublet; dd, double doublet; ddd, double doublet doublet; dddd, double doublet doublet doublet; qd, quartet doublet; t, triplet; tt, triplet triplet; q, quartet; m, multiplet and the coupling constants J are quoted in Hz. ^{13}C NMR spectra were recorded at 75 MHz on a DPX 400 in deuterated chloroform ($CDCl_3$).

MS data: High Resolution Mass Spectra (HRMS) were acquired on an Agilent Technologies 5977B MSD using electrospray (ESI) making use of the Mass Works software ver. 4.0.0.0. (Cerno Bioscience) for the formula identification. MassWorks is a

MS calibration software, which calibrates for isotope profile as well as for mass accuracy allowing highly accurate comparisons between calibrated and theoretical spectra.1 Obtained data are expressed in mass/charge (m/z) units.

(Universidad Aútonoma de Madrid) High Resolution Mass Spectra (HRMS) were acquired on an Agilent Technologies 5977B MSD using electrospray (ESI) making use of the Mass Works software ver. 4.0.0.0. (Cerno Bioscience) for the formula identification. MassWorks is a MS calibration software, which calibrates for isotope profile as well as for mass accuracy allowing highly accurate comparisons between calibrated and theoretical spectra.1 Obtained data are expressed in mass/charge (m/z) units..

HPLC Profiles: Optical rotations were measured on a Perkin-Elmer 241 polarimeter at room temperature and [α]20 D values are given in deg•cm•g-1•dm-1; concentration *c* is listed in g•(100 mL)-1. The enantiomeric excess (ee) of the products were determined by SFC using mixtures of supercritical CO_2 and methanol and Chiralpak IA, IB-3, IC, ID, IG-3, OJ-H columns as chiral stationary phases.

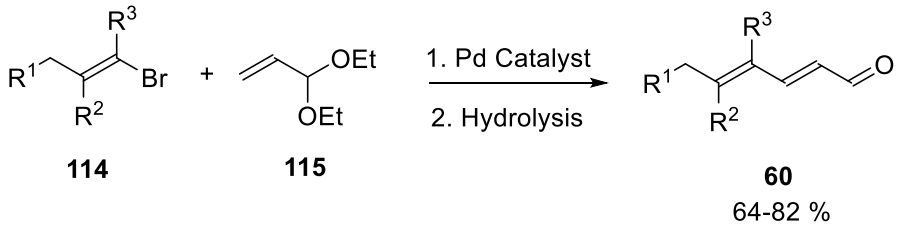
(Universidad Aútonoma de Madrid) Optical rotations were measured on a Perkin-Elmer 241 polarimeter at room temperature and [α]20 D values are given in deg•cm•g-1•dm-1; concentration *c* is listed in g•(100 mL)-1. The enantiomeric excess (ee) of the products were determined by SFC using mixtures of supercritical CO_2 and methanol and Chiralpak IA, IB-3, IC, ID, IG-3, OJ-H columns as chiral stationary phases.

7.1. Synthesis of aldehydes used for aminocatalysis:

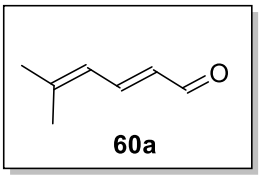
7.1.1. Synthesis of 2,4-dienals

A) General procedure to synthesize substituted 2,4-dienals using Pd-catalyst: To a stirred solution of vinyl bromides **114** in DMF were added acrolein diethyl acetal **115,** $Pd(OAc)_2$, 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

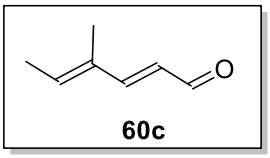
over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography. (Scheme 49).[149]



Scheme 48: *Synthesis of 2,4-dienals.*



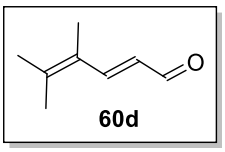
(*E*)-5-methylhexa-2,4-dienal (60a): To a stirred solution of 1-bromo-2-methylprop-1-ene (7.41 mmol, 0.76 mL) in DMF (50.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.22 mmol, 50.0 mg), nBu_4NOAc (14.8 mmol, 4.47 g), K_2CO_3 (11.1 mmol, 1.52 g), and KCl (7.41 mmol, 552.2 mg). The mixture was stirred for overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 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 (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).



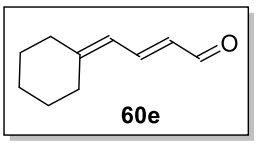
(2*E*,4*E*)-4-methylhexa-2,4-dienal (60c): To a stirred solution of 1-bromo-2-methylprop-1-ene (5.5 mmol, 0.56 mL) in DMF (30.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.17 mmol, 37.0 mg), nBu_4NOAc (11.0 mmol, 3.32 g), K_2CO_3 (8.26 mmol, 1.13 g), and KCl (5.5 mmol, 410 mg). The mixture was stirred for overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 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 (pentane/diethyl ether 19:1). Yellow oil; 76% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.54

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

(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).



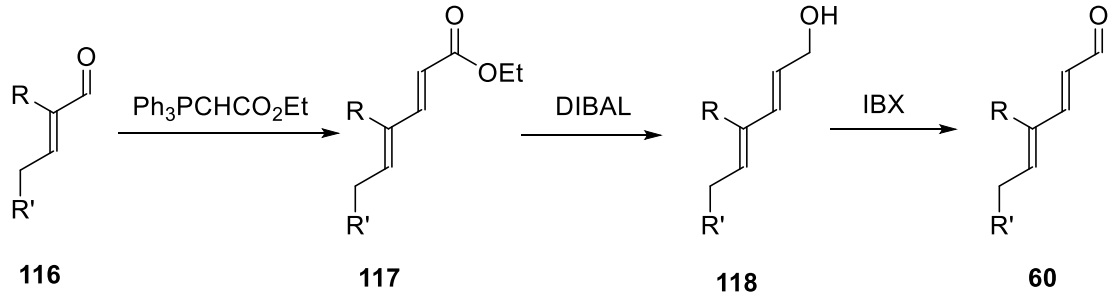
(*E*)-4,5-dimethylhexa-2,4-dienal (60d): To a stirred solution of 1-bromo-2-methylprop-1-ene (5.5 mmol, 0.64 mL) in DMF (30.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.17 mmol, 37.0 mg), nBu_4NOAc (11.0 mmol, 3.32 g), K_2CO_3 (8.26 mmol, 1.13 g), and KCl (5.5 mmol, 410 mg). The mixture was stirred for overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 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 (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).



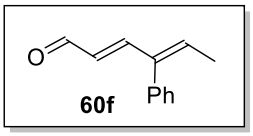
(*E*)-4-cyclohexylidenebut-2-enal (60e): To a stirred solution of 1-bromo-2-methylprop-1-ene (5.5 mmol, 0.73 mL) in DMF (30.0 mL) were added acrolein diethyl acetal, $Pd(OAc)_2$ (0.17 mmol, 37.0 mg), nBu_4NOAc (11.0 mmol, 3.32 g), K_2CO_3 (8.26 mmol, 1.13 g), and KCl (5.5 mmol, 410 mg). The mixture was stirred for overnight at 90 °C. After cooling 2N HCl was slowly added and the reaction mixture was stirred at RT for 10 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 (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).

B) General procedure to synthesize phenyl substituted 2,4-dienals: NaH (4.5 mmol) was added in small portions during 5 minutes to a solution of Ph_3PCHCO_2Et (3 mmol) in THF (20 mL) at 0 °C. 10 minutes later, enal (2.5 mmol) was added. After the reaction completed (monitored by TLC), the mixture was quenched with H_2O. THF was evaporated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The

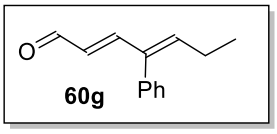
combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was diluted with 20 mL toluene at -78 °C under an argon atmosphere, and DIBAL-H (4.5 mol) was added. After the reaction completed (monitored by TLC), the mixture was quenched with aqueous NH_4Cl. The solid was removed by filtration through celite. The filtrate was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was diluted in 5 mL DMSO, and IBX (4.5 mol) was added in small portions. After the reaction completed (monitored by TLC), the solid was removed by filtration through celite. The filtrate was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (Scheme 50). (*These 2,4-dienals are not very stable and should be stored in pentane in cold condition.)*[150]



Scheme 49: *Synthetic procedure B2 for the preparation of 2,4-dienals*



(2*E*,4*E*)-4-phenylhexa-2,4-dienal (60f): Yellow oil; compound was isolated by flash-chromatography (pentane/diethyl ether 90:10) Yield= 66%; **^{1}H NMR (300 MHz, $CDCl_3$):** 9.58 (d, *J* = 8.0Hz, 1H), 7.42-7.28 (m, 4H), 7.11-7.09 (m, 2H), 6.37 (q, *J* = 7.2 Hz, 1H), 5.72 (dd, *J* = 15.6, 8.0 Hz, 1H), 1.74 (d, *J* = 7.2 Hz, 3H) ppm.



(2*E*,4*E*)-4-phenylhepta-2,4-dienal (60g): Yellow oil; compound was isolated by flash-chromatography (pentane/diethyl ether

[150] Jia, Z.-J.; Zhou, Q.; Zhou, Q. Q.; Chen, P. Q.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638-8641.

90:10) Yield= 62%; **^{1}H NMR (300 MHz, $CDCl_3$):** 9.58 (d, *J* = 8.0 Hz, 1H), 7.41-7.28 (m, 4H), 7.11-7.09 (m, 2H), 6.26 (t, *J* = 8.0 Hz, 1H), 5.71 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.08 (q, *J* = 7.6 Hz, 2H), 1.01 (t, *J* = 7.6 Hz, 3H) ppm.

7.1.2. Synthesis of 2-methyl-indole acrylaldehyde[151]

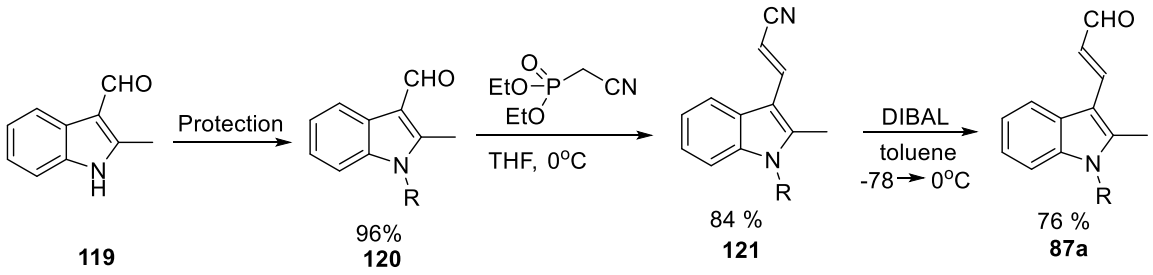
B) General procedure to synthesize phenyl substituted 2,4-dienals:

Step-I: The protection of each aldehyde carried out as per procedure mentioned in each case from literature.[152]

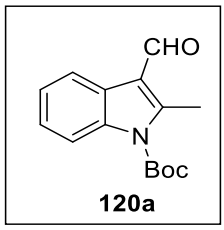
Step-II: To a solution of diethylcyanomethyl phosphonate **120** (1.3 equiv.) in anhydrous THF at 0°C, BuLi (2.5M in hexanes, 1.2 equiv.) was added dropwise and the mixture was stirred for 1h at the same temperature. A solution of the aldehyde (1 equiv.) in anhydrous THF was prepared and the solution 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 purified as per mentioned in each case to achieve corresponding nitrile **121**.

Step-III: A solution of the nitrile **121** (1 equiv.) in anhydrous toluene was cooled down to -78 °C and at that temperature, a solution of diisobutylaluminium hydride DIBAL in heptane (1M, 1.2 equiv.) 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 at -78 °C. The reaction flask could warm to room temperature then stirred with 1M HCl for two minutes. The solution was diluted with EtOAc and the organic phase was separated. The aqueous layer was extracted twice with 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.

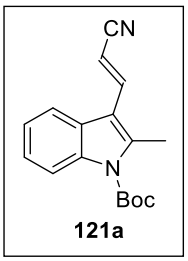
[151] Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212-15218.
[152] Dhayalan, V.; Clement, J. A.; Jagan, R.; Mohanakrishnan, A. K. *Eur. J. Org. Chem.* **2009**, 531–546.



Scheme 50: *Synthesis of 2-methyl-3-(3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylate derivatives.*



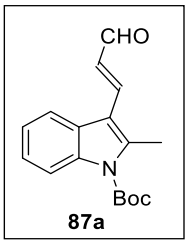
tert-butyl 3-formyl-2-methyl-1*H*-indole-1-carboxylate: To a solution of 2-methyl-1H-indole-3-carbaldehyde **119** (25.1 mmol, 4 g) in CH_3CN (65 mL), DMAP (2.5 mmol, 307 mg) and di-tert-butyl dicarbonate (30 mmol, 6.9 mL) were added and stirred at room temperature for 4 h. The solvent was removed and 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 **120a**.[153] 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).



tert-butyl (*E*)-3-(2-cyanovinyl)-2-methyl-1*H*-indole-1-carboxylate: To a solution of diethylcyanomethyl phosphonate **120a** (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 **121a**(84%). White solid; compound was isolated by flash-chromatography (20% EtOAc/hexanes). Yield = 84 %;

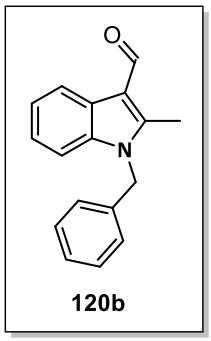
[153] Dhayalan, V.; Clement, J. A.; Jagan, R.; Mohanakrishnan, A. K. *Eur. J. Org. Chem.* **2009**, 531–546.

^{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.



87a

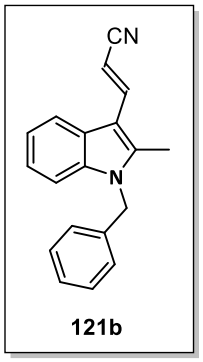
tert-butyl (*E*)-2-methyl-3-(3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate (87a): A solution of the nitrile **121a** (7 mmol, 2 g) in anhydrous toluene (30 mL) was cooled down to -78 °C and at that temperature, a solution of diisobutylaluminium hydride (DIBAL) in heptane (1M, 8.5 mL) was added dropwise 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.



120b

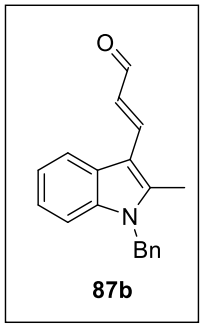
1-benzyl-2-methyl-1H-indole-3-carbaldehyde (120b): To a solution of 2-methyl-1H-indole-3-carbaldehyde **119** (10.0 mmol, 1.59 g) in DMF (25 mL), BnBr (10.0 mmol, 1.2 mL) and potassium carbonate (15.0 mmol, 2.1 g) were added and stirred at 90 °C for overnight. The solvent was removed and then extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine and then dried ($NaSO_4$). The crude product was purified by column chromatography (20% EtOAc/hexane). White powder, 97.6% yield (9.63 mmol, 2.48 g). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.26 – 10.20 (m, 1H), 8.34 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.28 (m, 5H), 7.26 (dd, *J* = 6.3, 1.8 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 2H), 5.38 (d, *J* = 3.3 Hz, 2H), 2.69 (dd, *J* = 3.6, 2.5 Hz, 3H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 184.36, 147.50, 136.84, 135.74, 129.10, 127.92, 125.97, 125.88, 123.39, 122.94, 121.00, 114.72, 109.70, 46.68, 10.62.



121b

(E)-3-(1-benzyl-2-methyl-1H-indol-3-yl)acrylonitrile (121b): To a solution of diethylcyanomethyl phosphonate **120b** (9.31 mmol, 1.51 mL) in anhydrous THF (15 mL) at 0°C, BuLi (2.5M in hexanes, 8.59 mmol, 3.4 mL) was added dropwise and the mixture was stirred for 1h at the same temperature. A solution of the aldehyde (7.16 mmol, 1.8 g) in anhydrous THF (10 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 5h. The solvent was removed and then extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine and then dried ($NaSO_4$). The product was recrystallized from pentane/DCM to give 1.64 g (83.4% yield, 6.02 mmol) of the corresponding nitrile **121b**. pale yellow solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.74 – 7.66 (m, 1H), 7.53 (d, *J* = 16.4 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.20 – 7.13 (m, 4H), 6.91 (t, *J* = 8.3 Hz, 2H), 5.71 (d, *J* = 16.4 Hz, 1H), 5.28 (d, *J* = 9.3 Hz, 2H), 2.38 (d, *J* = 5.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.06, 141.44, 137.46, 136.16, 129.07, 127.85, 125.91, 125.28, 122.92, 122.02, 120.65, 119.67, 110.15, 109.63, 89.01, 46.93, 10.71.



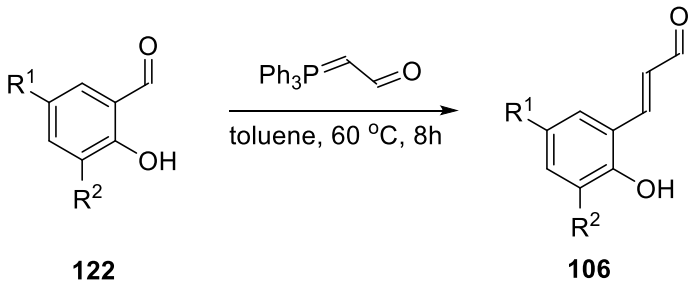
87b

(E)-3-(1-benzyl-2-methyl-1H-indol-3-yl)acrylaldehyde (87b): A solution of the nitrile **121b** (5.5 mmol, 1.5 g) in anhydrous toluene (25 mL) was cooled down to -78 °C and at that temperature, a solution of diisobutylaluminium hydride (DIBAL) in heptane (1M, 6.61 mmol, 6.6 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 (30% EtOAc/hexane) to give the desired product. Orange brown solid; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.63 (s, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.74 (d,

J = 15.6 Hz, 1H), 7.33 – 7.26 (m, 5H), 7.26 – 7.22 (m, 1H), 7.00 (d, J = 6.9 Hz, 2H), 6.83 (dd, J = 15.6, 7.8 Hz, 1H), 5.38 (s, 2H), 2.53 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 194.36, 146.13, 143.02, 137.72, 136.16, 129.18, 127.96, 126.01, 125.77, 123.88, 123.13, 122.30, 120.37, 110.33, 110.16, 47.12, 11.01; **HRMS** (ESI^+) calculated for $C_{27}H_{24}N_2O_5$ $[M+nH]^+$: 276.1383, found: 276.1396.

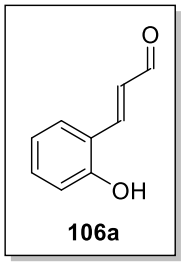
7.1.3. Synthesis of hydroxyphenyl Aldehydes

C) 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 52).



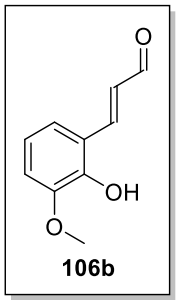
122 **106**

Scheme 51: *synthesis of 2-hydroxyphenyl acrylaldehyde*



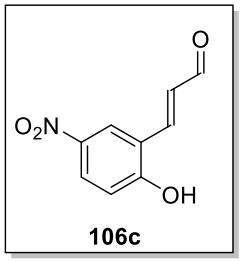
106a

(E)-3-(2-hydroxyphenyl)acrylaldehyde (106a): A mixture of a 2-hydroxy-5-benzaldehyde (24.6 mmol, 3.0 g) with Ph_3P=CHCHO (29.5 mmol, 9.0 g) 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.



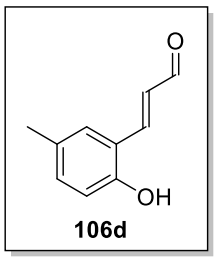
106b

(E)-3-(2-hydroxy-3-methoxyphenyl)acrylaldehyde (106b): A mixture of a 2-hydroxy-3-methoxybenzaldehyde (6.6 mmol, 1.0 g) with Ph_3P=CHCHO (7.9 mmol, 2.4 g) 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.



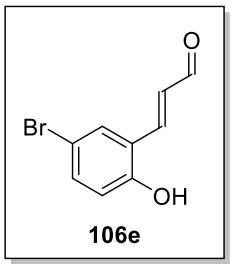
106c

(E)-3-(2-hydroxy-5-nitrophenyl)acrylaldehyde (106c): A mixture of a 2-hydroxy-5-nitrobenzaldehyde (6.0 mmol, 1.0 g) with Ph_3P=CHCHO (7.9 mmol, 2.4 g) 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.



106d

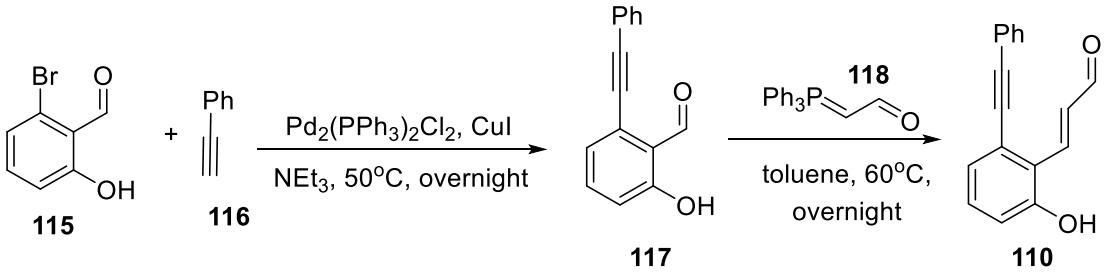
(E)-3-(2-hydroxy-5-methylphenyl)acrylaldehyde (106d): A mixture of a 2-hydroxy-5-methylbenzaldehyde (7.3 mmol, 1.0 g) with Ph_3P=CHCHO (7.9 mmol, 2.4 g) in toluene (10.0 mL) was stirred at 60 ºC for 8 h under nitrogen. The crude product was directly purified by silica gel column directly eluting with 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.



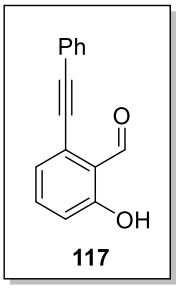
106e

(E)-3-(5-bromo-2-hydroxyphenyl)acrylaldehyde (106e): A mixture of a 2-hydroxy-5-bromobenzaldehyde (5.0 mmol, 1.0 g) with Ph_3P=CHCHO (7.9 mmol, 2.4 g) 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.

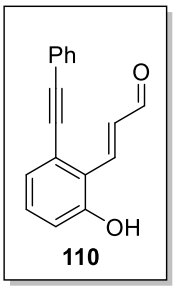
7.1.4. Synthesis of 2-hydroxy-6-(phenylethynyl)phenyl)acrylaldehyde



Scheme 52: *Synthesis of 2-hydroxy-6-(phenylethynyl)phenyl)acrylaldehyde.*



2-hydroxy-6-(phenylethynyl)benzaldehyde (117): To a flask containing 2-hydroxy-6-bromobenzaldehyde (4 mmol, 1.004 g), CuI (0.1 mmol, 19 mg) $Pd_2Cl_2(PPh3)_2$ (0.1 mmol, 70 mg) and Et_3N (solvent, 30 mL) was added ethynylbenzene (4.20 mmol, 0.55 mL) dropwise. The resulting mixture was stirred at 50 °C under nitrogen atmosphere. Upon completion as by TLC, the mixture was filtered through pad of celite rinsing with Et_2O. It was then concentrated under reduced pressure and residue were purified by column. (Silica 50g, ethyl acetate/cyclohexane 1:9), yield 62%; white solid; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 11.70 (s, 1H), 10.57 (s, 1H), 7.57 (s, 2H), 6.97 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 192.76, 164.94, 138.85, 131.41, 131.41, 128.66, 128.51, 128.51, 127.68, 123.39, 123.33, 121.79, 120.25, 80.33, 74.95.



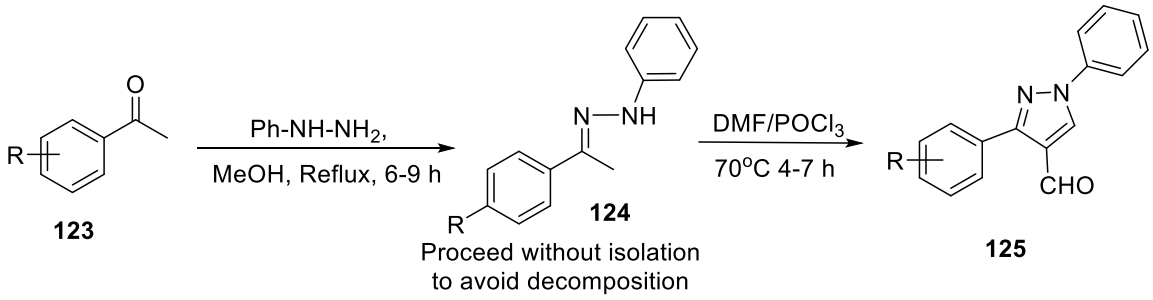
110

(E)-3-(2-hydroxy-6-(phenylethynyl)phenyl)acrylaldehyde (118): To a solution of 2-hydroxy-6-(phenylethynyl)benzaldehyde (4.05 mmol, 900 mg) in toluene (25 mL) was added 2-(triphenyl-l5-phosphanylidene)acetaldehyde (6.08 mmol, 1.85 mg) and reaction were heated at 60 °C overnight. Upon completion of reaction, the mixture was concentrated under reduced pressure and the residue were purified by column chromatography. (Silica gel 50g, ethyl acetate/cyclohexane 1:9), yield 90%; faint yellow solid; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.72 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 15.9 Hz, 1H), 7.58 (d, *J* = 3.5 Hz, 4H), 7.49 – 7.33 (m, 3H), 7.29 (s, 1H), 7.28 (s, 1H), 6.95 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 191.94, 155.70, 151.38, 135.54, 131.41, 131.41, 129.05, 128.66, 128.51, 128.51, 128.04, 127.95, 123.97, 123.33, 119.32, 80.33, 74.95.

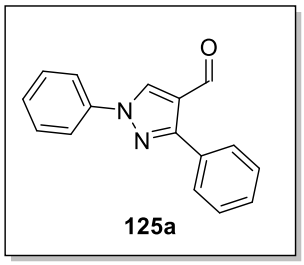
7.2. Synthesis of pyrazole: carbaldehydes, dienophiles, chiral cycloadducts (Scope) and derivatization:

7.2.1. Synthesis of pyrazole carbaldehydes

D) General procedure to synthesize pyrazole carbaldehyde: In a flask containing acetophenone (1 equiv.) dissolved in methanol was added phenyl hydrazine (1 equiv.) followed by 2-3 drops of concentrated H_2SO_4 and refluxed for 6-9 hours. The reaction mixture was allowed to cool until solid appeared in the flask. The mixture was filtered and dried manually (highly unstable) and collected in the flask containing DMF (1.5 equiv.) added $POCl_3$ dropwise at 0 °C. The reaction was heated at 70 °C for 4-7 hours. After cooling the mixture, $NaHCO_3$ were added until neutralisation and was extracted with ethyl acetate and dried over reduced pressure. The residue was purified by column chromatography. 56-88% yield (Scheme 54).

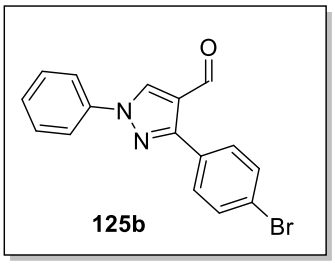


Scheme 53: *Synthesis of pyrazole carbaldehyde.*



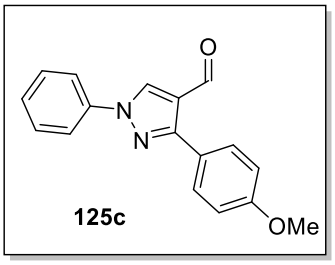
1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (125a): In a flask containing acetophenone (8.6 mmol, 1 mL) dissolved in methanol (10 mL) was added phenyl hydrazine (8.6 mmol, 0.85 mL) followed by 3 drops of concentrated H_2SO_4 and refluxed for 5 hours. The reaction mixture was allowed to cool until solid appeared in the flask. The mixture was filtered and dried manually and collected in the flask containing DMF (1.8 mL) added $POCl_3$ (9.0 mL) dropwise at 0 °C. The reaction was heated at 70 °C for 4 hours. After cooling the mixture, $NaHCO_3$ were added until neutralisation and was extracted with ethyl acetate and dried over reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane, 1:9), white solid,

88% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.98 (s, 1H), 8.47 (s, 1H), 7.77 – 7.70 (m, 4H), 7.46 – 7.39 (m, 5H), 7.32 (t, *J* = 7.4 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 185.38, 154.96, 139.15, 131.46, 131.07, 129.82, 129.44, 129.10, 128.91, 128.11, 122.64, 119.90, 77.16.



125b

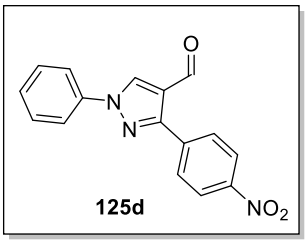
3-(4-bromophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (125b): In a flask containing 4'-bromoacetophenone (5.02 mmol, 1 g) dissolved in methanol (10 mL) was added phenyl hydrazine (5.02 mmol, 0.5 mL) followed by 3 drops of concentrated H_2SO_4 and refluxed for 5 hours. The reaction mixture was allowed to cool until solid appeared in the flask. The mixture was filtered and dried manually and collected in the flask containing DMF (1.5 mL) added $POCl_3$ (7.5 mL) dropwise at 0 °C. The reaction was heated at 70 °C for 6 hours. After cooling the mixture, $NaHCO_3$ were added until neutralisation and was extracted with ethyl acetate and dried over reduced pressure. The residue was purified by Recrystallization (DCM/pentane), bluish white solid, 83% yield. **^{1}H NMR (500 MHz, DMSO)** δ 9.99 (s, 1H), 9.37 (s, 1H), 7.99 (dt, *J* = 3.1, 1.7 Hz, 2H), 7.96 – 7.91 (m, 2H), 7.75 – 7.69 (m, 2H), 7.62 – 7.55 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 1H). **^{13}C NMR (126 MHz, DMSO)** δ 184.48, 151.19, 138.50, 135.73, 131.51, 130.62, 130.49, 129.74, 127.83, 122.69, 122.17, 119.26, 39.52.



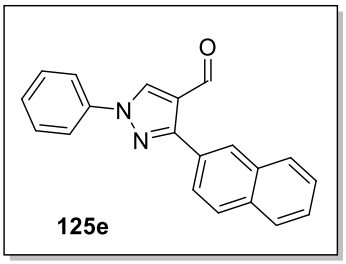
125c

3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (125c): In a flask containing 4'-methoxyacetophenone (6.66 mmol, 1 g) dissolved in methanol (10 mL) was added phenyl hydrazine (6.66 mmol, 0.66 mL) followed by 3 drops of concentrated H_2SO_4 and refluxed for 5 hours. The reaction mixture was allowed to cool until solid appeared in the flask. The mixture was filtered and dried manually and collected in the flask containing DMF (1.6 mL) added $POCl_3$ (8.0 mL) dropwise at 0 °C. The reaction was heated at 70 °C for 14 hours. After cooling the mixture, $NaHCO_3$ were added until neutralisation and was extracted with ethyl acetate and dried over reduced pressure. The residue was purified by Recrystallization (DCM/pentane), pale yellow solid, 85% yield. **^{1}H NMR (500 MHz,**

DMSO) δ 9.97 (s, 1H), 9.29 (s, 1H), 7.98 (dd, *J* = 8.6, 0.9 Hz, 2H), 7.92 – 7.89 (m, 2H), 7.59 – 7.55 (m, 2H), 7.42 (dd, *J* = 9.6, 5.2 Hz, 1H), 7.08 – 7.05 (m, 2H), 3.83 (s, 3H). **^{13}C NMR (126 MHz, DMSO)** δ 184.60, 172.01, 162.30, 160.07, 152.42, 138.62, 135.01, 130.05, 129.70, 127.61, 123.64, 121.96, 119.17, 113.97, 55.24, 39.52.

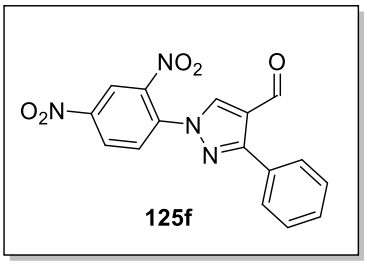


3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (125d): In a flask containing 4'-nitroacetophenone (6.1 mmol, 1 g) dissolved in methanol (10 mL) was added phenyl hydrazine (6.1 mmol, 0.6 mL) followed by 3 drops of concentrated H_2SO_4 and refluxed for 5 hours. The reaction mixture was allowed to cool until solid appeared in the flask. The mixture was filtered and dried manually and collected in the flask containing DMF (1.5 mL) added $POCl_3$ (7.5 mL) dropwise at 0 °C. The reaction was heated at 70 °C for 2 hours. After cooling the mixture, $NaHCO_3$ were added until neutralisation and was extracted with ethyl acetate and dried over reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane, 1:1), pale yellow solid, 92% yield. **^{1}H NMR (500 MHz, DMSO)** δ 10.03 (s, 1H), 9.44 (s, 1H), 8.39 – 8.33 (m, 2H), 8.30 – 8.25 (m, 2H), 8.04 – 7.99 (m, 2H), 7.63 – 7.58 (m, 2H), 7.47 (t, *J* = 7.4 Hz, 1H). **^{13}C NMR (126 MHz, DMSO)** δ 184.41, 149.89, 147.63, 138.41, 137.62, 136.55, 129.80, 129.74, 128.07, 123.68, 122.62, 119.38, 39.52.



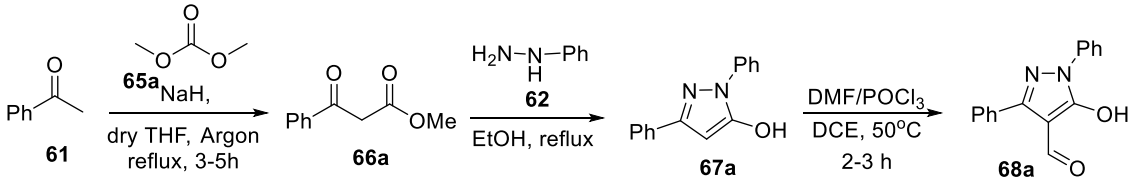
3-(naphthalen-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (125e): In a flask containing 2-acetonaphthone (5.9 mmol, 1 g) dissolved in methanol (10 mL) was added phenyl hydrazine (5.9 mmol, 0.58 mL) followed by 3 drops of concentrated H_2SO_4 and refluxed for 5 hours. The reaction mixture was allowed to cool until solid appeared in the flask. The mixture was filtered and dried manually and collected in the flask containing DMF (1.4 mL) added $POCl_3$ (7.0 mL) dropwise at 0 °C. The reaction was heated at 70 °C for 4 hours. After cooling the mixture, $NaHCO_3$ were added until neutralisation and was extracted with ethyl acetate and dried over reduced pressure. The residue was purified by Recrystallization (Methanol), pale yellow solid, 90% yield. **^{1}H NMR (500 MHz, DMSO)** δ 10.09 (s, 1H), 9.38 (s, 1H), 8.56 (s, 1H), 8.10 – 7.96 (m, 6H), 7.65 – 7.55 (m, 4H), 7.49 – 7.41 (m, 1H).

^{13}C NMR (126 MHz, DMSO) δ 184.82, 152.58, 138.62, 134.98, 133.07, 132.77, 129.74, 128.72, 128.46, 128.17, 128.04, 127.78, 127.61, 126.87, 126.59, 126.12, 122.42, 119.30, 39.52.

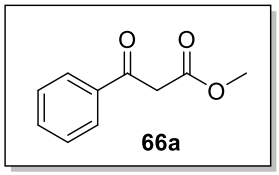


1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (125f): In a flask containing acetophenone (8.6 mmol, 1 mL) dissolved in methanol (10 mL) was added 2,4-dinitrophenyl hydrazine (8.6 mmol, 1.7 g) followed by 3 drops of concentrated H_2SO_4 and refluxed for 5 hours. The reaction mixture was allowed to cool until solid appeared in the flask. The mixture was filtered and dried manually and collected in the flask containing DMF (1.8 mL) added $POCl_3$ (9.0 mL) dropwise at 0 °C. The reaction was heated at 70 °C for 7 hours. After cooling the mixture, $NaHCO_3$ were added until neutralisation and was extracted with ethyl acetate and dried over reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane, 2:3), Orange-yellow solid, 64% yield. **^{1}H NMR (500 MHz, DMSO)** δ 10.01 (s, 1H), 9.36 (s, 1H), 8.95 – 8.87 (m, 1H), 8.69 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.30 (d, *J* = 8.9 Hz, 1H), 7.80 – 7.78 (m, 2H), 7.52 – 7.47 (m, 3H). **^{13}C NMR (126 MHz, DMSO)** δ 184.73, 153.90, 146.46, 143.09, 138.74, 135.08, 130.36, 129.68, 128.91, 128.71, 128.63, 128.25, 126.66, 125.70, 122.90, 121.28, 107.22, 39.52.

Preparation of 5-hydroxy-1,3-diphenyl-1H-pyrazole-4-carbaldehyde (68a):

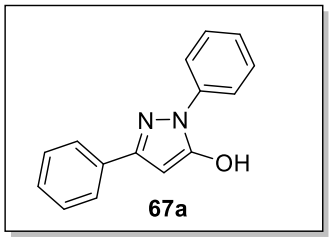


Scheme 54: *Synthesis of 5-hydroxy-1,3-diphenyl-1H-pyrazole-4-carbaldehyde*



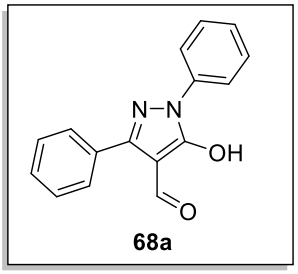
methyl 3-oxo-3-phenylpropanoate (66a): To a suspension of NaH (51.4 mmol, 1.23 g) and dimethyl carbonate **65a** (34.4 mmol, 3 mL) in dry THF was added a solution of substituted acetophenone **61** (17.2 mmol, 2 mL) in dry THF dropwise under reflux. The mixture was refluxed for 5 hours under argon then quenched with

saturated NH_4Cl aq. Solution. The mixture was extracted with ethyl acetate three times and combined with organic phase was washed with brine dried with Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by column. (Silica 100 g, ethyl acetate/cyclohexane 15:85), colourless liquid, 86% yield, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.99 – 7.89 (m, 2H), 7.63 – 7.55 (m, 1H), 7.51 – 7.44 (m, 2H), 4.01 (d, *J* = 2.3 Hz, 2H), 3.74 (d, *J* = 2.0 Hz, 3H).



67a

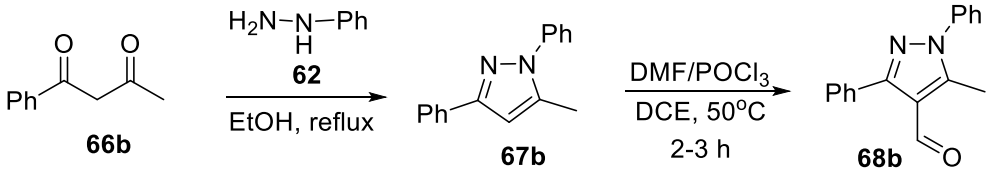
5-hydroxy-1,3-diphenyl-1*H*-pyrazole (67a): To a solution of methyl 3-oxo-3-phenylpropanoate **66a** (11.2 mmol, 2 g) in ethanol was added phenyl hydrazine **62** (12.4 mmol, 1.2 mL) with stirring. The reaction was heated to reflux until complete consumption of starting material. The reaction was allowed to cool to RT and solid that formed was collected by filtration, washed with cold ethanol and dried over reduced pressure. White powder Yield 68% **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.40 – 7.24 (m, 11H), 2.17 (d, *J* = 0.9 Hz, 1H).



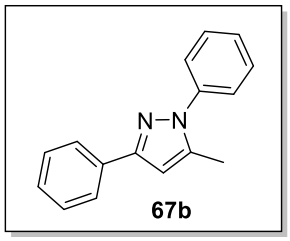
68a

5-hydroxy-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (68a): A mixture of DMF (60 mL) and $POCl_3$ (60 mL) was stirred at 0 °C for 5 minutes under argon then warm to RT and stirred for 30 minutes. Reaction mixture was added to the pyrazole **67a** (5 mmol, 1.2 g) dissolved in DCE (300 mL) and stirred for 2h at 50 °C. Cool the mixture to RT and slowly added sat. $NaHCO_3$ at 0 °C. Warm the mixture to RT and stirred for 30 minutes. Wash with water twice, separated organic layer dried over $MgSO_4$. The yellow residue was purified by column chromatography. (Silica 100 g, ethyl acetate/cyclohexane 20:80), 88% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 10.07 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.82 (dd, *J* = 6.5, 3.2 Hz, 3H), 7.67 – 7.61 (m, 2H), 7.53 (dd, *J* = 9.1, 6.5 Hz, 4H), 1.43 (s, 1H).

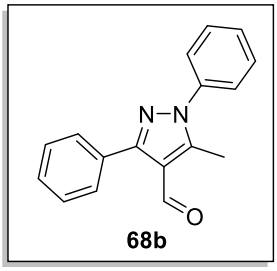
Preparation of 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (68b):



Scheme 55: *Synthesis of 5-methyl-1,3-diphenyl-1H-pyrazole-4-carbaldehyde*



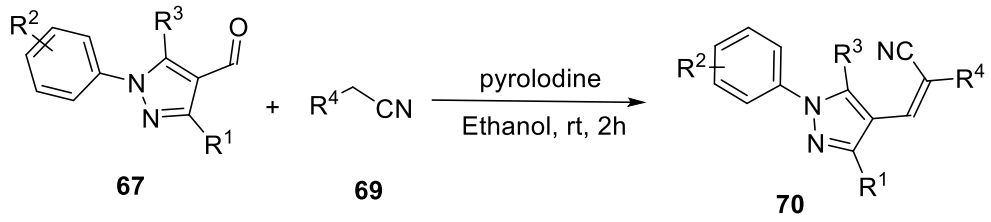
5-methyl-1,3-diphenyl-1*H*-pyrazole (67b): To a solution of 1-phenylbutane-1,3-dione **66b** (18.5 mmol, 3 g) in ethanol was added phenyl hydrazine **62** (22.2 mmol, 2.2 mL) with stirring. The reaction was heated to reflux until complete consumption of starting material. The reaction was allowed to cool to RT and solid that formed was collected by filtration, washed with cold ethanol and dried over reduced pressure; White powder; Yield 68%; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.37 – 7.19 (m, 11H), 2.42 (s, 3H).



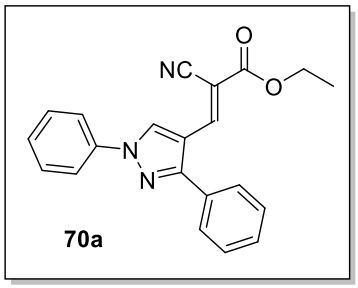
5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (68b): A mixture of DMF (30 mL) and $POCl_3$ (30 mL) was stirred at 0 °C for 5 minutes under argon then warm to RT and stirred for 30 minutes. Reaction mixture was added to the 5-methyl-1,3-diphenyl-1H-pyrazole **67b** (2.5 mmol, 576 mg) dissolved in DCE (300 mL) and stirred for 2h at 50 °C. Cool the mixture to RT and slowly added sat. $NaHCO_3$ at 0 °C. Warm the mixture to RT and stirred for 30 minutes. Wash with water twice, separated organic layer dried over $MgSO_4$. The yellow residue was purified by column chromatography. (Silica 100 g, ethyl acetate/cyclohexane 20:80), 88% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.79 (s, 1H), 7.43 (d, J = 7.0 Hz, 3H), 7.36 – 7.25 (m, 7H), 2.64 (d, J = 6.4 Hz, 3H).

7.2.2. Synthesis of dienophiles (olefinic pyrazole) (54):

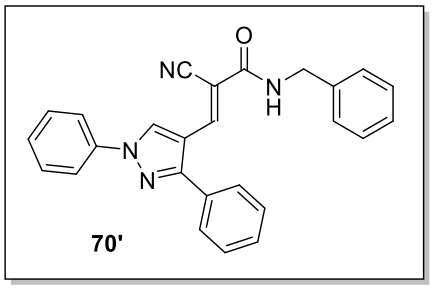
E) General procedure to synthesize dienophile: To a solution of aryl cyano-derivative (1 eq.) and pyrazole aldehyde (1.1 eq.) in ethanol (0.2 M) was added pyrrolidine (0.05 eq.). The resulting solution was stirred for 2 hours until complete formation of solid. This was then extracted with ethyl acetate (4 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a solid crude material which was then purified by column chromatography (silica gel, ethyl acetate/hexane). This was further purified by crystallization using varying mixtures of dichloromethane and petroleum ether. Yield 92-98% (Scheme 57).



Scheme 56: *Synthesis of olefinic pyrazole*



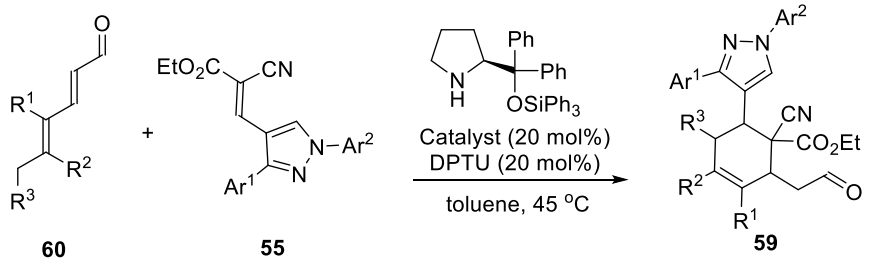
ethyl (E)-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylate (70a): To a solution of ethyl-cyanoester (1 eq.) and pyrazole aldehyde (1.1 eq.) in ethanol (0.2 M) was added pyrrolidine (0.05 eq.). The resulting solution was was stirred for 2 hours until complete formation of solid. This was then extracted with ethyl acetate (4 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a solid crude material which was then purified by column chromatography (silica gel, ethyl acetate/hexane). Recrystallise by using dichloromethane and petroleum ether. Yield 98%. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.14 (s, 1H), 8.31 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.62 (dt, *J* = 8.2, 2.0 Hz, 2H), 7.56 – 7.46 (m, 5H), 7.44 – 7.37 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.40 – 1.35 (m, 3H).; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.83, 156.54, 146.40, 139.03, 131.00, 129.83, 129.51, 129.43, 129.31, 129.15, 128.30, 120.10, 116.84, 115.10, 100.00, 77.16, 62.54, 14.34.



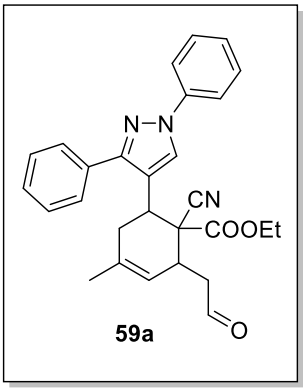
(E)-N-benzyl-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide: To a solution of cycnobenzyl amine (1 eq.) and pyrazole aldehyde (1.1 eq.) in ethanol (0.2 M) was added pyrrolidine (0.05 eq.). The resulting solution was was stirred for 2 hours until complete formation of solid. This was then extracted with ethyl acetate (4 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a solid crude material which was then purified by column chromatography (silica gel, ethyl acetate/hexane). Recrystallise by using dichloromethane and petroleum ether. Yield 91%. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.94 (s, 1H), 8.37 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.59 – 7.54 (m, 2H), 7.48 – 7.38 (m, 5H), 7.37 – 7.20 (m, 6H), 6.45 (t, *J* = 5.4 Hz, 1H), 4.52 (d, *J* = 5.7 Hz, 2H).

7.2.3. Synthesis of pyrazole cycloadduct:

F) General procedure B for the trienamine mediated [4+2] cycloaddition reaction: A dry 5 mL vial equipped with a magnetic stirrer bar and was charged with the corresponding aminocatalyst (0.02 mmol), and corresponding dienal (0.2 mmol). toluene (0.5 mL) was added to dissolve the compounds, there upon the dienophile (0.1 mmol) was added to the mixture. The reaction mixture was stirred at 45 °C for the time indicated in each case. After completion, full conversion was determined by ^{1}H NMR, which delivers the final products **59**. The crude product was purified by flash column chromatography on silica gel (eluents are mentioned in each case) (Scheme 58).

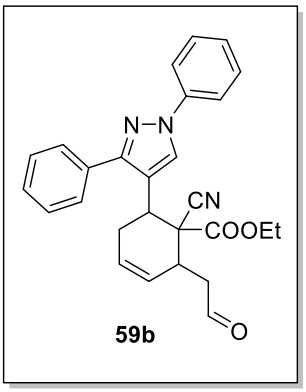


Scheme 57: *synthesis of chiral pyrazole-cyclohexyl adducts.*



59a

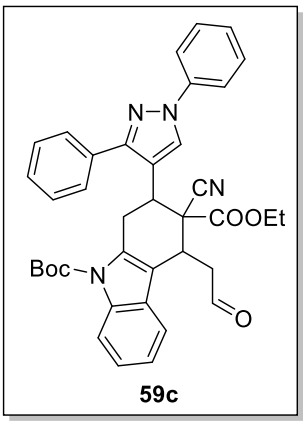
ethyl 1-cyano-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-methyl-2-(2-oxoethyl)cyclohex-3-ene-1-carboxylate (59a): From **60a** (0.1 mmol) and catalyst (0.02 mmol), following the general procedure F (70 ºC, 60 h), compound **59a** was obtained in 82% yield as a yellow oil. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15). The dr was determined by ^{1}H proton of crude sample and was observed 9:1. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 9.61 (s, 1H), 8.33 (s, 1H), 7.75 (d, *J* = 1.1 Hz, 1H), 7.73 (d, *J* = 0.9 Hz, 1H), 7.67 (t, *J* = 1.7 Hz, 1H), 7.66 (s, 1H), 7.49 (d, *J* = 1.3 Hz, 1H), 7.44 (dd, *J* = 2.5, 1.2 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.40 (d, *J* = 1.4 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.29 (s, 1H), 5.90 (d, *J* = 10.1 Hz, 1H), 5.74 – 5.69 (m, 1H), 4.07 – 4.02 (m, 1H), 3.97 – 3.92 (m, 1H), 3.63 – 3.59 (m, 1H), 3.52 (dd, *J* = 10.4, 6.6 Hz, 1H), 2.91 (dd, *J* = 18.9, 7.9 Hz, 1H), 2.52 (d, *J* = 1.1 Hz, 1H), 2.49 (d, *J* = 4.6 Hz, 1H), 1.25 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C **NMR (126 MHz, CDCl$_3$)** δ 198.77, 167.52, 152.80, 139.93, 135.47, 133.27, 129.58, 128.82, 128.74, 128.34, 126.74, 125.00, 120.79, 119.30, 119.15, 77.16, 63.07, 51.82, 46.03, 38.17, 37.13, 23.07, 13.81.



59b

ethyl 1-cyano-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-methyl-2-(2-oxoethyl)cyclohex-3-ene-1-carboxylate (59b): From **60b** (0.1 mmol) and catalyst (0.02 mmol), following the general procedure F (70 ºC, 60 h), compound **59b** was obtained in 65% yield as a yellow oil. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15). The dr was determined by ^{1}H proton of crude sample and was observed 9:1. Yellow solid; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 9.61 (s, 1H), 8.33 (s, 1H), 7.75 (d, *J* = 1.1 Hz, 1H), 7.73 (d, *J* = 0.9 Hz, 1H), 7.67 (t, *J* = 1.7 Hz, 1H), 7.66 (s, 1H), 7.49 (d, *J* = 1.3 Hz, 1H), 7.44 (dd, *J* = 2.5, 1.2 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.40 (d, *J* = 1.4 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.29 (s, 1H), 5.90 (m, *J* = 10.1 Hz, 2H), 5.74 – 5.69 (m, 1H), 4.07 – 4.02 (m, 1H), 3.97 – 3.92 (m, 1H), 3.63 – 3.59 (m, 1H), 3.52 (dd, *J* = 10.4, 6.6 Hz, 1H), 2.91 (dd, *J* = 18.9, 7.9 Hz, 1H), 2.52 (d, *J* = 1.1 Hz, 1H), 2.49 (d, *J* = 4.6 Hz, 1H), 1.25 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 198.77, 167.52, 152.80, 139.93,

135.47, 133.27, 129.58, 128.82, 128.74, 128.34, 126.74, 125.00, 120.79, 119.30, 119.15, 77.16, 76.32 63.07, 51.82, 46.03, 38.17, 37.13, 23.07.



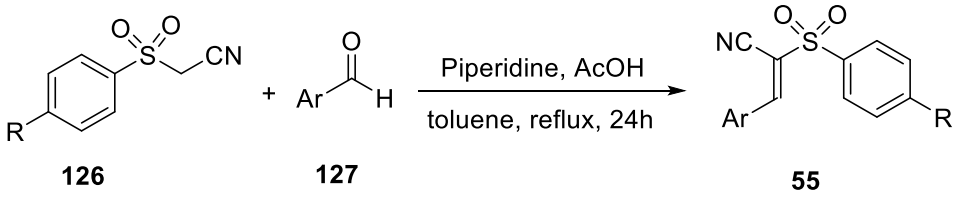
59c

9-(tert-butyl) 3-ethyl 3-cyano-2-(1,3-diphenyl-1H-pyrazol-4-yl)-4-(2-oxoethyl)-1,2,3,4-tetrahydro-9H-carbazole-3,9-dicarboxylate (59c): From **60b** (0.1 mmol) and catalyst (0.02 mmol), following the general procedure F (70 ºC, 60 h), compound **59c** was obtained in 65% yield as a yellow oil. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15). The dr was determined by ^{1}H proton of crude sample and was observed 9:1. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.71 (s, 3H), 9.65 (s, 3H), 7.78 – 7.67 (m, 6H), 7.67 – 7.58 (m, 12H), 7.55 (d, *J* = 3.3 Hz, 2H), 7.55 – 7.45 (m, 20H), 7.37 (s, 3H), 4.63 (d, *J* = 11.5 Hz, 6H), 4.25 – 4.13 (m, 6H), 3.95 (s, 2H), 3.41 (s, 3H), 2.73 (s, 2H), 2.48 (s, 2H), 1.54 – 1.50 (m, 27H), 1.41 – 1.37 (m, 9H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 201.77, 186.56, 167.70, 160.59, 150.83, 139.97, 138.24, 133.87, 133.00, 131.08, 129.70, 129.11, 128.62, 128.18, 128.03, 125.44, 121.83, 120.86, 120.71, 119.95, 117.61, 116.91, 114.91, 93.09, 80.96, 71.85, 62.47, 52.81, 43.94, 36.73, 32.90, 28.41, 22.41, 14.69.

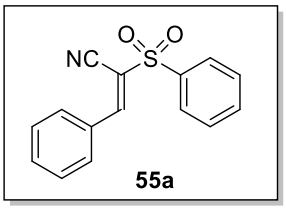
7.3. Synthesis of sulfones: cyanosulfones, chiral cycloadducts (Scope) and derivatization:

7.3.1. Synthesis of cyanosulfones

G) General procedure for α,β-unsaturated α,α-disubstituted aryl cyanosulfones: To a solution of aryl cyanosulfone (1 eq.) and aryl aldehyde (1.1 eq.) in toluene (0.2 M) was added piperidine (0.05 eq.) and acetic acid (0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, ethyl acetate/cyclohexane). This was further purified by crystallization using varying mixtures of dichloromethane and hexane. Unless otherwise stated, the reported yields are prior to crystallization (Scheme 59).

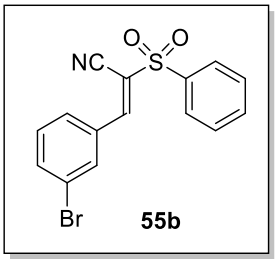


Scheme 58: *Synthesis of aryl cyanosulfones*

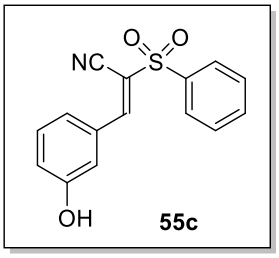


α-Phenylsulfonyl cinnamonitrile 55a: To a solution of (phenylsulfonyl)acetonitrile (3 g, 16.57 mmol) and benzaldehyde (1.84 mL, 18.23 mmol, 1.1 eq.) in toluene (50 mL) was added piperidine (0.08 mL, 0.83 mmol, 0.05 eq.) and acetic acid (0.28 mL, 4.97 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 30% ethyl acetate/cyclohexane). 85% yield, Colorless plates, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.24 (s, 1H), 8.08 – 7.98 (m, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.72 (t, *J* = 6.9 Hz,

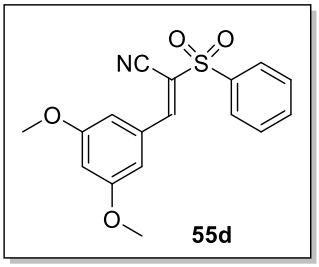
1H), 7.61 (dd, *J* = 15.5, 7.7 Hz, 3H), 7.51 (t, *J* = 7.3 Hz, 2H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 113.2, 114.7, 128.7, 129.5, 129.7, 130.1, 131.1, 134.2, 134.7, 137.9, 151.6.



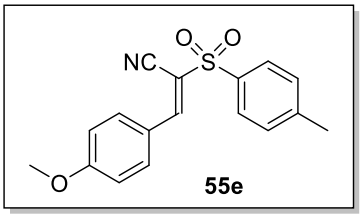
α-Phenylsulfonyl-3-bromocinnamonitrile 55b: To a solution of (phenylsulfonyl)acetonitrile (1 g, 5.52 mmol) and 3-bromobenzaldehyde (0.71 mL, 6.08 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.03 mL, 0.27 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.66 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semisolid crude material which was then purified by column chromatography (silica gel, 25% ethyl acetate/cyclohexane). 84% yield, Colorless cotton like solid, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.13 (s, 1H), 8.01 – 7.90 (m, 2H), 7.65 – 7.55 (m, 4H), 7.39 (s, 1H), 7.24 (s, 1H), 7.15 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 112.6, 116.5, 123.5, 128.8, 128.9, 129.8, 130.9, 132.0, 133.8, 134.9, 136.8, 137.5, 149.6.



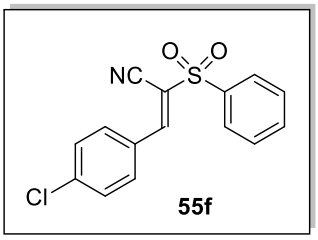
α-Phenylsulfonyl-3-hydroxycinnamonitrile 55c: To a solution of (phenylsulfonyl)acetonitrile (1 g, 5.52 mmol) and 3-hydroxybenzaldehyde (0.74 g, 6.08 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.03 mL, 0.27 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.66 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semisolid crude material which was then purified by column chromatography (silica gel, 30% ethyl acetate/cyclohexane). 84% yield, Yellow plates; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.13 (s, 1H), 8.01 – 7.90 (m, 2H), 7.61 (t, *J* = 9.0 Hz, 3H), 7.11 (s, 1H), 6.88 (d, *J* = 6.2 Hz, 2H), 6.69 (s, 1H), 3.84 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 113.1, 114.9, 116.3, 121.6, 124.5, 128.7, 129.7, 130.8, 131.4, 134.7, 137.7, 151.2, 156.2.



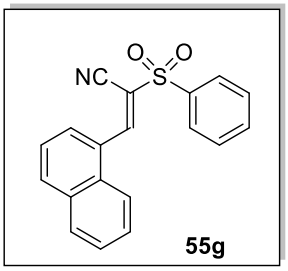
α-Phenylsulfonyl-3,5-dimethoxycinnamonitrile 55d: To a solution of (phenylsulfonyl)acetonitrile (1 g, 5.52 mmol) and 3,5-dimethoxybenzaldehyde (0.74 g, 6.08 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.03 mL, 0.27 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.66 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 25% ethyl acetate/cyclohexane). 87% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.14 (s, 1H), 8.01 – 7.90 (m, 2H), 7.61 (t, *J* = 9.2 Hz, 3H), 6.64 – 6.60 (m, 2H), 6.48 (s, 1H), 3.84 – 3.80 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 55.6, 106.9, 108.5, 113.2, 115.0, 128.7, 129.7,131.7, 134.7, 137.9, 151.8, 161.2.



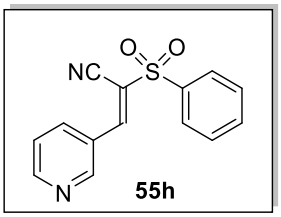
α-p-Toluenesulfonyl-4-methoxycinnamonitrile 55e: To a solution of 2-tosylacetonitrile (1 g, 5.13 mmol) and 4-methoxybenzaldehyde (0.69 mL, 5.64 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.025 mL, 0.26 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.54 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 30% ethyl acetate/cyclohexane). 85% yield, Yellow plates, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.14 (s, 1H), 7.98 – 7.84 (m, 2H), 7.54 – 7.40 (m, 2H), 7.37 – 7.23 (m, 2H), 6.95 – 6.81 (m, 2H), 3.83 – 3.79 (m, 3H), 2.38 – 2.34 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 21.7, 55.7, 111.2, 113.9, 115.0, 123.0, 128.5, 130.2, 133.6, 135.5, 145.6, 150.5, 164.4.



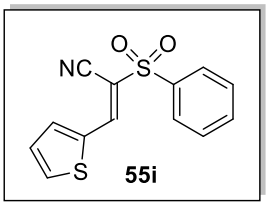
α-Phenylsulfonyl-4-chlorocinnamonitrile 55f: To a solution of (phenylsulfonyl)acetonitrile (1 g, 5.52 mmol) and 4-chlorobenzaldehyde (0.85 g, 6.08 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.03 mL, 0.27 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.66 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 25% ethyl acetate/cyclohexane).86% yield, Yellow needle, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.11 (s, 1H), 7.90 – 7.78 (m, 2H), 7.62 (s, 1H), 7.58 – 7.52 (m, 2H), 7.33 – 7.19 (m, 3H), 7.19 – 7.12 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 112.9, 115.2, 128.6, 128.7, 129.8, 129.9, 132.2, 134.8, 137.6, 140.6, 149.9.



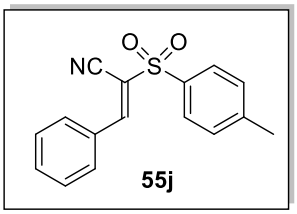
α-Phenylsulfonyl-3-(1-naphthyl)acrylonitrile 55g: To a solution of (phenylsulfonyl)acetonitrile (1 g, 5.52 mmol) and 1-naphthaldehyde (0.8 mL, 6.08 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.03 mL, 0.27 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.66 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 25% ethyl acetate/cyclohexane). 77% yield, Yellow prism, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.49 (s, 1H), 8.00 – 7.89 (m, 2H), 7.86 – 7.75 (m, 3H), 7.58 (t, *J* = 7.7 Hz, 3H), 7.47 (dd, *J* = 4.7, 1.4 Hz, 4H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 113.2, 116.9, 122.5, 125.3, 126.7, 127.1, 128.3, 128.3, 128.8, 129.3, 129.8, 131.6, 133.5, 134.4, 134.7, 137.7, 148.9.



α-Phenylsulfonyl-3-(3-pyridyl)acrylonitrile 55h: To a solution of (phenylsulfonyl)acetonitrile (1 g, 5.52 mmol) and nicotinaldehyde (0.5 mL, 6.08 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.03 mL, 0.27 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.66 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 50% ethyl acetate/cyclohexane). 70% yield, Yellow plates, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.41 (s, 1H), 8.30 (s, 1H), 8.17 (s, 1H), 7.97 – 7.86 (m, 2H), 7.68 (s, 1H), 7.59 (t, *J* = 8.4 Hz, 3H), 7.21 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 112.6, 117.4, 124.2, 126.3, 128.9, 129.9, 135.0, 135.9, 137.3, 147.9, 152.8, 154.2.



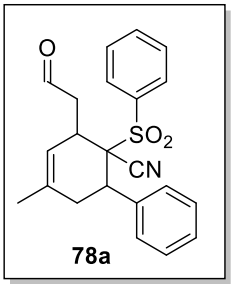
α-Phenylsulfonyl-3-(2-thiophenyl)acrylonitrile 55i: To a solution of (phenylsulfonyl)acetonitrile (1 g, 5.52 mmol) and 2-thiophene carboxaldehyde (0.57 mL, 6.08 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.03 mL, 0.27 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.66 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 25% ethyl acetate/cyclohexane).80% yield, Yellow needle, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.11 (s, 1H), 7.88 – 7.73 (m, 2H), 7.50 – 7.35 (m, 2H), 7.29 – 7.20 (m, 5H), 2.37 – 2.33 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 110.9, 113.2, 128.4, 129.0, 129.7, 134.5, 134.5, 136.1, 137.9, 138.4, 143.7.



α-p-Toluenesulfonyl cinnamonitrile 55j: To a solution of 2-tosylacetonitrile (1 g, 5.13 mmol) and benzaldehyde (0.57 mL, 5.64 mmol, 1.1 eq.) in toluene (25 mL) was added piperidine (0.025 mL, 0.26 mmol, 0.05 eq.) and acetic acid (0.09 mL, 1.54 mmol, 0.3 eq.). The resulting solution was heated to reflux using a Dean-Stark trap to remove water. After 24 h, the reaction was cooled to room temperature and water was added. This was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a semi-solid crude material which was then purified by column chromatography (silica gel, 20% ethyl acetate/cyclohexane). 85% yield, Colorless plates, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.11 (s, 1H), 7.88 – 7.73 (m, 2H), 7.50 – 7.35 (m, 2H), 7.29 – 7.20 (m, 5H), 2.47 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 21.8, 113.2, 115.1, 128.8, 129.5, 130.2, 130.4, 131.0, 134.0, 134.8, 146.0, 151.0.

7.3.2. Synthesis of sulfone adducts

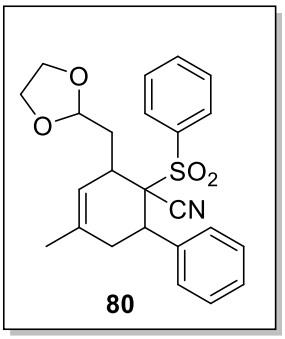
H) General procedure for [4+2] cycloaddition reaction C: To a solution of 2,4-dienal (2 equiv.) and (R)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (20 mol%) in chloroform (0.2 M) was added α,β-unsaturated α,α-disubstituted aryl cyanosulfones (1 equiv.) and the reaction mixture was stirred for 3 days at 0 °C. After completion, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel 25g, ethyl acetate/hexane 10:90).



5-methyl-3-(2-oxoethyl)-2-(phenylsulfonyl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carbonitrile: To a solution of (*E*)-5-methylhexa-2,4-dienal (2 equiv.) and (R)-2-(diphenyl((trimethylsilyl) oxy)methyl)pyrrolidine (20 mol%) in solvent (0.2 M) was added α-phenylsulfonyl cinnamonitrile (1 equiv.) and the reaction mixture was stirred for 3 days at 0 °C. After completion, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel 25g, ethyl acetate/hexane 10:90). Yellow thick oil, 80 yield, 78% ee, 2:3 dr**, ^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.77 (s, 1H), 7.47 – 7.36 (m, 4H), 7.22 – 7.08 (m, 6H), 5.21 (s, 1H),

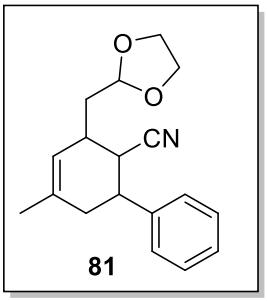
4.00 (d, *J* = 8.4 Hz, 1H), 3.74 – 3.63 (m, 1H), 3.62 – 3.51 (m, 2H), 2.70 (ddd, *J* = 18.6, 10.1, 1.1 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.14 (dd, *J* = 18.0, 4.1 Hz, 1H), 1.70 (s, 3H).

7.3.3. Synthesis of Sulfone derivatives



80

3-((1,3-dioxolan-2-yl)methyl)-5-methyl-2-(phenylsulfonyl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carbonitrile (80): After confirmation of obtaining **78a** by ^{1}H NMR, 3 equiv. of ethylene glycol were added, and reaction were stirred for another 6 hours. The desired product **80** was isolated by column chromatography (cyclohexane/ethyl acetate = 90:10), 77% yield, yellow oil; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.01 – 7.90 (m, 4H), 7.60 (t, *J* = 8.9 Hz, 6H), 7.42 – 7.33 (m, 4H), 7.33 – 7.27 (m, 4H), 7.18 (s, 2H), 5.37 (s, 2H), 4.90 (s, 2H), 4.84 (s, 2H), 4.18 (s, 2H), 3.98 – 3.94 (m, 3H), 3.92 – 3.88 (m, 3H), 2.45 (s, 2H), 2.30 (s, 2H), 1.86 – 1.82 (m, 6H), 1.62 – 1.52 (m, 4H).

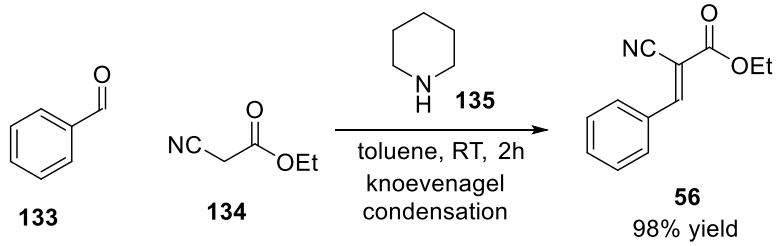


81

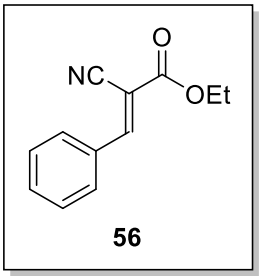
3-((1,3-dioxolan-2-yl)methyl)-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carbonitrile (81): To an excess solution of Raney Ni in THF, compound **80** was added, and was refluxed for 8 hours. Reaction mixture was allowed to cool, and isolated by column chromatography (cyclohexane/ethyl acetate = 80:20), 52% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.31 – 7.24 (m, 4H), 7.17 (s, 1H), 5.37 (s, 1H), 4.90 (s, 1H), 4.00 – 3.96 (m, 2H), 3.94 – 3.90 (m, 2H), 3.38 (s, 1H), 3.14 (s, 1H), 2.93 (s, 1H), 2.37 (s, 1H), 2.17 (s, 1H), 1.85 – 1.81 (m, 3H), 1.59 – 1.55 (m, 2H).

7.4. Synthesis of THC's: trienamine mediated chiral cycloadducts

7.4.1. Synthesis of cyanophenylacrylate:



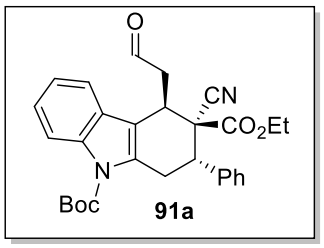
Scheme 59: *Synthesis of dienophile*



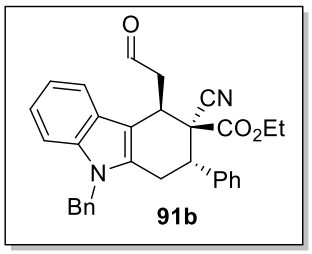
ethyl (E)-2-cyano-3-phenylacrylate (56): To a solution of a benzaldehyde (12.7 mmol) and ethyl 2-cyanoacetate (13 mmol) in toluene (1.1 mL), pyrrolidine (2.3 mmol) was added and stirred at RT for 2 hours. Crude product was recrystallized by DCM and pentane. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.50, 155.06, 133.32, 131.49, 131.08, 129.29, 115.50, 103.05, 62.75, 14.17.

7.4.2. Synthesis of chiral phenyl isocyanate cycloadducts

I) General procedure B for the trienamine mediated [4+2] cycloaddition reaction: A dry 5 mL vial equipped with a magnetic stirrer bar and was charged with the corresponding aminocatalyst (5 mg, 0.01 mmol), and corresponding 2-methylindole acrylaldehyde (0.1 mmol). toluene (0.5 mL) was added to dissolve the compounds, there upon the cyanophenylacrylate (0.05 mmol) was added to the mixture. The reaction mixture was stirred at 70 °C for the time indicated in each case. After completion, full conversion was determined by ^{1}H NMR, which delivers the final products **91**. The crude product was purified by flash column chromatography on silica gel and then preparative plate (eluents are mentioned in each case).

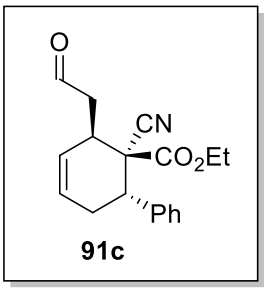


9-(tert-butyl) 3-ethyl (2S,3S,4R)-3-cyano-4-(2-oxoethyl)-2-phenyl-1,2,3,4-tetrahydro-9H-carbazole-3,9-dicarboxylate (91a): From **87** (28.5 mg, 0.1 mmol) and **5** (10.0 mg, 0.05 mmol), following the general procedure I (70 ºC, 60 h), compound **91a** (19.2 mg, 0.039 mmol) was obtained in 79% yield as a yellow solid. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15). The dr was determined by ^{1}H proton of crude sample and was observed 62:38. The *ee* was determined by Chiralcel OD-H, hexane/*i*-PrOH (90:10), 1 mL/min, T=35 ºC, τ_{max} = 8.72 min, τ_{min} = 6.99 min, ***ee***= 98%. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.73 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.28 (m, 6H), 4.58 (d, *J* = 9.6 Hz, 1H), 3.94 – 3.89 (m, 2H), 3.66 (d, *J* = 14.7 Hz, 1H), 3.60 – 3.46 (m, 3H), 2.84 (d, *J* = 19.5 Hz, 1H), 1.65 (s, 9H), 1.01 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.69, 167.25, 150.35, 138.57, 136.34, 134.31, 128.78, 128.76, 128.23, 127.31, 124.67, 123.16, 118.49, 117.25, 116.15, 115.37, 84.53, 63.06, 51.26, 45.82, 42.59, 34.48,3 1.93, 28.35, 13.62. **HRMS** (ESI^+) calculated for $C_{27}H_{24}N_2O_5$ $[M+nH]^+$: 487.2227, found: 487.2237.



ethyl (2S,3S,4R)-9-benzyl-3-cyano-4-(2-oxoethyl)-2-phenyl-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate (91b): From **87** (27.4 mg, 0.1 mmol) and **5** (10.0 mg, 0.05 mmol), following the general procedure I (70 ºC, 60h), compound **91b** (21.4 mg, 0.045 mmol) was obtained in 84% yield as a amber color cotton type solid. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15). The dr was determined by ^{1}H proton of crude sample and was observed 92:8. The *ee* was determined by Chiralcel OD-H, hexane/*i*-PrOH (90:10), 1 mL/min, T=35 ºC, τ_{max} = 18.24 min, τ_{min} = 15.01 min, ***ee***= 98%. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.98 (s, 1H), 7.46 – 7.09 (m, 12H), 6.69 (d, *J* = 7.1 Hz, 2H), 5.29 (s, 2H), 4.65 - 4.61 (m, 1H), 3.96 – 3.91 (m, 2H), 3.65 (dd, *J* = 12.3, 4.8 Hz, 1H), 3.56 (ddd, *J* = 19.2, 4.4, 1.2 Hz, 1H), 3.45 – 3.38 (m, 1H), 3.15 (ddd, *J* = 19.2, 6.5, 1.1 Hz, 1H), 3.01 (dd, *J* = 16.5, 4.4 Hz, 1H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 199.71, 167.66, 138.04, 137.50, 137.09, 134.29, 129.08, 128.87, 128.59, 128.56, 127.68, 125.94, 125.39, 121.97, 120.03, 118.68, 117.12, 110.05, 107.37, 62.96, 57.89, 47.47, 42.62, 46.43, 36.64,

27.44, 13.64; **HRMS** (ESI^+) calculated for $C_{27}H_{24}N_2O_5$ $[M+nH]^+$: 477.2182, found: 477.2173.

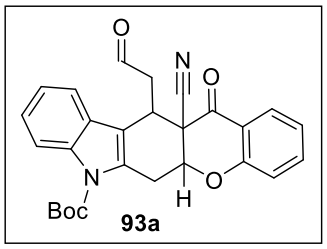


91c

ethyl (1S,2R,3R)-2-cyano-3-(2-oxoethyl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (91c): From **60a** (20.0 mg, 0.1 mmol) and **5** (10.0 mg, 0.05 mmol), following the general procedure I (70 ºC, 60h), compound **91c** (18.4 mg, 0.045 mmol) was obtained in 84% yield as amber color oil. The crude product was purified by column chromatography (gradient hexane/AcOEt 90:10). The dr was determined by ^1H proton of crude sample and was observed 96:4. ^1H **NMR (500 MHz, $CDCl_3$)** δ 9.59 (s, 1H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.23 – 7.18 (m, 2H), 5.92 – 5.86 (m, 1H), 5.69 – 5.63 (m, 1H), 3.88 – 3.79 (m, 2H), 3.53 (d, *J* = 6.4 Hz, 1H), 3.18 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.07 (dd, *J* = 18.8, 7.9 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.51 (dd, *J* = 18.8, 4.6 Hz, 1H), 2.38 (dt, *J* = 18.8, 4.8 Hz, 1H), 0.92 (t, *J* = 7.1 Hz, 3H).

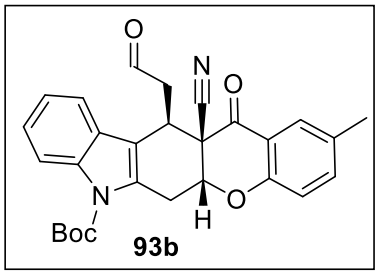
7.4.3. Synthesis of chiral cyanochromene cycloadducts

J) General procedure A for the trienamine mediated [4+2] cycloaddition reaction: A dry 5 mL vial equipped with a magnetic stirrer bar and was charged with the corresponding aminocatalyst (0.02 mmol), and the 2-methylindole acrylaldehyde (0.15 mmol). toluene (0.5 mL) was added to dissolve the compounds, there upon the corresponding cyanochromene (0.1 mmol) and PhCOOH (0.02 mmol) was added to the mixture. The reaction mixture was stirred at 70 °C for the time indicated in each case. After completion, full conversion was determined by ^1H NMR, which delivers the final products **93**. The crude product was purified by flash column chromatography on silica gel and then preparative plate (eluents are mentioned in each case).



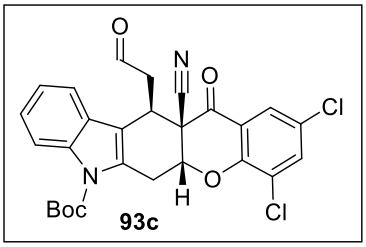
93a

tert-butyl (5aR,12R,12aR)-12a-cyano-13-oxo-12-(2-oxo ethyl)-6,12,12a,13-tetrahydrochromeno [2,3-b] carbazole -7(5aH)-carboxylate (93a): From **87** (43.0 mg, 0.15 mmol) and cyanochromene **56a** (17.2 mg, 0.1 mmol), catalyst (10.0 mg, 0.02 mmol) and PhCOOH (2.5 mg, 0.02 mmol), following the general procedure A (70 ºC, 18h), compound **93a** (32.6 mg, 0.071 mmol) was obtained in 71% yield as a red solid. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15) followed by preparative plate (gradient hexane/AcOEt 95:5). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.88 (s, 1H), 8.20 – 8.16 (m, 1H), 7.95 – 7.92 (m, 1H), 7.59 – 7.55 (m, 1H), 7.32 – 7.27 (m, 2H), 7.18 (d, *J* = 4.1 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 5.16 (s, 1H), 4.41 (d, *J* = 18.9 Hz, 1H), 3.81 (ddd, *J* = 19.0, 4.1, 2.7 Hz, 1H), 3.70 (dd, *J* = 13.7, 5.4 Hz, 1H), 3.50 – 3.38 (m, 2H), 1.72 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.49, 150.13, 137.63, 136.26, 135.41, 128.66, 126.97, 124.55, 123.17, 123.07, 118.26, 118.15, 116.12, 115.16, 84.86, 77.16, 51.08, 47.63, 44.36, 38.83, 34.21, 28.37, 27.63, 22.43, 14.16.



93b

tert-butyl (5aR,12R,12aR)-12a-cyano-2-methoxy-13-oxo-12-(2-oxoethyl)-6,12,12a,13-tetrahydrochromeno [2,3-b]carbazole-7(5aH)-carboxylate (93b): From **87** (43.0 mg, 0.15 mmol) and cyanochromene **56b** (18.5 mg, 0.1 mmol), catalyst **3x** (10.0 mg, 0.02 mmol) and PhCOOH (2.5 mg, 0.02 mmol), following the general procedure A (70 ºC, 30h), compound **93b** was obtained in 66% yield as a red solid. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15) followed by preparative plate (gradient hexane/AcOEt 95:5). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.65 (s, 1H), 8.42 (s, 1H), 7.55 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.26 (s, 1H), 7.19 (s, 1H), 7.03 (s, 1H), 5.53 (s, 1H), 4.68 (s, 1H), 3.86 (s, 1H), 3.20 (s, 1H), 2.73 (s, 1H), 2.48 (s, 1H), 2.35 – 2.27 (m, 3H), 1.53 – 1.46 (m, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 201.77, 188.30, 158.95, 150.83, 138.24, 136.90, 130.93, 129.89, 129.11, 126.92, 125.44, 121.83, 121.51, 120.86, 120.51, 117.59, 114.91, 109.86, 80.96, 73.09, 43.94, 31.75, 28.41, 23.79, 21.20.

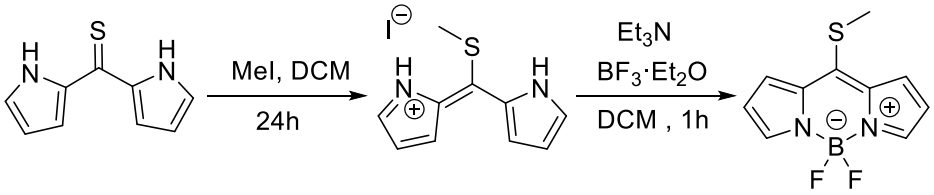


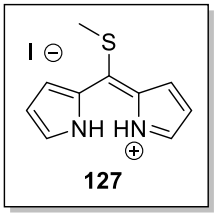
93c

tert-butyl (5aR,12R,12aR)-2,4-dichloro-12a-cyano-13-oxo-12-(2-oxoethyl)-6,12,12a,13-tetrahydrochromeno [2,3-b]carbazole-7(5aH)-carboxylate (93c): 87 (43.0 mg, 0.15 mmol) and cyanochromene **56c** (24.0 mg, 0.1 mmol), aminocatalyst (10.0 mg, 0.02 mmol) and PhCOOH (2.5 mg, 0.02 mmol), following the general procedure A (70 ºC, 60h), compound **93c** was obtained in 54% yield as a red solid. The crude product was purified by column chromatography (gradient hexane/AcOEt 85:15) followed by preparative plate (gradient hexane/AcOEt 95:5). The *ee* was determined by **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.65 (s, 1H), 8.49 (s, 1H), 7.93 (s, 1H), 7.64 (s, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.40 (s, 1H), 5.47 (s, 1H), 3.86 (d, *J* = 1.3 Hz, 2H), 3.24 (s, 1H), 2.73 (s, 1H), 2.48 (s, 1H), 1.58 – 1.42 (m, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 201.77, 187.24, 157.19, 150.83, 138.24, 133.67, 129.89, 129.11, 127.40, 126.63, 125.44, 125.37, 122.78, 121.83, 120.86, 120.51, 114.91, 109.86, 80.96, 74.04, 43.94, 31.75, 28.41, 23.79.

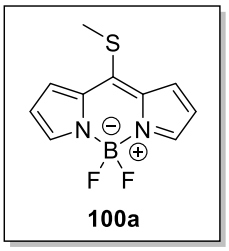
7.5. Synthesis of BODIPY's (starting material): thiomethyl BODIPY's, iodo BODIPY's, alkenyl BODIPY's.

7.5.1. Synthesis of thiomethyl BODIPY's[154]





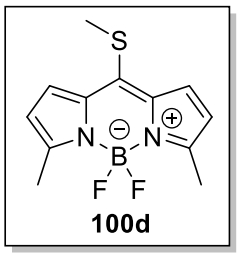
(*E*)-2-((methylthio)(1*H*-pyrrol-2-yl)methylene)-2*H*-pyrrol-1-ium iodide (127): To a stirred solution of the thioketone (2.60 g, 14.86 mmol, 1 equiv.) in anhydrous DCM (50 mL), MeI (4.8 mL, 74.3 mmol, 5.8 equiv.) was added and the mixture was stirred at room temperature for 24h. Then, the solvent and the MeI in excess were removed under reduced pressure obtaining the iodide thioether as a black solid (4.73 g) in quantitative yield. The product was used without further purification. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 12.0 (brs, 2H), 7.91 – 89 (m, 2H), 7.29 – 7.26 (m, 2H), 6.68 – 6.66 (m, 2H), 2.91 (s, 3H).



5,5-difluoro-10-(methylthio)-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinine (100a): To a stirred solution under argon atmosphere of the iodide thioether (450 mg, 1.4 mmol, 1 equiv.) in anhydrous DCM (11 mL), triethylamine (0.35 mL, 4.76 mmol, 3.5 equiv.) was added and the mixture was stirred at room temperature for 30 minutes. Then, the solution was cooled to 0 ºC and $BF_3{\cdot}Et_2O$ (0.9 mL, 7.3 mmol, 5 equiv.) was added dropwise. The reaction mixture was led to reach room temperature and was stirred for an additional 30 minutes. The solvent was removed under reduced pressure and the crude was purified by column chromatography on silica gel, eluting with Cy/AcOEt

[154] T. V. Goud, T. V.; Tutar, A.; Biellmann, J. -F. *Tetrahedron*, **2006**, *62*, 5084.

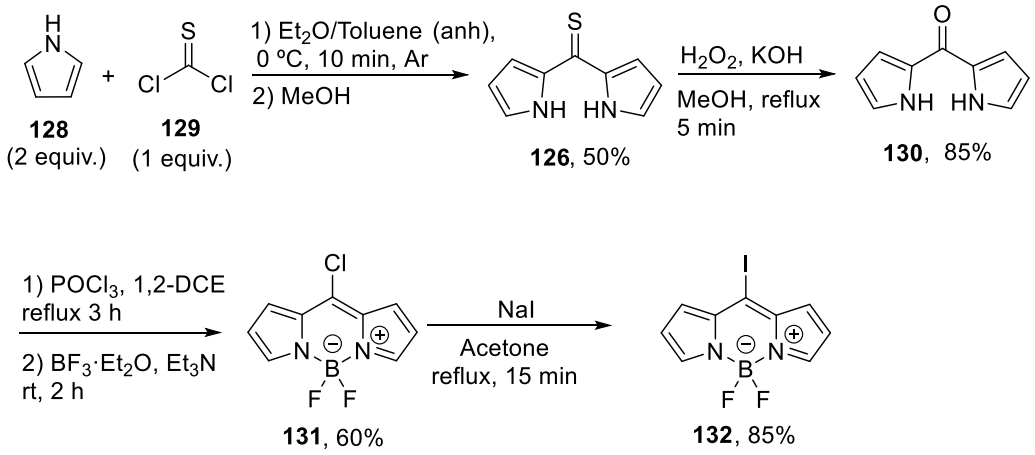
(3:1) obtaining the final product as a red solid (85 mg, 25% yield). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.80 (brs, 2H), 7.43 – 7.41 (m, 2H), 6.54 – 6.52 (m, 2H), 2.92 (s, 3H).



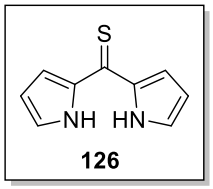
100d

5,5-difluoro-3,7-dimethyl-10-(methylthio)-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine (100d): Red solid; 50% yield;

7.5.2. Synthesis of 8-iodoBODIPY's[155,156]



Scheme 60: *Synthesis of 8-iodo BODIPY*



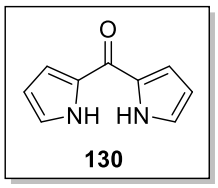
126

di(1*H*-pyrrol-2-yl)methanethione (126): To a stirred solution under argon atmosphere of pyrrole (4.14 mL, 59 mmol, 2 equiv.) in anhydrous diethyl ether (90 mL) at 0 ºC, a solution of thiophosgene (2.25 mL, 29.5 mmol, 1 equiv.) in anhydrous toluene (78 mL) was added dropwise. The mixture was stirred at 0 ºC for 10 minutes. After completion, the reaction mixture reached rt, MeOH was added and the reaction mixture was stirred for 30 min. Then, the solvents were evaporated under reduced pressure and the crude was purified by flash chromatography (eluent: Cy:AcOEt 7:1). The thioketone was obtained as a red solid with

[155] Plater, M. J.; Aiken, S.; Bourhill, G. *Tetrahedron*, **2002**, *58,* 2405.

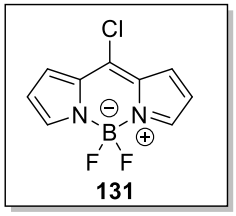
[156] Leen, V.; Yuan, P.; Wang, L.; Boens, N.; Dehaen, W. *Org. Lett.*, **2012**, *14*, 6150.

a 50% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.78 (brs, 2H), 7.25 – 7.16 (m, 2H), 7.10 – 7.01 (m, 2H), 6.46 – 6.37 (m, 2H).



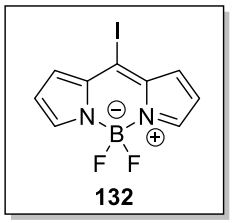
130

di(1*H*-pyrrol-2-yl)methanone (130): To a stirred solution of the thioketone (2.6 g, 15 mmol, 1 equiv.) in 82 mL of MeOH, KOH (3.25 g, 58 mmol, 4 equiv.) was added and the mixture was stirred for 5 min at 0 °C. Then, H_2O_2 (30%, 11 mL, 67 mmol, 4.5 equiv.) was added dropwise and the reaction crude was reflux. After 5 minutes, the reaction is cooled to room temperature and water (130 mL) is added. Finally, the crude is again cooled to 0 ºC. The solid obtained was filtered obtaining the ketone as a white solid in 85% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.79 (s, 2H), 7.17 – 7.16 (m, 2H), 7.10 – 7.08 (m, 2H), 6.36 – 6.35 (m, 2H).



131

10-chloro-5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinine (131): To a solution of the ketone (1.2 g, 7.5 mmol, 1 equiv.) in DCE (40 mL), phosphorus(V) oxychloride (1.5 mL, 15 mmol, 2 equiv.) was added and the reaction mixture was reflux (85 °C) for 3 hours. Then, the crude was cooled to 0 °C and triethylamine (12.5 mL, 75 mmol, 10 equiv.) was added dropwise. After stirring for 5 minutes, boron trifluoride diethyl etherate (12.5 mL, 82.5 mmol, 11 equiv.) was added and the mixture was stirred at rt for 2 hours. After completion, the crude was dissolved in water and extracted with Et_2O. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuum*. The residue was purified by column chromatography on silica gel, eluting with Cy/DCM (1:1) obtaining the final chloride product as a red solid in 60% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88 (brs, 2H), 7.41 (d, 2H, J = 3.8 Hz), 6.58 (brs, 2H).



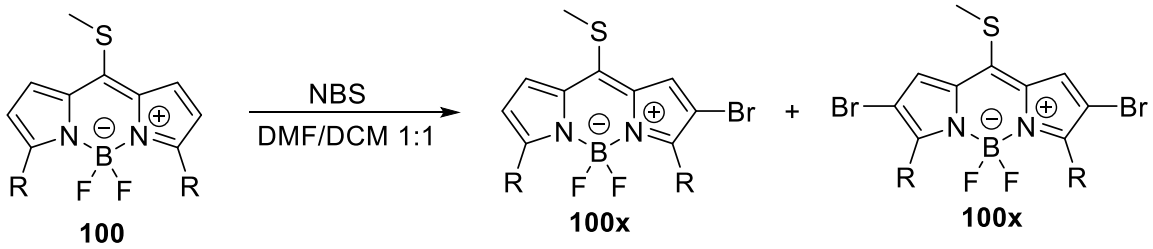
132

5,5-difluoro-10-iodo-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinine (132): A solution of the chloride product (1.15 g, 3.62 mmol, 1 equiv.) and sodium iodide (3.05 g, 14.5 mmol, 4 equiv.) in acetone (36 mL) under argon atmosphere was refluxed (65 °C) for 15 min. Then, the reaction mixture was left to rise rt and was dissolved in water and extracted with Et_2O. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuum*. The residue was purified by column chromatography

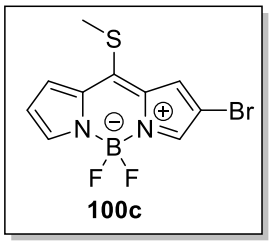
on silica gel, eluting with Cy/DCM (1/1) obtaining the final iodide product as a red solid in 85% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.98 (brs, 2H), 7.29 (d, 2H, *J* = 3.8 Hz), 6.53 (brs, 2H).

7.5.3. Bromination of 8-thiomethylBODIPY's

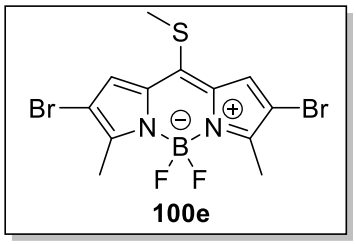
A two-necked round-bottom flask equipped with a stir bar was purged with nitrogen and charged with 8-methylthio-3, 5-dimethylBODIPY (1 equiv), dry DMF and dry dichloromethane (1:1). A solution of NBS (mentioned in each case) in dry DCM was added dropwise with an addition funnel at rt. The reaction mixture was stirred for (mentioned in each case) h, after which brine was added. The organic phase was separated and washed with brine (2 × 150 mL). The aqueous phase was further extracted with EtOAc (2 × 150 mL). The organic phases were combined, dried with $MgSO_4$, and filtered, and the solvent was removed in vacuum. The product was purified by column chromatography (SiO_2 gel, EtOAc−hexanes gradient).



Scheme 61: *Bromination of 8-thiomethyl BODIPY*



2-bromo-5,5-difluoro-10-(methylthio)-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine (100c): NBS (1.2 equiv.); reaction time = 1 hour; purple crystals, yield = 83%: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.35 (d, J = 4.2 Hz, 1H), 7.28 (s, 1H), 6.32 (d, J = 4.3 Hz, 1H), 2.71 (s, 3H), 2.60 (s, 3H), 2.57 (s, 3H).



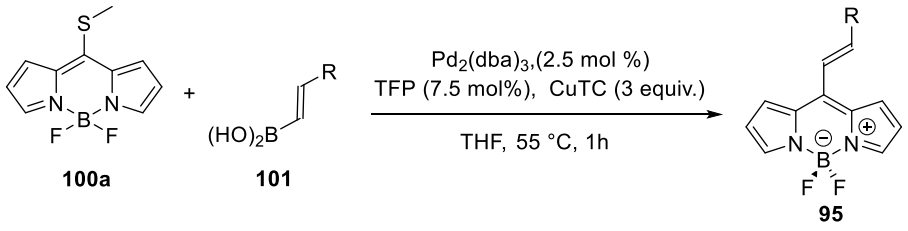
100e

2,8-dibromo-5,5-difluoro-3,7-dimethyl-10-(methylthio)-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine (100e): NBS (2.1 equiv.); reaction time = 2 hours; Black solid; 48% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.35 (s, 2H), 2.74 (s, 3H), 2.58 (s, 6H).

7.5.4. Synthesis of Alkenyl BODIPY's

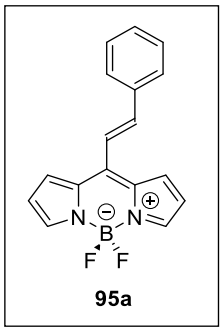
K) General procedure B for the synthesis of Alkenyl BODIPY's by a Liebeskind-Srogl coupling reaction.[157]

A two-neck round bottom flask equipped with a magnetic stir bar and a reflux condenser, under argon atmosphere, was charged with the corresponding boronic acid (3 equiv.) and thioether compound (1 equiv.) in anhydrous THF (10 mL). To this solution, copper thiophene-2-carboxylate (3 equiv.), $Pd_2(dba)_3$ (0.025 equiv.) and tri(2-furyl)phosphine (0.075 equiv.) were added and the mixture was heated at 55 °C for 24 hours. After completion, the solvent was concentrated in vacuum and the residue was purified by column chromatography on silica gel, eluent indicated each case.



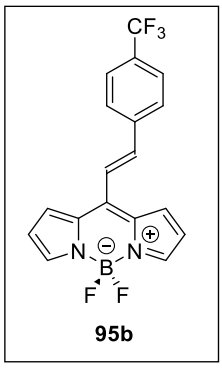
Scheme 62: *Synthesis of Alkenyl BODIPY's by a Liebeskind-Srogl coupling reaction.*

[157] Arroyo, I.; Hu, R.; Tang, B. Z.; Lopez, F.; Peña-Cabrera, E. *Tetrahedron,* **2011**, *67*, 7244.



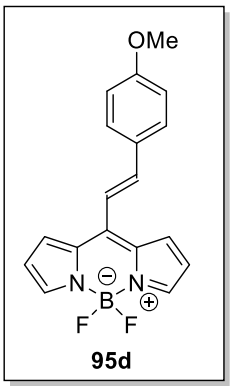
95a

(*E*)-5,5-difluoro-10-styryl-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-c:2',1'-*f*][1,3,2]diazaborinine (95a): The compound was isolated by flash-chromatography, 20% EtOAc/hexanes), the solid product was crystallized from CH_2Cl_2/petroleum ether. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.85 (s, 2H), 7.61-7.58 (m, 2H), 7.44-7.41 (m, 5H), 7.32 (d, *J* = 3Hz, 2H), 6.52 (d, *J* = 3Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 145.0, 144.0, 143.2, 135.8, 134.1, 130.8,129.4, 128.5, 128.2, 121.4, 118.1.



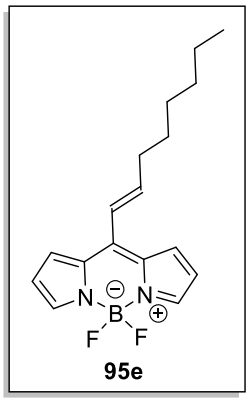
95b

Preparation of (*E*)-5,5-difluoro-10-(4-(trifluoromethyl)styryl)-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-c:2',1'-*f*][1,3,2]diazaborinine: The compound was isolated by flash-chromatography (20% EtOAc/hexanes). the solid product was crystallized from CH_2Cl_2/petroleum ether. Reaction time 15 min. dark red needles; yield= 76%; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.87 (s, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 14.2 Hz, 1H), 7.37 (s,2H), 7.32 (d, *J* = 12.0 Hz, 1H), 7.00(d, *J* = 9.0 Hz, 2H), 6.56 (m,2H); **^{13}C (126 MHz, $CDCl_3$)** δ 162.0, 145.2, 144.5, 142.5, 133.9, 130.1, 128.7, 128.0, 119.1, 117.7, 114.9, 55.7.



95d

(*E*)-5,5-difluoro-10-(4-methoxystyryl)-5H-4λ^4,5λ^4-dipyrrolo[1, 2-*c*:2',1'-*f*][1,3,2] diazaborinine (95d): From *trans*-2-(4-methoxyphenyl)vinylboronic acid (326 mg, 1.83 mmol, 3 equiv.), thioether compound (145 mg, 0.61 mmol, 1 equiv.), copper thiophene-2-carboxylate (349 mg, 1.83 mmol, 3 equiv.), $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol, 0.025 equiv.) and tri(2-furyl)phosphine (10.7 mg, 0.046 mmol, 0.075 equiv.), compound **95d** was obtained in 40% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). Spectroscopic data are in agreement with the published data. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.87 (brs, 2H), 7.61 – 7.49 (m, 3H), 7.38 – 7.31 (m, 3H), 7.02 – 6.94 (m, 2H), 6.57 – 6.52 (m, 2H), 3.89 (s, 3H).



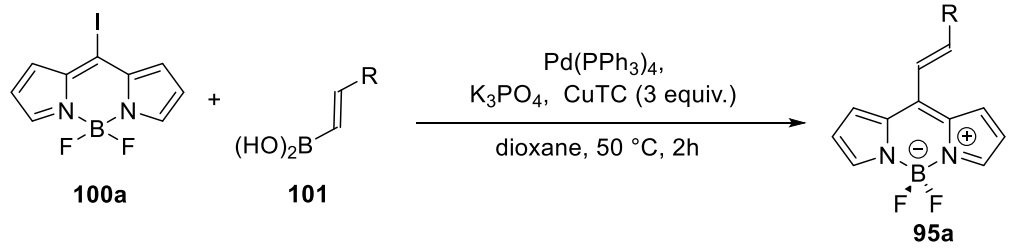
95e

(*E*)-5,5-difluoro-10-(oct-1-en-1-yl)-5H-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinine (95e): From *trans*-1-octenylboronic acid (98.3 mg, 0.63 mmol, 3 equiv.), thioether compound (50.0 mg, 0.21 mmol, 1 equiv.), copper thiophene-2-carboxylate (120.2 mg, 0.63 mmol, 3 equiv.), $Pd_2(dba)_3$ (4.8 mg, 0.005 mmol, 0.025 equiv.) and tri(2-furyl)phosphine (3.7 mg, 0.016 mmol, 0.075 equiv.), compound **95e** was obtained in 90% yield as a red oil. The crude product was purified by flash column chromatography (gradient pentane/AcOEt from 9:1 to 5:1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.85 (brs, 3H), 7.25 (d, *J* = 4.1 Hz, 3H), 6.85 – 6.61 (m, 2H), 6.59 – 6.50 (m, 2H), 2.39 (td, *J* = 7.3, 5.9 Hz, 2H), 1.66 – 1.51 (m, 2H), 1.48 – 1.18 (m, 6H), 0.98 – 0.81 (m, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 149.4, 144.3, 142.9, 133.7, 128.5, 123.2, 117.7, 34.3, 31.6, 28.9, 28.6, 22.6, 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -145.95 (dd, *J* = 57.2, 28.6 Hz, 2F). **HRMS** (ESI^+) calculated for $C_{17}H_{23}N_2BF_2$ $[M+H]^+$: 303.1953, found: 303.1930.

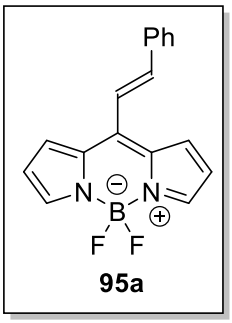
L) General procedure for the synthesis of Alkenyl BODIPY's by a Suzuki coupling reaction.[158]

A two-neck round bottom flask equipped with a magnetic stir bar and a reflux condenser, under argon atmosphere, was charged with the corresponding boronic acid (2 equiv.), the iodide compound (1 equiv.) and anhydrous dioxane (24 mL). To this solution, tetrakis(triphenylphosphine)palladium(0) (0.05 equiv.) and K_3PO_4 (3 equiv.) were added, and the mixture was heated at 60 °C for 2 hours. After completion, the solvent was concentrated in vacuum and the residue was purified by column chromatography on silica gel, eluting with Cy/AcOEt (9:1) obtaining the final products indicated each case.

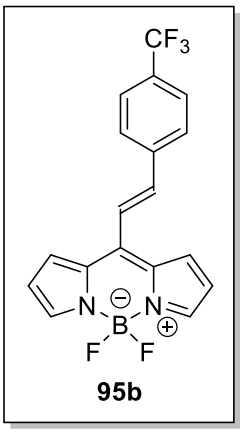
[158] Leen, V.; Yuan, P.; Wang, L.; Boens, N.; Dehaen, W. *Org. Lett*., **2012**, *14*, 6150.



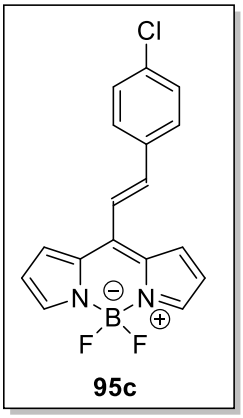
Scheme 63: *Synthesis of Alkenyl BODIPY's by a Suzuki coupling reaction.*



(*E*)-5,5-difluoro-10-styryl-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*] [1,3,2]diazaborinine (95a): From *trans*-2-phenylvinylboronic acid (493 mg, 3.34 mmol, 2 equiv.), iodide compound (530 mg, 1.67 mmol, 1 equiv.), tetrakis(triphenylphosphine)palladium(0) (96.3 mg, 0.08 mmol, 0.05 equiv.) and K_3PO_4 (1.061 g, 5.00 mmol, 3 equiv.), following *general procedure L*, compound **95a** was obtained in 60% yield as a purple solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.89 (brs, 2H), 7.65 – 6.59 (m, 2H), 7.50 – 7.32 (m, 7H), 6.56 (brs, 2H).



(*E*)-5,5-difluoro-10-(4-(trifluoromethyl)styryl)-5H-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*] [1,3,2]diazaborinine (95b): From *trans*-2-[4-(Trifluoromethyl)phenyl]vinylboronic acid (271.7 mg, 1.26 mmol, 2 equiv.), iodide compound (200.0 mg, 0.63 mmol, 1 equiv.), tetrakis(triphenylphosphine)palladium(0) (36.4 mg, 0.03 mmol, 0.05 equiv.) and K_3PO_4 (400.6 mg, 1.89 mmol, 3 equiv.), following *general procedure L*, compound **95b** was obtained in 72% yield as a red solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.92 (brs, 2H), 7.72 (brs, 4H), 7.48 (brs, 2H), 7.35 (d, J = 4.3 Hz, 2H) 6.58 (d, J = 3.7 Hz, 2H).



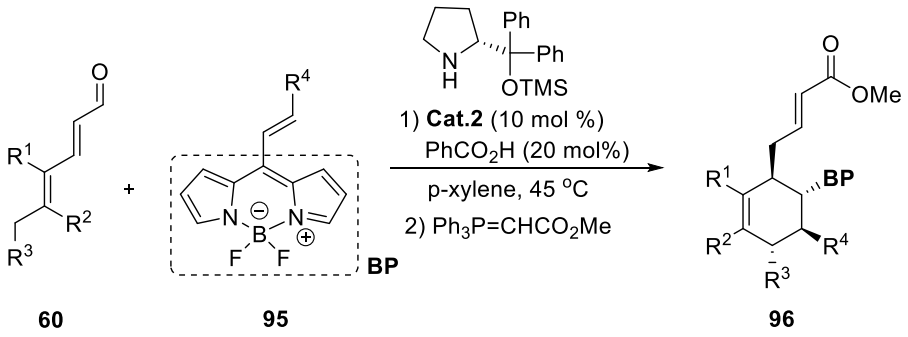
95c

***(E)*-10-(4-chlorostyryl)-5,5-difluoro-5H-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinine (95c):** From *trans*-2-(4-Chlorophenyl)vinylboronic acid (229.8 mg, 1.26 mmol, 2 equiv.), iodide compound (200.0 mg, 0.63 mmol, 1 equiv.), tetrakis(triphenylphosphine)palladium(0) (36.4 mg, 0.03 mmol, 0.05 equiv.) and K_3PO_4 (400.6 mg, 1.89 mmol, 3 equiv.) following *general procedure L*, compound **95c** was obtained in 55% yield as a red solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88 (brs, 2H), 7.64 – 7.57 (m, 2H), 7.49 – 7.40 (m, 4H), 7.34 (d, *J* = 4.3 Hz, 2H), 6.57 – 6.51 (m, 2H).

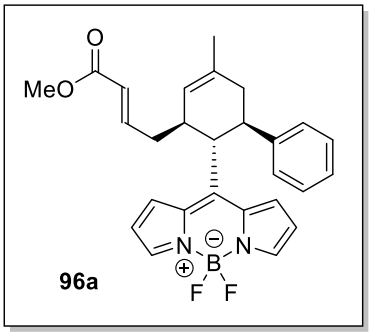
7.6. Synthesis of BODIPY cycloadducts by trienamine and one-pot reactions.

7.6.1. Synthesis of BODIPY cycloadducts by trienamine catalysis.

M) General procedure C for the organocatalytic [4+2] cycloaddition reaction: A dry vial equipped with a magnetic stir bar was charged with the corresponding aminocatalyst **3** (0.01 mmol, 0.1 equiv.), PhCOOH (0.01 mmol, 0.1 equiv.) and the corresponding dienal (0.25 mmol, 2.5 equiv.). *p*-Xylene (1 mL) was added to dissolve the compounds, there upon the corresponding BODIPY (0.1 mmol, 1 equiv.) was added to the mixture. The reaction mixture was stirred at 45 °C for the time indicated in each case. After completion, full conversion was determined by ^{1}H NMR, *p*-xylene (1 mL) and (methoxycarbonylmethylene)triphenylphosphorane (0.25 mmol, 2.5 equiv.) were added to derivatize to the final products **5**. The crude product was purified by flash column chromatography on silica gel (eluent indicated in each case).

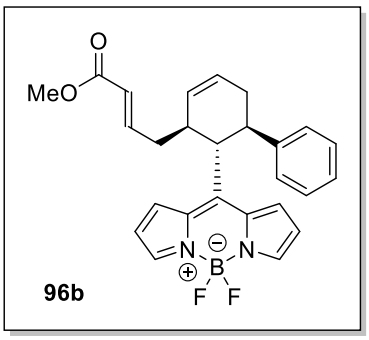


Scheme 64: *Synthesis of BODIPY cycloadducts by trienamine catalysis*



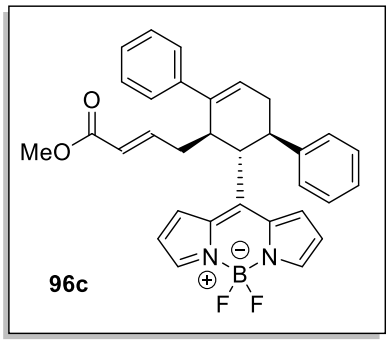
Methyl (*E*)-4-((1*S*,2*S*,3*R*)-2-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)but-2-enoate (99a): From **60a** (27.5 mg, 0.25 mmol) and BODIPY **95a** (29.4 mg, 0.1 mmol), following the general procedure M (45 ºC, 18h), compound **99a** (35.9 mg, 0.078 mmol) was obtained in 78% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to

5:1). The *ee* was determined by SFC using Chiralpak IC column [CO_2/MeOH (90:10), 120 bar, 40 °C)]; 3.0 mL/min. τ_{max} = 6.994 min, τ_{min} = 7.535 min, ***ee***= 96%. **[α]$^{20}_{D}$** = +945 (*c* 0.031, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.72 (brs, 2H), 7.53 (brd, *J* = 4.4 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.10 – 6.78 (m, 6H), 6.56 (brd, *J* = 4.2 Hz, 1H), 6.40 (brd, *J* = 4.4 Hz, 1H), 5.70 (d, *J* = 15.5 Hz, 1H), 5.48 (brs, 1H), 3.73 (s, 3H), 3.61 – 3.47 (m, 1H), 3.22 – 3.13 (m, 2H), 2.53 – 2.27 (m, 3H), 2.17 – 2.02 (m, 1H), 1.82 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.6, 152.3, 145.6, 144.6, 141.8, 141.7, 137.3, 135.6, 133.0, 129.6, 128.4, 128.2 (2C), 127.4 (2C), 126.9, 123.6, 123.1, 117.9, 117.6, 51.5, 50.5, 48.8, 43.8, 39.7, 37.1, 23.3. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -145.09 (ddd, *J* = 105.7, 58.4, 29.4 Hz, 1F), -147.68 (ddd, *J* = 105.1, 56.0, 27.7 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{27}H_{31}N_3O_2BF_2$ $[M+NH_4]^+$: 478.2586, found: 478.2566.

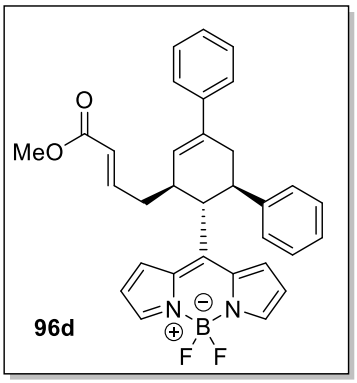


96b

Methyl (*E*)-4-((1*S*,2*S*,3*R*)-2-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)but-2-enoate (96b): From **60b** (28 µL, 0.25 mmol) and BODIPY **95a** (29.4 mg, 0.1 mmol), following the general procedure M (45 ºC, 48h), compound **96b** (32.1 mg, 0.072 mmol) was obtained in 72% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak IA column [CO_2/MeOH (90:10), 120 bar, 40 °C]; 3.0 mL/min. τ_{max} = 9.547 min, τ_{min} = 9.088 min, ***ee***=92% **[α]$^{20}_{D}$** = -47.6 (*c* 0.043, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.71 (s, 2H), 7.53 (d, *J* = 4.3 Hz, 1H), 7.19 (d, *J* = 4.4 Hz, 1H), 7.06 – 6.99 (m, 3H), 6.92 – 6.79 (m, 3H), 6.59 – 6.52 (m, 1H), 6.42 – 6.35 (m, 1H), 6.04 – 6.00 (m, 1H), 5.78 (d, *J* = 10.4 Hz, 1H), 5.71 (d, *J* = 15.7 Hz, 1H), 3.71 (s, 3H), 3.59 – 3.43 (m, 1H), 3.28 – 3.21 (m, 2H), 2.50 – 2.46 (m, 2H), 2.40 – 2.32 (m, 1H), 2.17 – 2.06 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.4, 151.9, 145.2, 144.7, 141.9, 141.6, 137.3, 133.0, 129.6, 128.8, 128.4, 128.2 (2C), 128.0, 127.5 (2C), 126.9, 123.8, 118.0, 117.7, 51.5, 50.5, 48.3, 43.6, 36.7, 34.6. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -145.07 (ddd, J = 105.4, 58.3, 29.1 Hz, 1F), -147.70 (ddd, *J* = 105.5, 56.0, 28.0 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{26}H_{29}BF_2N_3O_2$ $[M + NH_4^+]$ = 464.2430, found: 464.2451.

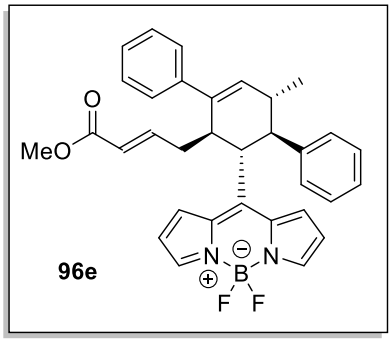


Methyl (*E*)-4-((2'*S*,3'*R*,4'*S*)-3'-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-2',3',4',5'-tetrahydro-[1,1':4',1''-terphenyl]-2'-yl)but-2-enoate (96c): From **60c** (43 mg, 0.25 mmol) and BODIPY **95a** (29.4 mg, 0.1 mmol), following the general procedure M (45 ºC, 18h), compound **96c** (40.7 mg, 0.078 mmol) was obtained in 78% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak IC column [CO_2/MeOH (90:10), 120 bar, 40 °C)]; 3.0 mL/min. τ_{max} = 8.794 min, τ_{min} = 11.848 min, ***ee***=95% **[α]$^{20}_D$** = +1096 (*c* 0.031, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.76 (s, 1H), 7.72 (s, 1H), 7.63 (d, *J* = 4.3 Hz, 1H), 7.41 – 7.20 (m, 6H), 7.11 – 6.98 (m, 4H), 6.96 – 6.89 (m, 2H), 6.76 (ddd, *J* = 15.1, 8.9, 5.7 Hz, 1H), 6.63 (dd, *J* = 4.3, 1.9 Hz, 1H), 6.35 (dd, *J* = 4.4, 1.8 Hz, 1H), 6.31 (m, 1H), 5.56 (d, *J* = 15.5 Hz, 1H), 3.92 – 3.80 (m, 1H), 3.72 (s, 3H), 3.60 – 3.46 (m, 1H), 3.40 (dd, *J* = 11.9, 8.9 Hz, 1H), 2.67 – 2.57 (m, 2H), 2.44 – 2.31 (m, 1H), 2.29 – 2.15 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.4, 152.5, 145.3, 144.2, 141.6, 141.5, 140.6, 139.6, 137.0, 133.0, 130.0, 128.7 (2C), 128.33, 128.29 (2C), 127.9, 127.4, 127.3 (2C), 127.0, 126.3 (2C), 124.3, 118.1, 117.7, 51.5, 50.5, 48.8, 44.7, 34.3, 33.7. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -144.44 (ddd, *J* = 105.1, 58.5, 29.1 Hz, 1F), -148.03 (ddd, *J* = 105.1, 55.6, 27.7 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{32}H_{29}N_2O_2BF_2$ $[M+NH_4]^+$: 540.2743, found: 540.2692.



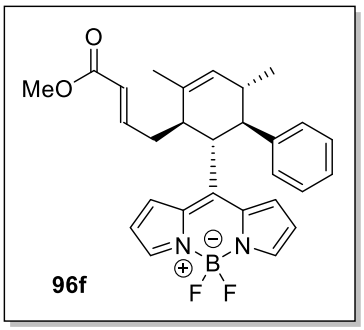
Methyl (*E*)-4-((1'*S*,5'*R*,6'*S*)-6'-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)but-2-enoate (96d): From **60d** (21.5 mg, 0.12 mmol) and BODIPY **95a** (14 mg, 0.048 mmol), following the general procedure M (45 ºC, 18h), compound **96d** (20.0 mg, 0.038 mmol) was obtained in 80% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (90:10), 120 bar, 40 °C)]; 2.0 mL/min. τ_{max} = 5.816 min, τ_{min} = 6.623 min, ***ee***= 95 %. **[α]$^{20}_D$** = -10.3

(*c* 0.205, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.74 (s, 2H), 7.58 (d, *J* = 4.3 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.40 – 7.27 (m, 3H), 7.24 (d, *J* = 4.5 Hz, 1H), 7.13 – 7.02 (m, 3H), 7.02 – 6.95 (m, 2H), 6.89 (ddd, *J* = 15.1, 8.9, 5.6 Hz, 1H), 6.58 (dd, *J* = 4.3, 1.9 Hz, 1H), 6.42 (dd, *J* = 4.4, 1.8 Hz, 1H), 6.18 – 6.11 (m, 1H), 5.75 (d, *J* = 15.7, 1H), 3.72 (s, 3H), 3.76 – 3.62 (m, 1H), 3.46 – 3.28 (m, 2H), 2.97 – 2.83 (m, 2H), 2.55 – 2.39 (m, 1H), 2.30 – 2.13 (m, 1H) **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.4, 151.8, 145.2, 144.8, 142.0, 141.4, 140.5, 138.2, 137.4, 132.9, 129.6, 128.5, 128.4, 128.3, 127.7, 127.5, 127.1, 125.5, 125.3, 124.0, 118.1, 117.7, 51.5, 50.2, 48.8, 44.4, 37.3, 37.1. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -145.00 (ddd, *J* = 105.3, 58.1, 28.9 Hz, 1F), -147.62 (ddd, *J* = 105.3, 56.0, 28.0 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{32}H_{34}N_3O_2BF_2$ $[M+NH_4]^+$: 540.2743, found: 540.2680.

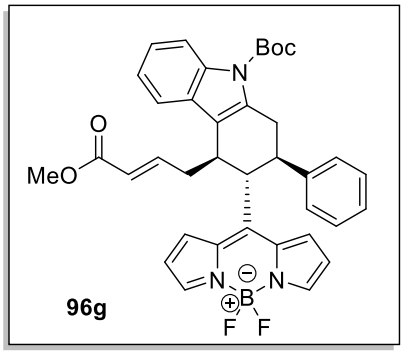


96e

Methyl (*E*)-4-((2'*S*,3'*S*,4'*S*,5'*R*)-3'-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborin-in-10-yl)-5'-methyl-2',3',4',5'-tetrahydro-[1,1':4',1''-terphenyl]-2'-yl)but-2-enoate (96e): From **60e** (46.5 mg, 0.25 mmol) and BODIPY **95a** (29.4 mg, 0.1 mmol), following the general procedure M (45 ºC, 48h), compound **96e** (49.4 mg, 0.092 mmol) was obtained in 92% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (90:10), 120 bar, 40 °C]; 2.0 mL/min. τ_{max} = 2.007 min, τ_{min} = 3.194 min, ***ee***=98% **$[\alpha]^{20}_D$** = -282 (*c* 0.023, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.82 (s, 1H), 7.68 (s, 1H), 7.61 (d, *J* = 4.3 Hz, 1H), 7.47 (d, *J* = 4.3 Hz, 1H), 7.40 – 7.28 (m, 6H), 7.11 – 7.04 (m, 3H), 7.04 – 6.93 (m, 2H), 6.80 (ddd, *J* = 15.6, 8.9, 5.5 Hz, 1H), 6.60 – 6.52 (m, 2H), 6.32 (dd, *J* = 6.3, 1.6 Hz, 1H), 5.60 (dt, *J* = 15.8, 1.5 Hz, 1H), 3.91 – 3.82 (m, 2H), 3.74 (s, 3H), 2.72 – 2.59 (m, 1H), 2.44 – 2.30 (m, 1H), 2.30 – 2.16 (m, 1H), 1.07 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.3, 152.8, 144.8, 144.4, 142.0, 140.7, 139.6, 138.2, 137.5, 135.0, 133.5, 129.5, 129.0 (2C), 128.7 (2C), 128.3, 127.9 (2C), 127.4, 126.8, 126.5 (2C), 124.2, 118.3, 118.0, 51.52, 51.49, 45.6, 42.0, 37.2, 33.5, 15.3. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -144.64 (ddd, *J* = 105.6, 58.5, 29.2 Hz, 1F), -147.64 (ddd, *J* = 105.7, 55.7, 27.9 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{33}H_{35}N_3O_2BF_2$ $[M+NH_4]^+$: 554.2899, found: 554.2894.

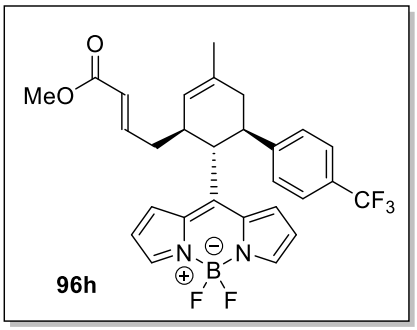


Methyl (*E*)-4-((1*S*,2*S*,3*S*,6*R*)-2-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-4,6-dimethyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)but-2-enoate (96f): From **60f** (31 mg, 0.25 mmol) and BODIPY **95a** (29.4 mg, 0.1 mmol), following the general procedure M (45 ºC, 48h), compound **96f** (37.0 mg, 0.078 mmol) was obtained in 78% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak IA column [CO_2/MeOH (95:5), 120 bar, 40 °C]; 3.0 mL/min. τ_{max} = 8.013 min, τ_{min} = 6.898 min, ***ee***=93% **[α]$^{20}_D$** = -221 (*c* 0.019, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.80 (s, 1H), 7.63 (s, 1H), 7.44 (dd, *J* = 14.9, 4.4 Hz, 2H), 7.08 – 6.98 (m, 4H), 6.98 – 6.90 (m, 2H), 6.90 – 6.80 (m, 1H), 6.58 – 6.52 (m, 1H), 6.51 – 6.44 (m, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 5.89 – 5.75 (m, 1H), 3.77 (s, 3H), 3.76 – 3.70 (m, 2H), 3.07 (brs, 1H), 2.59 (dtd, *J* = 16.2, 5.0, 2.3 Hz, 1H), 2.49 – 2.36 (m, 1H), 2.28 (ddd, *J* = 16.4, 8.5, 3.2 Hz, 1H), 1.80 (s, 3H), 0.93 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.4, 153.0, 144.4 (2C), 141.9, 139.9, 137.6, 133.3, 132.4, 132.1, 129.4, 129.0, 128.6, 127.8, 126.5, 124.5, 118.1, 117.7, 51.8, 51.6, 47.6, 42.0, 37.0, 32.2, 21.4, 15.5. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -144.61 (ddd, *J* = 105.3, 58.2, 29.3 Hz, 1F), -147.78 (ddd, *J* = 106.5, 55.0, 27.9 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{28}H_{33}N_3BF_2O_2$ $[M+NH_4]^+$: 492.2743, found: 492.2767.



tert*-Butyl (2*S*,3*R*,4*S*)-3-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-4-((*E*)-4-methoxy-4-oxobut-2-en-1-yl)-2-phenyl-1,2,3,4-tetrahydro-9*H*-carbazole-9-carboxylate (96g):** From **60g** (71.3 mg, 0.25 mmol) and BODIPY **95a** (29.4 mg, 0.1 mmol), following the general procedure M (45 ºC, 18h), compound **96g** (42.6 mg, 0.067 mmol) was obtained in 67% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak ID column [CO_2/MeOH gradient (from 5% to 40% of MeOH), 120 bar, 40 °C], 2.0 mL/min τ_{max} = 3.652 min, τ_{min} = 3.384, ***ee=82%. **[α]$^{20}_D$** = +280 (*c*

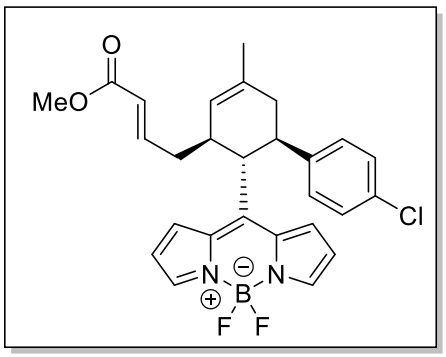
0.051, CH_2Cl_2) **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.20 (d, *J* = 8.3 Hz, 1H), 7.74 (s, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 4.2 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.29 – 7.22 (m, 2H), 7.13 (d, *J* = 4.4 Hz, 1H), 7.11 – 7.02 (m, 3H), 7.00 – 6.92 (m, 2H), 6.64 (ddd, *J* = 15.6, 9.1, 5.3 Hz, 1H), 6.54 (dd, *J* = 4.3, 1.9 Hz, 1H), 6.40 (dd, *J* = 4.4, 1.9 Hz, 1H), 5.67 (d, *J* = 15.9 Hz, 1H), 4.18 – 4.07 (m, 1H), 3.67 (s, 3H), 3.71 – 3.45 (m, 3H), 3.36 (ddd, *J* = 18.8, 11.9, 2.4 Hz, 1H), 3.09 (dtd, *J* = 15.5, 5.4, 2.0 Hz, 1H), 2.69 – 2.56 (m, 1H), 1.68 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.3, 151.7, 150.3, 145.2, 143.8, 141.7, 140.8, 137.2, 136.5, 136.3, 133.0, 130.1, 128.2 (2C), 127.8, 127.5 (2C), 127.1, 124.7, 124.0, 122.8, 118.6, 118.1, 117.6, 116.0, 115.8, 84.3, 51.5, 50.5, 49.6, 40.8, 34.9, 34.1, 28.2. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -144.81 (ddd, *J* = 104.8, 58.4, 29.2 Hz, 1F), -147.75 (ddd, *J* = 105.1, 55.7, 27.7 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{37}H_{40}BF_2N_4O_4$ [M + NH_4^+] = 653.3220, found: 653.3278.



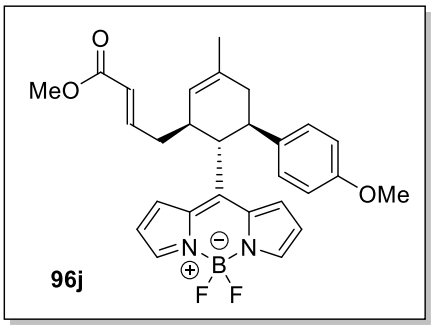
96h

Methyl (*E*)-4-((1*S*,2*S*,3*R*)-2-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazabor-inin-10-yl)-5-methyl-4'-(trifluoromethyl)-1,2,3,6 -tetrahydro-[1,1'-biphenyl]-3-yl)but-2-enoate (96h): From **60a** (27.5 mg, 0.25 mmol) and BODIPY **95h** (36.2 mg, 0.1 mmol), following the general procedure M (45 ºC, 18h), compound **96h** (40.2 mg, 0.076 mmol) was obtained in 76% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak OJ-H column [CO_2/MeOH (90:10), 120 bar, 40 °C)]; 3.0 mL/min. τ_{max} = 2.432 min, τ_{min} = 2.195 min, ***ee***= 94 %. **$[\alpha]^{20}_D$** = +5722 (*c* 0.005, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.73 (d, *J* = 5.6 Hz, 2H), 7.51 (d, *J* = 4.2 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 4.3 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.83 (ddd, *J* = 14.9, 8.9, 5.7 Hz, 1H), 6.56 (dd, *J* = 4.5, 2.0 Hz, 1H), 6.42 (dd, *J* = 4.6, 2.0 Hz, 1H), 5.70 (d, *J* = 15.7 Hz, 1H), 5.50 (s, 1H), 3.71 (s, 3H), 3.68 – 3.51 (m, 1H), 3.26 – 3.11 (m, 2H), 2.50 – 2.23 (m, 3H), 2.16 – 2.02 (m, 1H), 1.81 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.5, 151.3, 145.9 (q, J_{C-F} = 1.1 Hz), 145.3, 145.1, 142.2, 137.2, 135.2, 132.8, 129.4, 129.1 (q, J_{C-F} = 32.5 Hz), 128.2, 127.8 (2C), 125.2 (q, J_{C-F} = 3.7 Hz), 123.9 (q, J_{C-F} = 272.0 Hz), 123.8, 123.3, 118.3, 117.8, 51.5, 49.9, 48.5, 43.7, 39.7, 36.9, 23.3. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -62.6 (s,

CF_3), -144.95 (ddd, *J* = 104.9, 58.2, 29.0 Hz, 1F), -147.79 (ddd, *J* = 104.9, 55.6, 27.9 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{28}H_{30}BF_5N_3O_2$ [M + NH_4^+] = 546.2460, found: 546.2411.

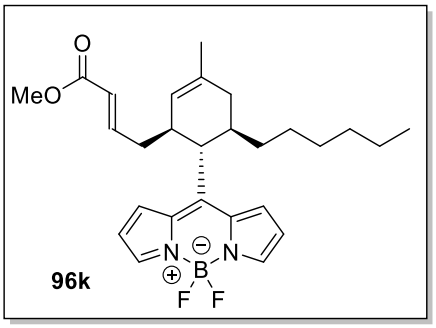


Methyl (*E*)-4-((1*S*,2*S*,3*R*)-4'-chloro-2-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*] [1,3,2] diazaborinin-10-yl)-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)but-2-enoate (5i): From **60a** (27.5 mg, 0.25 mmol) and BODIPY **2i** (32.9 mg, 0.1 mmol), following the general procedure M (45 ºC, 48h), compound **5i** (30.7 mg, 0.062 mmol) was obtained in 62% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak OJ-H column [CO_2/MeOH (95:5), 120 bar, 40 °C)]; 3.0 mL/min. τ_{may} = 8.685 min, τ_{min} = 6.575 min, *ee*= 95 %. $[\alpha]^{20}_D$ = +1170 (*c* 0.025, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 4.3 Hz, 1H), 7.18 (d, *J* = 4.5 Hz, 1H), 7.02 and 6.85 (AA'BB' system, 4H), 6.89 – 6.76 (m, 1H), 6.55 (dd, *J* = 4.3, 2.0 Hz, 1H), 6.42 (dd, *J* = 4.4, 1.9 Hz, 1H), 5.69 (d, *J* = 15.7, 1H), 5.48 (s, 1H), 3.72 (s, 3H), 3.58 – 3.44 (m, 1H), 3.22 – 3.06 (m, 2H), 2.48 – 2.22 (m, 3H), 2.14 – 1.95 (m, 1H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 151.7, 145.4, 145.0, 142.1, 140.3, 137.2, 135.4, 132.8, 132.5, 129.4, 128.7, 128.4, 128.3, 123.7, 123.3, 118.2, 117.7, 51.5, 50.2, 48.1, 43.8, 39.8, 37.0, 23.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ -144.80 (ddd, *J* = 104.3, 58.8, 29.3 Hz, 1F), -147.72 (ddd, *J* = 104.8, 55.2, 27.5 Hz, 1F). HRMS (ESI$^+$) calculated for $C_{27}H_{30}BF_2N_3O_2Cl$ [M + NH_4^+] = 512.2197, found: 512.2175.



Methyl (*E*)-4-((1*S*,2*S*,3*R*)-2-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-4'-methoxy-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl) but-2-enoate (96j): From **60a** (27.5 mg, 0.25 mmol) and BODIPY **95j** (32.4 mg, 0.1 mmol), following the general procedure M (45 ºC, 18h), compound **96j** (39.2 mg, 0.08 mmol) was obtained in 80% yield as a red

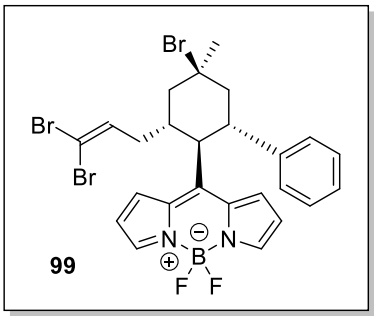
solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using a Chiralpak OJ-H column [CO_2/MeOH (95:5), 120 bar, 40 °C)]; 3.0 mL/min. τ_{may} = 8.714 min, τ_{min} = 6.591 min, ***ee***= 95 %. **[α]$^{20}_{D}$** = +1437 (*c* 0.021, CH_2Cl_2) **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.72 (s, 2H), 7.52 (d, *J* = 4.0 Hz, 1H), 7.18 (d, *J* = 4.2 Hz, 1H), 6.89 – 6.76 (m, 3H), 6.65 – 6.49 (m, 3H), 6.40 (d, *J* = 3.9 Hz, 1H), 5.68 (d, *J* = 15.7 Hz, 1H), 5.46 (s, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.60 – 3.39 (m, 1H), 3.21 – 3.07 (m, 2H), 2.50 – 2.21 (m, 3H), 2.15 – 1.97 (m, 1H), 1.80 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.6, 158.2, 152.7, 145.7, 144.6, 141.7, 137.4, 135.7, 133.8, 133.0, 129.6, 128.3 (3C), 123.6, 123.1, 118.0, 117.5, 113.7, 55.1, 51.5, 50.7, 47.9, 43.9, 40.0, 37.1, 23.3. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -144.66 (ddd, *J* = 105.7, 58.7, 29.2 Hz, 1F), -147.83 (ddd, *J* = 105.7, 55.7, 27.8 Hz, 1F). **HRMS (ESI$^+$)** calculated for $C_{28}H_{33}BF_2N_3O_3$ [M + NH_4^+] = 508.2692, found: 508.2563.



96k

Methyl (*E*)-4-((1*R*,5*S*,6*R*)-6-(5,5-difluoro-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2] diazaborinin-10-yl)-5-hexyl-3-methylcyclohex-2-en-1-yl)but-2-enoate (96k): From **60a** (27.5 mg, 0.25 mmol) and BODIPY **95k** (30.2 mg, 0.1 mmol), following the general procedure M (45 ºC, 15h), compound **96k** (35.3 mg, 0.075 mmol) was obtained in 75% yield as a red solid. The crude product was purified by flash column chromatography (gradient Cy/AcOEt from 9:1 to 5:1). The *ee* was determined by SFC using Chiralpak IA column [CO_2/MeOH (95:5), 120 bar, 40 °C)]; 3.0 mL/min. τ_{may} = 8.017 min, τ_{min} = 7.121 min, ***ee***= 88 %. **[α]$^{20}_{D}$** = -182.5 (*c* 0.079, CH_2Cl_2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.92 (s, 1H), 7.82 (s, 1H), 7.39 (d, *J* = 4.3 Hz, 1H), 7.27 (d, *J* = 4.3 Hz, 1H), 6.76 (ddd, *J* = 15.1, 9.0, 5.6 Hz, 1H), 6.56 – 6.48 (m, 2H), 5.64 (d, *J* = 15.7 Hz, 1H), 5.36 (s, 1H), 3.70 (s, 3H), 3.04 – 2.88 (m, 1H), 2.66 (t, *J* = 10.9 Hz, 1H), 2.40 – 2.12 (m, 3H), 2.06 – 1.87 (m, 1H), 1.76 (s, 3H), 1.39 – 0.90 (m, 11H), 0.79 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.6, 154.2, 145.9, 144.6, 142.2, 137.5, 135.1, 132.7, 129.3, 128.3, 123.3, 123.2, 118.1, 117.7, 51.4, 50.5, 43.8, 40.8, 37.0, 36.9, 34.2, 31.6, 28.8, 26.3, 23.5, 22.5, 14.0. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -145.08 (ddd, *J* = 106.1, 57.9, 28.8 Hz, 1F), -146.39 (ddd, *J* = 106.3, 56.8, 28.2 Hz, 1F). **HRMS (ESI$^+$) calculated** for $C_{27}H_{40}N_3O_2BF_2$ [M+NH_4]$^+$: 486.3212, found: 486.3100.

7.6.2. Derivatization of BODIPY cycloadduct by Ramirez reaction.

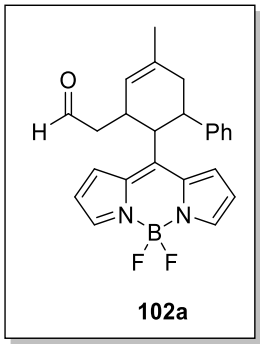


99

10-((1S,2R,4R,6S)-4-bromo-2-(3,3-dibromoallyl)-4-methyl-6-phenylcyclohexyl)-5,5-difluoro-5H-4l4, 5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine (99): A dry vial equipped with a magnetic stir bar was charged with the aminocatalyst **Cat.2** (3.3 mg, 0.01 mmol, 0.1 equiv.), PhCOOH (1.2mg, 0.01 mmol, 0.1 equiv.) and dienal **60a** (29.4mg, 0.25 mmol, 2.5 equiv.). *p*-Xylene (1 mL) was added to dissolve the compounds, then the BODIPY **95a** (27.4mg, 0.1 mmol, 1 equiv.) was added to the mixture. The reaction mixture was stirred at 45 °C for 18h affording the crude with the product **96'**. After that, the reaction crude was added dropwise over a solution of ylide, prepared by reaction of CBr_4 (248.7 mg, 0.75 mmol, 3 equiv.) and PPh_3 (393.5 mg, 1.5 mmol, 6 equiv.) in DCM at -5 °C following the procedure described in the literature.[159] The mixture was stirred at -5 °C during 10 minutes (full conversion was determined by TLC). The crude product was purified by flash column chromatography (gradient of Cy/AcOEt from 9:1 to 4:1) achieving the desired product 8 (32.9mg, 0.05mmol) in 50% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 4.3 Hz, 1H), 7.79 (s, 1H), 7.69 (s, 1H), 7.14 – 6.97 (m, 4H), 6.96 – 6.86 (m, 2H), 6.64 (dd, *J* = 4.3, 1.9 Hz, 1H), 6.33 (dd, *J* = 4.4, 1.9 Hz, 1H), 6.24 (dd, *J* = 8.5, 6.4 Hz, 1H), 3.88 (td, *J* = 11.6, 3.4 Hz, 1H), 3.10 – 2.94 (m, 1H), 2.88 (t, *J* = 11.4 Hz, 1H), 2.49 – 2.35 (m, 2H), 2.01 (s, 3H), 2.14 – 1.83 (m, 3H), 1.49 (dd, *J* = 14.7, 11.3 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 150.9, 144.7, 142.4, 140.8, 136.97, 136.9, 134.9, 132.8, 129.1, 128.8, 128.5 (2C), 127.3 (2C), 127.2, 118.0, 91.4, 68.9, 53.3, 49.5, 48.6, 47.9, 40.8, 37.5, 35.4. **^{19}F NMR (282 MHz, $CDCl_3$)** δ -144.90 (ddd, *J* = 105.1, 58.0, 29.0 Hz), -147.53 (ddd, *J* = 105.2, 56.2, 28.1 Hz). **HRMS (ESI^+)** calculated for $C_{25}H_{25}N_2BBr_3F_2$ $[M+H]^+$: 638,9623, found: 638,9640.

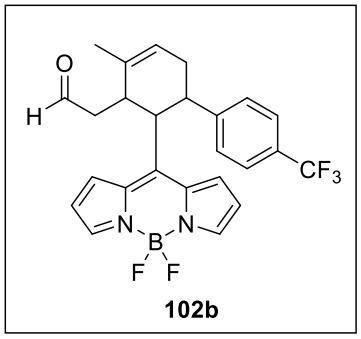
[159] Albrecht, Ł.; Cruz Acosta, F.; Fraile, A.; Albrecht, A.; Christensen, J.; Jorgensen, K. A. *Angew. Chem. Int. Ed.*, **2012**, *51*, 9088.

7.6.3. Synthesis of BODIPY cycloadducts by one-pot trienamine catalysis



102a

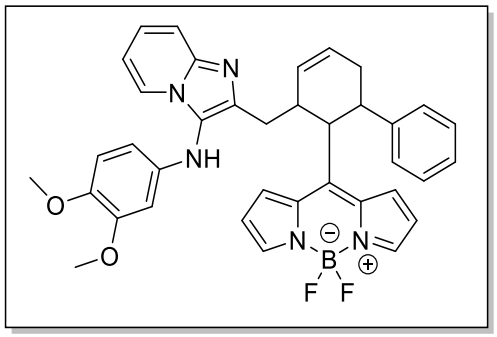
2-(2-(5,5-difluoro-5*H*-4λ⁴,5λ⁴-dipyrrolo[1,2-c:2',1'-*f*][1,3,2]diazaborinin-10-yl)-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl) acetaldehyde (102a): Compound **102a** was isolated by column chromatography (20 % ethyl acetate/hexane); brown shiny solid; fluorescent; yield= 84%; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.67 (s, 1H), 7.72 (s, 2H), 7.57 (s, 1H), 7.24 (s, 1H), 7.03 (dd, *J* = 13.1, 7.2 Hz, 4H), 6.93 (s, 1H), 6.56 (s, 1H), 6.43 (s, 1H), 5.47 (s, 1H), 3.59 – 3.52 (m, 1H), 3.48 (s, 1H), 3.34 – 3.28 (m, 1H), 2.56 – 2.51 (m, 1H), 2.44 (d, *J* = 11.7 Hz, 1H), 2.38 – 2.32 (m, 2H), 1.79 (s, 3H).



102b

2-(2-(5,5-difluoro-5*H*-4λ⁴,5λ⁴-dipyrrolo[1,2-c:2',1'-*f*][1,3,2]diazaborinin-10-yl)-4-methyl-4'-(trifluoromethyl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)acetaldehyde (102b): Compound **102b** was isolated by column chromatography (20 % ethyl acetate/hexane); brown shiny solid; fluorescent; yield= 82%; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.71 (s, 1H), 7.74 (d, 2H), 7.51 (d, *J* = 4.2 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 4.3 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.58 – 6.56 (m, 1H), 6.43 – 6.41 (m, 1H), 5.80 (d, *J* = 4.5 Hz, 1H), 3.75 (dd, *J* = 11.8 Hz, 1H), 3.53 (td, *J* = 11.8, 4.7 Hz, 1H), 3.28 (d, 1H), 2.79 (dd, *J* = 17.6 Hz, 1H), 2.50 (dd, *J* = 4.4 Hz, 1H), 2.49 – 2.45 (m, 1H), 2.44 – 2.40 (m, 1H), 1.78 (d, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 201.39, 146.03, 142.52, 134.04, 133.18, 130.21, 128.46, 128.21, 128.16, 125.68, 125.65, 125.62, 124.41, 122.42, 119.13, 118.29, 108.33, 49.80, 48.91, 44.48, 44.33, 34.86, 22.17.

7.6.4. Derivatization of BODIPY cycloadduct by GPP reaction

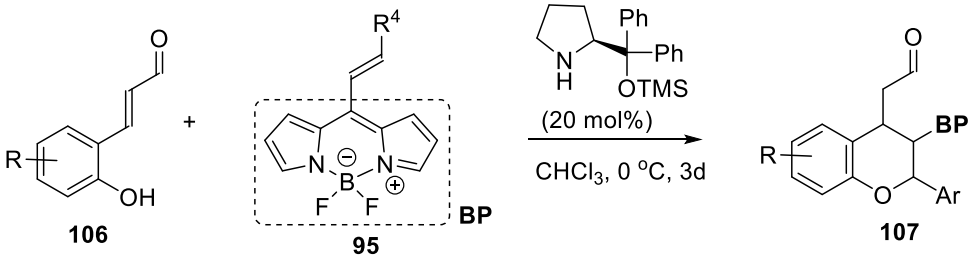


2-((2-(5,5-difluoro-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)methyl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridine-3-amine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.43 (s, 1H), 7.27 – 7.09 (m, 9H), 6.86 – 6.44 (m, 6H), 6.18 (d, *J* = 8.1 Hz, 2H), 5.99 (s, 1H), 5.89 (s, 1H), 5.61 (s, 1H), 5.55 (s, 1H), 3.86 – 3.81 (m, 6H), 3.24 (s, 1H), 2.67 – 2.56 (m, 3H), 2.36 (d, *J* = 10.0 Hz, 2H), 2.14 (s, 1H).

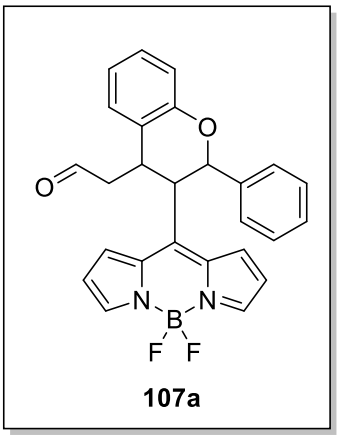
7.7. Synthesis of BODIPY's: Iminium ion mediated chiral cycloadducts (Scope) and derivatization

7.7.1. Synthesis of iminium ion mediated cycloadducts:

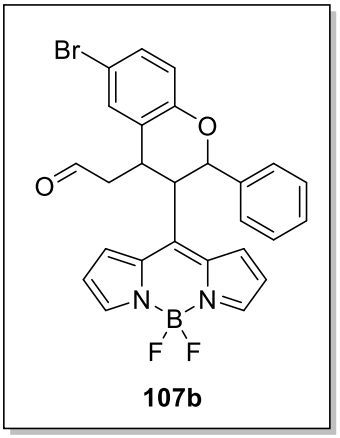
N) General procedure C for the organocatalytic [4+2] cycloaddition reaction: A dry vial equipped with a magnetic stir bar was charged with the corresponding aminocatalyst **Cat.1** (0.01 mmol, 0.1 equiv.) and the corresponding 2-hydroxyacrylaldehyde (0.1 mmol, 1 equiv.). chloroform (0.3 mL) was added to dissolve the compounds, there upon the corresponding BODIPY (0.12 mmol, 1.2 equiv.) was added to the mixture. The reaction mixture was stirred at 4 °C for the time indicated in each case. After completion, full conversion was determined by ^{1}H NMR, to achieve final products **107**. The crude product was purified by flash column chromatography on silica gel (eluent indicated in each case).



Scheme 65: *Synthesis of iminium ion mediated cycloadducts.*

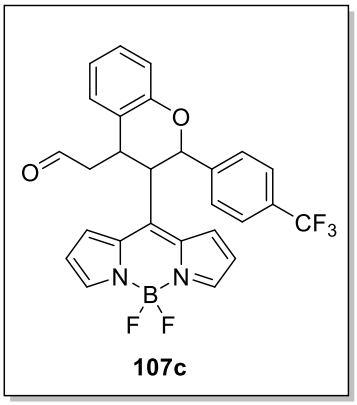


2-(3-(5,5-difluoro-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f] [1,3,2] diazaborinin-10-yl)-2-phenylchroman-4-yl) acetaldehyde (107a) : From **106a** (15.0 mg, 0.1 mmol) and BODIPY **95a** (23.0 mg, 0.12 mmol), following the general procedure N (4 ºC, 60h), compound **107b** was obtained in 86% yield as a red solid. The crude product was purified by column chromatography (gradient hexane/AcOEt from 9:1 to 5:1).



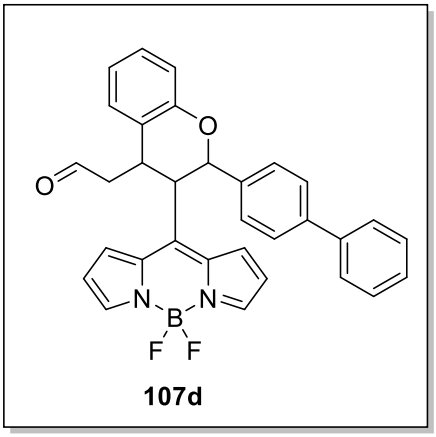
107b

2-(6-bromo-3-(5,5-difluoro-5H-4l4,5l4-dipyrrolo[1,2-c:2', 1'-f][1,3,2]diazaborinin-10-yl)-2-phenylchroman-4-yl) acetaldehyde (107b): From **106b** (22.7 mg, 0.1 mmol) and BODIPY **95a** (23.0 mg, 0.12 mmol), following the general procedure N (4 ºC, 60h), compound **107b** was obtained in 77% yield as a red solid. The crude product was purified by column chromatography (gradient hexane/AcOEt from 9:1 to 5:1). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.76 (s, 1H), 7.91 (s, 1H), 7.84 (s, 1H), 7.80 – 7.68 (m, 1H), 7.50 (d, *J* = 3.3 Hz, 1H), 7.42 (dt, *J* = 30.5, 11.4 Hz, 3H), 7.22 (d, *J* = 2.6 Hz, 2H), 7.10 (d, *J* = 3.5 Hz, 1H), 7.05 – 6.84 (m, 2H), 6.74 (s, 1H), 6.46 (d, *J* = 3.5 Hz, 1H), 5.52 (d, *J* = 10.2 Hz, 1H), 4.31 – 4.25 (m, 1H), 3.97 (t, *J* = 10.7 Hz, 1H), 3.19 (dd, *J* = 18.7, 4.0 Hz, 1H), 2.90 (dd, *J* = 18.8, 4.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 199.77, 154.29, 146.23, 143.00, 137.29, 135.05, 132.16, 131.49, 130.12, 129.80, 129.11, 128.67, 128.61, 126.57, 126.20, 119.88, 118.32, 114.31, 82.58, 77.16, 49.73, 46.61, 38.26.



107c

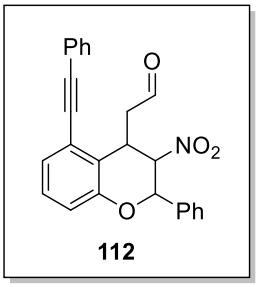
2-(3-(5,5-difluoro-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f] [1,3,2]diazaborinin-10-yl)-2-(4-(trifluoromethyl)phenyl) chroman-4-yl)acetaldehyde (107c): From **106a** (15.0 mg, 0.1 mmol) and BODIPY **95b** (44.0 mg, 0.12 mmol), following the general procedure N (4 ºC, 60h), compound **107b** was obtained in 73% yield as a red solid. The crude product was purified by column chromatography (gradient hexane/AcOEt from 9:1 to 5:1). **^{1}H NMR (500 MHz, $CDCl_3$)**



107d

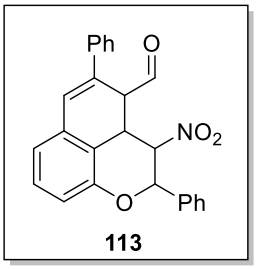
2-(2-([1,1'-biphenyl]-4-yl)-3-(5,5-difluoro-5H-4l4, 5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)chroman-4-yl)acetaldehyde (107d): From **106a** (15.0 mg, 0.1 mmol) and BODIPY **95c** (45.0 mg, 0.12 mmol), following the general procedure N (4 ºC, 60h), compound **107b** was obtained in 81% yield as a red solid. The crude product was purified by column chromatography (gradient hexane/AcOEt from 9:1 to 5:1). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.61 (s, 1H), 7.76 (s, 1H), 7.70 – 7.64 (m, 1H), 7.40 (d, *J* = 7.2 Hz, 3H), 7.32 (dd, *J* = 15.9, 8.0 Hz, 4H), 7.23 (dd, *J* = 17.3, 10.0 Hz, 2H), 7.14 (dd, *J* = 16.9, 9.0 Hz, 3H), 7.03 – 6.92 (m, 3H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.28 (d, *J* = 3.6 Hz, 1H), 5.44 (d, *J* = 10.2 Hz, 1H), 4.19 (dt, *J* = 16.2, 5.3 Hz, 1H), 3.83 (t, *J* = 10.7 Hz, 1H), 3.01 (dd, *J* = 18.2, 4.4 Hz, 1H), 2.73 (dd, *J* = 18.2, 4.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 200.09, 154.92, 146.06, 140.96, 136.57, 131.41, 130.05, 129.61, 128.69, 128.59, 128.47, 128.26, 127.43, 127.37, 127.18, 127.11, 127.01, 126.94, 126.26, 123.86, 123.20, 122.06, 120.36, 117.98, 82.20, 50.28, 46.99, 38.49. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -143.89 – -145.11 (m), -146.97 – -148.20 (m).

7.8. Synthesis of cooperative catalysed cycloadducts.



112

2-(3-nitro-2-phenyl-5-(phenylethynyl)chroman-4-yl)acetaldehyde (112): To a solution of (E)-3-(2-hydroxy-6-(phenylethynyl)phenyl)acrylaldehyde (0.12 mmol, 30 mg) and (R)-2-(diphenyl((trimethylsilyl) oxy)methyl)pyrrolidine (0.02 mmol, 6.6 mg) in DCM (0.2 M) was added nitrostyrene (0.1 mmol, 15 mg) and sodium acetate (0.02 mmol, 1.7 mg) the reaction mixture was stirred for overnight at RT. After completion, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel 25g, ethyl acetate/hexane 12:88). Brown solid, 82% yield, 99% ee, 1:4 dr, **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.56 (t, *J* = 8.8 Hz, 1H), 7.44 – 7.32 (m, 13H), 5.62 (d, *J* = 6.2 Hz, 1H), 5.23 (d, *J* = 6.0 Hz, 1H), 4.61 – 4.47 (m, 1H), 3.25 (dd, *J* = 19.5, 2.9 Hz, 1H), 2.67 (dd, *J* = 19.5, 9.4 Hz, 1H).



113

3-nitro-2,5-diphenyl-2,3,3a,4-tetrahydrobenzo[de]chromene-4-carbaldehyde (113): In a 5 mL vial of 2-(3-nitro-2-phenyl-5-(phenylethynyl)chroman-4-yl)acetaldehyde (0.05 mmol, 20 mg) and (R)-2-(diphenyl((trimethylsilyl) oxy)methyl)pyrrolidine (0.01 mmol, 3.3 mg) in solvent (0.4 mL) was added corresponding $Au(PPh_3)Nf_2$ (0.01 mmol, 15.8 mg) and *p*-TSA (0.03 mmol, 5.7 mg) the reaction mixture was stirred for corresponding time using different temperatures. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.72 (s, 2H), 7.46 – 7.32 (m, 4H), 7.32 – 7.20 (m, 16H), 7.16 (s, 2H), 7.11 (s, 2H), 6.91 (d, *J* = 14.4 Hz, 4H), 6.55 (s, 2H), 4.97 (s, 2H), 4.50 (s, 1H), 3.32 (s, 2H).

Chapter 8.

Summary, author contribution, acknowledgment and final personal remarks

I begin my Ph.D. with satisfying writing skills, that even I was not happy with it. In all this journey, reading articles, writing a predoctoral manuscript, a long article like "ApDOS concept", writing a review with 20 pages helped me to improve my writing skill to another level. Learning from skill writers, that how they turn blitz-second of action into chapter-long thrilling reading by their magical touch, which surely kept me awake for many nights. It was not that easy to write such concepts and learn English word-to-word to explain my point so that non-specialists can understand too. But thank to my professor Dr. David, his writing skills gave an indication that how a normal sentence can be converted into an attractive phrase. As a result, in this thesis, I had least struggle to write and conceptualize each point individually and I tried my best to make it more interesting reading for experts as well as outsiders of the field of organocatalysis.

In the first chapter, the brief concept, that how a chemical evolution meets asymmetric synthesis which results into a development of today's organocatalysis field. Also, a brief knowledge about aminocatalysis will help to understand the absolute concept and surely it will inspire other chemists to begin the work on such a field. In the third point, the information about catalytic system in aminocatalysis can explain the scope of field that I suppose to admit it that this section was not so important, as we used only the diaryl prolinol ethers and not the rest, however when it comes about aminocatalysis, I felt obligated to introduce the rest two points to explained overall field. Also, the beginners can surely improve their knowledge by understanding the future challenges in organocatalysis which is mentioned as a next separate point. In the fifth point, catalytic cascade reaction has been discussed from the advantages they offer in the synthesis to their general classification and nomenclature. I tried my best, to introduce the term "cooperative catalysis" in short notes to aim a better explanation that can help to understand chapter 6 more clearly. As an entity, I hope to have seized the reader's attention while providing the required background information for the upcoming scientific discussion in later chapters.

In chapter 2, a theoretical survey has been discussed. During my Ph.D., I was fascinated by the skilled writing of different review writers that inspired myself to write a review of my own. In addition, our research group came up with the "ApDOS concept" that make my dream come true to write my own words to make others understand my point. That inspired me to read the articles and understand the reader's mind carefully. Nevertheless, the hunger of writing more and to know more about the field, motivated me to write another review. All the backstage preparation for these two articles has been discussed in this chapter.

In third and forth chapter, a brief introduction about trienamine catalysis with the help of four different projects are discussed. As, this thesis is mainly focusing on the trienamine activation, I enjoyed explaining the term more briefly. During this study, some new dienophiles were discovered (pyrazole and sulfone containing olefins) whereas some previously used dienophiles were passed down to contribute in the medicinal field.

In chapter 5, three different projects are discussed. They are classified as individual chapter as, it was first time, BODIPY dye was used in asymmetric transformations to synthesize chiral fluorescent compounds. BODIPY is very important moiety in organic synthesis due to their fluorescent properties, that inspired our group to work with BODIPY's. Some of the important projects that carried out during my Ph.D. work are described in this chapter. Last but not least, a separate chapter to introduce "cooperative catalysis" which involve very attractive project with the combination of amino- and gold catalysis has been discussed. In the end a separate chapter (7^{th}) provided for the experimental section.

As concluding remark for this thesis, As, when I started my Ph.D., I was first and only doctorate student in the group, it was bit-slow to learn about the field and practical knowledge with some problems that a new lab suppose to face, I started my journey as doctorate student. The projects we start was with least help and some of the projects (including the projects that didn't worked) I handled individually. Additionally, all the projects (including concept and review) mentioned in this thesis, I am or I will be the first author of each, except the project "Alkenyl BODIPY as dienophile in trienamine reactivity" (section 0). But also, I must (again) underline that none of the work was possible without collaborated help from different groups, many colleagues and David to whom I

owe my everything in my short academic career. Moreover, it must also be stressed that I shall be held solely responsible for any error and mistakes in this dissertation.

Finally, I would like to thank Dr. David Cruz Cruz for taking me to his group. I am sincerely grateful to CONACyT for providing a strong economical support during my 4 years of Ph.D., I would like to thank a great collaboration with my committee member Dr. Eduardo Peña-Cabrera and Dr. Clarisa Villegas Gómez. Also, direct and indirect support from my codirector of thesis Dr. César Rogelio Solorio Alvarado and Dr. Miguel Angel Vasquez. I am also thankful to Dr. José Luis "Wicho" Belmonte for support in lab. I am thankful to Dr. José Luis Olivares-Romero from Instituto de Ecología AC, Xalapa for providing a help with HPLC. During my stay in Universidad Autonoma de Madrid, Spain, A great support by Dr. José Aléman-Lara and Dr. Alberto Fraile-Carrasco was priceless.

With these words, I mark the finish of my Ph.D. thesis, which hopefully provided some interesting reading and insight into my soon ended journey as a graduate student. I claimed in the preface that my objective of research is to demonstrate the applicability of aminocatalysis and show usefulness of these strategies in synthesis. I sincerely hope that I, at least in a part, have been successful in doing so (Otherwise CONACyT have to pay me another year, which doesn't look possible). As final words, Cheers, to myself and all the interested readers.

Appendix I.

Aminocatalytic Privileged Diversity-Oriented Synthesis (ApDOS): An Efficient Strategy to Populate Relevant Chemical Spaces

Tushar J. Pawar, Hao Jiang, Miguel A. Vazquez, Clarisa Villegas Gomez* and David Cruz Cruz.*

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EurJOC European Journal of Organic Chemistry

Microreview

The ApDOS Concept

Aminocatalytic Privileged Diversity-Oriented Synthesis (ApDOS): An Efficient Strategy to Populate Relevant Chemical Spaces

Tushar J. Pawar,[a] Hao Jiang,[a] Miguel A. Vázquez,[a] Clarisa Villegas Gómez*[a] and David Cruz Cruz*[a]

Abstract: Diversity-oriented synthesis and aminocatalysis constitute two important tools for access to important compounds. The extraordinary development in these two areas has allowed chemists to populate new regions in chemical space. As a consequence, new libraries of complex and diverse frameworks are becoming available for drug discovery. ApDOS is presented as a new concept that shows the scope of aminocatalysis for the synthesis and diversification of privileged structures.

Introduction

Molecular diversity, the extraordinarily vast set of organized chemical structures immersed over the whole of chemical space, has defined the development of emergent areas in chemistry and biology, such as chemical genetics and medicinal chemistry.

According to chemical genetics, biological processes can be dissected and modulated with the aid of small-molecule compounds. These powerful probes are able to bind selectively to one or multiple receptors and to exert important effects in the functions of biomacromolecules.[1] As a consequence, biological phenotypes can be induced, either in a preselected protein target (reverse chemical genetics) or with multiple proteins of interest (forward chemical genetics).[2] In particular, the forward chemical genetics approach is of special interest because it allows the discovery of new bioactive chemical structures and the exploration of biological pathways at the same time. Indeed, chemical genetics is closely related to drug discovery. However, the discovery of lead targeting compounds remains an important challenge. In this context, the screening of collections of structurally diverse small-molecule compounds facilitates the rapid identification of new biological modulators or lead compounds.[3] Therefore, libraries of structurally diverse molecules are of great value in the search for biologically active compounds.

In terms of diversity, nature has provided a vast supply of diverse and complex molecular architectures, which represent molecules distributed in all directions throughout chemical space. For years, these natural products have played an important role, because of their ability to modulate a variety of biological functions. However, their use as drugs has been limited due to the problems associated with their natural abundance, isolation, and characterization.[4] Nevertheless, their structures have inspired the development of new drugs through chemical synthesis.[5] Traditionally, the search for synthetic bioactive compounds has been pursued by the synthesis and/or modification of target molecules (Target-Oriented Synthesis, TOS);[6] however, the inherent low diversity of this methodology limits the probability of finding a lead compound. To address this issue, Diversity-Oriented Synthesis (DOS) has emerged as a powerful tool for maximizing molecular diversity through the creation of compound libraries.[7] In a DOS methodology, simple and similar compounds are transformed efficiently into several complex and diverse structures. In contrast to TOS, in which target compounds are prepared by retrosynthetic analysis and total synthesis (convergent synthesis), DOS follows a divergent process, a branched pathway, by which libraries with broad diversity are generated through a forward synthetic analysis.

Since the conceptualization of DOS by Schreiber in 2000, several original strategies have been developed for the generation of libraries containing complex compounds with different elements of diversity, such as appendage, functional group, stereochemistry, and chemical skeleton.[8] These structurally diverse collections populate new regions in chemical space, which in turn opens up new possibilities for the discovery of new therapeutic agents.

In order to maximize the potential of library synthesis and hit rate in drug design, privileged diversity-oriented synthesis has been introduced as a strategy for creating collections of small-molecule compounds based on privileged cores.[9] A privileged structure is defined as a single molecular framework capable of providing high-affinity ligands for more than one type of receptor.[10] Therefore, pDOS represent an efficient and rational strategy for creating libraries of relevant architectures that can populate bioactive regions in chemical space.

Coincidentally, during the DOS conceptualization, the renaissance of asymmetric catalysis facilitated by small-molecule or-

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ganic compounds also took place.[11] In the same year, the concept of organocatalysis was effectively demonstrated by the groups of MacMillan[12] and List,[13] who reported two ingenious synthetic methodologies simultaneously. Since then, the field of organocatalysis has experienced tremendous progress and has now come to be considered the third pillar of asymmetric catalysis.[14] In particular, aminocatalysis has played an important role, due to its ability to functionalize carbonyl compounds in a stereoselective manner. This type of catalysis has led to the development of a great variety of enantioselective transformations and constitutes a powerful tool for accessing a wide range of enantioenriched compounds.

Activation Modes in Aminocatalysis and the ApDOS Concept

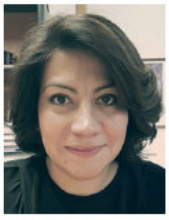
The success of aminocatalysis lies in the ability of chiral primary or secondary amines to condense effectively but also reversibly with aldehydes and ketones. This complementary amine/carbonyl pairing can promote different enantioselective transformations through a variety of activation processes in which organized and highly reactive intermediates are involved. Depending on the features of the aldehyde or ketone, a predictable activation mode can be formed, and as a result a rational methodology for desired products can be achieved. Currently, approximately seven activation modes have been successfully developed and have served as platforms for many asymmetric transformations.[15]

The essence of activation modes in aminocatalysis is in the fundamental reactivity-enhancing concepts of raising the HOMO and lowering the LUMO. The archetypal HOMO-raising process is *enamine activation*. In this strategy, enolizable carbonyl compounds are activated with catalytic amounts of chiral primary or secondary amines, which induces the formation of enamine intermediates. These nucleophilic enolate equivalents can then react with electrophilic reagents, and as a conse-

Tushar Janardan Pawar was born in 1992 in the Raigad district of Maharashtra, India. He obtained his M.Sc. in organic chemistry in 2015. For his Master's thesis he developed new methodologies to synthesize new giant heterocyclic moieties, under the supervision of Prof. Milind V. Gaikwad at Dr. D. Y. Patil A.C.S. college, affiliated to the University of Pune, India. Currently he is a Ph.D. student under the supervision of Prof. David Cruz Cruz at the Universidad de Guanajuato, Mexico (since 2016). His research interests include new modes of activation for remote functionalization by organocatalysis, as well as asymmetric synthesis and application of fluorescent compounds and development of cascade reactions with use of aminocatalysis.

Hao Jiang was born in Shanghai, P.R. China, in 1984. He studied chemistry at Aarhus University and received his Ph.D. degree in October 2011 under the supervision of Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University. Upon gruaduation, he continued to work at the Center for Catalysis as a postdoctoral researcher until 2014. He is currently working as a senior research scientist at a biopharmaceutical company.

Miguel Ángel Vázquez G. is a Professor at the University of Guanajuato, México. His major research interests cover practically all aspects of synthesis of heterocyclic molecules and application in industry and in medicinal chemistry. He received his PhD (2004) from the Instituto Politécnico Nacional in México City, under the supervision of Prof. Francisco Delgado, working on the synthesis and reactivity of Fischer carbenes. Afterwards he joined Polaquimia Company, where he became a lead researcher in the R&D department, working on the synthesis of surfactants, agrochemicals, and biodegradable lubricants. In 2007 he moved to the Department of Chemistry at Universidad de Guanajuato to establish his own research group.



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 the Universidad Nacional Autónoma de México, working on 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, Denmark. In 2016 she moved to the Department of Chemistry at the Universidad de Guanajuato as an Associate Professor. Her research is focused on the isolation of bioactive natural products, as well as on the synthesis of natural product scaffolds by new methodologies in organocatalysis inspired by the concept of Diversity-Oriented Synthesis.

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

quence, new C–C or C–heteroatom bonds α to carbonyl groups can be effectively formed in an enantioselective fashion.[15c–i]

On the other hand, lowering of the energy of the LUMO is the underlying principle of *iminium ion activation*. In this activation mode α,β-unsaturated aldehydes and ketones condense with chiral amines to generate iminium ion intermediates, and this facilitates both asymmetric nucleophilic additions at the β position and also pericyclic reactions.[15a,15b]

Additionally, once HOMO and LUMO activation were established, MacMillan and co-workers introduced SOMO activation. This term refers to one-electron oxidation of the enamine intermediate to generate a 3π-radical cation intermediate. This new species is then able to participate in a variety of asymmetric radical transformations.[16] Moreover, the development of this SOMO activation invention has influenced the combination of photoredox catalysis with aminocatalysis, to extend possibilities in this area.[17]

Thanks to both enamine and iminium ion activation modes, a great variety of methodologies for the enantioselective functionalization of carbonyl compounds at the α and β positions have been successfully developed. Moreover, these two classical activation strategies have been extended, leading to the discovery of new activation modes. Through the above reactivity concepts, aminocatalysis has been transformed with the development of the so-called dienamine,[15j,15k] linear trienamine,[15l,15m] cross trienamine,[18] tetraenamine,[15n,15o] and vinylogous iminium ion patterns,[15p,15q] by extension of π-conjugated systems in carbonyl compounds. These new activation modes have allowed the functionalization of remote centers (i.e., reactive sites located five to seven bonds distant from the catalyst).[19]

Together with the discovery of new activation modes, the development of new catalysts is also crucial. Aminocatalysts based on pyrrolidine-, imidazolidinone-, and cinchona-alkaloid-derived scaffolds have been designed and prepared not only to promote different activation modes but also to provide efficient chirality transfer. In these senses, both steric-shielding and hydrogen-bond bifunctional operational modes can be involved, depending on the features of the groups attached to the main core of the catalyst.

The success of aminocatalysis has been driven both by the development of new activation modes and by the design of new catalysts enabling efficient transfer of asymmetry and high rate enhancement. In terms of diversity, molecular architectures produced by aminocatalysis have allowed the population of new regions of chemical space. More importantly, biologically relevant regions have been targeted, with a wide variety of methodologies having been directed towards the synthesis and diversification of privileged structures.

In general, pDOS and aminocatalysis are closely related. According to their main goals, we envision 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 pathways typically involve a process that generates a common intermediate scaffold from simple molecules, which in turn serve as a platform for the synthesis of complex and diverse frameworks. These key intermediates represent the inflection point at which extensive molecular diversity arises. Therefore, in ApDOS, aldehydes and ketones are the simple, common molecular building blocks, able to participate in different activation modes. 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 1).

Here we present a conceptual review of recent literature, covering diversification of privileged structures with the aid of aminocatalytic processes, either through the utilization of a single activation mode or by combining multiple modes in a single process (cascade reactions). The aim of this paper is to demonstrate the broad utilization of aminocatalysis in asymmetric synthesis, since is serves as a genuine tool to amplify and diversify the chiral pool, and to create diverse chiral frameworks in relevant regions of chemical space. This contribution shows repre-

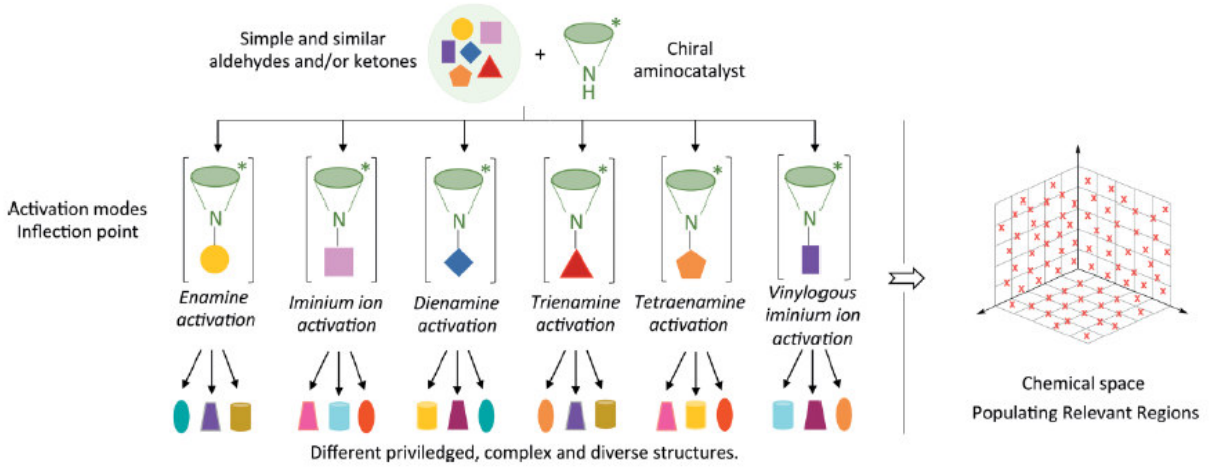


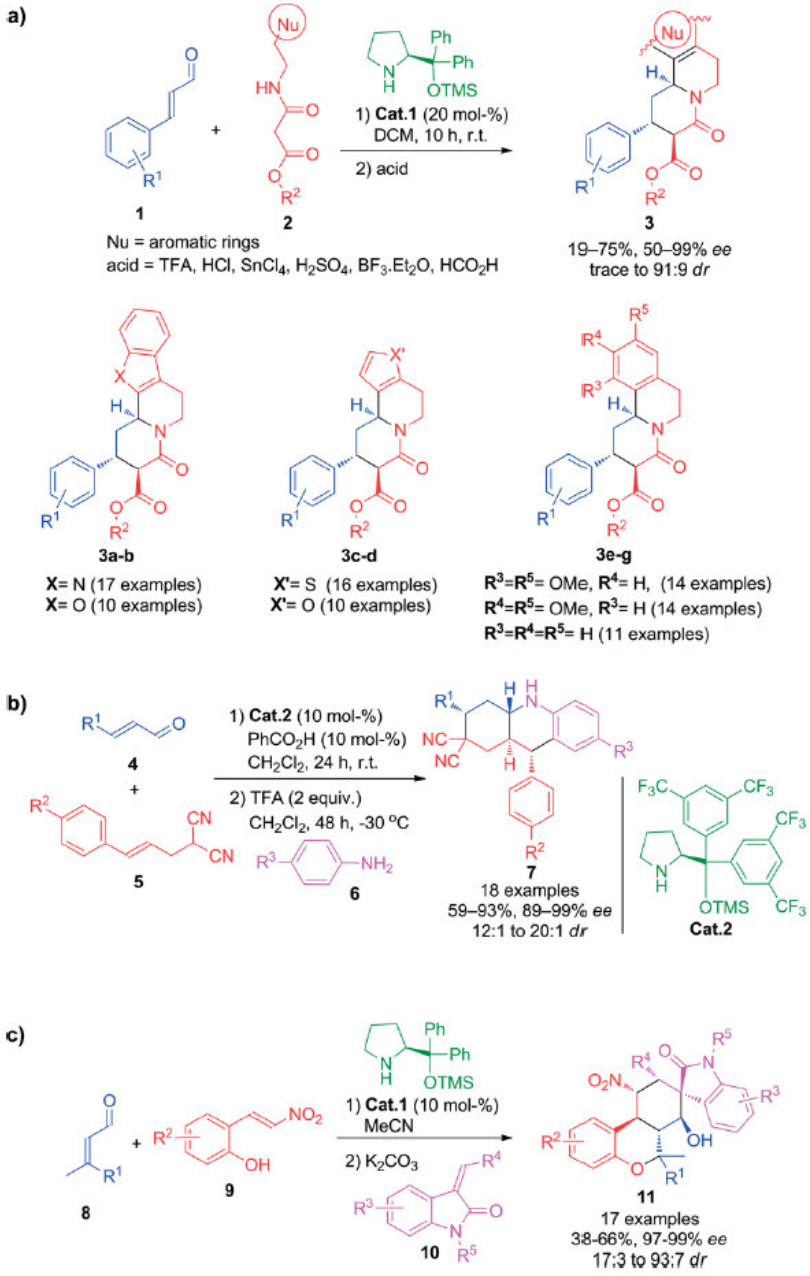
Figure 1. The ApDOS concept.

sentative examples of rapid assemblies of diverse product classes enabled by this strategy. It should be noted that only a conceptual overview of this topic – based on literature published after 2010 – is provided. A comprehensive or complete review of the field of research would be beyond the scope of this work.

ApDOS with Iminium Ion Catalysis

Iminium ion activation, considered one of the two classical aminocatalytic pathways, has been the subject of countless asymmetric methodologies, including those based on nucleophilic additions and on pericyclic reactions. In the seminal work by MacMillan and co-workers the ability of chiral iminium ion intermediates to undergo asymmetric Diels–Alder cycloaddition was demonstrated.[20] Thereafter, great efforts were devoted to developing innovative methodologies for the synthesis and diversification of optically active molecules of interest.

Aminocatalytic Michael reactions of α,β-unsaturated aldehydes represent one of the most important strategies for forming new C–C or C–heteroatom bonds β to carbonyl groups; the



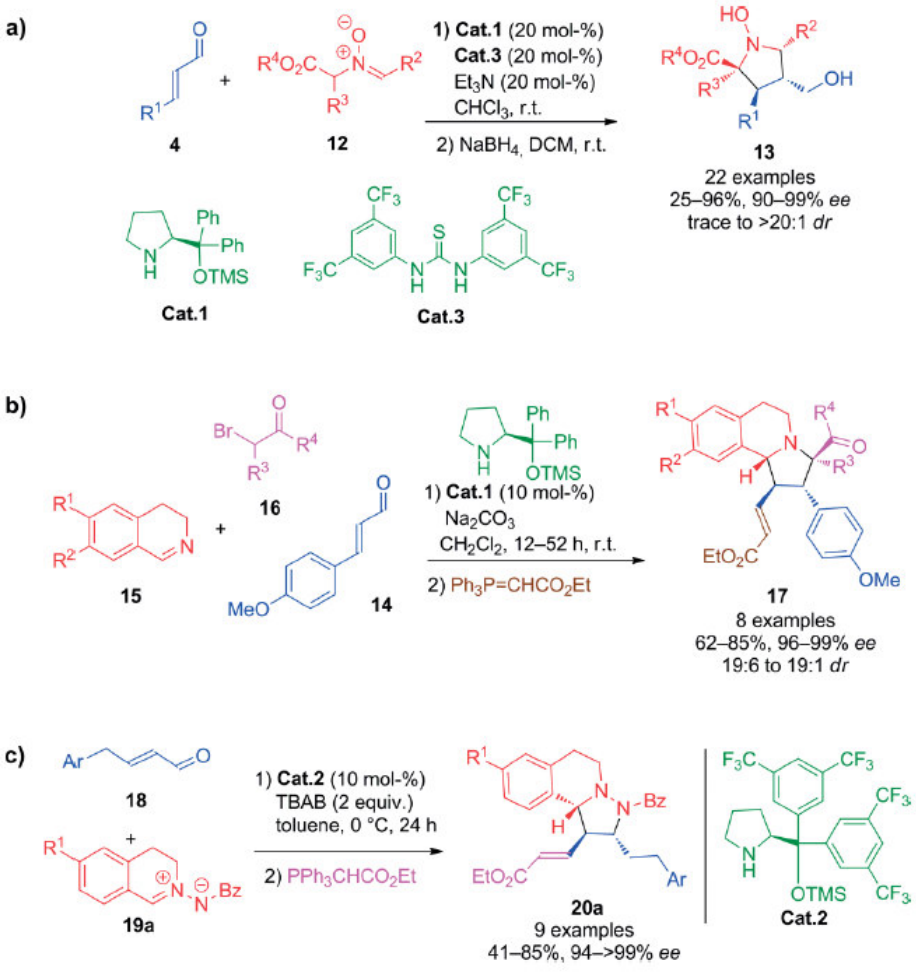
Scheme 1. (a) Stereoselective one-pot approach to the synthesis of asymmetric quinolizidine derivatives. (b) An asymmetric organocatalytic one-pot methodology for the synthesis of asymmetric octahydroacridine frameworks. (c) Asymmetric synthesis of chroman-fused spirooxindoles.

capability to introduce a variety of nucleophiles with different functional groups allows further inter- or intramolecular reactions after the aminocatalytic pathway, leading to the formation of complex compounds in one-pot fashion. As an example of this concept, a one-pot strategy for the construction of quinolizidines **3** was successfully developed. In this sequence, electron-deficient amides **2** underwent aminocatalytic conjugate addition with α,β-unsaturated aldehydes **1**, followed by ring-closing condensation and then acid-catalyzed cyclization, to afford the desired products **3a–g** in good yields and with excellent enantio- and diastereoselectivities (Scheme 1a).[21]

On the other hand, the aminocatalytic Michael addition of alkenyl-malononitrile derivatives **5** to α,β-unsaturated aldehydes **4**, followed by intramolecular Povarov reaction, promoted by the addition of anilines **6** to the corresponding adducts, leads to the formation of octahydroacridines **7**, an important class of tetrahydroquinolines with interesting potential biological properties, in good yields and with excellent stereocontrol. Notably, the high level of diversity stems from the different substituents on the three components (Scheme 1b).[22]

An interesting strategy for assembling chroman-fused spirooxindoles **11** involves an oxa-Michael/Michael/Michael/aldol sequence, in a three-component process. Through this methodology, a library of bioactive compounds was obtained in moderate to good yields and with excellent stereoselectivities (Scheme 1c).[23]

Five-membered heterocycles are of great interest because they are found in a broad variety of natural and pharmaceutical compounds, so 1,3-dipolar cycloadditions have played an important role in the synthesis of frameworks of this type. Aminocatalyst-bound iminium ion intermediates have served as activated dipolarophiles for different [3+2] cycloadditions. Several reports on the synthesis of isoxazolidines through the use of nitrones as dipoles have been published over the last 17 years.[24] Recently, an alternative aminocatalyzed [3+2] annulation strategy, involving the introduction of electron-withdrawing groups in nitrone moieties **12**, led to the *N*-hydroxypyrrolidines **13** rather than the expected isoxazolidines, in moderate to excellent yields and with high enantiocontrol (Scheme 2a).[25]



Scheme 2. (a) Bidentate reactivity of nitrones in [3+2] cycloaddition with enals with cooperative H-bonding catalysis/iminium ion activation. (b) New organocatalytic multicomponent reaction giving access to a series of hexahydropyrrolo-isoquinoline derivatives. (c) Iminium ion activation of enolizable α,β-unsaturated aldehydes.

Another example of an important methodology is cycloaddition with dihydroisoquinolinium ylides (generated in situ) to furnish highly enantioenriched hexahydropyrrolo-isoquinolines **17** in good yields (Scheme 2b).[26]

In 2014, an interesting organocatalytic [3+2] cycloaddition methodology based on the use of azomethine imines **19a** as dipoles was also reported. The ability of α,β-unsaturated β-arylmethyl-substituted aldehydes **18** to form iminium ion or dienamine intermediates selectively through appropriate choice of conditions leads to diversification in the form of tetrahydroisoquinolines **20a** in good yields and with excellent chemo- and stereoselectivities (Scheme 2c and Scheme 10).[27]

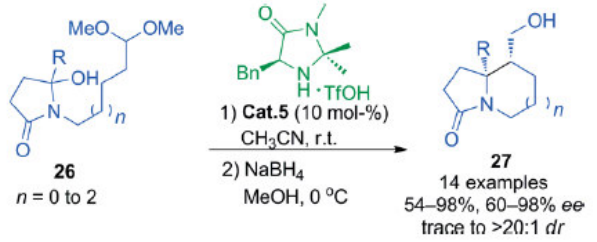
ApDOS Based on Enamine Catalysis

In 1971, the groups of Hajos and Parrish at Hoffmann–La Roche and Eder, Sauer, and Weichert at Schering AG independently described the first enantioselective intramolecular aldol condensation based on the use of proline as the catalyst.[28] The key to this strategy is the generation of an enamine intermediate to furnish bicyclic ketones. Although the formal conceptualization of organocatalysis is dated to the beginning of this century, these isolated reports constitute the origin of asymmetric organocatalysis. Moreover, the Hajos–Parrish–Eder–Sauer–Weichert reaction is an efficient strategy for gaining access to the Weiland–Miescher ketone, an important building block used in the total synthesis of a variety of natural products, such as sesquiterpenoids, diterpenoids, and steroids.[29] As such, it can be viewed as the initial seed that led to the later evolution of method development towards the generation of privileged structures facilitated by organocatalysis.

During the last two decades an impressive variety of methodologies involving enamines in asymmetric synthesis have been developed.[15c–15i] Nowadays, this activation mode has been effectively used to form nucleophilic equivalents in situ in conjugated addition reactions with a wide variety of electron-deficient olefins. Subsequent reactions may then furnish highly diverse and complex scaffolds. As a validation of this approach, treatment of *N*-protected 1-aminomethyl- or 1-hydroxymethyl-substituted nitroolefins **22** with enamines allows the rapid formation of six-membered *N*- or *O*-centered heterocycles **23**, each containing four contiguous chiral centers (Scheme 3a).[30]

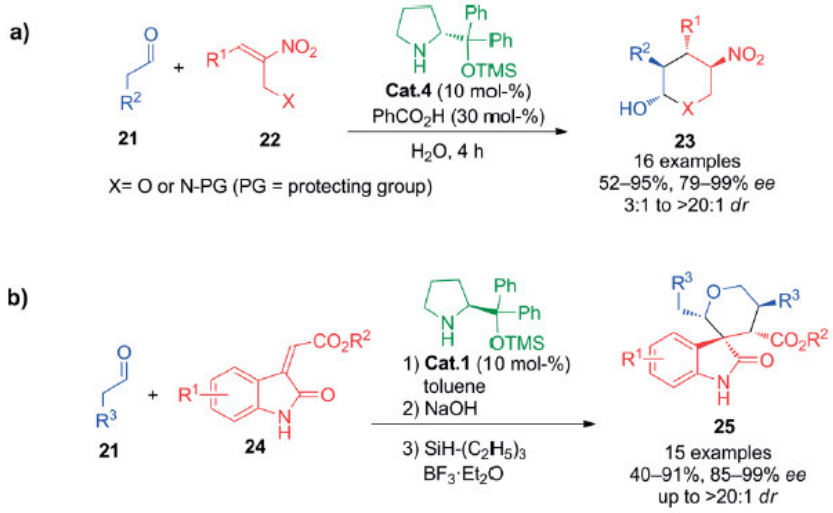
In order to prepare spirocyclic oxindole derivatives **25**, electron-deficient olefin oxindoles **24** were incorporated as Michael acceptors in the aminocatalytic process, and then an extra equivalent of aldehydes **21** triggered both aldol and hemiacetalization reactions. Finally, reduction to avoid low diastereoselectivities finalized the formation of spirocyclic oxindoles fused with tetrahydropyran moieties in moderate to good yields and with high stereoselectivities (Scheme 3b).[31]

Recently, an innovative strategy that involves an intramolecular acyl-Mannich cyclization of tethered acetal starting material **26** has provided access to izidine alkaloids **27**, carrying an aza-quaternary motif, with good to excellent yields and stereoselectivities. The reaction proceeds via the in situ generation of an *N*-acyl iminium ion and an aldehyde motif from the *N*,*O*-hemiaminal and the acetal group, respectively. Notably, this method is applicable to the assembly of five-, six-, and seven-membered rings (Scheme 4).[32]

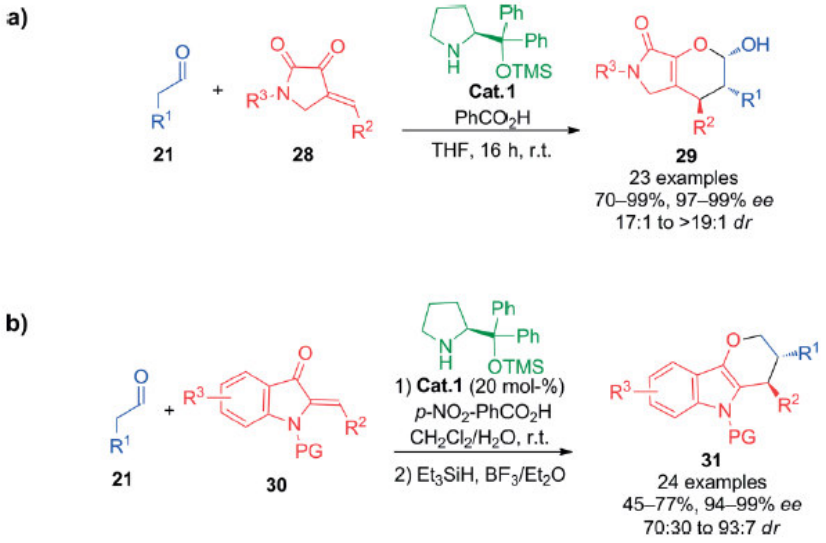


Scheme 4. Asymmetric synthesis of the aza-quaternary center of izidine alkaloids.

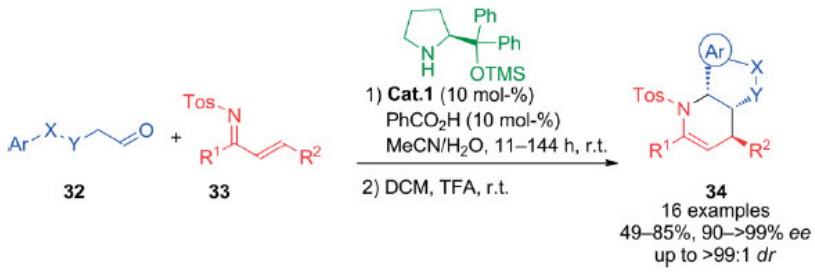
Inverse-electron-demand (IED) Diels–Alder cycloaddition constitutes a powerful tool for the construction of challenging frameworks. Catalyst-bound enamines have been successfully



Scheme 3. (a) Organocatalytic Michael addition of aldehydes to nitroolefins and subsequent aminalization. (b) Synthesis of spirocyclic oxindole derivatives through a Michael/aldol/ hemiacetalization cascade sequence.



Scheme 5. Asymmetric IED oxo-Diels–Alder cycloaddition between saturated aldehydes and (a) cyclic enones, or (b) heterodienes.



Scheme 6. IED aza-Diels–Alder cycloaddition between *N*-sulfonyl-1-azabuta-1,3-dienes and aminocatalytically generated enamines.

applied as electron-rich dienophiles for transformations of this type, leading to the population of important regions in chemical space.

As an example of the above, γ-lactam-derived cyclic enones **28** were shown to react with enamines to form fused bicyclic dihydropyrans **29** with different substituents and functionalities in good yields and with excellent stereocontrol through IED oxa-Diels–Alder cycloaddition (Scheme 5a).[33] Conceptually similarly, when *N*-protected (*Z*)-2-ylideneoxindoles **30** were deployed as electron-poor heterodienes, a library of densely functionalized hydropyrano[3,2-*b*]indoles **31** was prepared. In most cases the reactions proceeded with good yields and remarkable stereoselectivities (Scheme 5b).[34]

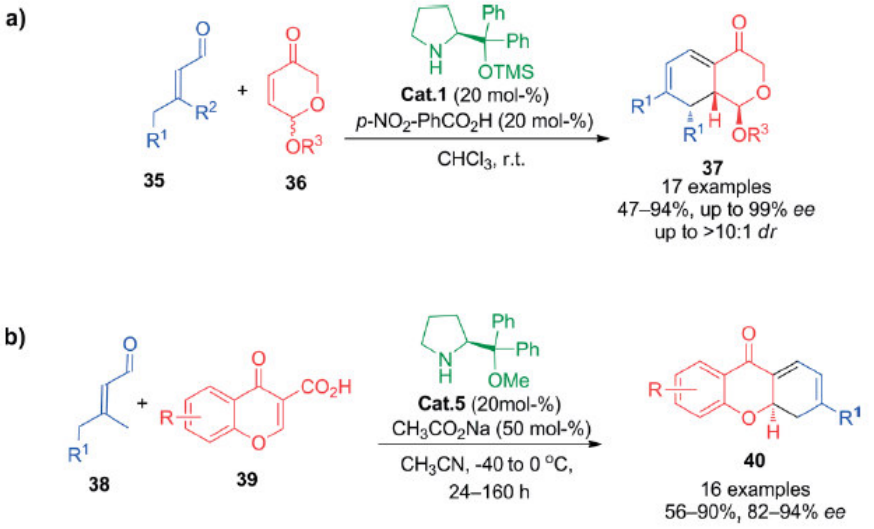
An attractive ApDOS methodology is the IED aza-Diels–Alder cycloaddition between *N*-sulfonyl-1-azabuta-1,3-dienes **33** and enamines aminocatalytically generated from **32**, followed by intramolecular Friedel–Crafts reaction, which allows access to complex and diverse fused piperidine derivatives **34** with high molecular complexity in good yields and with excellent enantioselectivities (Scheme 6).[35]

ApDOS with Dienamine Catalysis

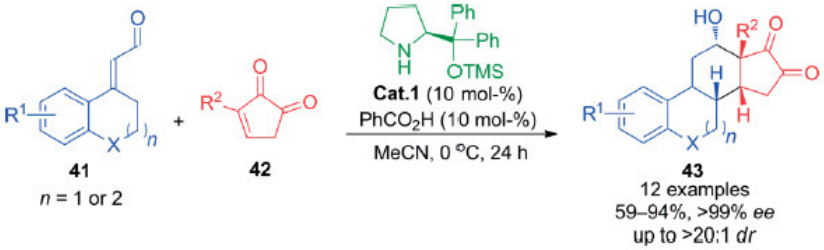
During the exploration of new reactivities in aminocatalysis, it was argued that the HOMO-raising concept should be extendable to the generation of reactive dienamine species, which would offer new opportunities for the construction of important architectures. Through the development of this aminocatalytic pathway, significant ApDOS strategies have been successfully accomplished.

The chromane skeleton is a prominent scaffold in the chemistry of natural products. A survey of the literature provides examples of how chromane derivatives, which are of great interest both in organic chemistry and in pharmaceutical science by virtue of their biological activities, have been discovered. In 2012, Vicario et al. synthesized isochromanes **37** from racemic 5-acyloxydihydropyranones **35** and enolizable α,β-unsaturated aldehydes **36** by way of a dienamine-catalyzed Diels–Alder/elimination cascade sequence in good yields and with excellent stereocontrol (Scheme 7a).[36] Recently, Albrecht and Bojanowski demonstrated diversification of substituted chromene carboxylic acids **39** through dienamine catalysis with α,β-unsaturated aldehydes **38** for the synthesis of optically active dihydroxanthone derivatives **40** in good yields and with *ee* values of up to 94 % (Scheme 7b).[37]

Privileged steroids have played a fundamental role in the evolution both of organic synthesis and of medicinal chemistry and biology. In 2014, Jørgensen et al. developed a new highly enantio- and diastereoselective one-step pathway for the preparation of enantioenriched 14β-steroids **43** from α,β-unsatu-



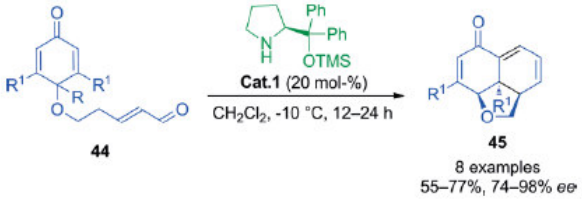
Scheme 7. (a) Dienamine-catalyzed Diels–Alder/elimination cascade sequence for the synthesis of substituted tetrahydro-7*H*-isochromanes. (b) Diversification of chromene carboxylic acids for the synthesis of 4,4a-dihydroxanthones.



Scheme 8. Highly enantio- and diastereoselective one-step methodology for the preparation of optically active steroids.

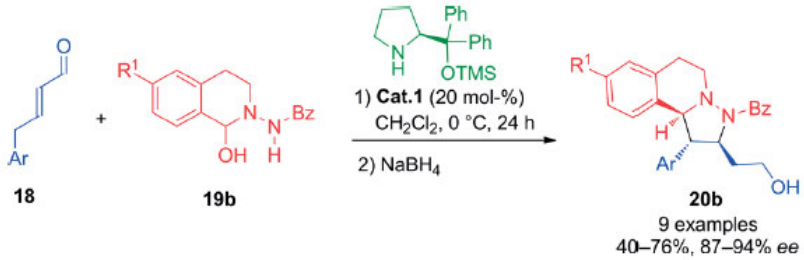
rated aldehydes **41** and five-membered cyclic dienophiles **42** (Scheme 8).[38] Notably, this reaction proceeds with a high yield and up to more than 99% *ee*. Steroids of this type are found in the naturally occurring Cardenolide family and are also used in a synthetic procedure for some natural products such as estrone and similar frameworks.

Interestingly, desymmetrization of cyclohexadienones promoted by intramolecular [4+2] cycloaddition assisted by dienamine activation leads to the synthesis of important optically active tricyclic derivatives **45**. In this highly stereoselective procedure, a large variety of substituents can be incorporated in good yields. In particular, these tricyclic motifs are found in bioactive compounds, in some natural products such as momilactone A, azadirachtin, oidiolacone, and nagilactone, and in the Ziegler intermediate etc. (Scheme 9).[39]

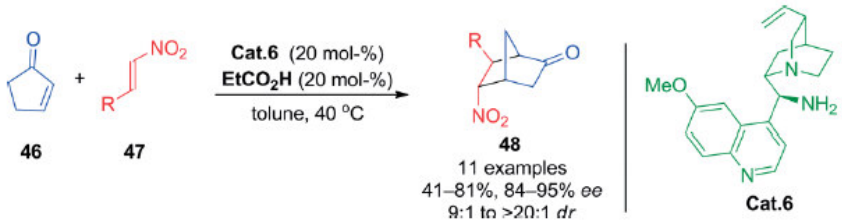


Scheme 9. Aminocatalytic intramolecular Diels–Alder/aldol cascade sequence for the construction of optically active tricyclic compounds.

As mentioned above, García Ruano et al. reported that, with appropriate choice of conditions, β-arylmethyl-substituted α,β-unsaturated aldehydes are able to react via iminium ion or dienamine intermediates in 1,3-dipolar cycloaddition with azomethine imines. The use of **Cat.1** (Scheme 10) promotes dienamine-



Scheme 10. Formation of optically active tricyclic compounds facilitated by dienamine catalysis.



Scheme 11. Direct access to multifunctionalized norcamphor scaffolds through asymmetric organocatalytic Diels–Alder cycloaddition.

catalyzed cycloaddition, leading to the corresponding tetrahydroisoquinoline derivatives **20b** with good yields and stereoselectivities.[27] In general, this strategy represents an important methodology for diversification of skeletons of this type through both activation modes.

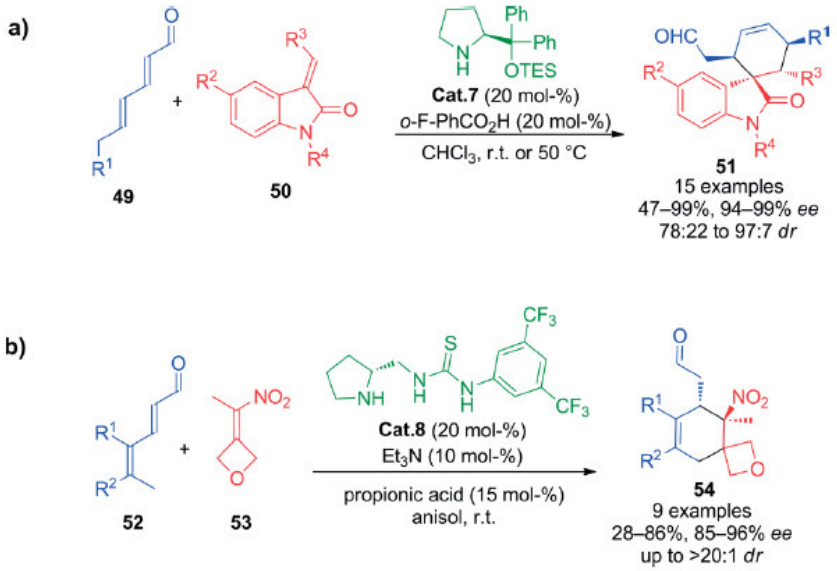
Although enamine catalysis has been widely used with aldehydes as precursors, α-enolizable α,β-unsaturated ketones such as **46** have been also incorporated to form cross-dienamine intermediates. Using this approach, Jørgensen et al. developed a simple but important strategy for access to norcamphor derivatives in good yields and with high levels of stereocontrol (Scheme 11).[40] Bicyclo[2.2.1]heptane scaffolds **48** are present in a large number of natural and synthetic compounds with a variety of biological activities, including antiviral, antifungal, antidiabetic, etc.

ApDOS with Trienamine Catalysis

It can be argued that a significant region of chemical design space is occupied by mono- and polycyclic structures and heterocycles with diverse substitution and functionalization patterns. Cycloaddition reactions and their formal variants still constitute one of the most prominent methods for ring annulation. To this end, aminocatalysis provides a unique opportunity for the assembly of enantioenriched cyclohexenes through formal asymmetric [4+2] cycloaddition.

In 2011 it was first demonstrated that optically pure amine **Cat.7** (Scheme 12a) and prochiral dienals **49** could form trienamines in situ, and that these could react with dienophiles **50** through a formal Diels–Alder pathway.[41] The process is believed to be stepwise, involving initial addition of the trienamine – at its remote alkene with the involvement of a *s-cis* configuration of its distal diene fragment – to the dienophile to form a high-energy zwitterionic species. This intermediate then undergoes rapid 1,4-addition to complete the annulation. As a proof of concept, olefinic oxindoles **50** were successfully used as dienophiles in this synthetic strategy, furnishing cyclohexenes **51**, each containing an all-carbon quaternary center, in high yields and with excellent enantiomeric excess (Scheme 12a).[41] This strategy was further explored to include the use of a range of various carbon-based dienophiles to form a plethora of diverse chemical libraries based on a cyclohexene core structure. An interesting example is the use of trisubstituted nitroolefins **53** as reaction partners to furnish highly enantioenriched spirocyclohexene oxetanes **54** with good yields and stereocontrol (Scheme 12b).[42]

Heterocycles play a pivotal role in medicinal chemistry, and hetero-Diels–Alder cycloaddition represents one of the most fundamental strategies for the assembly of six-membered het-

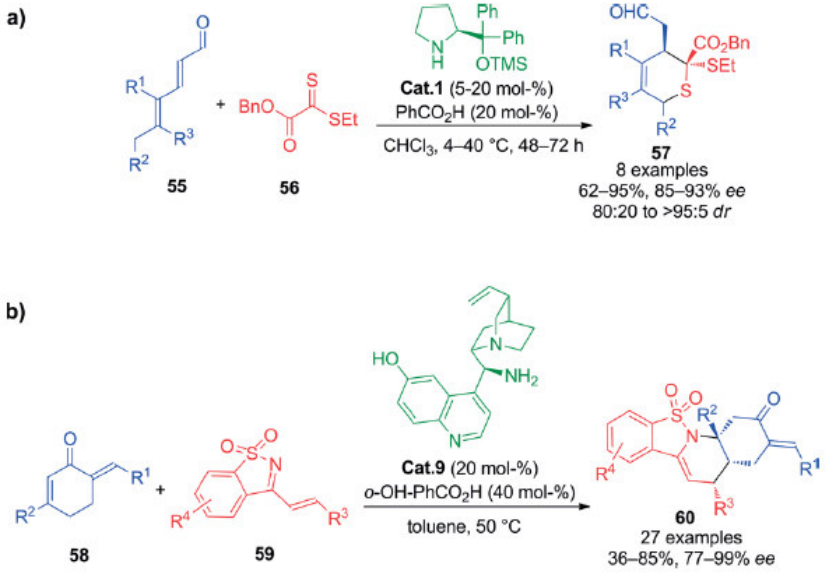


Scheme 12. (a) First use of trienamines in asymmetric organocatalytic Diels–Alder cycloaddition. (b) Cycloaddition between trisubstituted nitroolefins and dienals.

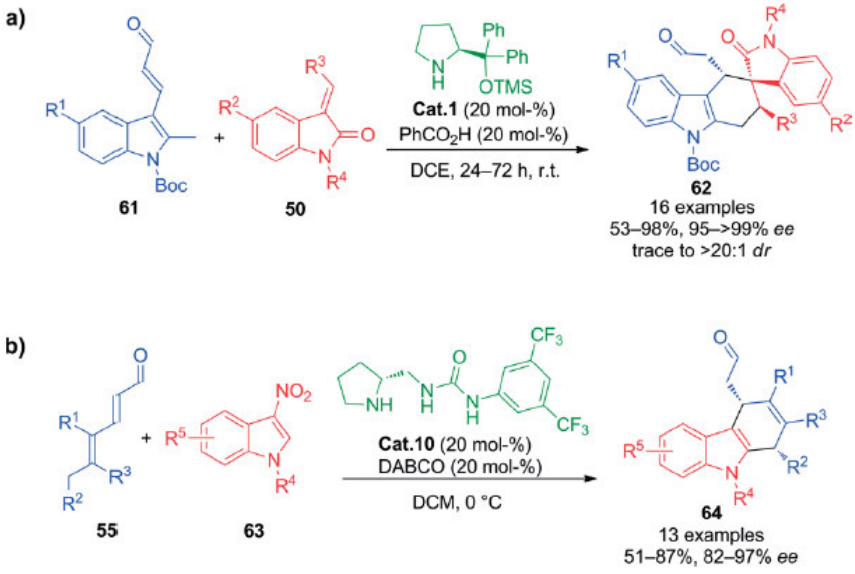
erocyclic structures. Trienamine catalysis has also been successfully utilized in the exploration of this chemical design space, with the use of dithioesters **56** as heteroatom-centered dienophiles to furnish products **57** in good yields and with excellent enantiomeric excess (Scheme 13a).[43] An alternative strategy involving reaction between catalyst-bound trienamine intermediates (generated in situ) and heterodienes was demonstrated on treatment of dienones **58** with **59** in the presence of **Cat.9** to furnish cycloadducts **60** with good yields and stereoselectivities (Scheme 13b).[44]

The indole motif is found abundantly in many natural products and biologically active compounds and represents one of the most important classes of heterocyclic compounds in life science. Trienamine catalysis can be used to create diverse libraries of fused polycyclic structures containing the indole motif. One strategy is to use compounds **61** as substrates; in the presence of **Cat.1** this leads to the in situ generation of heterocyclic *ortho*-quinodimethanes by dearomatization of the indole ring. Subsequent reaction with suitable dienophiles **50** leads to the formation of highly enantioenriched fused indole derivatives **62** in good yields (Scheme 14a).[45]

A different approach is to use 3-nitroindoles **63** as indolyne equivalents. These undergo formal Diels–Alder cycloaddition with dienals **55**, via trienamine intermediates, to form cycloadducts that readily eliminate and rearomatize to form **64** with good enantioselectivities and yields (Scheme 14b).[46]

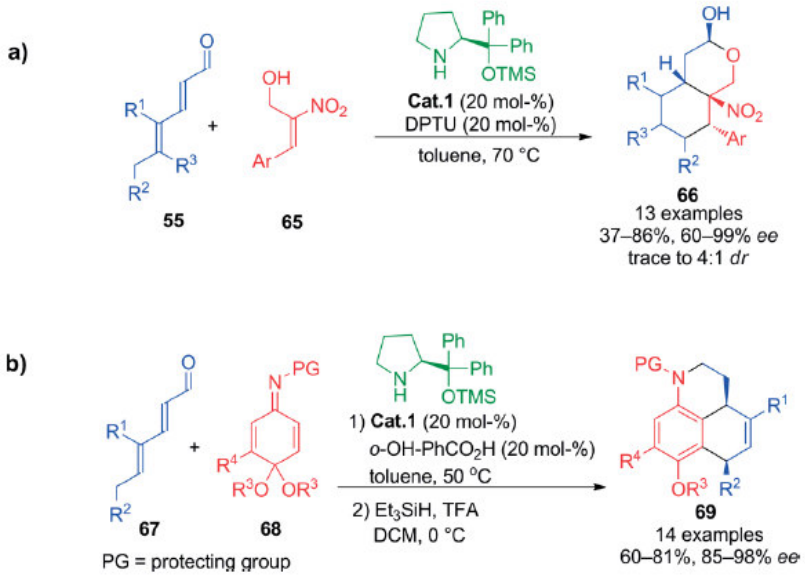


Scheme 13. (a) Trienamine-catalyzed thio-Diels–Alder cycloaddition. (b) Cross-conjugated trienamine-catalyzed aza-Diels–Alder cycloaddition.

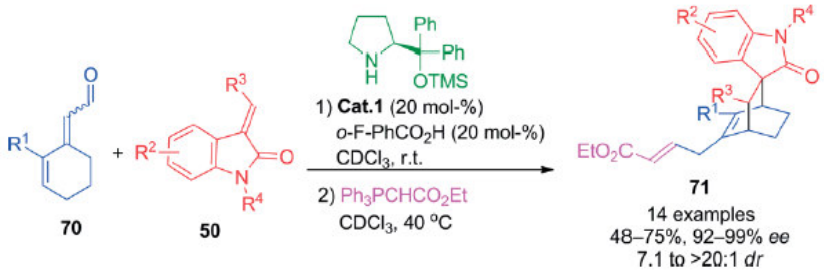


Scheme 14. (a) Trienamine-catalyzed Diels–Alder cycloaddition with heterocyclic *ortho*-quinodimethanes generated in situ. (b) Aminocatalytic [4+2] cycloaddition between dienals and 3-nitroindoles facilitated by trienamine catalysis.

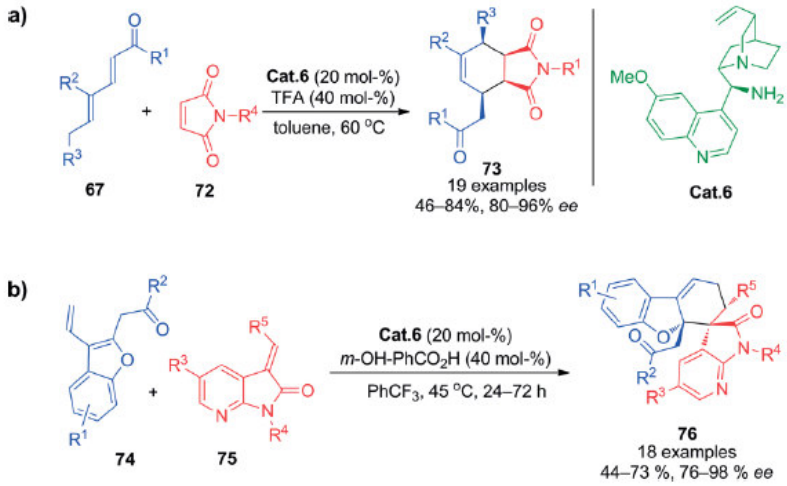
Trienamine catalysis can also provide a facile route to diverse carbon-centered polycyclic structures. One strategy is to utilize the fact that the formal cycloadducts of trienamine-mediated reactions contain aldehyde moieties, which can undergo further cyclization reactions. Thus, incorporation of dienophiles that bear addition nucleophilic functionalities could provide simple



Scheme 15. (a) Asymmetric [4+2] cycloaddition/nucleophilic ring-closing reaction cascade sequence. (b) Organocatalytic Diels–Alder cycloaddition/aromatization/intramolecular hemiaminal formation domino sequence.



Scheme 16. First cross-trienamine-mediated asymmetric synthesis of bicyclic compounds.



Scheme 17. Cinchona-based amine-catalyzed Diels–Alder cycloaddition, aided by trienamine activation, between dienones and (a) *N*-substituted maleimides, or (b) 3-olefinic-7-azaoxindoles.

access to structurally diverse polycyclic compounds. Two examples of this strategy are illustrated in Scheme 15, which shows the rapid formation of highly enantioenriched hydroisochromenes **66** and benzo[*de*]quinolones **69** by trienamine catalysis followed via an *O*- and *N*-centered nucleophilic ring closure, respectively.[47,48]

Instead of fused polycyclic structures, the formation of enantioenriched bridged bicyclic compounds can also be driven by chiral amine catalyst through the generation of cross-trienamines in situ. This was demonstrated for reactions between cyclic dienals **70** and different dienophiles to furnish highly enantioenriched products **71** in good yields (Scheme 16).[49]

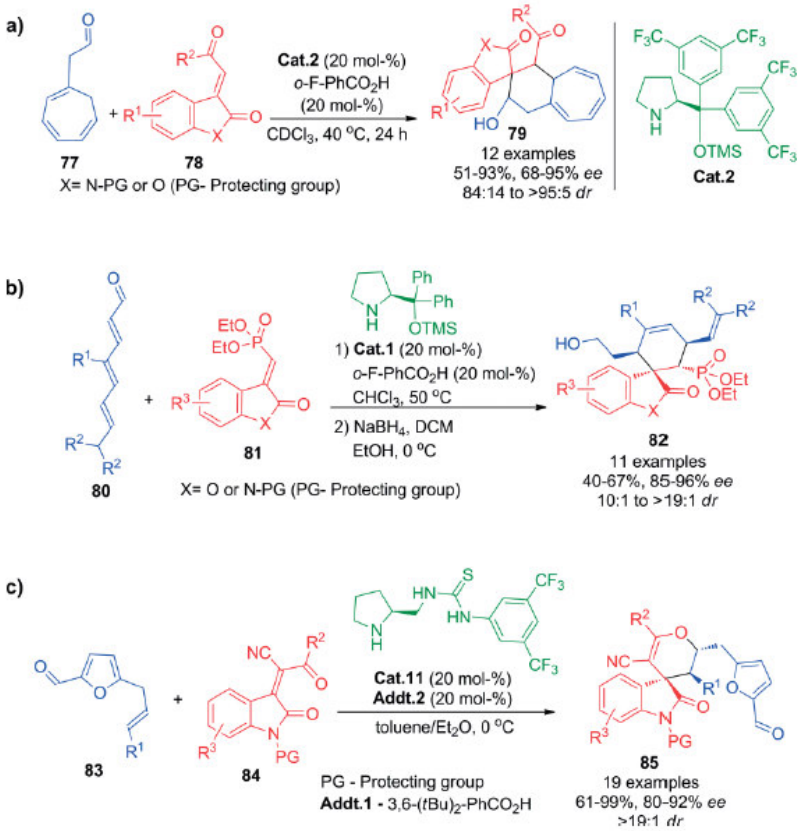
Although most trienamine catalysis has been achieved with aldehyde substrates as precursors for the generation of catalyst-bound trienamines in situ, the incorporation of ketones as substrates has also been shown to be viable. This further diversifies the complexity and variability with which trienamine catalysis can be used in ApDOS. Examples of this strategy are shown in Scheme 17. Intriguingly, despite multiple reactive site and/or enolization possibilities the desired products **73** and **76** are formed with good yields and stereoselectivities.[50,51]

ApDOS with Tetraenamine Catalysis

The knowledge that HOMO activation can be extended to dienamine and trienamine pathways, depending on the conjugation in the carbonyl group, meant that the tetraenamine activation mode also came to be viewed as offering new opportunities for challenging transformations. Despite the inherent problems associated with the reactivity and regioselectivity of species of this type, two methodologies have been successfully developed. In these two approaches, cyclic and linear trienals **77** and **80**, respectively, were specifically designed to react with olefinic oxindoles **78** and **81**, leading to the formation of spirocyclic oxindoles **79** and **82**, respectively, with high levels of stereocontrol and good yields.

Although the first report is limited to the aldehyde **77**, the molecular diversity comes from the different substitution patterns that can be introduced in the olefinic oxindoles **78** (Scheme 18a).[52] In the second methodology, the regioselectivity was controlled by introducing appropriate substituents in the trienal skeleton of **80** (Scheme 18b).[53] In both cases, benzofuranones can be also incorporated in place of oxindoles, thus improving the diversity of the libraries.

Prior to the publication of the present contribution, a new methodology for the construction of spirooxindoles aided by tetraenamine catalysis was reported. In that study, the tetraenamine intermediates were generated through the dearomatization of 5-allylic furfural derivatives **83** in the presence of **Cat.11** (Scheme 18c). Then the remote ζ,η-double bond was able to participate in IED oxa-Diels–Alder cycloaddition, leading to the corresponding spirooxindoles **85** with moderate to good yields and good stereoselectivites (Scheme 18c).[54]



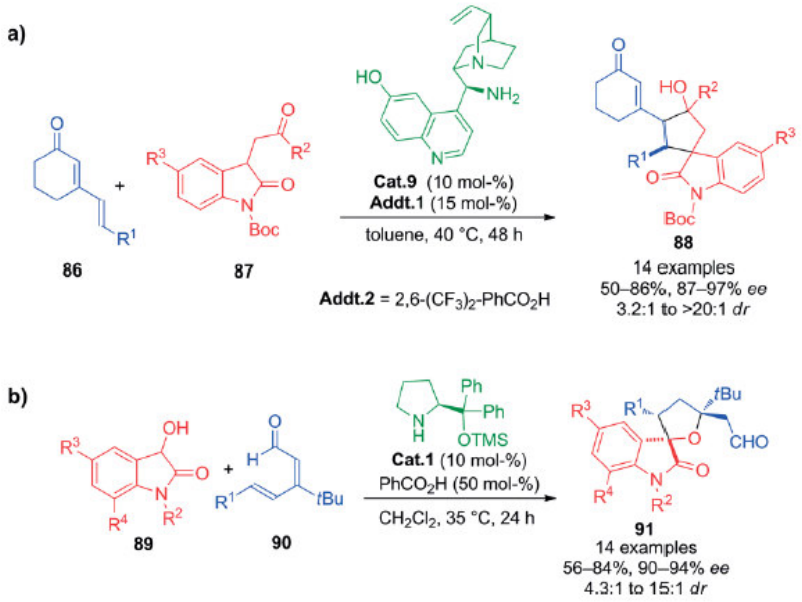
Scheme 18. Aminocatalytic cycloadditions aided by tetraenamine activation.

ApDOS with Vinylogous Iminium Ion Catalysis

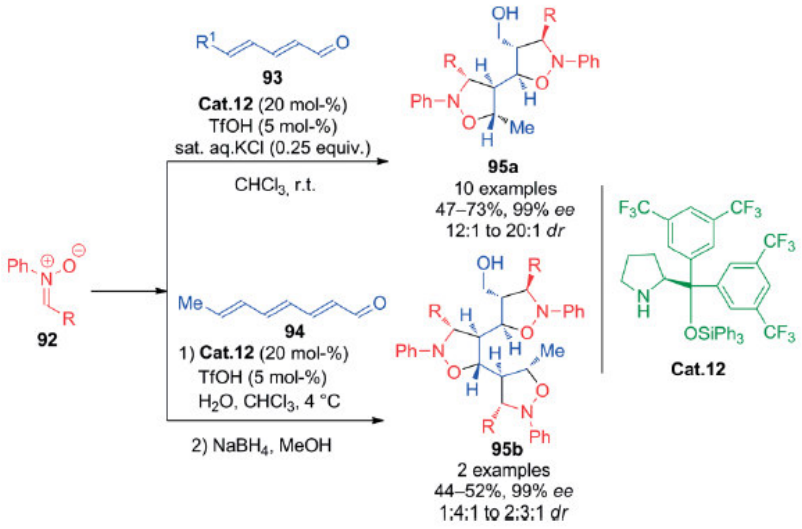
The success of aminocatalytic activation modes using the LUMO lowering effect is well documented in asymmetric synthesis. When the development in asymmetric aminocatalysis met the principle of vinylogy, a new activation mode, named vinylogous iminium ion catalysis, was created.[55] In previous work, iminium ion catalysis has served as a preeminent tool for the synthetic community to build complex natural products and bioactive frameworks.

The strategy of vinylogous iminium ion activation added some important features to the development of aminocatalysis. In 2013, Melchiorre et al. reported an important cascade process for the preparation of spirocyclopentane oxindoles **88** from cyclic dienones **86** and 3-substituted oxindoles **87** with excellent yields and high enantioselectivities (Scheme 19a).[56] This strategy enables the production of optically active spirocyclopentane oxindoles **88** in only one step. Later the same group demonstrated aminocatalytic 1,6-addition between oxindoles **89** and linear 2,4-dienals **90** facilitated by vinylogous iminium ion activation for the synthesis of tetrahydrofuran spirooxindoles **91** (Scheme 19b).[57]

Since 2000, iminium-ion-mediated 1,3-dipolar cycloaddition between nitrones and enals has served as an established pathway for the synthesis of isoxazolidines. This inspired further development of the concept, in which 2,4-dienals **93** and 2,4,6-



Scheme 19. (a) 1,6-Addition/intramolecular aldol condensation cascade sequence via vinylogous iminium ion intermediates catalyzed by a cinchona-based primary amine. (b) Synthesis of a tetrahydrofuran spirooxindole scaffold via vinylogous iminium ion intermediates.



Scheme 20. First vinylogous and bis-vinylogous iminium ion intermediates in the synthesis of bi- and tri-isoxazolidine frameworks through double and triple cascade 1,3-dipolar cycloaddition.

trienals **94** were subjected to double and triple 1,3-dipolar cycloaddition cascades, leading to bi- and tri-isoxazolidine derivatives **95a** and **95b** – with six and nine stereocenters, respectively – via vinylogous and bis-vinylogous iminium ions, respectively, with good yields and remarkable stereoselectivities (Scheme 20).[58]

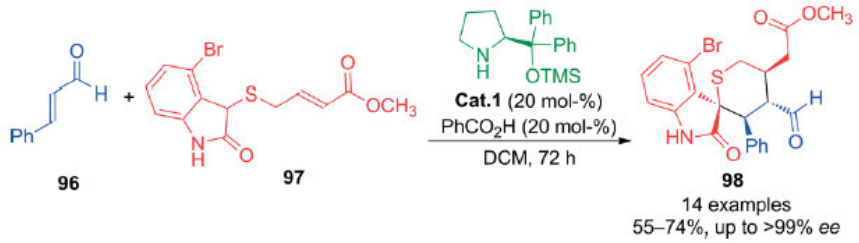
ApDOS based on Aminocatalytic Cascades

The combination of two or more aminocatalytic activation modes in a cascade manner enables the assembly of many useful classes of enantioenriched privileged chemical compounds with high structural diversity. Moreover, such cascade-type reactions may incorporate multiple reactants, which react in a cycle-specific manner, thereby leading to greater amplification of diversity and population of the chemical design space.

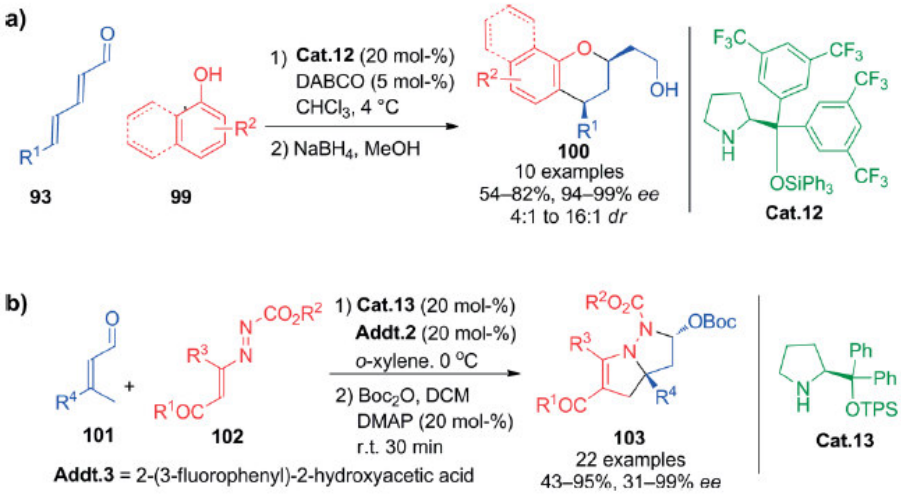
A classical approach to the design of aminocatalytic cascades involves the use of iminium and enamine catalysis. This strategy involves a catalyst-bound iminium ion, which reacts with a nucleophile resulting in the formation of an enamine species. This species will in turn react with an electrophilic reaction partner, leading to the final product after catalyst liberation. In a two-component reaction, the nucleophilic species responsible for the initial iminium-ion-mediated bond formation also bears an inherently electrophilic moiety for participation in the subsequent enamine pathway. An example of such a strategy is presented in Scheme 21,[59] which showcases the synthesis of **98**, a new class of p53-MDM2 inhibitors.

Other approaches to combining two aminocatalytic pathways include sequences involving two iminium ion-mediated cascades and the merger of dienamine and iminium ion catalysis. Scheme 22a shows an example of the reaction of di-nucleophilic species **99**, which first react with dienals **93** by 1,6-addition, followed by 1,4-addition, with both steps activated by a chiral aminocatalyst (**Cat.12**).[60] Scheme 22b shows the synthesis of a class of enantioenriched bicyclopyrazolidines **103** through a dienamine-iminium cascade with β,β-disubstituted enals **101** as reactants.[61]

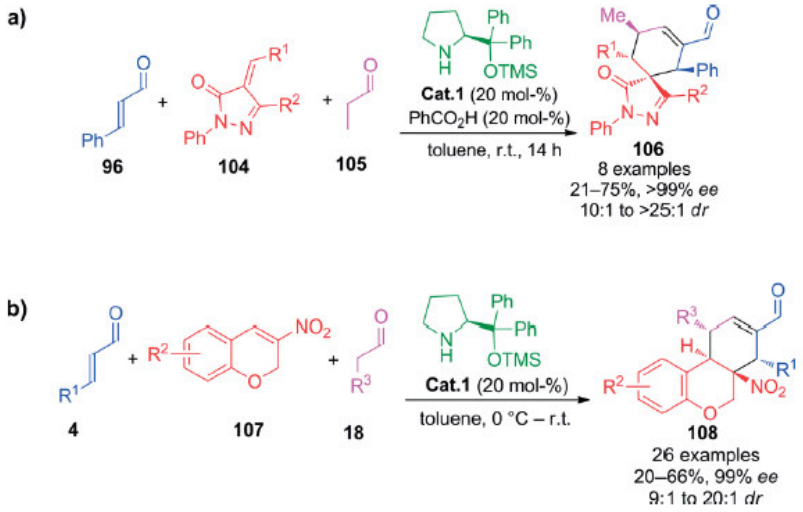
Multicomponent aminocatalytic cascades provide a rapid means for the formation of complex molecular structures with several variable side chains. The combination of activation modes can be designed by selecting suitable reactants. Two examples of three-component triple cascades facilitated by aminocatalysis are shown in Scheme 23.[62,63] Common to these works is the selection of reactants, which includes an enal (either **96** or **4**), a saturated aldehyde, and a Michael acceptor. Both reactions are initiated by the reaction between the saturated aldehyde and the Michael acceptor aided by enamine catalysis (with **Cat.1**). Upon reaction, the reaction intermediate reveals a nucleophilic site, which reacts with the enal compo-



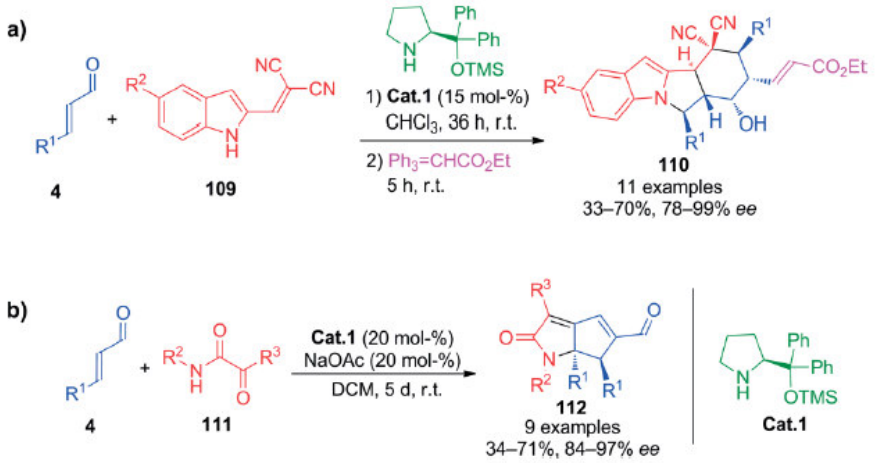
Scheme 21. Organocatalytic asymmetric synthesis of spiro-tetrahydrothiopyran-oxindoles.



Scheme 22. (a) Organocatalytic enantioselective 1,6-Friedel–Crafts/1,4-oxa-Michael cascade sequence. (b) Asymmetric synthesis of bicyclopyrazolidine derivatives from 1,2-diaza-1,3-dienes facilitated by dienamine-iminium activation.



Scheme 23. (a) Organocatalytic synthesis of chiral spiropyrazolones. (b) Organocatalytic triple domino reaction for the synthesis of chromans.



Scheme 24. (a) Asymmetric aza-Michael/Michael/Michael/aldol cascade sequence for the synthesis of polycyclic indole structures. (b) Organocatalytic quadruple cascade sequence for the synthesis of tetraaryl-substituted 2-azabicyclo[3.3.0]octadienones.

nent through the iminium ion pathway. Final ring annulation through a second enamine-mediated reaction furnishes the final products **106** and **108** with good yields and selectivities. It is noteworthy that the starting materials of the two reactions differ only in the nature of the Michael acceptor. However, two structurally different classes of compounds are generated.

Aminocatalytic cascades can be further extended to quadruple cascades. Scheme 24 shows two examples of iminium ion/enamine/iminium ion/enamine cascades, which both proceed in a cycle-specific manner.[64,65] Starting materials in both reaction sequences include two equivalents of an enal component **4** in combination with a reactant that structurally possesses both a nucleophilic and an electrophilic moiety. The initial iminium ion/enamine cascade assembles a cyclic intermediate from one equivalent of the enal **4** and the reactant **109** or **111**. The resulting cyclic intermediate is nucleophilic and adds to another enal **4** molecule in the presence of **Cat.1**. Final enamine-mediated annulation followed by **Cat.1** liberation completes the domino reaction sequence, providing the two highly structurally differentiated classes of products **110** and **112**.

Conclusions

In conclusion, we present a concept article that describes how aminocatalysis, through its different activation modes, contributes to the synthesis and diversification of privileged structures. A concise review with selected contributions from last decade demonstrates the extraordinary progress that has been made in this field. Currently, efforts in aminocatalysis are focused on the development of simple and efficient methodologies for the construction of relevant architectures with increasingly complexity and functionalization. The ApDOS concept represents a general definition of methodologies in which simple, similar compounds are transformed into important frameworks through common reactive intermediates (activation modes). We envision that this concept may attract more attention in this

area. As a consequence, new regions in chemical space can be populated, and libraries of new diverse small-molecule compounds will be available for biological screening.

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Keywords: Aminocatalysis · Diversity-oriented synthesis · Privileged structures · Chemical space · Molecular diversity · Multicomponent reactions · Enantioselectivity

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Appendix II.

Enantioselective synthesis of tetrahydrocarbazoles (THC's) via trienamine catalysis and their anxiolytic-like activity.

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Enantioselective synthesis of tetrahydrocarbazoles (THC's) via trienamine catalysis and their anxiolytic-like activity.

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ABSTRACT

The first study about the anxiolytic activity of two chiral THC´s is presented. The new chiral THC´s were prepared through an organocatalytic strategy via trienamine activation. The *in situ ortho*-quinodimethane species, formed by the condensation of the *N*-protected 2-methylindole acrylaldehyde with a sterically hindred diarylsilylprolinol ether derivative as catalyst, easily participate in a Diels–Alder reaction with the ethyl cyanophenyl acrylate as dienophile, in good yields and excellent stereoselectivity. These THC's showed activity against anxiety and mood disorders that can possibly contribute in the discovery of new drugs. In addition, the use of *N*-protected 2-methylindole acrylaldehyde will set a new base for the synthesis of medically and pharmacologically important THC's via trienamine catalysis.

Chiral tetrahydrocarbazoles (THC's) are the most widely recognized class of natural indole alkaloids.[1] In the interest of its biological and pharmaceutical development which is consistently encouraging the discovery of new efficient synthetic pathways to establish novel chiral THC framework.[2] It has been observed over the century that the discovery of novel chiral THC's always appears with new extraordinary bioactivities as well as bunch of naturally occurring THC alkaloids are found in ancient medicines.[3] For instance, *Dasycarpidone* **I** and *Uleine* **II** exhibited antiplasmodial activity in vitro against *P. falciparum* and *T. cruzi*.[3a-b] Also, a novel synthetic drug with a THC core, the (*R*)-*Ramatroban* **III**, used in the treatment of allergic rhinitis, asthma and coronary artery disease.[3c-d] In the same way, *Fischambiguine B* **IV** showed inhibitory activity against *M. tuberculosis*.[3e] Nevertheless, some great examples of structurally simple synthetic drugs can explain a potential use of THC core, for example, the 1-ethyl-8-*n*-propyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid **V** was found to be a novel anti-inflammatory agent as well as 6-Chloro-1,2,3,4-tetrahydrocarbazole-2-carboxylic acid **VI** was discovered as clinically active in the treatment of acute gout (Figure 1).[3f]

From the past 20 years, it has been observed that depression, anxiety and mood disorder are the cause of morbidity in the developed nations. Hence, the circumstance call for research for the discovery of new drugs or medicines that possess anxiolytic activity with no toxicity and withdrawal effect.[4] In this era, a number of drugs has been reported with this type of activity,

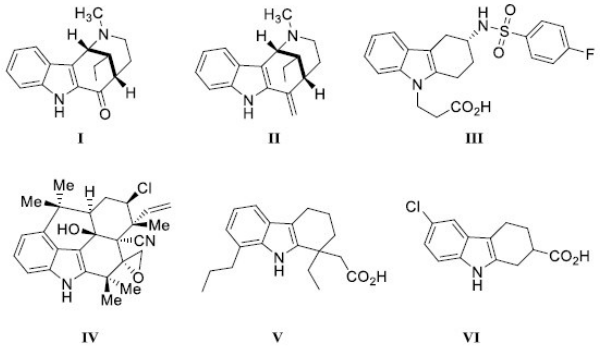


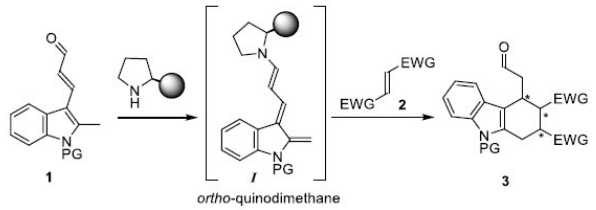
Figure 1. Some examples of THC's that possess potent biological activities

whereas chiral THC alkaloids are pharmacologically important compounds that make worthy to synthesize it and perform biological tests to disclose forbidden activities of these structures.

Consequently, over the past decades, chemists are focusing more towards new methodologies to synthesize known or novel chiral THC frameworks. At the same time, the newly developed trienamine catalysis strategy has attracted considerable attention for the synthesis of chiral privileged structures.[5] In fact, during its conceptualization, a new methodology was developed to synthesize chiral THC´s by using 2-methylindole acrylaldehyde **1** as a masked 2,4-dienal.[6] In this strategy, the condensation of a chiral secondary amine with the acrylaldehyde **1** lead to the formation of a *ortho*-quinodimethane intermediate ***I***, which is an

active trienamine species with the ability to react with a variety of dienophiles **2** and construct different chiral THC derivatives **3** (Scheme 1). Recently, many asymmetric transformations have been reported using this strategy along with the modification of previous reports but none of the chiral THC was studied before.[7]

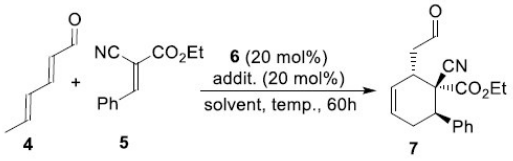
The purpose of this study is to synthesize novel THC's, which can be biologically and pharmacologically important and can be considered as a member of alkaloids. Herein, we report the asymmetric synthesis of two novel THC's efficiently via Diels–Alder cycloaddition reaction. In addition, the resulting THC's turn up with outstanding biological activities, that contribute to the medicinal field.

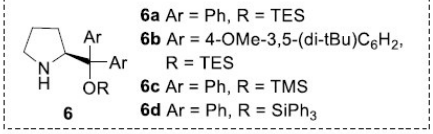


Scheme 1. The concept of THC synthesis via trienamine catalysis

We started this work by analysing the first report of trienamine strategy by Jørgensen.[8] In this study, the 2,4-dienal **4** condense with chiral amine **6a-b** to form the corresponding trienamine intermediate, which through a Diels–Alder cycloaddition with ethyl cyanophenyl acrylate **5** lead to the expected cyclohexene **7** (Table 1, entries 1 and 2). We initiate our work by improving the previous conditions. Initially, we check the reaction with different solvents, with or without additives and by varying the temperature (r.t. to 70 °C). By using toluene as solvent and without additive, the reaction response was satisfied at 70 °C. In the trial of use Jørgensen-Hayashi catalyst **6c**, the stereoselectivity was improved (entry 3). However, to our glad the best results (98% ee and 96:4 dr) were obtained in presence of more sterically hindered catalyst **6d** (entry 4). Thus, we improved the stereoselectivity of the reaction far better than the

Table 1. Optimization table

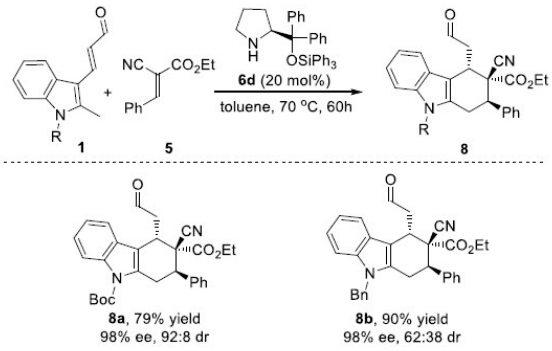




Entry	Cat.	T (°C)	Solvent	Addit	Yield (%)[d]	dr	ee (%)
1[a]	**6a**	50	$CHCl_3$	*o*FBA	81	86:14	89
2[a]	**6b**	50	$CHCl_3$	*o*FBA	87	80:20	86
3[b]	**6c**	70	toluene	-	75	82:18[c]	93[d]
4[b]	**6d**	70	toluene	-	73	96:4[c]	98[d]

[a]Conditions of previous report, [b]reactions were carried out in the scale of 0.1 mmol of dienophile, 0.2 mmol of aldehyde, and 0.02 mmol of catalyst for 60 h. [c]all values were calculated by ^{1}H NMR analysis, [d]detrminated after isolation of the product, by HPLC on a chiral stationary phase.

previous report. Although, best conditions were obtained, subsequently same conditions were tried with *N*-protected 2-methyl indole acrylaldehyde **1** along with individual optimization



Scheme 2. Synthesis novel THC's via trienamine catalysis.

for compound **1** were performed consequently, earlier condition was found to be the best as well (Scheme 2).

Under the optimized conditions, we synthesized two different THC's **8a** and **8b** with different *N*-protecting groups, Boc and benzyl respectively. On the basis of this result as well as by considering the THC motif, we started performing different biological activity tests on **8a** and **8b**.

The findings showed that these THC molecules, orally administered 1h before the experiment, reduced the anxiety-like behaviour in a dose-dependent fashion in Balb/c mice in the cylinder exploratory test (Fig. 2 A and B), which is commonly used for the screening of drugs with anxiogenic or anxiolytic actions in rodents. The maximal effect shown by these compounds were: 72% (25 mg/kg, **8a)** and 83.4% (25 mg/kg, **8b**). These effects were almost comparable to those found with 1.5 mg/kg CNZ. (Fig. 2 A and B). The values for the effective dose 50 were: 3.3 mg/kg (**8a**) and 7.7 mg/kg (**8b**). Molecules **8a** and **8b** slightly reduced the time on the rotarod in a dose-dependent impairment. However, this effect was not significant compared to the vehicle group (Fig. 2C). Only molecule **8b** (100 mg/kg) significantly ($p<0.05$) reduced the time on rotarod at 60 min-post-treatment. However, this was a partial effect since mice recover their motor coordination 60 min later (Fig. 2D).

Although the anxiolytic-like actions of these two molecules were not comparable to those found with CNZ, these two molecules did not significantly affect motor coordination in mice at doses lower than 25 mg/kg (Fig.2). Pre-treatment with 0.7 bicuculline (an antagonist of GABAA receptor) partially abolished the anxiolytic-like effects of molecules 8a and 8b, whereas pre-treatment with ketanserin (a blocker of 5-hydroxytryptamine 2 receptor) or yohimbine (an α2-adrenoceptor blocker) did not change the anxiolytic-like effects of molecules 8a and 8b (Fig. 3). These findings suggest the partial participation of the GABAergic system in the anxiolytic-like actions of molecules **8a** and **8b**. However, other studies will confirm this hypothesis.

Our results showed that these THC molecules possess anxiolytic-like activity and can be used as lead compounds in the drug discovery area. In further studies, the anxiolytic-like activity of molecules 8a and 8b will be corroborated in other models of anxiety-induced in rodents. Also, the trienamine methodology for the synthesis of THC will set a new base for the organic chemists to contribute to the medicinal field as it is necessary to uncover this kind of chiral THC compounds and their biological activities.

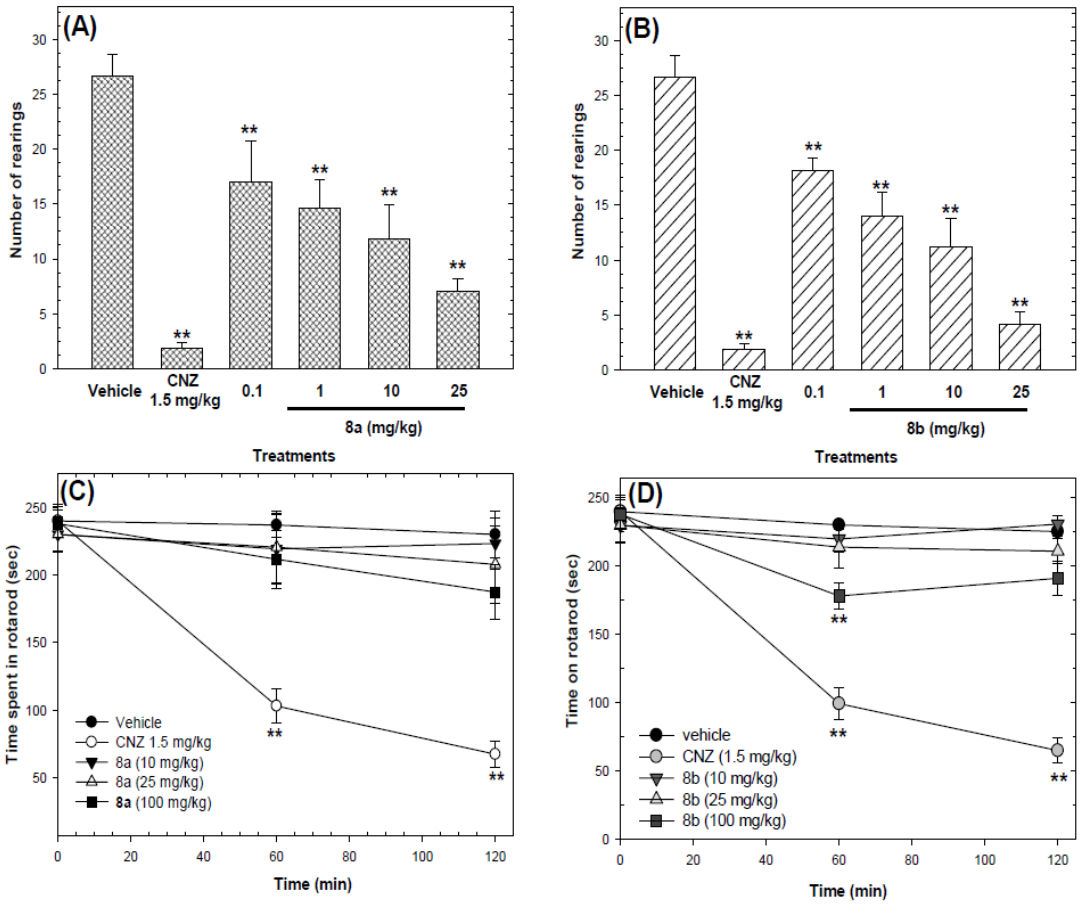


Figure 2. Anxiolytic-like and locomotor effects of molecules **8a** and **8b**. The anxiolytic effects of **8a** and **8b** (0.1–25 mg/kg p.o.) were evaluated using the cylinder exploratory test, recording the number of readings (A and B). The effects of **8a** and **8b** (10-100 mg/kg) on locomotion in mice were evaluated with the rotarod test (C and D). Additional groups were administered with 1.5 mg/kg clonazepam (CNZ) as the positive control or the vehicle (saline solution). Data are demonstrative of two parallel experiments (n = 8). Results represent the mean ± standard error media (SEM). ** represents $p \leq 0.05$ in comparison to the vehicle group, using ANOVA and Dunnett´s *post hoc* test.

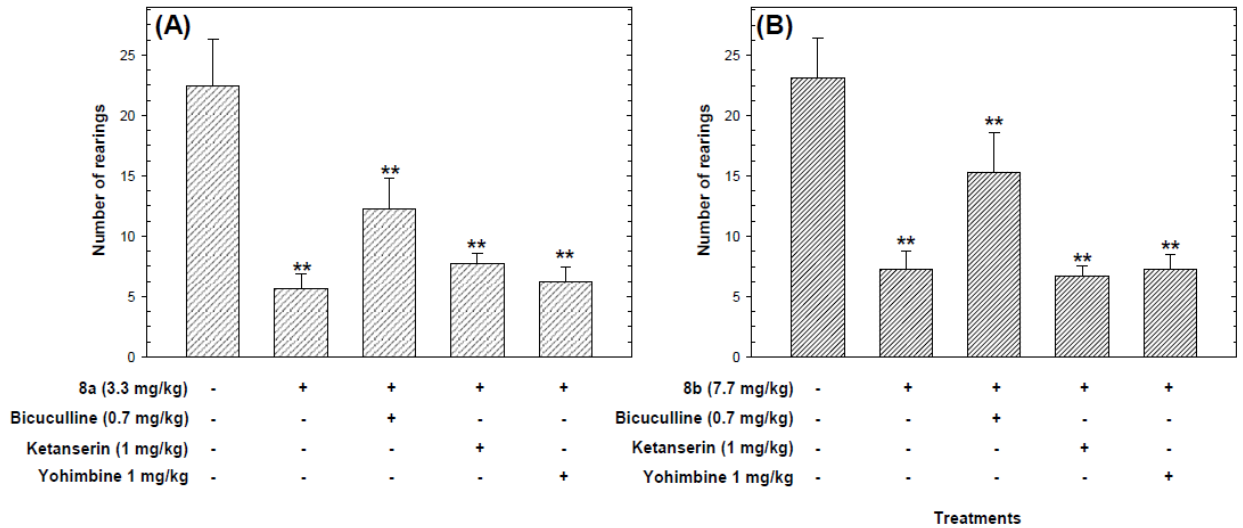


Figure 3. Possible mechanism of action of the Anxiolytic-like effects of molecules **8a** (A) and **8b** (B) in the cylinder exploratory test during 5-min exposure. Bars represent mean values (± SEM) for the experimental group. ** P<0.05, compared to the vehicle group.

Acknowledgments

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Appendix III.

BODIPY as electron withdrawing group for the activation of double bonds in asymmetric cycloaddition reactions

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BODIPY as electron withdrawing group for the activation of double bonds in asymmetric cycloaddition reactions†

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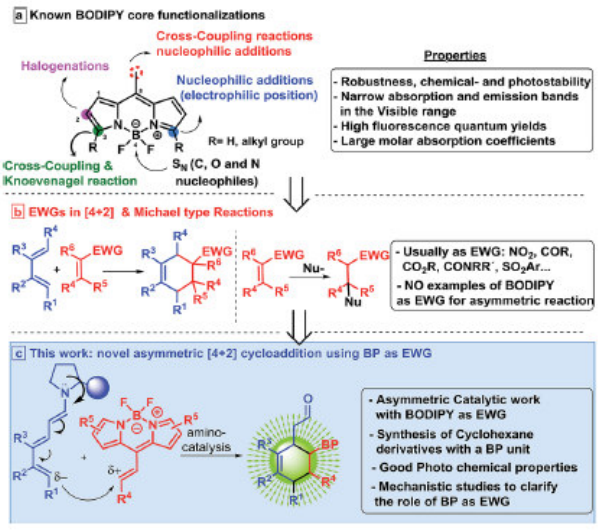
In this work we have found that a BODIPY can be used as an electron withdrawing group for the activation of double bonds in asymmetric catalysis. The synthesis of cyclohexyl derivatives containing a BODIPY unit can easily be achieved *via* trienamine catalysis. This allows a new different asymmetric synthesis of BODIPY derivatives and opens the door to future transformation of this useful fluorophore. In addition, the Quantum Chemistry calculations and mechanistic studies provide insights into the role of BODIPY as an EWG.

Introduction

BODIPY dyes (BOron DIPYrromethene) are a remarkable family of fluorophores that have been studied in recent years due to their excellent robustness, and chemical- and photo-stability.[1] The structure of the BODIPY derivatives is formed by two pyrrole units linked by a carbon and complexed with a di-substituted boron atom, mainly a BF_2 motif, which forms the core scaffold (see top, Scheme 1). They show impressive spectroscopic properties such as narrow absorption and emission bands in the visible wavelength range, high fluorescence quantum yields and large molar absorption coefficients among others.[1b,2] As a result of these interesting characteristics, this class of fluorophores has attracted a lot of attention due to their numerous applications, for instance, as labelling reagents, in the bioimaging of living cells,[3] as radiotracers for positron emission tomography,[4] photocatalysts[5] or photodynamic therapy (PDT).[6] In addition, the introduction of stereogenic centres in these type of structures is of great importance as it is possible to modulate the BODIPY photophysics. Therefore, chiroptical applications based on circular dichroism (CD) and circularly polarized luminescence (CPL) can be used in devices for optical storage and enantioselective CPL sensors, among others.[7a,b]

Different modes of functionalization of BODIPY dyes have been described in the literature. They present eight different positions that can be modulated, causing changes and modifications of the spectral and photochemical properties.[1,7c] Initial studies into the reactivity and derivatization of these important building blocks have been carried out by Werz,[8a,b] Ziessel,[8c]



Scheme 1 Background and present work in the [4 + 2] cycloaddition reaction *via* trienamine with alkenyl BODIPY derivatives (BP = BODIPY).

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† Electronic supplementary information (ESI) available. CCDC 1880124. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc00959k

Shinokubo,[8d] Burgess,[8e] Liras,[8f] Bröring,[8g] de la Moya,[8h,i] and us.[8j]

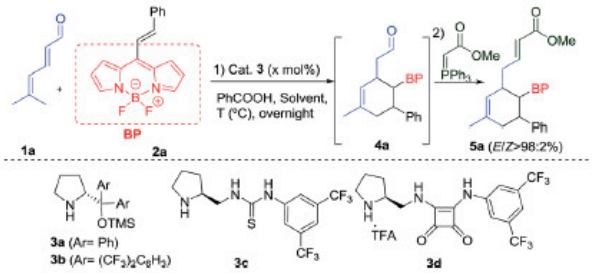
However, in spite of these efforts, very little is known about the catalytic asymmetric synthesis of BODIPY derivatives. Two main reactivities can be found: aromatic type reactivities (see top Scheme 1 coloured green, pink and blue), which are related to the direct regioselective halogenations that can be performed at different positions,[9] aromatic substitutions,[10] as well as cross-coupling reactions;[11] and reactivity at the methyl of the methylene bridge, the most acidic position (see top Scheme 1 coloured red), although the number of these examples is scarce.[1a,11] This latter position can be deprotonated and can react with diethyl ketomalonate,[8a] or aldehydes.[12] Moreover, de la Moya group have shown that boron functionalization can be easily achieved as well, introducing different alcohol or amine derivatives.[8h,i]

One of the most used strategies to polarize double bonds in asymmetric catalysis is the employment of Electron Withdrawing Groups (EWGs, middle Scheme 1), which decrease the energy of the LUMO, thus favouring the interaction with the HOMO of the nucleophile. This strategy has been widely used for Michael-type nucleophilic additions or stepwise [4 + 2] cycloadditions. For this latter reaction, trienamine catalysis[13] has shown to be one of the most prominent strategies,[14] using double bonds activated with nitro,[14c,d] azlactones[14a] or cyanoacetate groups[14b] as dienophiles (middle Scheme 1). These authors have described this [4 + 2] reaction as an asynchronous cycloaddition,[15] *via* a Michael addition followed by an intramolecular iminium ion reaction. In all these examples, very strong EWGs, *e.g.* nitro group, or two nitriles, at the double bond were used in order to achieve the desired reactivity. Therefore, based on electron-withdrawing character of the BODIPY core,[16] we wondered if it would be possible to use this interesting fluorescent moiety as an EWG of a double bond located at the 8-position to perform an asymmetric [4 + 2] cycloaddition (bottom Scheme 1). In this work, we describe the catalytic asymmetric synthesis of chiral BODIPY cyclohexane derivatives, using trienamine aminocatalysis *via* a Diels–Alder reaction (Scheme 1c). In addition, the optical properties of the adducts and DFT calculations, which explain the mechanism and the role of the BODIPY as an EWG have been performed.

Results and discussion

We started the present study with the reaction between the dienal **1a** and the BODIPY **2a** in the presence of the Jørgensen–Hayashi catalyst **3a** in chloroform at room temperature. We

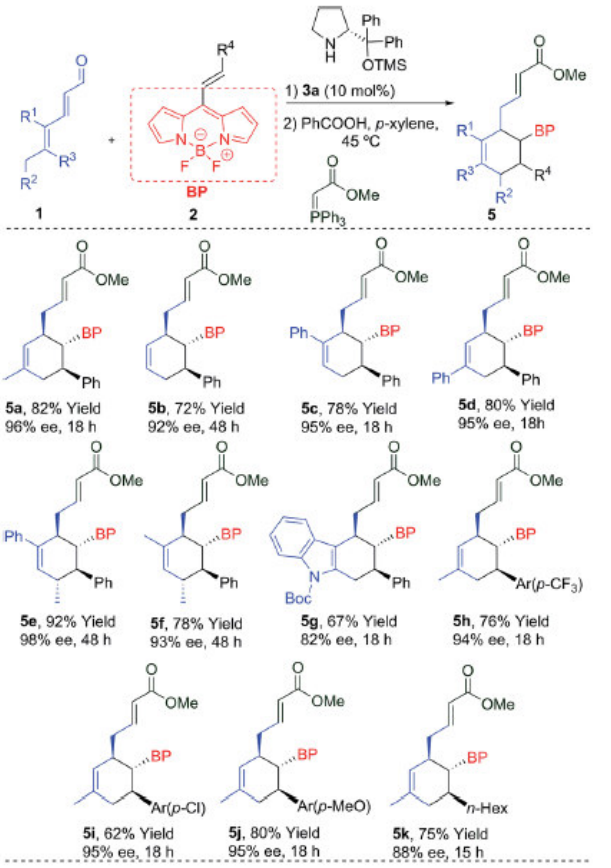
Table 1 Screening of reaction conditions for the synthesis of **5a**[a]



Entry	Cat. [mol%]	Solvent	Temp (°C)	Conv[b] (%)	ee[c] (%)
1[d]	**3a** (20)	$CHCl_3$	rt	9	—
2	**3a** (20)	$CHCl_3$	rt	32	92
3	**3a** (20)	$CHCl_3$	45	100	84
4	**3b** (20)	$CHCl_3$	45	n.r.	—
5	**3c** (20)	$CHCl_3$	45	n.r.	—
6	**3d** (20)	$CHCl_3$	45	n.r.	—
7	**3a** (20)	CH_2Cl_2	45	15	n.d.[f]
8	**3a** (20)	THF	45	c.m.[e]	—
9	**3a** (20)	Toluene	45	100	94
10	**3a** (20)	*p*-Xylene	45	100	96
11	**3a** (10)	*p*-Xylene	**45**	**100 (82)**[g]	**96**
12	**3a** (5)	*p*-Xylene	45	10	n.d.[f]

[a] 0.05 mmol of **2a**, 0.13 mmol of **1a** in 0.5 mL of the indicated solvent and the same amount of $PhCO_2H$ as catalyst loading. [b] Conversion and *Z*/*E* ratio determined by ^1H NMR analysis of the crude mixture. [c] Determined by SFC. [d] Without $PhCO_2H$. [e] Complex mixture. [f] Not determined. [g] Isolated yield after FC in brackets.

Table 2 Scope of reaction with different aldehydes **1** and BODIPYs **2**[a]



[a] Conditions: 0.1 mmol of **2**, 0.25 mmol of **1**, 10 mol% of **3a** and 10 mol% of $PhCO_2H$ in 1.0 mL of *p*-xylene. Enantiomeric excess determined by SFC.

found that the reaction gave the desired product **5a** with a very low conversion (entry 1, Table 1). In order to improve this preliminary result, we tested the addition of benzoic acid as an additive (entry 2), increasing the conversion to 32%. Latterly, when the temperature was increased to 45 °C, full conversion was achieved (entry 3). Following this, different aminocatalysts **3b–d** were tried (entries 4–6). Interestingly, the bulkiest catalyst **3b** or the hydrogen bond type catalysts **3c** and **3d** did not provide any conversion to the product **5a**. Different solvents under **3a** catalysis were then examined (entries 7–10). Chlorinated solvents and THF gave only modest results, but very apolar solvents such as toluene and *p*-xylene provided full conversions and very high enantioselectivities (94 and 96% ee). The catalytic loading was decreased to 10 mol%, achieving the

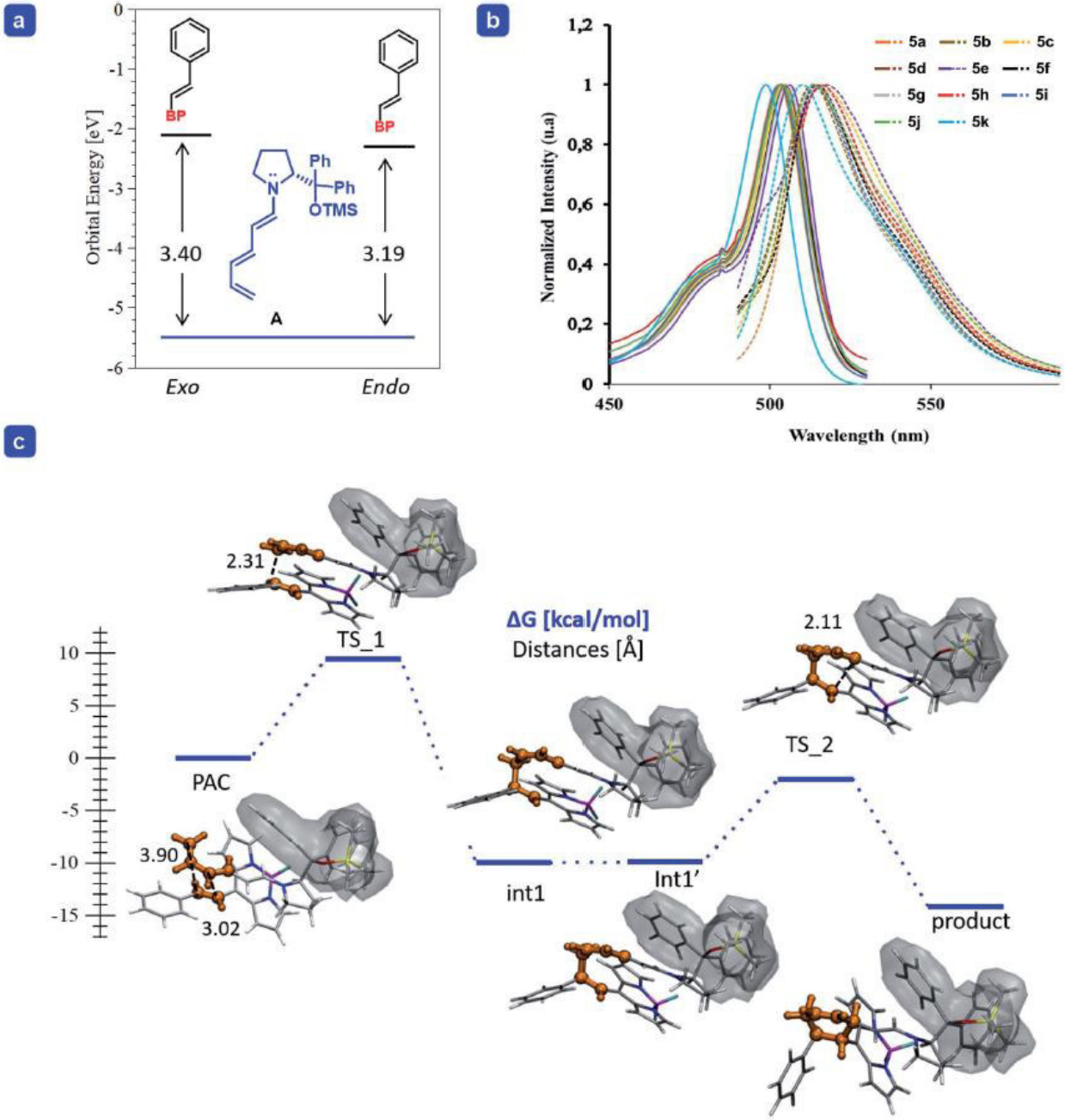


Fig. 1 (a) Energy (in eV) of the frontier molecular orbitals calculated for trienamine **A**, and the BODIPY **2a** for the *endo* and *exo* approaches. (b) Absorption and emission (dash-line) spectra of BODIPYs **5a–k** (see ESI for details†). (c) Gibbs free energy profile of the *endo*-[4 + 2] cycloaddition of the trienamine formed from **1b** and catalyst **3a** to the double bond **2a**. The reactive part is highlighted in orange and the shadow wraps the catalyst. Energies in kcal mol^{-1}. Geometry optimization was carried out at the M06-2X/6-31G(d,p) level of theory and single point energies including solvent at the $SMD_{(p\text{-xylene})}$/M06-2X/6-31+G(d,p) level of theory.

product **5a** with 96% ee, full conversion, and 82% isolated yield (entry 11). However, when the catalyst loading was 5 mol%, only 10% conversion was found (entry 12). Once the best conditions had been determined, we carried out the scope of the reaction using different aldehydes **1** and BODIPYs **2** (Table 2).

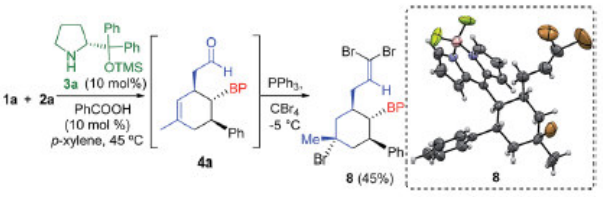
The reaction worked even when all substituents were hydrogen ($R^1 = R^2 = R^3 = H$), giving **5b** with a 92% ee and a 72% yield. The cyclohexanes **5c** and **5d**, with different substitutions at R^1 or R^3 (Ph), were also obtained with excellent yields and enantioselectivities after 18 h. An additional stereogenic centre can be also obtained using **1e** ($R^1 = Ph$, $R^2 = R^3 = Me$) and **1f** ($R^1 = R^2 = R^3 = Me$), that allows access to the products **5e** and **5f** with complete stereocontrol at the four stereogenic centres. An interesting indole derivative **5g** was obtained with a very good ee and a good yield. The use of different EDGs (*p*-MeO) and EWGs (*p*-CF_3 or *p*-Cl) at the aromatic ring of the double bond, gave the final products **5h–j** with good results. Aliphatic derivatives (**5k**) were also tolerated. We also measured the absorption and emission spectra of these new BODIPYs (**5a–k**), which are comparable with other previously related derivatives,[1b,7] described in the literature (top-right, Fig. 1b).

The absolute configuration was determined by derivatization of the intermediate **4a**, yielding the olefin **8** with concomitant bromination of the cyclohexene double bond (Scheme 2). Therefore, we assigned the configuration of compounds **5** as 1′*S*, 2′*S*, 3′*R* using X-ray analysis.[17]

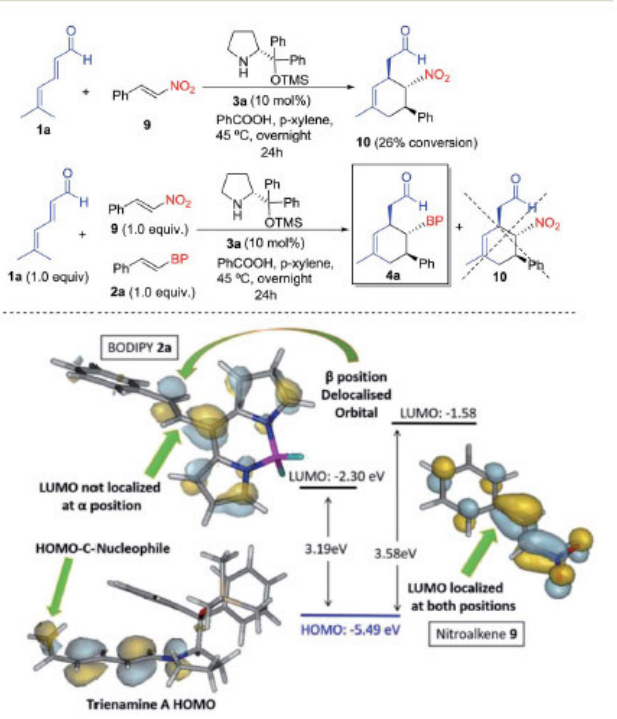
In order to shed light onto the reactivity, we performed a Frontier Molecular Orbital (FMO) analysis, using the density functional theory (DFT),[18] frequently employed to explain the reactivity in pericyclic reactions[19] as in the one presented here (for more details see ESI†). The orbitals of the reagents in the ground state are used to predict the way the reaction proceeds (both orientation and reaction rate). The addition of trienamine **A** (**1b**) to the double bond of BODIPY **2a** is governed mainly by the overlap between the Highest Occupied Molecular Orbital of the nucleophile ($HOMO_{trienamine}$) and the Lowest Unoccupied Molecular Orbital of the electrophile ($LUMO_{dienophile}$), leading to the correct orientation. In addition, the HOMO–LUMO energy gap is related to the reaction rate (k), which is enhanced when the gap decreases.[20] Therefore, if we compare the reaction of two different electrophiles with the same nucleophile, the lowest HOMO–LUMO gap will explain the highest catalytic efficiency. The energy difference between the frontier orbitals in the reaction of **A** with **2a**, the energy gap (ΔE = LUMO−HOMO) was higher, and too large, for the *exo*- than for the *endo*-approach (3.40 and 3.19 eV respectively, top-left, Fig. 1a).[21] Therefore, we only considered the reaction energy profile for the *endo*-approach (bottom, Fig. 1c).

We found that the reaction takes place in a stepwise fashion (bottom, Fig. 1c) as reported in previous examples in the literature.[15] Once the pre-association complex (PAC) is formed,[22] the first C–C bond between the terminal carbon of the trienamine **A** and the β-carbon of **2a** is formed with a barrier of 9.5 kcal mol^{-1} (**TS_1**), which is the stereoselective limiting step barrier. Then, after a series of rotations with negligible energy cost (from the intermediate **Int-1** to **Int-1′**) it forms the second C–C bond with a barrier of 7.9 kcal mol^{-1} (**TS_2**) to yield the final adduct which is easily cleaved, *via* hydrolysis, releasing the catalyst **3a** and the desired product **4a**.

Finally, to study the relative reactivity of BODIPY **2a**, we compared its reaction with other known dienophiles in trienamine chemistry such as the nitrostyrene.[14d] The reaction of dienal **1a** with nitroalkene **9** yielded **10** with a 26% conversion after 24 h under the same reaction conditions (top, Scheme 3). We then carried out a competitive reaction between **2a** and **9**, and found that only the BODIPY derivative reacted, without any traces of product **10**, thus highlighting the higher reactivity of **2a**. The origin of this notable difference in the reactivity was analyzed with the frontier orbitals of trienamine **A**, and dienophiles **2a** and **9** (bottom, Scheme 3). The HOMO orbital of trienamine **A** is delocalized over the two central double bonds, between the nitrogen and the terminal nucleophilic carbon atom that will attack the β position of the BODIPY double bond. The LUMO orbital of **2a** is delocalized over the BODIPY with an



Scheme 2 Derivatization of compound **4a** and X-ray analysis of compound **8**.



Scheme 3 Top: reaction and reactivity comparison of BODIPY **2a** with nitroalkene **9**. Bottom: orbital analysis of **2a**, **9** and trienamine **A**.

important contribution at the β position of the double bond and without any contribution at the α position. This explains the regioselectivity, as the β carbon of **2a** is the first to react. However, in the case of nitroalkene **9**, the LUMO orbital is fully delocalized through the molecule with contributions from α and β carbon atoms. In addition, the HOMO–LUMO gap is much lower for **2a** (3.19 eV) than for **9** (3.58 eV). This means that the BODIPY is a better EWG than the NO_2 for this reaction and explains the higher reactivity of the BODIPY derivatives **2** when compared with nitrostyrene **9**.

Conclusions

In conclusion, we have shown that the BODIPY can be used as an electron withdrawing group for the activation of double bonds in asymmetric catalysis. Indeed, the BODIPY acts as a stronger EWG than the nitro group. In this work, we have applied this characteristic for the synthesis of asymmetric cyclohexyl derivatives *via* trienamine catalysis, that contain a BODIPY unit in their structure, allowing a new functionalization of these fluorophores. In addition, we have been able to explain the observed reactivity with Quantum Chemistry calculations, confirming the role of the BODIPY as an EWG in the double bond. The new reactivity here presented can be used in the future for further asymmetric transformations.

Conflicts of interest

There are no conflicts to declare.

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***Note: The spectral information will be provided separately on demand.**