エナンチオ選択的反応に用いる新規ハイブリッド型スクアラミドアミノアルコール有機分子触媒の開発

THE DEVELOPMENT OF NEW HYBRID TYPE SQUARAMIDE FUSED AMINO ALCOHOL ORGANOCATALYSTS FOR ENANTIOSELECTIVE REACTIONS

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Mr. Madhu Chennapuram

Supervisor
Professor Hiroto Nakano

DEPARTMENT OF APPLIED SCIENCES
GRADUATE SCHOOL OF ENGINEERING
MURORAN INSTITUTE OF TECHNOLOGY
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博士論文申請者：工学専攻先端環境創生工学コース：　Madhu Chennapuram
（マデュー チェンアプラム）

博士論文題目：The Development of New Hybrid Type Sqauaramide Fused Amino Alcohol Organocatalysts for Enantioselective Reactions

論文内容要旨

医薬品を含む多くの生物活性化合物は光学活性物質であり，その鏡像異性体は異なる生体内活性を示すことが多いため，有効な一方の鏡像異性体を高選択的に合成するための不斉合成反応の開発が重要である．ごく少量の不斉分子によって触媒化される触媒的不斉合成反応の開発は省エネルギーや環境調和の観点から有機合成化学領域の最も重要な研究課題の一つであり，金属を含有しない有機分子触媒は空気中で安定であり取り扱いやすく安価であるという利点なども有するため，次世代の環境調和型触媒として現在活発に研究開発が行なわれている．

著者は，新規多点認識型有機分子触媒としてアミノアルコールとスクアラミドが融合したハイブリッド型触媒（SFAA 触媒）を設計し，それを，エナンチオ選択的 (1) イサチン類とニトロアルケン類との不斉ニトロアルドール反応，(2) 3-ヒドロキシ-2-ピリドン類とマレイミド類との塩基触媒不斉ディールス・アルダー (DA) 付加環化反応，さらに (3) インダノン類と1,3-ジカルボニル類とのドミノマイケル付加環化反応にそれぞれ適用し，その有機分子触媒としての機能性を検討した．

(1) SFAA 有機分子触媒 **A** を合成し，触媒 **A** を用いるイサチン類とニトロアルカン類との不斉ニトロアルドール反応を検討した．その結果，触媒 **A** が不斉触媒活性を示し，本反応によって優れた化学収率と良好な光学収率で光学活性オキシインドール誘導体を与えることを見出した． 得られるオキシインドール誘導体は，抗癌作用を持つドナキサリジン誘導体などの有用な合成中間体である．

(2) SFAA 有機分子触媒 **A** を用いる 3-ヒドロキシ-2-ピリドン類とマレイミド類との不斉ディールス・アルダー反応を検討した．その結果，触媒 **A** が不斉触媒活性を示し，本反応によってほぼ完全な化学収率と優れた光学収率で光学活性イソキヌクリジン誘導体が得られることを見出した。得られるイソキヌクリジン誘導体は，タミフルなどの抗ウイルス活性化合物の有用な合成中間体である．

(3) SFAA 有機分子触媒 **A** を用いるインダノン類と 1,3-ジカルボニル類との不斉ドミノマイケル付加環化反応を検討した．その結果，触媒 **A** が不斉触媒活性を示し，本反応によってほぼ完全な化学収率と優れた光学収率で光学活性スピロ-2-アミノピラン類が得られることを見出した。得られるスピロ-2-アミノピラン誘導体は，寄生原虫病であるリーシュマニア症に有効な化合物を合成するための有用な合成中間体である．

本研究において著者は，その分子中に「基質との 3 点の水素結合部位と 1 点の塩基性部位を併せ持つ多点認識機能を持つアミノアルコール-スクアラミドハイブリッド型触媒 (SFAA 触媒)」を開発することに成功し，それらが創薬に有効な不斉ニトロアルドール反応，不斉ディールス・アルダー付加環化反応および不斉ドミノマイケル付加環化反応においてそれぞれ良好な不斉触媒活性を示すことを明らかにした．また，本反応によって得られる化合物は様々な医薬品をはじめとする生物活性化合物の合成中間体として有用であることから，本研究の成果は，新薬創製の合成開発研究に大きく貢献できると期待される．

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Research summary

Many biologically active compounds, including pharmaceuticals, are optically active. Often, only one of the enantiomers is required because the enantiomers display different in vivo activities. In pharmaceuticals in particular, differences in the absolute configuration can affect not only the pharmacological activity but also the toxicity. Catalytic asymmetric synthesis, in which a low amount of a chiral molecular catalyst theoretically enables infinite production of an optically active compounds, is among the most important current challenges in organic synthetic chemistry; it is also important in terms of energy saving and environmental friendliness. Environmental effects now have to be considered in chemical syntheses, and environmentally benign organic syntheses have been receiving attention. The chiral catalysts used in catalytic asymmetric syntheses can be divided into two categories: organometallic catalysts and metal-free chiral organocatalysts. Particularly, organocatalysts are stable in air, easy to handle, and inexpensive, so they are being focused on as next-generation, environmentally friendly catalysts.

On these backgrounds, author aimed to develop the new hybrid type squaramide fused amino alcohol (SFAA) organocatalysts. This SFAA organocatalyst was successfully prepared from commercially available amino esters by using simple organic transformations and the catalytic activity were demonstrated in the enantioselective (1) nitroaldol, (2) Diels-Alder and (3) domino Michael addition cyclization reactions.

(1) The enantioselective nitroaldol reaction was established with various isatins and nitromethanes using SFAA organocatalysts. This protocol provides chiral 3-substituted 3-hydroxyoxindoles in excellent chemical yields and high enantioselectivities. The obtained 3-substituted 3-hydroxyoxindoles are important synthetic precursors for many biological active and natural compounds such as donaxaridine (*anti*-cancer drug).

(2) The enantioselective Diels-Alder reaction was established with 3-hydroxy-2-pyridones and maleimides using SFAA organocatalysts. This protocol provides the chiral 4-hydroxyisoquinnuclidines in both excellent chemical yields and enantioselectivities. The obtained chiral 4-hydroxyisoquinnuclidines are synthetic intermediates for many biological active compounds such as oseltamivir phosphate (*anti*-influenza drug).

(3) The enantioselective domino Michael addition cyclization reaction was established with 3-dicyano-2-indanones and 1,3-cyclic carbonyl compounds using SFAA organocatalysts. This protocol provides the chiral spiro-conjugated 2-aminopyrans in both excellent chemical yields and enantioselectivities. The obtained chiral spiro-conjugated 2-aminopyrans are significant synthetic intermediates for many biological compounds such as 2-amino-tetrahydrochromene (*anti*-leishmaniasis).

In this study, author revealed that the new explored new hybrid type squaramide fused amino alcohol (SFAA) organocatalyst having both three hydro-bonding sites and a basic site in the compound with a substrate shows satisfactory catalytic activity in the enantioselective (1) nitroaldol, (2) Diels-Alder and (3) domino Michael addition cyclization reactions. It is expected that this result might be able to greatly contribute the development of new drug and its related compounds.

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Chapter 1

Introduction

1.1 Introduction

The enantioselective organocatalysis is most important and well-explored area in synthetic organic chemistry for synthesizing biological active chiral molecules. Because of its does not involve any toxic metals or costly enzyme catalysts to carry out the stereoselective organic reactions. From the last few years, organocatalysis leading explored into one of the most breathtaking and precipitously emerging area in synthetic organic chemistry.[1,2] The enantioselective synthesis provides a practical and cost-effective synthesis of chiral molecules, but designing of simple and efficient synthetic strategies are interesting and often more challenging.

Author PhD objectives were to design and develop the new hybrid type squaramide fused amino alcohol (SFAA) organocatalysts for asymmetric reactions. The new hybrid type SFAA oragnocatalysts were developed and used in this thesis mainly concentrated on four sections (i) The development new hybrid type squaramide fused amino alcohol organocatalysts, (ii) Nitro-aldol (Henry), (iii) Diels-Alder and (iv) Domino Michael addition cyclization reactions. The brief discovery and applications of these enantioselective reactions are discussed in the following sections.

1.2 Catalysis

The catalysis mainly classified in to three major parts, such as metal, enzyme and organocatalysis. Currently, enantioselective organocatalysis is known as an independent synthetic research area among enantioselective metallic catalysis and enzymatic catalysis for the synthesis of optically active compounds. Among the metal and enzyme catalysis, the organocatalysis gains its own importance's due to non-toxic, availability and easy to synthesis. They are mostly stable under aerobic conditions, and the organocatalytic reactions do not require very dry conditions to carry out the reactions.[3]

1.3 Chirality

According to Mislow,[4] for chiral molecule the definitions is defined as follows "A molecule may be chiral if it is non-identical to its mirror images" if it not obeys the above said definition such compounds are known be achiral, the chirality concept can be also explained by following way, our right and left hands are mirror images of each other, but cannot be superimposed on each other when palms are fronting to the same direction. The below depicted generic chiral amino acid is able to exist as mirror images of each other. (Figure 1).

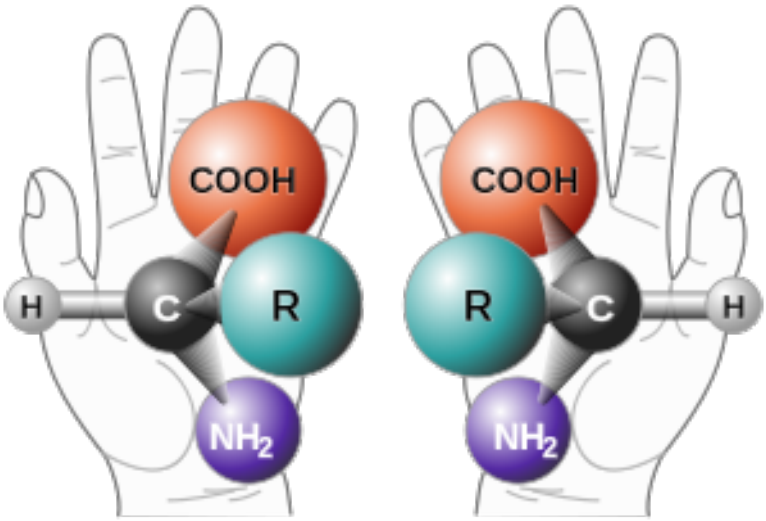


Figure 1. Two enantiomers of a generic amino acids

1.4 Asymmetric synthesis and its importance

Asymmetric synthesis as defined by Morrison and Mosher,[5] is a chemical reaction in which an achiral unit in a group of molecules is converted into a chiral unit, in such course of reaction unequal amounts of stereoisomers are produced. For example, the (*R*)-thalidomide shows the activity towards for morning sickness, while the (*S*)-thalidomide causes the embryo growth restriction or death of embryo (Figure 2).

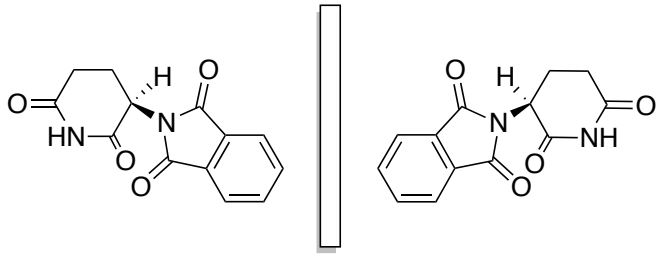


Figure 2. Biological role of thalidomide isomer

Ibuprofen is a nonsteroidal anti-inflammatory drug, in human body its functions as an antipyretic and analgesic agent. Ibuprofen is commonly used for treatment of acute and chronic pain, osteoarthritis, rheumatoid arthritis diseases. The pharmacokinetics of ibuprofen differs as the in form of *R*-(-)-ibuprofen and *S*-(+)-ibuprofen (Figure 3), in which the (*S*)-ibuprofen shows anti-inflammatory activity while (*R*)-ibuprofen is found to be non-active.[6]

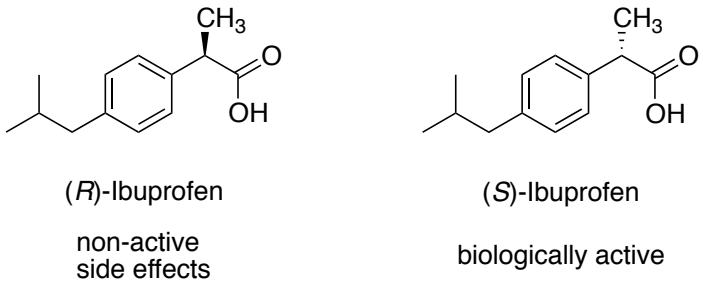


Figure 3. The biological role of ibuprofen isomers

1.5 Advantages of organocatalysis

The advantages of organocatalysis gains its own consideration when compared to metal and enzyme catalysis, because the catalysts are usually inexpensive and easy to synthesis and widely available in a large number, suitable for small-scale to gram-scale reactions, additionally catalysts are non-toxic and eco-friendly. By these own advantages of organocatalysts many researchers are focused in development new class of catalysts for enantioselective reactions. For example, the following organocatalysts are widely and well-studied in the field of synthetic organic chemistry. (Figure 4).[7]

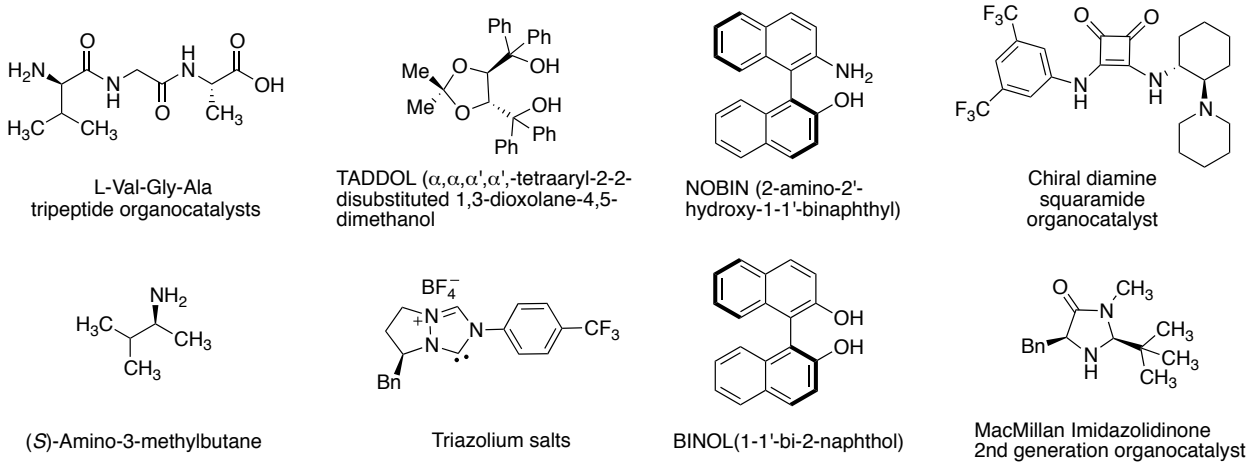
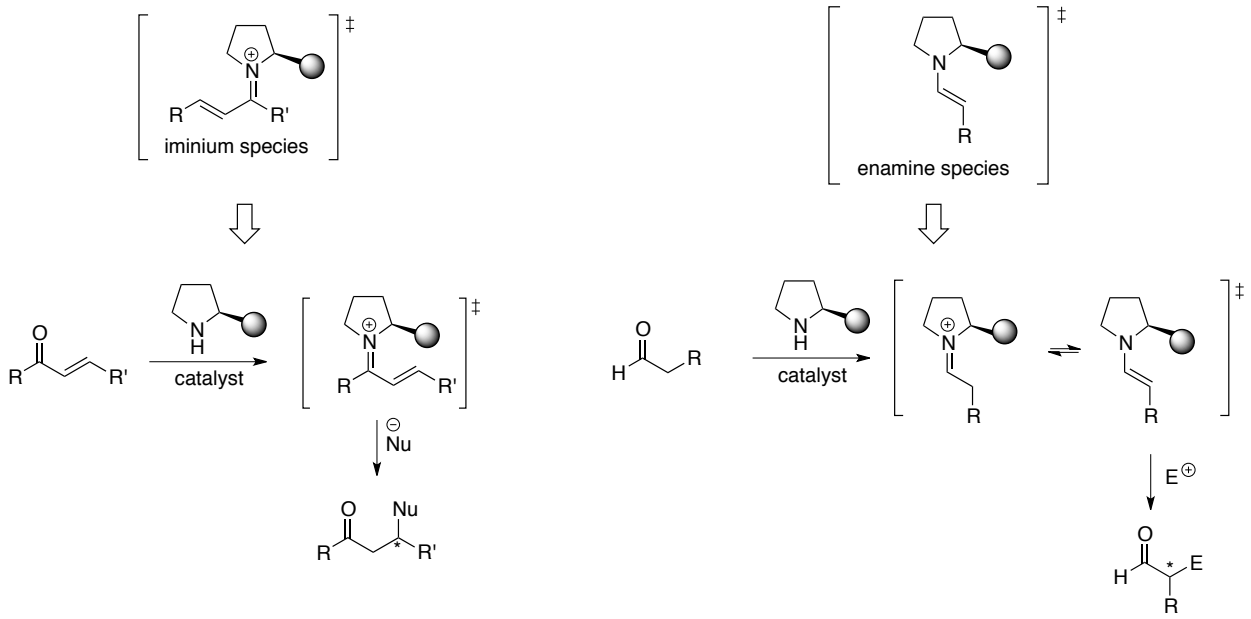


Figure 4. Widely used organocatalysts in asymmetric synthesis

1.6 Covalent modes of activation

In covalent modes of activation iminium and enamine catalysis are well studied in enantioselective synthesis. The iminium catalysis involves the condensation of a secondary amine with an electrophilic carbonyl containing as substructure, which generates the electrophilic iminium cation species which are attacked by appropriate nucleophiles to form a chiral product (Scheme 1).[8] Regarding to enamine catalysis is one of the very examined exploration study in the area of enantioselective catalysis. Enamine activation perception is as follows the reversible condensation of an amine catalyst of electron deficient carbonyl compounds to form an iminium intermediate that, upon tautomerization to generate the enamine reactive species which is reacts with an available electrophile.



Scheme 1. Covalent modes of activation

As an example of covalent modes of activation (*S*)-proline, β-amino alcohols and imidazolidinone catalysts (Figure 5) are well explored in enantioselective synthesis.[9]

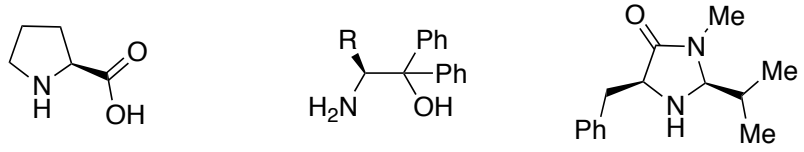
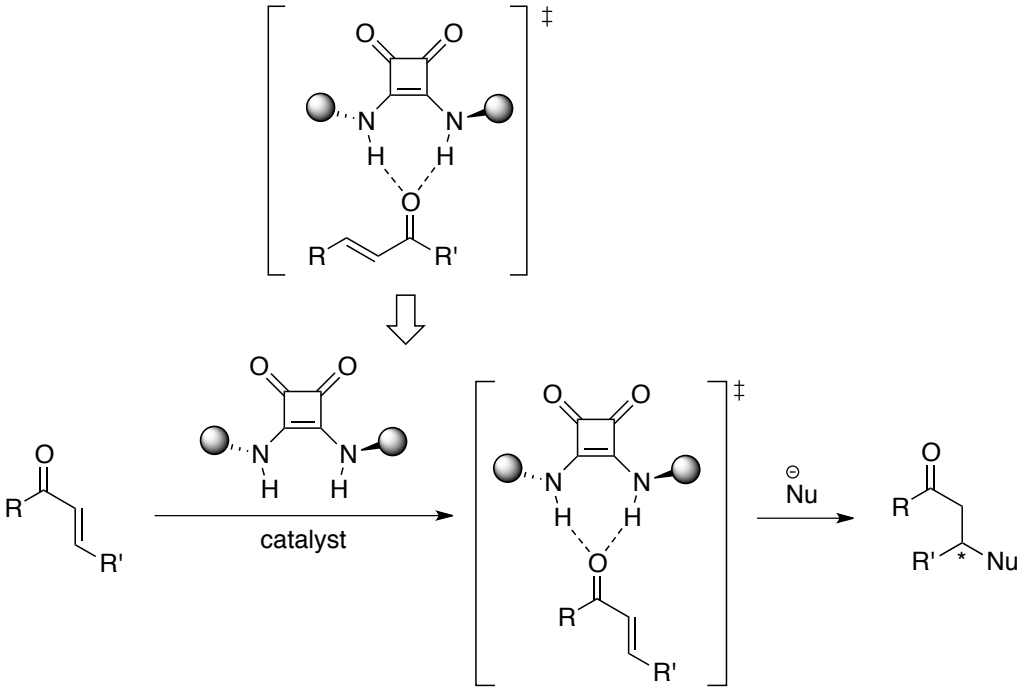


Figure 5. Covalent type organocatalysts

1.7 Non-covalent modes of activation

In non-covalent modes of activation usually hydrogen bond-donor catalysis plays a primitive role for activation of substrates, which is a well explored research area in enantioselective catalysis. Among them, non-covalent modes of activation squaramide and thiourea based organocatalysts are well studied.[10] The squaramide catalyst usually forms a multiple hydrogen bonding's mode with the substrates (mainly electron deficient conjugated ketones) which allows an electrophilic site to attack an appropriate nucleophile on it to which subsequently affords the chiral products (Scheme 2).



Scheme 2. Non-covalent modes of activation

The chiral phosphoric acids, phase transfer catalyst and cinchona based squaramide catalysts are well explored in field of non-covalent organocatalysts (Figure 6).

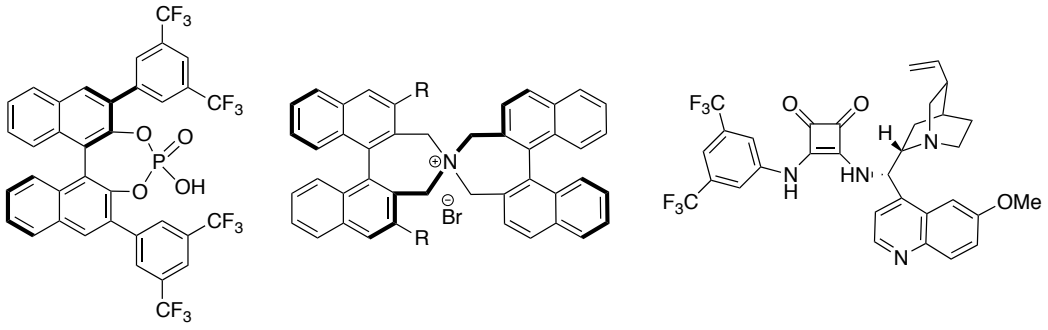
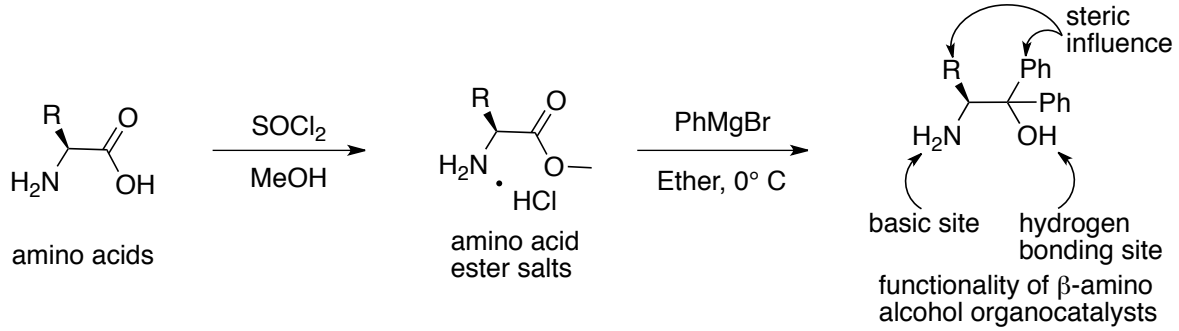


Figure 6. Non-covalent type organocatalysts

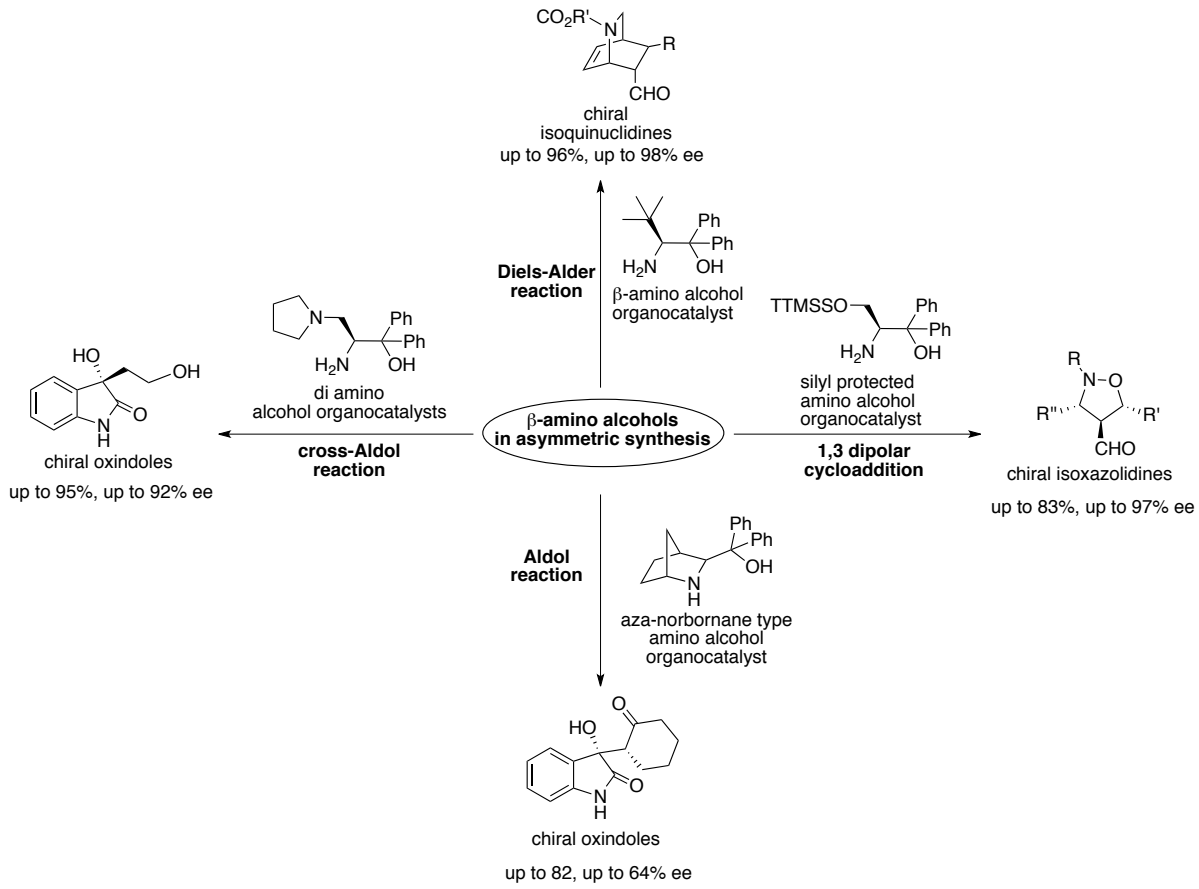
1.8 β-Amino alcohol organocatalysis in asymmetric synthesis

The simple β-amino alcohols and their derivatives can be easily prepared in a single-step from their related compounds such as accessible amino acids. These chiral precursors could be serves as an independent chiral catalyst in enantioselective organocatalysis.[11] There are many benefits of using simple primary β-amino alcohols as new class of organocatalysts, such as easy to prepare, stability on air/water, and which can be used as both covalent (iminium) and non-covalent (hydrogen bonding donor) interactions.



Scheme 3. Preparation method for β-amino alcohols

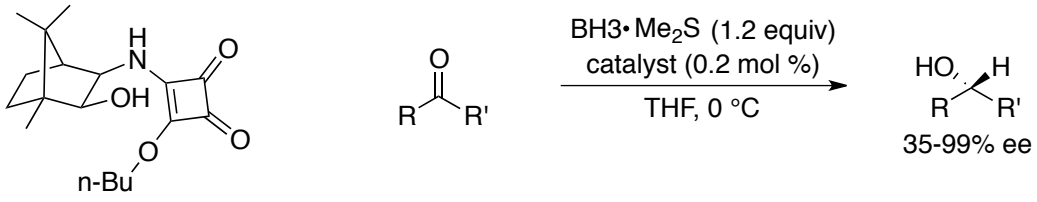
The β-amino alcohols can be easily prepared from corresponding amino acids ester salts using simple organic transformation (Scheme 3). The simple primary β-amino alcohols can be easily derived in to a di amino alcohol, aza-norbornane type amino alcohol and silyl protected amino alcohol as organocatalysts. By introducing new functional groups on amino alcohol catalyst, there might be possibility in increasing the enantiomeric phase of catalysts. The primary β-amino alcohols and their derivatives successfully showed the catalytic activity in important asymmetric reaction such as Diels-Alder and 1,3-dipolar cycloadditions, Aldol and cross-aldol reactions to afford the valuable chiral biological synthetic intermediates in satisfactory chemical yields and enantioselectively (Scheme 4).[12]



Scheme 4. The β-amino alcohol organocatalysts for enantioselective reactions

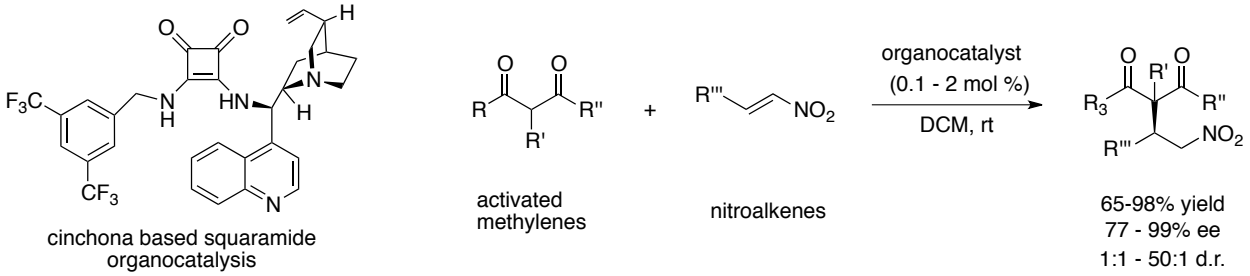
1.9 Recent progress in squaramide organocatalysis

The first example bearing squaramide unit in enantioselective synthesis was described by[13] W. Xie and his research is for the enantioselective reduction of pro-chiral ketones which stood by with borane dimethyl sulfide in the presence of chiral squaramide amino alcohols catalyst (Scheme 5), to afforded chiral secondary alcohols in excellent enantioselectivities (99 % ee).



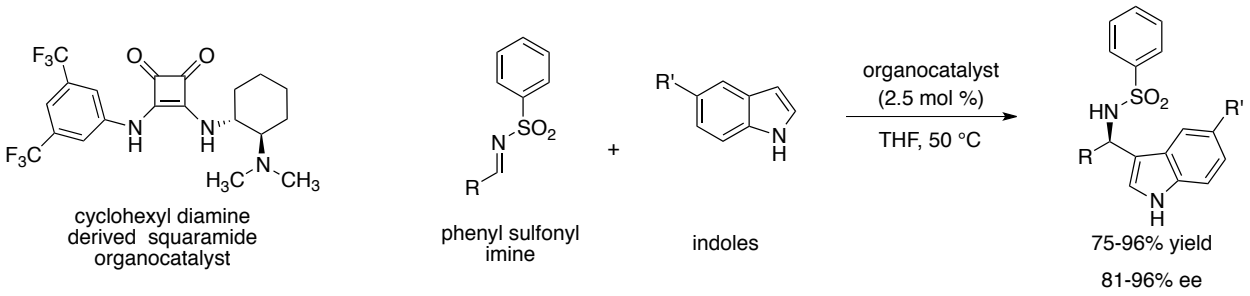
Scheme 5. Bicyclic amino alcohol squaramide organocatalysts for reduction of prochiral ketones

V. H. Rawal and his research group demonstrated cinchona based squaramide catalyst in enantioselective Michael reaction with active C-H functions of nitroalkenes, which afforded anticipated Michael products in both satisfactory chemical yields and enantiomeric excess (Scheme 6).[14]



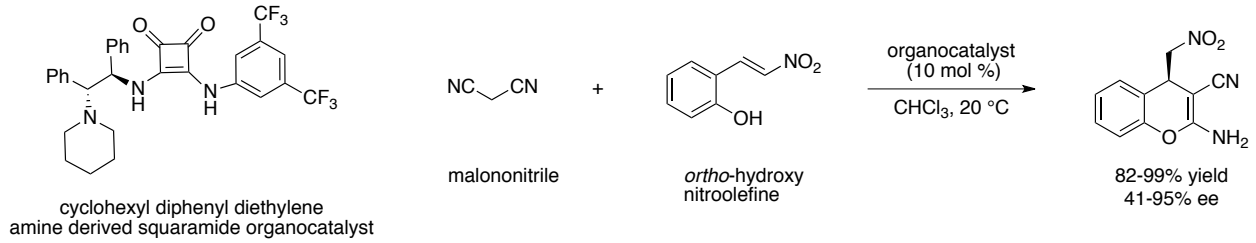
Scheme 6. Cinchona based squaramide organocatalysts for Michael addition reaction

Furthermore, V. H. Rawal and his research group[15] has also reported the enantioselective Friedel-Craft reaction of indoles with arylsulfonylimines using with cyclohexyl amine derived squaramide organocatalyst (Scheme 7). The organocatalysts was afforded the indolyl-sulfonamides, in good excellent chemical yield (up to 96%) and in excellent enantioselectivities (up to 96% ee).



Scheme 7. Cyclohexyl amine based squaramide catalysts for Friedel-Craft reaction

C. Tang and his research group[16] reported the tandem Michael addition and intramolecular cyclization concept with Michael donors and *ortho*-hydroxynitroolefines to afford the chiral 2-aminopyrans using cyclohexyl diphenyldethyleneamine derived squaramide oragnocatalyst. The catalyst was found to be good H-bonding catalyst for affording the chiral 2-aminopyrans in good to excellent enantioselctivities (41-95%), using with 10 mol % of oragnocatalyst (Scheme 8).



Scheme 8. Cyclohexyl diphenyl diethylamine derived squaramide catalyst for Michael addition

1.10 Structural judgement of thioureas between squaramides

The squaramide have the its own structural arrangements and works very effectively when compared to thiourea and guanidine type of catalysts. The following figure represents the bond distances and resonance on thioureas and squaramido units (**I-IV**).[17] The two -NH functions bond forming distance is measured practically as 2.13 Å of thiourea (**I**), the thiourea units exhibits the resonance effect from sulphur atom to -NH functions (**II-III**). In the case of squaramido unit the two -NH functions bond forming distances is 2.71Å (**IV**), the resonance effect is allowing from oxygen atoms of cyclobutanedione ring towards -NH functions of squaramido unit (**V-VI**).

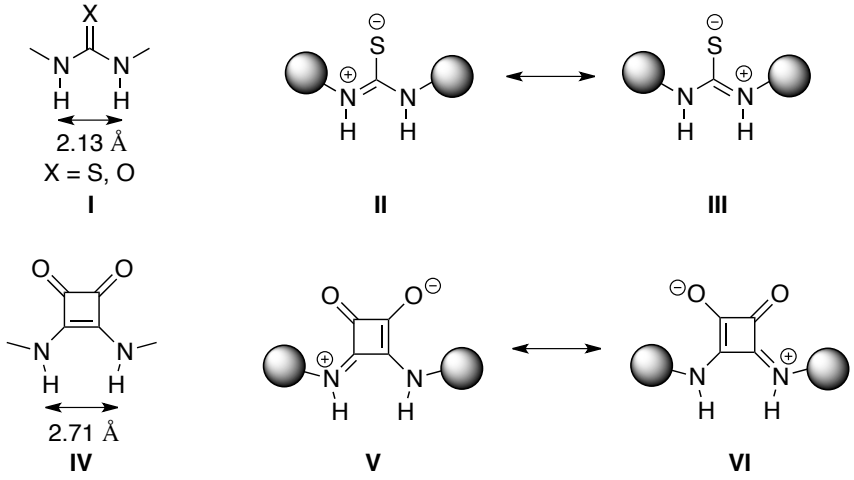
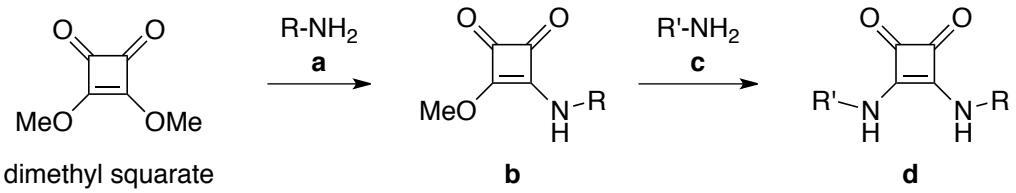


Figure 7. Structural comparisons between thiourea and squaramide unit

1.11 General preparation method for squaramide organocatalysts

The squarate esters was easily prepared from squaric acid, which is also called as quadratic acid because of its four carbon atoms approximating to from a square, is an organic compound with chemical formula $C_4H_2O_4$. Squaric acid is also used as reagent for chemical synthesis, used for instance to make photosensitive squaric dyes and inhibitors of protein tyrosine phosphatases.

Recently the squarate esters were gained importance in field of organocatalysts, and its widely explored as starting materials for synthesizing many squaramide bifunctional organocatalysts. In addition, the synthesis involves a condensation reaction with dimethyl squarate of amine **a**, again respected by a parallel substitution reaction using with a chiral primary amine **c** affording the bifunctional squaramide units **d** (Scheme 9).[18]



Scheme 9. Common synthesis method for the squaramide organocatalysts

1.12 Binding modes of squaramide motif with different substrates

The squaramide motif is serves as an effective activation function for hydrogen bonding's with variety of substrates such as nitro-olefins (**VII**), conjugated ketones (**VIII**), pyruvate ketones (**IX**), oxazolidinone ketones (**X**) and imino-ester (**XI**) (Figure 8).[19]

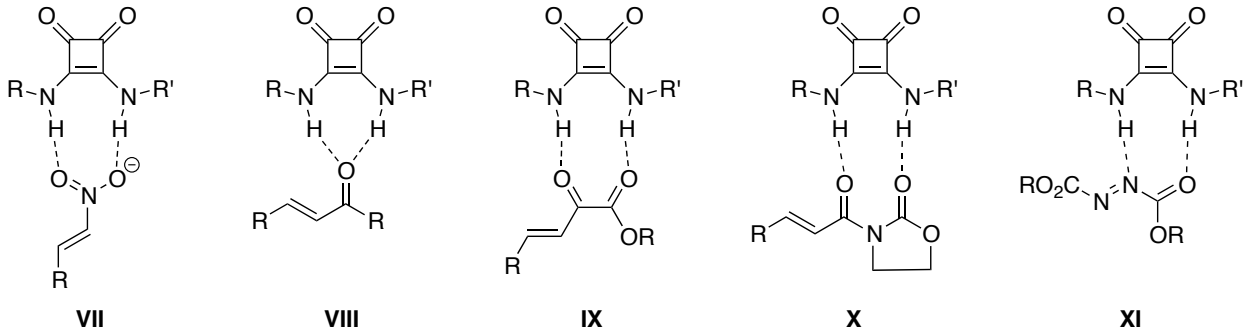


Figure 8. Possible bindings modes of squaramides unit to various hydrogen bonds acceptors

1.13 Author strategy

Author aimed to develop new hybrid type squaramide fused amino alochol organocatalysts by using simple primary β-amino alcohol as chiral precursors, the squaramide organocatalysts are remarkable four membered ring systems derived from squaric acid. The squaramide unit of the catalyst part can contribute two proximate and polarized -NH fragments (Figure 9). The squaramide catalysts function as an effective activation unit for hydrogen-bond donor catalysis when compared with urea/thiourea and guanidine type catalysts. By these advantages of squaramide catalysts author concentrated to the synthesis of usual and new hybrid type squaramide fused amino alcohol organocatalysts by using amino alcohols.

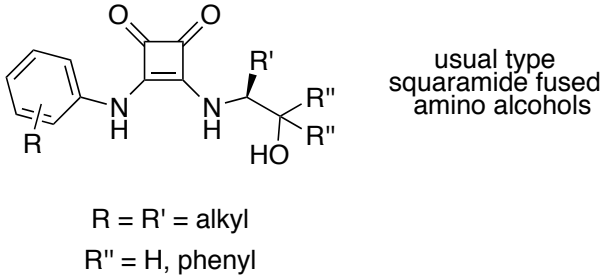
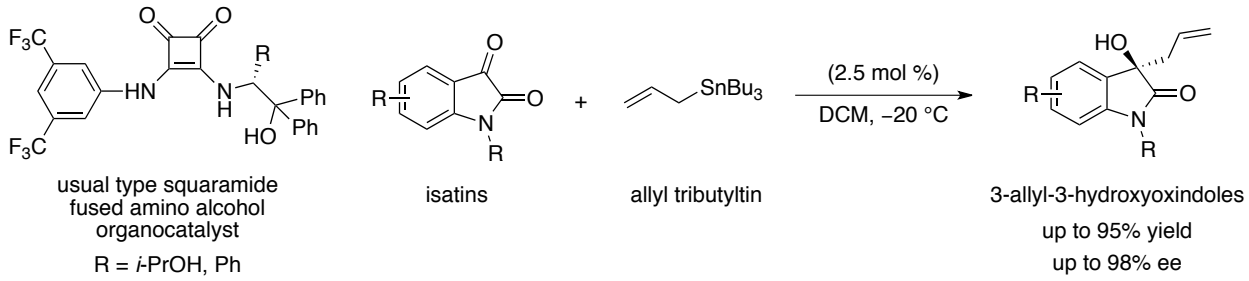


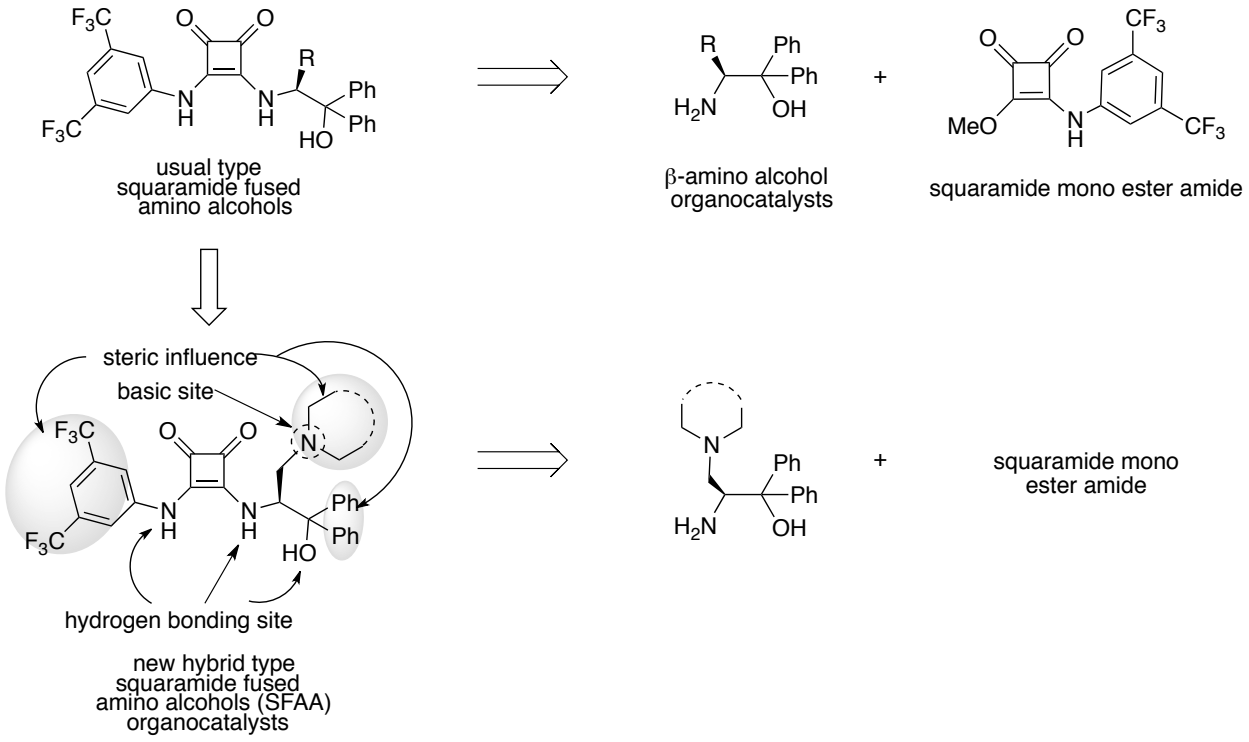
Figure 9. General structure of squaramide organocatalysts

However, recently the usual type squaramide fused amino alcohols are reported in the literature by Hari C. Bajaj[20] and his research group described the synthesis of usual type squaramide fused amino alcohol organocatalysts using with β-amino alcohol as chiral precursors having isopropyl and phenyl groups at side chain of the catalyst (Scheme 10). And demonstrated their catalytic activity in enantioselective allylation reaction of isatins with allyl tributyltin to afford the corresponding chiral 3-allyl-3-hydroxyindoles in high and enantioselectivities. Moreover, the usual type squaramide fused amino alcohol organocatalysts contains only hydrogen bonding and steric influences on the molecule.



Scheme 10. Enantioselective allylation of isatins

And its didn't have any basic site to abstract the proton from pro-nucleophiles to affords high enantioslectivities, additionally, the usual type squaramide fused amino alcohol organocatalysts are not well studied in the field of enantioselective synthesis. By these drawbacks of usual type squaramide fused amino alcohol organocatalysts, author aimed to synthesis new hybrid type squaramide fused amino alcohol organocatalysts by introducing Brønsted basic site on the molecule. After several attempts, author successfully developed the new hybrid type squaramide fused amino alcohol (SFAA) having multiple activation sites such as two amino and one hydroxy group as the hydrogen-bonding sites, three steric influences from phenyl groups and side chain of the SFAA catalysts contains cyclic tertiary amino group that can act as a Brønsted base. And two amino and one hydroxy group that can form hydrogen bonds with both substrates. By owing these properties of SFAA catalysts might be act as trifunctional organocatalysts (Scheme 11).

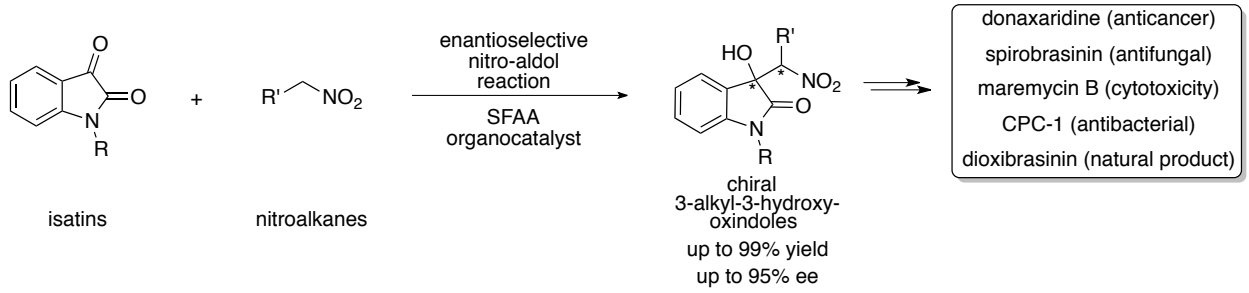


Scheme 11. Concept of SFAA catalyst design

The newly developed hybrid type SFAA organocatalysts having hydrogen bonding, steric influences and Brønsted basic sites demonstrated its catalytic activity for enantioselective reactions such as nitro-aldol reaction, Diels-Alder reaction and domino Michael addition cyclization reaction to afford the corresponding biologically active synthetic intermediates in high enatioselectivities.

i) Enantioselective nitro-aldol reaction

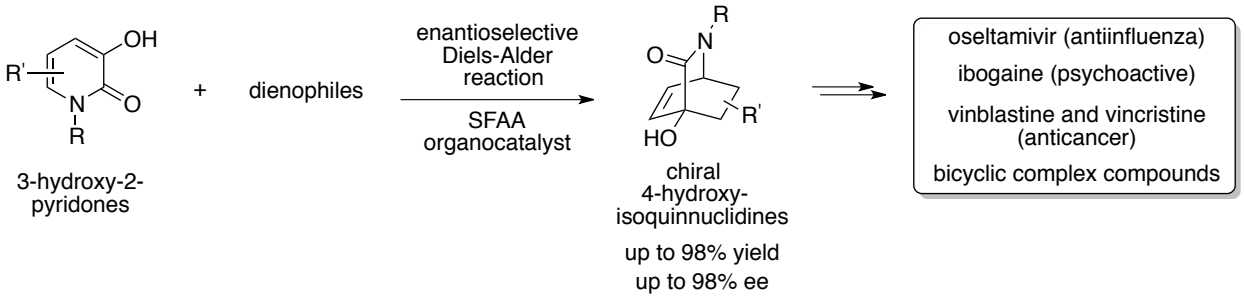
Author initially tried and explored the catalytic activity of SFAA organocatalysts for enantioselective nitro-aldol reaction of isatins with nitromethane to affords the chiral 3-alkyl-3-hydroxyoxindoles in excellent chemical yields (up to 99% yield) and enantioselectivies (up to 95% ee). The chiral 3-alkyl-3-hydroxyoxindoles are the prominent synthetic intermediates for many biologically active compounds. Such as the donaxaridine (anticancer), spirobrasinin (antifungal), maremycin B (cytotoxicity), CPC-1 (antibacterial agent) and dioxibrasinin (natural product) (Scheme 12).[21]



Scheme 12. SFAA organocatalyst for enantioselective nitro-aldol reaction

ii) Enantioselective Diels-Alder reaction

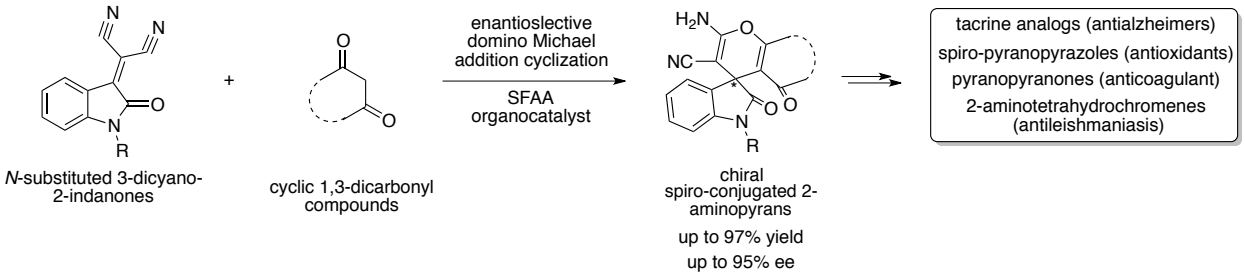
Furthermore, the author has applied the newly prepared SFAA organocatalysts for enantioselective Diels-Alder reaction of 3-hydroxy-2-pyridones with dienophiles to accesses the chiral 4-hydroxyisoquinuclidines in both excellent chemical yield (up to 98%) and enantioselectivities (up to 98%) (Scheme 13).[22] The chiral 4-hydroxyisoquinnuclidines are key synthetic intermediates for bicyclic complex structures and many biological active compounds such as oseltamivir (antiinfluenza drug), ibogaine (psychoactive drug) and vinblastine and vincristine (anticancer drugs).



Scheme 13. SFAA organocatalysts for enantioselective Diels-Alder reaction

iii) Enantioselective domino Michael addition cyclization reaction

Moreover, author also successfully applied the SFAA organocatalysts for enantioselective domino Michael addition cyclization reaction of 3-dicyano-2-indanones with cyclic 1,3-dicarbonyl compounds for affording the chiral spiro-conjugated 2-aminopyrans in both excellent chemical yield (up to 97% yield) and enantioselectivities (up to 95% ee). The domino Michael addition cyclization reaction of electron withdrawing indanones with active methylene's accesses the chiral quaternary streogenic 2-aminopyrans. The chiral spiro-conjugated 2-aminopyrans are the vital synthetic intermediates for many biologically active derivatives, such as tacrine derived 2-aminopyrans (antialzheimers), spiro-pyranopyrazoles (antioxidants), pyranopyranones (anticoagulant) and 2-aminotetrahydrocromenes (antileishmaniasis) (Scheme 14). The detailed discovery of SFAA organocatalysts preparations and its application for enantioselective reactions will be discussed in following sections.



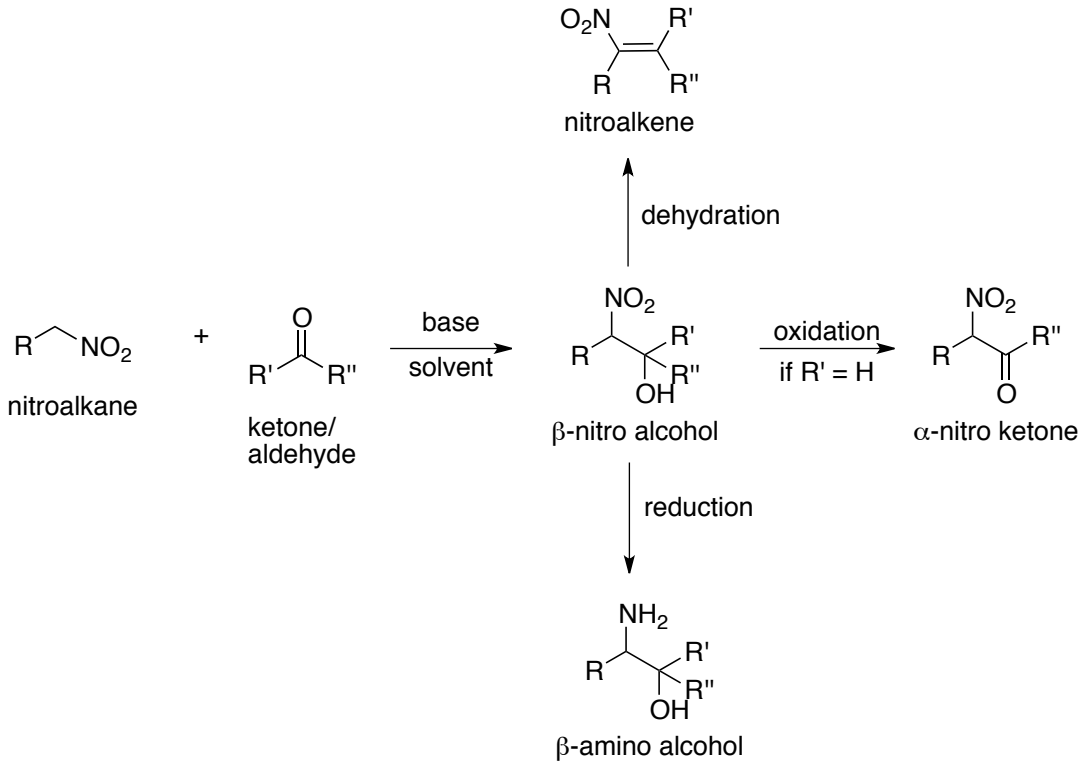
Scheme 14. SFAA organocatalysts for enantioselective domino Michael addition cyclization reaction

Chapter 2

The New Hybrid Type Squaramide Fused Amino Alcohol Organocatalysts For Enantioselective Nitro-Aldol Reaction of Nitromethane with Isatins

2.1 Introduction

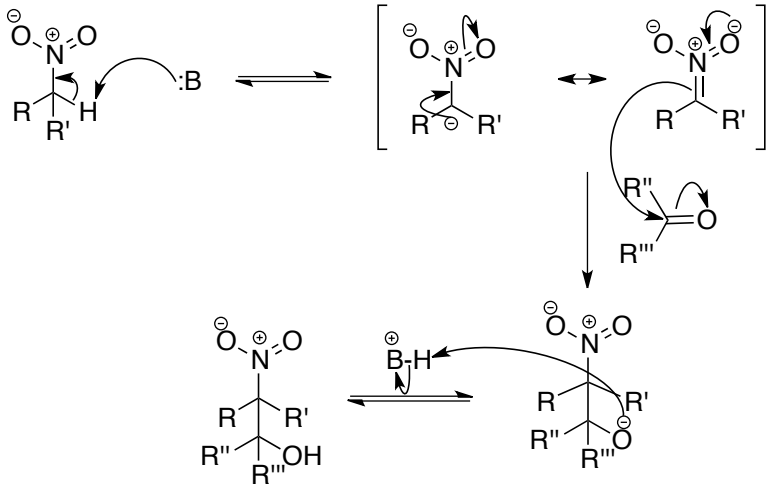
The nitro-aldol reaction is also referred as (Henry reaction) which is a well-studied reaction in synthetic organic chemistry. The nitro-aldol reaction was discovered by Belgian chemist Louis Henry during the year of 1895. The nitro-aldol reaction is the usually takes place between nitroalkane and an electron deficient (ketone/aldehyde) in the presence of catalytic amount of basic additives to afford the β-nitro alcohol. The obtained β-nitroalcohols can be easily converted into other functional derivatives such as, nitroalkenes, α-nitro ketones and β-amino alcohols (Scheme 15).[23]



Scheme 15. General representation of nitro-aldol reaction

2.2 Mechanism

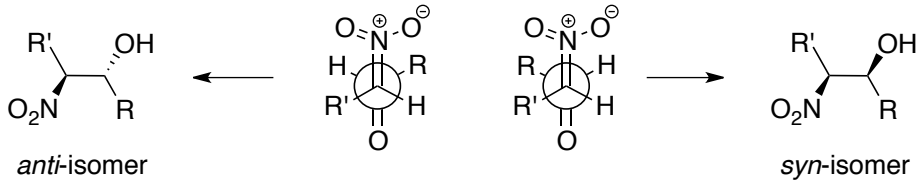
The nitro-aldol reaction mechanism leads with deprotonation of nitro-alkane in the presence of base which forms carbanion at α-position. The active species of carbanion reacts with electron deficient (ketone/aldehyde) to form the diastereomeric β-nitro alkoxide. The protonation of the alkoxide from the reaction medium forms the β-nitro alcohol as desired product. In nitro-aldol course of reaction all the steps are reversible (Scheme 16).[24]



Scheme 16. Mechanism of nitro-aldol reaction

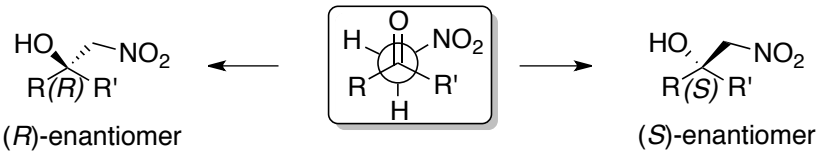
2.3 Stereochemical course of the nitro-aldol reaction

In a stereochemical course of the nitro-aldol reaction usually produces the unequal amount of the isomers. In many enantioselective nitro-aldol reactions *syn* or *anti*-isomer can be observed in the course of the reaction. The steric influences of the substrates usually determine the stereochemical outcome of the products in nitro-aldol reaction (Scheme 17).[25]



Scheme 17. The *anti*/*syn* stereochemical approach of nitro-aldol reaction

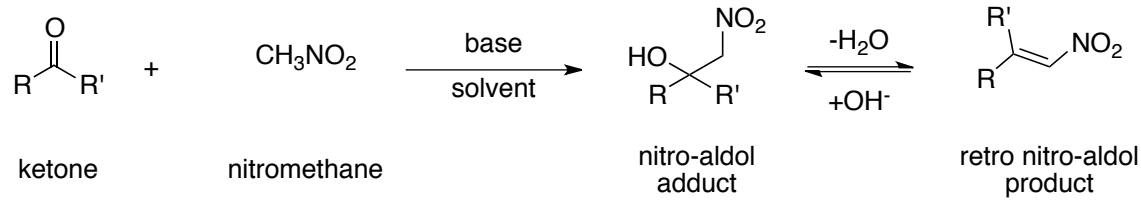
When it's come to the one chiral center bearing of nitro-aldol products the stereochemistry assigned as (*R*) or (*S*) its depends on the R groups on the substrates of ketone/aldehyde and nitroalkane. The stereochemistry of resultant nitro-aldol products also obeys the enantiomeric face approach of the corresponding nitromethane to electrophilic ketones (Scheme 18).



Scheme 18. (*S*) or (*R*) enantiomers of the nitro-aldol reaction

2.4 Limitations of the nitro-aldol reaction

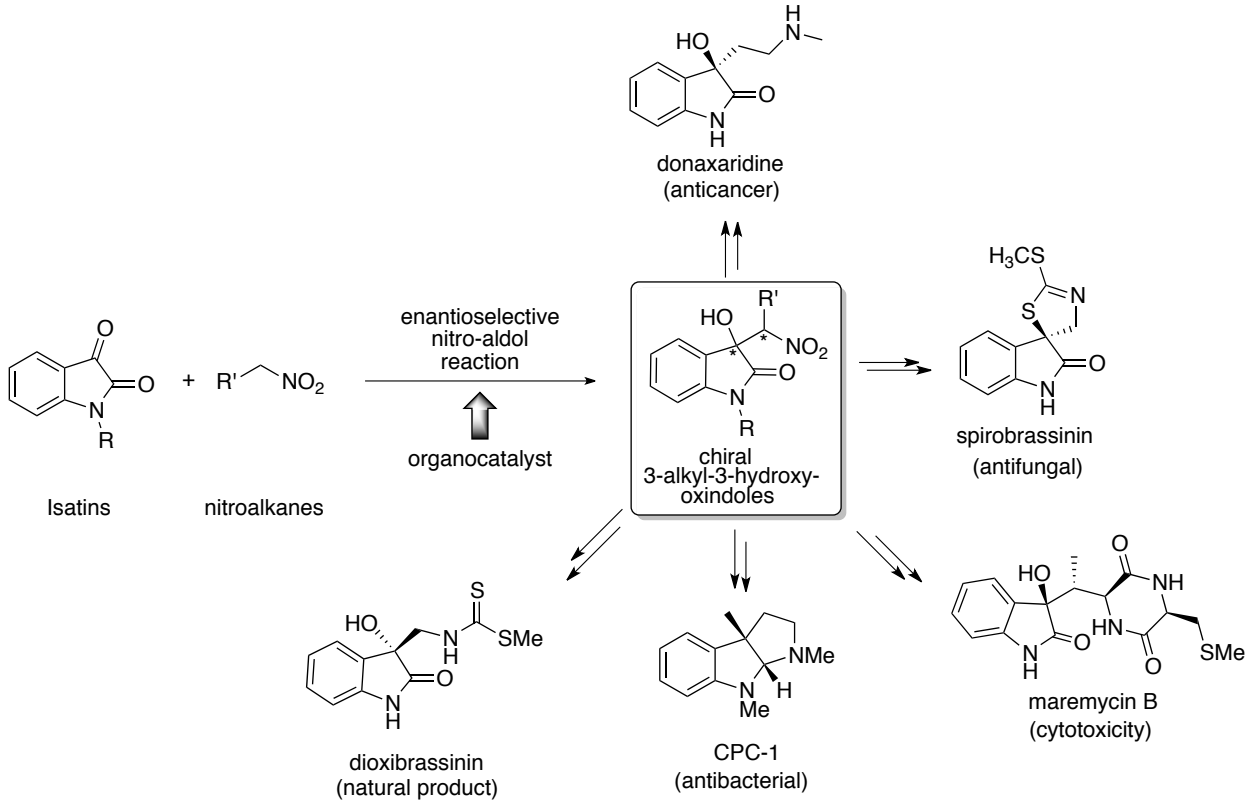
The main drawback of the nitro-aldol reaction is producing the potential side products in the course of the reaction. In the following reaction the nitromethane reacts with ketone in the presence of basic medium to form the nitro-aldol adduct. The nitro-aldol adduct has the tendency to undergo retro nitro-aldol reaction to afford retro nitro-aldol product (nitro-alkene) in the presence of protic solvent medium. (Scheme 19).



Scheme 19. General representation of the retro nitro-aldol reaction

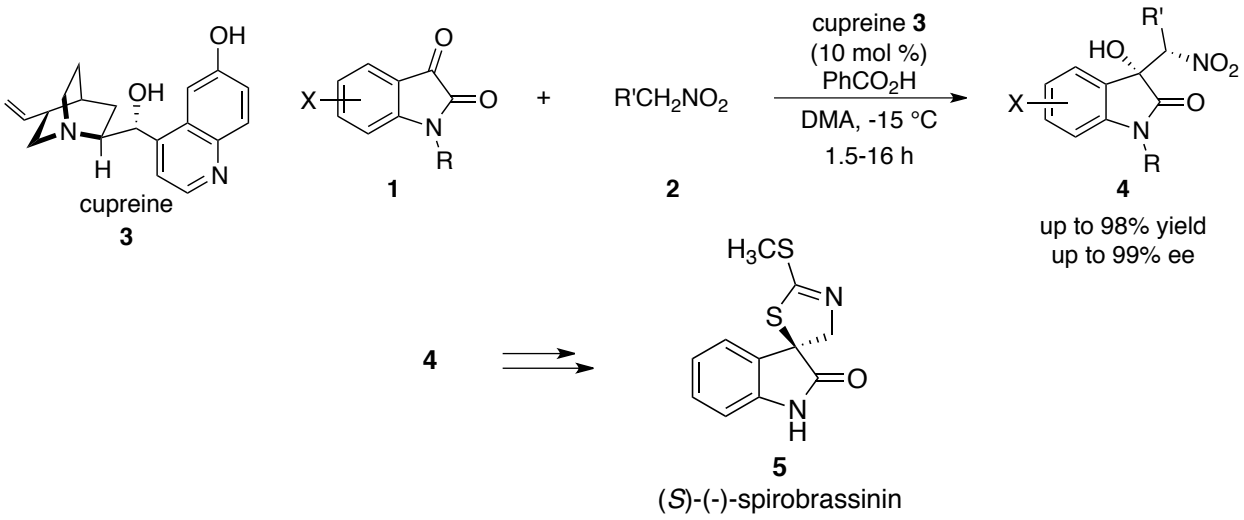
2.5 The enantioselective nitro-aldol reaction of isatins with nitroalkanes

The enantioselective nitro-aldol reaction of isatins with nitroalkanes affords synthetically valuable chiral 3-alkyl-3-hydroxyoxindoles.[26] The 3-substituted 3-hydroxyoxindoles are the core structural unit in a large array of fascinating natural products with broad spectrum of intriguing biological activities (Scheme 20). The resulting heterocycles are important synthetic precursors for many biologically active natural products such as CPC-1 (antibacterial activity), maremycin B (cytotoxicity against K562 human leukemia cell lines), spirobrassinin (anti- fungal, antitumor, and oviposition stimulation activity), donaxaridine (anticancer activity), and dioxibrassinin (important natural product).



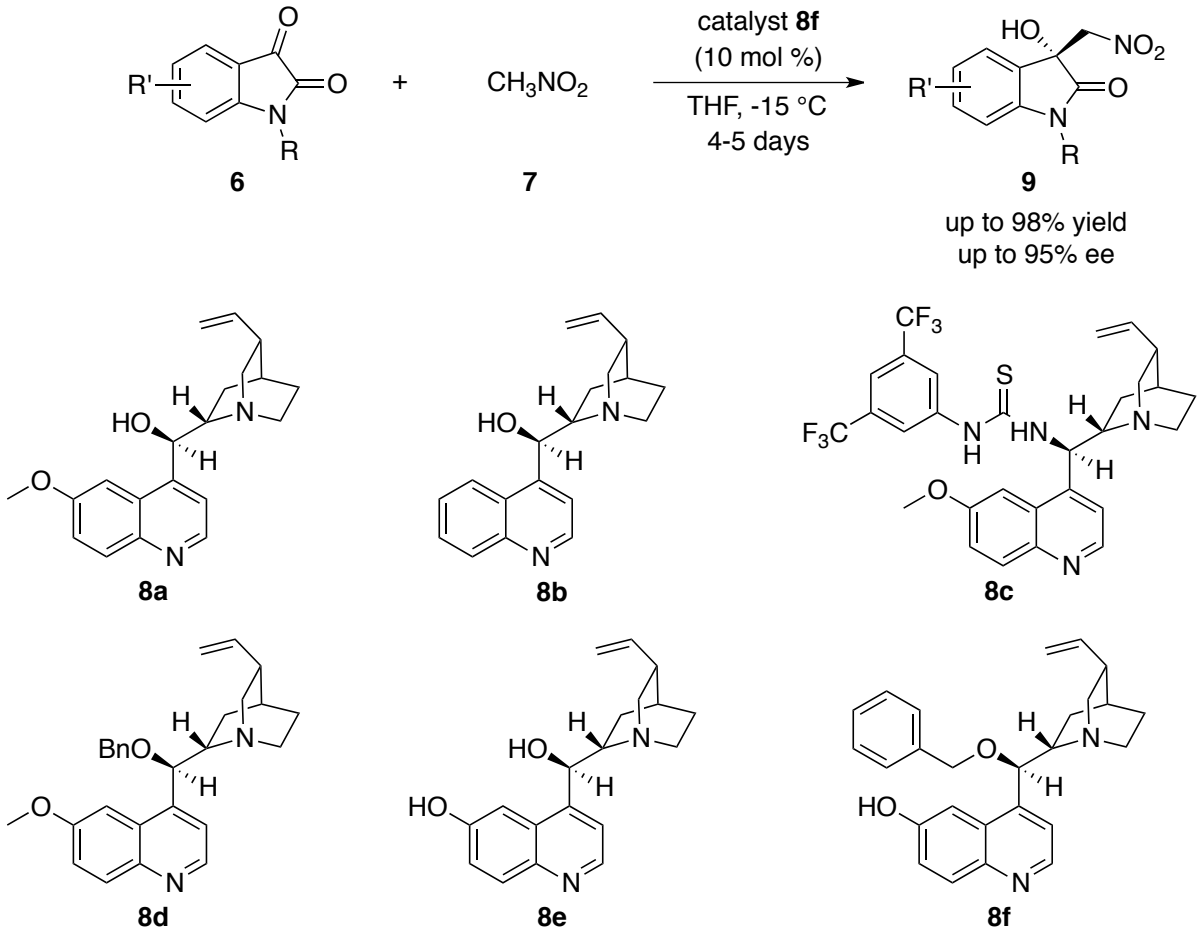
Scheme 20. General representation of the nitro-aldol reaction of isatins with nitroalkanes using organocatalyst

W. Wang and his research group[27] reported enantioselective nitro-aldol reaction of isatins **1** with nitroalkanes **2** using cupreine **3** as organocatalyst to afford the nitro-aldol adducts in excellent yields (up to 98%) and with good to excellent enantioselectivities (up to 99%) under the mild reaction conditions (Scheme 21). And this strategy relying on non-covalent bond-mediated catalysis which is a different approach from other organocatalytic of nitro-aldol reaction. In this methodology, they also demonstrated the synthetic utility of 3-susbstituted 3-hydroxyoxindoles **4** to afford (*S*)-(-)-spirobrassinin **5**. The (*S*)-(-)-spirobrassinin is a natural product isolated from *Pseudomonas cichorii* (Japanese radishes) in 1987. The compound displays various biological properties including plant defense, antifungal and antitumor activities.



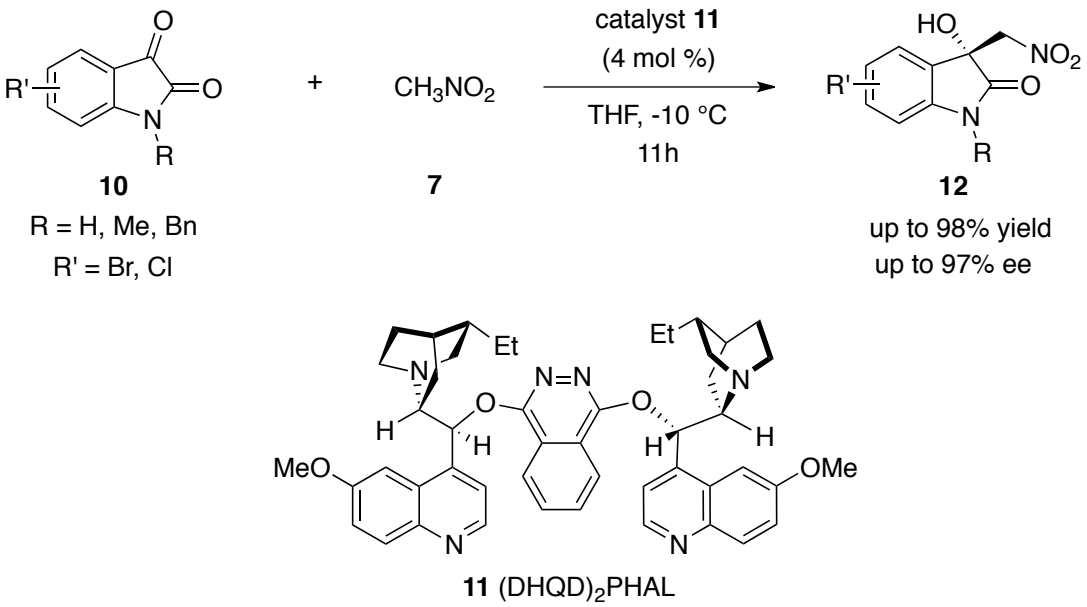
Scheme 21. The enantioselective nitro-aldol reaction using cupreine alkaloid

X. -W. Wang and his research group[28] reported the enantioselective nitro-aldol reaction of isatins with nitroalkanes using with bifunctional cinchona alkaloid derivatives as organocatalysts. In the course of enantioselective nitro-aldol reaction they prepared a series of cinchona alkaloid derivatives **8a-f**, among them **8f** has showed the excellent catalytic activity in enantioselective nitro-aldol reaction of isatins **6** with nitromethane **7** to afford 3-hydroxy-3-(nitromethyl)indolin-2-ones **9** in both excellent yields (up to 98%) and enantioselectivities (up to 95%) (Scheme 22).



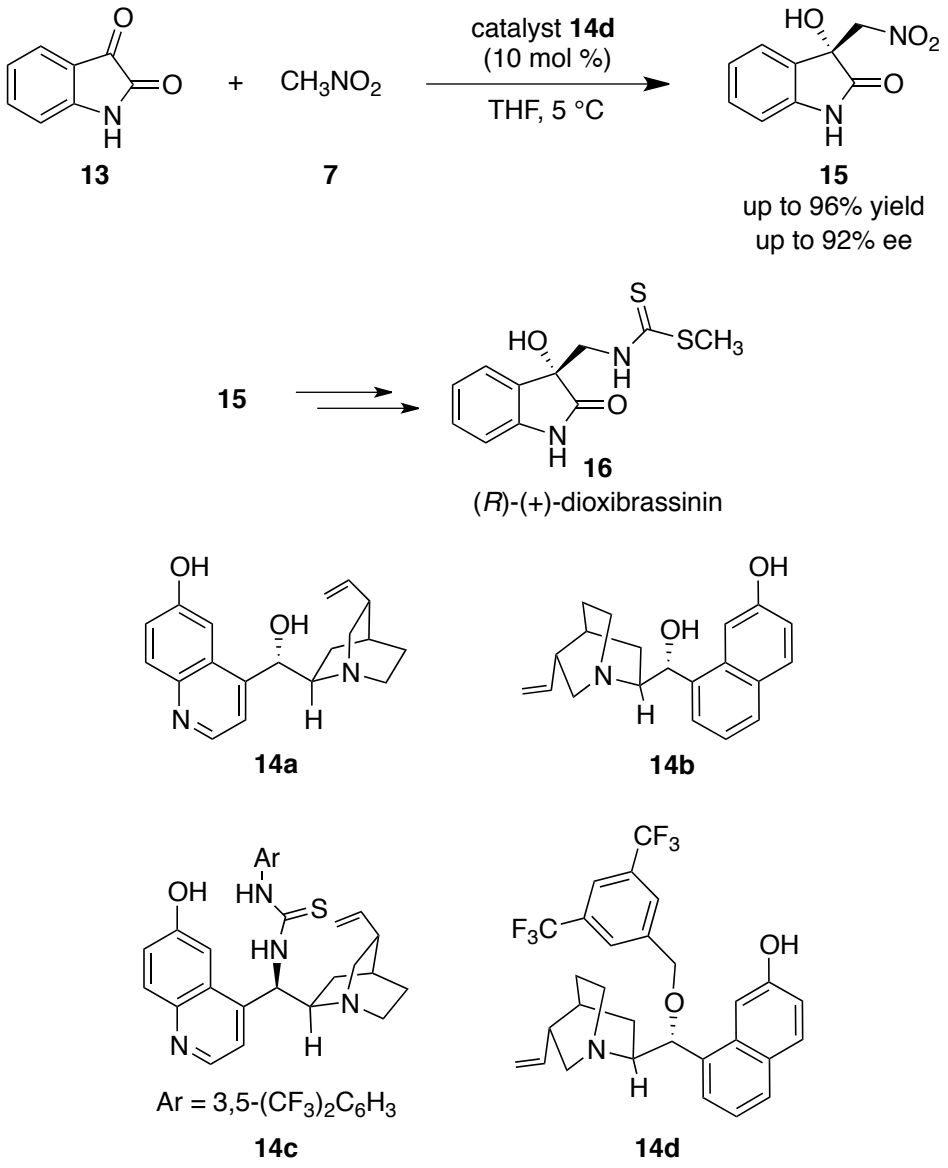
Scheme 22. The enantioselective nitro-aldol reaction of isatins with nitromethane using cinchona alkaloids

Pravin R. Likhar and his research group[29] reported the enantioselective nitro-aldol reaction of isatins **10** with nitromethane **7** in the presence of bis-cinchona based $(DHQD)_2PHAL$ **11** alkaloid as organocatalyst. They prepared a series of bifunctional cinchona alkaloid catalysts possessing pthalazine as a cross linker in between two cinchona alkaloids. They successfully demonstrated the prepared catalysts catalytic activity in enantioselective nitro-aldol reaction to afford the 3-hydroxyoxindoles **12** in both good to excellent chemical yields (up to 98%) and enantioselectivities (up to 97%) (Scheme 23).



Scheme 23. The enantioselective nitro-aldol reaction using cinchona based $(DHQD)_2PHAL$

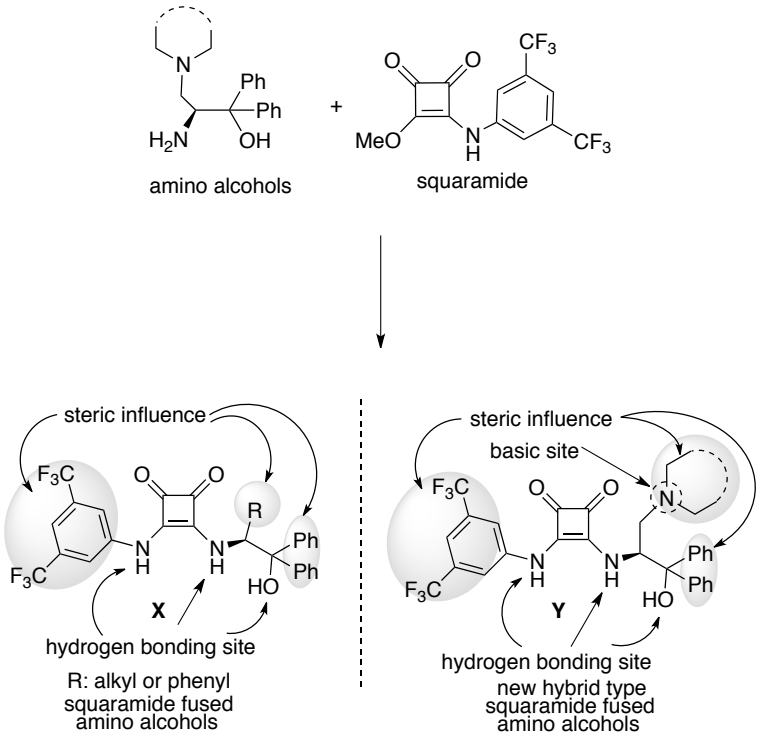
Wang and his research group[30] has reported the organocatalytic enantioselective nitro-aldol reaction of isatins **13** with nitromethane **7** using cinchona alkaloid catalysts **14a-d**, among them catalyst **14d** have showed the excellent catalytic activity for affording the 3-hydroxyoxindoles **15** in excellent yield (up to 96%) and high enantioselectivites (up to 92%). And this method effectively useful for the synthesis of (*R*)-(+)-dioxibrasinin **16**, the dioxibrasinin belongs to phytoalexins class, with possessing potent antimicrobial activity (Scheme 24).



Scheme 24. The enantioselective nitro-aldol reaction using cinchona alkaloids

2.6 Author strategy

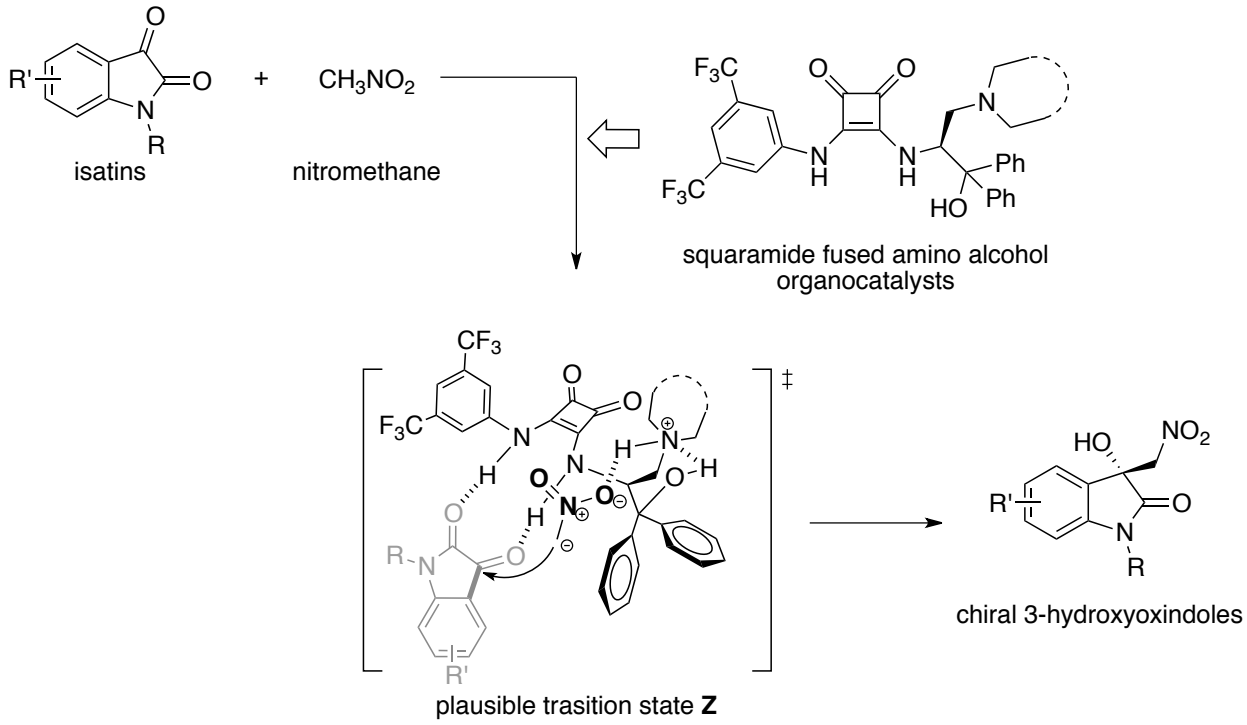
As part of author research work aim to develop the simple primary β-amino alcohols as a new class of organocatalysts in enantioselective synthesis. Author successfully prepared the new hybrid type squaramide fused amino alcohol (SFAA) organocatalysts using with simple primary β-amino alcohol as chiral precursors. The SFAA catalysts posses with distinctive properties such as ease to synthesis, stability upon exposure to air, potential towards steric site modifications, and capability act as trifunctional (enamine activation, non-covalent activation and basic site) catalyst. The SFAA catalysts can be a more hydrogen bonding possibilities compared to those with urea/thiourea and guanidine catalyst providing more superior rate of enhancements and stereoselective controls in enantioselective reactions. An advantage of chiral SFAA as organocatalysts is the simple and modular preparation, which offers a facile route to a wide range of trifunctional organocatalysts. By this point of view, author synthesized the new hybrid type SFAA organocatalysts which contains a cyclic tertiary amino group that can act as a Brønsted base, sterically bulky groups, and two amino and one hydroxy group that can form hydrogen bonds with both substrates (Scheme 25). The SFAA catalysts **X** and **Y** can be easily prepared by the condensation reaction of a squaramide and the corresponding amino alcohol.



Scheme 25. Properties of squaramide fused amino alcohol organocatalysts **X** and **Y**

2.7 Results and discussions

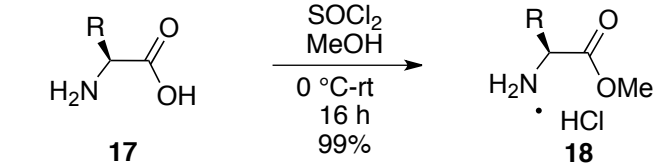
The newly developed SFAA organocatalysts posses with multiple hydrogen bonding sites and steric influence sites within one molecule, it might have shown strong stereochemical influence in the enantioselective nitro-aldol reaction of isatins with nitromethane. As shown in the plausible transition state **Z**, where isatin and nitromethane can be conformationally fixed by four hydrogen-bonding interaction, that is between the two amino groups of the squaramide and the two carbonyl groups of the isatins. Between the cyclic ammonium site of squaramide and oxygen atom of the nitro enolate moiety, and between the cyclic ammonium site and the hydrogen atom of the hydroxy group in the ammonium alcohol intermediate (Scheme 26). Then, the reaction may proceed stereoselectively to afford the nitro-aldol product with high enantioselectivity.



Scheme 26. Conceptualization of enantioselective nitro-aldol reaction using SFAA oraganocatalysts

2.7.1 Synthesis of usual type squaramide fused amino alcohol organocatalysts

Initially, according previous literature procedures,[20] author prepared usual type of squarmide fused amino alcohol organocatalysts by employing coupling reaction of squarate monoester amide with corresponding β-amino alcohol which were easily prepared from Grignard reaction of commercially available amino esters salts. First, author synthesized a series of amino acids ester salts **18** from corresponding amino acids **17** by reaction with thionyl chloride at 0 °C - rt conditions, the amino acids salts were obtained with excellent yields up to 99% (Scheme 27).



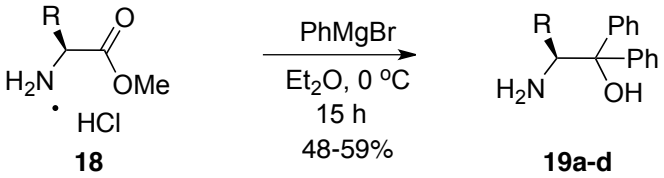
17

R = Me, Ph, Bn, *i*-Pr

18

Scheme 27. Synthesis of amino acid salts from amino acids

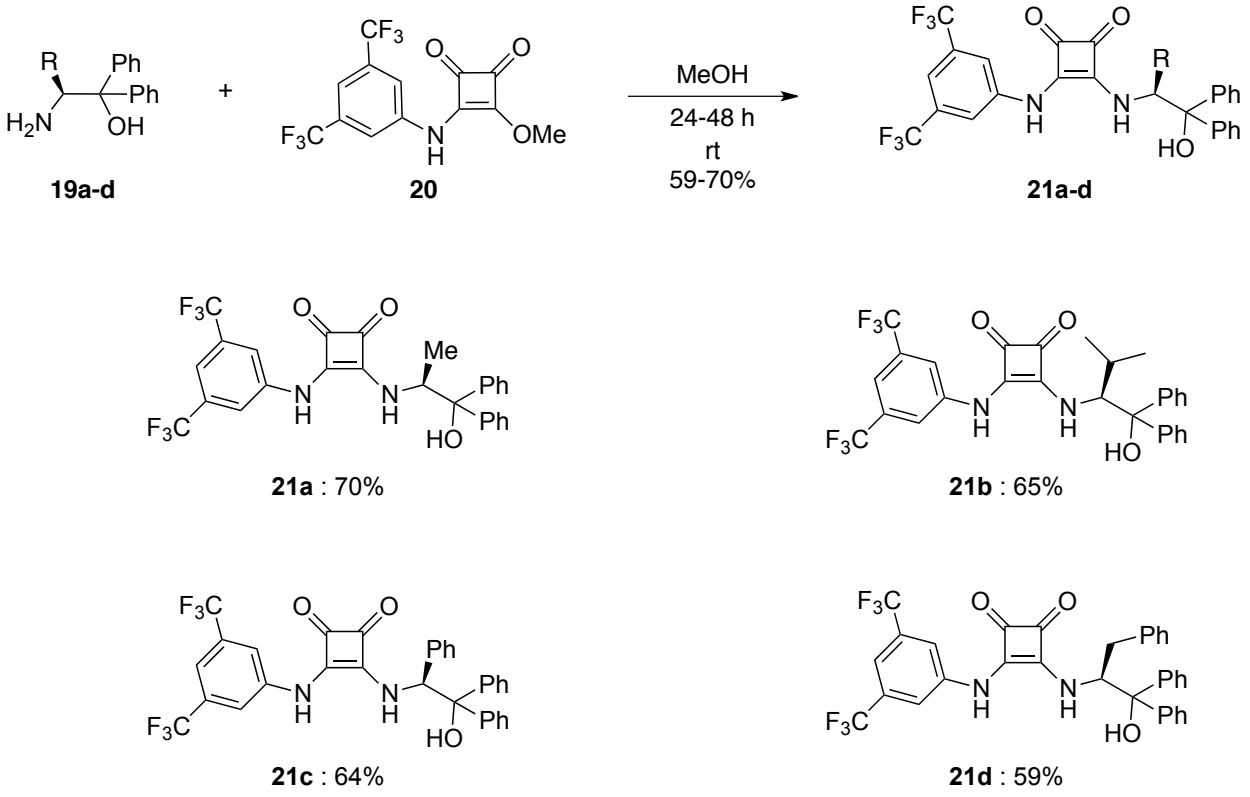
The obtained amino acids salts were reacted with PhMgBr in argon atmosphere to using dry ether at 0 °C temperature to afford the β-amino alcohols organocatalysts **19a-d** in moderate yields up to 48-59% (Scheme 28). Furthermore, the obtained β-amino alcohol organocatalysts **19a-d** were fused with squaramide mono ester amide **20** in dry MeOH solvent at room temperature to furnish the usual type squaramide fused amino alcohol organocatalyst **21a-d** in moderate to good yields 59-70% (Scheme 29)



18

19a-d

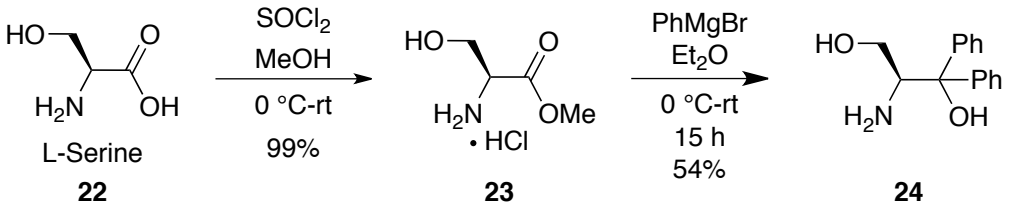
Scheme 28. Synthesis of β-amino alcohol organocatalysts from amino acid salts



Scheme 29. Synthesis of usual type squaramide fused amino alcohol organocatalysts

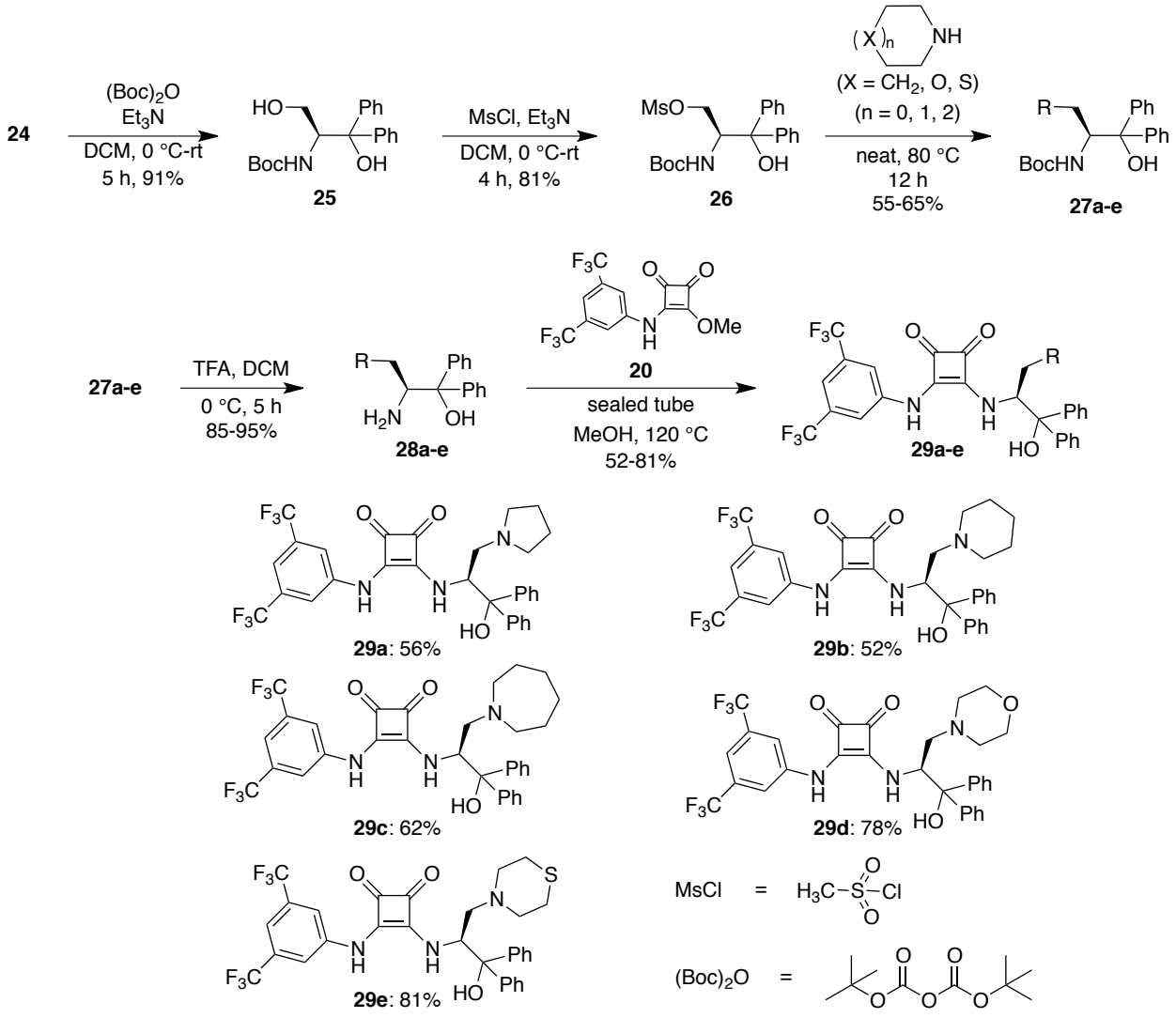
2.7.2 Synthesis of new hybrid type squaramide fused amino alcohol organocatalysts

Furthermore, by employing previous literature procedures[11] author prepared new type hybrid squaramide fused amino alcohol organocatalysts from using L-Serine amino acid **22** as starting material. The serine was reacted with thionyl chloride in MeOH at 0 °C to afford the serine methyl ester hydrochloride salt **23** with 99% yield. The obtained salt **23** were reacted with PhMgBr to afford the serine β-amino alcohol **24** with 54% yield (Scheme 30). Moreover, the amino group of obtained serine amino alcohol **24** was protected with $(Boc)_2O$ to afford compound **25** with 91% yield.



Scheme 30. Synthesis of serine β-amino alcohol

Next, the primary hydroxy group of compound **25** protected with MsCl in the presence of Et_3N to afford **26** with 81% yield. Furthermore, the compound **26** reacted with cyclic amines (pyrrolidine, piperdine, azapane, morpholine and thiomorpholine) in neat reaction conditions to afford the compounds **27a-e** in 55-65% chemical yields respectively. The Boc group on nitrogen function of compounds **27a-e** was de-protected using with excess amount of TFA in dichloromethane as solvent at 0 °C to afford the desired amino alcohols **28a-e** with 85-95% yields. The obtained diamine alcohol **28a-e** were fused with squramide mono ester amide **20** using MeOH in sealed tube at 120 °C for 12h to afford the targeted new hybrid type squaramide fused amino alcohol organocatalysts **29a-e** in moderate to good yields (up to 81%) (Scheme 31).



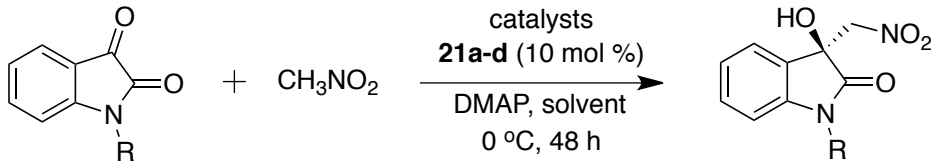
Scheme 31. Synthesis of new hybrid type squaramide fused amino alcohol organocatalysts

The newly synthesized hybride type squaramide fused amino alcohol organocatalysts were characterized with ^{1}H-NMR, ^{13}C-NMR, HRMS, and IR spectroscopy. Next, author examined the catalytic activity of prepared catalysts **29a-e** for enantioselective nitro-aldol reaction of isatins **30a-c** with nitromethane **7**.

2.7.3 The nitro-aldol reaction of isatin with nitromethane using catalysts 21a-d

Author desire to examine the catalytic activity of catalysts **21a-d** for enantioselective nitro-aldol reaction (Table 1), initially, author carried out the reaction of simple isatin **30a** with nitromethane **7** using catalyst **21a** in THF at 0 °C without using of any basic additives. However, the expected aldol product **31a** was not observed even after 48h and the starting compound **30** recovered completely (entry 1). Then author hypothesized that addition of a basic additive might initiate the reaction. To implement this hypothesis, the basic additives such as TEA, DIPEA and DMAP were used in the course of reaction to abstract the proton from nitromethane (entries 2-4).

Table 1. Enantioselective nitro-aldol reaction using catalysts **21a-d**



30a-c **7** **31a-c**

entry[a]	catalysts **21a-d**	R	base	solvent	**31a-c**	yield [%][b]	ee [%][c]
1[d]	**a**	H	---	THF	---	---	---
2	**a**	H	TEA	THF	**a**	12	8
3	**a**	H	DIPEA	THF	**a**	25	11
4	**a**	H	DMAP	THF	**a**	83	38
5	**b**	H	DMAP	THF	**a**	82	32
6	**c**	H	DMAP	THF	**a**	83	31
7	**d**	H	DMAP	THF	**a**	82	32
8	**a**	Me	DMAP	THF	**b**	62	23
9	**a**	Bn	DMAP	THF	**c**	75	11
10	**a**	H	DMAP	DCM	**a**	92	*rac*
11	**a**	H	DMAP	$CHCl_3$	**a**	85	*rac*

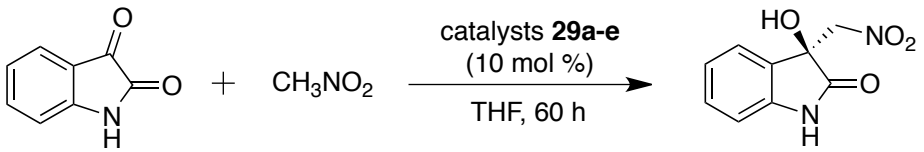
[a]The reaction were carried out with **30a-c** (0.13 mmol), **7** (0.67 mmol) in above mentioned solvents (2.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined on chiral HPLC using Chiralpak AD-H column. [d]Without using any base

By using these basic additives, the reaction was proceeded smoothly and afforded aldol product **31a**, but the better results was observed by using DMAP as additive (entry 4, 83%, 38% ee). Then, different SFAA catalysts **21b-d** were tested and each catalyst showed considerable catalytic activity and furnished the product **31a** in good yields (up to 83%), although the enantioselectivities was not satisfactory obtained (entries 5-7, up to 32% ee). Among the examined catalysts, **21a** was found to be the best one to afford aldol product **31a** in good chemical yield, although the satisfactory enantioselectivity was not afforded. Furthermore, different substituted isatins were examined using catalyst **21a** under the same reaction conditions. The reactions of *N*-methylated isatin **30b** and *N*-benzylated isatin **30c** respectively, afforded the corresponding aldol products **31b** and **31c** in moderate chemical yields with poor enantioselectivities (entries 8, 9). The nitro-aldol reaction was performed in different polar and non-polar solvents. The reaction proceeded efficiently in DCM and $CHCl_3$ respectively, the aldol product **31a** were obtained in good chemical yield, although in racemic (entries 10, 11). These results shown that catalysts **21a-d** were inefficient to afford the aldol products with satisfactory enantioselectivities and it revealed that a basic additive is necessary to proceed the reaction. By observed results in (Table 1) author assumed that the introduction of basic site into the core structure of SFAA catalyst could improve the enantioselectivity of the nitro-aldol reaction.

2.7.4 Nitro-aldol reaction using catalysts 29a-e

Next, author examined the catalytic activity of catalysts **29a-e** using the best solvent *i.e.* THF (Table 2). As the first attempt, catalyst **29a** bearing pyrrolidine ring system as a basic site was tested in the nitro-aldol reaction of simple isatin **30a** with nitromethane **7** at 0 °C. As expected, aldol product **31a** was obtained in excellent chemical yield (99%) with moderate enantioselectivity (64% ee) (entry 1). Furthermore, author examined the catalytic activity of other SFAA catalysts **29b-e** for this reaction. Catalyst **29b** bearing piperidine ring system afforded **31a** with excellent chemical yield (92%) but with low enantioselectivity (39%) (entry 2). The best enantioselectivity (81% ee) with good chemical yield (92%) was obtained by using catalyst **29c** bearing azepane ring system (entry 3). On the other hand, other two catalysts bearing morpholine and thiomorpholine ring systems **29d-e**, afforded the nitro-aldol product **31a** in only trace amounts (entries 4, 5).

Table 2. The enantioselective nitro-aldol reaction using catalysts **29a-e**



30a **7** **31a**

entry[a]	catalysts **29a-e**	temp. (°C)	yield [%][b]	ee [%][c]
1	**a**	0	99	64
2	**b**	0	92	39
3	**c**	0	92	81
4	**d**	0	*trace*	---
5	**e**	0	*trace*	---
6	**d**	RT	85	61
7	**e**	RT	98	59

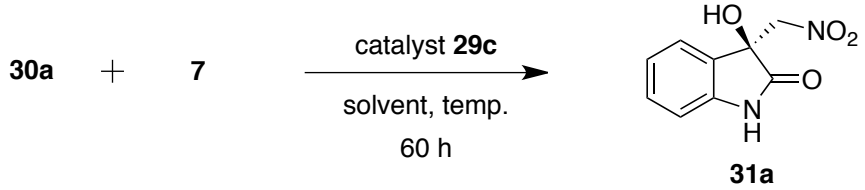
[a]The reaction were carried out with **30a** (0.13 mmol), **7** (0.67 mmol) in dry THF (2.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined by chiral HPLC on chiralpak AD-H column

Fortunately, performing these reactions at room temperature successfully afforded the desired aldol product **31a** in good chemical yields with moderate enantioselectivities (**29d**: 85%, 61% ee; **29e**: 98%, 59% ee) (entries 6, 7), but these results were not better than those obtained with catalyst **29c**. From these observed results, the catalyst **29a** is superior in the nitro-aldol reaction of isatin **30a** with nitromethane **7**. Furthermore, author investigated optimization reaction condition for enantioselective nitro-aldol reaction using catalyst **29c** with isatin **30a** and nitromethane **7**.

2.7.5 Optimization of nitro-aldol reaction conditions using catalyst 29c

Author next inspected the effect of solvent, molar ratio of catalyst, and reaction temperature (entries 1-20, Table 3). Changing the molar ratio of catalyst **29c** to 5 mol% and 20 mol% also provided the aldol product **31a** in good chemical yields and enantioselectivity (5 mol%: 82%, 74 % ee, 20 mol%: 93%, 64% ee), respectively (entries 1, 2). Author also optimized the nitro-aldol reaction at lower temperature (-20 ^{o}C), in these reaction condition author observed decreases in both the chemical yield (70%) and enantiomeric excess (78%) (entry 3).

Table 3. Optimization of reaction conditions using catalyst **29c**

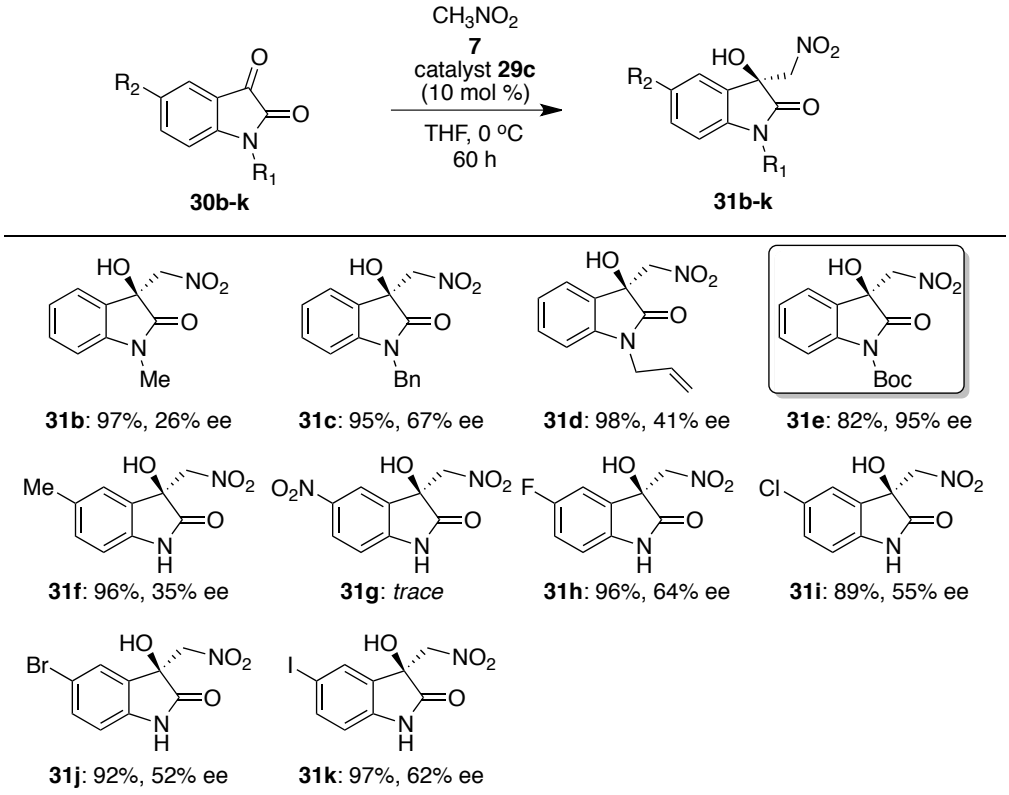


entry[a]	catalyst **29c** (mol %)	solvent	temp (°C)	yield [%][b]	ee [%][c]
1	5	THF	0	82	74
2	20	THF	0	93	64
3	10	THF	-20	70	78
4	10	toluene	0	89	*rac*
5	10	benzene	0	98	*rac*
6	10	*m*-xylene	0	95	*rac*
7	10	DCM	0	86	2
8	10	diisopropylether	0	93	2
9	10	CPME	0	86	*rac*
10	10	1,4-Dioxane	rt	94	55
11	10	Et_2O	0	93	21
12	10	THP	0	*trace*	---
13	10	TFE	0	94	*rac*
14	10	ACN	0	91	53
15	10	DMA	0	43	74
16	10	DMF	0	57	64
17	10	DMSO	rt	*trace*	---
18	10	MeOH	0	92	*rac*
19	10	water	rt	92	*rac*
20	10	neat	0	96	*rac*

[a]The reaction were carried out with **30a** (0.13 mmol), **7** (0.67 mmol) in above mentioned dry solvents (2.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined by using chiral HPLC on chiralpak AD-H column

The use of non-polar aromatic solvents also afforded **31a** with excellent chemical yields (89-95%), but completely in racemic form (entries 4-6). Furthermore, the reaction in chlorinated and different ethereal solvents afforded **31a** in good to excellent chemical yields (86-94%) (except THP, in which case only trace amount of **31a** was formed), but very poor to moderate enantioselectivities were observed (entries 7-12). Moreover, the effect of polar solvents such as TFE, ACN, DMA, DMF, DMSO and MeOH were also investigated. Unfortunately, satisfactory chemical yields and enantioselectivities were not obtained (entries 13-18). The reaction was also conducted in water and in neat conditions (nitromethane used as solvent and reactant). Although the product **31a** was obtained in fairly good chemical yields, good enantioinduction was not observed (entries 19 and 20). From these results, after screening of catalysts, catalyst loadings, additives, solvents and reaction temperatures, author decided to set the conditions as (catalyst **29c** (10 mol %), in THF at 0 °C for 60 h) as optimal conditions for this reaction and started to explore the substrate scope for enantioselective nitro-aldol reaction.

2.7.6 Substrate scope for enantioselective nitro-aldol reaction using catalyst 29c



Scheme 32. Substrate scope of nitro-aldol reaction using SFAA catalyst **29c**

In a substrate scope of nitro-aldol reaction, a variety of isatins **30b-k** with nitromethane **7** were afforded the nitro-aldol products **31b-k** in good to excellent chemical yields and moderate to good enantioselectivities (Scheme 32). The reactions of *N*-alkylated isatins such as *N*-methyl-isatin **30b**, *N*-benzyl-isatin **30c** and *N*-allyl-isatin **30d** with nitromethane **7** afforded the desired aldol products **31b-d**, respectively, in excellent chemical yields (95-98%) but with low to moderate enantioselectivities (26-67% ee). On the other hand, the nitro-aldol reaction using *N*-Boc isatin **30e** afforded the product **31e** in good chemical yield (82%) with excellent enantioselectivity (95% ee). 5-Methyl-isatin **30f** provided the aldol product **31f** in excellent chemical yield (96%) with low enantioselectivity (35% ee). Moreover, only trace amount of the aldol product **31g** was obtained from the reaction of 5-NO_2-isatin **30g** with **7**, although the exact reason was not clear. The use of halogenated isatins **30h-k** provided the corresponding nitro aldol products **31h-k** with fairly good to excellent chemical yields (89-97%), but with moderate enantioselectivities (52-64% ee).

2.7.7 Mechanistic investigation of nitromethane and isatin with squaramido unit

Finally, the enantioselective reaction mechanistic pathway of this reaction using author developed squaramide-fused amino alcohol catalyst **29c** was considered based on both the high enantiopurity (81% ee) of the chiral aldol product (*S*)-**31a** which was obtained from the reaction of isatin **30a** with nitromethane **7** and the calculation analysis (**1**: natural bonding orbital (NBO) analysis of the hydrogen bonding of simple squaramide **I** with isatin **30a** or nitromethane **7**, **2**: the hydrogen bonding distance calculations of complexes **A** or **B**, **3**: electron density of isatin **30a**) (Figure 10). Thus, (1) NBO analysis was performed subsequently on the optimized structures to quantify the donor-acceptor. The stabilization energies ($E^{(2)}$) of intermolecular interactions of all complexes (complexes **A** and **B**) were performed by using second order perturbation theory. As the calculation result, the stability of **A** ($E^{(2)}$ / kcal·mol^{-1} = 1.56) was increased as compared with that of **B** ($E^{(2)}$ / kcal·mol^{-1} = 0.25). This result might be consistent with the stability of the complexes. Furthermore, (2) the hydrogen bonding distance of complex **A** was also shorter than that of complex **B**. In addition, (3) the place of the highest electron density (Mulliken charge distribution) was on oxygen of amide in isatin **30a**.

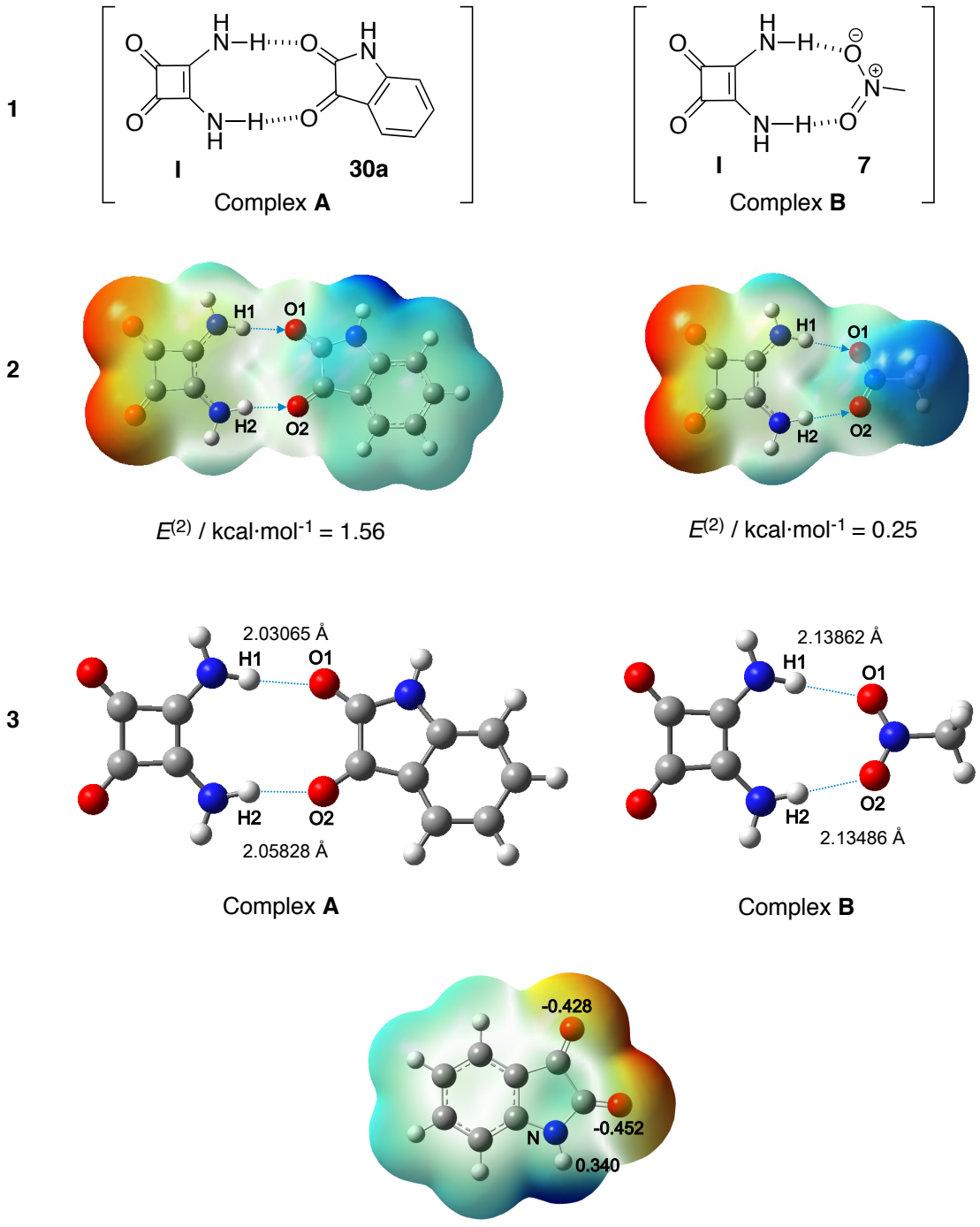
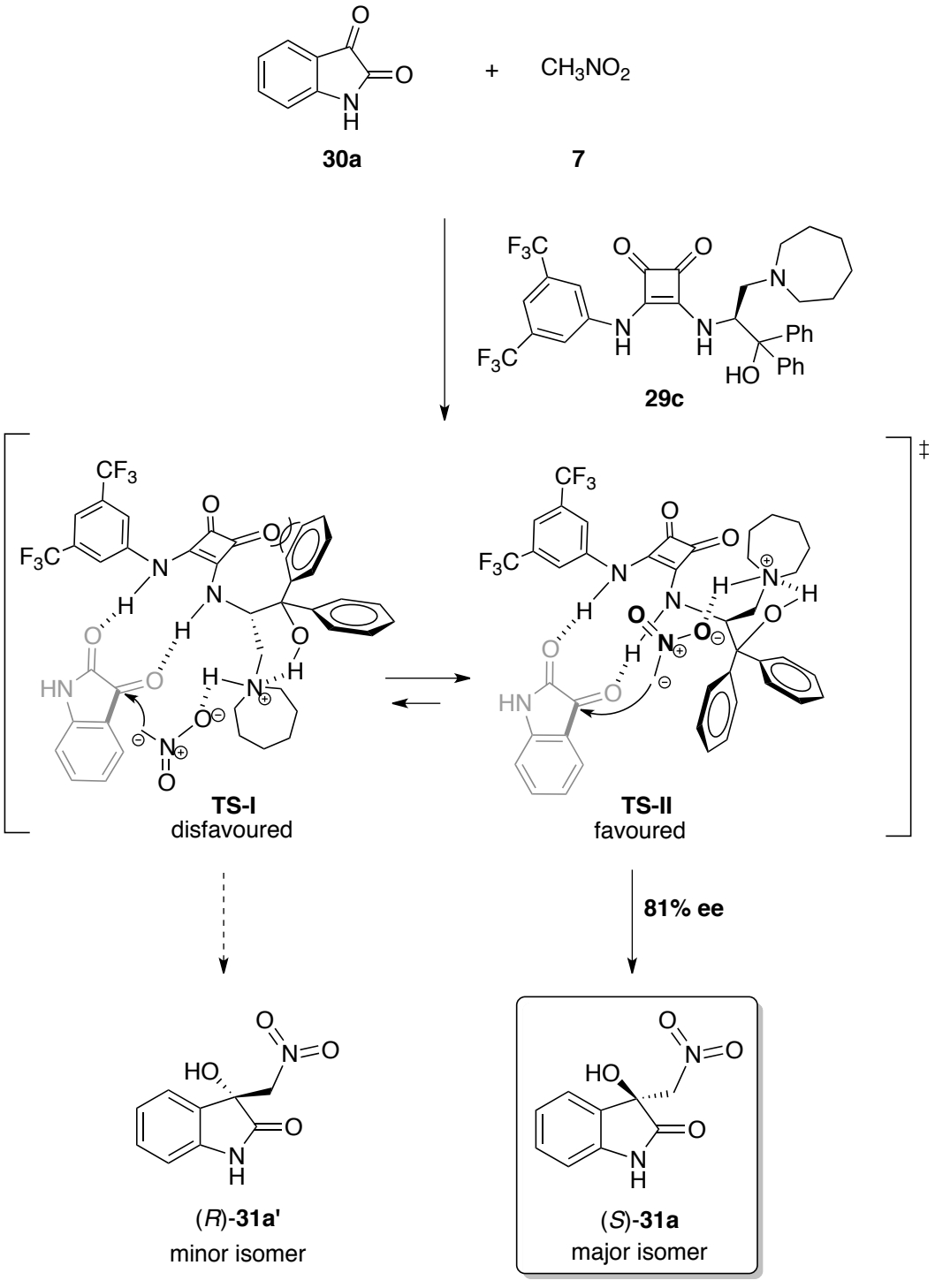


Figure 10. (1) The calculated second order perturbation energies (E (2) / kcal, E^{a}mol^{-1}) of the second donor (H-bond donor of squaramides) and acceptor (oxygenatoms of isatin **30a** and nitrate **7**) interaction for the complexes **A** and **B**, (2) the calculated hydrogen bond distances of the complexes **A** and **B**, (3) The electron density map and Mulliken charge distribution of isatin **30a**



Scheme 33. Plausible reaction course for nitro-aldol reaction

From the mechanistic investigation of isatin **30a** and nitromethane **7** with squaramido unit **I** (Figure 12). A model for the enantioselective nitro-aldol reaction a mechanistic pathway is proposed. First, the active methylene proton of nitromethane is abstracted by basic tertiary amino group on azepane ring in catalyst **29c** to form nitro enolate, which might also induce the strong hydrogen bonding interaction between the hydrogen atom of the ammonium moiety on azepane ring in catalyst and oxygen atom of nitro enolate. Next, isatin **30a** might fixed with catalyst **29c** through two hydrogen bonds between two carbonyl oxygen atom on isatin **30a** and two primary amino groups on squaramide site in catalyst. When isatin **30a** makes the hydrogen bonding to catalyst, one carbonyl oxygen atom of amide on isatin **30a** might binds with the hydrogen atom of amino group with 3,5-bis(trifluoromethyl)phenyl group as an electron-withdrawing group on squaramide site in catalyst and other carbonyl oxygen atom on isatin **30a** might binds with the hydrogen atom of another amino group on squaramide in catalyst. In addition, the side chain containing ammonium alcohol moiety on catalyst might be fixed by the hydrogen bonding interaction between hydrogen atom on the hydroxyl group and ammonium moiety on azepane ring on the side chain. Among the possible two transition states **TS-I** and **TS-II**, **TS-II** has less steric interaction than that of **TS-I**, which has strong steric repulsion between four membered squaramide skeleton and di-phenyl groups on catalyst. Hence the reaction might proceed *via* the transition state **TS-II**, in which nitroenolate coordinated to ammonium moiety on azepane ring could attack on the isatin from the upper side leading to the formation of (*S)*-**31a** as major enantiomer, whereas minor isomer (*R*)-**31a'** might be obtained *via* the unfavorable transition state **TS-I** (Scheme 33).

2.8 Summary

In summary, author prepared new hybrid type SFAA catalysts **29a-e** from commercial available amino esters *via* simple organic transformations and demonstrated their catalytic efficiency in the enantioselective nitro-aldol reaction of various isatins **30a-k** and nitromethane **7**. This protocol provides the chiral 3-substituted 3-hydroxyoxindoles **31a-k** in excellent chemical yields (up to 99%) and excellent enantioselectivities (up to 95% ee). Especially, catalyst **29c** bearing azepane ring system as basic site showed best catalytic activity for this reaction. The obtained 3-alkylsubstituted 3-hydroxyoxindoles could be important intermediates for the synthesis of many significant biologically active scaffolds. The feasible mechanistic path of this reaction using newly prepared catalyst **29c** was also explained by calculated the second order perturbation

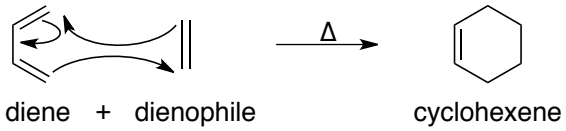
energies of second donor [H-bond donor of squaramide] and acceptor (oxygen atoms of isatin **30a** and nitromethane **7**) and hydrogen bond distances between catalyst **29c** and isatin **30a**, and nitromethane **7**.[12]

Chapter 3

The New Hybrid Type Squaramide Fused Amino Alcohol Organocatalysts For Enantioselective Diels-Alder Reaction of 3-Hydroxy-2-Pyridones with Maleimides

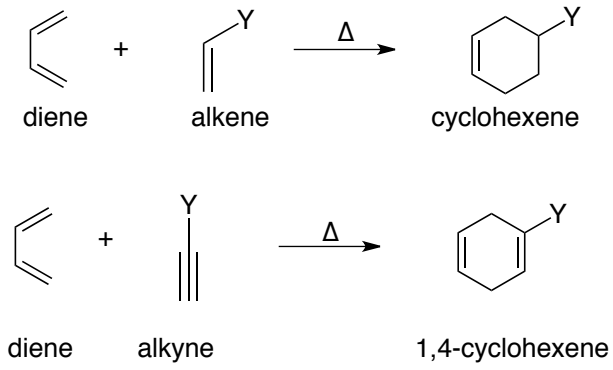
3.1 Introduction

The Diels-Alder reaction is a classical organic reaction using with conjugated diene and dienophile to form a cyclohexene system, it's also refered as a [4+2] cycloaddition reaction. The DA reaction discovered by Otto Diels and Kurt Alder in 1928 (Scheme 34). For their tremendous contribution presented Nobel prize in chemistry in the year of 1950. The Diels-Alder reaction is also reliable practical method for constructing the complex bicyclic compounds in synthetic organic chemistry.



Scheme 34. General representation of Diels-Alder reaction

The [4+2] cycloaddition reaction usually employs with a diene with electron deficient dienophile, in which the diene and dienophile involves an electrocyclic reaction the where diene contributes 4π-electrons while the dienophile contributes 2π-electrons to afford the cyclohexene framework. In the case of an alkynyl dienophile, the initial adduct can still react as a dienophile if not too sterically hindered (Scheme 35).[31]



Scheme 35. Diels-Alder reaction using different dienophiles

3.1.1 Mechanism of Diels-Alder reaction

The mechanism of Diels-Alder reaction obeys concerted pericyclic reaction pathway. The reaction follows in a single concerted pathway, during the course of reaction no intermediates are formed. In the mechanism of Diels-Alder reaction the electron rich diene reacts with electron withdrawing dienophile. Usually it follows [4πS+2πS] cycloaddition, representative that it proceeds through the suprafacial-suprafacial interactions of a 4π-electron system of the diene with a 2π-electron system of dienophile, an interaction that is thermally allowed called as [4n+2] cycloaddition (Figure 11).

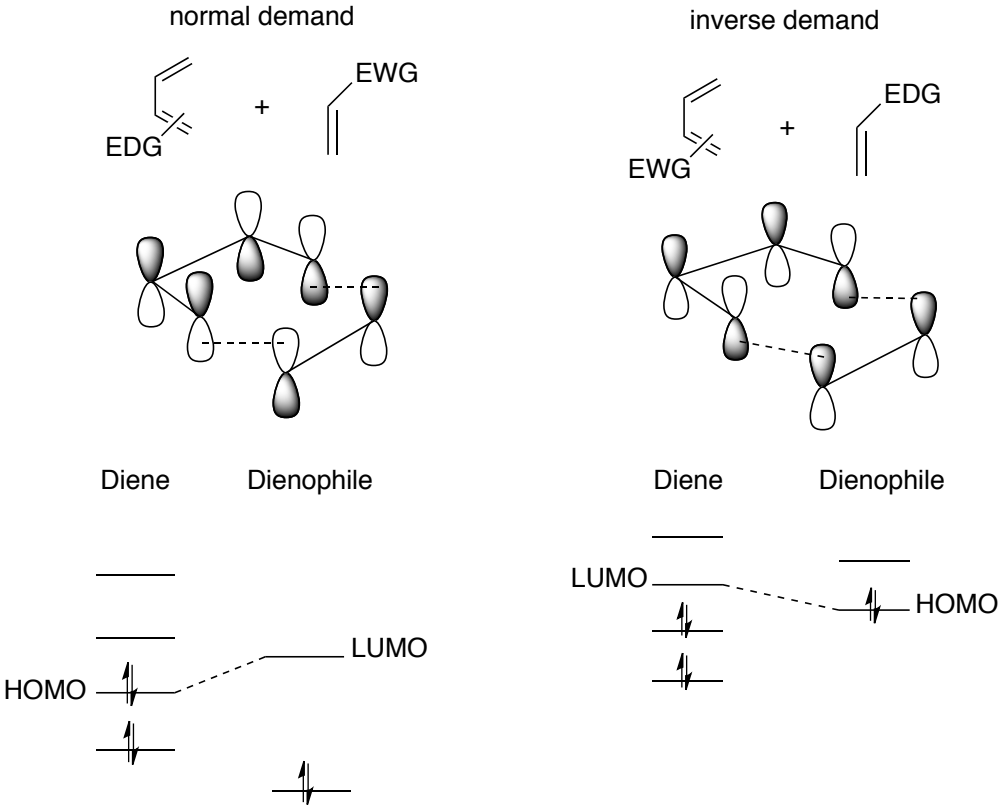


Figure 11. Pictorial representations of frontier molecular orbitals of Diels-Alder reactions

In a normal electron-demand DA reaction predominately occurs between electron rich dienes and electron deficient dienophiles, while in the case of inverse electron demand DA reaction is controlled by electron withdrawing dienes with electron rich dienophiles to afford the DA adducts.[32]

3.1.2 Regioselectivity of Diels-Alder reaction

The frontier molecular orbital (FMO) analysis is used to explain the regioselectivity outlines in Diels-Alder reactions. The diene and dienophile resonance effects can be taken in consideration to assume the regioselectivity of the DA reaction. The figure depicted below shows the partial moment of resonance charges in a diene creates more electron density towards electron donating group. In the case of dienophile, the partial resonance charges moment is towards electron withdrawing group, by these phenomena of resonance effects in diene and dienophiles it's easy to predict the regioselectivities of DA reaction (Figure 12).

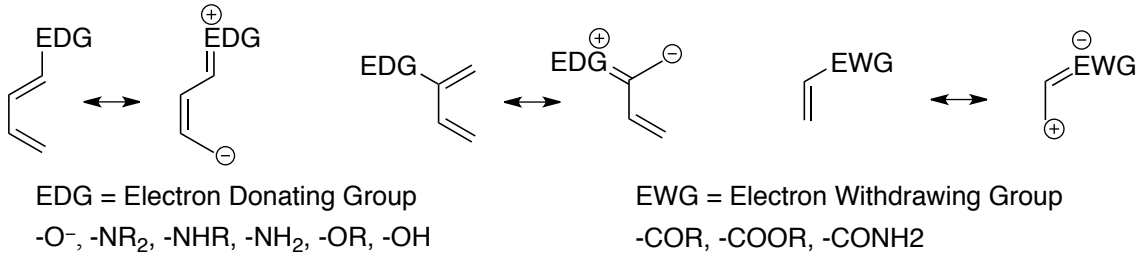
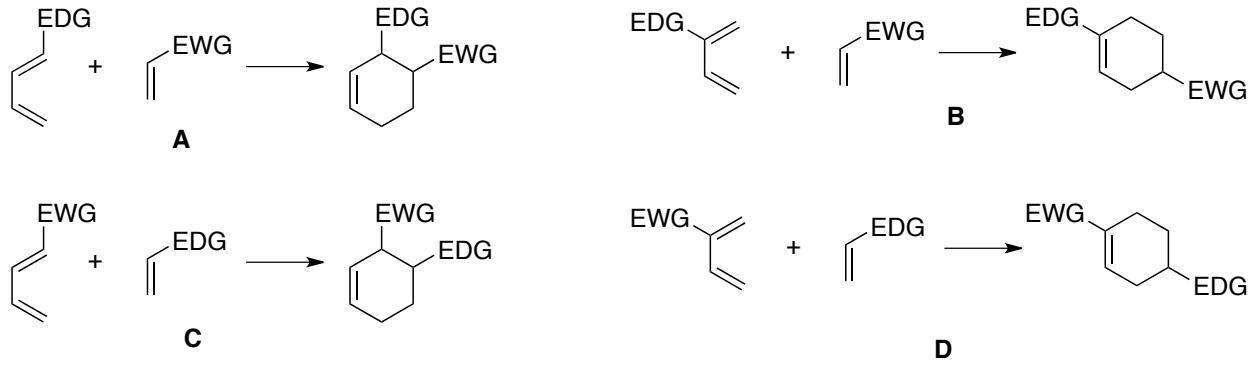


Figure 12. Diene, dienophile charge distribution

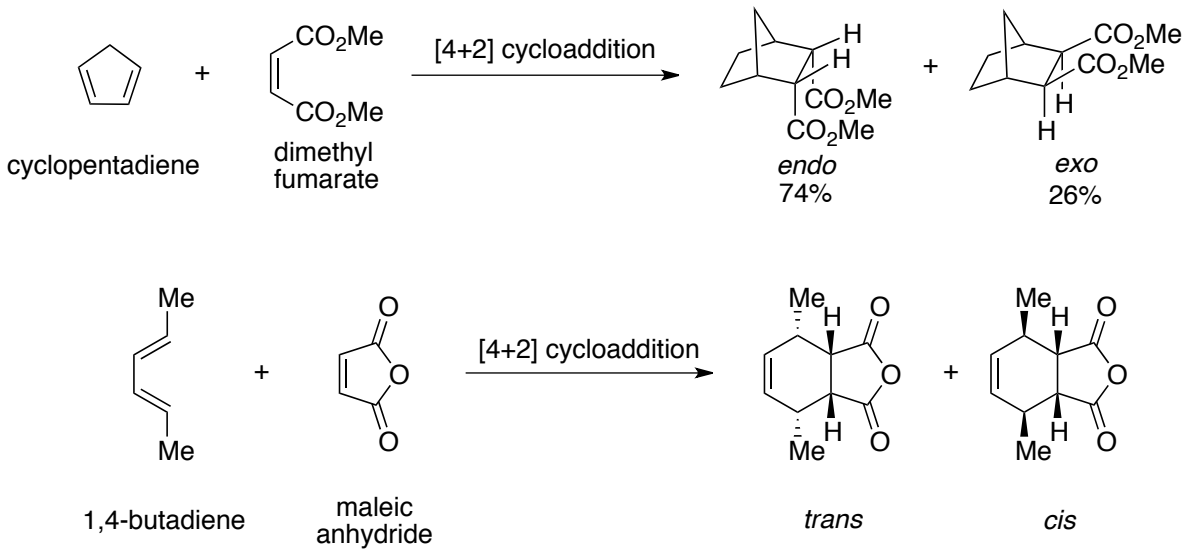
In a normal-demand DA reaction, the diene is bearing with an electron donating group at C1 position takes its major HOMO amount at C4, although the dienophile has the largest LUMO factor at C2 combination of these factors affords the "ortho" product **A**. The diene containing at C2 position as in case of **B** underneath has the more HOMO factor at C1, which allows the "para" adduct. Parallel approach for the equivalent inverse-demand DA reaction takes place which gives rice to related adduct depicted as **C** and **D** (Scheme 36).



Scheme 36. Regioselectivity in Diels-Alder reaction

3.1.3 Stereoselectivity in Diels-Alder reaction

The Diels-Alder (DA) reaction are concerted cycloaddition reactions i.e. the stereochemistry of the reactants which involves in DA reaction as retains in their corresponding products. For example, the DA reaction of cyclopentadiene with dimethyl fumarate affords two different products, the *endo* and *exo*, might conceivably be formed depending on the manner in which the diene and dienophile are disposed in the transition state. According to the *endo* addition rule, in diene addition reaction two components arrange themselves in parallel planes. The afforded bicyclic products as two isomers *endo* (74% yield) along with *exo* (26% yield) isomers is depicted in following reaction. In a similar manner the DA reaction of *trans*-1,4-butadiene with maleic anhydride produces two unequal amounts of *trans* and *cis* isomers in the course of DA reaction. In this reaction the stereochemistry of the butadiene retains in the *trans* DA adduct as major product (Scheme 37).[33]



Scheme 37. General representation of stereoselectivity in Diels-Alder reaction

3.1.4 The diene

The well explored dienes in DA reaction consists 1-methoxy-3-trimethylsiloxy-1,3-butadiene moiety, it's also referred as Danishefskys diene **E**, it has precise synthetic value for providing unsaturated 1,2-cyclohexenone systems. Additionally, the Brassard developed 1,3-alkoxy-1-trimethylsiloxy-1,3-butadienes **F**, and Rawal explored 1-dialkylamino-3-trimethylsiloxy-1,3-butadienes **G** are well-studied in the course of DA reactions. And these

unsaturated systems (dienes) with appropriate dienophiles provides synthetically valuable complex motifs in the synthetic organic chemistry (Figure 13).[34]

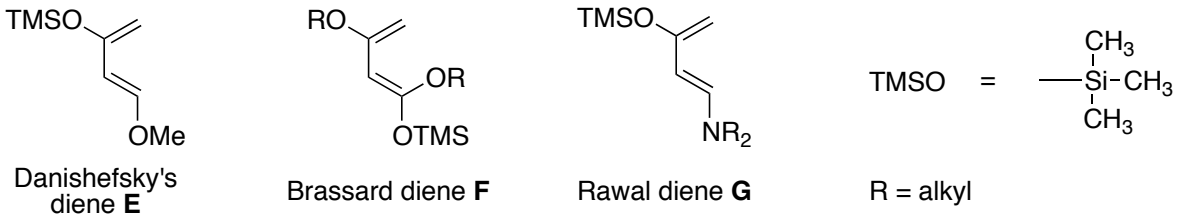
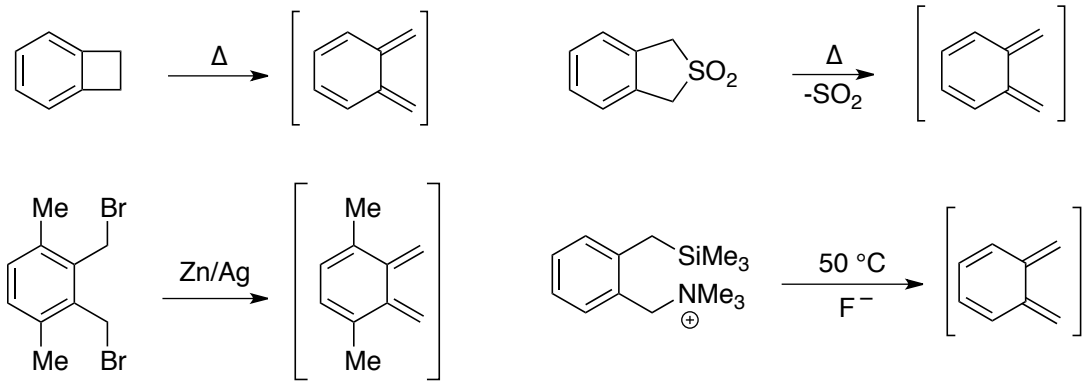


Figure 13. Most investigated dienes in Diels-Alder reaction

Most of the unstable *o*-quinodimethanes dienes usually generated by in-situ in the course of the DA reaction at elevated reaction temperature. For generating *o*-quinodimethanes reactive species pyrolysis method usually employed. For example, the benzocyclobutenes, benzosulfones, 1,4-elimination of *ortho*- benzylic silanes, and sulfonyls, produces the unstable *o*-quinodimethanes diene reactive species at high reaction temperatures and which can easily participate in the DA reactions. Additionally, the reduction of α,α'-ortho benzylic dibromides results in the formation of unstable dienes (Scheme 38).



Scheme 38. In-situ generation unstable *O*-quinodimethanes dienes

3.1.5 The dienophile

The dienophiles posses with electron withdrawing groups on it, many different kinds of dienophiles can take part in DA reactions.[35] Usually they may be the derivatives of acetylene or ethylene functional moiety containing simple acrylates, chromium bonded acrylates, cyclic

ketones, vinyl sulfones, allenes, thioketones, nitroso-benzene and electron withdrawing carboxylates.

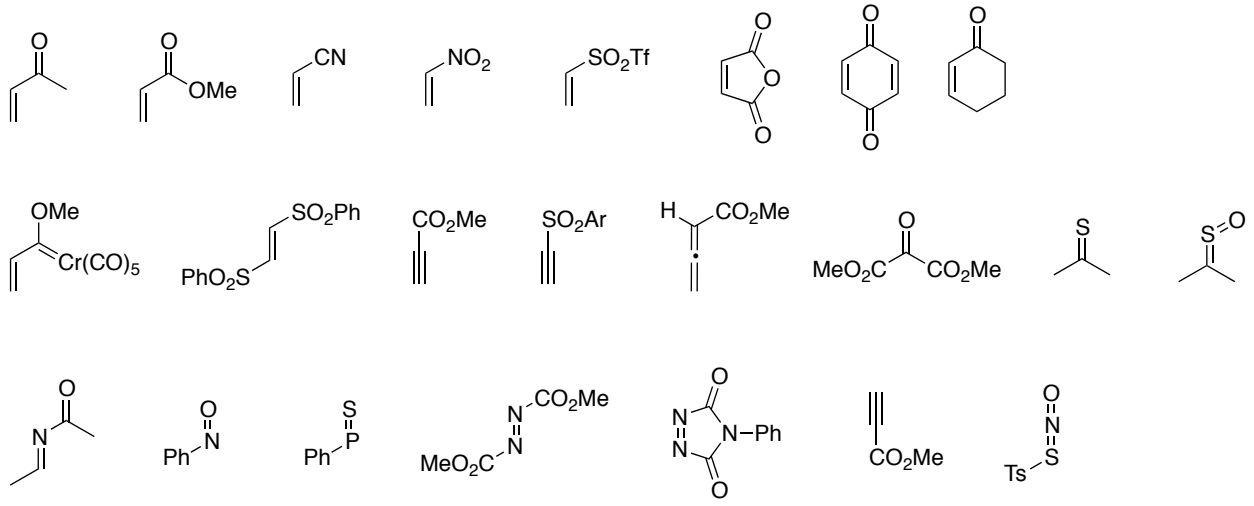
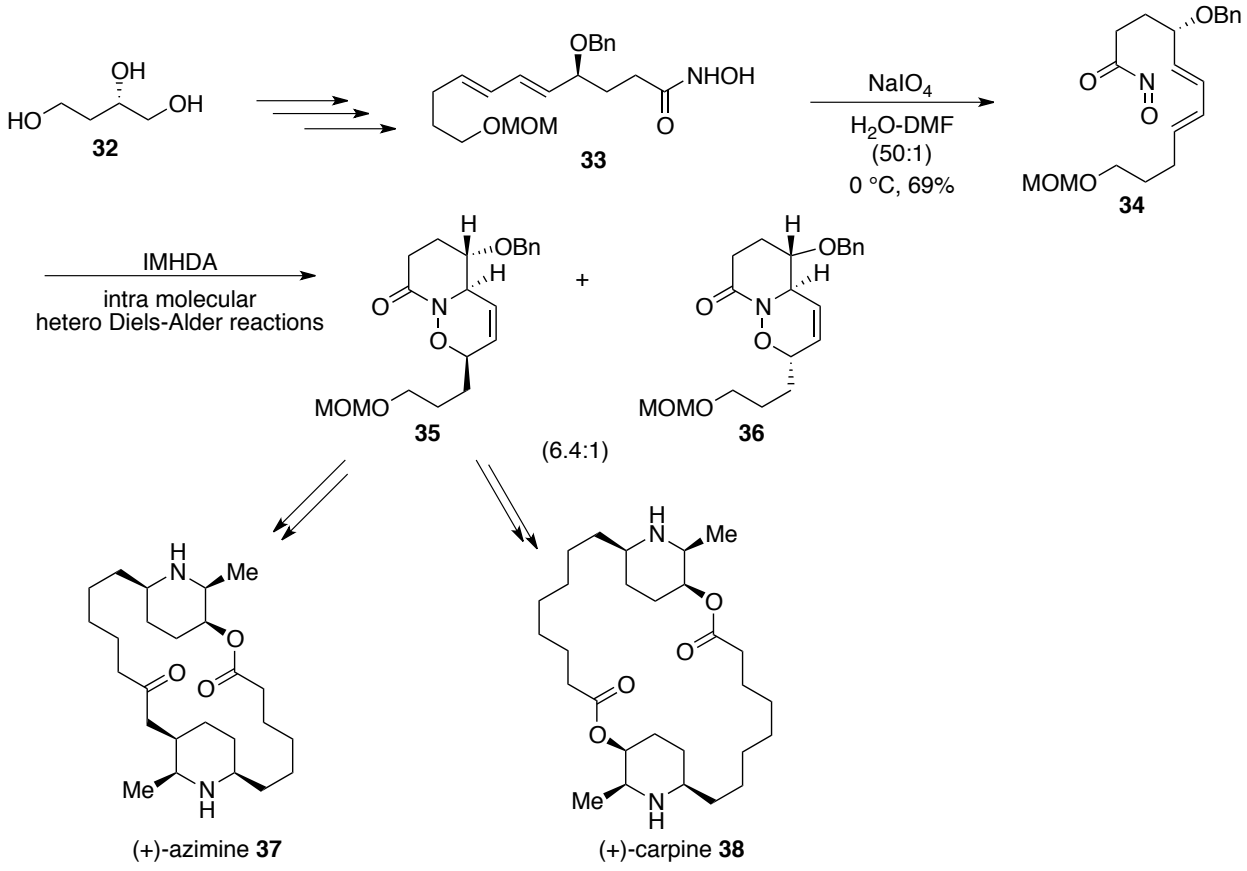


Figure 14. Different types of dienophiles that undergo Diels-Alder reaction

3.1.7 Intramolecular hetero Diels-Alder (IMHDA) reaction

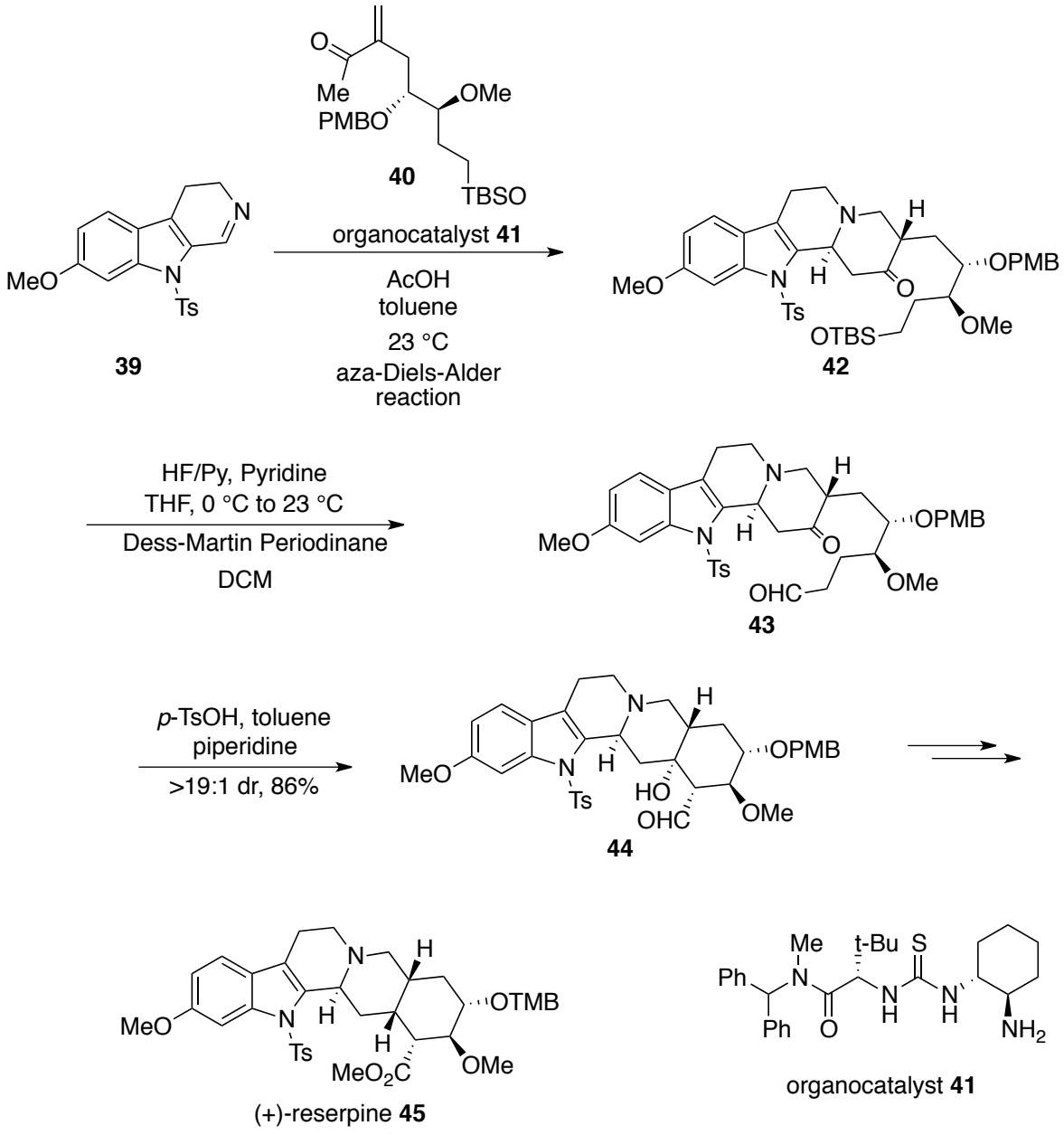
The intramolecular hetero-Diels-Alder (IMHDA) reaction is useful synthetic protocol in synthetic organic chemistry, it is an adaptable protocol for the synthesis of novel polycyclic systems. By using this protocol, it is easy to construct the natural products and biologically active compounds. Recently, Corey and Nicolaou[36] has applied the IMHDA protocol to synthesis macrocyclic dilactone family alkaloid such as, (+)-carpine and (+)-azimine, these natural products are constructed using, the acylnitroso-DA (IMHDA) protocol (Scheme 39). The synthesis began with optically active (*S*)-1,2,4-butanetriol **32** as starting material. After the successive synthesis of the compound **33** from **32** its reacted with $NaIO_4$ to afford the compound **34** which was underwent IMHDA reaction to afford the DA-adducts **35** and **36** as diastereomers. Among them the major diastereomer **35** was applied for the total synthesis of (+)-azimine **37** and (+)-carpine **38**.



Scheme 39. Importance of hetero Diels-Alder reaction in (+)-azimine and (+)-carpine synthesis

3.1.8 Intermolecular aza-Diels-Alder reaction

The catalytic enantioselective intramolecular aza-Diels-Alder reaction is remains most adorable protocol for synthesizing many natural products. The aza-Diels-Alder reaction transforms imines and dienes into a biologically active tetrahydropyridines. The significance of the aza-Diels-Alder reaction is for the construction of a six-membered ring containing nitrogen functional. Recently, Jacobson and his research group[37] reported the total synthesis of (+)-Reserpine by employing an aza Diels-Alder reaction strategy.

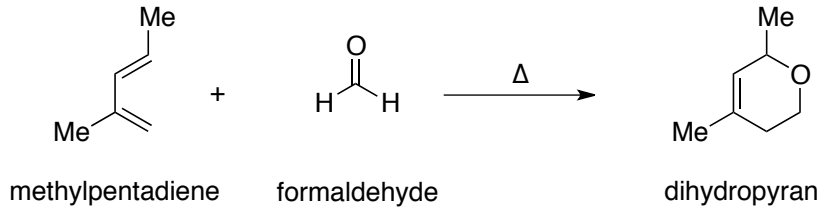


Scheme 40. Importance of aza-Diels-Alder reaction in (+)-reserpine synthesis

A highly diastereoselective catalyst-controlled aza-Diels-Alder reaction between imine **39** and α-substituted enone **40** were observed in the presence of chiral amino organocatalyst **41** providing the desired DA-adduct **42**. The obtained DA-adduct can undergo oxidation in the presence of Dess-Martin periodinane to afford the aldehyde **43**. Further, the compound **43** was cyclized in the presence of piperidine and *p*-TsOH in toluene to afford compound **44** with 86% yield. Additional manipulation of compound **44** involving aldehyde oxidation/esterification, elimination/reduction of alcohol, de-protection of PMB ether and tosyl amine, and installation of the trimethoxybenzoyl (TMB) ester which led to the formation of targeted (+)-reserpine **45** (Scheme 40).

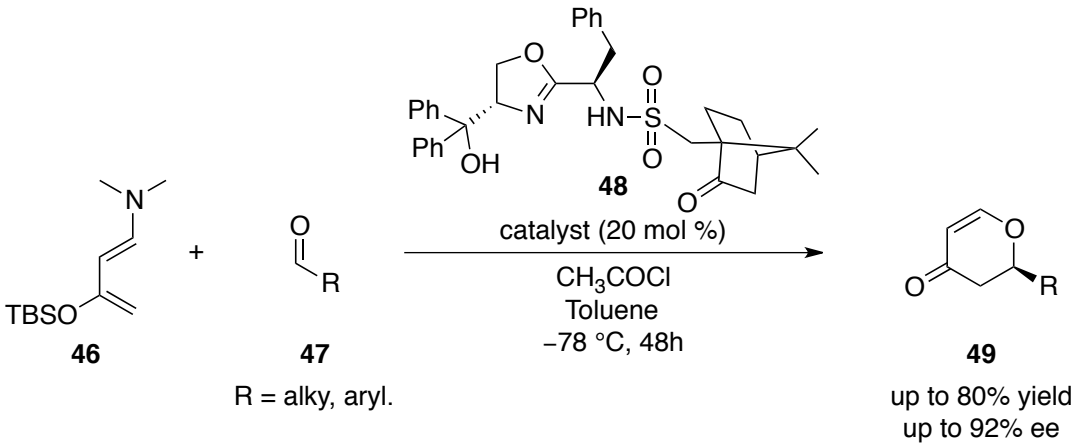
3.1.9 Oxo-Diels-Alder reaction

The oxo-Diels-Alder reaction usually employs of methyl pentadiene with formaldehyde to afford the dihydropyran ring systems. The oxo-Diels-Alder reaction was first reported in 1949 using a methyl pentadiene with formaldehyde (Scheme 41).[38b]



Scheme 41. Oxo-Diels-Alder reaction

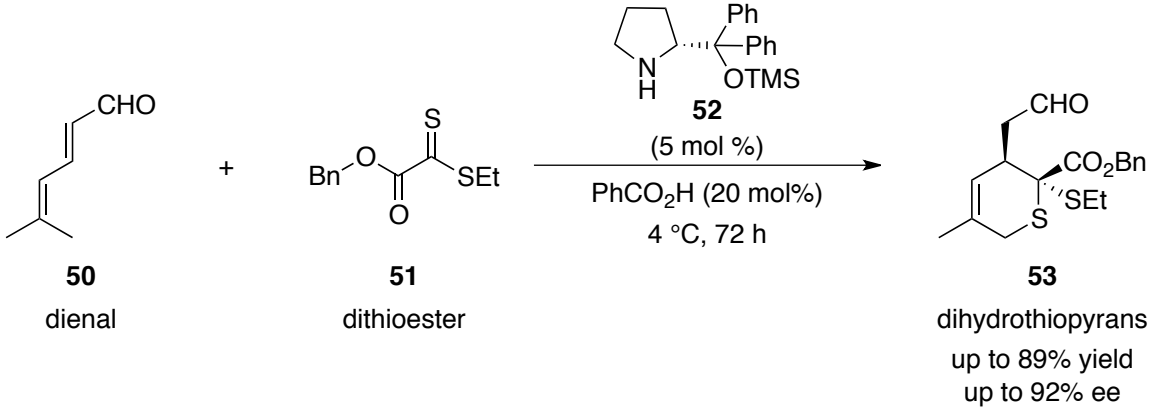
M. S. Sigman and his research group[38a] reported the enantioselective oxo-Diels-Alder reaction using oxazoline **48** based hydrogen bond catalyst. They developed the new elegance of segmental oxazoline catalysts that trigger aldehydes **47** *via* hydrogen bond formation. The activated aldehydes can participate in highly enantioselective oxo-Diels-Alder reaction with diene **46** (Scheme 42).



Scheme 42. Importance of oxo-Diels-Alder reaction for chiral dihydro-pyrans

3.1.10 Thio-Diels-Alder reaction

Recently K. A. Jørgensen and his research group[39] reported a enantioenriched sulfur-based heterocycles by TMS prolinol organocatalyst **52**. The catalytic enantioselective Diels-Alder reaction of dienal **50** with dithioester **51** affords the corresponding chiral dihydrothiopyrans **53** in both good chemical yields (up to 89%) and enantioselectivities (up to 92% ee) (Scheme 43).

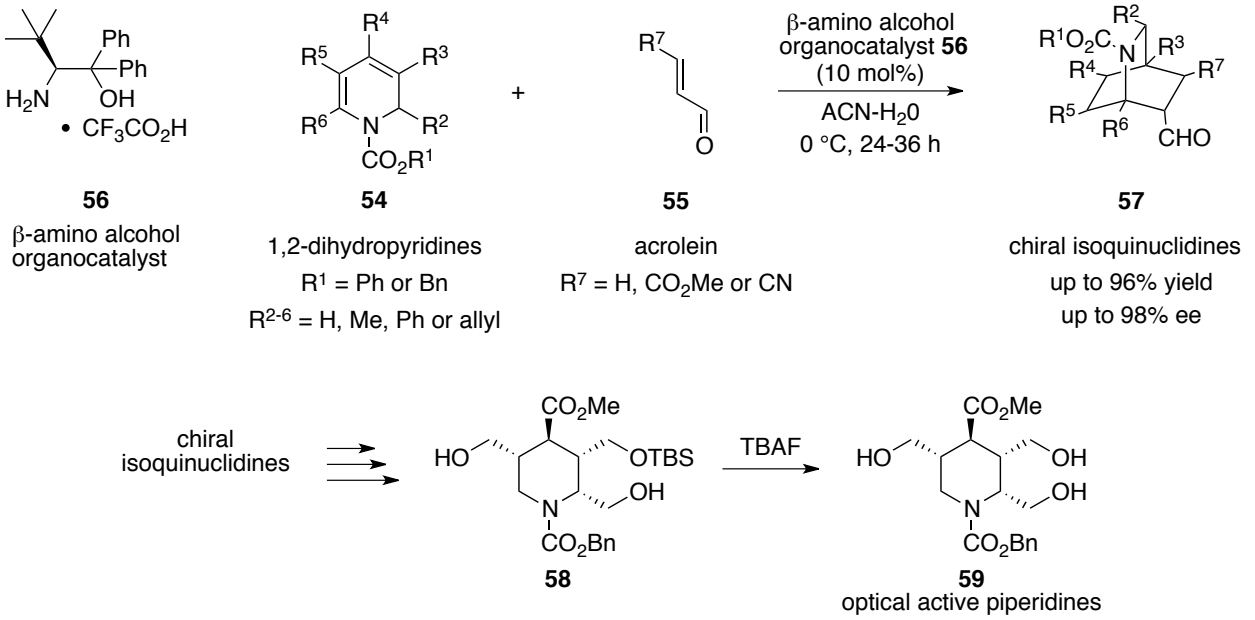


Scheme 43. The oxo-Diels-Alder reaction to synthesis of chiral dihydrothiopyrans

3.1.11 Amino alcohol catalyzed enantioselective Diels-Alder reaction

Recently from author research group[11f] reported the enantioselective Diels-Alder reaction of 1,2-dihydropyridines **54** with acrolein **55** using a simple primary β-amino alcohol catalyst **56** which afforded the, chiral isoquinuclidines **57** in both excellent chemical yields (up to 96%) and enantiomeric excess (up to 98% ee). In addition, the obtained chiral isoquinuclidines are

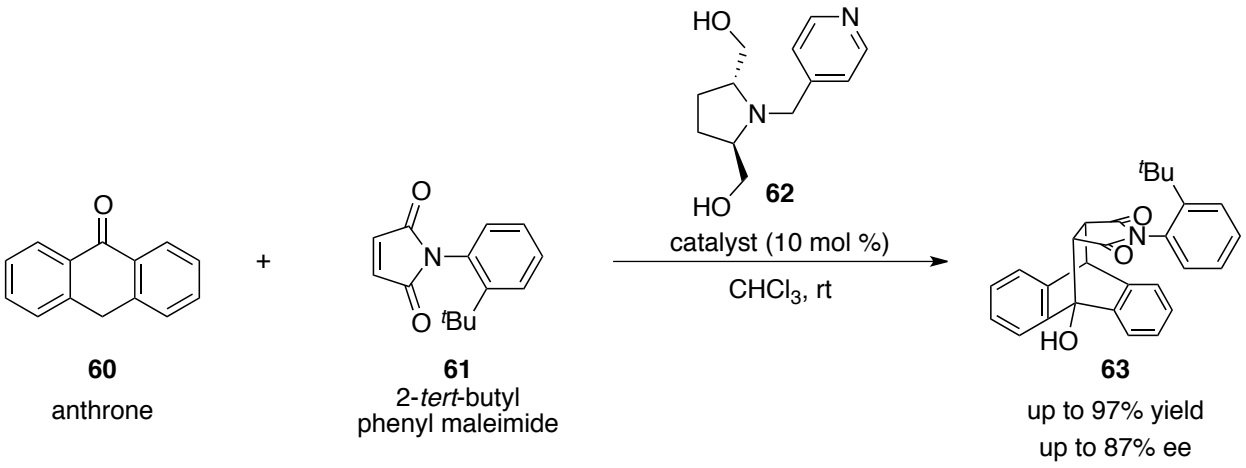
successfully converted in to TBS protected chiral piperidines **58** which upon de-protection in the presence of TBAF afforded the optically aactive chiral piperidine **59** having four continuous stereogenic-centers (Scheme 44).



Scheme 44. β-Amino alcohol organocatalyst catalyzed enantioselective Diels-Alder reaction

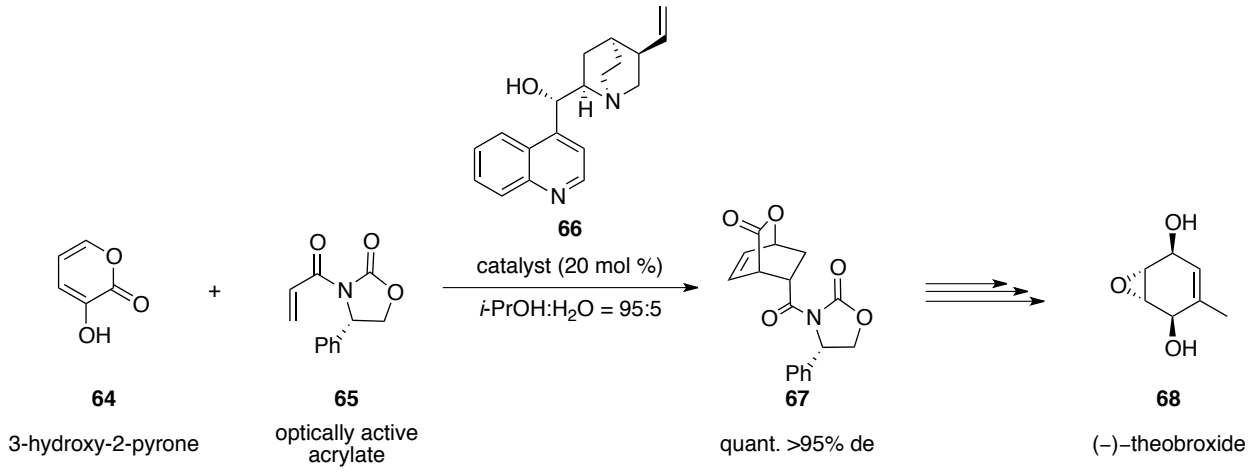
3.2 Base catalyzed Diels-Alder reactions

Y. Yamamoto and his research group[40] reported the enantioselective base catalyzed Diels-Alder reaction of anthrone **60** with 2-*tert*-butyl-phenylmaleimide **61** using pyrrolidine derivative as basic organocatalysts **62**. They obtained the corresponding DA-adduct **63** in excellent chemical yield (up to 97%) and with good enantioselectivities (up to 87%) (Scheme 45).



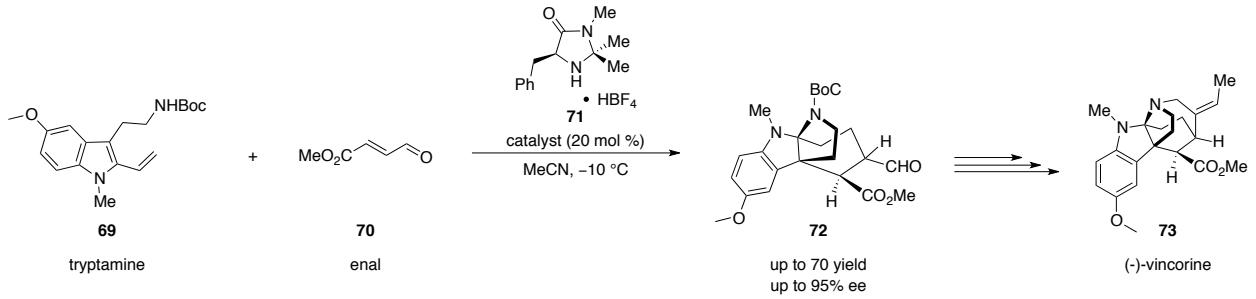
Scheme 45. The base catalyzed Diels-Alder reaction of anthrone with 2-tert-butyl-phenyl maleimide

H. Okamura and his research group[41] reported the enantioselective base catalyzed Diels-Alder reaction of 3-hydroxy-2-pyrone **64** with optically active acrylate **65** using with catalyst **66**, to afford DA-adduct **67** with >95% de. They also demonstrated the synthetic utility of obtained DA-adduct for synthesizing (-)-theobroxide **68** (Scheme 46).



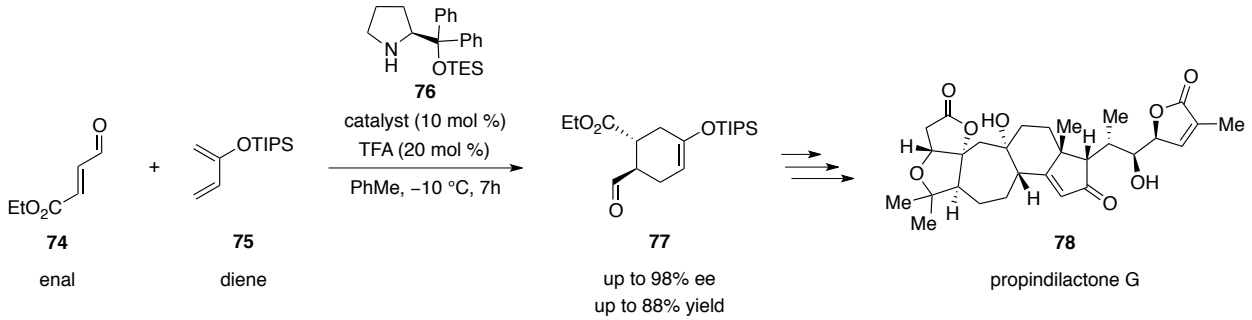
Scheme 46. The base catalyzed Diels-Alder reaction of 3-hydroxy-2-pyrone with acrylate

D. W. C Macmillan and his research group[42] reported the enantioselective Diels-Alder reaction using secondary amine imidazolidinone basic catalyst **71** of tryptamine **69** with enal **70** *via* iminium pathway. Which afforded the structurally complex DA-adduct **72** in moderate yields (up to 70%) and in excellent enantioselectivities (up to 95%). The obtained DA-adduct **72** was successfully applied in the total synthesis (-)-vincorine **73** natural product using Diels-Alder/amine cyclization cascade reaction strategy (Scheme 47).



Scheme 47. The base catalyzed Diels-Alder reaction of tryptamine with enal

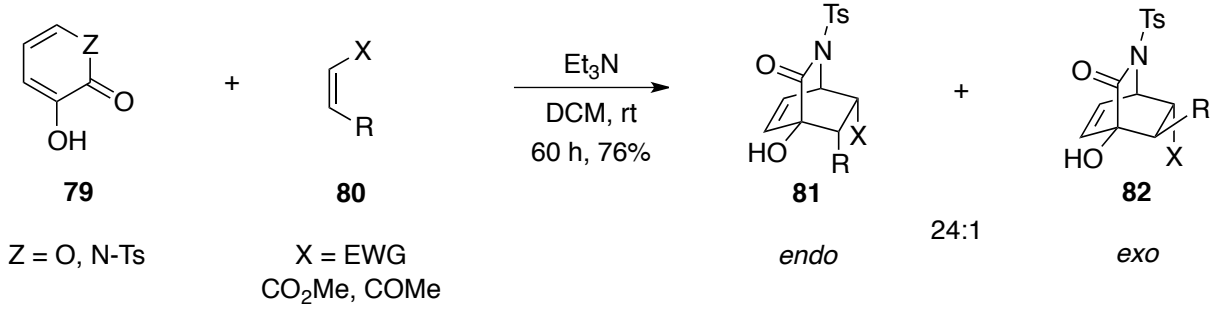
W. Yang and his research group[43] reported the enantioselective Diels-Alder reaction of enal **74** with diene **75** using catalyst **76** to afford the DA-adduct **77** in good chemical yield (up to 88%) and in excellent enantioselectivities (up to 98%). And also, they demonstrated the synthetic utility of obtained DA-adduct **77** for the total synthesis of (+)-propindilactone G **78** (Scheme 48).



Scheme 48. The base catalyzed Diels-Alder reaction of enal with diene

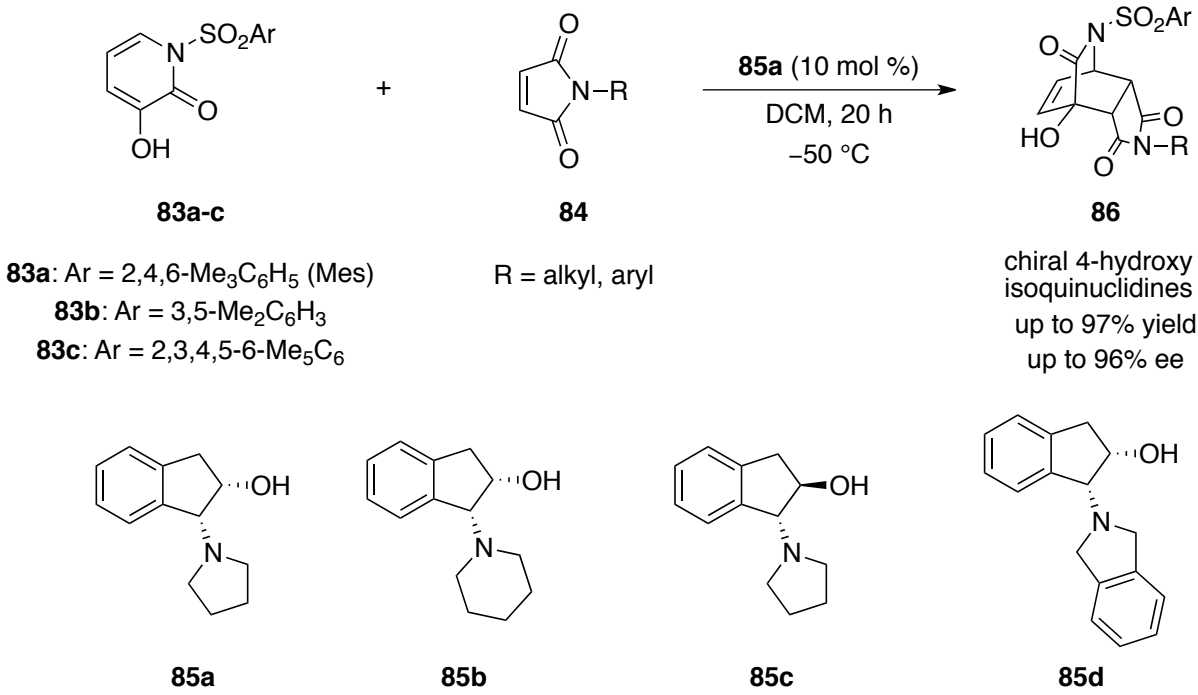
3.3 Previous reports on enantioselective Diels-Alder reaction of 3-hydroxy-2-pyridones with electron withdrawing dienophiles.

H. Okamura and his research group[41a] reported base catalyzed Diels-Alder reaction of 3-hydroxy-2-pyridones **79** with dienophiles **80** using triethyamine as base, to afford 4-hydroxyisoquinuclidines **81** and **82** with 76% yield (Scheme 49).



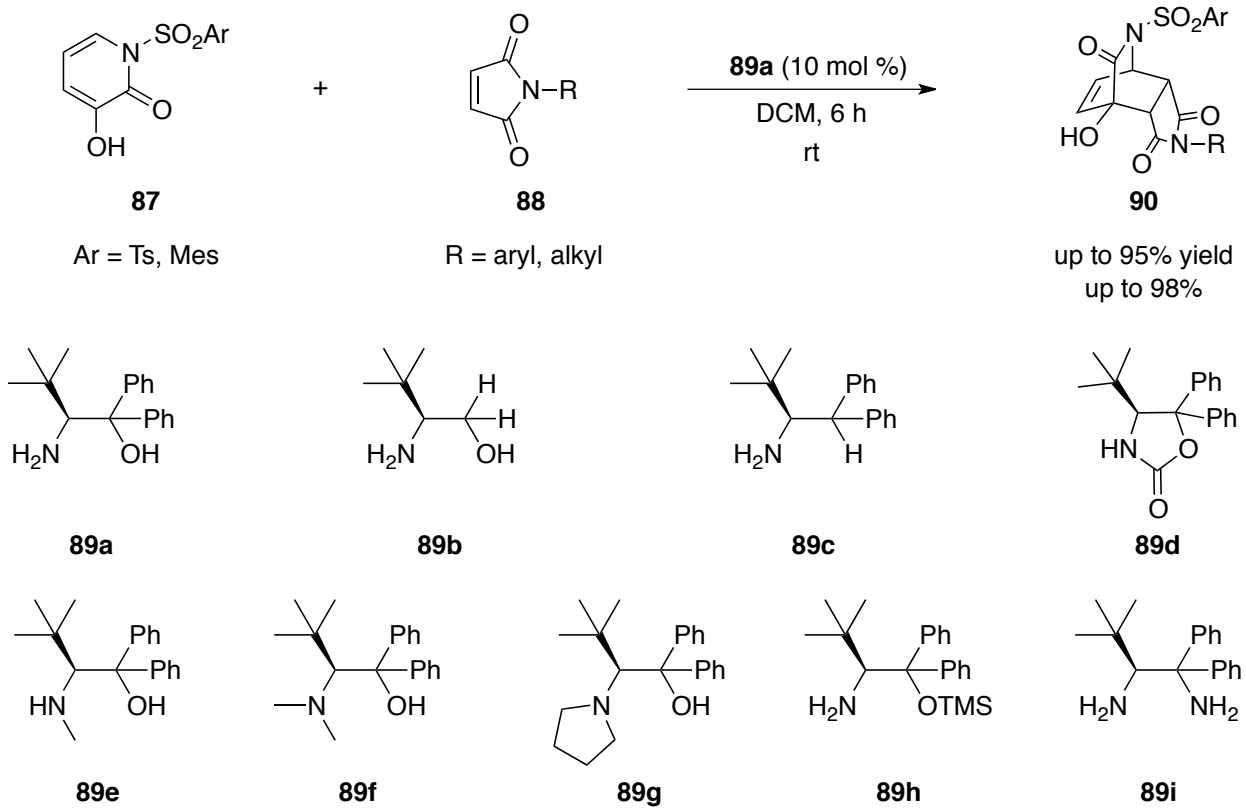
Scheme 49. The base catalyzed Diels-Alder reaction of 3-hydroxy-2-pyridones with dienophiles

C.-H Tan and his research group reported[44] the enantioselective Diels-Alder reaction using 3-hydroxy-2-pyriodones **83a-c** with maleimides **84** using a simple new type bifunctional amino-indanol catalysts **85a-d**, among the optimized catalysts, the catalyst **85a** have showed the best catalytic activity for afford the chiral 4-hydroxyisoquinuclidines in both excellent chemical yields (up to 97% yield) and enantioselectivities (up to 96% ee) (Scheme 50).



Scheme 50. Enantioselective Diels-Alder reactions of 3-hydroxy-2-pyridones with maleimides using amino-indanol organocatalysts

Recently from author research group reported the simple primary β-amino alcohol[45] catalyzed Diels-Alder reaction of 3-hydroxy-2-pyridones **87** as dienes with *N*-substituted maleimides **88** as dienophiles to afford the highly substituted optically active isoquinuclidines **90** as a single diastereomers in excellent enantioselectivities (up to 98%) with excellent chemical yields (up to 95%). In this study, a range of simple β-amino alcohols **89a-i** were synthesized from the corresponding inexpensive amino acids and their catalytic activity was examined for this reaction. Among them, catalyst **89a** was found to be best catalyst for affording the chiral 4-hydroxyisoquinuclidines (Scheme 51).



Scheme 51. β-amino alcohol oraganocatalyzed Diels-Alder reaction of 3-hydroxy-2-pyridone with maleimides

3.4 Author strategy

Author aimed to develop the simple primary β-amino alcohol **X** and their derivatives as a new class of organocatalysts, since they are easy to synthesize, stable on exposure to air, an inexpensive alternative to the other primary amino organocatalysts such as a chiral diamines and cinchona derived primary amines (Figure 15). Most recently, author successfully developed the new hybrid type squaramide fused aminoalcohol (SFAA) **Y** and revealed the utility as the organocatalyst in the enantioselective nitro-aldol reaction of nitroalkanes with isatins to afford chiral 3-alkyl-3-hydroxyoxindoles, which is useful intermediate for biologically active compounds. The Diels-Alder (DA) reaction using 3-hydroxy-2-pyridones **91** as dienes in the presence of dienophiles using SFAA organocatalysts provides synthetically valuable multifunctional chiral 4-hydroxy-isoquinuclidines **92**.

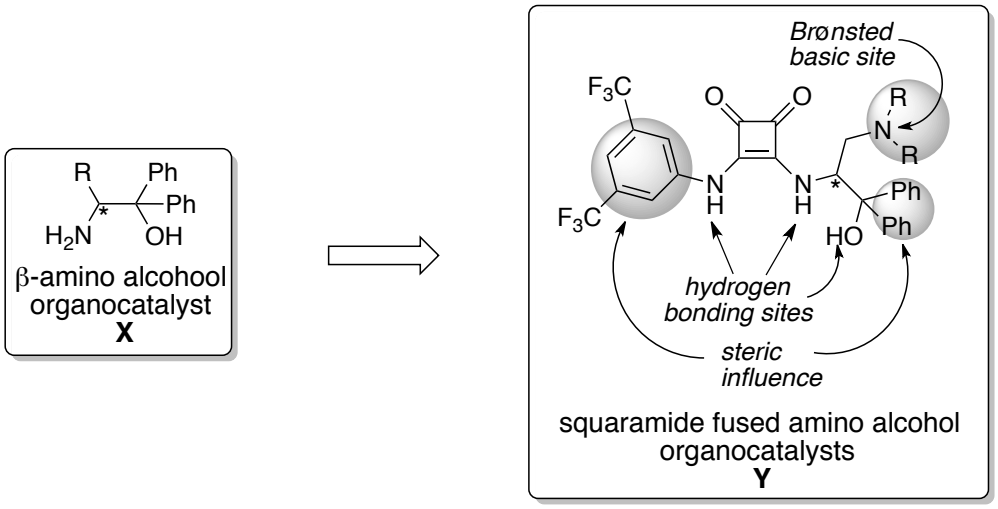
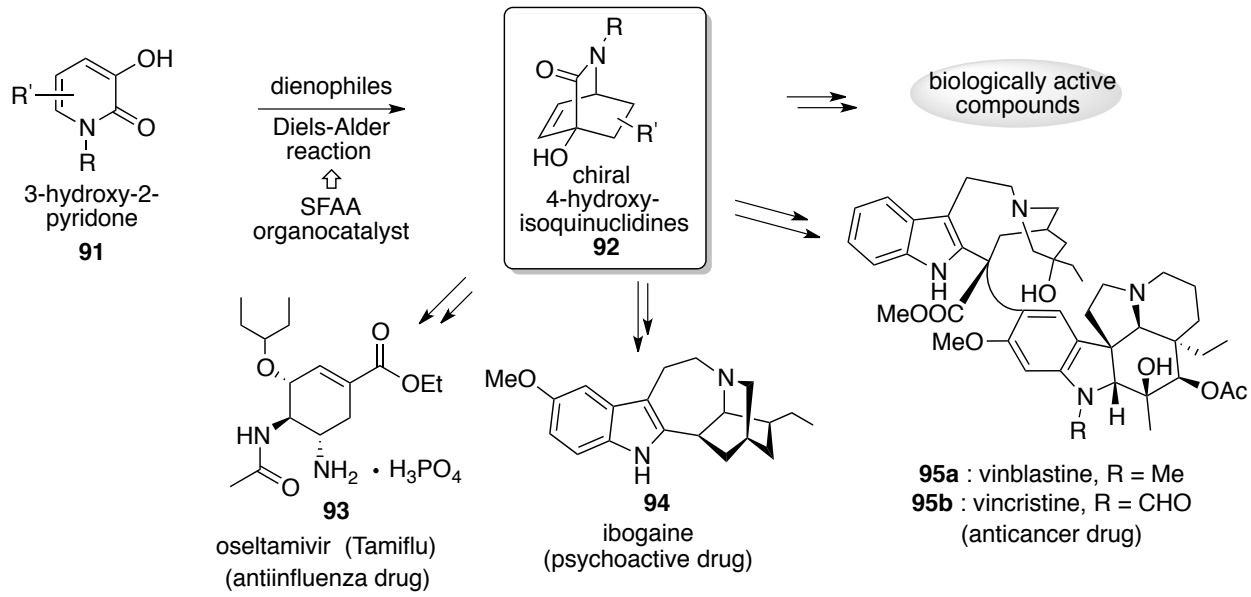


Figure 15. Functionality of squaramide fused amino alcohol (SFAA) organocatalysts

The obtained isoquinuclidines can be easily access to the many biological active compounds such as oseltamivir (Tamiflu) **93** to prevent both influenza A and B virus. Furthermore, DA adduct also plays key precursors for the synthesis of ibogaine **94** which is a naturally occurring psychoactive compound and anticancer drug. And also, isoquinuclidines are the primitive intermediates for synthesis of vinblastine **95a** and vincristine **95b** natural products, these natural products play key role in chemotherapy medication (Scheme 52).

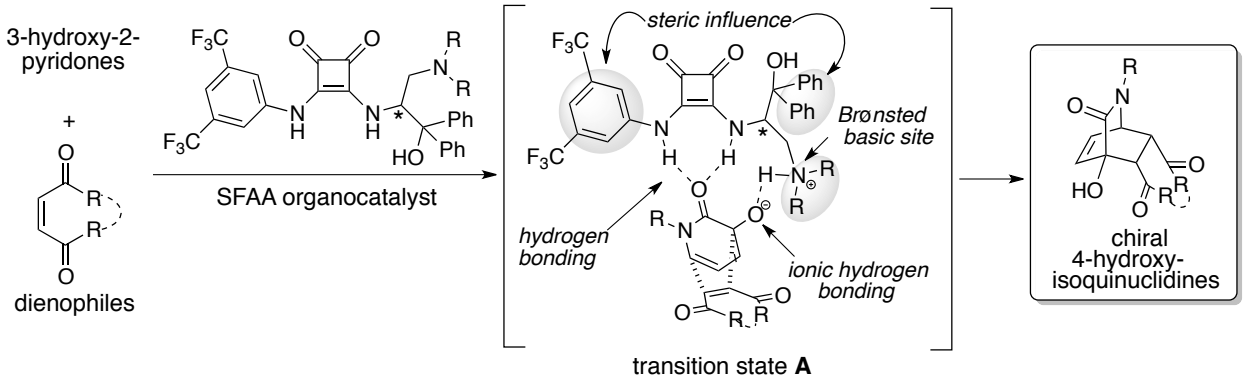


Scheme 52. Synthetic utilities of 4-hydroxyisoquinuclidines

3.4.1 Results and discussions

To further expand the efficiency of SFAA as an organocatalyst, author tried the DA reaction of 3-hydroxy-2-pyridones with dienophiles using chiral SFAA organocatalyst. As a concept of the expression of enantioselectivity in this reaction using SFAA catalyst, the reaction might be proceeding through a transition state **A**, in which the anionic oxygen at 3-position on the pyridones might be fixed by the hydrogen bonding interactions with the ammonium site on catalyst (Scheme 53). Furthermore, the amide oxygen atom of pyridones might be fixed by the hydrogen bonding interactions with two amino hydrogen atoms of the squaramide part on the catalyst, then dienophiles might attack stereoselectively from the less steric interaction site of the fixed dienes to furnish the chiral isoquinuclidines. The hybrid type squaramide fused amino alcohol (SFAA) having both Brønsted basic site and hydrogen bonding site in the molecule showed high catalytic activity as an organocatalyst in the enantioselective Diels-Alder reaction (DA) of 3-hydroxy-2-pyridones with maleimides to afford the chiral *endo*-4-hydroxy-2-azabicyclo[2.2.2]octanes (4-hydroxy-isoquinuclidines) with excellent chemical yields and enantioselectivities (up to 95%, up to 98% ee). Particularly, the use of 4-brominated 2-pyridones afforded the corresponding chiral 4-hydroxyisoquinuclidines in both excellent chemical yield and enantioselectivity (95%, 98% ee) having an opposite absolute stereochemistry in comparison with the chiral *endo*-DA adduct from the reactions using common 3-hydroxy-2-pyridones. The obtained DA adducts could be used as

synthetic precursors for the synthesis of several natural products that have a broad spectrum of fascinating biologically activities.

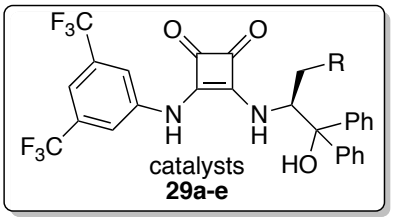


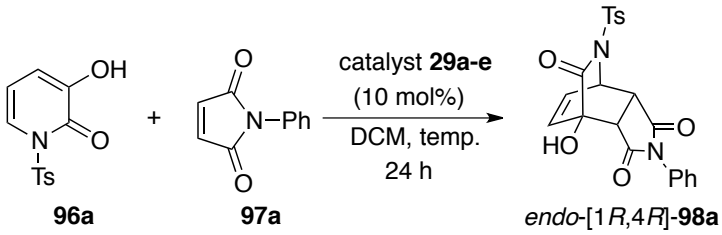
Scheme 53. Concept of SFAA orgaanocatlysts for Diels-Alder reaction

3.4.2 Enantioselective Diels-Alder reaction using catalysts 29a-e

First, author examined the catalytic ability of SFAA catalysts **29a-e** in the DA reactions of common 3-hydroxy-1-tosyl-2-pyridone **96a** and *N*-phenylmaleimide **97a** in DCM as a solvent at 0°C (entries 1-5, Table 4). All reactions using catalysts **29a-e,** which were easily prepared by author previous reported method, afforded the *endo*-DA adduct [1*R*,4*R*]-**98a** as a major isomer.

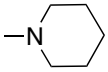
Table 4. Enantioselective DA reaction using catalysts **29a-e**

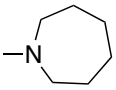


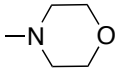


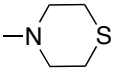
96a **97a** *endo*-[1*R*,4*R*]-**98a**

29a: R= 

29b: R= 

29c: R= 

29d: R= 

29e: R= 

entry[a]	catalyst **29a-e**	temp. (°C)	yield [%][b]	ee [%][c]
1	**a**	**0**	**87**	**64**
2	**b**	0	95	21
3	**c**	0	89	28
4	**d**	0	49	14
5	**e**	0	43	5
6	**a**	-20	67	28
7	**a**	-80	57	23

[a]The reactions were carried out with **96a** (0.07 mmol), **97a** (0.08 mmol) in DCM (1.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined on chiral HPLC using Chiralpak AS-H column.

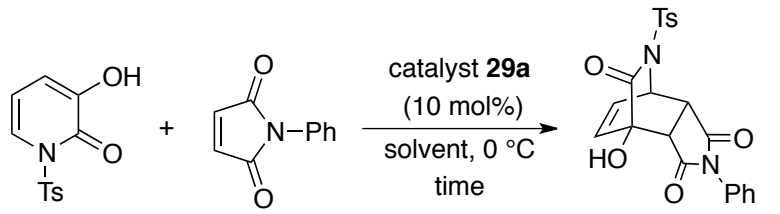
The catalyst **29a** having a basic pyrrolidine ring at side chain showed a good catalytic activity and afforded the DA adduct **98a** with good chemical yield and moderate enantioselectivity (87%, 64% ee, entry 1). However, both catalysts, **29b** having piperidine ring and **29c** having azepane ring, at side chain gave **98a** with low enantioselectivities, although chemical yields were fairly good (entries 2,3). Furthermore, catalyst **29d** having morpholine ring or catalyst **29e** having thiomorpholine ring at side chain did not show satisfactory catalytic activities in this reaction conditions (entries 4,5). In addition, the reaction using superior catalyst **29a** also tried at low temperatures (-20°C and -80°C). Although expecting enantioselectivity were not afford anymore, chemical yields were moderate (entries 6,7). From the above results, author revealed that catalyst **29a** having five membered pyrrolidine ring system as a Brønsted basic site at side chain is better

for obtaining satisfactory results for chemical yield and enantioselectivity.

3.4.3 Optimization of DA reaction conditions using catalyst 29a

In order to optimize the reaction conditions using the superior catalyst **29a**, author next examined the effect of the molar ratio of catalyst **29a**, the effect of solvent and reaction time (Table 5). The decrease of catalytic loading of **29a** to 5 mol% resulted in a slight decrease in the chemical yield (50%) and a substantial decrease the enantioselectivity (42% ee) (entry 1). The increase of catalytic loading of **29a** to 20 mol% resulted in a slight increase in the chemical yield (90%), but enantioselectivity was decreased to 32% ee (entry 2) than that of the reaction containing 10 mol% of **29a** (entry 1, Table 5), although the reason is not clear. To further improve the enantioselectivity, author also examined the solvent effects on this reaction. Commonly used aprotic nonpolar ($CHCl_3$, $ClCH_2CH_2Cl$, MTBE, Et_2O, THF, 1,4-dioxane, toluene, PhCl, xylene) and polar protic (MeOH) solvents were screened, respectively (entries 3-12). The *endo*-[1*R*,4*R*]-**98a** were obtained in all solvents with moderate to good chemical yields (62-92%), but enantioselectivity were poor to low (2-42% ee, entries 3-12). Unfortunately, no improvements in enantioselectivity were observed in these solvents in comparison with the use of CH_2Cl_2 (entry 1, Table 5). Under the best reaction conditions (DCM, **29a**: 10 mol%, 0°C), the reaction time was extended to 48 h and 96 h, respectively, led to an increase in the chemical yields, although the satisfactory enantioselectivities were not observed in both reaction times (entries 13,14). From these results, author clarified that the use of 10 mol% of catalyst, 0°C of the reaction temperature, and 24 h of reaction time is the best reaction conditions.

Table 5. Optimization of DA reaction using catalyst **29a**



96a **97a** *endo*-[1*R*,4*R*]-**98a**

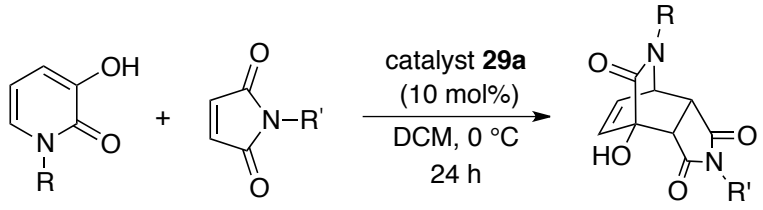
entry[a]	catalyst (mol %)	time (h)	solvent	yield [%][b]	ee [%][c]
1	5	24	DCM	50	42
2	20	24	DCM	90	32
3	10	24	$CHCl_3$	85	7
4	10	24	DCE	82	28
5	10	24	MTBE	82	–9
6	10	24	Et_2O	72	7
7	10	24	THF	70	37
8[d]	10	24	1,4-dioxane	62	10
9	10	24	toluene	78	23
10	10	24	PhCl	92	37
11	10	24	xylene	87	42
12	10	24	MeOH	85	–2
13	10	48	DCM	92	33
14	10	96	DCM	98	38

[a]The reactions were carried out with **96a** (0.07 mmol), **97a** (0.08 mmol) in above mentioned solvents (1.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined on chiral HPLC using Chiralpak AS-H column. [d]The reaction was conducted at room temperature.

3.4.4 Substrate scope for enantioselective DA reaction using catalyst 29a

Under the optimized reaction conditions, wide ranges of the DA reaction with 2-pyridones **96a**,**b** and maleimides **97b-k** were investigated using superior catalyst **29a** to afford the corresponding *endo*-DA adducts **98b-k** and the results are shown in Table 6. First, the reaction of 2-pyridone **96a** with several maleimides **97a-i** using catalyst **29a** (10 mol%) were examined under optimized reaction condition (DCM, 0°C, 24 h), respectively. The use of *N*-methylmaleimide **97b** afforded the corresponding DA adduct **98b** in an excellent chemical yield (96%), although the enantioselectivity was low (22% ee) (entry 1). The use of *N*-ethylmaleimide **97c** also afforded **98c** in a fairly good chemical yield (90%) and the enantioselectivity also slightly increased to 25% ee (entry 2). Moreover, the reaction of **96a** with maleimides **97d-i** having electron-donating or electron-withdrawing groups at 4-position on phenyl group.

Table 6. Substrate scope for DA reaction of pyridones using catalyst **29a**



96a,b **97b-k** **98b-k** *endo only*

entry[a]	diene **96**	R	dienophile **97**	R'	DA adduct **98**	yield [%][b]	ee [%][c]
1	**a**	Ts	**b**	Me	**b**	96	22
2	**a**	Ts	**c**	Et	**c**	90	25
3	**a**	Ts	**d**	4-MePh	**d**	90	20
4	**a**	Ts	**e**	4-NO_2Ph	**e**	nd[d]	nd
5	**a**	Ts	**f**	4-FPh	**f**	89	36
6	**a**	Ts	**g**	4-ClPh	**g**	85	34
7	**a**	Ts	**h**	4-BrPh	**h**	92	42
8	**a**	Ts	**i**	4-IodoPh	**i**	78	37
9	**b**	SO_2Mes	**j**	Ph	**j**	92	22
10	**b**	SO_2Mes	**k**	4-BrPh	**k**	95	39

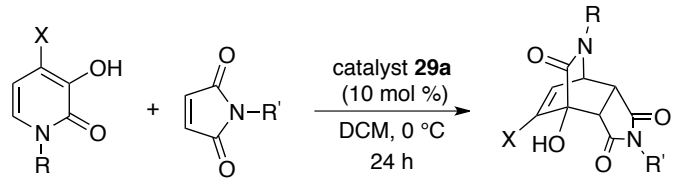
[a]The reactions were carried out with **96a,b** (0.07 mmol), **97b-k** (0.08 mmol) in DCM (1.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined on chiral HPLC using Chiralpak AS-H column. [d]Not determined

Additionally, *N*-(4-methylphenyl)maleimide **97d** did not afford the corresponding DA adduct **98d** in a satisfactorily enantioselectivity (20% ee), although the chemical yield was fairly good (90%) (entry 3). The reaction with *N*-(4-nitrophenyl)maleimide **97e** having a strong electron-withdrawing nitro group at 4-position on phenyl group was not proceed to obtained the *endo*-**98e**, why the reason is not clear (entry 4). Furthermore, the use of maleimides **97f-i** having halogeno group at 4-position on phenyl group afforded the corresponding DA adducts **98f-i** in good chemical yields (78-92% ee), but satisfactory enantioselectivities were not obtained (34-42% ee) (entries 5-8) in the optimized reaction conditions. Author also examined the DA reaction of more steric hindered 3-hydroxy-1-(2,4,6-trimethylphenylsulfonyl)-2-pyridone **96b** with maleimides **97j**,**k** respectively. However, contrary to expectation, the desired *endo*-DA adducts **98j**,**k** did not obtained with satisfactorily enantioselectivity (**98j**: 22% ee, **98k**: 39% ee) (entries 9, 10), but, the chemical yields were sufficient (**98j**: 92%, **98k**: 95%) similar to most of used maleimide dienophiles **97a-d**,**f-i**.

3.4.5 Enantioselective DA reaction of substituted pyridones using catalyst 29a

Author next evaluated the asymmetric DA reactions of 4-halogenated or bulky alkylated 3-hydroxy-2-pyridones **99a-d** with maleimides **100a-f** using catalyst **29a** (10 mol%) at the optimized reaction conditions (DCM, 0°C, 24 h) (Table 7).

Table 7. Substrate scope for DA reaction of substituted pyridones using catalyst **29a**



entry[a]	diene	R	X	dienophile	R'	DA adduct	yield [%][b]	ee [%][c]
	99			**100**		**101**		
1[d]	**a**	**Ts**	**Br**	**a**	**Ph**	**a**	**95**	**98**
2	**a**	Ts	Br	**b**	4-BrPh	**b**	89	75
3	**a**	Ts	Br	**c**	Me	**c**	90	65
4	**b**	SO_2Mes	Br	**d**	Ph	**d**	92	64
5	**c**	Ts	Allyl	**e**	Ph	**e**	93	74
6	**d**	Ts	Propyl	**f**	Ph	**f**	90	50

[a]The reactions were carried out with **99a-d** (0.07 mmol), **100a-f** (0.08 mmol) in DCM (1.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined on chiral HPLC using Chiralpak AS-H and chiralcel OD-H columns. [d]The aboslute configuration of **101a** was determined by X-ray.

First, author tried the reaction using 2-pyridones **99a-d** having halogeno group at 4-position on pyridone ring. The enantioselective were observed to increase in all reactions with corresponding *endo*-DA adducts **101a-f** moderate to excellent enantioselectivities (64-98% ee) and in excellent chemical yields (89-95%, entries 1-6). In particular, a dramatic increase in enantioselectivity (98% ee, entry 1) was observed in the reaction of 4-brominated-2-pyridone **99a** with **100a** to afford the DA adduct (1*R*,4*S*)-**101a**, which has the opposite absolute configuration in comparison with DA adduct (1*R*,4*R*)-**101a** obtained from the reaction of **99a** with **100a** (entry 1, Table 7). The absolute stereochemistry of [1*R*,4*S*]-**101a** was determined by X-ray analysis (Figure 16). And also, an improvement of enantioselectivity was conformed in the reactions using 2-pyridones having allyl and propyl functional groups at 4-position on pyridone ring (entries 5, 6). Although the reactions afforded the corresponding DA adducts **101e**,**f** with high chemical yields, the enantioselectivity were moderate to good (**101e**: 93%, 74% ee, **101f**: 90%, 50% ee) (entries 5, 6). From these results, it might be indicated that the steric influence of substituent group at 4-position on pyridone ring might participate to fix the direction of diene in the transition state for increasing of enantioselectivity.

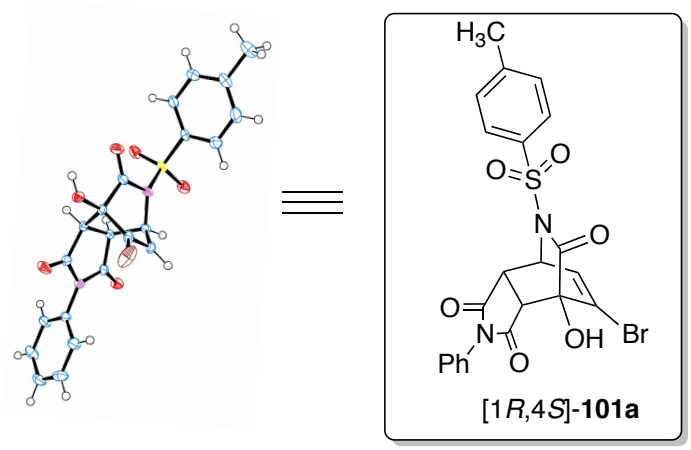
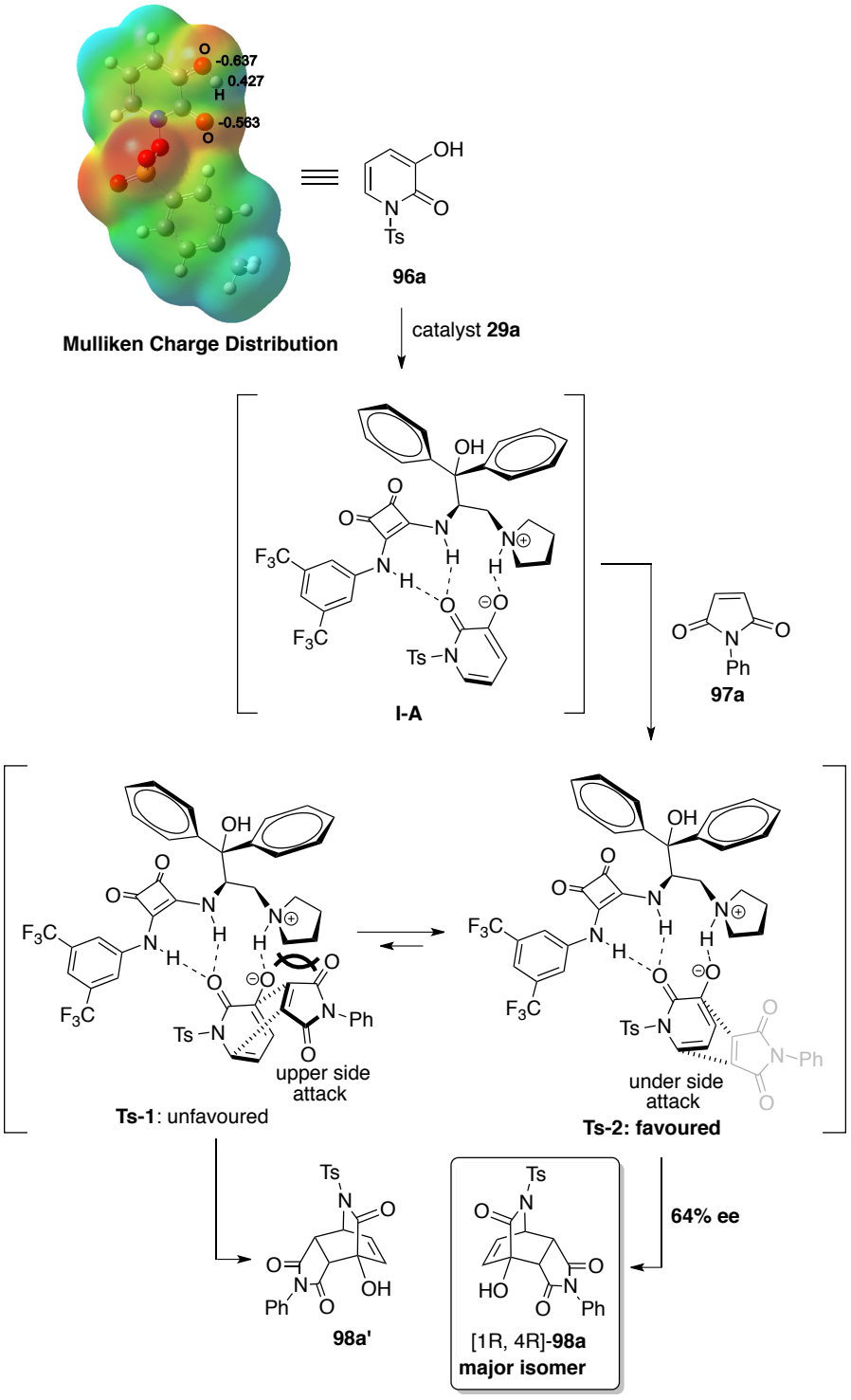


Figure 16. Absolute stereochemistry of DA-adduct **101a** by X-ray analysis

3.4.6 Plausible reaction course of the 3-hydroxy-2-pyridone 96a with *N*-phenyl maleimide 97a using catalyst 29a.

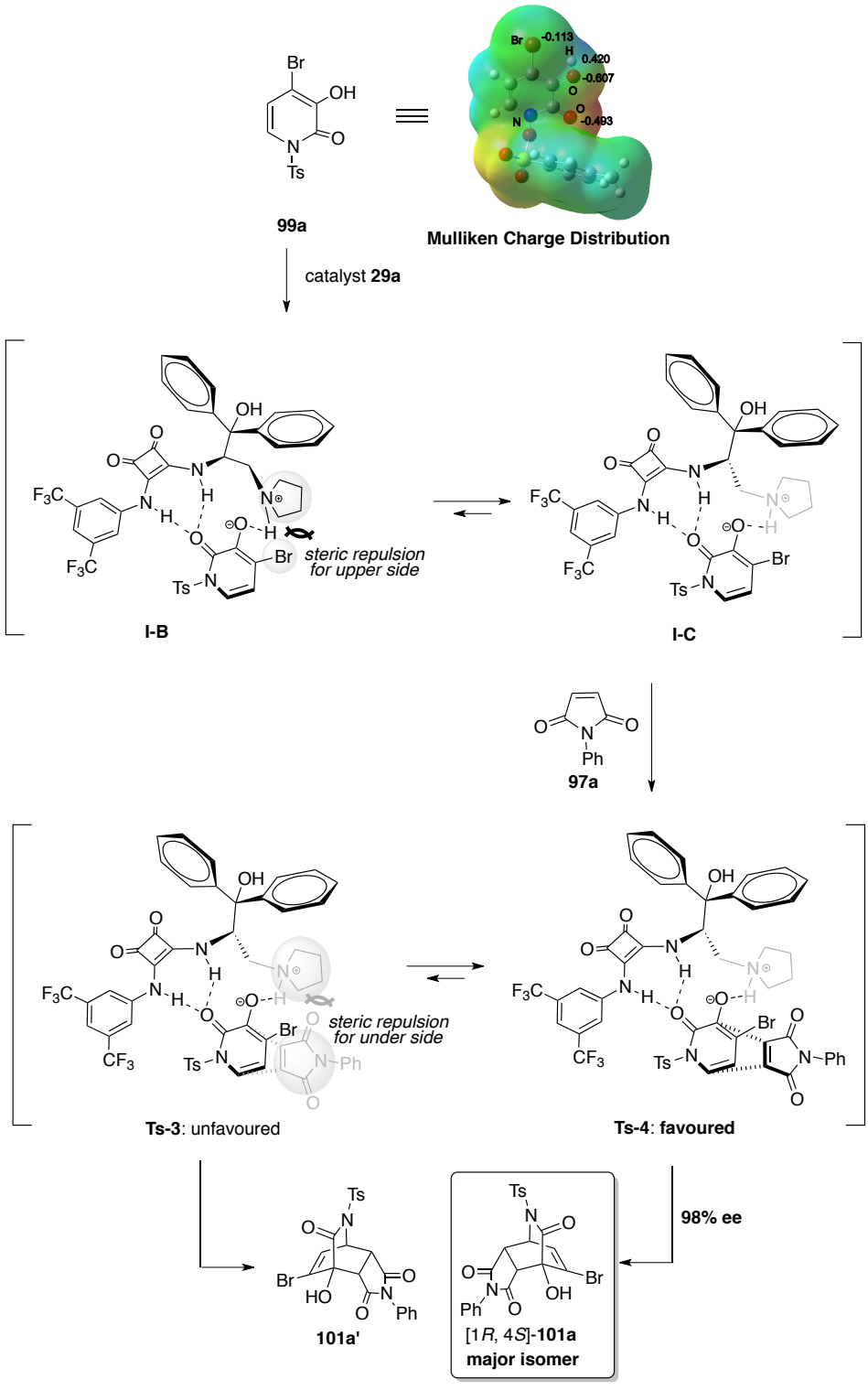


Scheme 54. Plausible reaction course of pyridone **96a** with *N*-phenyl maleimide **97a** using catalyst **29a**

Based on the both observed enantiopurities (**98a**: 64% ee, entry 1, Table 4; **101a**: 98% ee, entry 1, Table 7) of chiral DA adducts **98a** or **101a** that were obtained from the reactions of **96a** with **97a** or **99a** with **100a**, and site of the highest electron density (Mulliken charge distribution) in **96a** and **99a** the following enantioselective reaction mechanism were proposed (Schemes 54 and 55). First, the reaction with **96a** might proceed through the more stable transition state **Ts-2** than **Ts-1** to afford [1*R*,4*R*]-**98a**. Thus, 3-hydroxy-2-pyridone **96a** might be fixed with catalyst **29a** through the hydrogen bonding interactions of both between the amide oxygen atom of **96a** and the two primary amino hydrogen atoms on the squaramide part of **29a** and between the hydrogen atom of the ammonium moiety on the pyrrolidine ring of **29a** and the anionic oxygen atom at 3-position of **96a** (intermediate: **I-A**). Then, when dienophile **97a** attacks on pyridone moiety, the reaction might proceed through the upper face of anionic pyridone coordinated to catalyst in the transition state (**Ts-2**) that has less steric interactions between the diamino alcohol part on catalyst **29a** and **96a** than that of **Ts-1** that has more steric interactions (Scheme 54).

3.4.7 Plausible reaction course of the reaction of 4-bromoro-3-hydroxy-2-pyridone 99a with with maleimide 100a using catalyst 29a.

On the other hand, the reaction of **99a** with **100a** affording [1*R*,4*S*]-**101a** might proceed through **Ts-4** than **Ts-3** (Scheme 55), based on three facts (a)-(c): (a) the reaction proceeded with a high enantioselectivity (98% ee), (b) the obtained DA adduct **101a** has an opposite absolute stereochemistry in comparison with the DA adduct **98a** obtained from the reactions using **96a** and **97a**, and (c) the site of the highest electron density (Mulliken charge distribution) of **99a** was on the oxygen atom of the amide moiety. Thus, the hydroxyl proton is abstracted from **99a** by the basic tertiary amino group of the pyrrolidine ring of **29a** to form intermediates **B** or **C**, which might be fixed by two places of hydrogen bonding interactions both between the hydrogen atom of the ammonium moiety of the pyrrolidine ring of **29a** and the anionic oxygen atom at 3-position of **99a** and between two primary amino hydrogen on the squaramide part of **29a** and the amide oxygen atom of **29a**. In the intermediates **I-B** or **I-C**, the intermediate **I-B** might be more advantageous than **I-A** that has larger steric interactions between the bromine atom on pyridone and the pyrrolidine ring of catalyst. And then, the reaction with dienophle **100a** might proceed through the transition state **Ts-4** that has less steric interactions between the catalyst part and **99a** than **Ts-3** that has more steric interactions (Scheme 55).



Scheme 55. Plausible reaction course of 4-bromo-3-hydroxy-2-pyridone **99a** with *N*-phenyl maleimide **97a** using catalyst **29a**

3.5 Summary

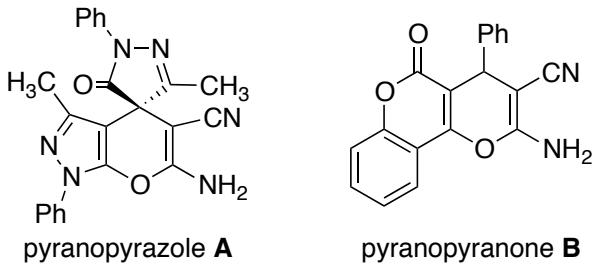
Author demonstrated that new hybrid type squaramide fused aminoalcohol (SFAA) **29a** containing both Brønsted basic site and hydrogen bonding site in the molecule showed highly catalytic activity as an organocatalyst in the enantioselective Diels-Alder reaction of 3-hydroxy-2-pyridones **96a**,**b** and **99a-d** with maleimides **97a-k**, **100a-f** with excellent chemical yields and enantioselectivities (up to 95%, up to 98% ee).[46] Particularly, the reaction of 4-brominated 2-pyridone **99a** with maleimides **97a** afforded the corresponding 4-hydroxyisoquinuclidines **101a** in both excellent chemical yield and enantioselectivity (95%, 98% ee) having an opposite absolute stereochemistry in comparison with the DA adduct **98a** from the reactions using common 3-hydroxy-2-pyridone **96a**.

Chapter 4

The New Hybrid Type Squaramide Fused Amino Alcohol Organocatalysts For Enantioselective Domino Michael Addition Cyclization Reaction

4.1. Introduction

The class of 2-amino-pyrans has been known for several decades. The first representative's pyranopyrazole **A** and pyranopyranone **B** are from the late 1950s to the early 1960s. Spiro-conjugated pyranopyrazole **A** was obtained in studies on pyrazolone dyestuffs, while pyranopyranone **B** served as a precursor for the blood anticoagulant warfarin (Figure 17).



pyranopyrazole **A** pyranopyranone **B**

Figure 17. The first representatives of 2-aminopyrans

The formation of the pyran ring, bearing an amino group in 2-position, tends to be reversible. The presence of a strong electron-withdrawing substituent in 3-position (e.g., CN, COR, CO_2R) seems to be crucial for the stability of these compounds. Since the middle 1970s there has been rapid progress in the chemistry of 2-amino-4*H*-pyrans, studies on their physicochemical properties, as well as various types of biological activity. In recent years, modern techniques were applied to aminopyran synthesis, such as, catalytic electro generation, microwave and ultra-sonic assistance, the use of "green" solvents, and solid-phase synthesis. Reviving interest in 2-aminopyrans can be attributed to the discovery of new types of biological activity compounds.[47]

4.1.1 Appearance

Most of the 2-amino-pyrans are colorless, pale-yellow, or pale-cream crystals with high melting points. They are readily soluble in aromatic hydrocarbons, alcohols, acetone, acetonitrile, chloroform, DMF, and DMSO, and nearly insoluble in hexane and water.

4.1.2 UV spectroscopy of 2-aminopyrans

UV spectroscopy is used as a supplementary method for characterization of 2-aminopyrans and most correspond to π-π* and π-*n* electron transfers of C=C-O and C=C-N fragments, as well as to π-π* transfers of aryl substituents. Compound **C** 13 reveal a single absorption maximum at 296-305 nm, more recently at 206, 243, and 297 nm (when X = CN), and 208, 265, and 298 nm (when = COOMe). Signal maxima at 225-230 nm characterize 2-aminopyrans, while the

tetrahydrochromene **D** shows maxima at 220 and 269 nm (Figure 18).[48]

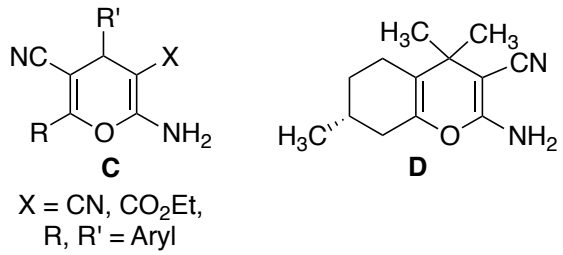
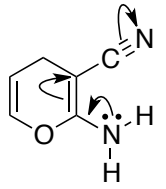


Figure 18. Prominent functional groups of 2-aminopyrans in UV spectroscopy

4.1.3 IR spectroscopy of 2-aminopyrans

Stretching vibrations of an -NH_2 group 3450-3200 cm^{-1} are always present in IR spectra of 2-aminopyrans. special analysis of IR and Raman spectra on a series of non-annulated pyrans has been carried out. One or several bands in the 1650-1590 cm^{-1} region, attributed to bending vibrations of -NH_2 and stretching vibrations of C=C, are also characterstics for aminopyrans. More propably, these bands correspond to the superposition of *d* (NH_2) and *v* (C=C) vibrations. A general feature of 3-cyanopyrans is the presence of a highly intense stretching band of the -CN group (2205-2180 cm^{-1}). The very high intensity and low-frequency shift possibly can be connected with a developed system of electron π-π-conjugation in an enamino nitrile moiety. Notably, starting and intermediate nitriles used in the synthesis of 2-amino-3-cyanopyrans **E** show moderate to weak nitrile group absorption at 2260–2220 cm^{-1} nitrile band is very characteristic (Figure 19).



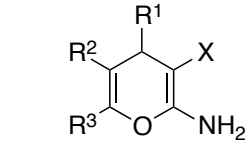
2-amino-3-cyanopyran **E**

Figure 19. Characteristic vibrations of amine and nitrile functional groups in IR spectroscopy

4.1.4 NMR spectroscopy of 2-aminopyrans

NMR spectroscopy is the main method for characterization of 2-amino-4*H*-pyrans. Most ^1H NMR data were obtained using DMSO-d_6 and $CDCl_3$. The spectra always contain a signal for NH_2 protons (br. s, 2H), but its chemical shift strongly depends on the nature of a 3-substituent and conditions. The majority of known 2-aminopyrans contain a single alkyl or aryl substituent

R^1. So 4*H* reveals its very characteristic signal at 4.10-4.60 ppm. When R^1 is an aryl group with strong electron-withdrawing substituent in *o*- or *m*-positions, the 4*H* proton singlet shifts downfield to 4.50–5.50 ppm. When R^1 is 2-$O_2NC_6H_4$, a weak intramolecular hydrogen bond forms. A small series of 6-unsubstituted 2-aminopyrans reveal an H(6) peak in the region 7.15-7.91ppm in DMSO-d_6 (Figure 20).[48b]



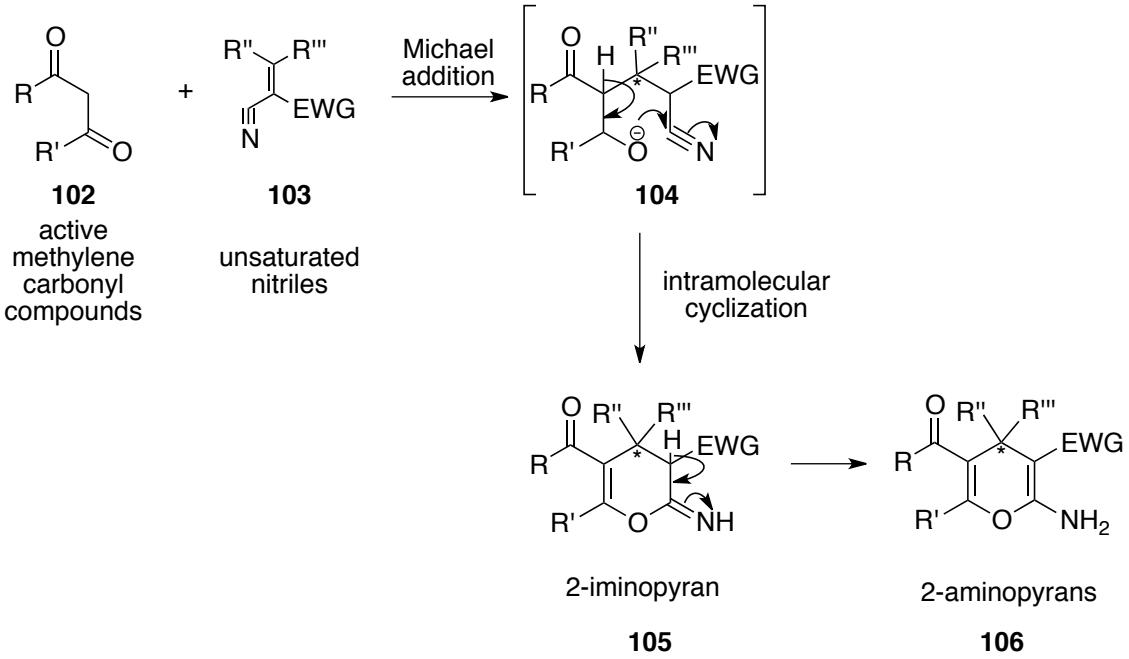
R^1 = alkyl, aryl.
R^2 = aryl, COR, CO_2R, CN
R^3 = alkyl, aryl
X = CN, CO_2R

substituent X	solvent	chemical shift (ppm)
CN	$CDCl_3$	4.50-4.82
	DMSO-d_6	6.50-7.50
CO_2R	$CDCl_3$	6.20-6.30
	DMSO-d_6	6.50-7.50

Figure 20. Prominent ^{1}HNMR signals of 2-aminopyrans

4.1.5 Methods of synthesis

The most widely known 2-aminopyrans contain a primary amino group, generalized in (Scheme 56).



102 active methylene carbonyl compounds

103 unsaturated nitriles

104

2-iminopyran **105**

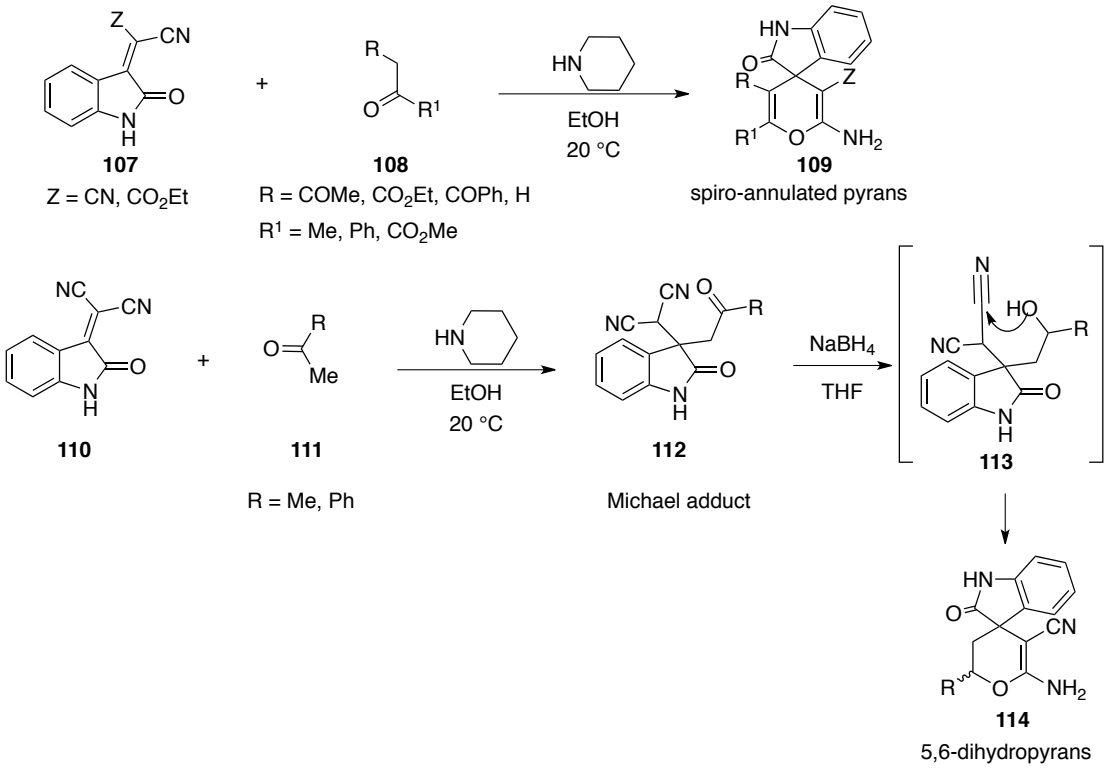
2-aminopyrans **106**

Scheme 56. General method of 2-aminopyran synthesis

The general synthetic approach involves cyclization of Michael adducts **104** *via* nucleophilic addition of an enolic oxygen **102** to a nitrile group **103** and subsequent tautomeric shift of the resultant 2-iminopyran **105** to 2-aminopyran **106**.[49]

4.2 Synthesis of spiro-conjugated 2-aminopyrans

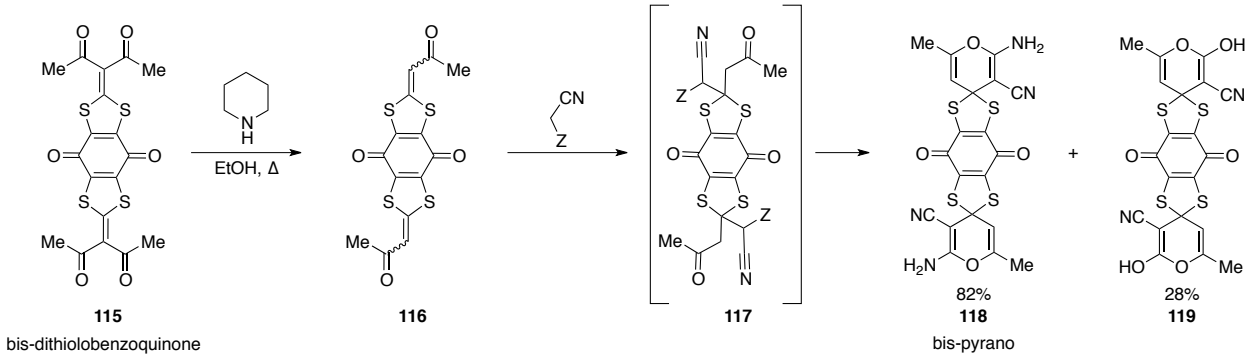
In contrast to acyclic monoketones, which usually do not form aminopyrans, reactions of cyclic ketones or their cyanomethylene derivatives with methylene-active carbonyl compounds gives spiro-conjugated 2-aminopyrans. Their syntheses are represented by fewer examples relatively to 4-arylpyrans, but many them latter draw attention due to their promising biological activities. The first example of reaction of 3-cyanomethyleneindol-2-one **107** with 1,3-dicarbonylcompounds **108** results in the formation of a series of spiro-annulated pyrans **109** (Scheme 57). The *tert*-butylacetoacetate also reacts with 3-(dicyanomethylene)-indo-2-one **110** in the similar manner. Acetone and acetophenone **111** undergo Michael addition toward, but adducts **112** do not cyclize into pyrans due to their relatively low degree of enolization. On reduction of the latter adduct **113** by sodium borohydride, the -OH group thus formed immediately attacks the nitrile group with cyclization into 5,6-dihydropyrans **114**.[49c]



Scheme 57. Synthesis of spiro-annulated and 5,6-dihydropyrans

4.2.1 Synthesis of dispiro-dipyrano-benzoquinones

The synthesis of dispiro-dipyrano compounds is an important challenge, weather both ring contributing to its structure is unique identical, or whether they are carbocyclic or heterocyclic-owing the practical implications of tetra-functionalizing the center spiro atoms. spiropyran is type of organic compounds known for photochromic properties that provides this molecules ability's for being used in the field of medical and material sciences. Spiro-pyrans usually possess a photochromic property's, photochromic is a property which forms a change of color in a material by incident radiation. The A. K. El-shafei and his research group[50] developed the synthesis of dispiro-dipyrano-benzoquinones from the starting material of bis-dithiolobenzoquinone **115** which upon reaction with piperdine in the presence of ethanol at elevated temperatures afford the oxopropylidene-bis-dithilo-benzoquinone compound **116**, which upon further condensation with malononitrile afford the Michael adduct **117**, which undergoes the cyclization give the mixture of products of dispiro-dipyrano-benzoquinone **118** and **119** (Scheme 58). The spiro-pyrans plays a key role in photochromic, thermochromics, solvatochromic, and electrochromic properties makes them especially important in field of technological. Nowadays the spiro-pyrans are most used as molecular logic devise, photochromic and electro optical devices.

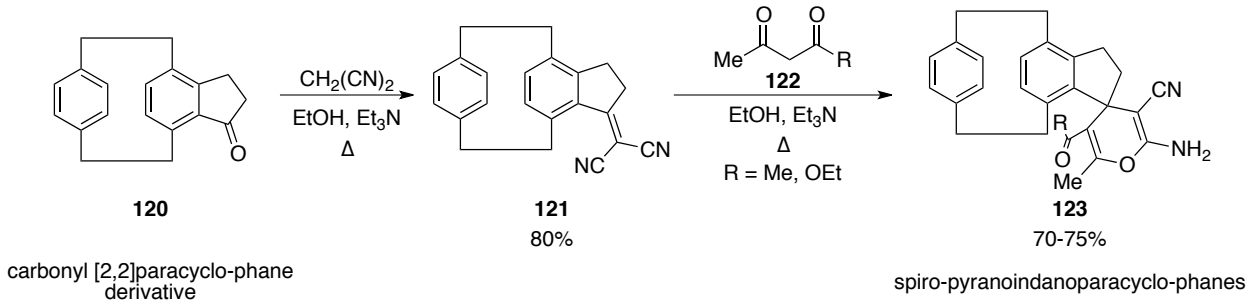


Scheme 58. Synthesis of dispiro-dipyrano-benzoquinones

4.2.2 Synthesis of cyclophan 2-aminopyrans

A cyclophane is a hydrocarbon consisting of an aromatic unit and an aliphatic chain that forms a bridge between two non-adjacent positions of the aromatic ring. More than 50 years after the first reported synthesis of [2.2]paracyclophane, and its chemistry is still challenging field of

ongoing research. The investigation of their physical and stereochemical properties were attractive point of the [2_n]cyclophanes in organic chemistry. Undoubtedly, research with future generation of cyclophanes will continue to contribute some of the most fascinating developments in the field of supramolecular chemistry. The A. A. Aly and his research group[51] were developed the first synthesis of spiro-pyranoindanoparacyclophanes **123**. In which the carbonyl [2.2]paracyclophane compound was condensed with malononitrile in basic medium to afford the compound **121**, the compound later allowed to reacted with acetonyl acetone or keto-esters **122** to afford the cyclophan 2-aminopyrans **123** with good to moderate chemical yields (Scheme 59).

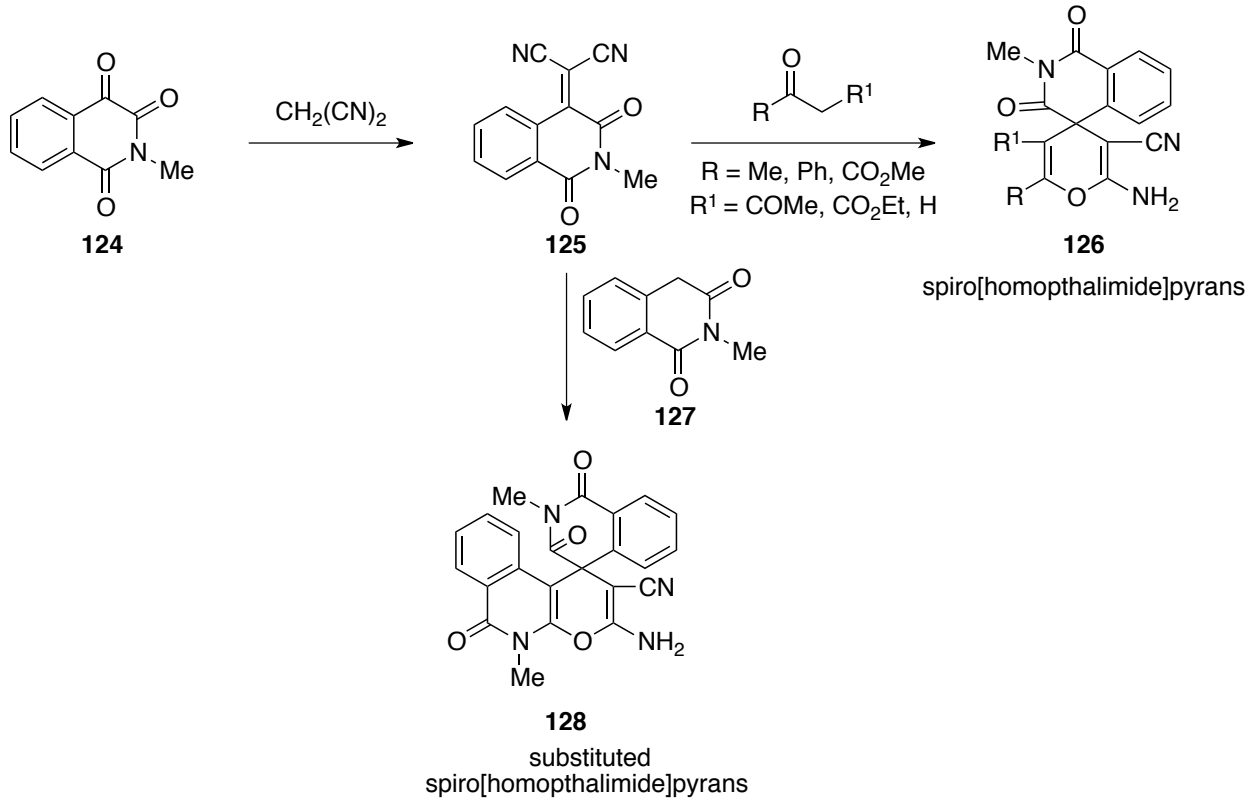


Scheme 59. Modular synthesis of spiro-pyanoindanoparacyclo-phanes

4.2.3 Synthesis of spiro-homophthalimidepyrans

The H. Otomasu and his research group[52] reported the spiro-homophthalimide pyrans (scheme 60). Their preparation started with the oxohomophthalimide **124** with malononitrile in the presence of basic medium will give the knoevenagel adduct **125** which further reacts with acetyl acetones or keto-esters which led to the formation of desired spiro-pyrans **126**. In the same way, the *N*-heterocyclic oxindole **127** when reacted with 1,3-carbonyl compounds such as acetylacetone or keto-esters led to formation of carbocyclic spiropyrans **128**. The spiro-homophthalimidepyrans possess a structural feature with an -CO-N-(R)-CO and an imide ring these feautures help them to be biologically active and pharmaceutically useful motifs. The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis over many years. Among them the spiro-homophthalimidepyrans in organic chemistry, imide is a functional group consisting of two carbonyl groups bound to nitrogen. They are hydrophobic and neutral, and can therefore cross biological membranes in *vivo*. These compounds are structurally

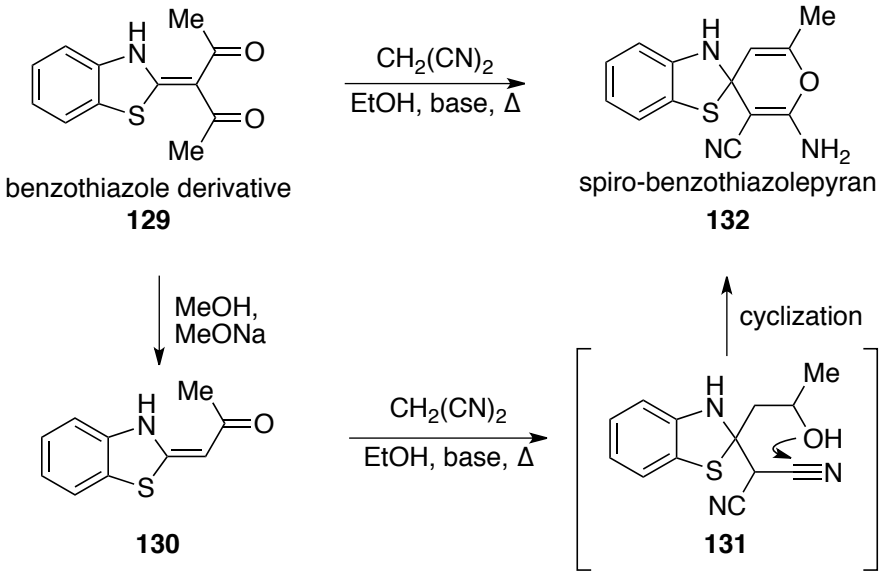
related to acid anhydrides. The spiro-homophthalimidepyrans have received attention due to their androgen receptor antagonists, anticonvulsant, antimicrobial, hypoglycemic, anti HIV-1 activities.



Scheme 60. Synthesis of spiro-homophthalimidepyrans

4.2.4 Synthesis of spiro-benzothiazolepyrans

The spiro-benzothiazole belongs to the family of bicyclic heterocyclic compounds having benzene nucleus fused with five-membered ring comprising nitrogen and sulfur atoms. spiro-benzothiazole is an important scaffold with a wide array of interesting biological activities and therapeutic functions including antitubercular, antimicrobial, antimalarial, anticonvulsant, anthelmintic, analgesic, antiinflammatory, antidiabetic and antitumor activities. A. K. El-shafei and his research group[53] were reported the spiro-benzothiazolepyrans **132** from diacylated benzothiazole **129** as a starting material which upon reaction with sodium methoxide in polar protic solvents afforded the mono acylated benzothiazole compound **130** which upon condensed with malononitrile to afford the Michael adduct **131** which underwent cyclization to afford the spiro-benzothiazolepyrans **132** (Scheme 61).



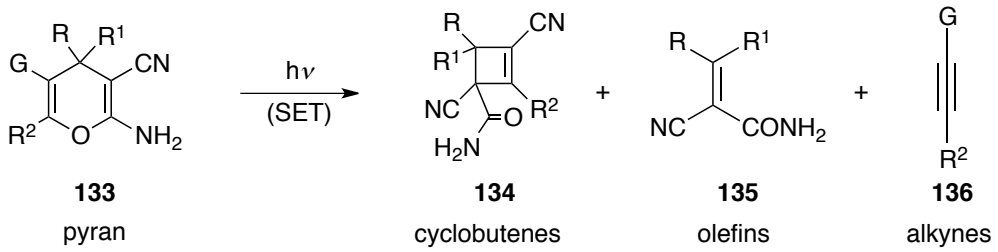
Scheme 61. Synthesis of spiro-benzothiazolepyrans

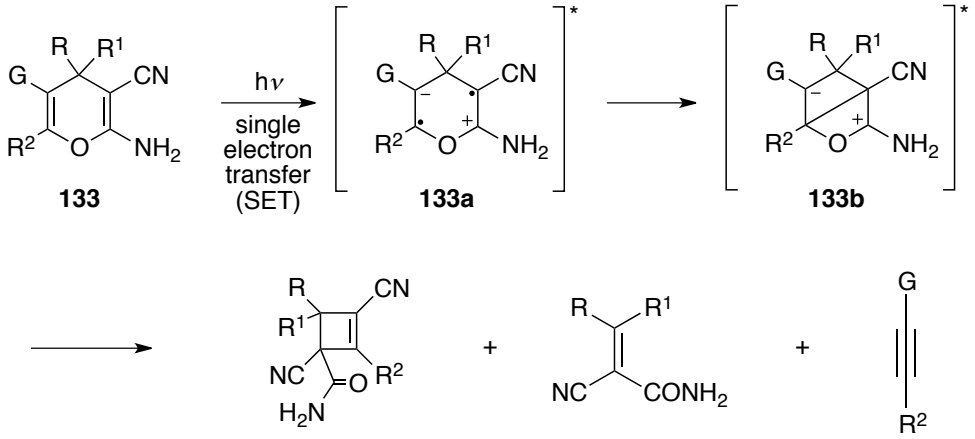
4.3 Chemical properties of 2-aminopyrans

The reactivity of 2-amino-4*H*-pyrans as well as their chemical properties has been poorly studied because of their weak stability toward many reactants. They undergo ring opening and re-cyclization in the presence of strong acids and bases, nucleophiles, and so on. But this feature can be turned to advantage in the synthesis of various heterocycles *via* re-cyclization. Thus, the enamino moiety in 2-amino-4*H*-pyran-3-carbonitriles and 2-amino-4*H*-pyran-3-carboxylic esters provides access to diverse derivatives, including fused pyrans. The available data on the chemical properties of 2-aminopyrans are not systematic, and, in certain cases, are contradictory.

4.3.1 Photochemical contraction of pyran ring

The Photochemical contraction of pyran ring in 2-aminopyrans **133** leads to the formation of mixtures of cyclobutenes **134**, not easily accessible, accompanied with olefins **135** and alkynes **136**.





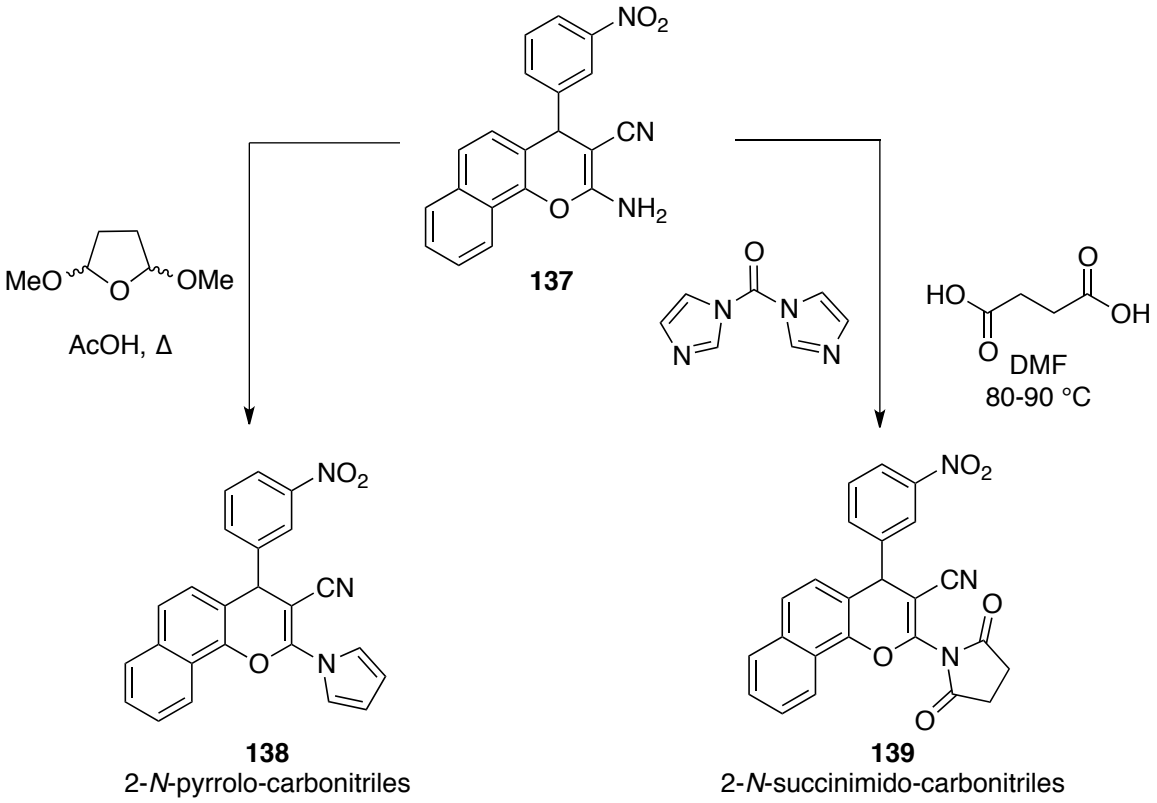
Scheme 62. Photochemical contraction of aminopyrans

A mechanistic scheme involves intramolecular single-electron transfer (SET) from the enamino moiety toward C-5 of the ring, and subsequent transannular interaction in zwitter-ionic biradical **133a** with formation of stabilized zwitter-ion **133b** opening of the oxetane ring in leads to cyclobutene **134**, while the secondary photolysis of latter gives the olefin **135** and alkyne **136** (Scheme 62).[54]

4.3.2 Synthesis of 2,4-disubstituted naptholpyrans.

Graham N. Wishart and his research group[55] reported the synthetic utility of naphtho-carbocyclic 2-aminopyrans under following conditions. The naphtho-carbocyclic 2-aminopyrans **137** was reacted with 2,5-dimethoxytetrahydrofuran under elevated temperatures in the presence

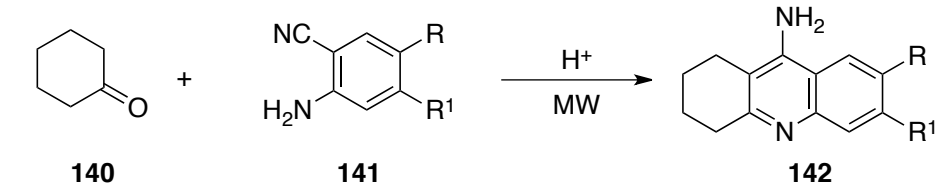
of acetic acid as solvent medium to afford the 2-*N*-pyrrolo-carbonitriles **138**. In the same way naphtho-carbocyclic 2-aminopyrans were reacted with *N*,*N*-carbonyldiimidazole and succinic acid in dimethylformamide solvent at 80-90 °C, to afford the 2-*N*-succinimido-carbonitriles **139** (Scheme 63). They synthesized a series of 2,4-disubstituted naptholpyrans under the acidic conditions and found their biological activity for antiinflammatory activity.



Scheme 63. Synthetic utility of naphthocarbonitrile

4.3.3 Synthesis of tacrine-like analogs from 2-aminopyrans

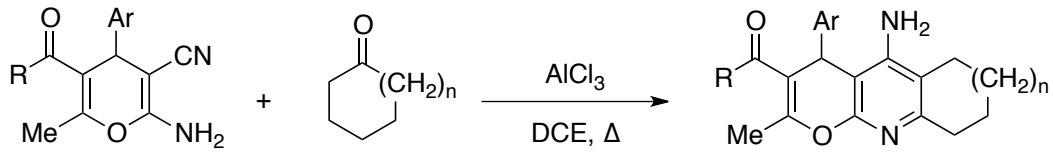
In 1993 tacrine (9-amino-1,2,3,4-tetrahydroacridine, THA) was the first acetylcholinesterase inhibitor (AChEI) approved in the United States for the treatment of Alzheimers disease (AD). The tacrine and its analogs **142** were prepared using sloid-phase synthesis, using cyclohexanone **140** and anthranilonitriles **141** under the microwave irradiation (Scheme 64).



140 cyclohexanone | **141** anthranilonitrile | **142** tacrine

Scheme 64. General methodology for synthesis of tacrine

Macro and his research group[56] reported the synthesis of different tacrine derivatives from fuctionalized 2-amino-3-cyano-4*H*-pyrans **143** with cyclic ketones **144** undergoes Friedlander annulation in the presence of aluminum chloride catalyst under reflux conditions to afford the new acridine-type tacrines **145**. The Friedlander annulation is a straight forward method for the synthesis of aza-heterocyclic compounds. And also, its well-appreciated tool for the generation of large libraries of related heterocyclic compounds which are related to pharmacological activities.



143 2-amino-4*H*-pyrans, R = ethyl, propyl. | **144** cyclic ketones, n = 0, 1, 2 | **145** tacrine analogs

Scheme 65. Synthetic utility of 2-aminopyrans for tacrine synthesis

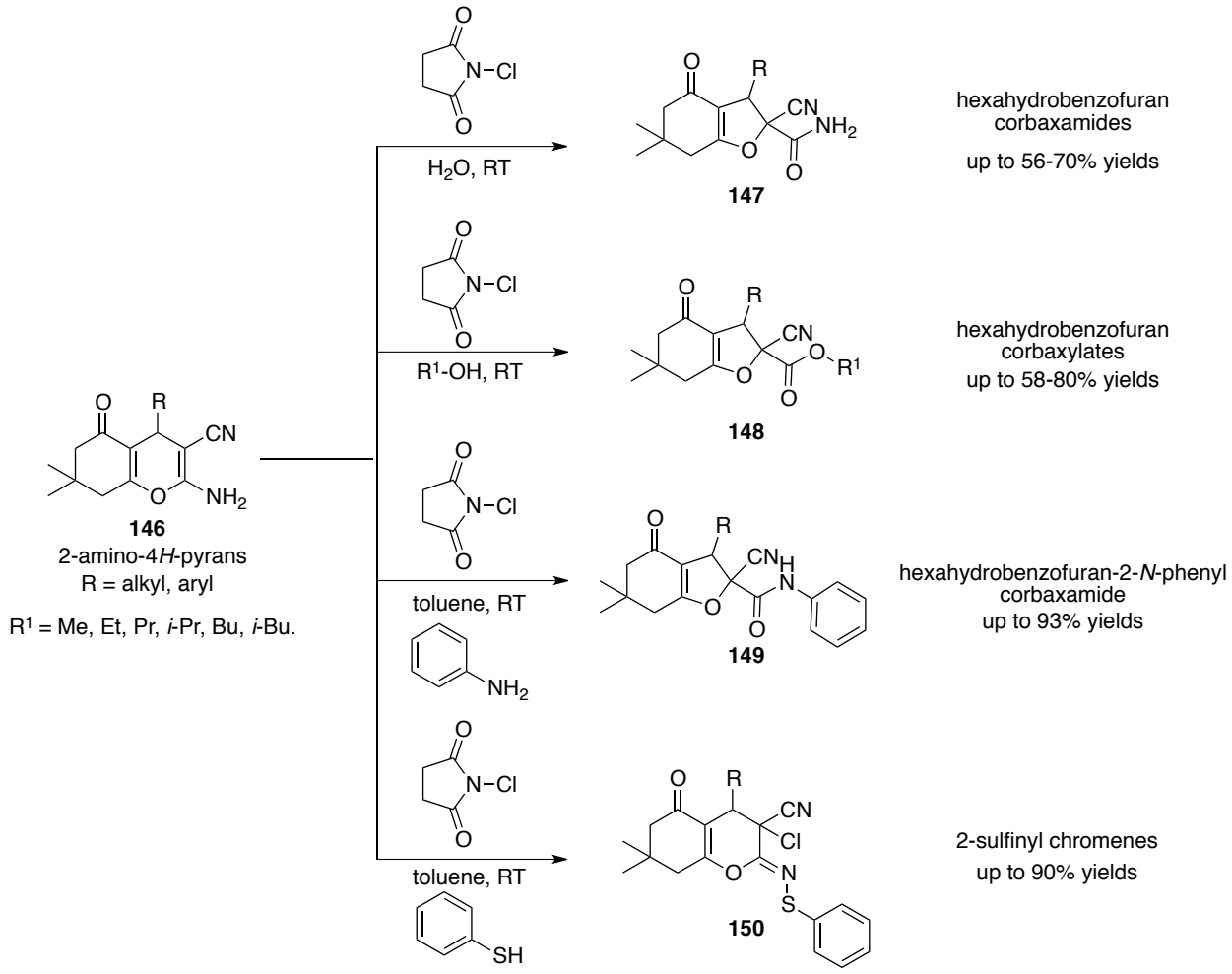
And they tested the prepared tacrine analogs showed the ability towards to inhibit the acetylcholinesterease (AChE) butyrylcholinesterease (BChE) and neuronal uptake of serotonin and noradrenaline. Changes in the size of the carbocyclic ring of tacrine produced modest potency against cholinesterase enzymes (Scheme 65).

4.3.4 Synthetic utility of 2-aminopyrans for dihydrofurans and 2-sulfinylimine-chromenes

Dihydrofurans and chromenes and their hetero-fused compounds are important molecular structures in synthetic organic chemistry. Such as, fungicidal agents, potential antioxidants and pharmaceuticals compounds. Further, these compounds are extensively used in photo chromic

materials and also as precursors to flavylium dyes. Recently A. Krishnaiah and his research group[57] reported a one pot four component reaction for dihydrofurans *via* simple, efficient, catalyst free green protocol in water medium. First 2-amino-4*H*-pyrans **146** were synthesized using multicomponent reaction strategy, then 2-aminopyrans were treated with *N*-chlorosuccinimide in water medium to obtained hexahydrodihydrofuran-carboxamides **147**. When 2-aminopyrans were treated with *N*-chlorosuccinimide in alcoholic medium furnishes the hexahydrodihydrofuran-carboxylates **148**.

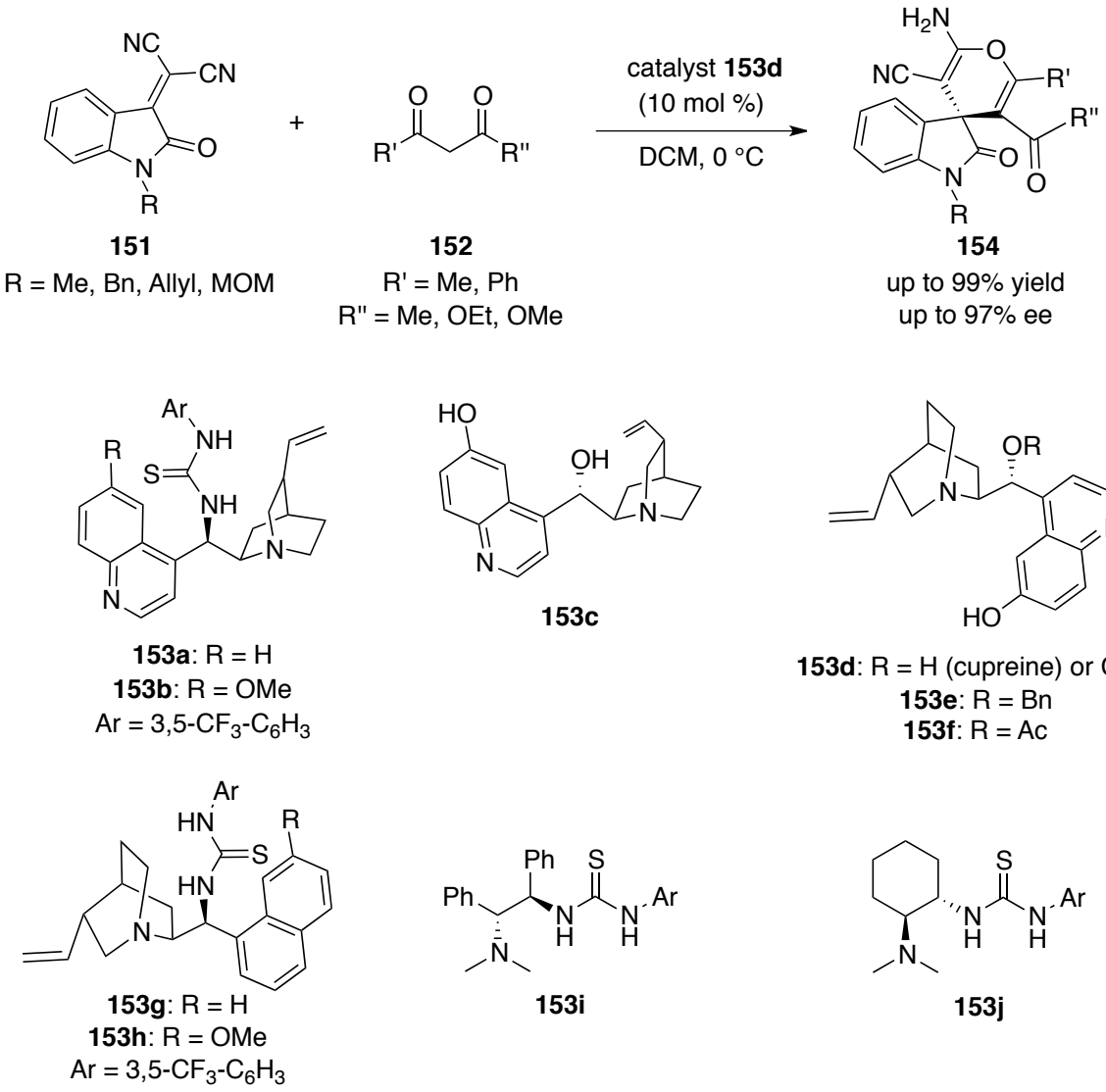
In another methodology A. Krishnaiah and his research group reported the synthetic utility of 2-amino-4*H*-pyrans **146**, using multi-component reaction strategy. Initially they were synthesized 2-aminocromenes using three components in one pot reaction of aldehyde, 1,3-dicarbonylcompound and malononitrile to construct the 2-aminopyrans, in the next stage 2-aminopyrans were reacted with *N*-chlorosuccinimide and aryl amine *via* sequential addition, to afford hexahydrobenzofuran-2-*N*-phenyl-corbaxamide **149** derivatives. In same way to 2-aminopyrans *N*-chlorosuccinimide and thiophenol in sequential addition to afford the 2-*N*-sulfinylimines **150** (Scheme 66).



Scheme 66. Synthetic utility of 2-aminochromenes for the construct of dihydrobenzofurans and 2-sulfinyl chromenes

4.4 Previous report on enantioselective synthesis of spiro-conjugated 2-aminopyrans

W. C. Yuan and his research group reported[58] the enantioselective construction of spiro-conjugated 2-aminopyrans (spiro-[4H-3,3'-oxindoles] through domino knoevenagel/Michael/cyclization sequence catalyzed by cupreine (CPN) organocatalyst. In this study, they synthesized a wide range of optically active spiro-conjugated 2-aminopyrans with good to excellent enantioselectivities (up to 97%) under mild reaction conditions (Scheme 67).

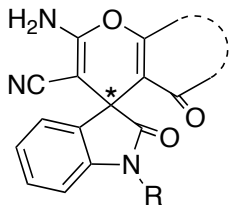


Scheme 67. Synthesis of optically active spiro-conjugated 2-aminopyrans

They reported the Michael addition reaction of unsaturated isatin nitriles **151** with linear1,3-diketones **152** using cupreines **153d-f** and cinchona-based alkaloids **153a-b** as organocatalysts. Among them, the catalyst **153d** have showed the excellent catalytic activity to afford chiral spiro-conjugated-2-aminopyrans **154** in both excellent chemical yields and enantioslectivities. However, this method failure to construct the chiral spiro-conjugated-2-aminopyrans using with cyclic 1,3-dicarbonyl compounds.

4.5 Author strategy

Author aimed to develop the new hybrid type sqauaramide fused amino alcohol (SFAA) organocatalysts for chiral spiro-conjugated 2-aminopyrans from readily available Michael acceptors and cyclic 1,3-dicarbonyl compounds using domino Michael addition cyclization reaction as strategy. However, the construction of one unique spirocyclic-oxindole, incorporating a 2-amino- 4*H*-pyran-3-carbonitrile ring at the C3 position of oxindole, is still limited in synthetic organic chemistry (Figure 21).

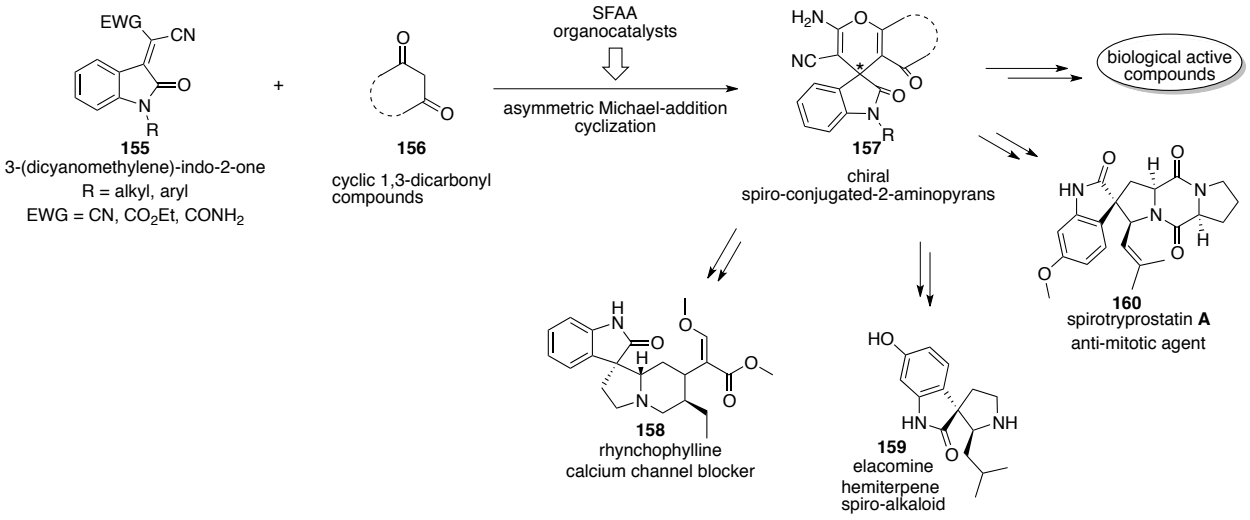


chiral spiro-conjugated 2-aminopyrans

Figure 21. The hybrid structure of chiral spiro-conjugated 2-aminopyrans

4.5.1 Synthetic utility of chiral spiro-conjugated 2-aminopyrans

The most fascinating application of spiro-conjugated 2-aminopyrans **157** in organic synthesis is undoubtedly due to the highly substituted spiro system of the molecules. The reactions of the amino and nitrile functional groups of spiro-conjugated 2-aminopyrans, mostly by nucleophilic additions or spiro-annulation, transform them into a 2-oxindole derivatives. The oxindoles skeletons system can be easily derived into a wide range of biologically active compounds, such as rhynchophylline (calcium channel blocker), elacomine (hemiterpene spiro-alkaloid) and spirotryprostatin A (anti-mitotic agent). And also, the bifunctional -NH_2 and -CN of spiro conjugated-2-aminopyrans shows reactivity towards electrophilic chlorination and brominating reactions.



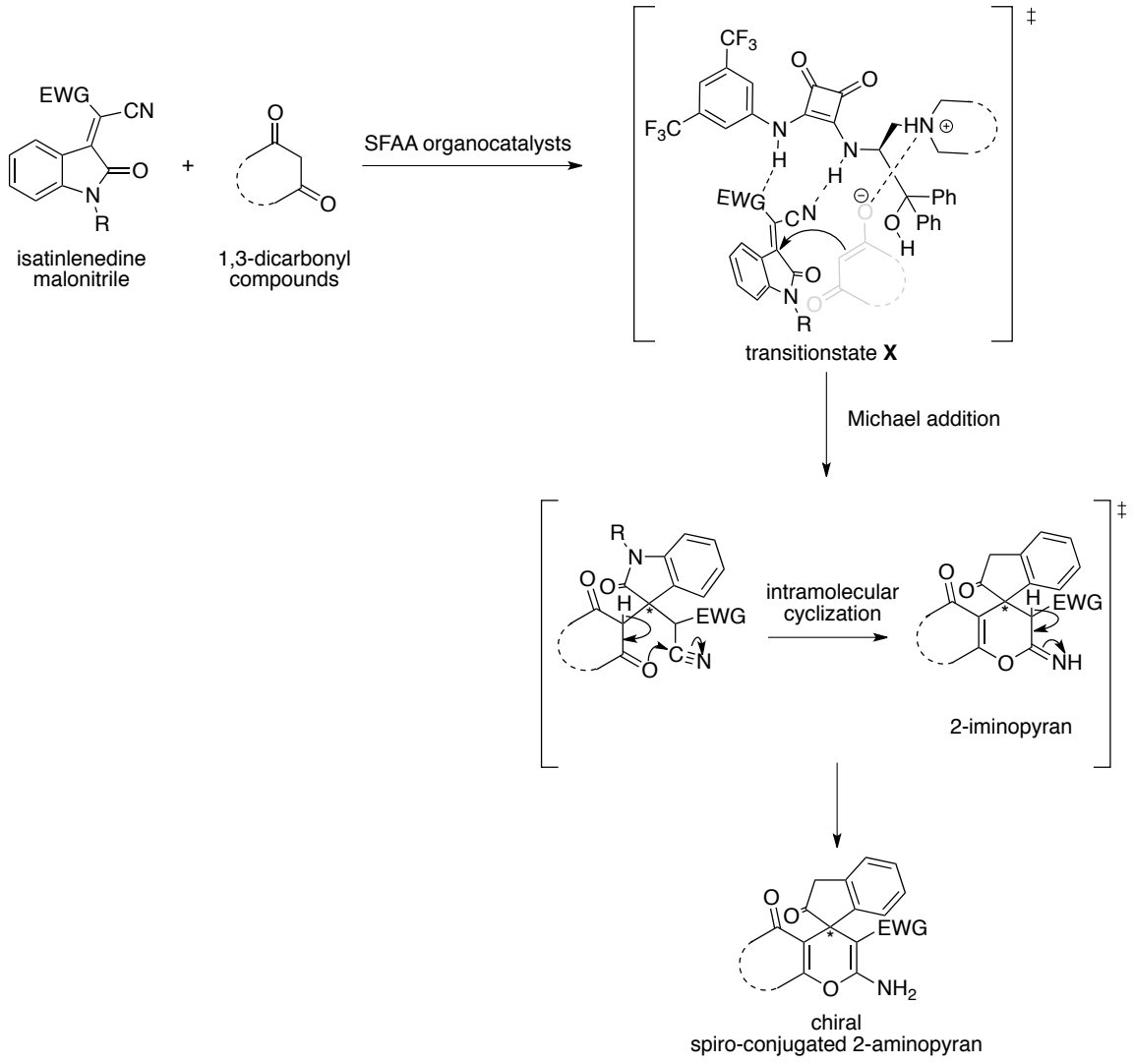
Scheme 68. Synthetic utility of chiral spiro-conjugated 2-aminopyrans

chiral spiro-conjugated 2-aminopyrans, especially those which are spiro-fused to other cyclic frameworks have drawn tremendous interest for researchers in the area of synthetic organic chemistry and medicinal chemistry. In particular, rhynchophylline **158**, is an alkaloid found in certain uncaria species (Rubiaceae), rhynchophylline is a non-competitive NMDA antagonist and calcium channel blocker. And also, the spiro-oxindole moiety's easily access to the synthesis of elacomine **159** hemiterpene spiro-alkaloid and spirotryprostatin **A 160** which is an indolic alkaloid from the 2,5-diketopiperazine class of natural products found in the *Aspergillus fumigatus* fungus (Scheme 68).

4.5.2 Results and discussions

In continuation of author efforts towards expanding the scope of amino alcohols and their derivatives as organocatalysts, author focused on the synthesis of squaramide fused amino alcohols and their applications for enantioselective reactions. The SFAA organocatalysts possess the multiple hydrogen-bonding and stereoinduction sites within the same molecule, and evaluated their catalytic activity in the Michael addition cyclization reaction to synthesis chiral spiro-conjugated 2-aminiopyrans using 3-methylenedicyano-indo-2-one and cyclic 1,3-dicarbonyl compounds. Additionally, SFAA catalysts contains a cyclic tertiary amino group that can act as a Brønsted base, sterically bulky groups, and two amino and one hydroxyl group that can form hydrogen bonds with both 3-dicyano-2-indanones and cyclic 1,3-dicarbonyl compound. As shown

in the plausible transition state **X** (Scheme 69). Thus, 3-dicyano-2-indanones and cyclic 1,3-dicarbonyl compound can be conformationally fixed by hydrogen-bonding interactions, that is, between the two amino groups of the squaramide and the two nitrile groups of the isatin, between the cyclic ammonium site of the squaramide and the oxygen atom of the 1,3-dicarbonyl enolate moiety, and between the cyclic ammonium site and the hydrogen atom of the hydroxyl group in the ammonium alcohol intermediate.



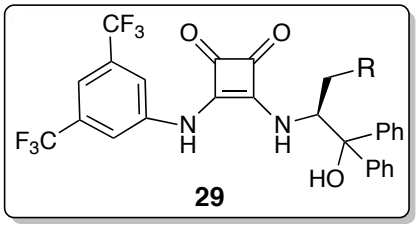
Scheme 69. Conceptualization of SFAA catalyzed enantioselective Michael addition cyclization reaction

Then, the Michael addition reaction may proceed stereo-selectively to afford the Michael adduct initially, which upon undergoes cyclization to produce the 2-iminopyrans subsequently the 2-iminiopyrans tautomerized into spiro-conjugated 2-aminopyrans to affords in a high enantioselectivities.

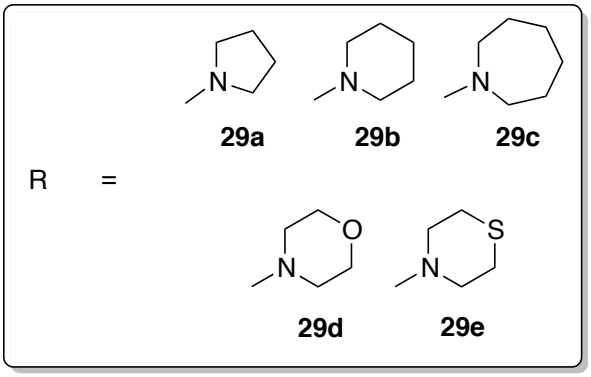
4.5.3 The enantioselective Michael addition cyclization reaction using catalysts 29a-e

First, author examined the catalytic ability of SFAA catalyst **29a** having a pyrrolidine ring at side chain of the catalyst for Michael addition cyclization reaction of 3-dicyano-2-indanone **161a** with dimedone **162a** in toluene at room temperature (entry 1, Table 8), afforded the spiro-pyran **163a** in trace amount. Next, catalyst **29b** is examined in toluene solvent at room temperature for 1h, afforded the spiro-pyran **163a** in good chemical yield (82%) with poor enantiomeric excess (9% ee) (entry 2). Furthermore, the reaction was conducted at room temperature and 0 °C using catalyst **29b** and **29c** respectively afforded the spiro-pyran **163a** in good to excellent chemical yields (catalyst **29c**: 90% yield with 7% ee, catalyst **29b**: 87% yield with racemic: entries 3,4). Moreover, reaction screened in THF solvent at 0 °C for 5h, afforded spiro-pyran **163a** in excellent chemical yield (90%) in racemic. Next reaction was examined with *N*-benzyl-3-dicyano-2-indanone **161b** with **162a** using catalyst **29b** in toluene solvent, afforded spiro-pyran **163b** in excellent chemical yield (95%) but the optical yield was not found (entry 6). Next, reaction is examined in THF solvent, for 24 h, at 0 °C, afforded chiral spiro-pyran in both good chemical yield (89%) and enantioselectivities (79 % ee) (entry 7). Subsequently the Michael reaction were optimized with catalysts **29a** and **29b** in THF solvent at 0 °C respectively, afforded chiral spiro-pyran **163b** in excellent chemical yields (92% and 95%) and good enantioselectivities (79% ee, 75% ee) (entries 8,9). Moreover, the reaction also screened with catalysts **29d** and **29e** having morpholine and thiomorpholine rings at side chain of the catalysts, which afforded the chiral spiro-pyran in excellent chemical yields (96%, 97%) but the enantiomeric excess was poor (entries 10,11). By observing these results, next author examined the optimization reaction conditions for Michael addition reaction of *N*-benzyl-3-dicyano-2-indanone **161b** with dimedone **162a** using catalyst **29a** in THF solvent at 0 °C for 48h.

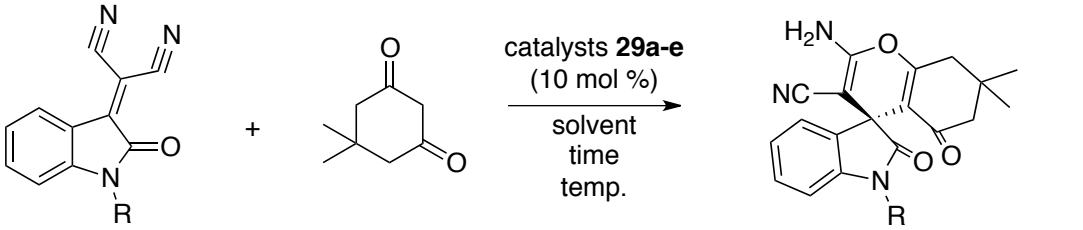
Table 8. The enantioselective Michael addition cyclization reaction using catalysts **29a-e**



29



29a **29b** **29c** **29d** **29e**



161a-b
3-dicyano-2-indanones
161a: H
161b: Bn

162a
dimedone

163a-b
chiral spiro-conjugated 2-aminopyrans

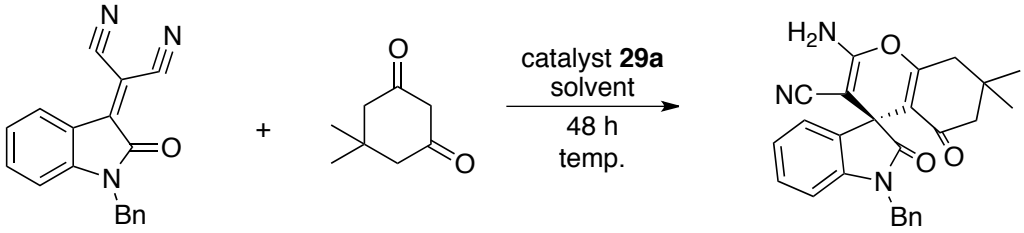
entry[a]	catalysts **29a-e**	indanones (R)	solvent	time (h)	temp. (°C)	yield [%][b]	ee [%][c]
1	**a**	H	toluene	24	RT	trace	----
2	**b**	H	toluene	1	RT	82	9
3	**c**	H	toluene	1	RT	90	7
4	**b**	H	toluene	5	0	87	rac
5	**b**	H	THF	5	0	90	rac
6	**b**	Bn	toluene	24	RT	95	rac
7	**b**	Bn	THF	24	0	89	77
8	**a**	**Bn**	**THF**	**48**	**0**	**92**	**79**
9	**c**	Bn	THF	48	0	95	75
10	**d**	Bn	THF	48	0	96	10
11	**e**	Bn	THF	48	0	97	rac

[a]The reactions were carried out with **161a**,**b** (0.1 mmol), **162a** (0.1 mmol) in above mentioned solvents (1.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined on chiral HPLC using Chiralpak AD-H and Chiralcel OD-H columns.

4.5.4 The optimization of reaction conditions for asymmetric Michael addition cyclization reaction using catalyst 29a

Next, author inspected various reaction temperatures, molar ratios and solvents for Michael addition reaction using catalyst **29a** for 48h (entries 1-15, Table 9). Changing the molar ratio of the catalyst **29a** to 20 and 5 mol% also provided the spiro-conjugated 2-aminopyran **163b** in excellent chemical yield with abnormal differences in enantiomeric excess, 20 mol % of the catalyst loading afforded the spiro-pyran with poor enantiomeric excess (7% ee).

Table 9. Optimization of reaction conditions using with catalyst **29a**



161b **162a** **163b**

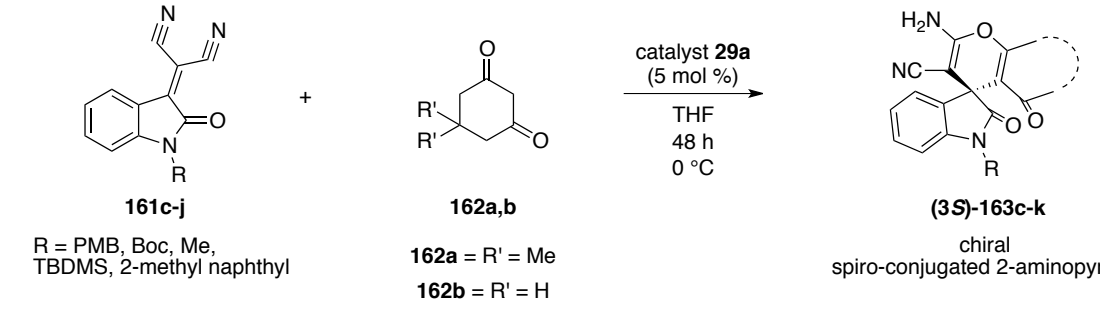
entry[a]	catalyst **29a** (mol %)	solvent	temp. (°C)	yield [%][b]	ee [%][c]
1	20	THF	0	96	7
2	**5**	**THF**	**0**	**95**	**83**
3	2	THF	0	92	81
4	5	THF	-10	92	73
5	5	THF	-50	90	81
6	5	THF	-80	87	77
7	5	Et_2O	0	82	67
8	5	DIPE	0	89	43
9	5	1,4-Dioxane	rt	98	5
10	5	DCM	0	96	7
11	5	chloroform	0	91	13
12	5	DCE	0	89	51
13	5	DMF	0	90	rac
14	5	DMA	0	89	rac
15	5	MeOH	0	92	rac

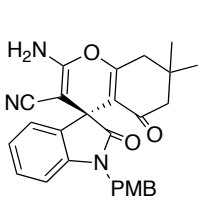
[a]The reactions were carried out with **161b** (0.1 mmol), **162a** (0.1 mmol) in above mentioned solvents (1.0 mL). [b]Isolated yields. [c]Enantiomeric excess was determined on chiral HPLC using Chiralpak AD-H column.

While the 5 mol % catalyst loading afforded **163b** with good enantiomeric excess 83% (entries 1,2). Next, the reaction screened with 2 mol % of catalyst **29a** afforded the spiro-pyran **163b** in 92% chemical yield with 81% enantiomeric excess (entry 3). Furthermore, Michael reaction was examined at lower temperature such as -10 °C, -50 °C and -80 °C afforded the spiro-pyran **163b** in decreasing chemical yields from (92% to 87%) and slight variations in enantioselectivities. At -10 °C afforded the spiro-pyran in 73% ee, at -50 °C afforded the spiro-pyran in 81% ee while -80 °C afforded the spiro-pyran with 77% ee (entries 4-6). Next, Michael reaction was optimized in ethereal solvent such as Et_2O, DIPE (diisopropyl ether) and 1,4-dioxane using catalyst **29a** afforded spiro-pyran **163b** with excellent chemical yields (82-98%) and poor to moderate enantioselectivities (5-67% ee) (entries 7-9). Furthermore, Michael reaction was also screened in chlorinated solvents such as DCM, chloroform and DCE using catalyst **29a** afforded the spiro-pyran **163b** in excellent chemical yields (89-96%) with poor to moderate enantioselectivities (7-51% ee) (entries 10-12). Subsequently the reaction was also optimized in polar solvents such as DMF, DMA and MeOH afforded the spiro-pyran in excellent chemical yields (89-92%) but the spiro-pyran **163b** was found in racemic (entries 13-15). Form above results, author optimized the reaction conditions (catalyst 5 mol %, at 0 °C, for 48h) for enantioselective domino Michael addition cyclization reaction.

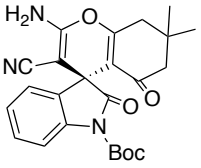
4.5.5 Substrate scope for the enantioselective domino Michael addition cyclization reaction

The generality of protocol for the enantioselective domino Michael addition cyclization reaction was fully demonstrated by evaluating the reactions with between *N*-substituted 3-dicayano-2-indanones **161c-j** and cyclic 1,3-dicarbonyl compounds **162a**,**b** using optimized catalyst **29a** in THF solvent at 0 °C for 48 h (Scheme 70). First, the author examined the *N*-(4-methoxybenzyl)-3-dicyano-2-indanone **161c** as Michael acceptor with dimedone **162a** using catalyst **29a**, afforded chiral spiro-pyran **163c** in both good chemical yields and enantiomeric excess (89%, 81% ee). Next the reaction was optimized with *N*-Boc group containing 3-dicyano-2-indanone **161d** with **162a** afforded the spiro-pyran **163d** in good chemical yield with poor enantioselectivity (5% ee).

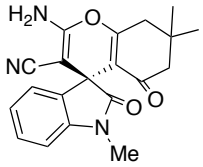




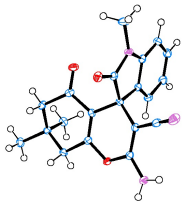
163c: 89%, 81% ee



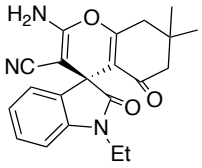
163d: 72%, 5% ee



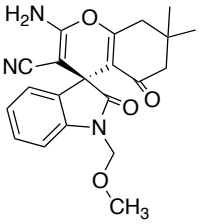
(3*S*)-163e: 92%, 95% ee



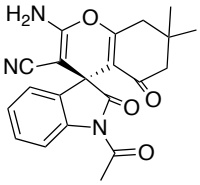
determination of absolute configuration of **163e** using X-ray crystalography



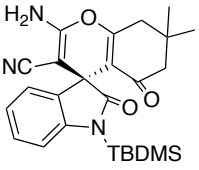
163f: 87%, 84% ee



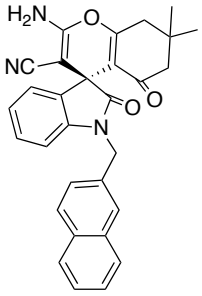
163g: 95%, 75% ee



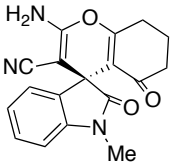
163h: 90%, 80% ee



163i: 72%, 76% ee



163j: 81%, 71% ee



163k: 90%, 76% ee

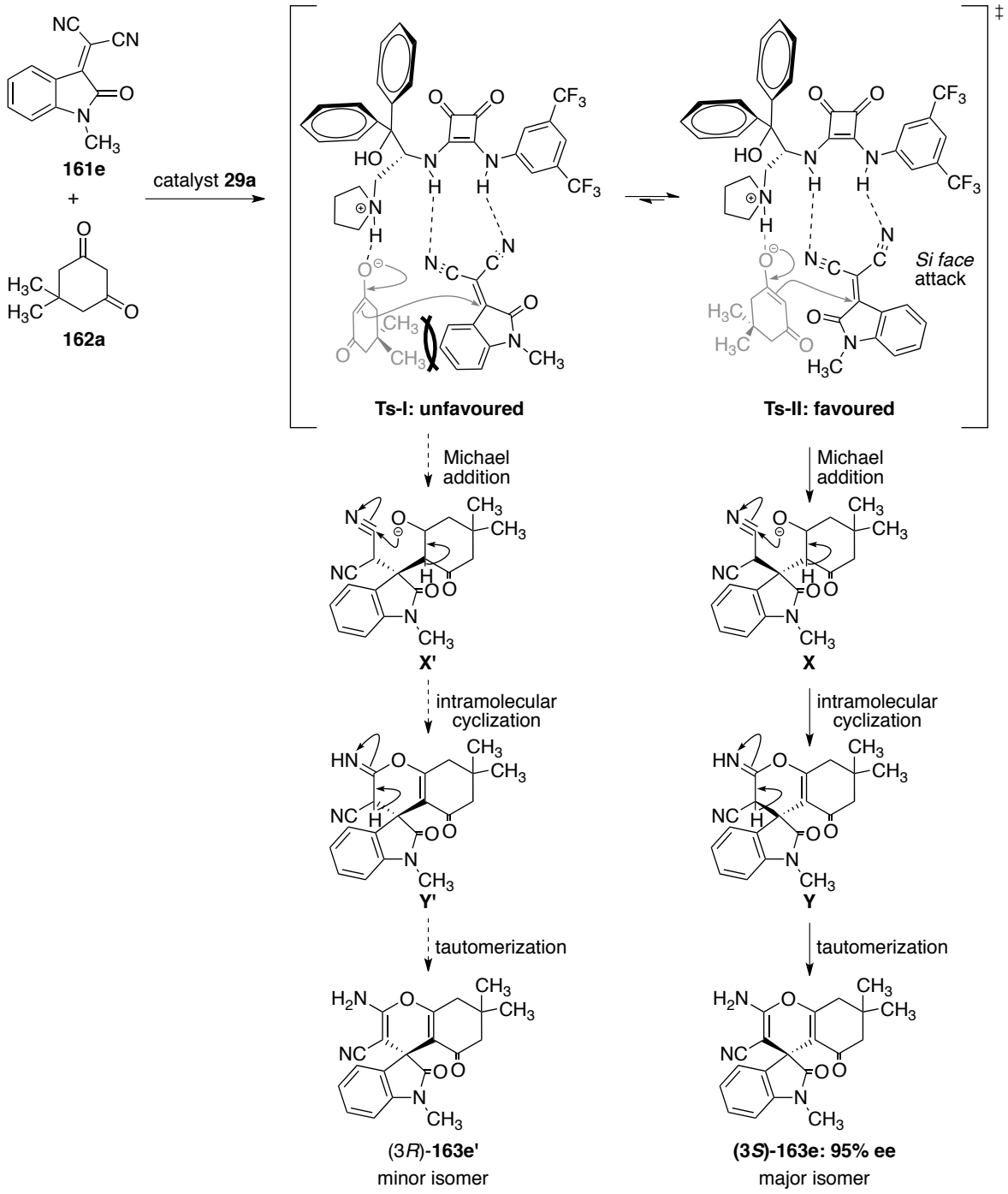
Scheme 70. Substrate scope for enantioselective domino Michael addition reaction

Furthermore, Michael reaction was screened with *N*-methyl-3-dicyano-2-indanones **161a** with **162a** afforded chiral spiro-pyran **163e** in both excellent chemical yields (92%) and enantiomeric excess (95%). The absolute configuration of chiral spiro-pyran **(3*S*)-163e** were determined using with X-ray crystallography. Next, The *N*-ethy-3-dicyano-2-indanone **161f** screened with **162a** using catalyst **29a** afforded chiral spiro-pyran in both good chemical yield (87%) and enantiomeric excess (84%). Additionally, the Michael reaction was screened with *N*-(monomethoxymethylether)-3-dicyano-2-indanone **161g** and *N*-(acetyl)-3-dicyano-2-indanone **143h** with dimedone **162a** using catalyst **29a** respectively, which afforded the chiral spiro-pyrans in excellent chemical yields (90 to 95%) and good to moderate enantioselectivities (75-80% ee). Furthermore, the enantioselective Michael addition reaction was screened with sterically bulky protected 2-methylene naphthyl and silyl protected 3-dicyano-2-indanones **161i** and **161j** with **162a** which afforded the chiral spiro-pyrans **163i** and **163j** respectively in both good chemical yields (72-81%) and enantioselctivities (71-76% ee). While changing the 1,3-cyclopentadione **162b** as Michael donor in reaction with *N*-methyl-3-dicyano-2-indanone **161e** using catalyst **29a** afforded the spiro-pyran **163k** in excellent chemical yield (90%) and with moderate enantiomeric excess (76% ee).

4.5.6 Plausible reaction course for domino Michael addition cyclization reaction

Based on the observed enantiopurities of chiral spiro-pyran **163e** in **95% ee** which afforded in Michael addition reaction with **161e** with **162a**, a model of mechanistic pathway for domino Michael addition cyclization reaction is proposed as follows (Scheme 72). First, the active methylene proton of dimedone is abstracted by basic tertiary amino group on pyrrolidine ring of catalyst **29a** to form enolate, which might also induce the strong hydrogen bonding interaction between the hydrogen atom of the ammonium moiety on pyrrolidine ring in catalyst and oxygen atom of enolate. Next, *N*-(methyl)-3-dicyano-2-indanone **161e** might fixed with catalyst **29a** through two hydrogen bonds between two nitriles functionalities of **161e** with two primary amino groups on squaramide unit of catalyst **29a**. In the two possible transition states **TS-I** and **TS-II**, the **TS-II** has less steric interaction than that of **TS-I**, which has strong steric repulsion between dimethyl groups from dimedone with amide carbonyl oxygen atom of **161e**. Hence the enantioselective Michael addition cyclization reaction might proceed *via* **TS-II**, in which the dimedone enolate co-ordinated to ammonium moiety on pyrrolidine ring could attack

stereoselectively on the electron deficient olefin carbon of **161e** from the above side (*Si* face) which leading to the formation of **(3*S*)-163e** as major isomer, whereas the minor isomer (3*R*)-**163e'** might be obtained through the unfavoured transition state **TS-I** (Scheme 71).



Scheme 71. Plausible reaction course for enantioselective domino Michael addition cyclization reaction using catalyst **29a**

4.6 Summary

In summary, author developed new hybrid type squaramide fused amino alcohol (SFAA) catalyst **29a** showed the significant catalytic activity in enantioselective domino Michael addition cyclization reaction with various *N*-substituted-3-dicyano-2-indanones **161a-j** and cyclic 1,3-dicarbonyl compounds **162a**,**b**. This protocol provides the chiral spiro-conjugated 2-aminopyrans **163a-k** in both excellent chemical yields (up to 98%) and enantioselectivities (up to 95% ee). The resulted chiral spiro-conjugated-2-aminopyrans could be crucial intermediates for the synthesis of many biologically active significant scaffolds.

5. Conclusion

Many biological active molecules, including pharmaceuticals, are optically active. In biological systems of human beings only one form of enantiomers plays key role in treatment of diseases. Therefore, synthesis of optically active molecules is often more challenging in the field of synthetic organic chemistry. The catalytic asymmetric synthesis is useful for the preparation of biologically active molecules including a drug. The enantioselective synthesis using organocatalysts is recognized as an independent synthetic tool besides asymmetric metal catalysis and enzyme catalysis, and the catalysts are easy to handle even on large scale and relatively less toxic compared to transition metals. In the present thesis, author aimed to develop an efficient new hybrid type squaramide fused amino alcohol (SFAA) organocatalysts for enantioselective reactions. The SFAA organocatalysts were prepared by using with simple amino alcohol with mono ester squaramide and the catalysts possess with multiple activation sites in the molecule such as, three hydrogen bonding sites from two amine functions and one hydroxy function. And also, contains an Brønsted basic site on the side chain of catalysts from cyclic amines (pyrrolidine, piperidine, azapane, morpholine and thiomorpholine) which can abstract the proton from pro-nucleophiles. By these properties of SFAA organocatalysts enables the formation of covalent and non-covalent intermediates with wide-variety of the substrates and allows one enantiomeric face for enantioselective reactions. The prepared SFAA organocatalysts successfully applied for enantioselective nitro-aldol (chapter 2), Diels-Alder (chapter 3) and domino Michael addition cyclization reactions (chapter 4).

In chapter 2, author discussed about the detailed application of SFAA organocatalysts for enantioselective nitro-aldol reaction. The usual and new hybrid type SFAA organocatalysts **21a-d** and **29a-e** were prepared and examined in enantioselective nitro-aldol reaction of isatins **30a-k** with nitromethane **7**. Among the prepared SFAA organocatalysts, the catalysts **29c** has showed the best catalytic activity to afford the chiral 3-alkylated-3-hydroxy-oxindoles **31a-k** in excellent chemical yields and enantioselectivities (up to 99%, up to 95% ee). The obtained chiral 3-alkylylated-3-hydroxy-oxindoles **31a-k** are prominent synthetic intermediates for many biologically active compounds such as the donaxaridine (anticancer), spirobrasinin (antifungal), maremycin B (cytotoxicity) and CPC-1 (antibacterial agent).

In chapter 3, author discussed about the detailed application of SFAA organocatalysts for enantioselective Diels-Alder reaction. The new hybrid type SFAA organocatalysts **29a-e** showed

catalytic activity for enantioselective Diels-Alder reactions of 3-hydroxy-2-pyridones **96a**,**b** and 4-substituted 3-hydroxy-2-pyridones **99a-d** with maleimides **97a-k** respectively. Among the optimized SFAA catalysts, the catalysts **29a** showed best catalytic activity to afford the chiral 4-hydroxyisoquinnuclidines **98a-k** and **101a-f** in excellent chemical yields and enantioselectivities (up to 95%, up to 98% ee) respectively. Particularly, the reaction of 4-brominated 2-pyridone **99a** with maleimides **97a** afforded the corresponding 4-hydroxyisoquinnuclidines **101a** in both excellent chemical yield and enantioselectivity (up to 95%, up to 98% ee) having an opposite absolute stereochemistry in comparison with the DA adduct **98a** from the reactions using common 3-hydroxy-2-pyridone **96a**. The obtained chiral 4-hydroxyisoquinnuclidines **98a-k** and **101a-f** are prominent synthetic intermediates for bicyclic complex structures and many biological active molecules such as oseltamivir (antiinfluenza drug), ibogaine (natural product) and vinblastine and vincristine (anticancer drug).

In chapter 4, author discussed about the detailed application of new hybrid type SFAA organocatalysts for enantioselective domino Michael addition cyclization reaction. The new hybrid type SFAA organocatalysts **29a-e** has showed catalytic activity for domino Michael addition cyclization reaction of cyclic 1,3-dicarbonyl compound **162a**,**b** with electron withdrawing 2-indanones **161a-j**. Among the optimized SFAA organocatalysts, catalyst **29a** has showed the best catalytic activity to afford chiral spiro-conjugated 2-aminopyrans **163a-k** in excellent chemical yields and enantioselectivities (up to 97%, up to 95% ee). The obtained chiral spiro-conjugated 2-aminopyrans **163a-k** are the prominent synthetic intermediates for many biologically active analogs, such as tacrine derived 2-aminopyrans (antialzheimers), spiro-pyranopyrazoles (antioxidants), pyranopyranones (anticoagulant) and 2-aminotetrahydrocromenes (antileishmaniasis).

In conclusion, author developed new hybrid type squaramide fused amino alcohol (SFAA) organocatalysts. The prepared SFAA organocatalysts successfully applied in enantioselective nitro-aldol, Diels-Alder and domino Michael addition cyclization reactions which afforded the biological active chiral synthetic intermediates in excellent chemical yields and enantioselectivities. It's expected that these results might be able to contribute greatly in the development of new synthetic drugs in the field of synthetic organic chemistry.

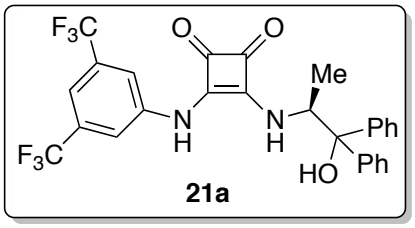
6. Experimental section

General information: All commercial reagents were purchased and used without further purification. All reactions were carried out under argon in flame-dried glassware with magnetic stirring. Thin layer chromatography was performed on silica gel 60 F_{254}, and the analytes were detected by using UV light (254 nm) and iodine vapor. Column chromatography was carried out on silica gel 60N (40-100 μm). Melting points were measured with a micro melting point apparatus. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data were recorded in either $CDCl_3$ or $(CD_3)_2SO$. The ^{1}H NMR spectral data are reported as follows: chemical shifts (δ) in ppm from tetramethylsilane (δ = 0.0 ppm) or the residual solvent as an internal standard [for $CDCl_3$: δ = 7.26 ppm; for $(CD_3)_2SO$: δ = 2.50 ppm], multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), and br. (broad)], coupling constants in Hertz (Hz), integration, and assignment. The ^{13}C NMR spectroscopic data were measured with complete proton decoupling. Chemical shifts are reported in ppm from the residual solvent as an internal standard (for $CDCl_3$: δ = 77.16 ppm). IR spectra were measured with an JASCO 4100 FT-IR spectrophotometer. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data were recorded using JEOL JNM-ECA500 instrument. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. HRMS data were obtained by EI and FAB using Hitachi RMG-GMG and JEOL JNX-DX303 sector instruments.

Chapter 2: **The New Hybrid Type Squaramide Fused Amino Alcohol Organocatalysts For Enantioselective Nitro-Aldol Reaction of Nitromethane with Isatins**

General procedure for the synthesis of compounds (21a-d): To a stirred solution of compound squaramide mono ester amide **20** (149 mg, 1 mmol) in dry MeOH (5 mL) was added the corresponding amino alcohol **19a-d** (1 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 12 h. Upon completion of the reaction indicated by TLC, the excess amount of MeOH was evaporated under reduced pressure to give the crude reaction mixture, which was purified by flash column chromatography (hexane/EtOAc, 6:4) to afford **21a-d** as pure compounds in moderate to good yields.

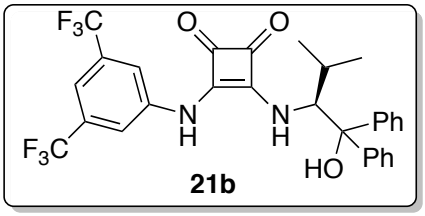
(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-1,1-diphenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (21a): Pale yellow solid (MeOH). 170 mg, 70% yield. m.p. 202-205 °C. $[\alpha]_D^{24} = -38$ (*c* = 0.5, MeOH). IR (neat) = 3223, 2980, 1687, 1417, 1115, 825 cm^{-1}.



21a

^1H NMR (500 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.03 (s, 2H), 7.99 (d, *J* = 10.50 Hz, 1H), 7.62 (s, 1H), 7.51 (t, *J* = 7.00 Hz, 3H), 7.40 (t, *J* = 7.50 Hz, 2H), 7.26-7.20 (m, 3H), 7.09 (t, *J* = 7.50 Hz, 1H), 6.42 (s, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.00 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 184.6, 180.0, 170.1, 161.8, 146.2, 145.3, 141.1, 128.3, 127.8, 126.8, 126.4, 125.7, 125.6, 124.2, 122.1, 117.9, 114.6, 81.1, 63.6, 28.7, 22.3, 17.5. EI-MS m/z: 534 $(M)^+$, 556.8 $(M + Na)^+$. HRMS (EI) calcd for $C_{27}H_{20}F_6N_2O_3$ m/z: 534.1378 $(M)^+$ found: 534.1390.

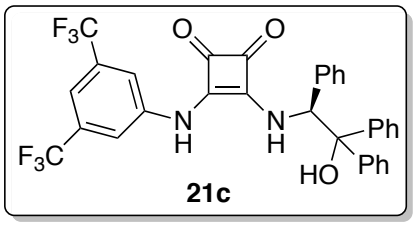
(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)amino)cyclobut-3-ene-1,2-dione (21b): White solid (ether). 150 mg, 65% yield. m.p. 197-198 °C. $[\alpha]_D^{24} = -647$ (*c* = 0.5, MeOH). IR (neat) = 3215, 2986, 1696, 1497,740 cm^{-1}. ^1H NMR



21b

(500 MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.21 (d, *J* = 11.00 Hz, 1H), 8.04 (d, *J* = 10.50 Hz, 1H), 7.50-7.43 (m, 4H), 7.34-7.23 (m, 4H), 7.20-7.11 (m, 1H), 5.76 (s, 1H), 5.68 (s, 1H), 5.12-5.10 (m, 1H), 4.40 (s, 1H), 4.19 (s, 1H), 0.93 (d, *J* = 7.00 Hz, 3H), 0.75 (t, *J* = 6.50 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.8, 182.4, 177.3, 173.1, 146.8, 130.2, 129.3, 128.8, 128.3, 128.1, 127.9, 127.5, 126.6, 126.0, 125.8, 125.6, 125.5, 125.0, 80.5, 63.7, 28.5, 22.4, 17.7. EI-MS m/z: 562 $(M)^+$. HRMS (EI) calcd for $C_{29}H_{24}F_6N_2O_3$ m/z: 562.1691 $(M)^+$ found: 562.1705.

(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-3-phenyl-1,1-diphenylbutan-2-yl)amino)cyclobut-3-ene-1,2-dione (21c): White solid (ether). 150 mg, 62% yield. m.p. 197-198 °C. $[\alpha]_D^{24} = -47$ (*c* = 0.5, MeOH). IR (neat) = 3215, 2986, 1696, 1497,740 cm^{-1}. ^1H NMR

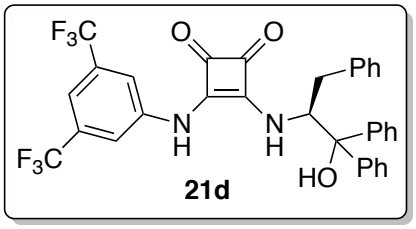


21c

(500 MHz, DMSO-d_6): δ 10.4 (s, 1H), 8.80-8.78 (d, J = 10 Hz, 1H), 8.01 (s, 2H), 7.64-7.69 (m, 3H), 7.35-7.38 (m, 2H), 7.08-7.25 (m, 11H), 6.75 (br, 1H), 6.22-6.24 (d, J = 10 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 184.64, 179.96, 168.35, 162.61, 145.61, 144.15, 140.82, 139.01, 131.36, 131.09, 128.93, 128.08, 127.52, 126.76, 126.62, 126.22,

126.15, 124.16, 121.99, 118.04, 114.8, 80.44, 63.38. EI-MS m/z: 596 $(M)^+$. HRMS (EI) calcd for $C_{32}H_{22}F_6N_2O_3$ m/z: 596.1581 $(M)^+$ found: 596.3181.

(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-1,1,3-triphenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (21d): White solid (MeOH). 100 mg, 59% yield. m.p. 253-255 °C. $[\alpha]_D^{24}$ = –25 (*c* = 0.5, MeOH). IR (neat) = 3265, 2986, 1686, 1446, 855 cm^{-1}. ^1H NMR

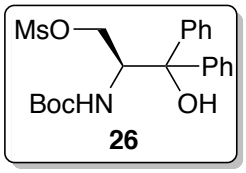


21d

(500 MHz, DMSO-d_6): δ 10.15 (s, 1H), 8.05 (d, *J* = 10.00 Hz, 1H), 7.93 (s, 2H), 7.66 (d, *J* = 7.50 Hz, 2H), 7.60 (s, 1H), 7.54 (d, *J* = 7.50 Hz, 2H), 7.46 (t, *J* = 7.50 Hz, 2H), 7.29 (t, *J* = 7.50 Hz, 1H), 7.19 (t, *J* = 7.50 Hz, 4H), 7.15-7.05 (m, 4H), 6.62 (s, 1H), 5.47-5.41 (m, 1H), 2.83 (d, *J* = 7.00 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 183.8, 179.6, 169.6, 160.9, 145.4, 145.1, 141.0, 137.9, 131.5, 131.2, 129.3, 128.6, 128.2, 127.9, 127.0, 126.4, 125.5, 124.2, 122.0, 117.6, 79.7, 62.2, 36.8. EI-MS m/z: 610 $(M)^+$, 633 $(M + Na)^+$. HRMS (EI) calcd for $C_{33}H_{24}F_6N_2O_3$ m/z: 610.1691 $(M)^+$ found: 610.1697.

General procedure for the synthesis of compound (26): To a stirred solution of compound **24** (1.0 g, 4.1 mmol) in dry DCM (20 mL) was added triethylamine (1.03 g, 10.2 mmol) and stirred for 5 min followed by addition of $(Boc)_2O$ (1.39 g, 6.3 mmol) then stirring was continued for 3 h at room temperature. After completion of the reaction indicated by TLC, reaction mixture was quenched with ice cold water and extracted with DCM (3x50 ml), solvent was evaporated under reduced pressure. The crude reaction mass of compound **25** (1.6 g, 4.6 mmol) was dissolved in dry DCM (20 mL) was added triethylamine (1.17 g, 11.6 mmol) and methanesulfonyl chloride (0.63 g, 5.5 mmol) at 0 °C and reaction was allowed to stir at room temperature for 5 h. Then reaction mixture was quenched with ice cold water and extracted with DCM (3x50 ml), solvent was removed under vacuum and the residue was purified by flash column chromatography (hexane/ethyl acetate 9:1) to afford the compound **26** in good yield.

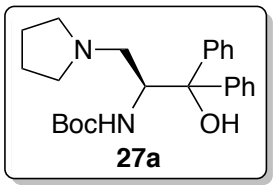
(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3,3-diphenylpropyl-methanesulfonate (26): White solid (Ether). 1.9 g, 85% yield. m.p. 152-154 °C. $[\alpha]_D^{21}$ = –57.14 (*c* = 0.7, EtOH). IR (neat): 3012, 2966, 2817, 1622, 1456, 1158, 1028 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 – 7.44 (m, 4H), 7.35 – 7.18 (m, 6H), 5.25 (d, *J* = 8.5 Hz, 1H), 4.92 – 4.85 (m, 1H), 4.38 – 4.27 (m, 2H), 3.94



(bs, 1H), 2.86 (s, 3H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 156.1, 144.4, 143.8, 128.8, 128.4, 127.6, 127.3, 125.6, 125.2, 80.4, 80.0, 69.5, 56.0, 37.3, 28.2. FAB-MS m/z: 422 $(M+H)^+$. HRMS (FAB) calcd for $C_{21}H_{28}NO_6S$ m/z: 422.1637 $(M+H)^+$: found: 422.1634.

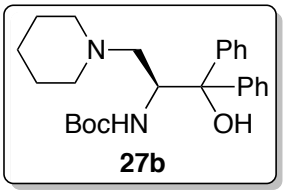
General procedure for the synthesis compounds (27a-c): The Compound **26** (1.0 mmol) was charged in 50 mL round bottomed flask and the corresponding cyclic amine (3 mmol) was added drop-wise at room temperature. After 5 min stirring the temperature was raised to 70° C and allowed to stirred for 12 h. After completion of the reaction, indicated by TLC, the crude reaction mixture was purified by flash column chromatography using (hexane/EtOAc, 7:3) to afford the compounds **27a-e** in moderate yield.

(*S*)-*tert*-butyl-(1-hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)carbamate (27a): White solid (Ether). 65% yield. m.p. 113-115 ^{o}C. $[\alpha]_D^{21}$ = –53.1 (*c* = 0.32, EtOH). IR (neat): 3096, 2918, 2817, 2834, 1725, 1565,1456, 1165, 1018 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 – 7.52



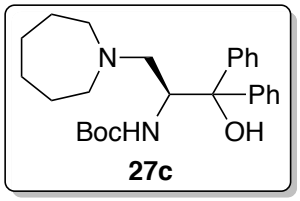
(m, 2H), 7.48 – 7.47 (m, 2H), 7.31 – 7.24 (m, 4H), 7.17 – 7.13 (m, 2H), 5.23 (d, *J* = 5.0 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 2.81 – 2.74 (m, 2H), 2.70 – 2.60 (m, 2H), 2.40 – 2.30 (m, 2H), 1.78 – 1.68 (m, 4H), 1.35 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.8, 146.8, 145.2, 128.4, 128.2, 126.68, 126.65, 125.3, 125.1, 81.7, 79.4, 56.3, 55.7, 54.3, 28.4, 28.3, 23.7. EI-MS m/z: 396 $(M)^+$. HRMS (EI) calcd for $C_{24}H_{32}N_2O_3$ m/z: 396.2413 $(M)^+$: found: m/z: 396.2417 $(M)^+$.

(*S*)-*tert*-butyl(1-hydroxy-1,1-diphenyl-3-(piperidin-1-yl)propan-2-yl)carbamate (27b): White solid (Ether). 62% yield. m.p. 85-87 ^{o}C. $[\alpha]_D^{21}$ = –88.0 (*c* = 0.25, EtOH). IR (neat): 3086, 2910,



2856, 1721, 1623, 1555, 1467, 1148, 1022 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 – 7.51 (m, 2H), 7.50 – 7.44 (m, 2H), 7.30 – 7.20 (m, 4H), 7.18 – 7.12 (m, 2H), 5.30 – 5.22 (m, 1H), 4.70 – 4.62 (, 1H), 2.76 – 2.73 (m, 1H), 2.56 – 2.42 (m, 2H), 2.10 – 2.02 (m, 2H), 1.60 – 1.52 (m, 4H), 1.42 – 1.30 (m, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155. 8, 147.5, 145.2, 128.4, 128.2, 126.7, 126.6, 125.3, 125.2, 81.4, 79.4, 59.1, 56.3, 54.0, 28.4, 26.3, 23.7. EI-MS m/z: 410 $(M)^+$. HRMS (EI) calcd for $C_{25}H_{34}N_2O_3$ m/z: 410.2569 $(M)^+$: found: m/z: 410.2565 $(M)^+$.

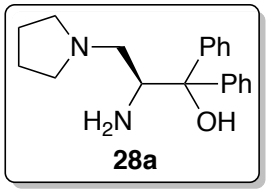
(*S*)-*tert*-butyl-(3-(azepan-1-yl)-1-hydroxy-1,1-diphenylpropan-2-yl)carbamate (**27c**): White solid (Ether). 55% yield. m.p. 67-69 °C. $[\alpha]_D^{21}$ = –80.0 (*c* = 0.25, EtOH). IR (neat): 3094, 2895, 2812, 1732, 1645, 1532, 1428, 1156, 1019 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, *J* = 5.0 Hz, 2H), 7.48 (d, *J* = 10.0 Hz, 2H), 7.30 – 7.24 (m, 4H), 7.18 – 7.12 (m, 2H), 5.28 – 5.20 (m, 1H), 4.68 – 4.62 (m, 1H), 3.00 – 2.92 (m, 1H), 2.44 – 2.36 (m, 2H), 1.70 – 1.52 (m, 8H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155. 7, 146.9, 145.3, 128.4, 128.2, 126.7, 126.6, 125.3, 81.5, 79.4, 59.0, 58.2, 54.0, 28.4, 27.9, 26.6. EI-MS m/z: 424 $(M)^+$. HRMS (EI) calcd for $C_{26}H_{36}N_2O_3$ m/z: 424.2726 $(M)^+$: found: m/z: 424.2728 $(M)^+$.



27c

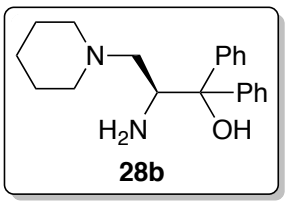
General procedure for the synthesis of compounds (28a-e): The compounds **27a-e** (1 mmol) were dissolved in DCM (10 mL) followed by slow addition of TFA (0.382 mL, 10 mmol) at 0 °C and stirred for 1 h at room temperature. After completion of reaction, indicated by TLC. The residue was basified using with saturated aq. $NaHCO_3$ solution and extracted with DCM (3x15 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford compounds **28a-e** in good to excellent yield.

(*S*)-2-amino-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-1-ol (28a): Light yellow solid (Ether). 135 mg, 90% yield. m.p. 113-115 °C. $[\alpha]_D^{24}$ = –74 (*c* = 1.09, EtOH). IR (neat) = 2933, 2803, 1556, 1448, 1355 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.50 Hz, 2H), 7.53 (d, *J* = 8.50 Hz, 2H), 7.33-7.25 (m, 4H), 7.20-7.13 (m, 2H), 3.92 (q, J_1 = 3.50, 7.00 Hz, 1H), 2.76 (q, J_1 = 7.00, 13.00 Hz, 1H), 2.62-2.60 (m, 2H), 2.42-2.40 (m, 2H), 2.28 (dd, J_1 = 3.50, 13.00 Hz, 1H), 1.76-1.70 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.3, 145.8, 128.4, 128.2. 126.6, 126.5, 125.9, 125.6, 79.9, 57.6, 55.1, 55.0, 23.7; FAB-MS m/z: 297 $(M+H)^+$. HRMS (FAB) calcd for $C_{19}H_{25}N_2O$ m/z: 297.1967 $(M+H)^+$ found: 297.1963.



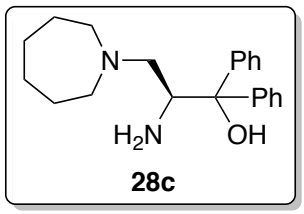
28a

(*S*)-2-amino-1,1-diphenyl-3-(piperidin-1-yl)propan-1-ol (**28b**): Pale yellow solid (Ether). 145 mg, 95% yield. m.p. 125-126 °C. $[\alpha]_D^{25}$ = –66 (*c* = 1.38, EtOH). IR (neat) = 3432, 2836, 2321, 1561, 1446 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.50 Hz, 2H), 7.51 (d, *J* = 7.50 Hz, 2H), 7.33-7.24 (m, 4H), 7.20-7.15 (m, 2H), 3.96 (q, J_1 = 4.50, 6.50 Hz, 1H), 2.62-2.39 (m, 3H), 2.20-2.16 (m, 3H), 1.57-1.50 (m, 4H), 1.38 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 145.2, 128.3, 128.2, 126.6, 126.5, 126.1, 125.8, 79.5, 59.1, 56.3, 54.0, 28.5, 26.3. FAB-MS m/z: 310 $(M+H)^+$. HRMS (FAB) calcd for $C_{20}H_{27}N_2O$ m/z: 311.2123 $(M+H)^+$: found: 311.2126.



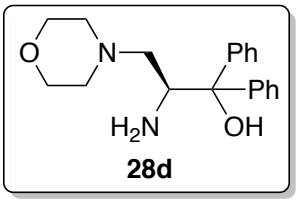
28b

(*S*)-2-amino-3-(azepan-1-yl)-1,1-diphenylpropan-1-ol (**28c**): Pale yellow solid (Ether). 131 mg, 86% yield. m.p. 145-146 °C. $[\alpha]_D^{23}$ = –40 (*c* = 2.4, EtOH). IR (neat) = 3504, 2933, 2326, 1615, 1452 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.50 Hz, 2H), 7.51 (d, *J* = 8.50 Hz, 2H), 7.33-7.24 (m, 4H), 7.21-7.155 (m, 2H), 3.92 (q, J_1= 4.50, 7.50 Hz, 1H), 3.71 (s, 3H), 2.69-2.65 (m, 2H), 2.57-2.52 (m, 3H), 2.48 (dd, J_1 = 4.50, 13.50 Hz, 1H), 1.63-1.56 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.3, 145.5, 128.4, 128.3, 127.3, 126.6, 126.1, 125.7, 79.8, 59.9, 56.8, 54.5, 28.0, 27.1. FAB-MS m/z: 325 $(M+H)^+$. HRMS (FAB) calcd for $C_{21}H_{29}N_2O$ m/z: 325.2280 $(M+H)^+$: found: 325.2279.



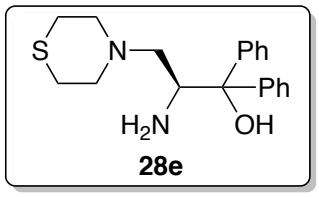
28c

(*S*)-2-amino-3-morpholino-1,1-diphenylpropan-1-ol (**28d**): Light yellow solid (Ether). 130 mg, 85% yield. m.p. 110-113 °C. $[\alpha]_D^{23}$ = –66 (*c* = 1.0, EtOH). IR (neat) = 3386, 3324, 2950, 1599, 1449, 1259 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 7.29 (d, *J* = 8.00 Hz, 2H), 7.18 (d, *J* = 8.00 Hz, 2H), 6.98 (t, *J* = 8.00 Hz, 2H), 3.76 (dd, J_1 = 3.00, 9.00 Hz, 1H), 2.20 (s, 2H), 2.10 (q, *J* = 9.00, 13.00 Hz, 1H), 1.88 (s, 2H), 1.83 (dd, *J* = 3.00, 12.50 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ: 147.6, 146.8, 129.5, 129.3, 127.9, 127.8, 127.2, 126.8, 80.7, 68.2, 61.2, 55.4, 54.6. FAB-MS m/z: 313 $(M+H)^+$. HRMS (FAB) calcd for $C_{19}H_{25}N_2O_2$ m/z: 313.1916 $(M+H)^+$: found: 313.1904.



28d

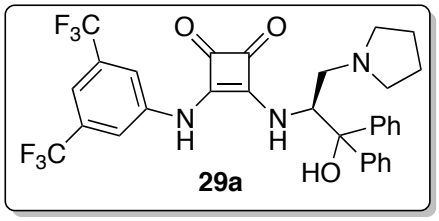
(*S*)-2-amino-1,1-diphenyl-3-thiomorpholinopropan-1-ol (**28e**): White solid (Ether). 131 mg, 85% yield. m.p. 94-96 °C. $[\alpha]_D^{25} = -74$ (*c* = 1.09, EtOH). IR(neat) = 3582, 2952, 2359, 1673, 1491 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 7.73 (s, 1H), 7.48 (d, *J* = 7.50 Hz, 2H), 7.39 (d, *J* = 7.50 Hz, 2H), 7.20-7.12 (m, 2H), 3.93 (s, 1H), 2.64 (s, 2H), 2.48 (s, 2H), 2.35 (s, 2H), 2.30-2.25 (m, 3H), 2.12 (d, *J* = 13.00 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 147.4, 146.8, 129.5, 129.3, 127.9, 127.8, 127.2, 126.2, 126.9, 80.7, 61.5, 57.2, 54.9, 28.9. EI-MS m/z: 328 $(M)^+$. HRMS (EI) calcd for $C_{19}H_{24}N_2OS$ m/z: 328.1609 $(M)^+$: found: 328.1608.



28e

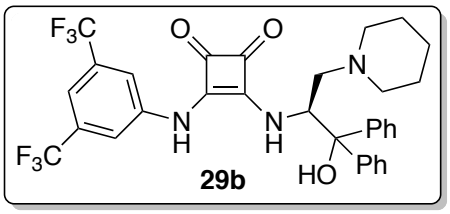
General procedure for the synthesis of compounds (29a-e): The compound **20** (100 mg, 1 mmol) and corresponding amino alcohol **28** (1 mmol) were charged in sealed tube in 20 mL MeOH solvent were added and the sealed tube was closed tightly without any air gap and the reaction mixture was stirred for 12 h at 120 °C. After completion of the reaction indicated by TLC, the excess solvent was evaporated under reduced pressure resulted the crude mass, which was purified directly by flash column chromatography using ($CHCl_3$/MeOH 9:1) to afford the compounds **29a-e** in moderate to good yield.

(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)amino)cyclobut-3-ene-1,2-dione (**29a**): Brown solid (Ether). 99 mg, 56% yield. m.p. 145-146 °C. $[\alpha]_D^{25} = -45$ (*c* = 1.0, $CHCl_3$). IR (neat): 3566, 3250, 3198, 2965, 1680, 1596 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 8.02 (s, 2H), 7.63 (d, *J* = 8.50 Hz, 2H), 7.55 (t, *J* = 7.50 Hz, 3H), 7.39 (t, *J* = 8.00 Hz, 2H), 7.26 (t, *J* = 7. 50 Hz, 1H), 7.21 (t, *J* = 7.50 Hz, 2H), 7.11 (t, *J* = 7.50 Hz, 1H), 5.45 (d, *J* = 6.50 Hz, 1H), 3.00 (d, *J* = 8.50 Hz, 1H), 2.77 (s, 2H), 2.60 (d, *J* = 13.00 Hz, 1H), 2.46 (s, 2H), 1.78 (s, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ 186.1, 182.0, 171.6, 164.0, 146.5, 146.3, 142.6, 129.7, 129.2, 128.4, 128.1, 127.0, 126.8, 127.0, 126.8, 125.8, 123.7, 119.2, 116.4, 58.9, 56.0, 24.5. EI-MS m/z: 603 $(M)^+$. HRMS (EI) calcd for $C_{31}H_{27}F_6N_3O_3$ m/z: 603.1957 $(M)^+$: found: 603.1948.



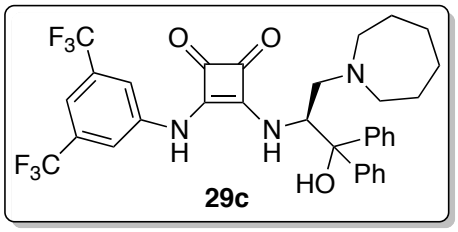
29a

(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-1,1-diphenyl-3-(piperidin-1-yl)propan-2-yl)amino)cyclobut-3-ene-1,2-dione (**29b**): Brown solid (Ether). 100 mg, 54% yield. m.p. 125-126° C. $[\alpha]_D^{25}$ = –23.0 (*c* = 1.0, EtOH). IR (neat): 3554, 3447, 1794, 1733, 1671, 1558 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 8.02, (s, 2H), 7.64 (d, *J* = 7.00 Hz, 2H), 7.56 (d, *J* = 9.00 Hz, 2H), 7.50 (s, 1H), 7.40 (t, *J* = 8.00 Hz, 2H), 7.27 (t, *J* = 7.50 Hz, 2H), 7.11 (t, *J* = 7.50 Hz, 1H), 5.53 (d, *J* = 7.50 Hz, 1H), 3.17-2.80 (m, 3H), 2.58 (s, 2H), 1.73-1.44 (m, 4H), 1.31-1.25 (m, 2H), 0.88 (t, *J* = 11.00 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 186.1, 182.0, 171.6, 164.2, 145.8, 142.4, 129.9, 129.3, 128.6, 128.3, 127.1, 126.8, 125.8, 123.6, 119.2, 116.7, 81.4, 60.9, 59.4, 56.1, 32.9, 26.0, 23.9, 14.6. FAB-MS m/z: 618 $(M+H)^+$. HRMS (FAB) calcd for $C_{32}H_{30}F_6N_3O_3$ m/z: 618.2191 $(M+H)^+$: found: 618.2203.



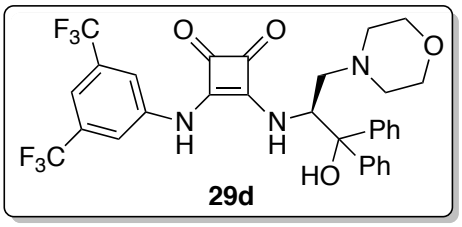
29b

(*S*)-3-((3-(Azepan-1-yl)-1-hydroxy-1,1-diphenylpropan-2-yl)amino)-4-((3,5-bis(trifluoromethyl)phenyl)amino)cyclobut-3-ene-1,2-dione (**29c**): Yellow solid (Ether). 117 mg, 62% yield. m.p. 161-162° C. $[\alpha]_D^{23}$ = –23.0 (*c* = 1.0, EtOH). IR (neat): 3522, 3493, 1793, 1648 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.64-7.52 (m, 4H), 7.46 (d, *J* = 6.00 Hz, 2H), 7.36 (t, *J* = 7.50 Hz, 3H), 7.23 (t, *J* = 6.00 Hz, 2H), 7.17-7.14 (m, 2H), 7.05 (t, *J* = 7.00 Hz, 1H), 5.44 (s, 1H), 3.12 (d, *J* = 14.00 Hz, 1H), 2.94 (s, 1H), 2.60 (s, 2H), 2.41 (s, 2H), 1.61-1.35 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.4, 181.7, 171.6, 162.4, 143.6, 143.0, 139.7, 129.2, 128.8, 127.7, 127.6, 125.2, 124.9, 124.0, 121.9, 117.7, 116.5, 115.3, 80.3, 59.7, 59.3, 57.8, 54.0, 27.1, 26.8, 23.6, 22.5. FAB-MS m/z: 632 $(M+H)^+$. HRMS (FAB) calcd for $C_{33}H_{32}F_6N_3O_3$ m/z: 632.2342 $(M+H)^+$: found: 632.2341.



29c

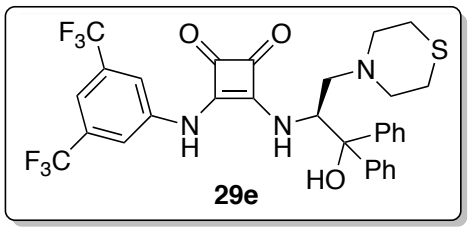
(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-3-morpholino-1,1-diphenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (**29d**): White solid (Ether). 142 mg, 78% yield. m.p. 238-240 °C. $[\alpha]_D^{25}$ = –8.00 (*c* = 1.10, EtOH). IR (neat): 3589, 3423, 1797, 1568, 1541 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 8.03 (s, 2H), 7.58 (t, *J* = 7.50 Hz, 4H), 7.53 (s, 1H), 7.37 (t,



29d

J = 7.50 Hz, 2H), 7.26-7.21 (m, 3H), 7.11 (t, *J* = 7.00 Hz, 2H), 5.48 (t, *J* = 4.50 Hz, 1H), 3.63-3.54 (m, 4H), 2.70 (q, J_1 = 9.50 Hz, 13.50 Hz, 3H), 2.54 (d, *J* = 12.00 Hz, 1H), 2.24 (s, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 186.3, 181.8, 171.8, 163.4, 146.6, 146.4, 142.6, 129.7, 129.3, 128.4, 128.0, 126.7, 125.8, 123.7, 119.2, 116.6, 80.8, 68.2, 61.4, 60.0, 55.5. FAB-MS m/z: 620 $(M+H)^+$. HRMS (FAB) calcd for $C_{31}H_{28}F_6N_3O_4$ m/z: 620.1984 $(M+H)^+$: found: 620.1984.

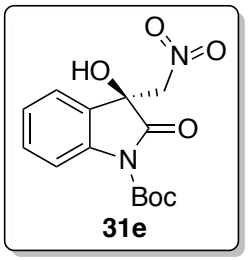
(*S*)-3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((1-hydroxy-1,1-diphenyl-3-thiomorpholinopropan-2-yl)amino)cyclobut-3-ene-1,2-dione (**29e**): White solid (Ether). 151 mg, 81% yield. m.p. 234-236 °C. $[\alpha]_D^{25}$ = –11.00 (*c* = 1.0, EtOH). IR (neat): 3522, 3462, 1800, 1652, 1573 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 8.03 (s, 2H), 7.58 (t, *J* = 7.50 Hz, 4H), 7.53 (s, 1H), 7.37 (t, *J* = 7.50 Hz, 2H), 7.26-7.21 (m, 3H), 7.11 (t, *J* = 7.00 Hz, 1H), 5.46 (m, 1H), 2.91 (t, *J* = 7.50 Hz, 2H), 2.69-2.49 (m, 8H). ^{13}C NMR (125 MHz, CD_3OD) δ: 186.2, 181.8, 171.8, 163.4, 146.7, 146.4, 142.5, 129.7, 126.3, 128.4, 128.0, 126.9, 126.6, 125.8, 123.6, 119.1, 116.6, 80.8, 61.6, 60.3, 57.2, 29.0. FAB-MS m/z: 636 $(M+H)^+$. HRMS (FAB) calcd for $C_{31}H_{28}F_6N_3O_3S$ m/z: 636.1756 $(M+H)^+$: found: 636.1760.



29e

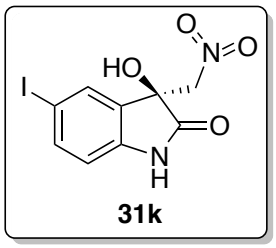
General Procedure for the synthesis of compounds (31b-k): To the stirred solution of isatins **30b-k** (20 mg, 1.0 equiv.) and catalyst **29c** (0.1 equiv.) in THF (2 mL) was added nitromethane **7** (5.0 equiv.) at 0 °C and stirring was continued for appropriate times at same temperature. After completion of reaction indicated by TLC, the excess solvent was removed under reduced pressure yields the crude mass, which was purified by flash column chromatography using (Hexane/EtOAC 6:4) solvent system to afford the nitro-aldol products **31b-k**. The enantiomeric were determined by chiral HPLC using ChiralPak AD-H and AS-H columns.

(*S*)-*tert*-butyl 3-hydroxy-3-(nitromethyl)-2-oxoindoline-1-carboxylate (**31e**): Yellow solid. 24 mg, 98% yield. m.p. 134-136 °C. $[\alpha]_D^{23}$ = +2.8 (*c* = 1.0, EtOH). IR (neat): 3995, 1732, 1616, 1540, 1191, 720 cm^{-1}. (^{1}H NMR, 500 MHz, $CDCl_3$): δ 10.19 (s, 1H), 7.77 (t, *J* = 8.00 Hz, 1H), 7.66 (t, *J* = 8.00 Hz, 1H), 7.44 (t, *J* = 9.00 Hz, 1H), 7.25-7.19 (m, 1H), 7.08 (s, 1H), 5.22 (q, J_1 = 14.00, 19.00 Hz, 2H), 1.58 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 148.9, 140.3, 131.2, 127.1, 125.3, 125.0, 115.3, 84.7, 78.5, 72.6, 28.4. EI-MS m/z: 308 $(M)^+$. HRMS (EI) calcd for $C_9H_8N_2O_4$ m/z: 208.0484 $(M\text{-}Boc)^+$: found: m/z: 208.0491 $(M\text{-}Boc)^+$. The enantiomeric excess was determined by HPLC; DAICEL chiralpak AD-H column, (solvent system (hexane/2-propanol) 85:15; flow rate 1.0 mL/min, detection UV 254 nm; retention time 10.27 min (major) and 17.46 min (minor), ee = 95 %).



31e

(*S*)-3-hydroxy-5-iodo-3-(nitromethyl)indolin-2-one (**31k**): Brown solid. 24 mg, 97% yield. m.p. 160-161 °C. $[\alpha]_D^{21}$ = +53.3 (*c* = 0.3, EtOH). IR (neat): 3991, 1730, 1615, 1543, 1182, 825 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.71 (d, J = 1.50 Hz, 1H), 7.57 (dd, J_1 = 1.50, 8.00 Hz, 1H), 6.79 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.02 (q, J_1 = 8.00, 39.50 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.3, 142.4, 138.6, 133.1, 130.7, 112.5, 84.6, 77.8, 72.4; EI-MS m/z: 333.9 $(M)^+$. HRMS (EI) calcd for $C_9H_7N_2O_4I$ m/z: 333.9450 $(M)^+$: found: 333.9460. The enantiomeric excess was determined by HPLC; DAICEL chiralpak AD-H column, (solvent system (hexane/2-propanol) 85:15; flow rate 1.0 mL/min, detection UV 254 nm; retention time 12.51 min (minor) and 16.89 min (major), ee = 95 %).



31k

Theoretical calculations

The gas phase geometry optimization of the molecules leading to energy minima was achieved using the B3LYP hybrid functional with the 6-31G(d) basis set as implemented in the Gaussian 09. For all optimized structures, vibrational normal mode analysis was carried out to ensure that the obtained structures were corresponding to minimum energy state.

1) Gaussian 09, Revision D.01,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

Table S1. Cartesian coordinates (Angstroms) for **7**.

Point Group: C1
Total energy = -414.73904622 hartree

Symbol	X	Y	Z
C	-0.69483	0.630929	-0.01183
C	0.694817	0.63089	-0.01182
C	0.773873	-0.85541	-0.00734
C	-0.77383	-0.85544	-0.00725
O	-1.6942	-1.64271	0.01256
O	1.694236	-1.64269	0.012404
N	-1.69573	1.541533	-0.04631
H	-2.62735	1.190591	0.136318
H	-1.5357	2.507005	0.201903
N	1.695716	1.541776	-0.04665
H	1.535579	2.506321	0.205273
H	2.627053	1.19038	0.136876

Table S2. Cartesian coordinates (Angstroms) for **30a**.

Point Group: C1
Total energy = -513.06346656 hartree

Symbol	X	Y	Z
C	-2.64303	0.801652	-0.00028
C	-2.75694	-0.59401	0.000096

C	-1.6325	-1.43064	0.0003
C	-0.3823	-0.82532	0.000254
C	-0.25463	0.5786	-0.00019
C	-1.37979	1.397911	-0.00049
H	-3.53775	1.416287	-0.00039
H	-3.74459	-1.04721	0.000185
H	-1.74092	-2.51126	0.000471
H	-1.25983	2.477471	-0.00073
C	1.181637	0.899999	0.000078
C	1.909511	-0.49268	-0.00011
O	1.749486	1.969806	0.000743
O	3.098802	-0.71151	-0.00062
N	0.884436	-1.42729	0.000258
H	1.053908	-2.42376	-0.00024

Table S3. Cartesian coordinates (Angstroms) for **30a**.

Point Group: C1
Total energy = -245.00932811 hartree

Symbol	X	Y	Z
N	0.173845	-0.00011	-0.01168
O	0.732444	1.092099	0.003192
O	0.730299	-1.09321	0.003236
C	-1.32526	0.001028	-0.0026
H	-1.66502	0.91265	-0.49085
H	-1.66722	-0.90041	-0.50823
H	-1.63506	-0.00883	1.045001

Table S4. Cartesian coordinates (Angstroms) for Complex **A** (**7** + **30a**).

Point Group: C1
Total energy = -927.82276495 hartree

Symbol	X	Y	Z
C	3.281111	0.736693	-0.14973
C	3.421373	-0.61779	0.149173
C	4.901437	-0.52533	0.223862
C	4.746214	0.974288	-0.11256
O	5.443092	1.955326	-0.28077
O	5.782951	-1.32968	0.45252
N	2.261307	1.574223	-0.4292
H	2.482575	2.560079	-0.46886
H	1.30178	1.331783	-0.20956
N	2.593896	-1.66162	0.358593
H	1.621988	-1.63231	0.070832
H	3.023265	-2.57459	0.424907

C	-5.2444	1.514967	0.319302
C	-5.82171	0.255126	0.116042
C	-5.04618	-0.89267	-0.1033
C	-3.66829	-0.73806	-0.11205
C	-3.07351	0.523839	0.091305
C	-3.85585	1.656968	0.30738
H	-5.87991	2.378689	0.485546
H	-6.9037	0.158461	0.127378
H	-5.51285	-1.86042	-0.2595
H	-3.38106	2.621244	0.461951
C	-1.62244	0.348343	0.018904
C	-1.40837	-1.18484	-0.24323
O	-0.72195	1.157301	0.123021
O	-0.35625	-1.77896	-0.36347
N	-2.67528	-1.71608	-0.30787
H	-2.85069	-2.69971	-0.46435

Table S5. Cartesian coordinates (Angstroms) for Complex **B** (**7** + **30a**).

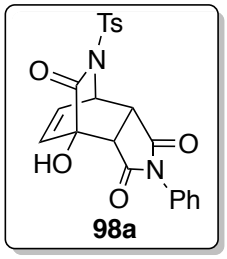
Point Group: C1
Total energy = -659.76437807 hartree

Symbol	X	Y	Z
C	-1.27292	-0.69431	-0.04863
C	-1.26923	0.69548	0.030308
C	-2.75259	0.775621	0.056425
C	-2.75692	-0.76842	-0.03533
O	-3.55337	-1.68333	-0.07685
O	-3.54407	1.693665	0.119141
N	-0.33966	-1.66479	-0.15501
H	-0.65798	-2.61754	-0.03886
H	0.62964	-1.47574	0.070069
N	-0.32937	1.662455	0.112317
H	0.632234	1.468876	-0.14012
H	-0.647	2.61599	0.000338
N	3.261333	-0.01106	-0.01538
O	2.702388	1.007235	-0.41407
O	2.698955	-1.03687	0.358079
C	4.755328	0.017801	0.057795
H	5.013172	0.471515	1.017662
H	5.114319	-1.00791	0.006076
H	5.116177	0.635958	-0.76241

Chapter 3: **The New Hybrid Type Squaramide Fused Amino Alcohol Organocatalysts For Enantioselective Diels-Alder Reaction of 3-Hydroxy-2-Pyridones with Maleimides**

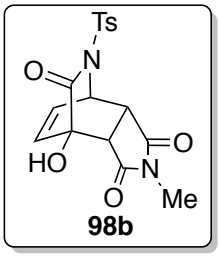
General procedure for the synthesis of compounds (98a-k) and (101a-f): To a 4-mL of sample vial containing catalyst **29a** (6 mg, 10 mmol), 3-hydroxy-2-pyridones **96a**,**b** and **99a-d** (20 mg, 0.07 mmol) and 1mL of DCM were added. The solution was allowed to stir at 0 °C for an hour, followed by maleimides **97a-k** (14 mg, 0.08 mmol) were added. After stirring for 23 h at same temperature, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (Hexane/EtOAc: 90:10 to 60:40) to afford the DA adducts **98a-k** and **101a-f**. The enantiomeric excess was determined by chiral HPLC using Chiralpak AS-H and Chiralcel OD-H columns.

(4*R*)-7-hydroxy-2-phenyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98a): White solid. 28 mg, 96 % yield. m.p. 241-242 °C. $[\alpha]_D^{23} = -14$ (*c* = 0.7, MeOH). IR (neat): cm^{-1} = 3449, 3065, 1781, 1712, 1449, 1351, 1240, 1159. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.89 (d, *J* = 8.00 Hz, 2H), 7.45 (t, *J* = 7.00 Hz, 2H), 7.40 (t, *J* = 7.50 Hz, 1H), 7.35 (d, *J* = 8.00 Hz, 2H), 7.16 (d, *J* = 8.00 Hz, 2H), 6. 48 (q, *J* = 6.00, 8.50 Hz, 1H), 6.39 (d, *J* = 7.50 Hz, 1H), 5.84-5.82 (m, 1H), 4.07 (s, 1H), 3.76 (q, *J* = 4.00, 8.00 Hz, 1H), 3.16 (d, *J* = 8.50 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.6, 172.1, 169.8, 146.4, 136.8, 134.6, 131.13, 130.14, 129.4, 129.33, 129.32, 128.2, 126.7, 78.0, 52.4, 47.4, 44.1, 21.9. MS (FAB): *m*/*z* = 439 $[M+H]^+$, HRMS (FAB): calcd. for $C_{22}H_{18}N_2O_6S$ *m/z* 439.0987; found: 439.0966. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H cloumn (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 21.66 min (major) and 33.31 min (minor), ee = 64%).



98a

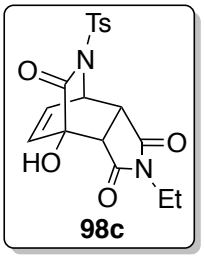
(4*R*)-7-hydroxy-2-methyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98b): White solid. 27 mg, 96 % yield. m.p. 231-232 °C. $[\alpha]_D^{24} = -15$ (*c* = 0.4, MeOH). IR (neat): cm^{-1} = 3456, 3072, 1778, 1709, 1458, 1360, 1238, 1154, 1112. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.85 (d, *J* = 8.50 Hz, 2H), 7.33 (d, *J* = 8.00 Hz, 2H), 6.35 (q, *J* = 5.50, 7.50 Hz, 1H), 6.24 (d, *J* = 8.00 Hz, 1H), 5.74-5.72 (m, 1H), 4.04 (s, 1H), 3.59 (q, *J* = 4.50, 8.00 Hz, 1H), 3.02 (d, *J* = 8.50 Hz, 1H), 2.93 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$,



98b

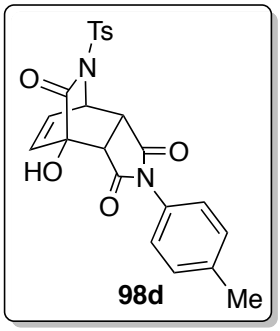
ppm): 173.9, 173.2, 169.9, 146.3, 136.3, 136.7, 134.5, 130.1, 129.1, 128.2, 77.8, 52.2, 47.5, 44.1, 25.4, 21.9. MS (FAB): *m/z* = 377 $[M+H]^+$, HRMS (FAB): calcd. for $C_{17}H_{16}N_2O_6S$ *m/z* 377.0814; found: 377.0809. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 18.99 min (major) and 22.18 min (minor), ee = 22%).

(4*R*)-7-hydroxy-2-ethyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98c): white solid. 26 mg, 90 % yield. m.p. 134.5 °C. $[\alpha]_D^{24}$ = –18 (*c* = 0.5, MeOH). IR (neat) cm^{-1} = 3458, 3070, 1771, 1700, 1451, 1355, 1218, 1144, 1113. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): *δ* 7.87 (d, *J* = 8.50 Hz, 2H), 7.34 (d, *J* = 8.00 Hz, 2H), 6.36 (q, *J* = 5.50, 8.00 Hz, 1H), 6.25 (dd, *J* = 4.50, 8.00 Hz, 1H), 3.50 (q, *J* = 7.00, 14.50 Hz, 2H), 2.99 (d, *J* = 8.00 Hz, 1H), 2.44 (s, 3H), 1.08 (t, *J* = 7.00 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 173.4, 172.9, 169.9, 146.3, 136.5, 134.5, 130.1, 129.0, 128.2, 77.8, 52.3, 47.3, 43.9, 34.3, 21.9, 12.9. MS (FAB): *m/z* = 391 $[M+H]^+$, HRMS (FAB): calcd. for $C_{18}H_{18}N_2O_6S$ *m/z* 391.0988; found: 391.0966. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 21.19 min (major) and 33.5 min (minor), ee = 26%).



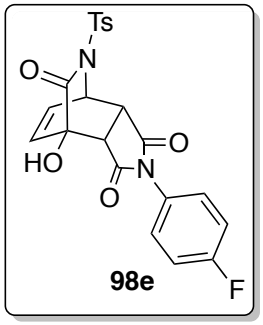
98c

(4*R*)-7-hydroxy-2-(p-tolyl)-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98d): White solid. 30 mg, 90 % yield. m.p. 236.1 °C. $[\alpha]_D^{23}$ = –20 (*c* = 0.2, MeOH). IR (neat): cm^{-1} = 3485, 2360, 1740, 1696, 1514, 1404, 1369, 1155, 1099. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): *δ* 7.89 (d, *J* = 8.50 Hz, 2H), 7.35 (d, *J* = 8.50 Hz, 2H), 7.25 (t, *J* = 7.00 Hz, 2H), 7.03 (d, *J* = 8.00 Hz, 2H), 6.46 (q, *J* = 6.00, 8.00 Hz, 1H), 6.38 (d, *J* = 7.00 Hz, 1H), 5.84-5.81 (m, 1H), 4.17 (s, 1H), 3.75 (q, *J* = 4.50, 8.50 Hz, 1H), 3.18 (d, *J* = 8.00 Hz, 1H), 2.44 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.8, 172.4, 169.8, 146.3, 139.4, 136.7, 134.5, 130.1, 130.3, 129.3, 128.4, 128.2, 126.0, 78.0, 52.4, 47.3, 43.9, 21.9, 21.3. MS (FAB): *m/z* = 453 $[M+H]^+$, HRMS (FAB): calcd. for $C_{23}H_{20}N_2O_6S$ *m/z* 453.1102; found: 453.1132. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 22.2 min (major) and 41.9 min (minor), ee = 25%).



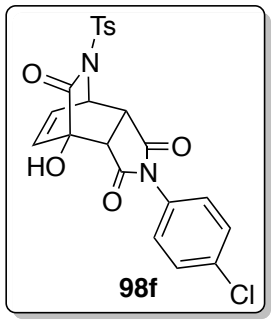
98d

(4*R*)-7-hydroxy-2-(4-fluorophenyl)-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98e): White solid. 30 mg, 89 % yield. m.p. 202-205 °C. $[\alpha]_D^{24} = -15$ ($c = 0.2$, MeOH). IR (neat): cm^{-1} = 3675, 1705, 1653, 1511, 1374, 1224, 1156, 1090. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.87 (d, J = 8.00 Hz, 2H), 7.34 (d, J = 8.50 Hz, 2H), 7.16-7.09 (m, 4H), 6.45 (q, J = 6.00, 8.00 Hz, 1H), 6.37 (dd, J = 1.00, 8.00 Hz, 1H), 5.82-5.80 (m, 1H), 4.27 (s, 1H), 3.80-3.77 (m, 1H), 3.23 (dd, J = 1.00, 8.50 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.7, 172.2, 169.8, 163.4, 161.5, 146.4, 136.7, 134.4, 130.1, 129.3, 128.2, 128.1, 126.9, 116.5, 116.3, 78.0, 52.3, 47.3, 43.9, 21.9. MS (FAB): m/z = 457 $[M+H]^+$, HRMS (FAB): calcd. for $C_{22}H_{17}FN_2O_6S$ m/z 457.0891; found: 457.0868. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 20.44 min (major) and 27.61 min (minor), ee = 36%).



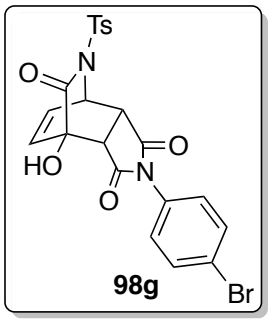
98e

(4*R*)-7-hydroxy-2-(4-chlorophenyl)-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98f): White solid. 30 mg, 85 % yield. m.p. 225.7 °C. $[\alpha]_D^{24} = -11$ (c = 0.2, MeOH). IR (neat): cm^{-1} = 3853, 1781, 1730, 1703, 1643, 1617, 1565, 1495, 1342, 1089. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.89 (d, J = 8.50 Hz, 2H), 7.42 (d, J = 9.00 Hz, 2H), 7.36 (d, J = 8.00 Hz, 2H), 7.14 (d, J = 8.50 Hz, 2H), 6.47 (q, J = 5.50, 8.00 Hz, 1H), 6.38 (q, J = 4.00, 8.00 Hz, 1H), 3.18 (d, J = 8.50 Hz, 1H), 2.45 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.4, 171.8, 169.7, 146.4, 136.8, 135.5, 134.5, 130.1, 129.6, 129.4, 128.2, 127.4, 78.0, 52.3, 47.4, 44.1, 21.9. MS (FAB): m/z = 473 $[M+H]^+$, HRMS (FAB): calcd. for $C_{22}H_{17}ClN_2O_6S$ m/z 473.0516; found: 473.0562. The enantiomeric excess was determined by chiral HPLC; CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 23.1 min (major) and 34.71 min (minor), ee = 35%).

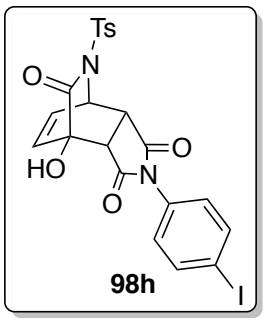


98f

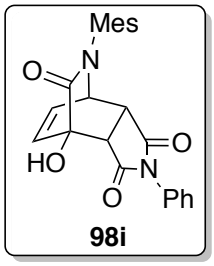
(4*R*)-7-hydroxy-2-(4-bromophenyl)-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98g): White solid. 35 mg, 92 % yield. m.p. 217.5 °C. $[\alpha]_D^{24}$ = –23 (*c* = 0.3, MeOH). IR (neat): cm^{-1} = 3735, 3352, 1711, 1595, 1490, 1364, 1272, 1165, 1087. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.89 (d, *J* = 8.50 Hz, 2H), 7.58 (d, *J* = 8.50 Hz, 2H), 7.36 (d, *J* = 8.50 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.47 (q, *J* = 6.00, 8.00 Hz, 1H), 6.38 (d, *J* = 7.50 Hz, 1H), 5.84-5.81 (m, 1H), 4.04 (s, 1H), 3.75 (q, *J* = 4.0, 8.50 Hz, 1H), 3.14 (d, *J* = 8.50 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.2, 171.7, 169.8, 146.4, 136.8, 134.6, 132.6, 130.16, 130.13, 129.4, 128.2, 127.7, 123.2, 78.0, 52.3, 47.4, 44.1, 21.9. MS (FAB): *m*/*z* = 517 $[M]^+$, HRMS (FAB): calcd. for $C_{22}H_{17}BrN_2O_6S$ *m/z* 517.0096; found: 517.0095. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 24.5 min (major) and 39.0 min (minor), ee = 49%).



(4*R*)-7-hydroxy-2-(4-iodophenyl)-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98h): White solid. 33 mg, 78 % yield. m.p. 202–205 °C. $[\alpha]_D^{24}$ = –19 (*c* = 0.1, MeOH). IR (neat): cm^{-1} = 3744, 3587, 2362, 1710, 1489, 1374, 1167, 1088, 993. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.89-7.87 (m, 2H), 7.76 (d, *J* = 9.00 Hz, 1H), 7.46-7.38 (m, 1H), 7.34 (d, *J* = 7.50 Hz, 2H), 7.16 (d, *J* = 7.50 Hz, 1H), 6.93 (d, *J* = 8.50 Hz, 1H), 6.49-6.44 (m, 1H), 6.38 (t, *J* = 7.50 Hz, 1H), 5.84-5.81 (m, 1H), 4.20 (s, 1H), 3.78 (q, *J* = 4.00, 8.00 Hz, 1H), 3.21 (d, *J* = 8.00 Hz, 1H), 2.44 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.7, 172.3, 171.8, 169.7, 146.4, 138.5, 136.7, 130.7, 130.1, 129.4, 128.2, 127.9, 126.2, 78.0, 52.4, 47.4, 44.0, 21.9. MS (FAB): *m*/*z* = 564 $[M]^+$, HRMS (FAB): calcd. for $C_{22}H_{17}IN_2O_6S$ *m/z* 564.9950; found: 564.9958. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 26.64 min (major) and 46.87 min (minor), ee = 36%).

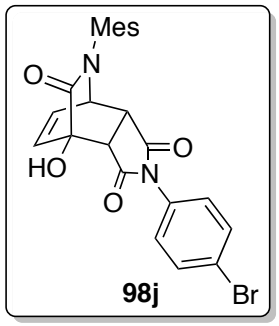


(4*R*)-7-hydroxy-2-phenyl-9-mesitylsulfonyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98i): White solid. 29 mg, 92 % yield. m.p. 234.1 °C. $[\alpha]_D^{24}$ = 57 (*c* = 0.4, CH_2Cl_2). IR (neat): cm^{-1} = 3213, 2970, 1787, 1517, 1456, 1345, 1125, 1109, 1098. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.46-7.38 (m, 3H), 7.17 (d, *J* = 8.00 Hz, 2H), 6.97 (s, 2H), 6.54 (t, *J* = 8.00 Hz, 1H), 6.50 (d, *J* = 5.50 Hz, 1H), 5.88 (t, *J* = 4.00 Hz, 1H), 4.10 (s, 1H), 3.90 (q, *J* = 4.50, 8.50 Hz, 1H), 3.24 (d, *J* = 8.50 Hz, 1H), 2.59 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.7, 172.2, 170.6, 144.8, 141.1, 137.3, 132.3, 131.6, 131.1, 129.3, 129.2, 129.0, 126.3, 78.1, 51.5, 47.9, 44.6, 22.7, 21.2. MS (FAB): *m*/*z* = 467 $[M+H]^+$, HRMS (FAB): calcd. for $C_{24}H_{22}N_2O_6S$ *m/z* 467.1204; found: 467.1272. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 23.3 min (major) and 31.8 min (minor), ee = 22%).



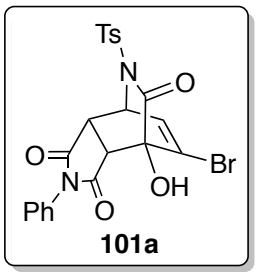
98i

(4*R*)-7-hydroxy-2-(4-bromophenyl)-9-mesitylsulfonyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (98j): White solid. 35 mg, 95 % yield. m.p. 221.5 °C. $[\alpha]_D^{24}$ = 90 (*c* = 0.4, CH_2Cl_2). IR (neat): cm^{-1} = 3821, 3742, 3567, 1780, 1700, 1670, 1489, 1373, 1188, 1079. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.57 (d, *J* = 8.50 Hz, 2H), 7.09 (d, *J* = 8.50 Hz, 2H), 6.98 (s, 2H), 6.55 (q, *J* = 5.50, 8.00 Hz, 1H), 6.49 (d, *J* = 8.00 Hz, 1H), 5.89-5.87 (m, 1H), 4.11 (s, 1H), 3.91 (q, *J* = 4.50, 8.50 Hz, 1H), 3.27 (d, *J* = 8.50 Hz, 1H), 2.59 (s, 6H), 2,30 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.3, 171.9, 170.5, 144.9, 141.1, 137.4, 134.4, 132.5, 132.4, 131.5, 130.1, 129.0, 127.7, 127.5, 123.1, 78.1, 51.4, 47.9, 44.7, 22.7, 21.2. MS (FAB): *m*/*z* = 545 $[M+H]^+$, HRMS (FAB): calcd. for $C_{24}H_{21}BrN_2O_6S$ *m/z* 545.0401; found: 545.0404. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 29.83 min (major) and 38.17 min (minor), ee = 38%).



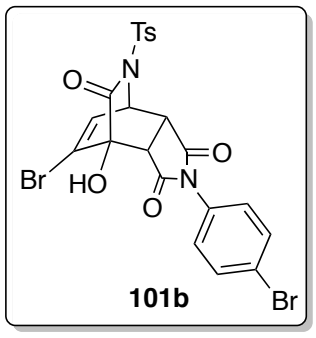
98j

(4*S*)-6-bromo-7-hydroxy-2-phenyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (101a): White solid. 28 mg, 95 % yield. m.p. 242.5 °C. $[\alpha]_D^{25}$ = 40 (*c* = 0.1, MeOH). IR (neat): cm^{-1} = 3815, 3734, 1716, 1596, 1495, 1394, 1342, 1291, 1205, 1153, 1086. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.91 (d, *J* = 8.00 Hz, 2H), 7.47-7.40 (m, 3H), 7.37 (d, *J* = 8.50 Hz, 2H), 7.16 (d, *J* = 7.00 Hz, 2H), 6.72 (d, *J* = 6. 00 Hz, 1H), 5.83 (q, *J* = 4.50, 7.00 Hz, 1H), 4.30 (s, 1H), 3.79-3.75 (m, 1H), 3.30 (d, *J* = 8.00 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.2, 171.1, 167.6, 146.6, 134.3, 130.9, 130.2, 129.5, 129.4, 129.0, 128.8, 128.3, 126.4, 78.5, 53.3, 47.9, 44.0, 21.9. MS MS (FAB): *m*/*z* = 517 $[M]^+$, HRMS (FAB): calcd. for $C_{22}H_{17}BrN_2O_6S$ *m/z* 517.0061; found: 517.0065. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 21.2 min (major) and 24.8 min (minor), ee = 98%).



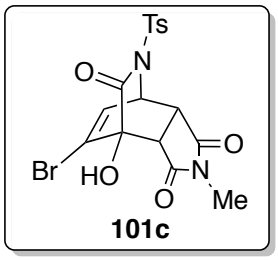
101a

(4*S*)-6-bromo-7-hydroxy-2-(4-bromophenyl)-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (101b): White solid. 30 mg, 89 % yield. m.p. 245 °C. $[\alpha]_D^{23}$ = 32 (*c* = 0.2, MeOH). IR (neat): cm^{-1} = 3769, 2355, 1712, 1595, 1490, 1364, 1272, 1165, 1087. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.89 (d, *J* = 8.50 Hz, 2H), 7.57 (d, *J* = 9.00 Hz, 2H), 7.36 (d, *J* = 8.50 Hz, 2H), 7.04 (d, *J* = 9.00 Hz, 1H), 6.71 (d, *J* = 6.50 Hz, 1H), 5.82 (q, *J* = 4.50, 7. 00 Hz, 1H), 4.37 (s, 1H), 3.82 (q, *J* = 4.50, 8.00 Hz, 1H), 3.35 (d, *J* = 7.50 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.0, 170.9, 167.6, 146.7, 134.2, 132.7, 130.2, 129.9, 129.0, 128.8, 128.3, 127.9, 123.3, 78,5, 53.2, 47.9, 44.1, 21.9. MS (FAB): *m*/*z* = 596 $[M]^+$, HRMS (FAB): calcd. for $C_{22}H_{16}BrN_2O_6S$ *m/z* 596.9130; found: 596.9131. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 23.55 min (major) and 29.03 min (minor), ee = 74%).



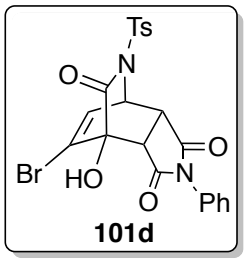
101b

(4*S*)-6-bromo-7-hydroxy-2-methyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (101c): White solid. 23 mg, 90 % yield. m.p. 248 °C. $[\alpha]_D^{24}$ = 40 (*c* = 0.5, MeOH). IR (neat): cm^{-1} = 3723, 2880, 1767, 1627, 1347, 1222, 1095, 1089. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.86 (d, *J* = 8.50 Hz, 2H), 7.34 (d, *J* = 8.00 Hz, 2H), 6.60 (d, *J* = 6.50 Hz, 1H), 5.73 (q, *J* = 4.50, 6.50 Hz, 1H), 4.25 (s, 1H), 3.60 (q, *J* = 4.00, 8.00 Hz, 1H), 3.19 (d, *J* = 8.00 Hz, 1H), 2.95 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 173.1, 172.1, 167.7, 146.6, 134.2, 130.2, 128.9, 128.6, 128.2, 78.3, 53.1, 47.8, 44.2, 25.5, 21.9. MS (FAB): *m/z* = 456 $[M+H]^+$, HRMS (FAB): calcd. for $C_{17}H_{15}BrN_2O_6S$ *m/z* 456.9817; found: 456.9893. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK AS-H column (solvent system: IPA:Hexane = 90:10; flow rate 0.5 mL/min; temp 25°C; detection UV 254 nm; retention time 28.0 min (major) and 37.6 min (minor), ee = 62%).



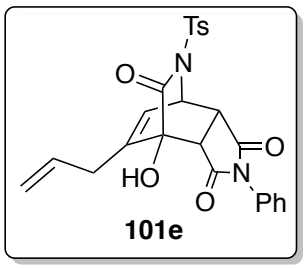
101c

(4*S*)-6-bromo-7-hydroxy-2-phenyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (101d): White solid. 26 mg, 92 % yield. m.p. 245 °C. $[\alpha]_D^{24}$ = 32 (*c* = 0.4, MeOH). IR (neat): cm^{-1} = 3931, 3869, 3488, 1603, 1505, 1457, 1339, 1281, 1102, 976. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.56 (d, *J* = 8.50 Hz, 2H), 7.08 (d, *J* = 8.50 Hz, 2H), 6.97 (s, 2H), 6.54 (q, *J* = 6.00, 8.00 Hz, 1H), 6.49 (d, *J* = 6.50 Hz, 1H), 5.89-5.86 (m, 1H), 4.10 (s, 1H), 3.91 (q, *J* = 4.00, 8.50 Hz, 1H), 3.26 (d, *J* = 8.50 Hz, 1H), 2.58 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.3, 171.9, 170.5, 144.9, 141.1, 137.4, 134.4, 132.5, 132.3, 131.5, 130.1, 129.0, 127.7, 127.4, 123.1, 78.1, 51.4, 47.9, 44.7, 22.7, 21.2. MS (FAB): *m/z* = 545 $[M]^+$, HRMS (FAB): calcd. for $C_{24}H_{21}BrN_2O_6S$ *m/z* 545.0345; found: 545.0357. The enantiomeric excess was determined by chiral HPLC; CHIRALPAK AS-H column (solvent system MeOH; flow rate 0.2 mL/min; temp 25°C; detection UV 254 nm; retention time 23.55 min (major) and 29.03 min (minor), ee = 74%).



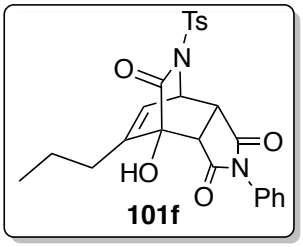
101d

(4*S*)-6-allyl-7-hydroxy-2-phenyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (101e): White solid. 29 mg, 93 % yield. m.p. 224 °C. $[\alpha]_D^{24}$ = 23 (*c* = 0.4, MeOH). IR (neat): cm^{-1} = 3976, 3748, 1708, 1596, 1497, 1353, 1296, 1226, 1188, 1084. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.89 (d, *J* = 8.00 Hz, 2H), 7.46-7.38 (m, 3H), 7.35 (d, *J* = 8.00 Hz, 2H), 7.11 (d, *J* = 7.50 Hz, 2H), 6.10-6.08 (m, 1H), 5.76 (q, *J* = 4.00, 6.00 Hz, 1H), 5.63-5.54 (m, 1H), 5.02 (dd, *J* = 9.00, 10.00 Hz, 1H), 4.88 (dd, *J* = 15.50, 17.00 Hz, 1H), 4.00 (s, 1H), 3.68 (q, *J* = 4.00, 8.00 Hz, 1H), 3.13 (d, *J* = 8.50 Hz, 1H), 2.95-2.81 (m, 2H), 2.46 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.7, 172.1, 170.1, 148.1, 146.3, 134.6, 132.5, 131.1, 130.1, 129.4, 129.3, 128.2, 126.3, 121.9, 118.7, 79.0, 52.2, 47.5, 44.2, 33.5, 21.9. MS (FAB): *m/z* = 479 $[M+H]^+$, HRMS (FAB): calcd. for $C_{25}H_{22}N_2O_6S$ *m/z* 479.1270; found: 479.1272. The enantiomeric excess was determined by chiral HPLC using CHIRALCEL OD-H column (solvent system: IPA/Hexane = 50/50; flow rate 0.5 mL/min; temp 25°C; detection UV 254 nm; retention time 24.8 min (major) and 50.3 min (minor), ee = 75%).



101e

(4*S*)-6-propyl-7-hydroxy-2-phenyl-9-tosyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3,8-(2*H*)-trione (101f): White solid. 28 mg, 90 % yield. m.p. 225.5 °C. $[\alpha]_D^{23}$ = 18 (*c* = 0.5, CH_2Cl_2). IR (neat): cm^{-1} = 3987, 3878, 3427, 2979, 1709, 1567, 1478, 1345, 1234, 1125, 1089. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.91(d, *J* = 8.50 Hz, 2H), 7.45 (t, *J* = 7.00 Hz, 2H), 7.40 (t, *J* = 7.50 Hz, 1H), 7.35 (d, *J* = 8.00 Hz, 2H), 7.11 (d, *J* = 7.0 Hz, 1H), 6.09-6.07 (m, 1H), 5.76 (q, *J* = 4.50, 6.00 Hz, 1H), 3.99 (s, 1H), 3.70 (q, *J* = 4.00, 6.00 Hz, 1H), 3.12 (d, *J* = 8.50 Hz, 1H), 2.44 (s, 3H), 2.23-2.17 (m, 1H), 2.08-2.01 (m, 1H), 1.36-1.211 (m, 2H), 0.74 (t, *J* = 7.50 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): 172.8, 172.3, 170.3, 149.5, 146.2, 134.7, 131.2, 130.0, 129.4, 129.2, 128.2, 126.1, 120.9, 79.2, 52.2, 47.6, 44.2, 31.2, 21.8, 20.1, 13.5. MS (FAB): *m/z* = 481 $[M+H]^+$, HRMS (FAB): calcd. for $C_{25}H_{24}N_2O_6S$ *m/z* 481.1421; found: 481.1431. The enantiomeric excess was determined by chiral HPLC using CHIRALPAK OD-H column (solvent system: IPA/Hexane: 50/50; flow rate 0.5 mL/min; temp 25°C; detection UV 254 nm; retention time 58.0 min (major) and 51.6 min (minor), ee = 51%).



101f

X-ray Crystallography of (101a):

Single crystals suitable for X-ray crystallography were obtained by a diffusion of 2-propanol into a dichloromethane solution of **101a**. X-ray diffraction data were collected at 150 K on a Rigaku XtaLAB mini diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71070 Å). The structure was solved by direct methods (SHELX 2013)[1] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement [2] on F^2 was based on 4752 observed reflections and 289 variable parameters and converged (largest parameter shift was 0.00 times its esd.) with unweighted and weighted agreement factors of:

$$R_1 = \Sigma \, ||F_o| - |F_c|| \, / \, \Sigma \, |F_o| = 0.0478$$
$$wR_2 = [\, \Sigma \, (w \, (F_o^2 - F_c^2)^2 \,) \, / \, \Sigma \, w(F_o^2)^2]^{1/2} = 0.1218$$

The goodness of fit[3] was 1.06. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.22 and -0.64 e-/Å^3, respectively. A total of 16453 reflections were measured and 4752 were unique (R_{int} = 0.0480). Crystal data and refinement statistics are shown in Table **S1**. Atomic coordinates Biso involving hydrogen atoms are listed in Table **S2**. Crystallographic data of **101a** has been deposited with Cambridge Crystallographic Data Center, deposition no. CCDC 1552298.

[1] Sheldrick, G.M. *Acta Cryst.,* **2008**, *A64*, 112-122.

[2] Least Squares function minimized: (SHELXL2013)
$\Sigma w(F_o^2 - F_c^2)^2$ where w = Least Squares weights.

[3] Goodness of fit is defined as:
$[\Sigma w(F_o^2 - F_c^2)^2/(N_o - N_v)]^{1/2}$
where: N_o = number of observations
N_v = number of variables

Table S1. Crystal data and structure refinement for **(101a)**:

A. Crystal Data

Empirical Formula	$C_{22}H_{17}BrN_2O_6S$
Formula Weight	517.35
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.400 X 0.400 X 0.350 mm
Crystal System	orthorhombic

Lattice Type	Primitive
Lattice Parameters	a = 8.6469(14) Å b = 10.2464(16) Å c = 23.712(4) Å V = 2100.9(6) Å^3
Space Group	Pca2$_1$ (#29)
Z value	4
D_{calc}	1.636 g/cm^3
F_{000}	1048.00
μ(MoKα)	21.056 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å) graphite monochromated
Voltage, Current	50kV, 12mA
Temperature	-123.0°C
Detector Aperture	75.0 mm (diameter)
Data Images	540 exposures
ω oscillation Range (χ=54.0, ϕ=0.0)	-60.0 - 120.0°
Exposure Rate	32.0 sec./°
Detector Swing Angle	30.00°
ω oscillation Range (χ=54.0, ϕ=120.0)	-60.0 - 120.0°
Exposure Rate	32.0 sec./°
Detector Swing Angle	30.00°
ω oscillation Range (χ=54.0, ϕ=240.0)	-60.0 - 120.0°
Exposure Rate	32.0 sec./°
Detector Swing Angle	30.00°
ω oscillation Range (χ=54.0, ϕ=0.0)	-60.0 - 120.0°
Exposure Rate	32.0 sec./°
Detector Swing Angle	30.00
ω oscillation Range (χ=54.0, ϕ=120.0)	-60.0 - 120.0°
Exposure Rate	32.0 sec./°
Detector Swing Angle	30.00°
ω oscillation Range (χ=54.0, ϕ=240.0)	-60.0 - 120.0°
Exposure Rate	32.0 sec./°
Detector Swing Angle	30.00°

Detector Position	50.00 mm
Pixel Size	0.073 mm
$2\theta_{max}$	55.0°No. of Reflections Measured Total: 16453
	Unique: 4752 (R_{int} = 0.0480)
	Parsons quotients (Flack x parameter): 1976
Corrections	Lorentz-polarization Absorption (trans. factors: 0.334 - 0.479)

C. Structure Solution and Refinement

Structure Solution	Charge Flipping (Superflip)
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\sigma^2(Fo^2) + (0.0315 \cdot P)^2 + 0.0000 \cdot P]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	55.0°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	4752
No. Variables	289
Reflection/Parameter Ratio	16.44
Residuals: R1 (I>2.00σ(I))	0.0344
Residuals: R (All reflections)	0.0375
Residuals: wR2 (All reflections)	0.0779
Goodness of Fit Indicator	1.063
Flack parameter (Parsons' quotients = 1976)	0.015(5)
Max Shift/Error in Final Cycle	0.001
Maximum peak in Final Diff. Map	0.22 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.64 $e^-/Å^3$

Table S2-1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
Br1	0.94209(4)	0.28893(4)	0.96282(2)	3.349(12)
S2	0.29923(12)	0.30199(8)	1.07492(3)	1.637(16)
O3	0.2253(3)	0.4116(2)	1.04920(10)	2.23(5)
O4	0.7312(3)	0.0150(2)	0.88084(10)	2.30(5)
O5	0.7736(3)	0.0524(2)	1.01117(9)	1.67(4)
O6	0.2187(3)	0.1807(3)	1.07844(11)	2.24(5)
O7	0.5685(3)	0.1199(3)	1.09159(9)	2.18(5)

O8	0.3225(3)	0.2892(2)	0.85400(10)	1.85(5)
N9	0.4596(3)	0.2798(3)	1.03545(11)	1.48(5)
N33	0.5338(3)	0.1502(3)	0.85392(11)	1.28(5)
C11	0.3700(4)	0.3443(3)	1.14157(14)	1.46(5)
C12	0.7288(4)	0.2713(3)	0.97342(13)	1.35(6)
C13	0.6192(4)	0.0786(3)	0.89295(12)	1.40(6)
C14	0.6253(4)	0.3624(3)	0.96085(14)	1.47(5)
C15	0.5611(4)	0.1786(4)	1.04755(14)	1.46(6)
C16	0.5610(4)	0.1439(3)	0.79415(13)	1.36(5)
C17	0.6623(4)	0.1447(3)	0.99622(13)	1.22(5)
C18	0.4182(4)	0.1970(3)	0.94146(13)	1.23(5)
C19	0.5455(3)	0.0951(3)	0.95042(13)	1.16(5)
C20	0.4615(4)	0.3211(3)	0.97519(12)	1.39(5)
C21	0.4133(4)	0.2209(3)	0.87872(14)	1.28(5)
C22	0.3419(4)	0.2588(4)	1.18597(15)	1.88(6)
C23	0.4425(4)	0.4628(4)	1.14940(16)	2.19(7)
C24	0.4633(4)	0.0696(4)	0.76135(15)	1.81(6)
C25	0.4561(4)	0.4155(4)	1.24935(15)	2.11(7)
C26	0.3852(5)	0.2961(3)	1.23979(14)	2.05(7)
C27	0.6103(5)	0.1289(4)	0.67940(14)	2.16(7)
C28	0.6833(5)	0.2117(4)	0.77045(14)	1.97(7)
C29	0.4988(5)	0.4565(5)	1.30860(18)	3.02(8)
C30	0.7078(4)	0.2032(4)	0.71280(17)	2.40(8)
C31	0.4896(4)	0.0611(4)	0.70363(15)	2.27(7)
C32	0.4876(5)	0.4961(4)	1.20411(16)	2.42(7)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table S2-2. Atomic coordinates and B_{iso} involving hydrogen atoms

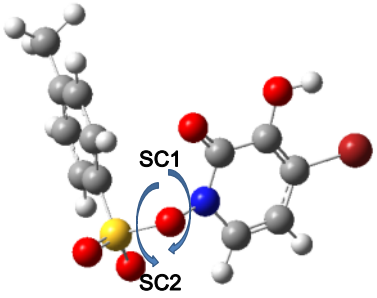
atom	x	y	z	B_{iso}
H5A	0.73884	0.00475	1.03706	2.009
H14	0.65089	0.44439	0.94464	1.761
H18	0.31649	0.16205	0.95474	1.470
H19	0.49858	0.01061	0.96280	1.390
H20	0.38624	0.39336	0.96812	1.664
H22	0.29417	0.17671	1.17950	2.256
H23	0.46114	0.52000	1.11859	2.625
H24	0.37883	0.02453	0.77801	2.172
H26	0.36610	0.23918	1.27062	2.455
H27	0.62662	0.12463	0.63982	2.591
H28	0.74954	0.26326	0.79338	2.366
H29A	0.59985	0.49973	1.30817	3.630
H29B	0.50360	0.37925	1.33292	3.630

H29C	0.42052	0.51696	1.32311	3.630
H30	0.79187	0.24868	0.69611	2.876
H31	0.42420	0.00857	0.68082	2.730
H32	0.54103	0.57577	1.21031	2.909

Theoretical calculations[1)]

The semiempirical molecular-orbital method (PM6) was used to perform the conformational analysis with Gaussian 09 program package. The gas phase geometry optimization of the molecules leading to energy minima was achieved using the B3LYP hybrid functional with the 6-31G(d) basis set as implemented in the Gaussian 09. For the optimized structures of the states, vibrational normal mode analysis was carried out to ensure that the obtained structures were corresponding to minimum energy state. The Mulliken charge distribution was calculated on B3LYP level with 6-31G (d) basis sets.

1) Gaussian 09, Revision D.01,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.



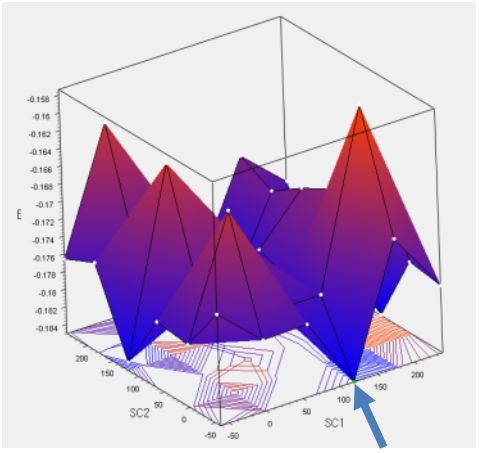


Figure S1. Scan of total energies of intermediate **99a** generated by varying two torsion angles (the dihedral scans showed with u-shaped arrows, as shown in the left structure). The arrow at the bottom represents the global energy minimum conformer.

Table S1. Cartesian coordinates (Angstroms) for **(99a)**:

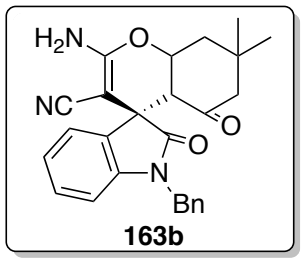
Point Group: C1
Total energy = -3863.932410 hartree

Symbol	X	Y	Z
C	1.346895	-1.99268	-0.14018
C	2.542824	-1.42262	-0.43711
C	2.785261	-0.09376	0.012257
C	1.868794	0.621205	0.736319
C	0.565705	0.035603	1.088738
H	1.047491	-2.99105	-0.42482
H	3.29116	-1.96654	-0.99719
O	-0.2987	0.585679	1.746126
O	2.036101	1.875519	1.201676
H	2.927871	2.176657	0.946108
N	0.408194	-1.2705	0.559344
S	-2.00604	-1.99123	-0.21631
C	-2.62766	-0.33177	-0.27424
C	-2.33525	0.464747	-1.38129
C	-3.40723	0.139543	0.785754
C	-2.83871	1.763558	-1.41977
H	-1.73945	0.068544	-2.19595
C	-3.89684	1.437584	0.72454
H	-3.62241	-0.49936	1.634939
C	-3.61699	2.270749	-0.37135
H	-2.62279	2.39192	-2.27971
H	-4.50356	1.81564	1.543079
C	-4.13049	3.689255	-0.40208
H	-3.53032	4.332517	0.25431
H	-4.08621	4.111891	-1.4103
H	-5.16679	3.747048	-0.05169
Br	4.465589	0.729387	-0.39927
O	-1.38222	-2.32206	-1.49394
O	-2.94548	-2.87299	0.456449
O	-0.73337	-1.94754	0.961139

Chapter 4: **The New Hybrid Type Squaramide Fused Amino Alcohol Organocatalysts For Enantioselective Domino Michael Addition Cyclization Reaction**

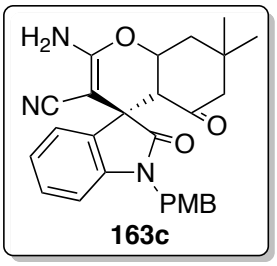
General procedure for the synthesis of compounds (163a-k): To a 4-mL sample vial containing dimedone **162a** (0.1 mmol) and catalyst **29a** (5 mol%) added anhydrous THF (1.0 mL). The reaction mixture allowed to stir at 0° C for 1 h, followed by added 3-dicyano-2-indanones **161a-j** (0.1 mmol) at same temperature. The reaction mixture was allowed stirred at the same temperature for 48 h. After completion of reaction, indicated by TLC, the residue was purified by using flash column chromatography (ethyl acetate/hexane, 4:6) to afford the desired products **163a-k** in moderate to excellent chemical yield. The enantiomeric excess was determined by chiral HPLC using Chiralpak AD-H and Chiralcell OD-H columns.

(3*S*)-2-amino-1-benzyl-7,7-dimethyl-2,5-doxo-tetrahydrospiro(chromene-4,3-indoline)-3-carbonitrile (163b): White solid. 92 mg, 98% yield. m.p. 250-251 °C. $[\alpha]_D^{24} = -22$ (c = 0.18, MeOH solvent). IR (neat): cm^{-1} = 2962, 2189, 1706, 1632, 1492, 1470. ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 7.55 (d, J = 7.00 Hz, 2H), 7.40-7.30 (m, 5H), 7.18 (t, J = 7.50 Hz, 1H), 7.02 (t, J = 8.00 Hz, 1H), 6.74 (d, J = 8.00 Hz, 1H), 4.96 (q, J = 16.50, 29.50 Hz, 2H), 2.66 (q, J = 17.50, 25.00 Hz, 2H), 2.27 (d, J = 16.50 Hz, 1H), 2.18 (d, J = 16.50 Hz, 1H), 1.10 (s, 3H), 1.07 (s, 3H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6, ppm): 195.2, 176.8, 164.6, 159.0, 142.6, 136.2, 133.6, 128.48, 128.40, 127.2, 127.1, 123.0, 122.7, 117.5, 110.7, 109.0, 57.2, 50.0, 46.6, 43.4, 32.0, 27.7, 27.12. MS (EI): m/z = 425 $[M]^+$, HRMS (EI): calcd. for $C_{26}H_{23}N_3O_3$ m/z 425.1748; found: 425.1745. The enantiomeric excess was determined by chiral HPLC; CHIRACELL OD-H column (solvent system (80:20) Hexane/IPA; flow rate 0.5 mL/min; temp 25°C; detection UV 210 nm; retention time 33.38 min (major) and 56.77 min (minor), ee = 83%).



163b

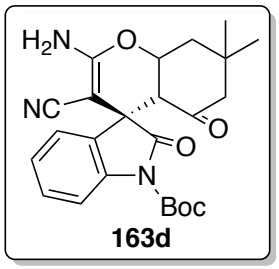
(3*S*)-2-amino-1-(4-methoxybenzyl)-7,7-dimethyl-2,5-doxo-tetrahydrospiro(chromene-4,3-indoline)-3-carbonitrile (163c): White solid. 70 mg, 89% yield. m.p. 147-149 °C. $[\alpha]_D^{24} = -21$ (c = 0.18, MeOH solvent). IR (neat): 2972, 2189, 1707, 1470, 1370 cm^{-1} = ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 7.41 (d, J = 8.50 Hz, 2H), 7.33 (s, 2H), 7.18-7.06 (m, 2H), 6.94 (t, J = 10.00 Hz, 1H), 6.86 (d, J = 5.00 Hz, 2H), 6.69 (d, J = 8.00 Hz, 1H), 4.83 (q, J =



163c

20.00, 23.50 Hz, 2H), 3.71 (s, 3H), 2.60 (q, J = 17.50, J = 29.00 Hz, 2H), 2.15 (dd, J = 16.00, 28.00 Hz, 2H), 1.04 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): 195.0, 176.6, 164.5, 158.9, 158.4, 142.6, 133.6, 128.9, 128.5, 128.2, 122.9, 122.5, 117.4, 113.7, 110.6, 109.0, 57.2, 55.0, 49.9, 46.5, 42.7, 32.0, 27.6, 27.0. MS (EI): m/z = 455 $[M]^+$, HRMS (EI): calcd. for $C_{27}H_{25}N_3O_3$ m/z 455.1834; found: 455.1838. The enantiomeric excess was determined by chiral HPLC; CHIRALCELL OD-H column (solvent system (80:20) Hexane: IPA; flow rate 0.5 mL/min; temp 25°C; detection UV 254 nm; retention time 48.74 min (major) and 92.45 min (minor), ee = 81%).

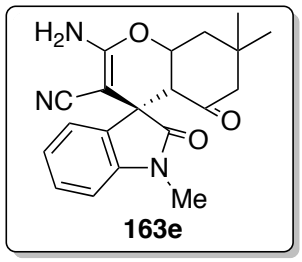
(3*S*)-2-amino-1-(*tertiarybutyloxy*)-7,7-dimethyl-2,5-doxo-tetrahydrospiro(chromene-4,3-indoline)-3-carbonitrile (163d): White solid. 57 mg, 72% yield. m.p.135-136 °C. $[\alpha]_D^{24} = -10$ (c = 0.18, MeOH solvent). IR (neat): cm^{-1} = 3309, 3179, 2189, 1720, 1715, 1610, 1407, 1309. ^{1}H



163d

NMR (500 MHz, DMSO-d_6, ppm): δ 7.87 (d, J = 8.00 Hz, 1H), 7.30 (t, J = 10.00 Hz, 1H), 7.12 (t, J = 7.50 Hz, 1H), 7.02 (d, J = 6.50 Hz, 1H), 4.99 (s, 2H), 2.56-2.46 (m, 2H), 2.23-2.13 (m, 2H), 1.65 (s, 12H), 1.11 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): 195.0, 175.5, 163.9, 158.3, 149.1, 139.8, 131.4, 129.4, 125.0, 123.2, 116.3, 115.5, 112.2, 84.6, 50.4, 40.9, 32.4, 28.6, 28.3, 27.9. MS (FAB): m/z = 436 $[M]^+$, HRMS (FAB): calcd. for $C_{24}H_{26}N_3O_5$ m/z 436.1845; found: 436.1863. The enantiomeric excess was determined by chiral HPLC; CHIRALCELL OD-H column (solvent system (Hexane/IPA) 90:10; flow rate 0.5 mL/min; temp 25°C; detection UV 254 nm; retention time 47.78 min (major) and 53.24 min (minor), ee = 5%).

(3*S*)-2-amino-1-methyl-7,7-dimethyl-2,5-doxo-tetrahydrospiro(chromene-4,3-indoline)-3-carbonitrile (163e): White solid. 86 mg, 92% yield. m.p.195-196 °C. $[\alpha]_D^{24} = -23$ (c = 0.18, MeOH solvent). IR (neat): cm^{-1} = 3308, 3176, 2189, 1720, 1715, 1612, 1432, 1402. ^{1}H NMR (500

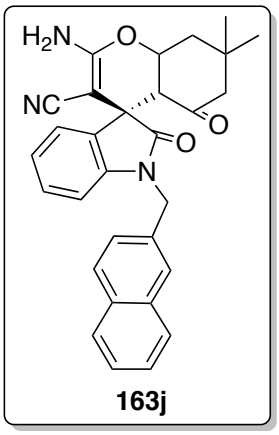


163e

MHz, DMSO-d_6, ppm): δ 7.29 (s, 1H), 7.25 (t, J = 8.00 Hz, 1H), 7.04 (d, J = 7.50 Hz, 1H), 7.00-6.96 (m, 2H), 3.12 (s, 3H), 2.56 (d, J = 4.00Hz, 2H), 2.11 (q, J = 16.00, 32.50 Hz, 2H), 1.02 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): 194.9, 176.6, 164.3, 158.9, 143.5, 137.4, 133.5, 128.9, 128.2, 125.3, 122.8, 122.4, 117.2, 110.7, 108.2, 57.0, 49.9, 32.0, 27.5, 27.0, 26.4, 21.1. MS (EI): m/z = 349 $[M]^+$, HRMS (FAB): calcd. for

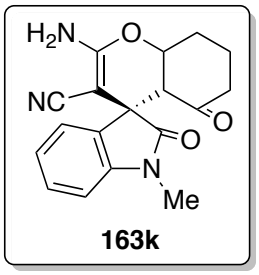
$C_{20}H_{19}N_3O_3$ *m/z* 349.3814; found: 349.3820. The enantiomeric excess was determined by chiral HPLC; CHIRALCELL OD-H column (solvent system (Hexane: IPA) 80:20; flow rate 0.5 mL/min; temp 25°C; detection UV 254 nm; retention time 95.54 min (major) and 48.69 min (minor), ee = 95%).

(3*S*)-2-amino-1-(methylenenaphthyl)-7,7-dimethyl-2,5-doxo-tetrahydrospiro(chromene-4,3-indoline)-3-carbonitrile (163j): White solid. 60 mg, 81% yield. m.p. 188-190 °C. $[\alpha]_D^{24} = -11$ (*c* = 0.18, solvent). IR (neat): cm^{-1} = 3395, 3196, 2996, 2189, 1782, 1676, 1610. ^1H NMR (500 MHz, DMSO-d_6, ppm): δ 8.03 (s, 1H), 7.90-7.87 (m, 2H), 7.79-7.77 (m, 1H), 7.61 (d, *J* = 8.50 Hz, 1H), 7.51-7.42 (m, 2H), 7.38 (s, 2H), 7.36 (s, 1H), 7.10 (t, *J* = 7.50 Hz, 2H), 6.96 (t, *J* = 7.50 Hz, 1H), 6.74 (d, *J* = 8.00 Hz, 1H), 5.08 (dd, *J* = 16.50, 68.00 Hz, 2H), 2.62 (q, *J* = 17.50, 28.00 Hz, 2H), 2.19 (dd, *J* = 16.00, 41.00 Hz, 2H), 1.06 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): 195.1, 176.8, 164.6, 159.0, 142.6, 133.7, 133.6, 132.9, 132.2, 128.3, 128.0, 127.6, 127.5, 126.2, 125.8, 125.5, 125.2, 123.0, 122.6, 110.7, 108.9, 57.1, 50.0, 46.7, 43.4, 32.0, 27.6, 27.0. MS (EI): *m/z* = 475 $[M]^+$, HRMS (FAB): calcd. for $C_{30}H_{25}N_3O_3$ *m/z* 475.1823; found: 475.1894. The enantiomeric excess was determined by chiral HPLC; CHIRALCELL OD-H column (solvent system 80:20, Hexane: IPA; flow rate 1.0 mL/min; temp 25°C; detection UV 254 nm; retention time 45.82 min (major) and 66.26 min (minor), ee = 71%).



163j

(3*S*)-2-amino-1-methyl-2,5-doxo-tetrahydrospiro(chromene-4,3-indoline)-3-carbonitrile (163k): White solid. 68 mg, 90% yield. m.p. 267-268 °C. $[\alpha]_D^{24} = -20$ (*c* = 0.18, MeOH solvent). IR (neat): cm^{-1} = 3302, 2187, 1723, 1671, 1629, 1293. ^1H NMR (500 MHz, DMSO-d_6, ppm): δ 7.30-7.22 (m, 3H), 7.08-7.05 (m, 1H), 7.00-6.95 (m, 2H), 3.12 (s, 3H), 2.70-2.61 (m, 2H), 2.25-2.14 (m, 2H), 1.936-1.88 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): 195.0, 178.8, 159.0, 144.5, 133.5, 128.4, 122.8, 122.5, 117.1, 110.5, 108.1, 57.0, 50.0, 46.5, 32.0, 27.6, 27.0, 26.5. MS (EI): *m/z* = 321 $[M]^+$, HRMS (EI): calcd. for $C_{18}H_{15}N_3O_3$ *m/z* 321.3312; found: 321.1145. The enantiomeric excess was determined by chiral HPLC; CHIRALPAK AD-H column (solvent system 80:20, Hexane: IPA; flow rate 1.0 mL/min; temp 25°C; detection UV 254 nm; retention time 12.81 min (major) and 28.44 min (minor), ee = 76%).



163k

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