不斉ヘテロ
ディールス・アルダー反応に用いる新規有機分子触媒複合系の開発

Development of New Organocatalyst Component System for Asymmetric Hetero Diels-Alder Reaction

Thesis

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by

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TITLE:

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(不斉ヘテロ ディールス・アルダー反応に用いる新規有機分子触媒複合系の開発)

NAME:

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ABSTRACT

Many biologically active compounds, including pharmaceuticals, are optically active and often only one of the enantiomer shows a high biologically activity. Therefore, it is important to develop the synthetic methodology for providing only necessary enantiomer. As the methodology, catalytic asymmetric synthesis, in which the use of a low amount of a chiral catalyst theoretically enables infinite production of optically active compounds, is the most efficient in the synthetic organic chemistry field. Moreover, this methodology is also important in terms of energy saving and environmental friendliness. The chiral catalysts used in catalytic asymmetric syntheses can be divided into two categories of organometallic catalyst and metal-free organocatalyst. Particularly, organocatalyst is stable in air, nontoxic, easy to handle, and inexpensive, so they are being focused on as next-generation, environmentally friendly catalysts.

Spirooxindoles are considered to be promising scaffolds in drug discovery. The structure of spirooxindoles is contained in many compounds having pharmacological activities such as contraceptive, anti-HIV, anticancer, antituberculosis, antimalarial, and antiproliferative drugs. Therefore, the development of an effective strategy for the preparation of highly optically pure spirooxindoles is a significantly challenging task in research. The hetero Diels–Alder (HDA) reaction is a versatile tool for effectively forming heterocyclic compounds. Especially, the catalytic asymmetric version of this reaction is the most efficient and convenient method for constructing a chiral heterocyclic skeleton, which acts as a precursor for many biologically active compounds and drugs. In this class of HDA reactions, the reaction of isatins with enones is one of the superior organic transformations for providing unique chiral spirooxindoles containing quaternary chiral carbon center on the structure.

Author tried to explore new catalysts component system for this reaction using isatins as diene and enones as dienophile. As a result, author developed a simple two catalysts component system consisting of primary β-amino alcohol as a catalyst and *N*-protected amino acid as a co-catalyst for the asymmetric HDA reaction of isatins with enones for the first time. This dual component system showed efficient catalytic activity to afford the chiral spirooxindoles that are efficient synthetic intermediates for many biologically active compounds and drug discovery, in good to excellent chemical yields and with enough stereoselectivities.

In this study, author revealed that the new explored catalysts component system showed excellent catalytic activity to the asymmetric HDA reaction of isatins with enones. It is expected that this results should be able to greatly contribute the development of new drug and its related compounds.

Tittle

Development of New Organocatalyst Component System for Asymmetric Hetero Diels-Alder Reaction

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 this background, Author developed the simple amino alcohol and simple amino silyl ether organocatalyst. The both organocatalyst are synthesized from commercially available from amino acids and amino alcohol. The catalytic activity of both organocatalyst were examined the asymmetric hetero Diels-Alder (hDA)reaction.

1.The asymmetric hetero Diels-Alder reaction was established with various isatins with enones using simple β-amino alcohol organocatalysts. This protocol provided spirooxindole tetrahydropyranones in good chemical yields and excellent diastereoselectives. The obtained chiral spirooxindole tetrahydropyanones are synthetic intermediate for preparing many biologically active compounds.

2.The asymmetric hetero Diels-Alder reaction was further established with various isatins with enones using simple β-amino silyl ether organocatalysts. This protocol provided spirooxindole tetrahydropyranones in excellent chemical yields and good diastereoselectives. The obtained chiral spirooxindole tetrahydropyanones are synthetic intermediate for preparing many biologically active compounds.

In this study author revealed that the simple amino alcohol organocatalysts having both covalent interaction (enamine formation site) and non-covalent interaction (hydrogen bond site) in a single molecule shows the good catalytic activity and simple amino silyl ether organocatalyst having covalent interaction (enamine formation site) in i) Enantioselective hetero Diels-Alder (hDA) reaction. It is expected that this work might be able to development of pharmaceutically active compounds.

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Chapter 1
Introduction

1. Introduction

Asymmetric organocatalysis has emerged as one of the most intensively investigated area in synthetic organic chemistry and one of the most powerful methods for the construct biologically active compounds.[1] Small organic molecules as catalysts can provide complex organic transformations with high levels of stereoselectivity transformations in an environmentally and economically friendly manner. It has most effective and attractive one because it doesn't involve the use either of toxic metals or of expensive biocatalysts to carry out stereoselective transformations. Particularly asymmetric organocatalysis have several advantages over organometallic and enzymatic catalysis and some of the organocatalysts are showing pharmaceutical activity also. Organocatalysts are usually in-expensive than metal based catalyst, non-toxic. Which is huge benefits preparation of pharmaceutical intermediate when compared with other metal catalyst.

Author PhD objectives were to design and develope the simple β-amino alcohol organocatalysts for asymmetric reactions. The simple β-amino alcohol oragnocatalysts were developed and used in this thesis mainly concentrated on three sections (i) The development of simple amino alcohol and amino silyl ether organocatalysts, (ii) simple β- amino alcohol organocatalysts for asymmetric hetero Diels-Alder (hDA) reaction, (iii) simple β- amino silyl ether organocatalysts for asymmetric hDA reaction, The detail study and applications of these enantioselective reactions are discussed in the following sections.

1.1 Chirality

Chirality is most important valuable function in biologically active compounds. Many research recent interest to the pharmaceutical industry and the U.S. Food and Drug Administration (FDA) is the production and sale of "chiral drugs," that is, drugs that contain a single enantiomer rather than a racemate. Because all chiral compounds have both enantiomer such as *R* (D) and *S* (L) have different nature of biologically activities. Generally the basic example of chirality is our human being left and right hands mirror image of each other and but cannot superimposed on each other (Figure 1)

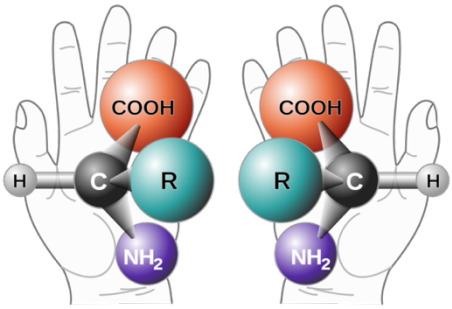
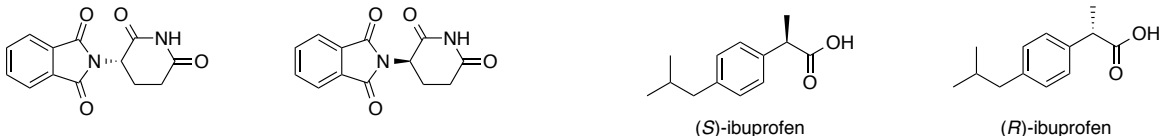


Figure 1. Two enantiomer of general amino acid

First synthesized in 1953, thalidomide was widely prescribed for morning sickness. The (*R*)-thalidomide shows the activity towards for morning sickness, while the (*S*)-thalidomide shows the sedative morning sickness. (*S*)- ibuprofen showed the anti-inflammatory activity and (*R*)-ibuprofen showing inactive even though (*R*)-isomer of ibuprofen is slowly converted into (*S*) isomer to the human body. (*S*)- methyldopa widely used as anti-hypertensive activity for primary chronic arthritis and (*S*)- methyldopa showing inactive. (*S*)- penicillamine commonly used as therapeutic activity and (*S*)- penicillamine showing inactive and also highly toxic (Figure 2).[3]



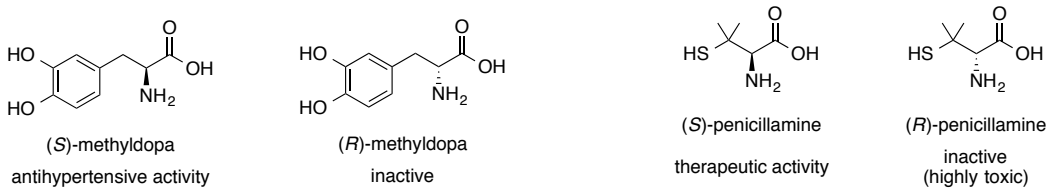


Figure 2. Biological activity of isomers

1.2 Asymmetric synthesis

Asymmetric synthesis is one of most significant area in synthetic organic chemistry. Asymmetric synthesis as defined by Morrison and Mosher,[2] is a chemical reaction in which an achiral molecule is converted into a chiral molecule the product unequal amounts of stereoisomers are formed. Most of the biologically active compounds have different functionality in biological system such as *R* and *S* enantiomers. Moreover, biologically active compounds requisite to synthesis the precise enantiomer using chiral catalyst through asymmetric synthesis.

1.3 Catalysis in asymmetric synthesis

The catalysis classified into three major parts, such as metal catalysis, enzyme or bio-catalysis and organocatalysis. Enantioselective organocatalysis is known as an independent synthetic research area in last two decades among enantioselective metallic catalysis and enzymatic catalysis for the synthesis of optically active compounds. Many of the metal based reactions necessary for glove box . Among the metal and enzyme catalysis, the organocatalysis has some assets like non-toxic, commercially availability, easy to synthesis and environmentally friendly. They are mostly stable under aerobic conditions, and the organocatalytic reactions do not require essential conditions to proceed the reactions.

1.4 Organocatalysis

Organocatalysis is a chemical process that catalyzed by non-metallic compounds, and this process has been attracting a great deal of attention to synthetic organic chemistry field for the last fifteen years. Organocatalysts are less expensive, more stable and exhibit superior solubility in both organic and aqueous solutions compared to organometallic and bioorganic counterparts and also economically and environmentally friendly manner. Most importantly, organocatalysis generally gives rise to outstanding stereoselectivity, which is significantly valuables of bioactive compounds and pharmaceutical agents.

Importance of organocatalyst

- It is stable in air and moisture.
- Non-toxic and environmental friendly manner.
- It is very cheaper than organic metal based catalyst.
- Easy to handle.

In recent years organocatalyst (Figure 2) is most trending in the field of synthetic organic chemistry. The advantages of organocatalyst as compared to metal based organometallic catalyst is non-toxic, easy available from nature and commercially available and environmentally friendly manner.[4]

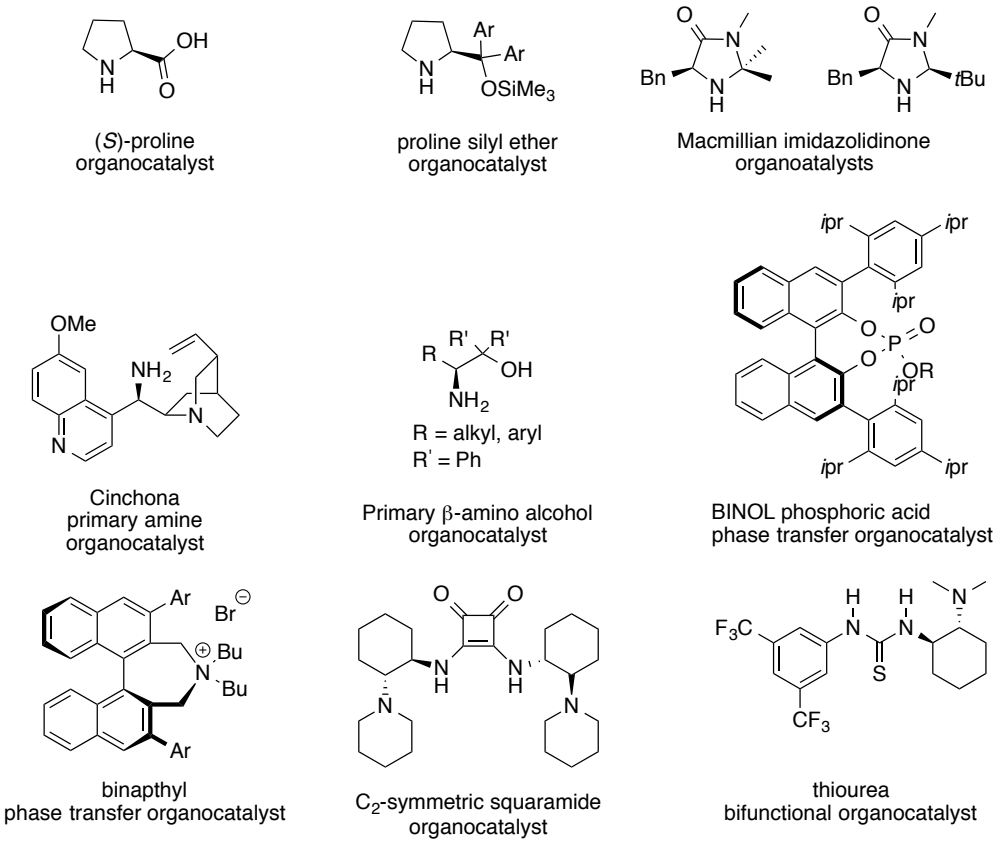


Figure 3. Commonly used organocatalysts

1.5 Types of organocatalysis activation mode in enantioselective reactions

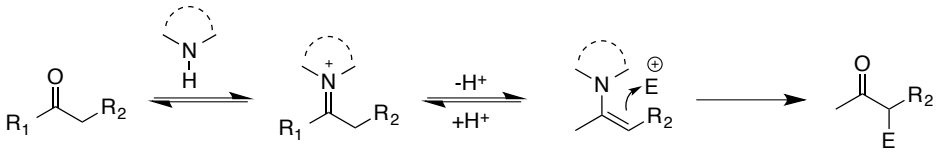
Organocatalysts are approach by two ways in enantioselective reaction.

1) **Covalent mode of activation-** amine based organocatalysts
2) **Non-covalent mode of activation-** hydrogen bond based organocatalysts

1.5.1 Covalent mode of organocatalysis activation

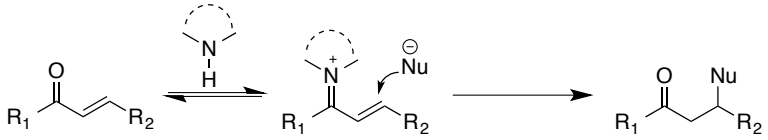
Generally, enamine catalysis might be better described as bifunctional catalysis because the amine-containing catalyst typically interacts with a ketone substrate to form an enamine intermediate but simultaneously engages with an electrophilic reaction partner through either hydrogen bonding or electrostatic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

Enamine activation

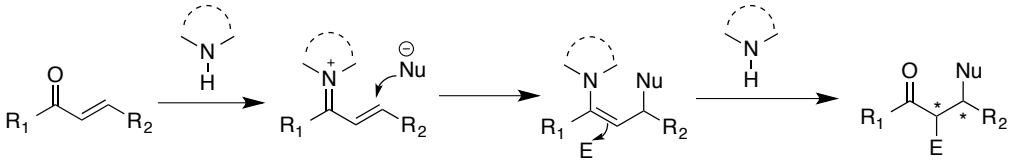


The concept was founded on the mechanistic hypothesis that the reversible formation of iminium ions from α,β-unsaturated aldehydes and chiral amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis (that is, lowest-unoccupied molecular orbital (LUMO)-lowering activation). With its tailor-made family of imidazolidinone catalysts, enamine, iminium catalysis is now used highly enantioselective protocols.

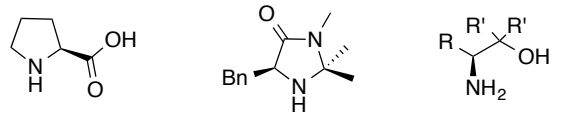
Iminium activation



Enamine and iminium activation



Example of covalent type organocatalyst such as (*S*)-proline, imidazolidinone and β-amino alcohol (Figure 4) are widely used in asymmetric synthesis.[5]

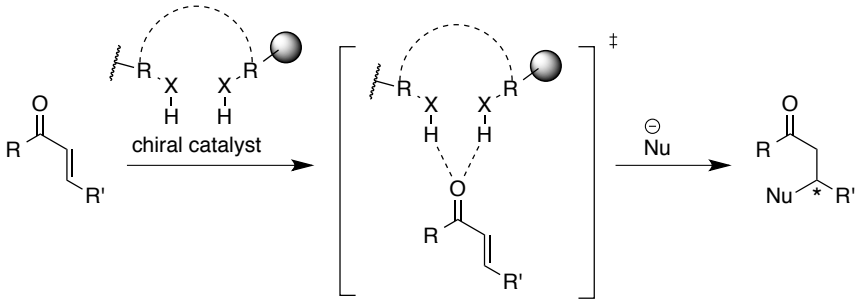


(*S*)-proline organocatalyst | imidazolidinone organocatalyst | β-amino alcohol organocatalyst

Figure 4. covalent type organocatalysts

1.5.2 Non-covalent mode of organocatalysis activation

Hydrogen-bonding organocatalysts is called as non-covalent organocatalysts. It activate imine electrophiles. 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 in last fifteen years. 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.



Example of Non-covalent type organocatalyst such as thiourea , squaramide and phosphoric acid organocatalysts (Figure 5) are widely used in asymmetric synthesis.[6]

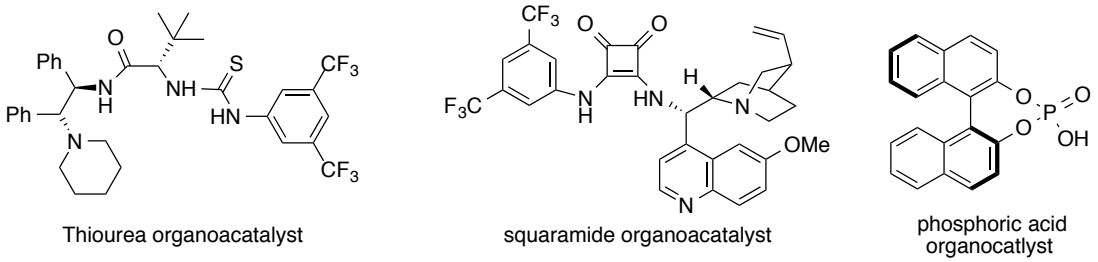
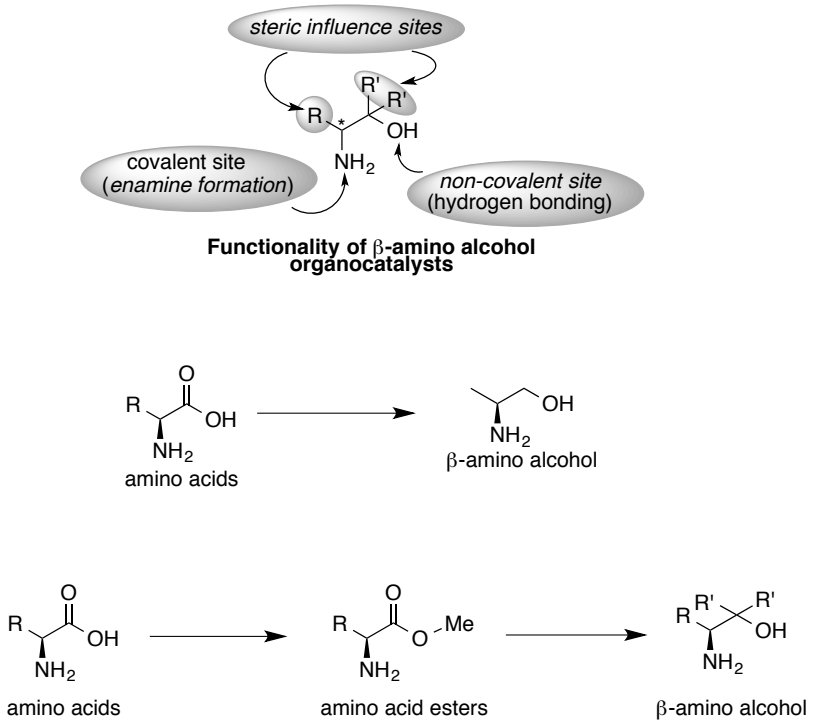


Figure 5. examples of non-covalent type organocatalysts

1.6 β-Amino alcohol organocatalysis importance in asymmetric synthesis

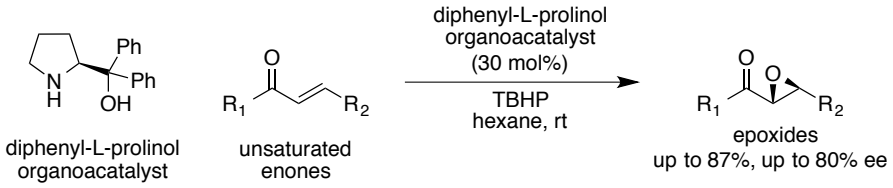
Simple β-amino alcohol and derivatives are synthesized from the commercially available corresponding amino acids by simple methods. The chiral of amino alcohol organocatalyst could be used as enantioselective reactions. They have many assets such as easy to synthesis, stable in air and moisture. It has covalent site for making enamine and imine formation and non-covalent site for making hydrogen bond in a single molecules (Scheme 1).



Scheme 1. Functionality and preparation of β-amino alcohol

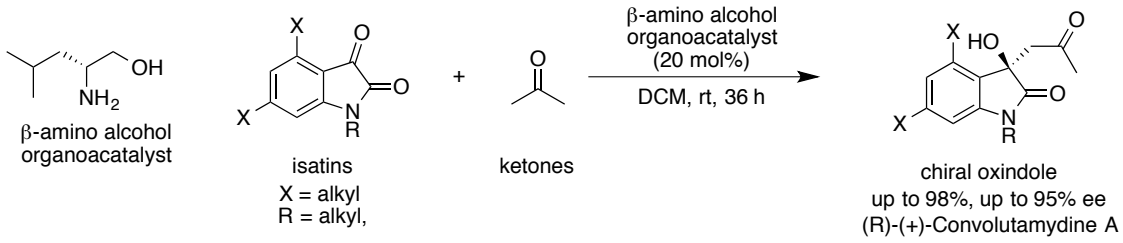
The β-amino alcohols can be easily prepared from corresponding amino acids and amino acid ester salts.The simple primary β -amino alcohols can be easily derived in to a di amino alcohol, squaramide fused amino alcohol. By introducing new functional groups on amino alcohol catalyst, there might be increasing the catalyst activity. The primary β -amino alcohols and their derivatives successfully showed the catalytic activity in important asymmetric reaction such as epoxidation, Diels-Alder and 1,3-dipolar cycloadditions, aldol cross-aldol reactions, domino Michael reaction and nitro aldol reaction to afford the chiral biological synthetic intermediates.

Alessandra lattanzi[7] reported the enantioselective epoxidation of unsaturated enone using diphenyl-L-prolinol as bifunctional organocatalyst to afforded the epoxides in good yield (up to 87%) and good enantioselectivities (up to 80%, Scheme 2).



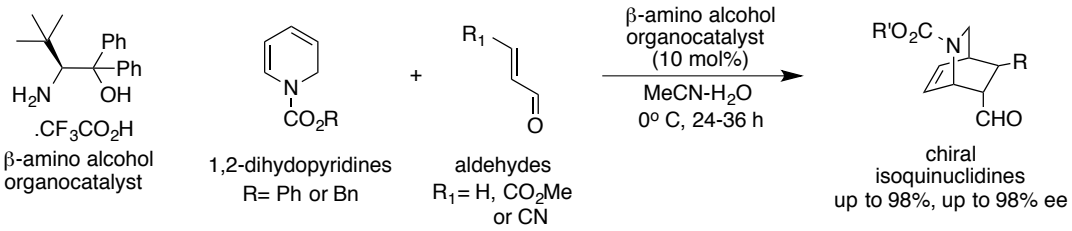
Scheme 2. Diphenyl-L-prolinol as bifunctional organocatalyst for epoxidation

Pavel Kocovsky[8] and co-workers reported the enantioselective Cross Aldol reaction of isatins with ketone using amino alcohol organocatalyst to afforded the chiral oxindole in excellent yield (up to 98%) and excellent enantioselectivities (up to 95%) amino alcohol (Scheme 3).



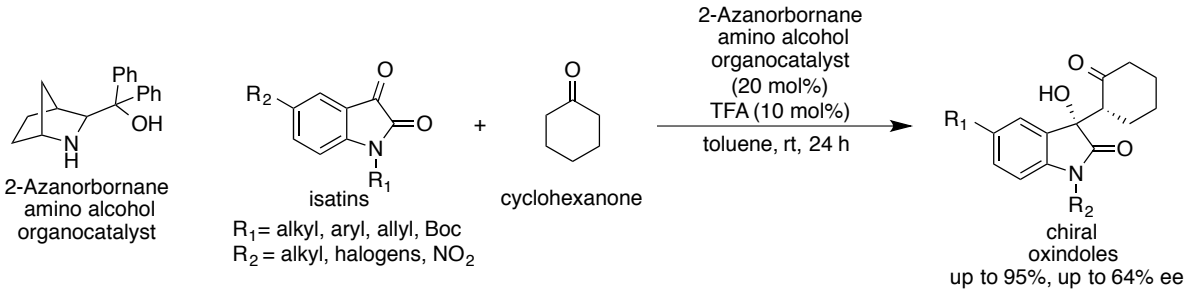
Scheme 3. Amino alcohol organocatalyst for Cross-Aldol reaction

Author research group[9] reported the chiral amino alcohol organocatalyst for enantioselective Diels Alder reaction of 1,2-dihydropylidines with aldehydes to afforded the chiral isoquinuclidines with excellent chemical yield (up to 98%) and excellent enantioselectivities (up to 98%, Scheme 4).



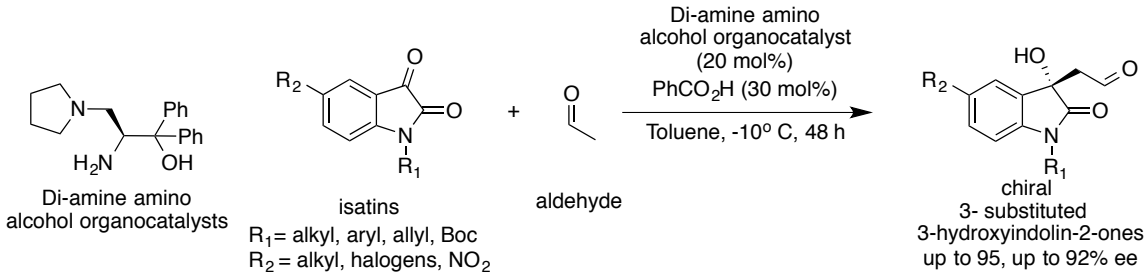
Scheme 4. Amino alcohol organocatalyst for enantioselective Diels-Alder reaction

Author research group[10] reported the optically active 2-azanorbornane amino alcohol organocatalyst for enantioselective aldol reaction of isatins with ketone to afforded the chiral oxindole with excellent chemical yield (up to 95%) and moderate enantioselectivities (up to 64%, Scheme 5).



Scheme 5. amino alcohol organocatalyst for aldol reaction

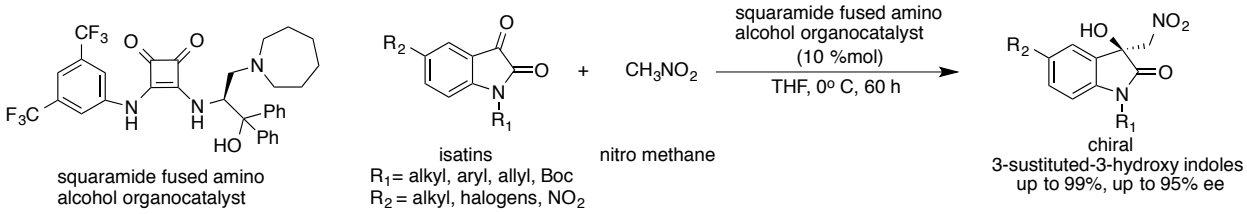
Author research group[11] reported the diamino alcohol organocatalyst for enantioselective aldol reaction of isatins with aldehyde to afforded the chiral 3-substituted-2-hydroxyindolin-2-one with excellent chemical yield (up to 95%) and excellent enantioselectivities (up to 92%, Scheme 6).



Scheme 6. Diamino alcohol organocatalyst for aldol reaction

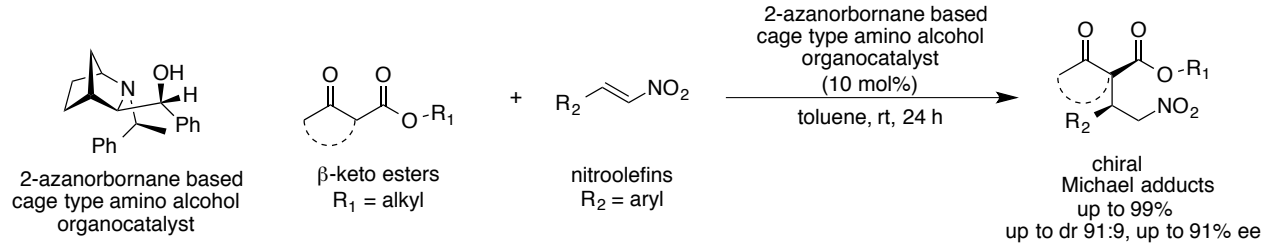
Author research group[12] reported the squaramide fused amino alcohol (SFAA) organocatalyst for enantioselective nitro aldol reaction of isatins with nitro methane to afforded the chiral 3-

substituted-3-hydroxy indoles with excellent chemical yield (up to 99%) and excellent enantioselectivities (up to 95%, Scheme 7).



Scheme 7. Squaramide fused amino alcohol organocatalyst for enantioselective nitro aldol reaction

Author research group[13] reported the 2-azanorbornane based cage type amino alcohol organocatalyst for enantioselective Michael reaction of b-keto ester with nitroolefins to afforded the chiral Michael adducts with excellent chemical yield (up to 99%) and moderate enantioselectivities (up to 91%, Scheme 8).



Scheme 8. 2-Azanorbornane based cage type amino alcohol organocatalyst for enantioselective Michael reaction

1.7 Spirooxindole importance in asymmetric synthesis

The spirooxindole framework bear spirocyclic ring fused at the 3-position and it has tetrasubstituted carbon. Synthesis of spirooxindoles core moieties still challenging task in asymmetric synthesis field. Chiral spiro oxindole core structure are one of the most important heterocyclic property and its showing biologically active (Figure 6) activities[14] such as anti-malarial activity,[15] MDM2 inhibitor, anti-tubercular activity, anti-proliferative activity. Synthetic spirooxindole also showed biological activity such as antimalarial, anti-HIV,[16] anticancer,[17] antituberculosis,[18] antiproliferative.[19]

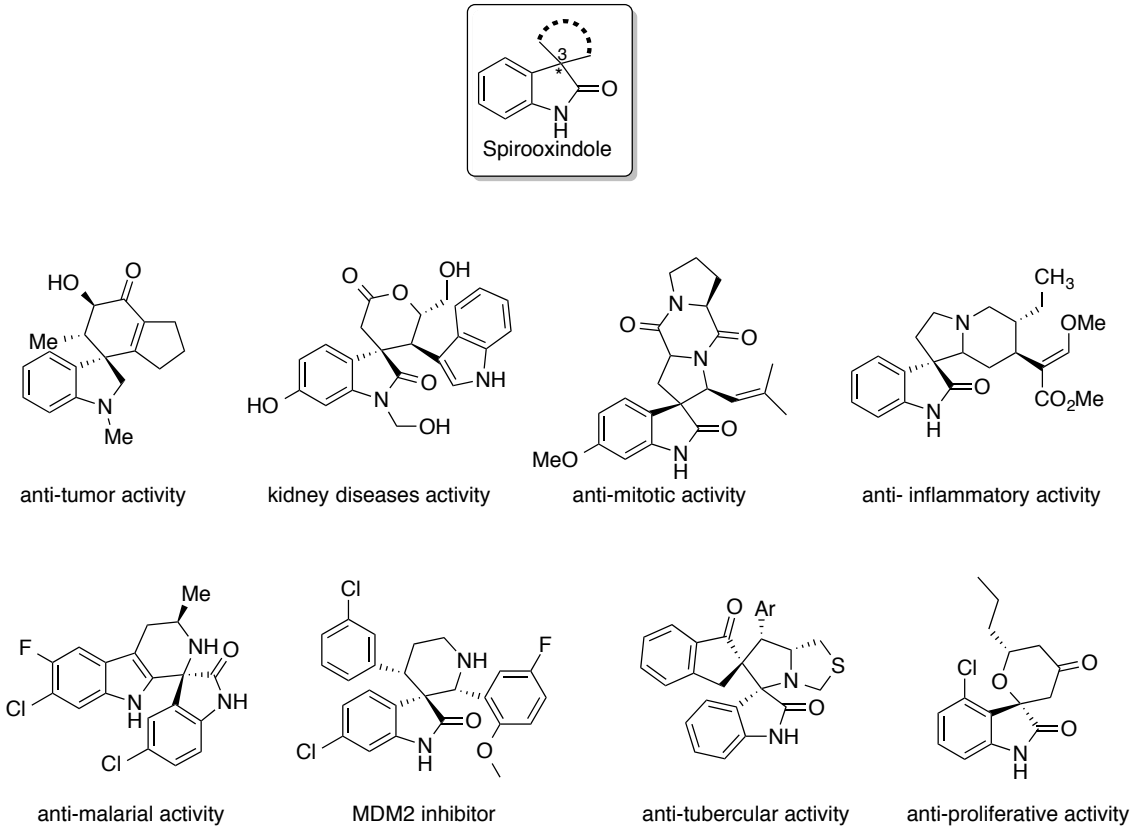


Figure 6. Spiro oxindoles containing biologically active compounds

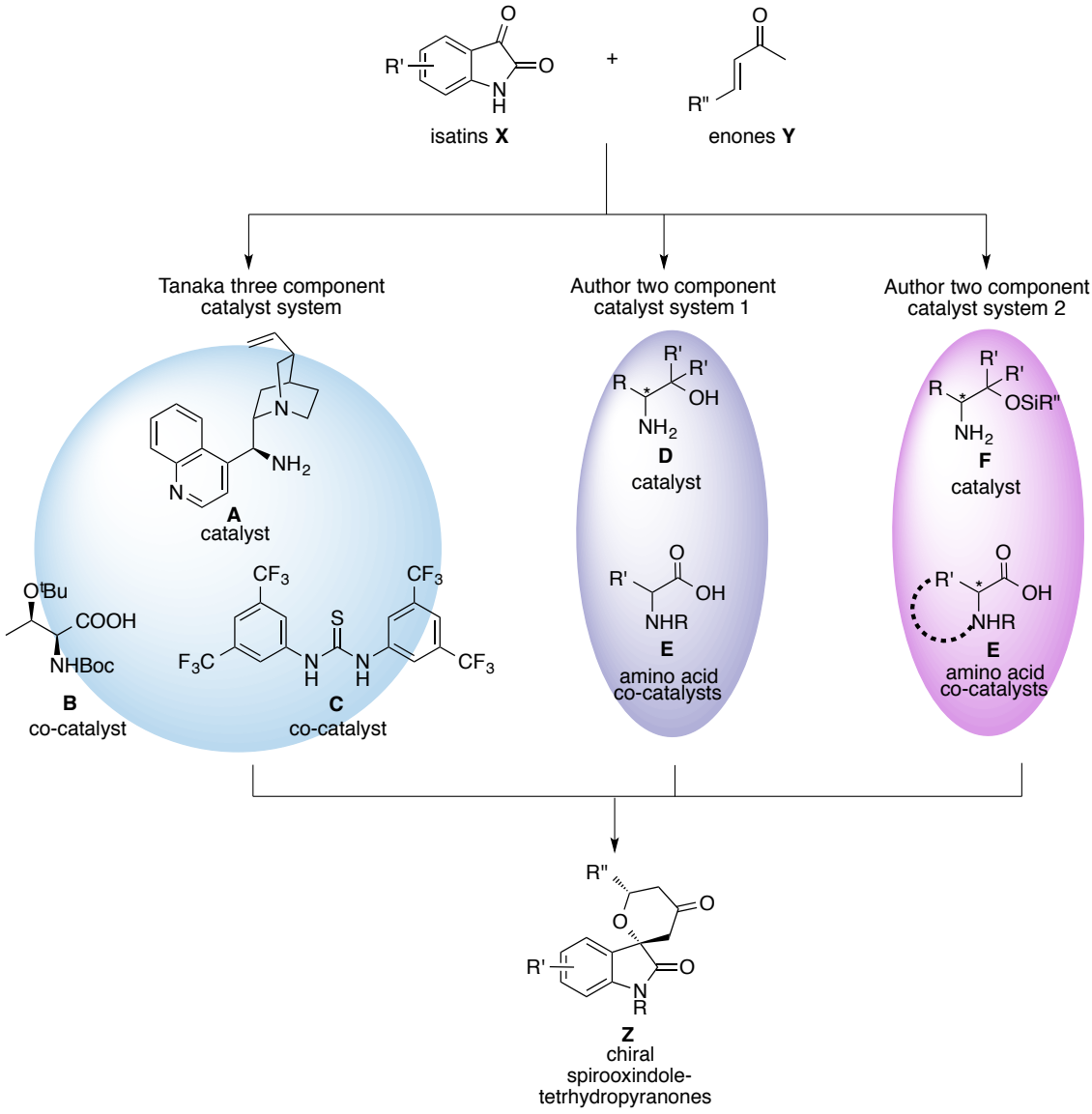
1.8 Author project

Functionality of spirooxindoles widely present in many an biologically active compounds and pharmaceiticals . Author decide to develop the simple amino alcohol and simple amino silyl ether organocatalyst to explored the hDA reaction of isatins with enones to afford the chiral spirooxindole tetrahydropyranones.

In order to develop the asymmetric hDA reaction of isatin with enones using two component catalyst system of simple β-amino alcohol organocatalyst **D** and *N*- protected amino acids as co-catalyst **E**. The functionality of amino alcohol has covalent site (enamine formation) and non-covalent site (hydrogen bond formation) in single molecule. Moreover, the bulky substitution at a substituent β-position works as a steric influence sites.

The asymmetric hDA reaction of isatin with enones using two component catalyst system of simple β-amino silyl organocatalyst **F** and *N*- protected amino acids as co-catalyst **E**. The functionality of amino silyl ether has covalent site (enamine formation). Moreover, the bulky substitution at a substituent β-position works as a steric influence sites.

In firstly Tanaka and co-workers developed three component catalyst system including, chinchona primary amine **A** (catalyst), *N*-Boc-amino acid **B** (co-catalyst) and thiourea **C** (co-catalyst) for asymmetric hetero Diels-Alder reaction of isatin with enones to afford the chiral spirooxindole tetrahydropyraones in good chemical yield (up to 87%), excellent diastereoselectivity and enantioselectivities (up to dr 95:5, up to 94% ee). The feature of cinchona alkaloid primary amine organocatalyst has aromatic quinoline act as steric influence site and bulky bicyclic quinuclidine is making hydrogen bond formation with *N*-Boc amino acid.Thiourea containing hydrogen is making hydrogen bond with isatin substrate. The advantage of three component catalyst system to furnish the good chemical yields and excellent stereoselectivities and disadvantage of that catalytic system using two chiral co-catalyst in situ (Scheme 9). As comparatively previous report amino alcohol having all functionality in a single molecule such as covalent site, non-covalent site and steric influence sites.



Scheme 9. Component system of hDA reaction

The author designed the simple two component catalyst system using simple β-amino alcohol organocatalyst **D** and *N*-protected-amino acid **E** act as co-catalyst and simple β-amino silyl ether organocatalyst **F** and *N*-protected-amino acid **E** The simple two component catalyst is altered from the Tanaka three component catalyst system.

The catalytic activity of simple two component catalyst system was examined in asymmetric hetero Diels-Alder reaction.

Author developed simple amino alcohol organocatalysts from amino acids. It has stability in air and moisture, covalent site for enamine formation , non-covalent site for hydrogen bond formation and remaining substitution act as steric influence site (Figure 7).

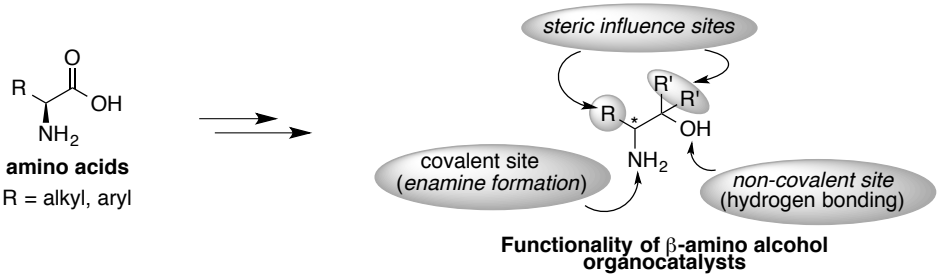
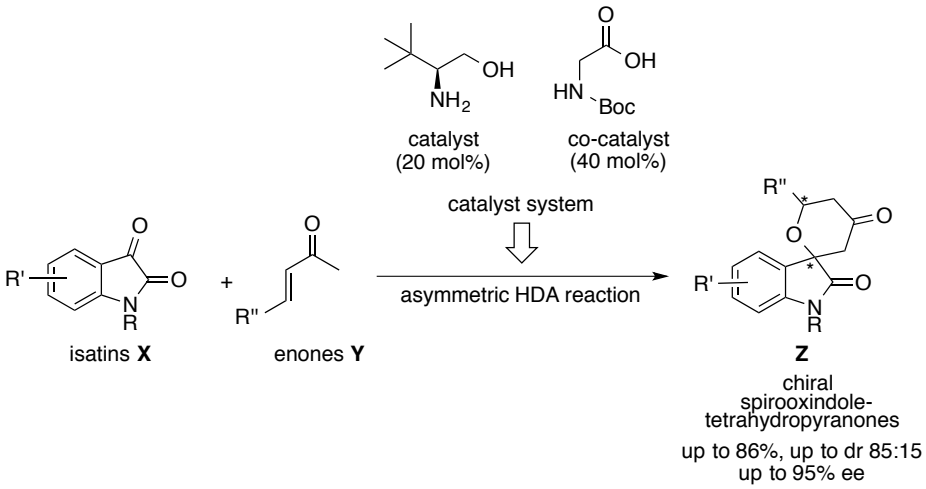


Figure 7. Functionality of β-amino alcohol organocatalyst

The author first examined the catalytic activities of simple two component catalyst of amino alcohols **2a-e, 4a-e** and *N*-Boc amino acids in the asymmetric hetero Diels-Alder reaction of isatin with enones to afforded the chiral Spiro oxindole tetrahydropyaranones good to excellent chemical yields, diastereoselectivities and enantioselectivities (up to 86%, up to dr = 85:15, up to 95% *ee*, Scheme 10).



Scheme 10. Amino alcohol organocatalyst for asymmetric hetero Diels-Alder reaction

Modified of that work the author developed simple amino silyl ether organocatalysts from amino alcohols organocatalyst. It has similar assets an amino alcohol like stability in air and

moisture, covalent for enamine formation and remaining substitution act as steric influence site (Figure 8).

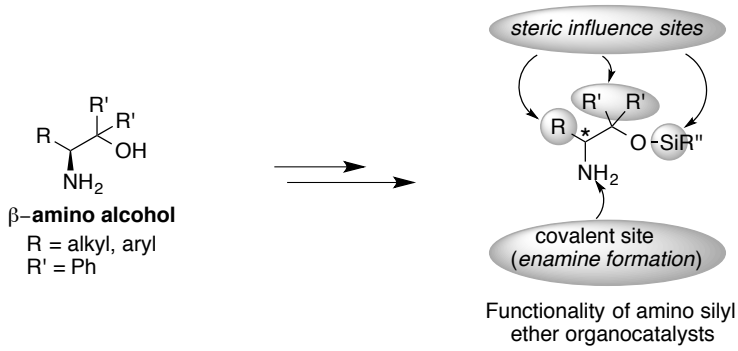
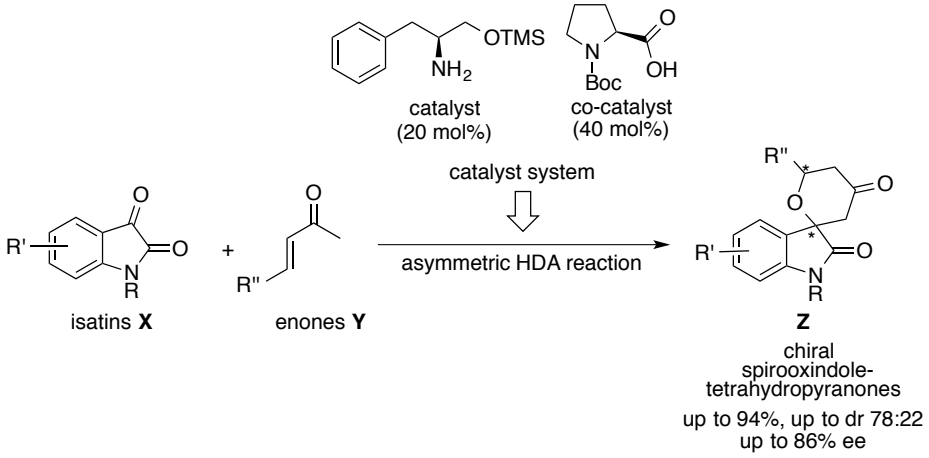


Figure 8. Functionality of amino silyl ether organocatalyst

In extension of previous work the author developed simple amino silyl ether oragnocatalyst **10a-o** and *N*-protected amino acid as a co-catalyst for enantioselective asymmetric hetero Diels-Alder reaction of isatin with enones to afforded the chiral spiro oxindole tetrahydropyaranones good to excellent chemical yields, diastereoselectivities and enantioselectivities (up to 94%, up to dr 78:22, up to 86% *ee*, Scheme 11). The detail of simple amino alcohol and amino silyl ether organocatalysts preparations and its application for enantioselective asymmetric reactions will be discussed in the following sections.



Scheme 11. Amino silyl ether organocatalyst for asymmetric hetero Diels-Alder reaction

Chapter 2

Simple organocatalyst component system for asymmetric hetero Diels-Alder reaction of isatins with enones

2. Simple organocatalyst component system for asymmetric hetero Diels-Alder reaction of isatins with enones

2.1 Author project

Author aimed to develop the simple β-amino alcohol organocatalyst component system for asymmetric hDA reaction of isatins with enones to afford the chiral spirooxindole tetrahydropyranones. The utility of amino alcohol has covalent site (enamine formation) and non-covalent site (hydrogen bond formation) in single molecule. Moreover, the bulky substitution at a substituent β-position works as a steric influence sites (Figure 9).

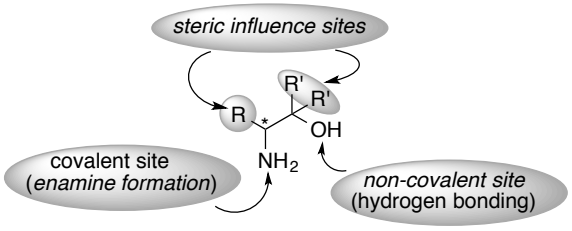
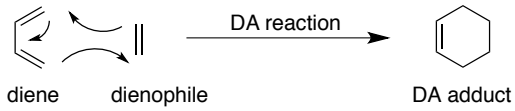


Figure 9. Functionality of β- amino alcohol organocatalyst

2.2 Diels-Alder reaction

The Diels-Alder (DA) reaction is a useful classical organic reaction using with conjugated diene and dienophile to form a cyclohexene system, it's also refered as a [4+2] cycloaddition reaction (Scheme 12). The DA reaction discovered by Otto Diels and Kurt Alder in 1928 for their tremendous contribution they received Nobel prize in chemistry in the year of 1950. The Diels-Alder reaction is also reliable practical method for constructing the six membered bicyclic compounds in synthetic organic chemistry.[20]



Scheme 11. General Diels-Alder reaction

2.3 Mechanism of Diels-Alder reaction

Diels-Alder reaction is also called as [4+2] cycloaddition reaction. In generally Diels-Alder reaction (Figure 10) proceed via two ways such as i) Normal electron demand Diels-Alder reaction,

ii) Inverse electron demand Diels-Alder reaction. Usually, normal electron demand Diels-Alder reaction is diene contain electron donating group and dienophile have electron withdrawing group. In the same way for Inverse electron demand Diels-Alder reaction is diene contain electron withdrawing group and dienophile have electron donating group to provide the six membered ring.[21]

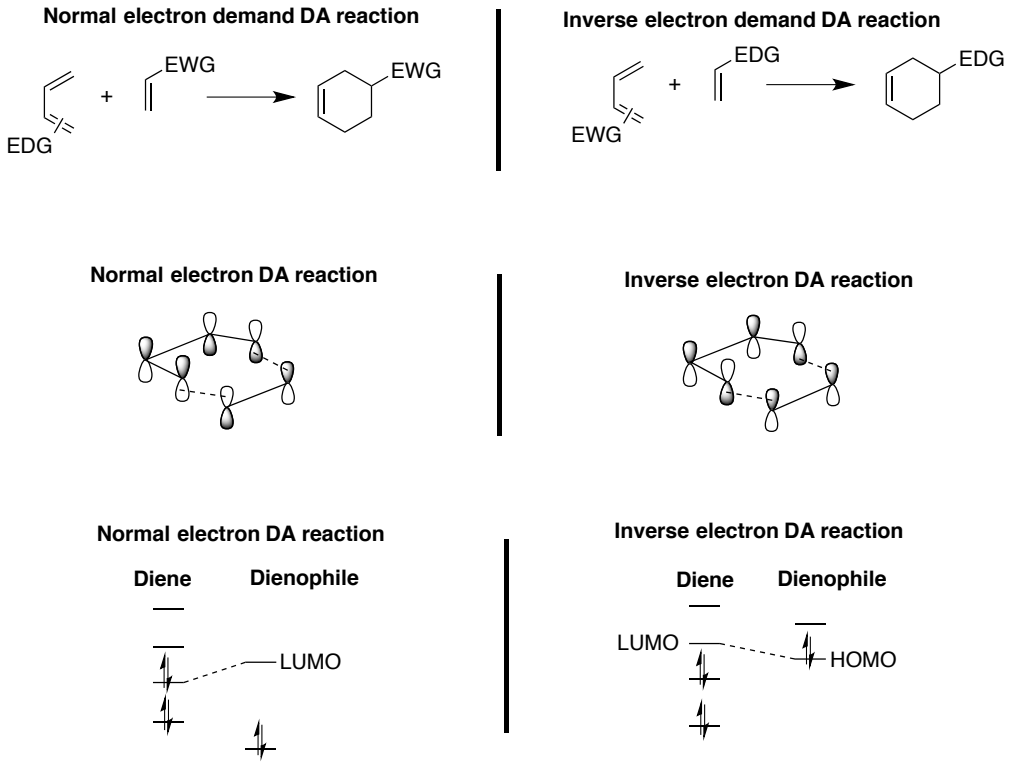
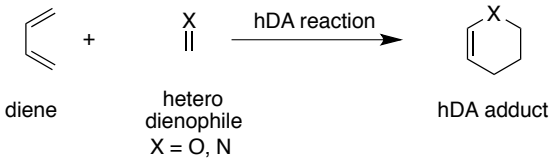


Figure 10. Pictorial representation of Diels-Alder reaction

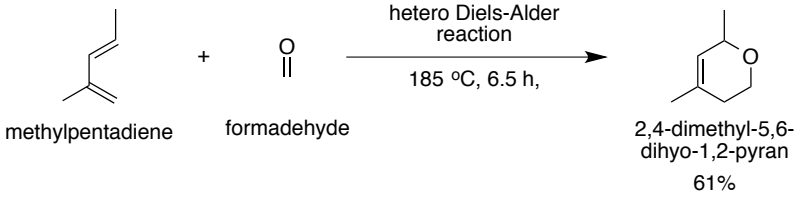
2.4 hetero Diels-Alder reaction

The hetero Diels-Alder (hDA) reaction (Scheme 12) is one of the most powerful transformations in the chemistry for the synthesis of heterocycles embodying multiple stereogenic centers. However, as compared to other cycloadditions, in particular the dipolar cyclo additions reaction, the hetero Diels-Alder reaction has been much less explored in organic synthesis. Nevertheless, this powerful transformation has opened up efficient and creative routes to biologically relevant small molecules and different natural products which contain six-membered oxygen or nitrogen ring systems.[22]



Scheme 12. General reaction for hetero Diels-Alder reaction

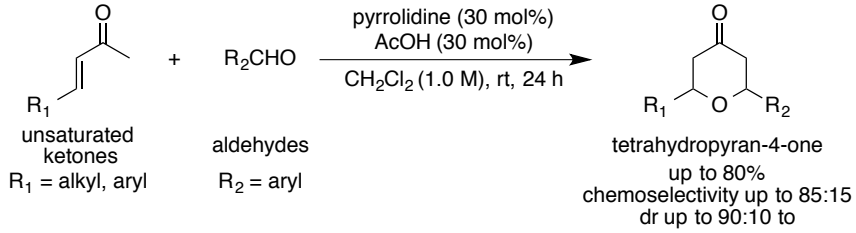
First hetero Diels-Alder reaction was reported by Thomas R. Steadman[23] in 1948 using methylpentadiene act as a diene and formaldehyde act as dienophile in the presence of 185 °C in 6.5 h to provide the 2,4-dimethyl-5,6-dihydro-1,2-pyran with yield (61%, Scheme 13).



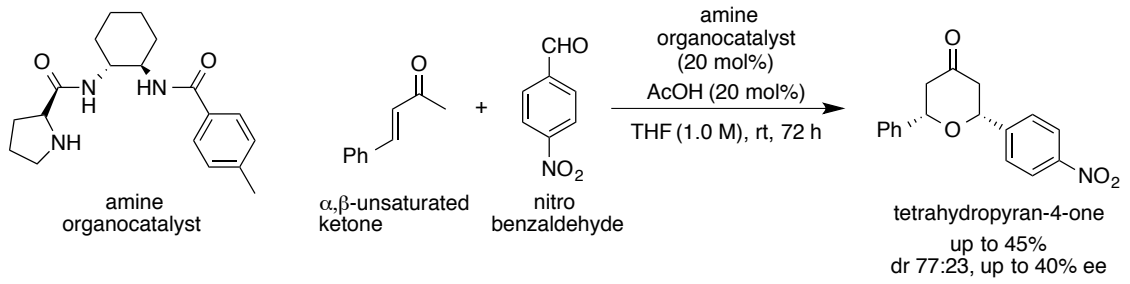
Scheme 13. hetero Diels-Alder reaction

2.4.1 Enantioselective oxa Diels-Alder reaction

Xiao and co-workers[24] reported the first organocatalytic oxa Diels-Alder reaction of α, β-unsaturated ketones with aldehydes to afforded the tethahydropyran-4-ones with good chemical yield up to 80% and diastereoselectivity up to 95:5 (scheme 14). Followed by they explored using amine organocatalyst for enantioselective reaction of α, β-unsaturated ketone with nitro benzaldehyde to afforded the tethahydropyran-4-ones (up to 45%, up to dr 77:23, up to 40% ee, Scheme 15).

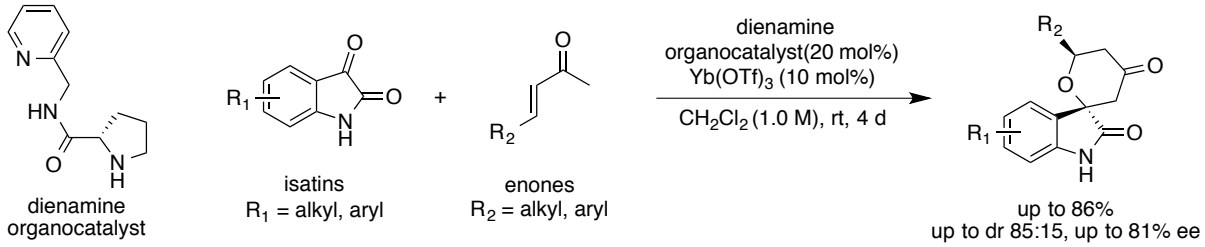


Scheme 14. Pyrrolidine organocatalyzed oxa Diels-Alder reaction



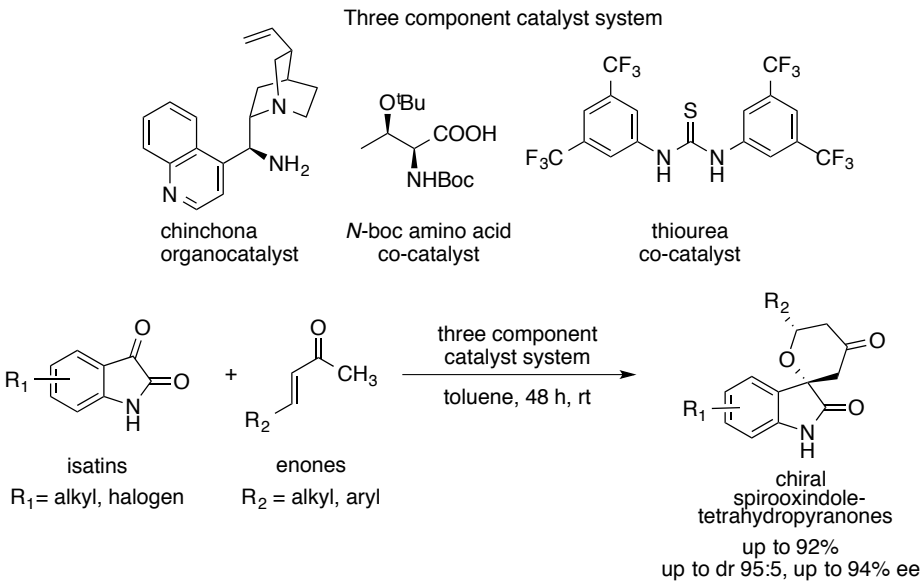
Scheme 15. Amine organocatalyst for enantioselective oxa Diels-Alder reaction

Wang and co-workers[25] developed the oxa Diels-Alder reaction of isatins with enones in the presence of dienamine and metal Lewis acid to afforded the spirooxindole tetrahydropyaranones with good chemical yield and stereoselectivities (up to 86%, up to dr 85:15, up to 81% ee, Scheme 16).



Scheme 16. Dienamine and metal Lewis acid organocatalyst for enantioselective oxa Diels-Alder reaction

Tanaka and co-workers[19] developed the oxa Diels-Alder reaction of isatins with enones using three component catalyst system to afforded the chiral spiro oxindole tetrahydropyaranones with excellent chemical yield (up to 92%) and excellent stereoselectivities (up to dr 95:5, up to 94% ee, Scheme 17). The provided chiral spiro oxindole tetrahydropyaranones is synthetic precursor for making many biological active compounds.



Scheme 17. Three component catalyst system for enantioselective oxa Diels-Alder reaction

2.5 Author strategy

Author aimed to develop the simple β-amino alcohol and derivatives organocatalysts (Figure 11). It has easy to synthesis from the commercially available amino acids, inexpensive than others like cinchona derived primary organocatalyst and stability towards the air and moisture. simple β-amino alcohol possess covalent site for enamine formation, non-covalent site for hydrogen bond formation and α, β-substitution act as steric influence sites in single molecules. Most recently, author developed the simple β-amino alcohol organocatalysts and the utility of this organocatalyst explored the asymmetric hetero Diels-Alder reaction of isatins with enones to afforded the chiral spiro oxindole tetrahydropyaranones. The obtained product is used in synthetic precursor for preparing many biologically active compounds.

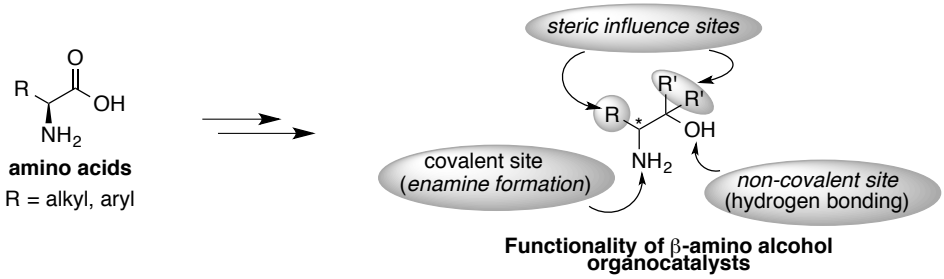
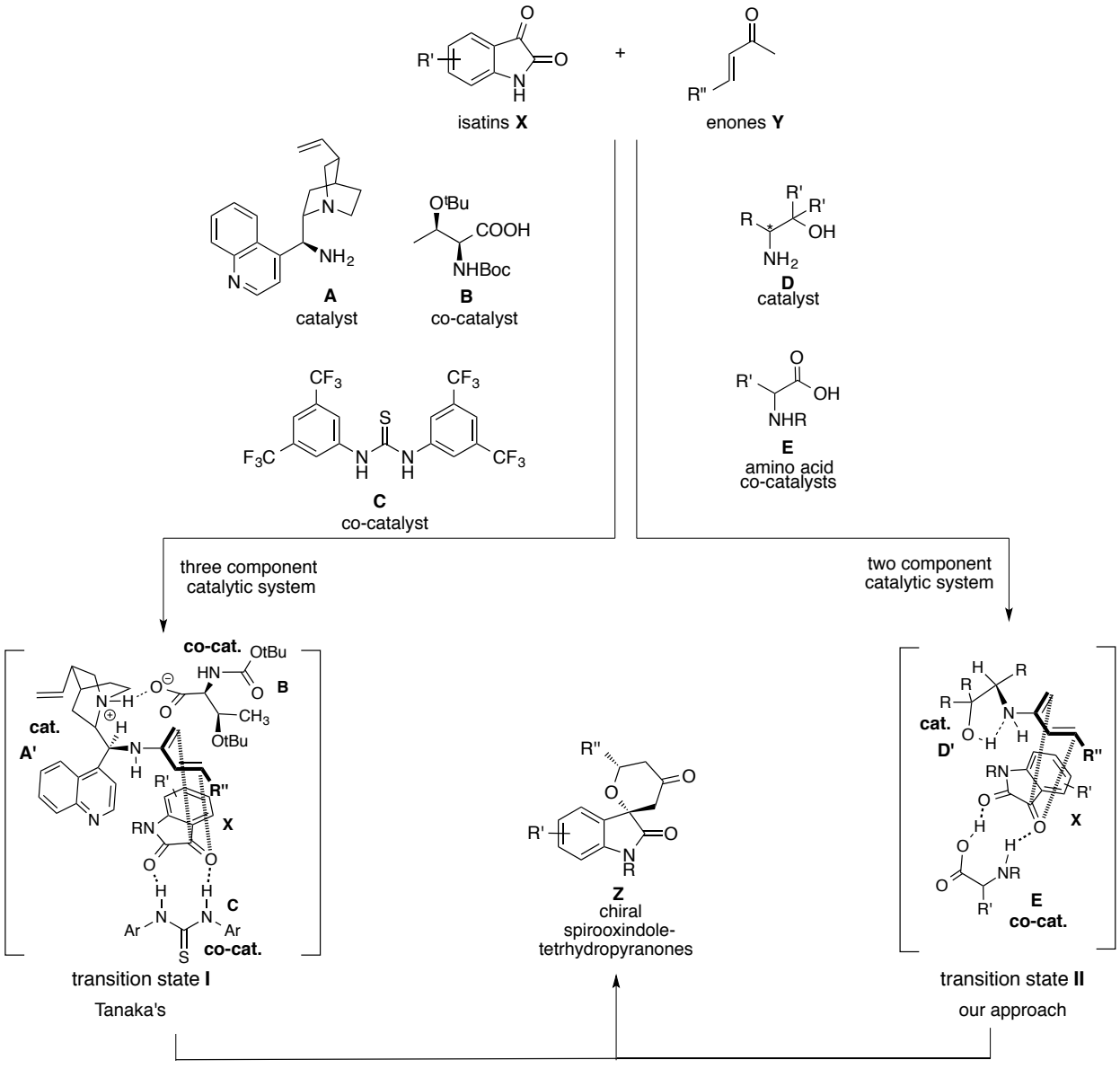


Figure 11. Functionality of β-amino alcohol organocatalysts

To further activity of simple β-amino alcohol organocatalysts, author examined the asymmetric hetero Diels-Alder reaction of isatin with enones using β-amino alcohol organocatalysts. As a concept of the enantioselectivity in this reaction using β-amino alcohol organocatalysts, the reaction might be proceeding via transition state **I**, the first amino alcohol react with enones to form diene (Scheme 18).



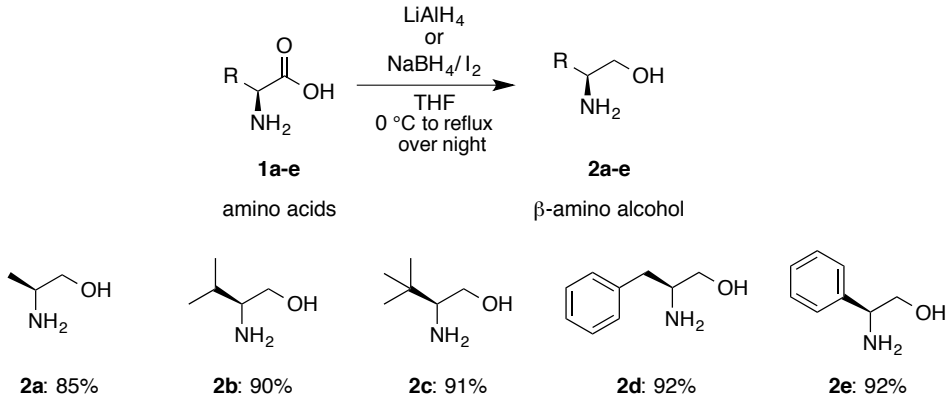
Scheme 18. Concept of β-amino alcohol organocatalysts for asymmetric hetero Diels-Alder reaction.

then isatin second oxygen atom make hydrogen bond interaction with acid group for *N*-protected amino acid and third oxygen make hydrogen bond interaction nitrogen atom of protected amino acid. The dienophile attack from the less steric hinderance side of diene intermediate to furnish the chiral spirooxindoles tetrahydropyranones. The simple β -amino alcohol organocatalysts has both covalent site for making enamine formation and non-covalent site for making hydrogen bond in a single molecule showed the catalytic activity in asymmetric hetero Diels-Alder reaction of isatin with enones to afforded the chiral spirooxindole tetrahydropyaranones.

2.7 Result and discussions

2.7.1 Synthesis of catalysts 2a-e

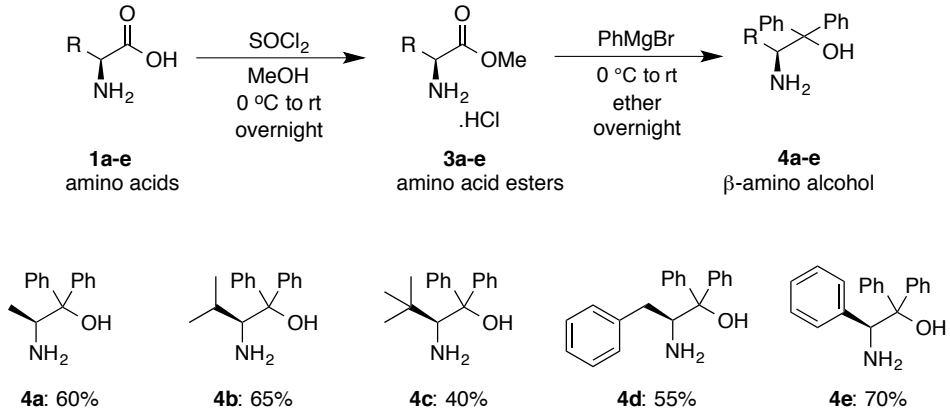
Author synthesized the simple β -amino alcohol organocatalysts **2a-e**[26] having no substitution at primary alcohol α-position for freely react with substrate were prepared from the commercially available corresponding amino acids **1a-e** by reduction of using lithium aluminium hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$)/iodine to afford the organocatalysts **2a-e (**Scheme 19).



Scheme 19. Synthesis of β-amino alcohol organocatalysts **2a-e**

2.7.2 Synthesis of catalysts 4a-e

Author synthesized the diphenyl β-amino alcohol organocatalysts **4a-e**[26] having diphenyl substitution at primary α-position for steric factor were synthesized from corresponding amino acid esters followed by Grignard reaction of using phenyl magnesium bromide to give organocatalysts **4a-e** (Scheme 20).



Scheme 20. Synthesis of β-amino alcohol organocatalysts **4a-e**

2.7.3 Various co-catalyst 5a-k to the asymmetric hetero Diels-Alder reaction of isatin with enones

The co-catalysts are playing crucial role in this asymmetric hetero Diels Alder reaction to increase the yield moreover with substrate to make more steric and hydrogen bond formation to provide results. Here author examined the listed of co-catalyst such as achiral **5a-b**, chiral of *N*-Boc and *N*-Cbz amino acids **5c-g**, organic acids **5h-j** and thiourea **5k** (Figure 12).

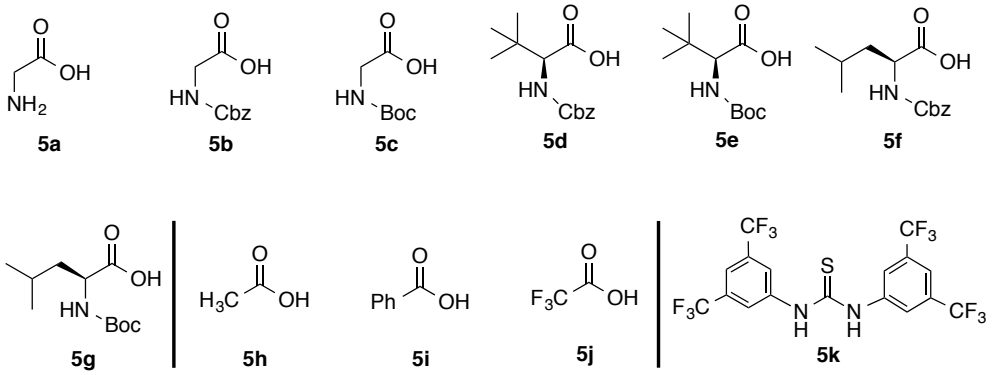


Figure 12. Various co-catalyst **5a-k** to the asymmetric hDA reaction

2.7.4 Optimized reaction condition for catalysts 2a-e and 4a-e in asymmetric hetero Diels-Alder reaction

In first author examined simple amino alcohol organocatalyst **2a-e** in asymmetric hetero Diels-Alder reaction model substrate is isatin with 3-hepten-2-one **7a** and *N*-Boc glycine **5c** as a model co-catalyst in the presence toluene at room temperature for 48 h in this reaction (entries 1-5) to afford the desired chiral spirooxindole tetrahydropyranones. All simple amino alcohol organocatalyst **2a-e** affords the desired chiral spirooxindole tetrahydropyranones with moderate to good chemical yield (16-86%), moderate to good diastereoselectivities (dr 50:50-80:20) and moderate to excellent enantioselectivities (72-92% ee). Catalyst **2b** having isopropyl group afford the less chemical yield (16%, entry 2). In extension with using simple amino alcohol diphenyl group contain at alpha position organocatalyst **4a-e** at same reaction condition instead of organocatalyst **2a-e** to afford the desired product with less chemical yield (14-28%, entries 6-10), moderate to good diastereoselectivities (dr 74:26-83:17) and less enantioselectivities (6-41% ee).

In contrast amino alcohol organocatalyst **4c** having diphenyl group at a-position did not affords the desired product because steric interaction between *tert*-butyl and diphenyl group. Concept of in this reaction amino alcohol as organocatalyst and acid as co-catalyst in the same way to continue

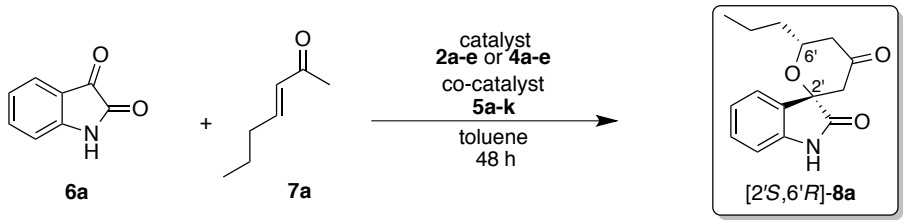
tertiary leucine amino acid **1a** has covalent site for enamine formation and acid group for making hydrogen bond formation for expect in this reaction but did not afford the desired product. The catalytic activity of amino acid **1a** (L-*tert*-leucine) with the primary amino group for generating diene species was also examined under the same reaction condition (entry 11). However, its catalytic activity was not confirmed at all, for a reason that neutral amino acids exist in betaine form which might not work for the generation of the diene species. Thus, amino alcohol alone worked as a catalyst for almost completely shielding one side of the enantiotopic face when diene attack to dienophile. These results indicated the necessity of our two catalysts component system comprising of amino alcohol catalyst for generating diene species and for controlling stereoselective reaction course and amino acid co-catalyst for activating isatin dienophile. These results indicated the necessity of our two catalysts component system comprising of amino alcohol catalyst for generating diene species and for controlling stereoselective reaction course and amino acid co-catalyst for activating isatin dienophile. The best organocatalyst is **2c,** from **2a-e**, **4a-e**. Author examined the one catalyst system using **2c** for in this reaction to furnish the desired the product with less chemical yield (14%, entry12), good diastereoselectivities (dr 85:15) and excellent enantioselectivity (92% ee).

Next, author tried the co-catalyst screening for in this reaction using best organocatalyst **2c** with co-catalysts **5a-b**, **5d-k**. Catalyst **2c** with unprotected glycine to afford the desired product with less chemical yield (14%, entry 13), moderate diastereoselectivity (dr 75:25) and excellent diastereoselectivity (95% ee). This system also same like one catalyst system. Next, tried with co-catalyst *N*-Cbz glycine **5b** to affords the desired product with god chemical yield (80%, entry 14) with good diastereoselectivity (dr 79:21) and excellent diastereoselectivity (91% ee). And also examine with chiral *N*-protected amino acid as co-catalyst **5d-g** to affords the desired product with good to excellent chemical yield (61-97%, entries 15-18), good diastereoselectivities (dr 72:28-82:18) and good enantioselectivities (84-88% ee). Next, tried with simple acid like acetic acid **5h**, benzoic acid **5i** to affords the desired product with good chemical yield (68%, entry 19-20), good diastereoselectivities (dr 75:25-84:16) and good enantioselectivities (86-87% ee). strong trifluoro acetic acid **5j** did not furnish the desired product. Next tried with thiourea **5k** to afford the desired product with less chemical yield (19%, entry 22), good diastereoselectivity (dr 73:27) and good enantioselectivity (75% ee). Moreover, three catalysts component system of catalyst **2c** and co-catalysts of both amino acid **5c** and thiourea **5k** also to affords the product (85%), good

diastereoselectivity (dr 75:25) and good enantioselectivity (82% ee). This three component catalyst showed less activity than two component system.

Furthermore, the best catalyst **2c** and co-catalyst **5c** conducted different reaction condition at 0 °C to afford low chemical yield 56% (entry 25) as compared with room temperature condition. Next, examined the molar ratio of catalyst **2c** and co-catalyst **5c** in this reaction of **6a** with **7a** (4 equiv) at room temperature (entries 26-30) to furnish the good chemical yield (52-60%), good diastereoselectivities (dr 78:22-81:19) and good enantioselectivities (87-89% ee). However, chemical yields comparatively decreased when the reaction was carried out under the molar ratio of 20 mol% of catalyst **2c** and 40 mol% of co-catalyst **5c** (entry 3).

Table 1. Asymmetric hetero Diels-Alder reaction of catalysts **2a-e, 4a-e** and co-catalysts **5a-k**



entry	enone **7a** (eq.)	catalyst **2a-f**, **4a-e** (20 mol%)	co-catalyst **5a-k** (40 mol%)	temp.	yield (%)[a]	dr[b]	ee (%)[c]
1	4	**2a**	**c**	rt	66	55:45	72
2	4	**2b**	**c**	rt	16	75:25	86
3	4	**2c**	**c**	rt	86	80:20	92
4	4	**2d**	**c**	rt	78	64:36	81
5	4	**2e**	**c**	rt	61	50:50	88
6	4	**4a**	**c**	rt	18	74:26	41
7	4	**4b**	**c**	rt	14	75:25	24
8	4	**4c**	-----	rt	*trace*	-----	-----
9	4	**4d**	**c**	rt	28	83:17	14
10	4	**4e**	**c**	rt	24	78:22	6
11	4	**1c**	-----	rt	*trace*	-----	-----
12	4	**2c**	-----	rt	15	85:15	92

continue to next page

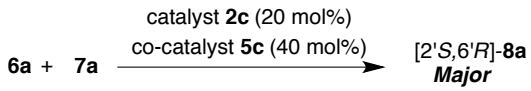
13	4	**2c**	**a**	rt	14	75:25	95
14	4	**2c**	**b**	rt	80	79:21	91
15	4	**2c**	**d**	rt	61	82:18	88
16	4	**2c**	**e**	rt	87	81:19	87
17	4	**2c**	**f**	rt	90	82:18	88
18	4	**2c**	**g**	rt	97	75:25	84
19	4	**2c**	**h**	rt	68	75:25	86
20	4	**2c**	**i**	rt	68	84:16	87
21	4	**2c**	**j**	rt	*trace*	-----	-----
22	4	**2c**	**k**	rt	19	73:27	75
23	2	**2c**	**c**	rt	47	77:23	90
24	1	**2c**	**c**	rt	17	73:27	89
25	4	**2c**	**c**	0 °C	56	81:19	93
26	4	**2c** (20 mol %)	**c** (20 mol %)	rt	54	78:22	89
27	4	**2c** (20 mol %)	**c** (10 mol %)	rt	52	79:21	87
28	4	**2c** (10 mol %)	**c** (10 mol %)	rt	54	78:22	89
29	4	**2c** (10 mol %)	**c** (20 mol %)	rt	60	81:19	89
30	4	**2c** (10 mol %)	**c** (5 mol %)	rt	52	79:21	87

[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture (major diastereomer: **8a**).[c]The ee value were determined by HPLC using Daicel chiralpak IB column.

2.7.5 Solvent screening for asymmetric hetero Diels-Alder reaction using catalyst 2c and co-catalyst 5c.

Next, examined the effects of various solvents and the reaction times to this reaction with an optimized catalyst combination of **2c** (20 mol%) and **5c** (40 mol%) at room temperature (Table 2). As a result, aromatic solvents toluene, benzene, xylene (entries 1-3) performed better giving good chemical yields (60-86%) Particularly, toluene was found to be effective in this reaction (entry 1). Also examined the non-polar such as cyclohexane affords the moderate chemical yield (66%, entries 4), and hexane did not afford (entry 5). Next tried with etherate solvent diethyl ether and diisopropylether and tetrahydrofuran to giving moderate chemical yields and stereoselectivities (40-68%, dr 77:23- 79:21, 82-90% ee). Furthermore, tried with and chlorinated solvent dichloromethane, chloroform and dichloroethane to furnish chemical yields and stereoselectivities (entries 9-11, 34-75%, dr 77:23-84:16, 88-90% ee). In addition that tried with polar solvent acetonitrile and methanol to giving less chemical yield (38-70%, entries 12,13) and satisfactory stereoselectivities (dr 68:32-75:25, 83-88% ee). Furthermore, no significant improvement in chemical yields and stereoselectivities was observed when the reaction times were shortened for 24 h and prolonged for 72 h and 96 h, respectively (entries 14-16). From these results, it was revealed that the catalyst combination of simple catalyst **2c** (20 mol %) and simple non-chiral *N*-Boc-glycine **5c** (40 mol %), toluene as solvent, room temperature and 48 h reaction time was best reaction condition for this reaction. While this reaction also slightly afforded aldol product **9** which is obtained by aldol reaction as a by-product. Similarly, This catalysts component system also slightly afforded similar aldol product **9** in low chemical yield (12%) and stereoselectivities (72:28 dr, 16% ee).

Table 2. Solvent screening for catalyst **2c** and co-catalyst **5c**



entry	solvent	time (h)	yield (%)[a]	dr[b]	ee (%)[c]
1	toluene	48	86	80:20	92
2	benzene	48	60	78:22	90
3	xylene	48	73	77:23	88
4	cyclohexane	48	66	74:26	89
5	hexane	48	*trace*	----	----
6	Et_2O	48	55	78:22	90
7	$^{i}Pr_2O$	48	68	77:23	89
8	THF	48	40	79:21	82
9	CH_2Cl_2	48	74	79:21	90
10	$CHCl_3$	48	34	84:16	92
11	$C_2H_4Cl_2$	48	75	77:23	88
12	CH_3CN	48	70	75:25	88
13	MeOH	48	38	68:32	83
14	toluene	24	73	79:21	90
15	toluene	72	86	78:22	86
16	toluene	96	76	78:22	86
17	neat	24	87	71:29	86
18	neat	48	75	68:32	82

[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture (major diastereomer: **8a**). [c]The ee value were determined by HPLC using Daicel chiralpak IB column.

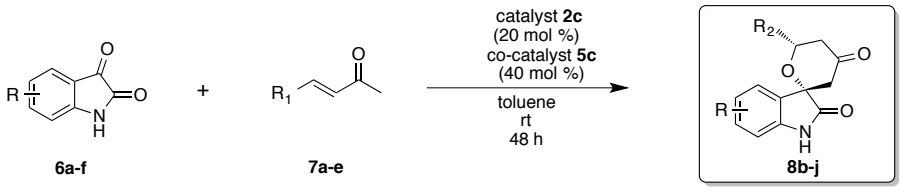
2.7.6 Substrate scope for asymmetric hetero Diels-Alder reaction using 6a-f and 7a-e.

After optimizing the reaction conditions, Next tried with application of using different isatin substrate **6b-f** and different enones **7a-e**. First tried with electron donating group contain 5-Me isatin **6b** with 3-hepten-2-one **7a** to furnish the desired chiral 5-Methyl spirooxindole tetrahydropyranone with good chemical yield (71%), good diastereoselectivity dr 78:22 and good enantioselectivity 86% ee. After that examined with isatin contain electron withdrawing group bromine and chlorine at fourth position to affords the desired chiral 4-bromo and 4-chloro spirooxindole tetrahydropyranone with moderate chemical yields (68-70%), did not afford the diastereoselectivities in this application and moderate enantioselectivities (56-66% ee) because it make with steric repulse between the isatin. Next tried with isatin contain electron withdrawing group bromine and chlorine at fifth and sixth position with moderate chemical yields (62-71%), good diastereoselectivity (dr 78:22)and good enantioselectivity 86-88% ee.

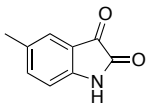
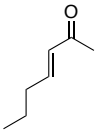
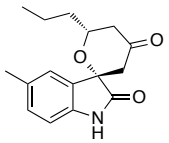
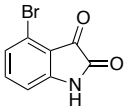
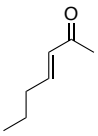
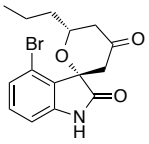
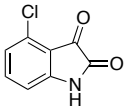
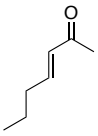
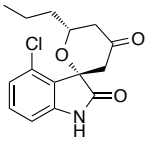
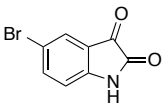
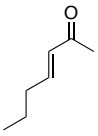
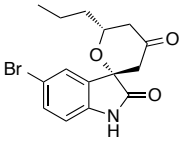
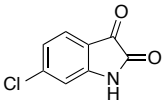
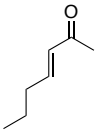
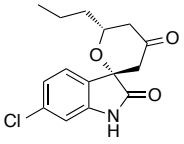
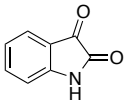
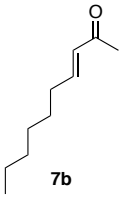
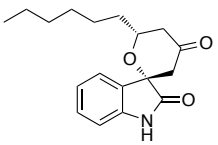
Furthermore, examined with long chain enone 3-decan-2-one **7b** with isatin **6a** to afford the desired chiral product with good chemical yield 68%, good diastereoselectivity dr 81:19 and good enantioselectivity 78% ee. In addition that examined with olefin contain enone **7c** with isatin **6a** to afford the desired chiral product with low chemical yield 25%, good diastereoselectivity dr 70:30 and excellent enantioselectivity 93% ee. Moreover that examined with 5-methyl-3-hexen-2-one **7d** with isatin **6a** to afford the desired chiral product with good chemical yield 66%, moderate diastereoselectivity dr 52:48 and good enantioselectivity 88% ee. Next, tried with benzalacetone **7e** with isatin **6a** did not afford the desired product.

Moreover, author examined the gram scale reaction of isatin **6a** with 3-hepten-2-one **7a** using optimized two component catalytic system catalyst **2c** and co-catalyst **5c**. As a result, the HDA adduct **8a** was successfully obtained with 87% chemical yield with good s good enantioselectivity (dr 80:20) and good enantioselectivity (85% ee). In overall the reaction carried out small scale to gram scale the desired product was formation slightly decrease was observed.

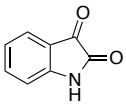
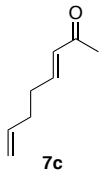
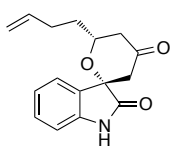
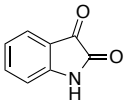
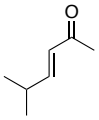
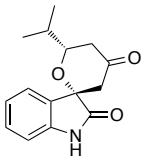
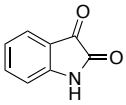
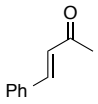
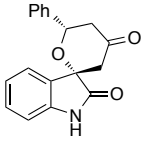
Table 3. Substrate scope for asymmetric HDA reaction



6a-f + **7a-e** → **8b-j**

entry	**6b-f** R	**7a-e** R_1	**8b-j**	yield (%)[a]	dr[b]	ee (%)[c]
1	 **6b**	 **7a**	 **8b**	71	78:22	86
2	 **6c**	 **7a**	 **8c**	70	-----	56
3	 **6c**	 **7a**	 **8d**	68	-----	66
4	 **6d**	 **7a**	 **8e**	71	78:22	88
5	 **6e**	 **7a**	 **8f**	62	78:22	86
6	 **6a**	 **7b**	 **8g**	68	81:19	78

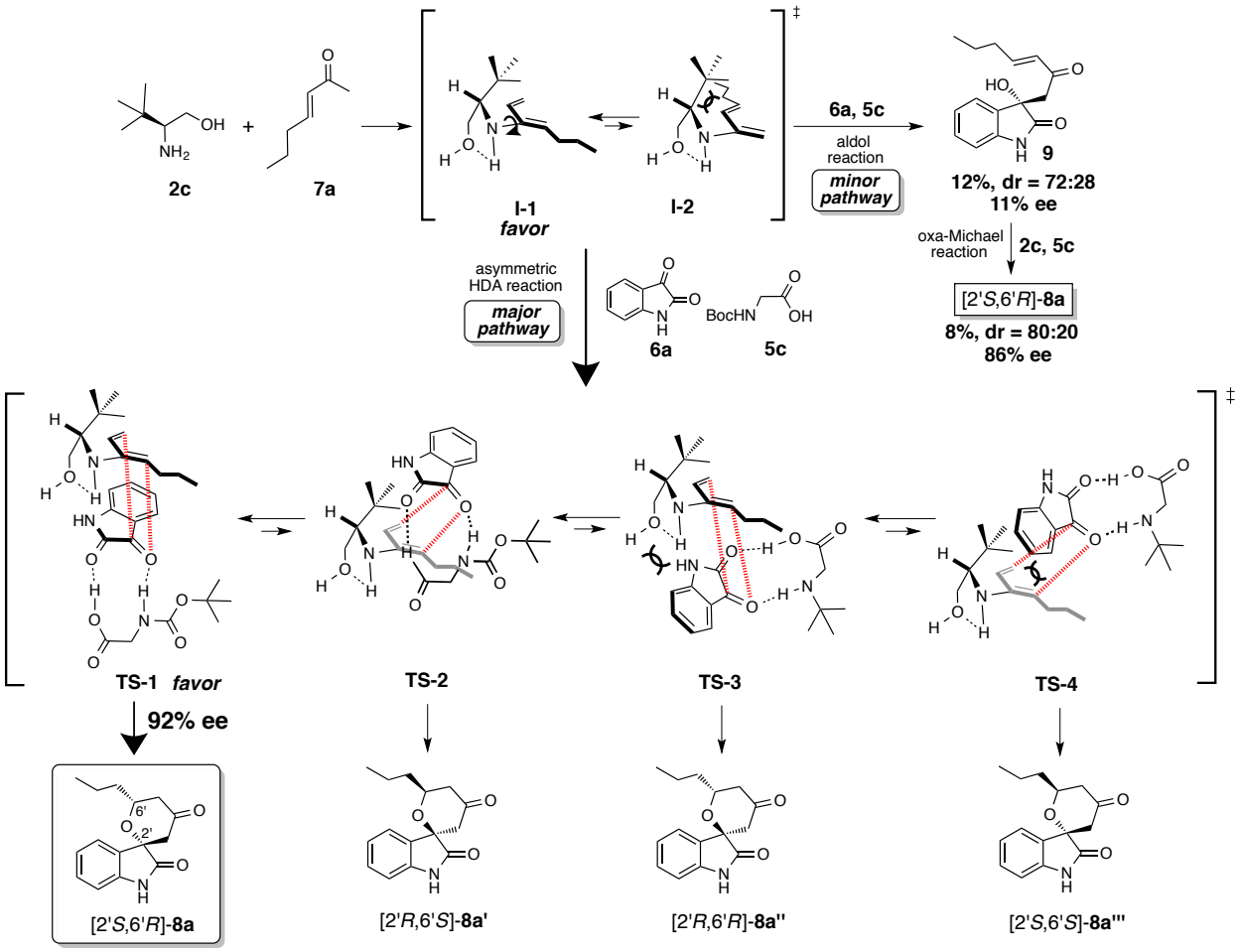
continue to next page

7	 **6a**	 **7c**	 **8h**	25	70:30	93
8	 **6a**	 **7d**	 **8i**	66	52:48	88
9	 **6a**	 **7e**	 **8j**	-----	-----	-----

[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture (major diastereomer: **8a**).[c]The ee value were determined by HPLC using Daicel chiralpak IB column.

2.7.7 Plausible Reaction mechanism for hetero Diels-Alder reaction using 6a and 7a with 2c and 5c

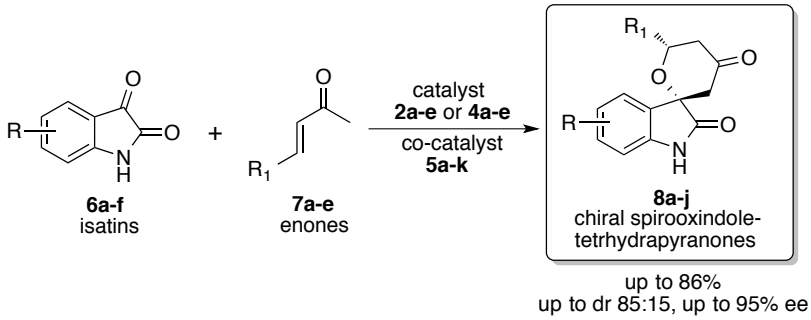
Based on the observed highly highly enantiopurity of the obtained HDA adduct [2*S*,6*R*]-**8a** (rt: 92% ee, 0°C: 93% ee, entries 6 and 25, Table1), the model of the enantioselective reaction course was proposed as shown in Scheme 4. First, the reaction of β-amino alcohol catalyst **2c** with enone **7a** forms the diene intermediate **I-1** that has less steric interaction of between amino alcohol that is fixed by intramolecular hydrogen bonding and substituted diene parts on generated diene **I-1** than that of intermediate **I-2**. Furthermore, isatin **6a** is activated by the two points of hydrogen bonding interactions with *N*-Boc amino acid co-catalyst **5c**. Then, the reaction might proceed through **TS-1** to afford **8a** that has a less steric interaction between **I-1** and dienophile **6a** than those of **TS-2-4** to afford **8a'-8a''** that have more steric interaction between **I-1** and **6a**. Thus, diene **I-1** might attack stereoselectively from less sterically hindered site of the incoming activated isatin dienophile **6a** to afford [2*S*,6*R*]-**8a** with excellent optically purity (92% ee). On the other hand, it is also expected that the formation of adduct **8a** via aldol reaction followed by oxa-Michael addition may be minor pathway based on the chemical yield and enantioselectivity of the obtained aldol product **9** and **8a** was quite low (**9**: 12%, dr 72:28., 16% ee, **8a**: 8%, dr 80:20., 86% ee, Scheme 21).



Scheme 21. Plausible reaction course for asymmetric hDA reaction

2.5 Summary

In summary, author developed a simple two catalysts component system consisting of primary β-amino alcohol **2c** as a catalyst and *N*-protected amino acid **5c** as a co-catalyst for the asymmetric hDA reaction of isatins with enones for the first time. This two component catalytic system showed excellent catalytic activity to afford the chiral spirooxindole-tetrahydropyranones **8a-j**. The obtained chiral spirooxindole-tetrahydropyranones are efficient synthetic intermediates for preparing many biologically active compounds and drug discovery, in good chemical yields (up to 86%), good diastereoselectivities (up to dr 85:15) and excellent enantioselectivities (up to 95% ee). Moreover, the single simple β-amino alcohol catalyst **2c** has *tert*-butyl also showed good catalytic activity for affording **8a** with an excellent enantioselectivity (92% ee) and chemical yield was very low.



Chapter 3

Simple amino silyl ether organocatalyst for asymmetric hetero Diels-Alder reaction of isatins with enones

3. Simple amino silyl ether organocatalyst for asymmetric hetero Diels-Alder reaction of isatins with enones

3.1 Author project

Author aimed to develop the further expand study of simple β-amino alcohol organocatalyst to simple β-amino silyl ether organocatalyst component system for asymmetric hDA reaction of isatins with enones to afford the chiral spirooxindole tetrahydropyranones. The function of amino silyl ether organocatalyst having covalent site (enamine formation), α, β and alcohol protected like silyl group act as steric influence site in a single molecule (Figure 13).

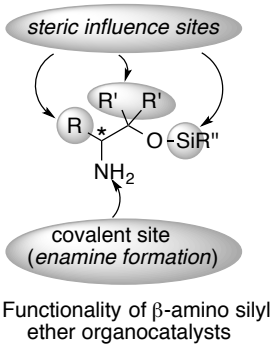


Figure 13. Functionality of β-amino silyl ether organocatalysts

3.2 Author strategy

Author aimed to develop the simple β-amino silyl ether and derivatives organocatalyst (Figure 14). It is synthesis from the β-amino alcohol and stability towards the air and moisture. simple β-amino silyl ether possess covalent site for enamine formation and remaining substitution act as steric influence site in single molecule. Most recently, author developed the simple β-amino silyl ether organocatalysts and the utility of this organocatalyst explored the asymmetric hetero Diels-Alder reaction of isatins with enones to afforded the chiral spirooxindole tetrahydropyaranones.

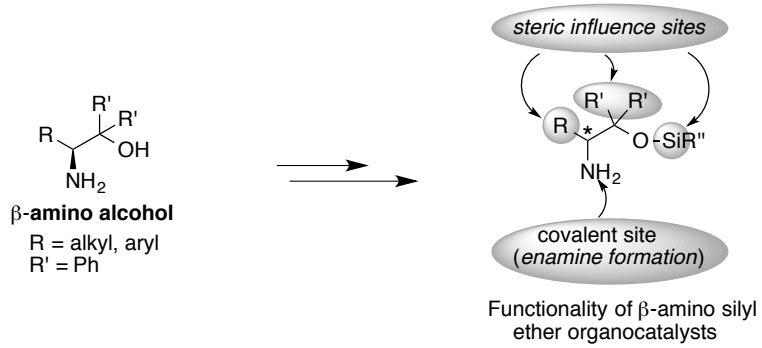
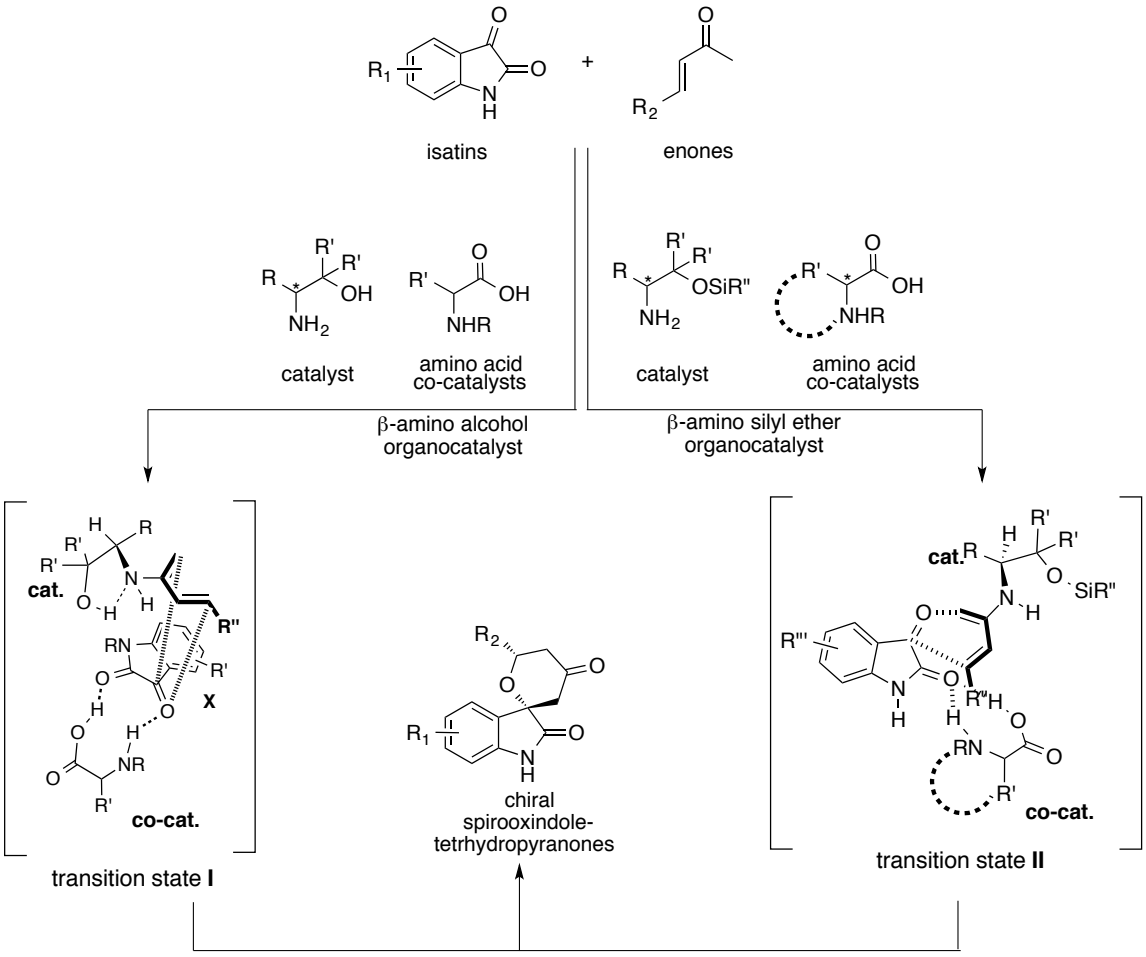


Figure 14. Functionality of β-amino silyl ether organocatalysts

To further activity of β-amino silyl ether organocatalysts, author tried to compare asymmetric hDA reaction of isatin with enones using β-amino alcohol and β-amino silyl ether organocatalysts (Scheme 22). As a concept of the enantioselectivity in this reaction using β-amino alcohol proceed via transition state **I** and β-amino silyl organocatalysts might be proceeding via transition state **II**, the first amino silyl ether react with enones to make act as diene. The second oxygen atom on isatin make hydrogen bond interaction with acid group for *N*-protected amino acid. The dienophile attack from the less sterichinderance side of diene intermediate to furnish the chiral spirooxindoles tetrahydropyranones.

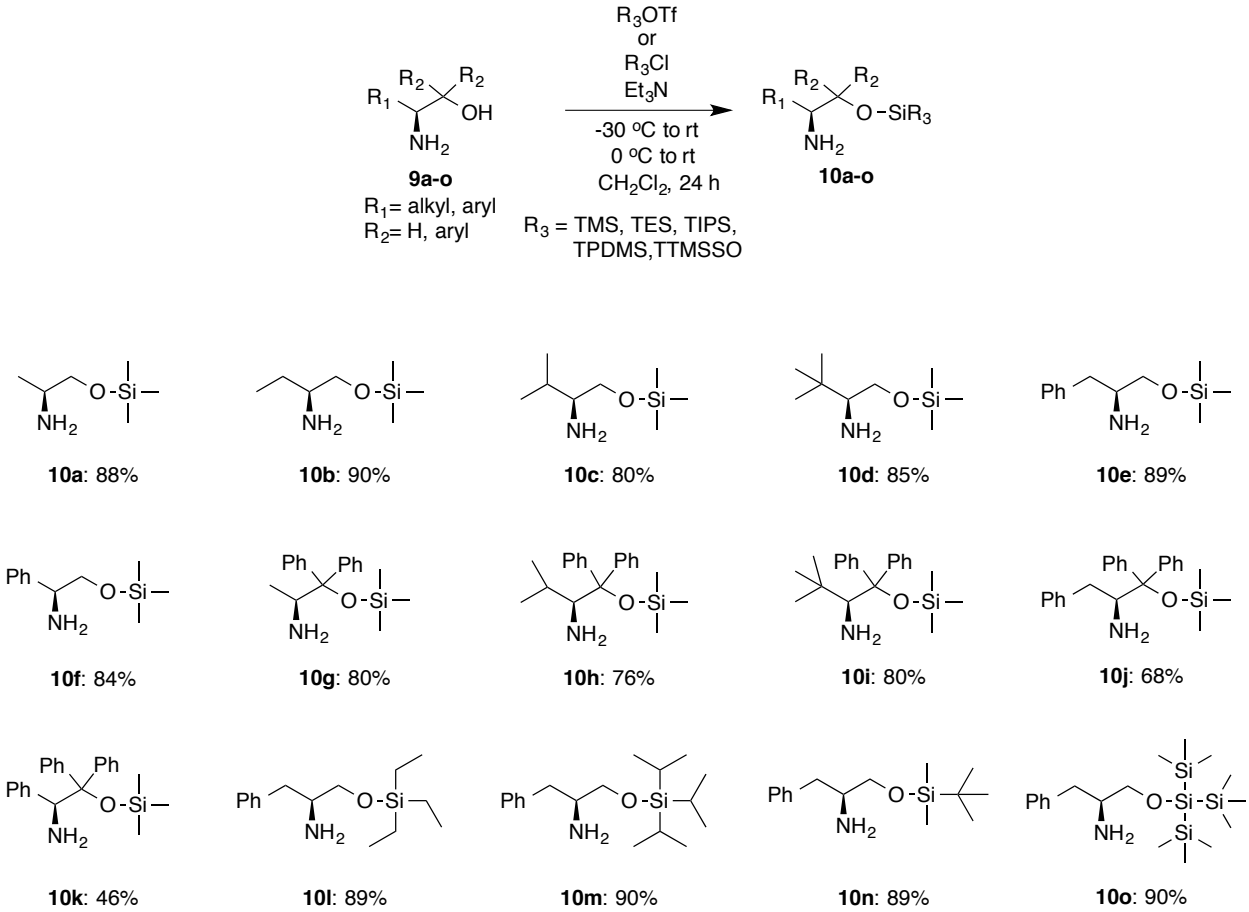


Scheme 22. Concept of amino silyl ether in asymmetric hDA reaction

3.3 Result and discussions

3.3.1 Preparation of simple amino silyl ether organocatalysts 10a-o

The desired amino silyl ethers **10a-o**[27] having several silyl groups on oxygen atom at a-position were easily prepared by the reactions of the corresponding β-amino alcohols **9a-o** with XCl [X= TMS (trimethylsilyl), TES (triethylsilyl), TIPS (triisopropylsilyl), TBDMS (*tert*-butyldimethylsilyl)], respectively, in good yields (Scheme 2). Furthermore, the bulkiest β-amino silyl ether catalyst **2o** having a super silyl [tris(trimethylsilyl)silyl: TTMSS] group on oxygen atom was also easily prepared from the reaction of the corresponding amino alcohols with TTMSSCl in moderate to good yields. Furthermore, several *N*-Cbz- and *N*-Boc-amino acids **11a-s** as co-catalysts were also easily derived from the corresponding commercially available non-protected acyclic and cyclic amino acids, respectively (Scheme 23).



Scheme 23. Preparation of organocatalysts **10a-o**

3.3.2 Various co-catalysts 5b-c, 5h-j, 11a-n employed in asymmetric hetero Diels-Alder reaction

The co-catalysts are participating essential role in asymmetric hetero Diels-Alder reaction to increase the yields and stereoselectivities. Additionally, interact with substrate to make more steric and hydrogen bond formation to afford them products. Here author listed the achiral **5b-c,** carboxylic acid **5i**, **11a-g**, organic acids **5h, 5j**, chiral of *N*-Boc and *N*-Cbz amino acids **11h-n** (Figure 15).

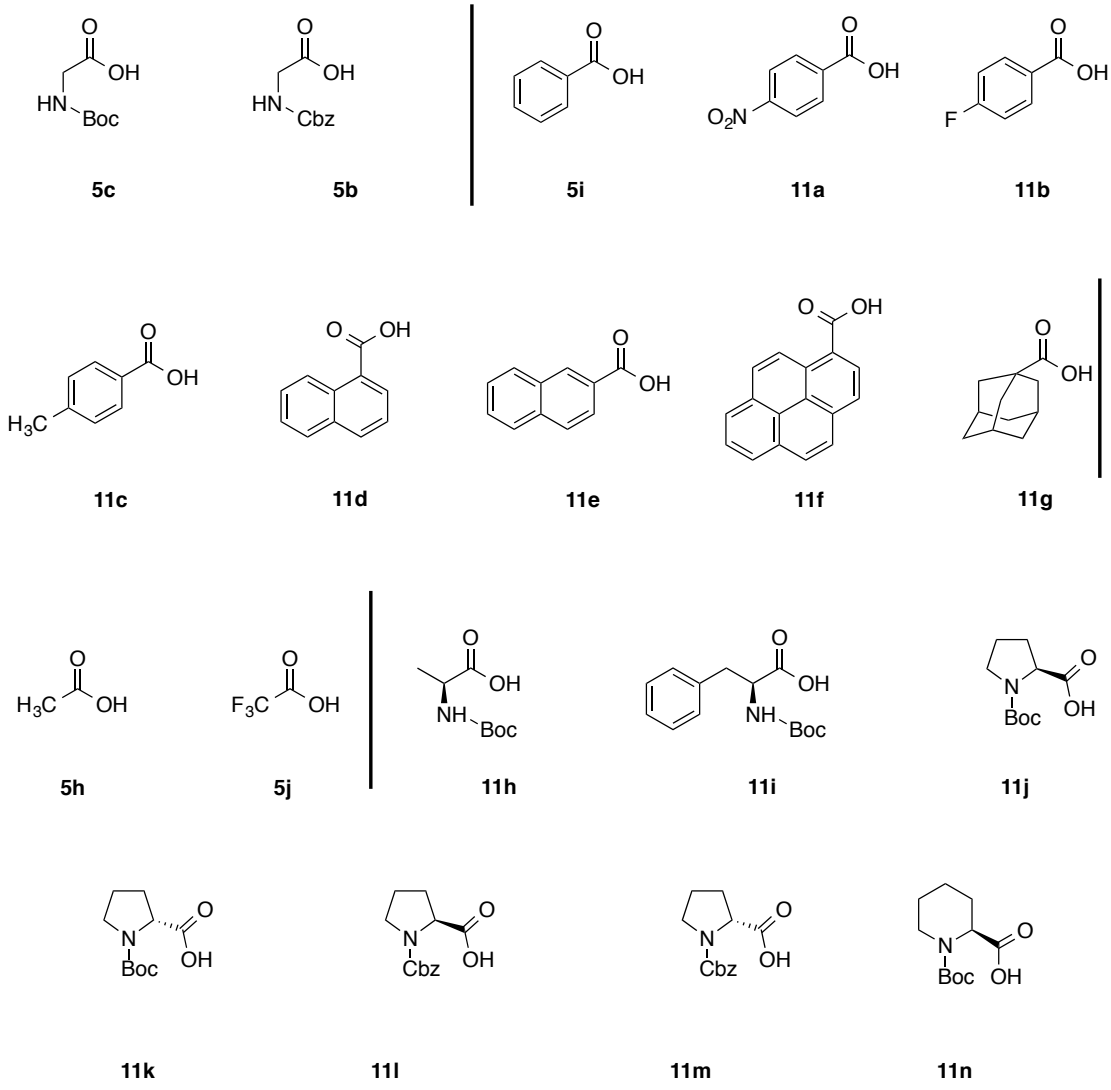
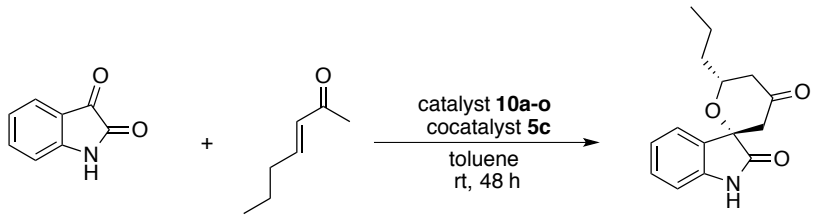


Figure 15. Various co-catalysts **5b-c**, **5h-j**, **11a-n** employed in asymmetric hDA reaction

3.3.3 Screening of catalyst 10a-o in asymmetric hetero Diels-Alder reaction

Author first examined the hDA reaction of isatin **6a** as a dienophile with heptene-2-one **7a** as a diene using the combinations of simple β-amino silyl ether organocatalysts **10a-f** with primary trimethylsiloxy (TMS) methyl or **10g-o** with bulkier TMS diphenylmethyl groups (20 mol %) with the simplest *N*-Boc-amino acid **5c** as a previous work best co-catalyst (40 mol %) at room temperature for 48 h (Table 4). As a result, every amino silyl ethers **10a-f** showed catalytic activities in this reaction and the corresponding HDA adduct [2'*S*,6'*R*]-**8a** was obtained in good enantioselectivities (72-85% ee) and with moderate diastereoselectivities (dr 53:47-67:33), although the chemical yield was the range of extremely low to good (2-77%, entries 1-6). In contrast catalyst **10d** contain *tert*-butyl bulky substituent and Trimethyl silyloxy (TMS) act as more steric hinderance because of that to afford the very low chemical yield (2%). Among these catalysts, the uses of catalysts **10e**, and **10f** having Bn and Ph bulkier substituents at β-position provides better catalytic activity (entries 5 and 6).

Table 4. Asymmetric hetero Diels-Alder reaction of catalyst **10a-o** and co-catalyst **5c**



6a **7a** [2*S*' 6*R*']-**8a**

entry	enone **7a** (eq)	catalyst **10a-o** (20 mol%)	co-catalyst (40 mol%)	yield (%)[a]	dr[b]	ee (%)[c]
1	4	**10a**	**5c**	11	54:46	72
2	4	**10b**	**5c**	9	64:36	79
3	4	**10c**	**5c**	44	67:33	85
4	4	**10d**	**5c**	2	63:37	76
5	4	**10e**	**5c**	74	67:33	81
6	4	**10f**	**5c**	77	53:47	72
7	4	**10e**	----	31	56:44	59
8	4	**10g**	**5c**	2	65:35	40
9	4	**10h**	**5c**	trace	-----	-----
10	4	**10i**	**5c**	trace	-----	-----
11	4	**10j**	**5c**	trace	-----	-----
12	4	**10k**	**5c**	9	74:26	14
13	4	**10l**	**5c**	64	61:39	75
14	4	**10m**	**5c**	46	69:31	15
15	4	**10n**	**5c**	65	66:34	18
16	4	**10o**	**5c**	84	51:49	51

[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture. [c]The ee value were determined by HPLC using Daicel chiralpak IB column.

Catalyst **10e** having bulkier benzyl group provided the adduct **8a** in good chemical yield (74%) and enantioselectivity (81% ee) with moderate diastereoselectivity (67:33)(entry 5). It might be for a steric factor. In addition that, examined with single catalyst **10e** at same reaction condition without co-catalyst to furnish the desired product **8a** with less chemical yield (31%), moderate diastereoselectivity (dr 56:44) and moderate enantioselectivity (59% ee). On the other hand, the

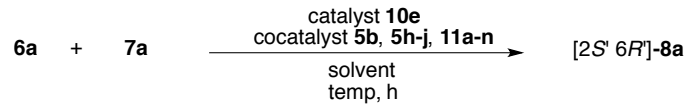
reactions using **10g-k** with bulkier TMSO diphenyl groups hardly proceeded. Catalyst **10g** and **10k** affords the product **8a** with very less chemical yields (2-9%) and enantioselectivity also considerably decreased (14-40% ee, entries 8-12). Moreover, catalyst **10h-j** did not afforded the product **8a**. Next, based on these best catalyst **10e** results, the reaction using different catalysts **2l-o** having different silyl groups on oxygen atom and co-catalyst **11a** were carried out under same reaction condition. However, these catalysts **10l-o** furnish the moderate to good chemical yield (46-84%, entry 13-16), moderate stereoselectivities (dr 51:49-61:39, 15-75% ee) bulkiest protecting having catalyst **10l-o** did not show better catalytic activity than **10e**. From these results, it was revealed that the best catalyst was β-amino silyl ether **10e** with primary TMSO siloxy group.

This reaction using two catalysts component system by our group mainly afforded HDA adducts **8a**, which was obtained by concerted HDA cycloaddition, while this reaction also slightly afforded aldol product **9**, which is obtained by aldol reaction as a by-product. Similarly, this catalysts component system also slightly afforded similar aldol product **9** in low chemical yield (10%) and enantioselectivity (9% ee) than previous two-component system using β-amino alcohol organocatalyst.

3.3.4 Screening of co-catalyst 5b, 5h-I, 11a-n using catalyst 10e in asymmetric hetero Diels-Alder reaction.

Next examined this reaction using the combinations of superior catalyst **10e** (20 mol%) with several acids **5b**, **5h-j**, **11a-n** as co-catalysts (40 mol%) at room temperature for 48 h (Table 5). First, the reactions using *N*-Cbz-amino acids **5b** and also common aromatic or aliphatic acids **5h-j**, **11a-g** as co-catalysts were carried out (entries 4–11). All co-catalysts **5b, 5h-j**, **11a-g** assisted the progress of the reaction for affording chiral **8a** with moderate to good chemical yields and stereoselectivities. However, bulkier aromatic acid **11f** only afforded **8a** in low chemical yields, although moderate to good stereoselectivities was observed. Furthermore, strongest trifluoro acetic acid (TFA) **5j** did not work as a co-catalyst in this reaction condition (entry 13). Unfortunately, these co-catalysts did not show better co-catalytic activity than the result of the combination of catalyst **10e** and co-catalyst **5c**. Next, the reactions using chiral *N*-Boc- or *N*-Cbz-amino acids **11h, i** as co-catalysts (40 mol%) were examined (entries 12,13). However, these co-catalysts **11h, i** also did not show better co-catalytic activity compared to the combination of catalyst **10e** and co-catalyst **5c**. Moreover, the utilities of combination of bulkier chiral *N*-Boc- or *N*-Cbz-prolines.

Table 5. asymmetric hetero Diels-Alder reaction of catalyst **10e** and co-catalyst **5b**, **5h-j, 11a-n**



entry	enone **7a** (eq)	catalyst (20 mol%)	co-catalyst **5b**, **5h-j**, **11b-s** (40 mol%)	temp	yield (%)[a]	dr[b]	ee (%)[c]
1	4	**10e**	**5b**	rt	69	65:35	82
2	4	**10e**	**5i**	rt	85	69:31	79
3	4	**10e**	**11a**	rt	76	68:22	79
4	4	**10e**	**11b**	rt	94	69:21	80
5	4	**10e**	**11c**	rt	85	70:30	78
6	4	**10e**	**11d**	rt	91	65:35	78
7	4	**10e**	**11e**	rt	90	68:32	80
8	4	**10e**	**11f**	rt	53	65:35	81
9	4	**10e**	**11g**	rt	80	67:33	80
10	4	**10e**	**5h**	rt	82	65:35	80
11	4	**10e**	**5j**	rt	trace	-----	-----
12	4	**10e**	**11h**	rt	79	76:24	80
13	4	**10e**	**11i**	rt	78	68:22	81
14	4	**10e**	**11j**	rt	85	77:23	82
15	4	**10e**	**11k**	rt	76	77:23	80
16	4	**10e**	**11l**	rt	79	67:33	81
17	4	**10e**	**11m**	rt	87	68:32	78
18	4	**10e**	**11n**	rt	75	57:43	78
19	4	**10e**	**11j**	0 °C	35	82:18	84
20	4	**10e**	**11j**	40 °C	79	77:23	76

[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture.
[c]The ee value were determined by HPLC using Daicel chiralpak IB column.

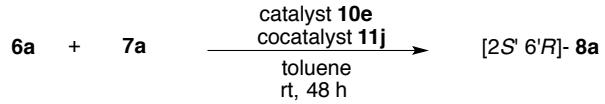
Co-catalyst **11j-m** and *N*-Boc-piperidine **11n** as a cyclic amino acid were also examined in this reaction condition (entries 19–22). Similarly to the results of general amino acids **5b-c**, **11h-i,** and common organic acids **5i**, **5j**, **11a-g**, these cyclic amino acids **11j-n** also showed moderate to good

catalytic activities for affording **8a** in good chemical yields and stereoselectivities. Particular, *N*-Boc-*L*-proline **11j** showed best co-catalytic activity and afforded **8a** in good chemical yield (85%, entry 14) and stereoselectivities(dr 77:23, 82% ee). However, the reaction of this combination of **10e** with **11j** at 0 °C brought about a large decrease in chemical yield up to 35% (entry 19), although good stereoselectivity (dr 82:18 , 84% ee) were kept. On the other hand, the reaction at 40 °C afforded **8a** in good chemical yield (79%, entry 20) and with stereoselectivity (dr 77:23, 76% ee). From these results, It was revealed that the combination of **10e** with **11j** was best combination in this reaction.

3.3.5 Optimization of mole amount used for superior catalysts system and substrates.

Next, examined the molar ratio of catalyst **10e** and co-catalyst **11j** in this reaction of **6a** (1 equiv) with **7a** (4 equiv.) at room temperature (entries 1-5, Table X) to afford the product **8a** with low to good chemical yield (17-85%) Satisfactory enantioselectivities (79-83% ee) and good diastereoselectivities(dr 69:31-75:25%) were confirmed under all of the molar ratios of **10e** and **11j**. However, chemical yields comparatively decreased when the reaction was carried out under the use of 10 mol% of catalyst **10e** (entry 6). Next, the ratio of substrate amounts **6a** and **7a** were examined in the presence of optimized **10e** (20 mol%) and co-catalyst **11j** (40 mol%) under same reaction condition (Table 6). Good chemical yield (48-92%) and stereoselectivity (dr 70:30-78:22, 76-81% ee) were observed under the uses of all of ratios, but the use of 1 equiv. of **7a** to **10e** brought about the decrease of chemical yield (48%).

Table 6. Optimization of asymmetric hetero Diels-Alder reaction of catalyst **10e** and co-catalyst **11j**



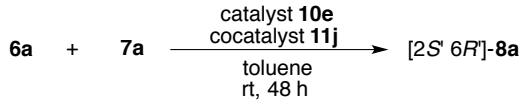
entry	enone **7a** (eq)	catalyst **10e**	co-catalyst **11j**	yield (%)[a]	dr[b]	ee (%)[c]
1	4	20 mol%	20 mol%	85	75:25	80
2	4	20 mol%	10 mol%	82	72:28	79
3	4	10 mol%	10 mol%	30	71:29	82
4	4	10 mol%	20 mol%	50	69:31	82
5	4	10 mol%	5 mol%	17	72:28	83
6	1	20 mol%	40 mol%	48	70:30	81
7	2	20 mol%	40 mol%	78	78:22	79
8	3	20 mol%	40 mol%	84	78:22	78
9	5	20 mol%	40 mol%	92	76:24	76

[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture . [c]The ee value were determined by HPLC using Daicel chiralpak IB column.

3.3.6 Solvent screening for catalyst 10e and co-catalyst 11j

Examined the effects of various solvents to this reaction with an optimized catalyst combination of **10e** (20 mol%) and **11j** (40 mol%) at room temperature (Table 7). As a result, aromatic solvents toluene, benzene, xylene performed better giving good to excellent chemical yields (85-92%) and stereoselectivities (dr 77:23, 77-82% ee ,entries 1-3). Also examined the non-polar like cyclohexane and hexane to affords the good chemical yield (75-86%, entries 4-5), satisfactory stereoselectivities (dr 51:49-67:33, 64-74% ee), Next tried with etherate solvent diethyl ether and diisopropylether to giving adequate yields and stereoselectivities (62-82%, dr 55:45, 71-75% ee). Furthermore, tried with polar aprotic and chlorinated solvent tetrahydrofuran, dichloromethane, chloroform and dichloroethane to furnish chemical yields and stereoselectivities (entries 9-11, 74-82%, dr 61:39-65:35, 78-70% ee). In addition that tried with polar solvent acetonitrile and methanol to giving less chemical yield (25-30%, entries 12,13) and satisfactory stereoselectivities(dr 53:47, 67-79% ee). Finally, examined the neat condition to affords the good chemical yield (82%, entry 13) and satisfactory stereoselectivity (dr 63:37, 73% ee). Particularly, toluene was found to be effective in this reaction (entry 1) for affording highly enantioselectivity. From these results, it was revealed that the catalyst combination of catalyst **10e** having TMS protection and Bn substituent at β-position (20 mol %) and simple chiral *N*-Boc-L-proline **11j** (40 mol %) in toluene at room temperature for 48 h was found as best reaction condition to obtain chiral DA adduct **8a** (entry 1).

Table 7. Solvent screening for catalyst **10e** and co-catalyst **11j**



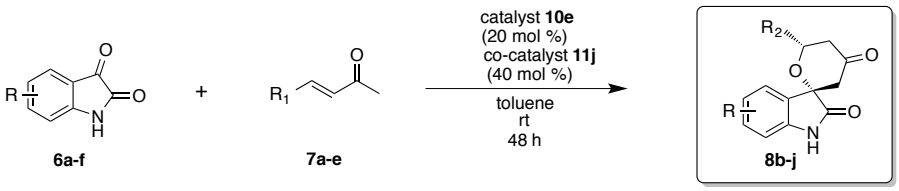
entry	solvent	yield (%)[a]	dr[b]	ee (%)[c]
1	toluene	85	77:23	82
2	benzene	92	77:23	77
3	Xylene	92	77:23	79
4	cyclohexane	86	51:49	74
5	hexane	75	67:33	64
6	Et_2O	62	67:33	75
7	iPr_2O	82	55:46	71
8	THF	35	70:30	74
9	CH_2Cl_2	82	61:39	78
10	$CHCl_3$	86	61:39	80
11	$C_2H_4Cl_2$	74	65:35	80
12	CH_3CN	30	53:47	79
13	MeOH	25	79:21	67
14	neat	82	63:37	73

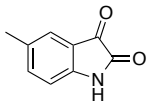
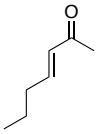
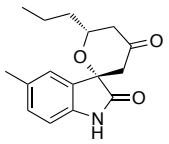
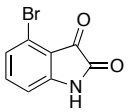
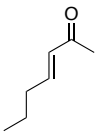
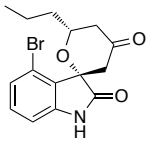
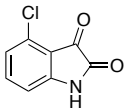
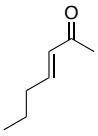
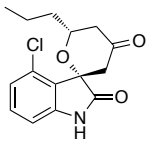
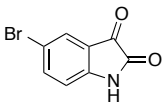
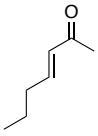
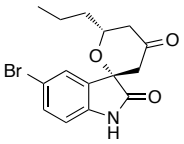
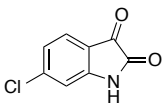
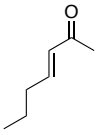
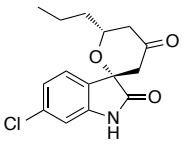
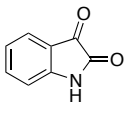
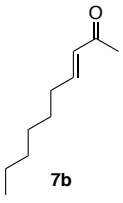
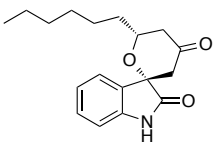
[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture. [c]The ee value were determined by HPLC using Daicel chiralpak IB column.

3.3.7 Substrate scope for asymmetric hetero Diels-Alder reaction using 6b-f and 7b-e.

After optimizing the reaction conditions, examined the generality of the developed superior two catalysts component system of **10e** and **11j** in the reactions of different isatins **6b-f** with enones **7a-d** (Table 8). This component system also showed catalytic activity in the reactions and afforded the corresponding chiral spirooxindole-tetrahydropyranones **8b–i** in moderate to good chemical yields and stereoselectivities. However, the reactions of **6a** with enones **7e** having bulky phenyl group hardly proceeded in this reaction condition to afford the corresponding adducts **8j** respectively.

Table 8. Substrates scope for asymmetric hetero Diels-Alder reaction



entry	6b-f R	7a-e R_1	8b-i	yield (%)[a]	dr[b]	ee (%)[c]
1	 **6b**	 **7a**	 **8b**	81	73:27	83
2	 **6c**	 **7a**	 **8c**	82	>99:1	40
3	 **6d**	 **7a**	 **8d**	57	77:23	43
4	 **6d**	 **7a**	 **8e**	92	77:23	77
5	 **6e**	 **7a**	 **8f**	90	63:37	84
6	 **6f**	 **7b**	 **8g**	76	78:22	78

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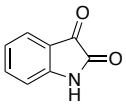
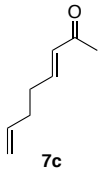
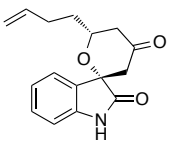
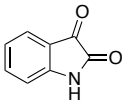
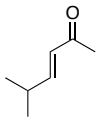
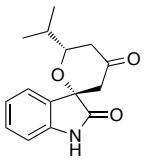
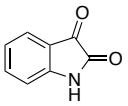
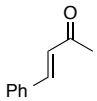
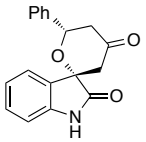
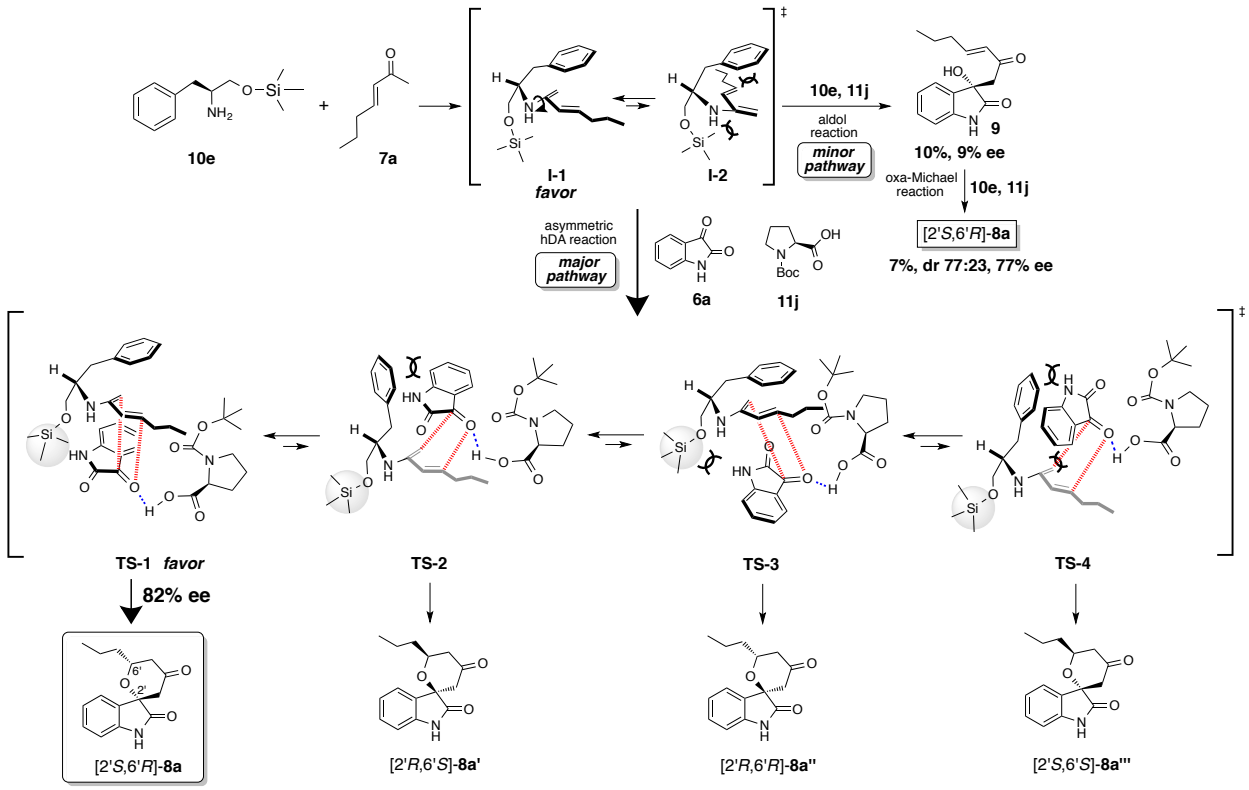
7	 **6a**	 **7c**	 **8h**	91	64:36	85
8	 **6a**	 **7d**	 **8i**	77	55:45	81
9	 **6a**	 **7e**	 **8j**	trace	-----	-----

[a]Isolated yields. [b]Diastereoselectivity (dr) was determined by ^{1}HNMR of the crude reaction mixture .[c]The ee value were determined by HPLC using Daicel chiralpak IB column.

3.3.8 Plausible reaction mechanism for asymmetric hetero Diels-Alder reaction of isatin with enone using catalyst 10e and co-catalyst 11j

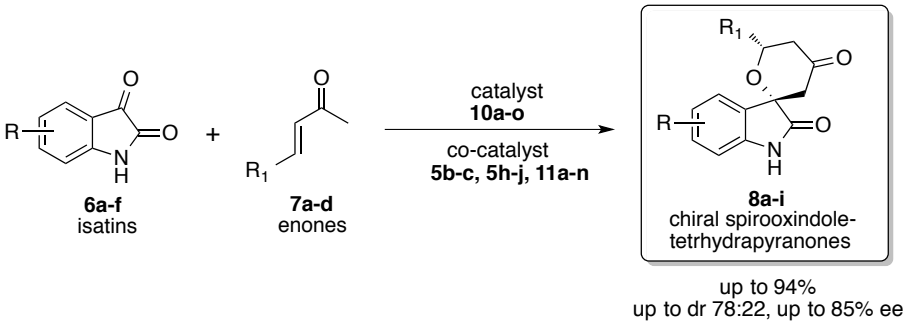
Based on the observed highly enantiopurity of the obtained hDA adduct [2*S*,6*R*]-**8a** (82% ee, Table 4), the model of the enantioselective reaction course was proposed. First, the reaction of β-amino silyl ether catalyst **10e** with enone **7a** forms the diene intermediate **I-1** that has less steric interaction of between amino silyl ether and substituted diene parts on generated diene **I-1** than that of intermediate **I-2**. Furthermore, isatin **6a** is activated by the two points of hydrogen bonding interactions with *N*-Boc proline co-catalyst **11j**. Then, the reaction might proceed through **TS-1** to afford **6a** that has a less steric interaction between **I-1** and dienophile **7a** than those of **TS-2**-**TS-4** to afford **8a'**-**8a'''** that have more steric interaction between **I-1** and **6a**. Thus, diene **I-1** might attack stereoselectively from less sterically hindered site of the incoming activated isatin dienophile **7a** to afford [2*S*,6*R*]- **8a** with excellent optically purity (82% ee). On the other hand, it is also expected that the formation of adduct **8a** *via* aldol reaction followed by oxa-Michael addition may be minor pathway based on the chemical yield and enantioselectivity of the obtained aldol product **9** and **8a** was quite low (**9**: 10%, 9% ee, **8a**: 7%, dr 77:23, 77% ee, Scheme 24).



Scheme 24. Plausible reaction course for asymmetric hetero Diels Alder reaction.

3.4 Summary

In summary author developed a simple two catalysts component system consisting of primary β-amino silyl ether **10e** as a catalyst and *N*-Boc-proline **11j** as a co-catalyst for the asymmetric hDA reaction of isatins with enones for the first time. This dual component system showed efficient catalytic activity to afford the chiral spirooxindole-tetrahydropyranones **8a-i** that are efficient synthetic intermediates for many biologically active compounds and drug discovery, in good chemical yields (up to 94%) and with enough stereoselectivities (up to dr 78: 22, 85% ee). In addition, the independent use of simple β-amino silyl ether catalyst **10e** also showed good catalytic activity for affording **8a** with an moderate enantioselectivity (59% ee), although chemical yield was low.



6a-f
isatins

7a-d
enones

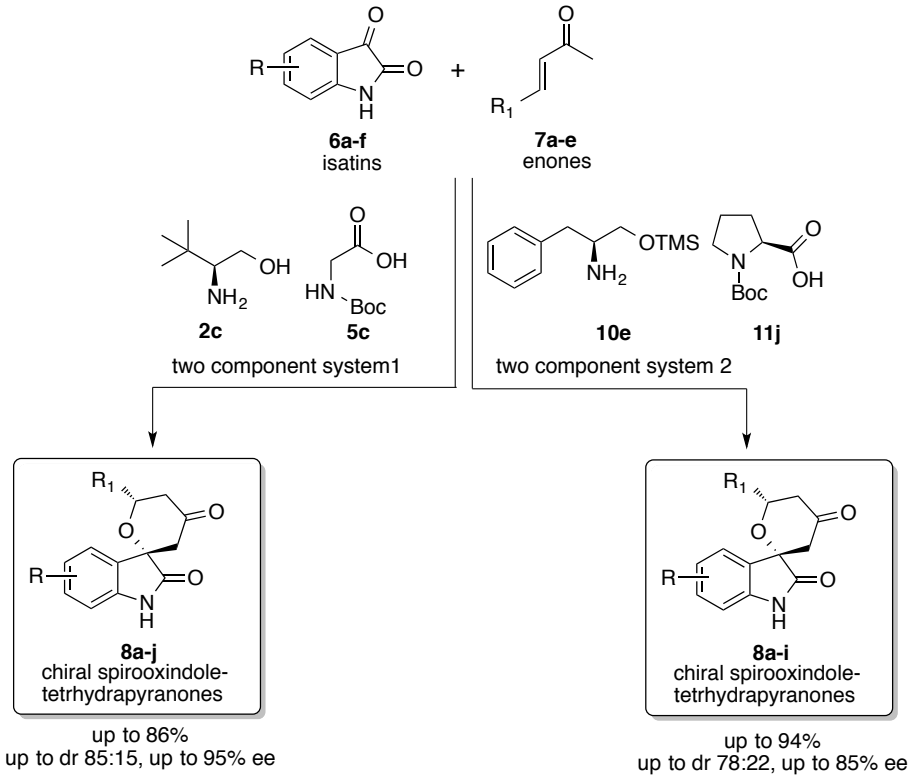
4. Conclusion

Many of the biologically active compounds are optically active. The way of biological systems of human beings only one form of enantiomers plays key role in treatment of particular diseases. Therefore, synthesis of optically active molecules is often more challenging task in the field of synthetic organic chemistry. The catalytic asymmetric synthesis is useful for the preparation of biologically active molecules including a drugs. 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 simple β-amino alcohol and simple β-amino silyl ether organocatalysts for asymmetric reactions. The simple amino alcohol organocatalysts were prepared by using with commercially available corresponding amino acids. Simple β-amino silyl ether organocatalysts were prepared from corresponding amino alcohol. The simple amino alcohol catalysts possess with multiple activation sites in the molecule such as, covalent site for making enamine formation and non-covalent site for making hydrogen bonding in single molecule. Simple β-amino silyl ether organocatalysts having covalent site for making enamine formation. By these properties of simple β-amino alcohol and amino silyl ether organocatalysts enables the formation of covalent and non-covalent intermediates with wide-variety of the substrates and allows for enantioselective reactions. The prepared amino alcohol and amino silyl ether organocatalysts successfully applied for asymmetric hetero Diels-Alder reaction (chapter 2 and 3).

In chapter 2, author discussed about the detailed application of simple β-amino alcohol organocatalyst for asymmetric hetero Diels-Alder reaction. The simple organocatalysts **2a-e, 4a-e** were prepared and examined in asymmetric hetero Diels-Alder reaction of isatins **6a-f** with enone **7**. Among the prepared simple amino alcohol organocatalysts, the catalysts **2c** has showed the best catalytic activity to afford the chiral spirooxindole tetrahydropyaranones in good chemical yields and stereoselectivities (up to 86%, up to dr 85:15, 95% ee). The obtained chiral spirooxindole tetrahydropyaranones **8a-j** are prominent synthetic intermediates for preparing many biologically active compounds.

In chapter 2, author discussed about the detailed application of simple amino silyl ether organocatalyst for asymmetric hetero Diels-Alder reaction. The simple organocatalysts **10a-o** were prepared and examined in asymmetric hetero Diels-Alder reaction of isatins **6a-f** with enone **7**. Among the prepared simple amino alcohol organocatalysts, the catalysts **10e** has showed the best catalytic activity to afford the chiral spirooxindole tetrahydropyaranones in excellent chemical yields and stereoselectivities (up to 94%, up to dr 78:22, 85% ee). The obtained chiral spirooxindole tetrahydropyaranones **8a-i** are prominent synthetic intermediates for preparing many biologically active compounds.

In conclusion, author developed simple β-amino alcohol and β-amino silyl ether organocatalysts. The prepared simple β-amino alcohol and β-amino silyl ether organocatalysts successfully applied in asymmetric hetero Diels-Alder reaction 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 pharmaceutical drugs in the field of synthetic organic chemistry.



5. Experimental section

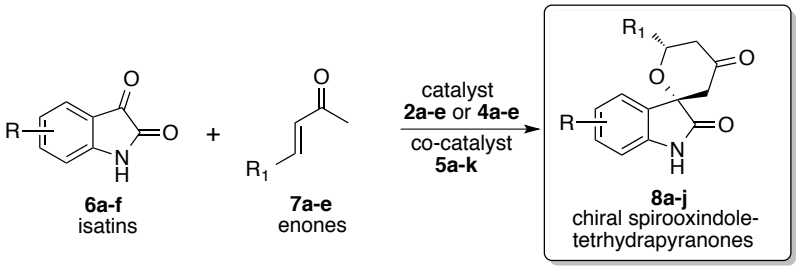
General information

All reagents and dry solvents were purchased from commercial vendors and used directly without further purification. All reactions were placed in dried sample vials inserted with magnetic beads. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates and the analytes were identified under UV light. Flash column chromatography was performed using silica gel pore size 60_N (40-100 μm). Melting points were recorded with a micro-melting point apparatus. IR spectra were recorded with a JASCO-4100 Fourier transform infrared spectrophotometer. ^1H and ^{13}C NMR spectroscopic data were recorded using a JEOL JNM-ECA500 instrument with tetramethyl silane as the internal standard. HPLC data were collected using the TOSOH instrument equipped with (UV-8020, DP-8020, and SD-8022) detectors using CHIRALPAK IB column. Optical rotations were recorded using a JASCO DIP-360 digital polarimeter. High-resolution mass spectrometry (HRMS) data were collected by electron impact (EI) modes using Hitachi RMG-GMG and JEOL JNX-DX303 sector instruments.

Chapter 2

Simple organocatalyst component system for asymmetric hetero Diels-Alder reaction of isatins with enones

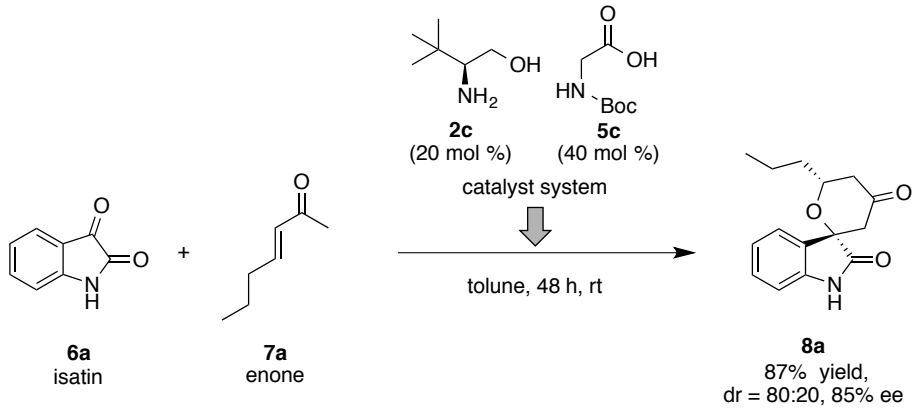
General procedure for the hetero Diels-Alder reaction of isatins (6a-f) with enones (7a-e)



To a solution of the corresponding isatins **6a-f** (0.2 mmol, 1 eq) and enones **7a-d** (0.8 mmol, 4 eq.) in anhydrous toluene (0.3 mL) were added catalysts **2a-e, 4a-e** (0.04 mmol, 20 mol%) and co-catalysts **5a-k** (0.08 mmol, 40 mol%) at room temperature and the mixture were stirred at that temperature for 48 h. The mixture was purified by flash column chromatography (SiO_2, hexane:ethyl acetate= 7:3) to afford the corresponding major hDA adducts **8a-i**. The

diastereoselectivity of the obtained hDA adducts were determined by the crude reaction mixture by ^{1}H-NMR. The enantiomeric excess of **8a-i** were determined by HPLC (CHIRALPAK-IB, hexane/*i*-PrOH = 90:10, 70:30 and 0.6ml/min, 1.0ml/min, λ = 245 nm).[19]

Large scale synthesis of 8a using hetero Diels-Alder reaction of isatins (6a) with enones (7a)

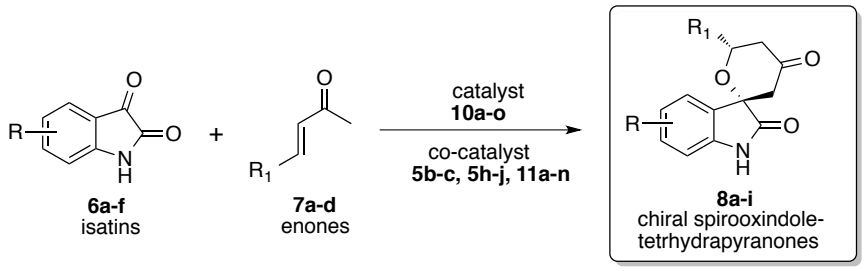


To a solution of the corresponding isatins **6a** (6.79 mmol, 1 eq) and enones **7a** (27.1 mmol, 4 eq) in anhydrous toluene (15 mL) were added catalysts **2c** and (1.35 mmol, 20 mol%) and co-catalysts **5c** (2.71 mmol, 40 mol%) at room temperature and the mixture were stirred at that temperature for 48 h. The mixture was purified by column chromatography (SiO_2, hexane:ethyl acetate= 7:3) to afford the corresponding major hDA adducts **8a** as a pale yellow amorphous solid (1.52g, 87% yield, dr 80:20 and major diastereomer 85% ee). The diastereoselectivity of the obtained hDA adducts were determined by the crude reaction mixture by ^{1}H NMR. The enantiomeric excess of **8a** were determined by HPLC (CHIRALPAK-IB, hexane/*i*-PrOH = 90:10 1.0mL /min, λ = 245 nm).[19]

Chapter 3

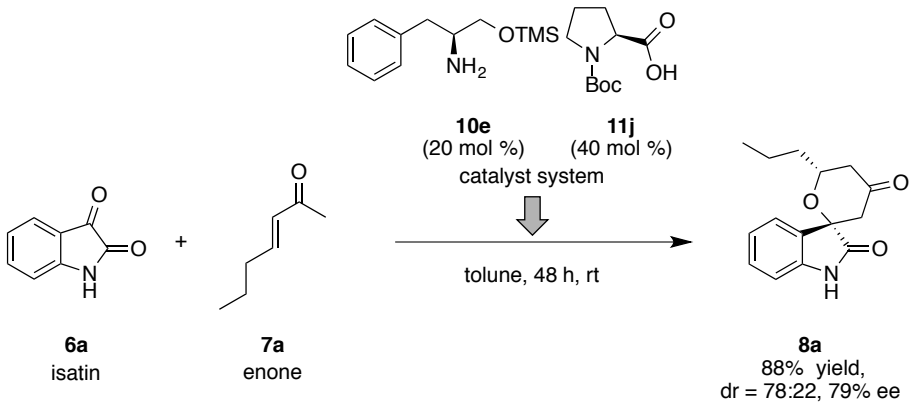
Simple amino silyl ether organocatalyst for asymmetric hetero Diels-Alder reaction of isatins with enones

General procedure for the hetero Diels-Alder reaction of isatins (6a-f) with enones (7a-d)



To a solution of the corresponding isatins **6a-f** (0.2 mmol, 1 eq) and enones **7a-d** (0.8 mmol, 4 eq) in anhydrous toluene (0.3 mL) were added catalysts **10a-o** (0.04 mmol, 20 mol%) and co-catalysts **5b-c**, **5h-j**, **11a-n** (0.08 mmol, 40 mol%) at room temperature and the mixture were stirred at that temperature for 48 h. The mixture was purified by flash column chromatography (SiO_2, hexane:ethyl acetate= 7:3) to afford the corresponding major hDA adducts **8a-i**. The diastereoselectivity of the obtained hDA adducts were determined by the crude reaction mixture by ^{1}H-NMR. The enantiomeric excess of **8a-i** were determined by HPLC (CHIRALPAK-IB, hexane/*i*-PrOH = 90:10, 95:5 and 0.6mL, 1.0ml/min, λ = 245 nm).[19]

Large scale synthesis of 8a using hetero Diels-Alder reaction of isatins (6a) with enones (7a)

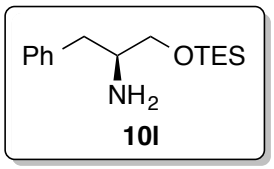


To a solution of the corresponding isatins **6a** (6.79 mmol, 1 eq) and enones **7a** (27.1 mmol, 4 eq) in anhydrous toluene (15 mL) were added catalysts **10e** and (1.35 mmol, 20 mol%) and co-catalysts **11j** (2.71 mmol, 40 mol%) at room temperature and the mixture were stirred at that temperature for 48 h. The mixture was diluted with ethyl acetate and washed with water. Separate the organic layer dried with sodium sulphate. The mixture was purified by column chromatography (SiO_2, hexane:ethyl acetate= 7:3) to afford the corresponding major hDA adducts **8a** as a pale yellow amorphous solid (1.52g, 87% yield, dr 78:22 and major diastereomer 79% ee). The diastereoselectivity of the obtained HDA adducts were determined by the crude reaction mixture by ^{1}H NMR. The enantiomeric excess of **8a** were determined by HPLC (CHIRALPAK-IB, hexane/*i*-PrOH = 90:10 and 0.6ml/min, λ = 254 nm).[19]

General procedure for synthesis of catalysts 10a-o:

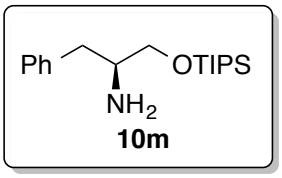
To a solution of the corresponding amino alcohol **2a-e, 4a-e** (6.79 mmol, 1 eq) in dry CH_2Cl_2 and cooled in 0 ºC or -30 ºC were added corresponding trialkyl silyl chloride or trifluoromethane sulfonate (1.2 eq) and triethylamine (1.2 eq) for 10 mins under argon atmosphere. The solution was stirred for 24 h at room temperature. Then reaction mixture was diluted with water and extracted with dichloromethane. Separate the organic layer dried with sodium sulphate. The mixture was purified by flash column chromatography (SiO_2, hexane:ethyl acetate= 7:3 and MeOH/CH_2Cl_2, 9:1) to give the corresponding amino silyl ether catalysts **10a-o**.

(S)-1-phenyl-3-((triethylsilyl)oxy)propane-2-amine (10l): light yellow oil. 89% yield. $[\alpha]_D^{24}$ = +6.24 (*c* = 0.48, DCM solvent). IR (neat): cm^{-1} = 3027, 2875, 1602, 1495, 1097, 794, 699.^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.25-7.30 (m, 2H), 7.20 (td, J = 5.0, 2.1 Hz, 3H), 4.11 (s, 2H), 3.62 (q, J = 4.6 Hz, 1H), 3.49 (dd, J = 9.7, 6.3 Hz, 1H), 3.21 (qd, J = 6.8, 4.3 Hz, 1H), 2.81 (dq, J = 46.5, 6.9 Hz, 2H), 0.87-0.99 (m, 9H), 0.56-0.63 (m, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.31, 129.37, 128.61, 126.56, 77.41, 77.17, 76.91, 65.35, 54.62, 38.90, 6.90, 4.42. MS (FAB): m/z : 265 $[M]^+$, HRMS (FAB): calcd for $C_{15}H_{27}NOSi$ m/z 265.47; found: 265.69.



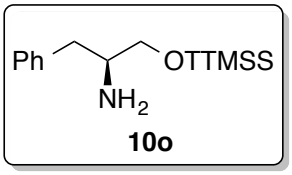
10l

(S)-1-phenyl-3-((triisopropylsilyl)oxy)propane-2-amine (10m): light yellow oil. 90% yield.



$[\alpha]_D^{24}$ = +1.84 (*c* = 0.55, DCM solvent). IR (neat): cm^{-1} = 2941, 2864, 1558, 1105, 782, 700. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.27-7.30 (m, 2H), 7.19-7.22 (m, 3H), 3.67 (q, J = 4.6 Hz, 1H), 3.56 (dd, J = 10.0, 6.0 Hz, 1H), 3.31 (s, 2H), 3.12-3.18 (m, 1H), 2.83 (q, J = 6.7 Hz, 1H), 2.66 (dd, J = 13.5, 7.7 Hz, 1H), 1.04-1.06 (m, 21H).^{13}C-NMR (125 MHz,$CDCl_3$) δ 138.26, 129.38, 128.68, 126.66, 77.39, 77.15, 76.89, 66.24, 54.89, 38.94, 18.06, 11.96. MS (FAB): m/z : 307 $[M]^+$, HRMS (FAB): calcd. for $C_{18}H_{33}NOSi$ m/z 307.55; found: 307.64.

(S)-1-((1,1,1,1,3,3,3-heptamethyl-2-(trimethylsilyl)-1-trissilan-2-yl)oxy)3-phenylpropane-2-amine- propane-2-amine (10o): Colourless liquid. 88% yield. $[\alpha]_D^{24}$ = -17.24 (*c* = 0.58, DCM solvent). IR (neat): cm^{-1} = 2947, 2892,1558,1540, 1070, 769, 699. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.27-7.29 (m, 2H), 7.17-7.20 (m, 3H), 3.37 (q, J = 4.6 Hz, 1H), 3.31 (dd, J = 9.5, 6.6 Hz, 1H), 2.99-3.04 (m, 1H), 2.72 (q, J = 6.3 Hz, 1H), 2.54 (q, J = 6.9 Hz, 1H), 1.45 (d, J = 22.3 Hz, 2H), 0.17 (s, 27H).^{13}C-NMR (125 MHz, $CDCl_3$) δ 139.16, 129.38, 128.53, 126.31, 77.39, 77.15, 76.89, 71.98, 54.82, 40.47, 0.39. MS (FAB): m/z : 397 $[M]^+$, HRMS (FAB): calcd. for $C_{18}H_{39}NOSi_4$ m/z 397.86; found: 397.91.



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