不斉マイケル付加反応に用いる糖型γ-アミノ有機分子触媒の開発

DEVELOPMENT OF SUGAR BASED γ-AMINO ORGANOCATALYSTS FOR ASYMMETRIC MICHAEL ADDITION

Thesis
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DOCTOR OF PHILOSOPHY
by

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TITLE:

Development of New Sugar Based γ-Amino Organocatalyst for Asymmetric Michael addition

（不斉 Michael 付加反応に用いる新規糖型γ−アミノアルコール有機分子触媒の開発）

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ABSTRACT

A lot of biologically active compounds, including drugs, are optically active and often only one of the enantiomer shows a high biologically activity. Therefore, it is important to develop a 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.

Author focused γ-amino alcohol as an organocatalyst. In contrast to β-amino alcohol as an organocatalyst, the utility of γ-amino alcohol was not much explored even though it is expected to have a high potential functionality as an organocatalyst similar to β-amino alcohol. As a compound, author selected a sugar based γ-amino alcohol and its derivative fixing 1,2-*O*-isopropylidene-D-xylofuranose structure as a backbone. This catalyst is expected to work as multipoint recognition catalyst having basic site, covalent and non-covalent hydrogen bonding sites in the single molecule. Proposed γ-amino alcohol contains an amino group acting as basic or covalent site and hydroxyl group acting as a non-covalent hydrogen bonding site and also sugar backbone acting as steric influence site for controlling stereoselective reaction course. Furthermore, this γ-amino alcohol can be easily prepared from commercially available D-xylose by few steps. As a reaction for providing the utility of the γ-amino alcohol, asymmetric Michael addition of β-keto esters with nitroolefins was selected. The Michael adducts from this reaction contain both quaternary and tertiary chiral carbon centers in the structure and the adducts work as an important synthetic precursor of the synthesis of many biologically active compounds including pharmaceuticals such as platencin (antibiotic).

Author tried this reaction of β-keto esters with nitroolefins using sugar based γ-amino alcohol and γ-amino silyl ether organocatalysts at first time. As a result, the both catalysts were showed good catalytic activity in this reaction and the desired chiral Michael adducts was obtained in good chemical yields, diastereoselectivities and enantioselectivities.

In this study, author revealed that the new explored sugar type γ-amino organocatalyst showed satisfactory catalytic activities in the Michael addition. It is expected that these results should be able to greatly contribute the development of new drug and its related compounds.

Contents

Chapter 1

Chapter 2

Chapter 3

Sugar based γ-amino silyl ether organocatalysts for asymmetric Michael addition of β-keto ester and nitroolefin

Chapter 1

Introduction

1. Introduction

Stereo-controlled organic molecules construction is highly challenging and most desirable technique for vast biologically active molecules creations. Development of effective catalytic system in stochiometric quantity requires to regulate the stereoselectivity of products such as metals, bio-active molecules, organic molecules.[1] Among various asymmetric catalysis, organocatalysis is leading as intensively appealing and essential tools in synthetic organic chemistry for chiral induction of biologically active molecules. Upon considering the complementary for other versions of asymmetric catalysis, this field existing as better alternative due to some valid reasons like, avoiding toxic metals or usage of costly enzyme catalysts to perform asymmetric organic reactions. In recent decades, enormous progress have been devoted on development of efficient small chiral molecule to control the stereoselectivity of substrates attracts much in biological as well as medicinal synthesis for few reasons such as, most of compounds were easy to handle, stability for long time usage, availability of both enantiomers and cost-efficiency. Asymmetric synthesis widely providing easy access for worthwhile synthesis of chiral molecules but designing synthetic strategies of small and effective organocatalysts are interesting though, frequently more difficult task.

PhD objectives of an author is to develop simple xylofuranose-based γ-amino organocatalysts and their use for asymmetric Michael reaction of β-keto esters and nitroolefins. The development of new γ-amino organocatalysts and their applications in this thesis were chiefly focused on three sections (i) The development of new xylofuranose-based γ-amino organocatalysts, (ii) xylofuranose-based γ-amino alcohol organocatalysts for asymmetric Michael addition, (iii) The development of new xylofuranose-based γ-amino silyl ether organocatalysts for asymmetric Michael addition. In the following sections, detailed findings and applications of these organocatalysts towards asymmetric Michael addition were discussed.

1.1 Chirality

Compound possessing chiral centers found often in biologically active compounds and natural products. In 1893, British mathematical physicist called Lord Kelvin who coined the term called "*Chirality*".[2] The field of asymmetric synthesis progressing totally based on that terminology which could be defined as follows, "organic molecule with same attachments and exhibiting non-super imposable behavior on its mirror image". One of the classical examples to clarify the chirality term is our human both left and right hands which are mirror images of each other and never be impose with each other across any axis (Figure 1).

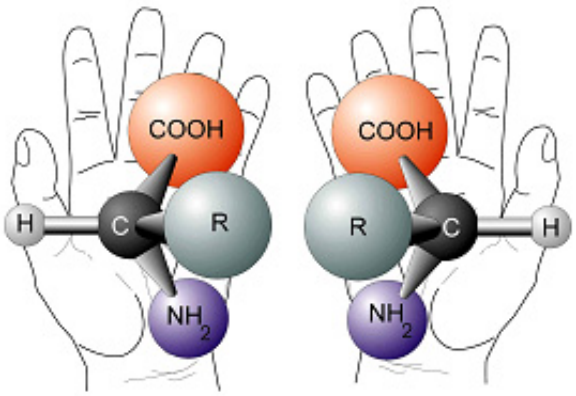


Figure 1. Example for chirality.

Amino acids are ubiquitous chiral molecules existing in both commercial and natural sources in two isomeric form which are frequently for organic synthetic applications. For instance, alanine amino acid in both *R* and *S* isomers has given bellow (Figure 2).

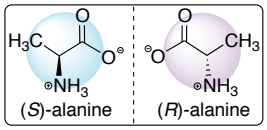
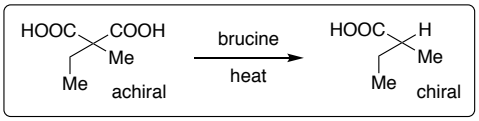


Figure 2. Two different enantiomers of alanine in zwitterionic form.

As Marckwald[3] (who found the first chiral compound) modernized definition for chiral compound synthesis "conversion of achiral compound into chiral by the use of small amounts of either chiral catalysts or reagents". Interestingly, the first report of selective decarboxylation of the

brucine salt of 2-ethyl-2-methyl-malonic acid witnessed asymmetric synthesis which could promote optically active compounds from achiral (Scheme 1).[4]



Scheme 1. Selective decarboxylation of 2-ethyl-2-methyl-malonic acid.

Optically active chiral centers are embedded in many bioactive compounds and pharmaceutical compounds administered to the human body. One enantiomer exists to be an active one of two enantiomers and another enantiomer displays no operation at all. In pharmaceutical and laboratory synthesis, therefore, synthesis of that one active enantiomer in gram and large-scale demands.

1.2 Asymmetric synthesis to catalysts

Asymmetric synthesis is one of the most essential and straightforward method in organic synthesis to develop molecules with chiral centers from achiral molecules.[5] Stereoisomers of products with imbalanced ratios were obtained during this course of asymmetric reaction by exploring catalysts. Numerous bio-active and natural compounds were not obtainable in both isomeric from nature and it requires to be synthesis from laboratory for small- and large-scale productions. Generally, each compound which are obtain with different stereochemistry as an outcome might possess distinctive biological applications. For instance, “Ibuprofen” preferred for non-steroidal anti-inflammatory and “Omeprazole” recommended for gastric acid-related disorders (Figure 3).[6]

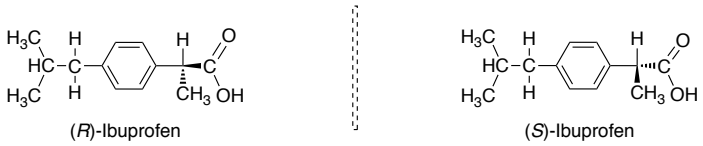


Figure 3. Stereoisomers of biologically active compound ibuprofen.

In the case of (*S*)-Ibuprofen, the drug has the ability to inhibit cyclooxygenase (COX), typically administered to the patients with pain, fever and inflammation, but another stereoisomer (R)-Ibuprofen expresses no action at all (Figure 4).

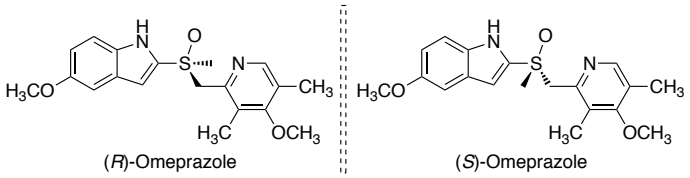


Figure 4. Stereoisomers of biologically active compound omeprazole.

Compound (*S*)-Omeprazole, on the other hand, currently a lead class proton pump inhibitor (PPN) drug to control the acid level in stomach. In the field of pharmaceutical, (*S*)-Omeprazole (esomeprazole) is preferred as a non-steroidal anti-inflammatory drug than (*R*)-omeprazole.

Based on this background, synthesis of those active compounds enantiomer in organic synthesis remains still as a challenging task.

1.3 Catalysis

A small chiral molecule that become involve in reaction and exponentially accelerate the rate of reaction to deliver the products in asymmetric organic transformation appeals predominantly on the scientific community. The catalysis field can broadly classify into three divisions such as, 1) Transition metal catalysis, 2) Enzyme catalysis, and 3) Organocatalysis.[7] In transition metal catalysis, catalysts incorporated with various metal atoms used for effective promotion of chiral products, but it has several disadvantages including, toxic metal usage, not cost-effective and highly sensitive. To avoid metal usage, biological compounds have demonstrated which also showed better performance on product formation in asymmetric synthesis. Moreover, they also possess some disadvantages such as, high sensitivity, vast compound structure and tedious synthesis process. From this background, to rectify these disadvantages organic molecules alone assisted chiral compounds were introduced in asymmetric synthesis for chiral induction.

1.4 Asymmetric synthesis to organocatalysts

In asymmetric synthesis, organocatalysis has become highly dynamic and powerful paradigm for chirality induction rather than other catalysis methods such as, transition metal catalysis and bio-catalysis.[8] Organocatalysis has owing some significant reasons including, the stability to withstand for long-term storage, vanishing the role of transition metals, easy to synthesis, and providing cost-efficacy research. Due to this reason, numerous chiral organic compounds have been developed and demonstrated in asymmetric reactions as an organocatalysts. Still, simple and effective organocatalysts development remains unsuccessful and highly demanded in asymmetric synthesis.

There are numerous valid reasons behind this expansion such as, cost-effective testing, the elevation of catalysts not requires tedious steps, it vanish toxic metal involvement, resistance to moisture and air stability, commercial accessibility of ingredients, environmentally benign, uncomplicated handling of catalysts and ambient reaction settings. In interpretation of these advantages, researchers have documented enormous reliable catalysts for chiral induction of bio-active molecule synthesis. For example, various chiral organocatalysts which delivers excellent results of stereochemical products that are shown in diagram below (Figure 5).[9]

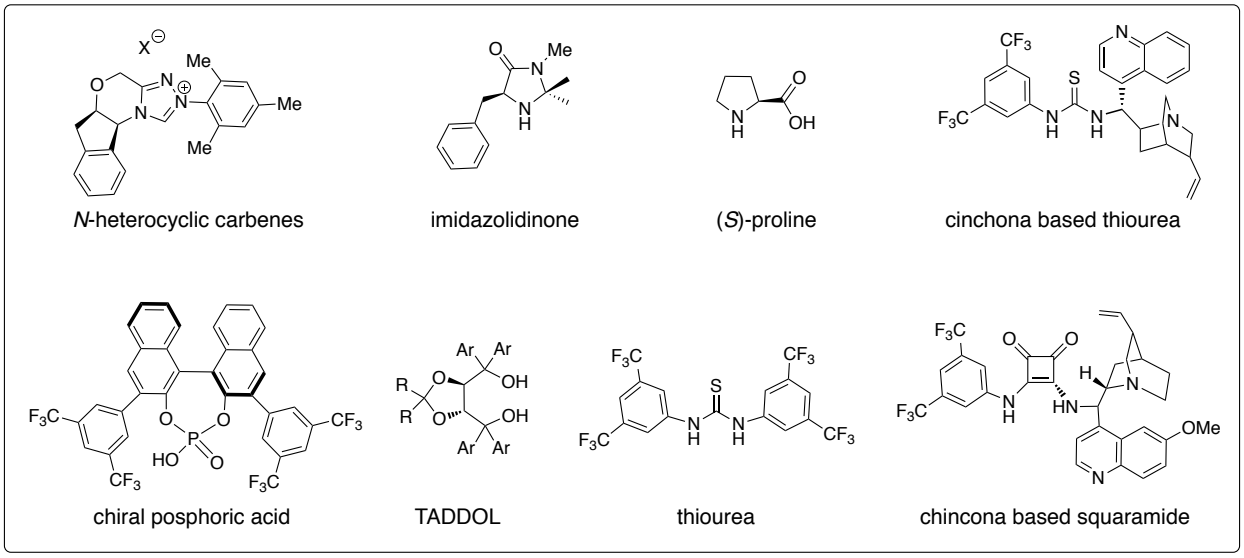


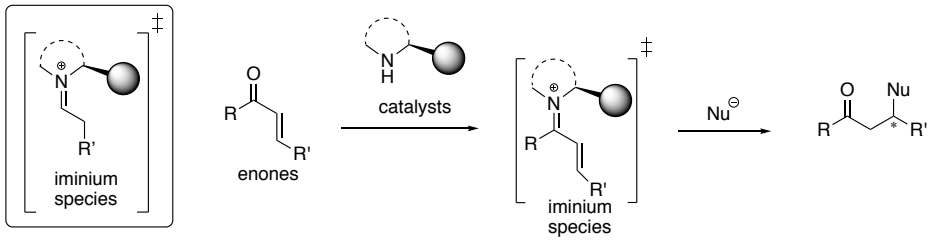
Figure 5. Various chiral organocatalysts in asymmetric synthesis.

1.5 Activation modes in organocatalysis

The field of amine-based organocatalysts attains satisfactory expansion and widely classified into two divisions such as, covalent catalysts and non-covalent catalysts. Generally, they classified on the basis of intermediate formation by catalysts and substrate.

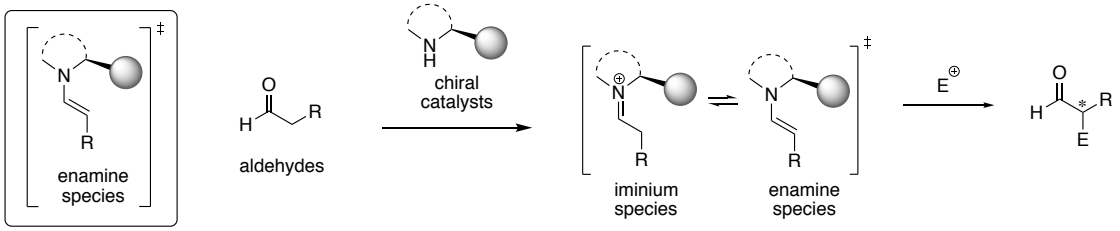
1.5.1 Covalent mode of activation

Secondary amine catalysts mostly involve in distinctive mechanism such as, iminium and enamine intermediate formations based on substrates which is reacting with catalysts. In iminium catalysis, condensation of catalysts with substructures containing electrophilic carbonyl carbons that make iminium stable intermediate cation during the course of reaction. Subsequently, an effective nucleophile attack on the intermediate contributes to the formation of products with chiral centers (Scheme 2).



Scheme 2. iminium mode of activation

In the case of enamine, after iminium cation formation, electrophilic deficient carbonyl carbon involves in condensation with the amino group of catalysts to generates enamine species. Followed by, nucleophilic attacks on enamine species contribute to the formation of chiral products. In both cases, catalysts are directly attached to substrates, catalysts often have high-level chiral dynamic response (Scheme 3).



Scheme 3. Enamine mode of activation

In recent decades, enormous progress on the development of various effective covalent organocatalysts which promotes chiral products with excellent optical purity in asymmetric organic reactions. These are the examples of covalent organocatalysts which were reported by various research groups (Figure 6).[10]

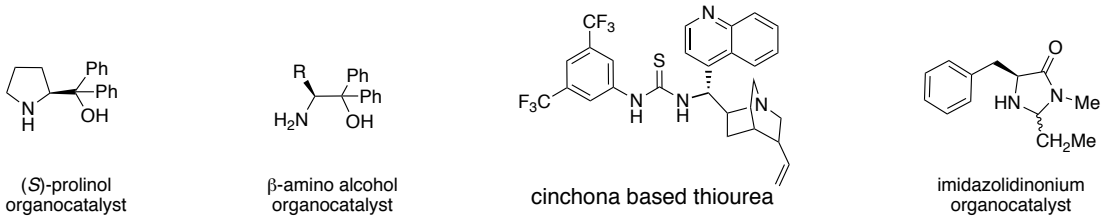
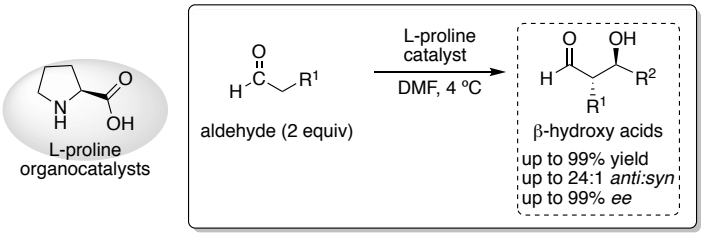


Figure 6. Examples for covalent organocatalysts.

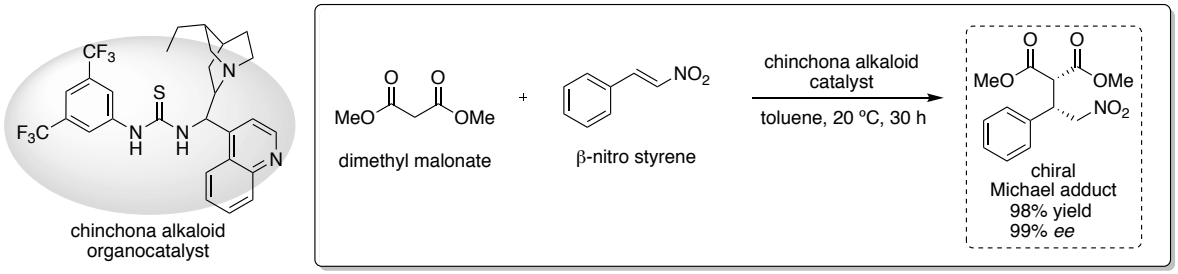
In 2005, W. C. McMillan and co-workers have reported L-proline as an organocatalysts to asymmetric aldol addition of aldehydes in DMF solvent afforded chiral β-hydroxy acids in excellent chemical yield, diastereoselectivity and enantioselectivity (99% yield, 24:1 *anti:syn*, 99% *ee*) (Scheme 4).[11]



Scheme 4. Proline catalyzed asymmetric aldol reaction.

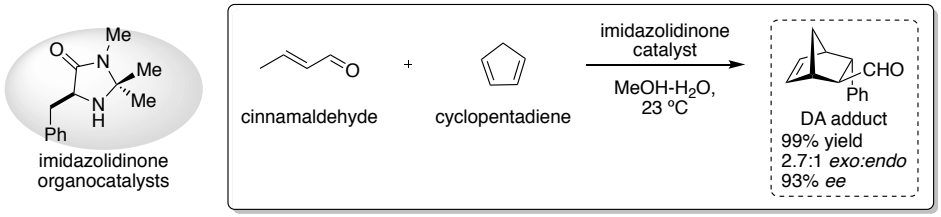
In 2005, Connon and co-workers reported chinchona alkaloid catalyzed asymmetric Michael addition of dimethyl malonate to nitroalkenes in presence of toluene solvent afforded chiral

Michael adduct in excellent chemical yield and enantioselectivity (98% yield, 99% *ee*) (Scheme 5).[12]



Scheme 5. Chinchona alkaloid catalyzed asymmetric Michael reaction.

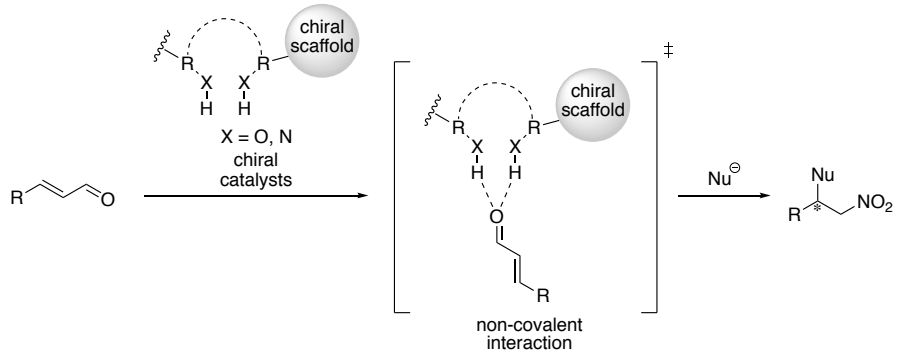
In 2000, McMillan and co-workers have reported that first L-proline catalyzed highly enantioselective organocatalytic Diels-Alder reaction. The chiral DA adducts were obtained in excellent chemical yield, diastereoselectivity and enantioselectivity (99% yield, 2.7:1 *anti:syn*, 93% *ee*) (Scheme 6).[13]



Scheme 6. Imidazolidinone catalyzed asymmetric Diels-Alder reaction.

1.5.2 Non-covalent mode of activation

On another class, non-covalent organocatalysts has also attained almost similar attention as like covalent catalysts on its catalytic efficiency towards chirality enhancement via forming electronic repulsions or non-covalent interactions between substrates and catalysts in asymmetric organic reactions. Generally, thiourea and squaramide based organocatalysts are often reported and delivers chiral products with considerably excellent results on asymmetric reactions.[14] During the reaction course, heteroatoms of reactants are interacted with hydrogen atom of catalysts through hydrogen bonding as a relatively shorter distance to lead the product formation. For instance, the non-covalent interaction of catalysts with substrates in asymmetric reaction has illustrated in general reaction bellow (Scheme 7).



Scheme 7. Hydrogen bonding non-covalent interaction of squaramide catalysts.

As an example of non-covalent hydrogen bonding catalysts, chiral phosphoric acid, Rawal's (TADDOL), Schreiner's thiourea, and cinchona based squaramide catalysts are listed below (Figure 7).[15]

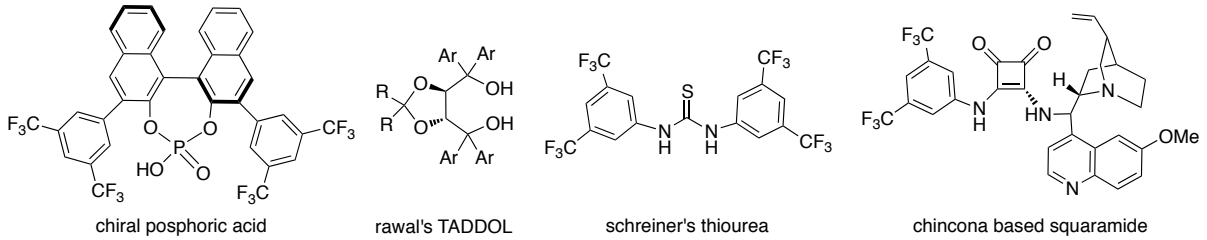
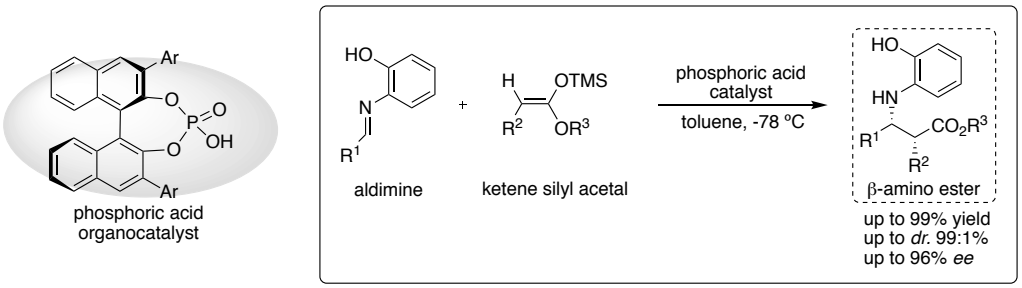


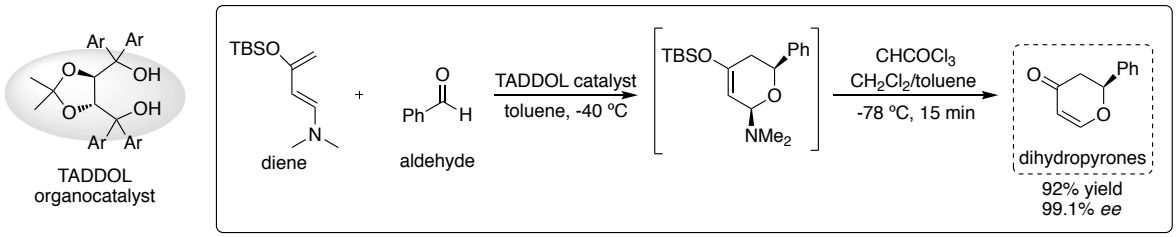
Figure 7. Various non-covalent organocatalysts utilized for asymmetric reaction.

Akiyama and co-workers reported phosphoric acid catalyzed asymmetric Mannich reaction of aldimine and ketene silyl acetal which promotes chiral β-amino esters in excellent chemical yield, diastereoselectivity and enantioselectivity (99% yield, dr. 99:1%, 96% ee) (Scheme 8).[16]



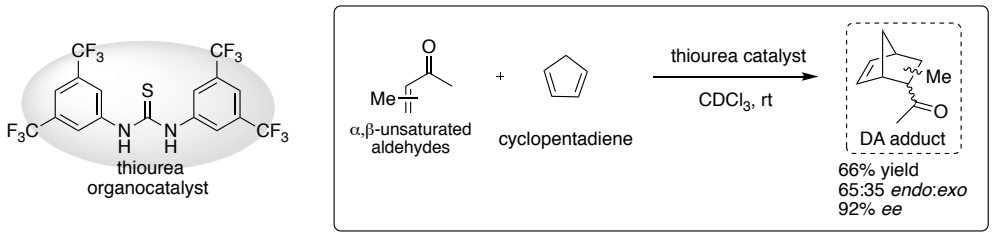
Scheme 8. Phosphoric acid catalyzed asymmetric reaction.

In 2003, Rawal and co-workers have reported the first example of chiral-diol as an organocatalysts that promotes asymmetric hetero Diels-Alder reaction of diene with aldehydes in presence of toluene solvent which effectively produce dihydropyrones in excellent chemical yield and enantioselectivity (92% yield, 99.1% *ee*) (Scheme 9).[17]



Scheme 9. TADDOL catalyzed asymmetric hetero Diels-Alder reaction.

In 2003, Schreiner and co-workers reported thiourea catalyzed Diels-Alder reactions of cyclopentadiene with several α,β-unsaturated carbonyl compounds that catalysts delivers chiral DA adduct in moderate chemical yield, diastereoselectivity and excellent enantioselectivity (66% yield, 65:35% *endo:exo*, 92% *ee*) (Scheme 10).[18]



Scheme 10. Thiourea catalyzed asymmetric hetero Diels-Alder reaction.

1.6 β-Amino alcohol organocatalysts in asymmetric synthesis

Organocatalysts associated with covalent and non-covalent active sites to promote asymmetric organic transformations attracts majority in scientific community. As an example, amino alcohol-based compounds are serving as an excellent bifunctional organocatalysts to deliver the valuable chiral synthons in asymmetric synthesis. Particularly, organocatalysts of β-amino alcohol has been reported often which delivers chiral products in various asymmetric reactions such as, hetero Diels alder, Michael addition, Aldol reaction. Advantages of those catalysts are, easy way of synthesis, stability for long term, atom economy and low catalysts loading. Further, it has amino group which can act as covalent site and hydroxy group that can perform as non-covalent site. Due to these reasons, various simple and effective amino alcohol containing catalysts from diverse starting materials have been developed and studied its catalytic activity in asymmetric organic reactions (Figure 8).[19]

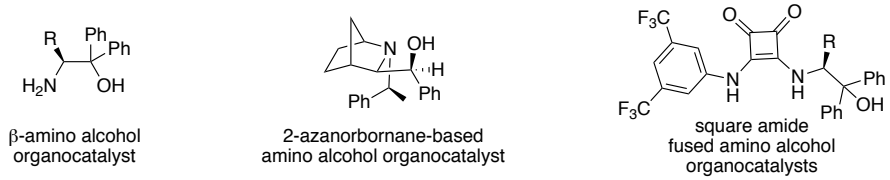
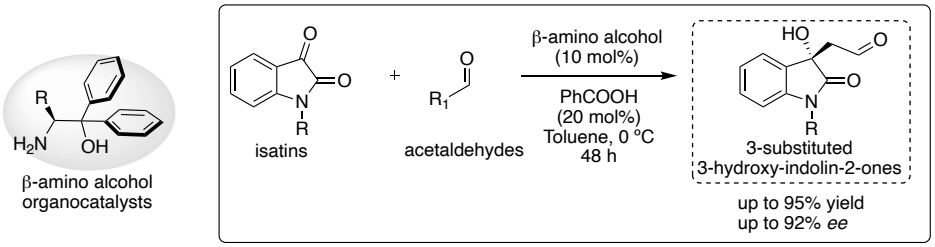


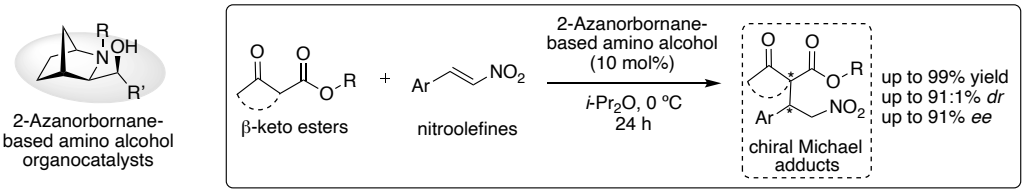
Figure 8. Various examples on β-amino alcohol organocatalysts.

β-amino alcohol organocatalysts developed by Nakano and group workers using commercial amino acids as a synthetic precursor which showed catalytic activity in asymmetric aldol reaction of isatins and acetaldehydes. Catalysts delivers the chiral 3-substituted-3-hydroxy-indolin-2-ones in excellent chemical yield and enantiomeric excess (Scheme 11).[20]



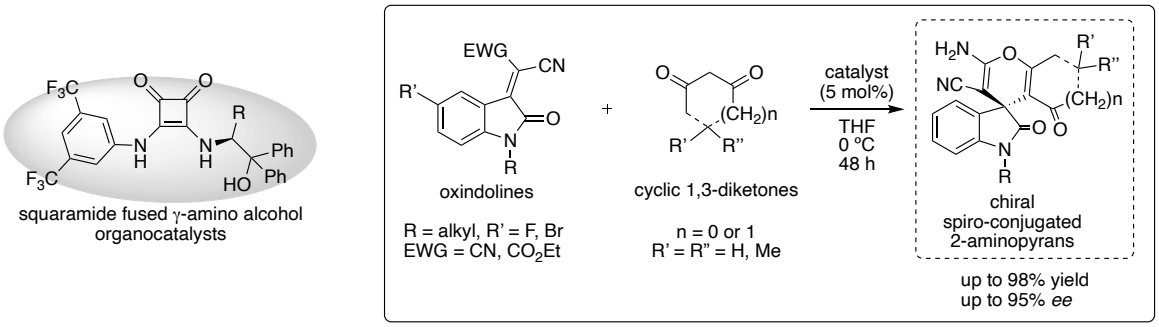
Scheme 11. β-Amino alcohol organocatalysts for asymmetric aldol reaction.

Followed by, β-amino alcohol incorporated with 2-azanorbornane backbone organocatalysts also developed by the same research group which showed same excellent results in both chemical yield and stereoselectivity (Scheme 12).[21]



Scheme 12. 2-Azanorbornane based amino alcohol organocatalysts for asymmetric Michael reaction.

Later, they introduced β-amino alcohol and squaramide moiety incorporated compound and utilized as an organocatalysts in asymmetric Michael addition followed by cyclization reaction of oxindoles and 1,3-diketones. Catalysts showed excellent activity on that reaction and delivers chiral spiro conjugated 2-aminopyrans in excellent chemical yield and enantioselectivity (Scheme 13).[22]

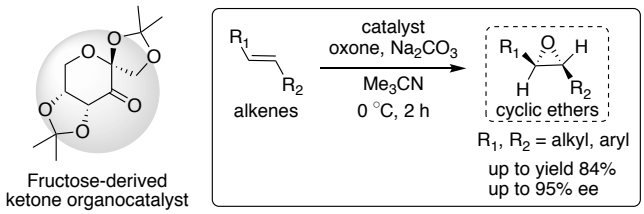


Scheme 13. squaramide fused amino alcohol organocatalysts for asymmetric domino Michael addition/cyclization.

1.7 Sugar-based organocatalysts in asymmetric synthesis

Long years ago, development of sugar moiety-based chiral auxiliaries and their utilization in asymmetric reaction as a catalyst has been considerably gaining attention over research community. Sugar moieties have contained several contagious chiral centers which centers are fine tunable with minimum efforts and multiple hydroxy functional groups might enable the easy access for structural modification. Moreover, it has several advantages including, sugar moieties are cheap chiral sources, stable towards air and moisture, and obtainable from both, commercially and naturally sources. Consequently, numerous sugar moiety-based various chiral amines associated catalysts has been developed and utilized for asymmetric reactions.

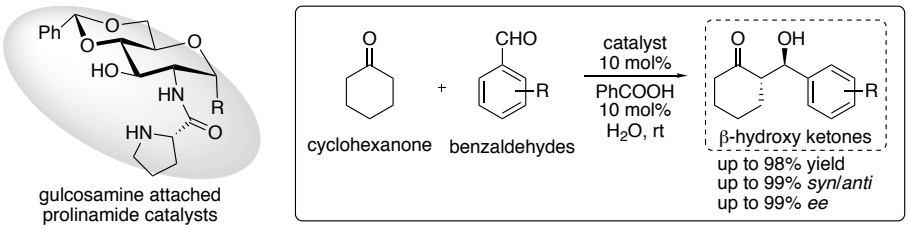
Shi and research crew reported first progress on sugar-derived organocatalysts for asymmetric epoxidation of alkenes which delivers corresponding chiral products in excellent results (Scheme 14).[23]



Scheme 14. Fructose-derived ketone organocatalysts for asymmetric epoxidation.

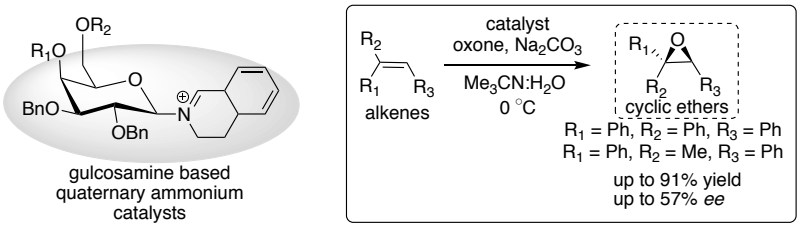
1.8 Progress on sugar based organocatalysts in asymmetric reactions

Zhang and co-workers develop glucose-derived prolinamide organocatalysts and examined in asymmetric aldol reaction of aromatic aldehydes and cyclic and acyclic ketones. Catalysts showed excellent catalytic activity and delivers chiral adducts in excellent chemical yield, diastereoselectivity and enantioselectivity (Scheme 15).[24]



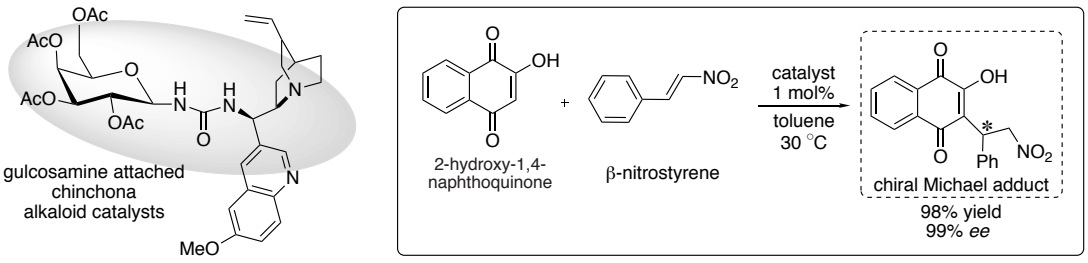
Scheme 15. Glucose-derived prolinamide organocatalysts for asymmetric aldol addition.

Page and research workers developed glucose-derived iminium salt organocatalysts for asymmetric epoxidation of unfunctionalized alkenes to afford chiral cyclic ethers with excellent chemical yield and moderate enantioselectivity (Scheme 16).[25]



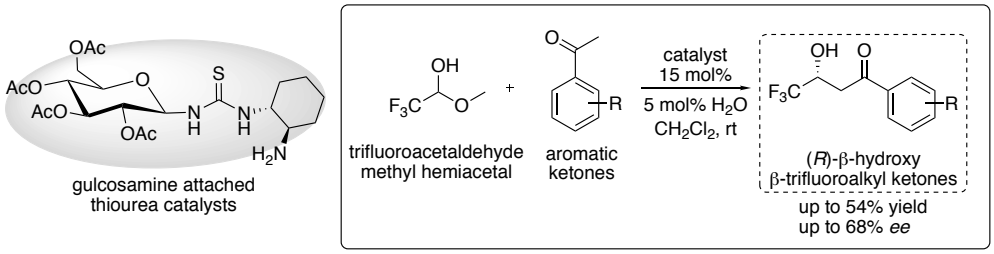
Scheme 16. Glucose-based quaternary ammonium organocatalysts for asymmetric epoxidation.

Followed by, Reddy and co-workers reported asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone and nitroolefins which affords chiral Michael adducts in excellent chemical yield and enantioselectivity (Scheme 17).[26]



Scheme 17. Glucose attached thiourea organocatalysts for asymmetric Michael addition.

Glucose based chiral bifunctional organocatalysts was developed and explored in asymmetric aldol addition by Ma and co-workers. Catalysts affords chiral β-hydroxy-β-trifluoroalkyl ketones in moderate chemical yield and enantioselectivity (Scheme 18).[27]

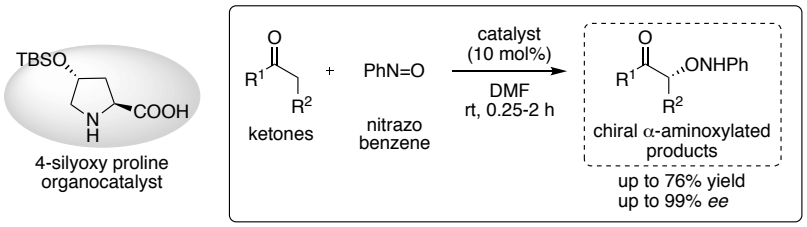


Scheme 18. Glucose-based chiral bifunctional organocatalysts for asymmetric aldol reaction.

1.9 Silyl ether group assisted organocatalysts in asymmetric synthesis

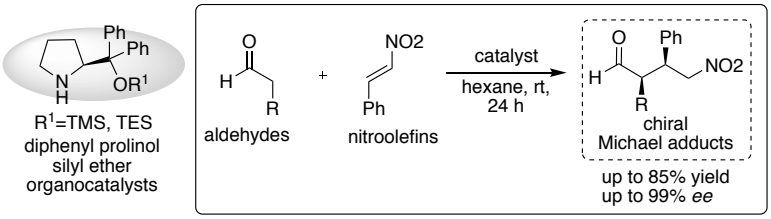
Organocatalysts incorporated with silyl ethers are often reported and employing for the natural and bio active synthesis. Silyl protected ether groups are serving as rigid cloud which can create steric influence for chirality enhancement of product formation in asymmetric synthesis. Still, silyoxy assited organocatalysts towards asymmeteric reactions has not well explored. There are few potential silyloxy assited organocatalysts developed by various groups and their applications are mentioned bellow.[28]

In 2005, Jorgenson and co-workers reported first 4-silyloxy proline organocatalysts for asymmetric nitrazo-aldol reaction of ketones with nitrazobenzene which afforded chiral α-aminoxylated product in excellent enantioselectivity (99% ee) as shown in (Scheme 19).[29]



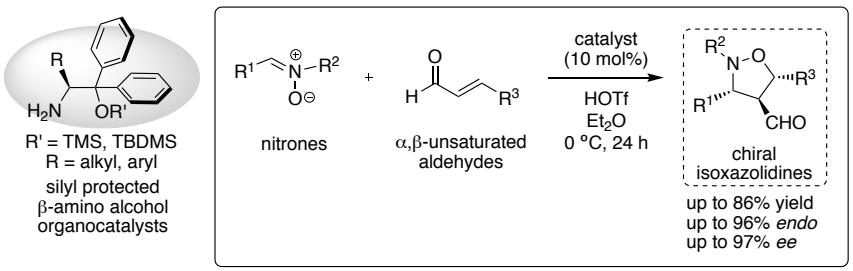
Scheme 19. Silyloxy proline catalyst for asymmetric nitrazo-aldol reaction.

Followed by, Hayashi and co-workers have found that diarylprolinol silyl ether as an organocatalysts for asymmetric Michael reaction of aldehydes with nitroolefins which afforded chiral Michael adducts in excellent enantioselctivity (99% ee) as shown in (Scheme 20).[30]



Scheme 20. Prolinol silyl ethers catalyst for asymmetric Michael reaction.

Few years back, Nakano and group workers developed silyloxy β-amino alcohol as an organocatalysts to asymmetric 1,3-dipolar cycloaddition reaction of nitrones and α,β-unsaturated aldehydes. Catalysts afforded chiral isoxazolidines with good chemical yield (86% yield), excellent diastereoselectivity (96% *endo*), and excellent enantioselctivity (97% ee) (Scheme 21).[31]



Scheme 21. Silyl protected amino alcohol catalyst for asymmetric 1,3-dipolar cycloaddition reaction.

Author project

Author aim to develop new type organocatalyst incorporated with sugar moiety and amino alcohol functional group together to demonstrate its catalytic activity in asymmetric synthesis. In the field of organocatalysis, development of catalysts using D-xylose as a chiral synthetic precursor have not explored. Hence, author preferred D-xylose as synthetic chiral precursor and developed sugar-based γ-amino alcohol organocatalysts and another new xylofuranose based γ-amino silyl ether organocatalysts. In contrast with β-amino alcohol, sugar-based γ-amino alcohol contains covalent site and non-covalent site together also expected to perform as an effective catalyst towards chiral induction. On the other hand, new sugar-based γ-amino silyl ether organocatalysts has protection of silyl groups on hydroxy atom which might expected to enhance the stereoselectivity in asymmetric reaction (Figure 9).

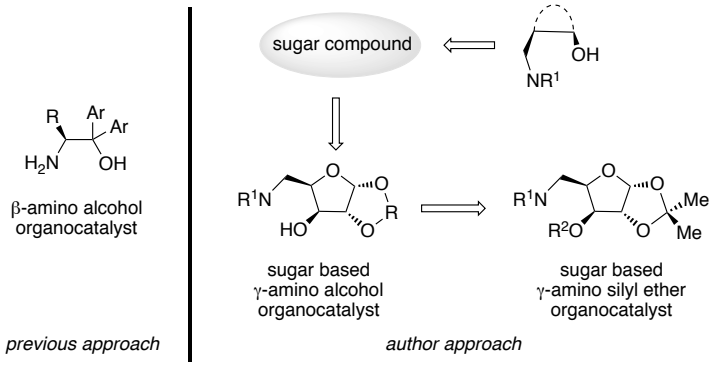
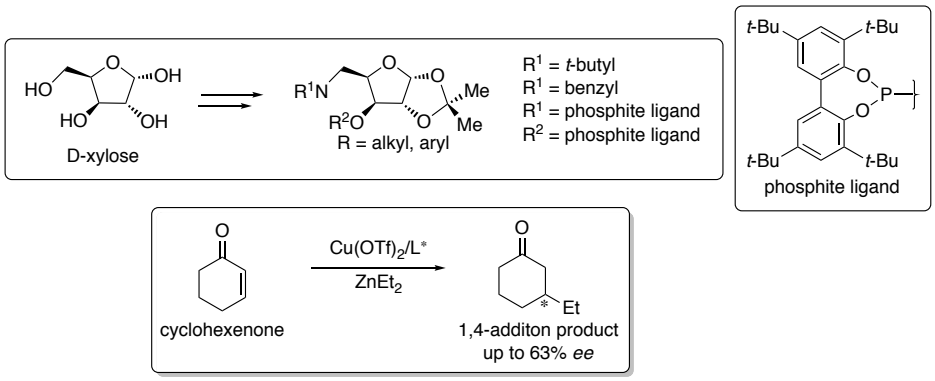


Figure 9. Author approach.

Xylofuranose based γ-amino alcohol compound as ligand along with metal triflates promoted asymmetric 1,4-addition of cyclohexanone and $ZnEt_2$ was reported by Dieguez and group members in the year of 2001 (Scheme 21).[32] After that, report on xylofuranose based γ-amino alcohol compound have not accessible till date.



Scheme 21. Asymmetric alkylation of cyclohexanone.

Further, xylofuranose based γ-amino alcohol contains required functionalities to undertake a catalysts role such as, amino group can perform as basic or covalent site, hydroxy group can involve on non-covalent interaction to substrate, substituents on nitrogen atom can act as steric influence site. Additionally, compound has xylofuranose ring on its core structure and 1,2-O-isopropylidene group was attached to it which all together could express steric influence on substrate. Consequently, sugar-based γ-amino silyl ether compound contains amino group can act as covalent or basic site, silyl ether group can act as rigid steric influence site along with substituents on amine atom and 1,2-O-isopropylidene backbone. Sugar based catalysts were synthesis from commercial D-xylose in simple steps (Figure 10). Author preferred Michael addition of β-keto ester and nitroolefin to demonstrate the catalytic activity of the obtained organocatalysts to affords chiral Michael adducts which has quaternary chiral center.

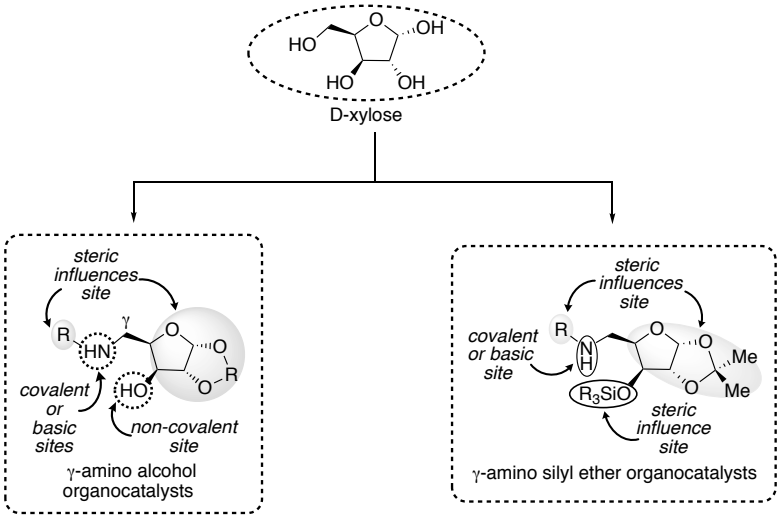
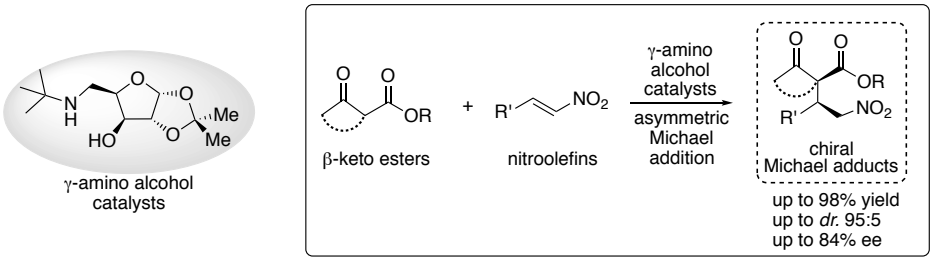


Figure 10. Concept of sugar-based γ-amino organocatalysts

The developed sugar-based γ-amino alcohol organocatalysts having amino group, hydroxy group and substituent on nitrogen atom as an organocatalysts was demonstrated to asymmetric Michael addition of β-keto ester and nitroolefin. Followed by, newly prepared sugar-based γ-amino silyl ether organocatalysts having amino group, silyl ether group and substituent on nitrogen atom demonstrated in asymmetric Michael addition of β-keto ester and nitroolefin.

i) Sugar-based γ-amino alcohol organocatalysts to asymmetric Michael addition

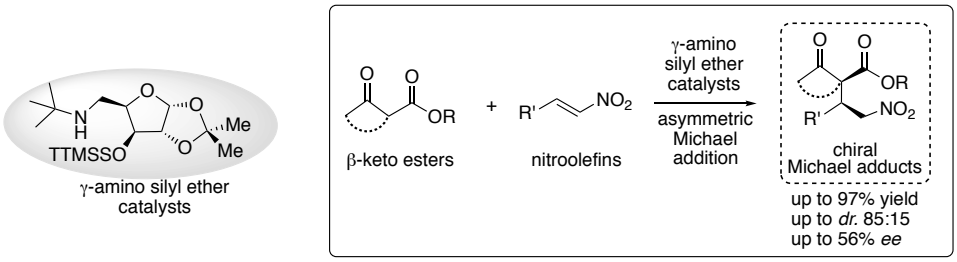
Initially, author prepared sugar-based γ-amino alcohol organocatalysts and explored in asymmetric Michael addition of β-keto ester and nitroolefin which afforded chiral Michael adduct in excellent chemical yield, excellent diastereoselectivity and good enantioselectivity (98% yield, *dr*. 95:5, 84% ee) (Scheme 22).



Scheme 22. Sugar-based γ-amino alcohol organocatalysts to asymmetric Michael addition.

ii) Sugar-based γ-amino silyl ether organocatalysts to asymmetric Michael addition

Followed by, author developed sugar-based γ-amino silyl ether organocatalysts and demonstrated in asymmetric Michael addition of β-keto esters and nitroolefins which afforded chiral Michael adducts in excellent chemical yield, good diastereoselectivity and moderate enantioselectivity (98% yield, *dr*. 95:5, 56% ee) (Scheme 23).



Scheme 23. Sugar-based γ-amino alcohol organocatalysts to asymmetric Michael addition.

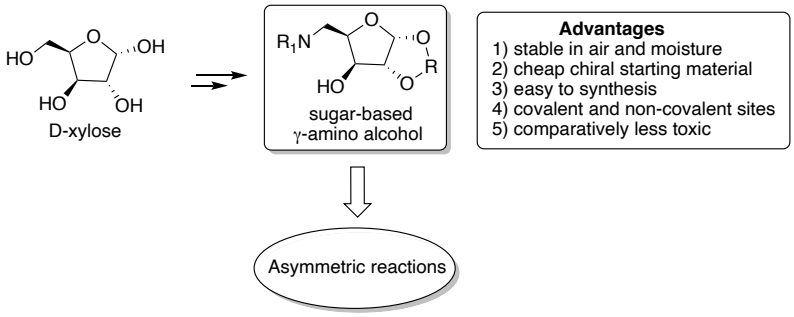
Chapter 2

Sugar based γ-amino alcohol organocatalysts for asymmetric Michael addition of β-keto ester and nitroolefin

2. Sugar based γ-amino alcohol organocatalysts for asymmetric Michael addition of β-keto ester and nitroolefin

2.1 Author approach

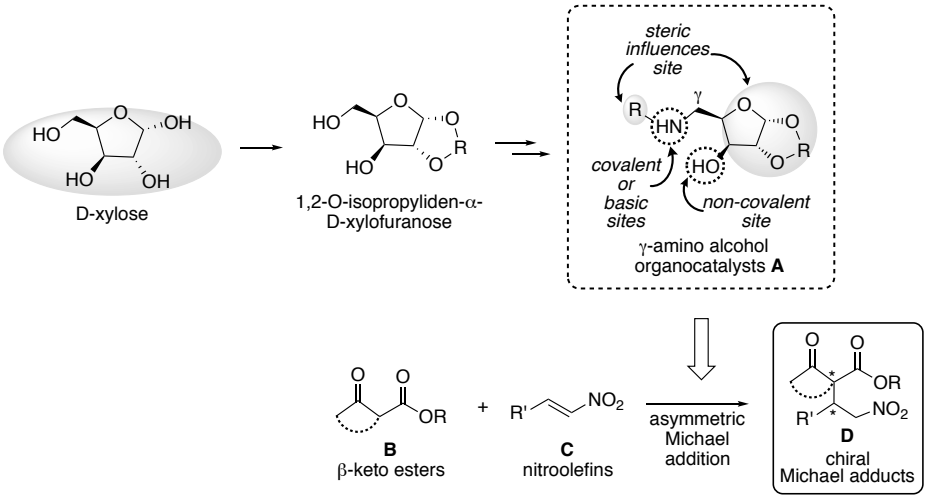
Advancement in new simple and chiral organocatalyst development from inexpensive chiral starting material is extremely demand in asymmetric synthesis. Sugar-based molecules are ubiquitous cheap chiral resources and utilized for multiple chiral based organic molecule transformations.[33] Compound of β-amino alcohol prepared from commercial amino acid precursors often reported as an organocatalysts to carry out the asymmetric reactions with excellent results. Based on this background, develop and explore compound of the sugar molecule associated γ-amino alcohol functions to catalyze the asymmetric reactions was decided by author. Particularly, xylofuranose-based γ-amino alcohol bearing various advantages including, stability on moisture and air, cost-efficacy, easy to synthesis and comparatively less toxic (Scheme 24). Additionally, compound sugar-based γ-amino alcohol can be synthesis with minimum efforts from utilizing D-xylose as synthetic precursor.



Scheme 24. Advantages of sugar-based γ-amino alcohol.

Author aim to develop new xylofuranose based γ-amino alcohol organocatalysts **A** having covalent and non-covalent functions using simple commercially available D-xylose. As a catalyst to induce chirality, it possesses multiple vital functionalities including, amino group could act as covalent or basic sites, hydroxy group as non-covalent site, and 1,2-O-isoprpylidene 5-membered ring back bone and substituent on nitrogen atom both might perform as steric influences site. Catalyst **A** having amino group and hydroxy group can synthesis from commercially available D-

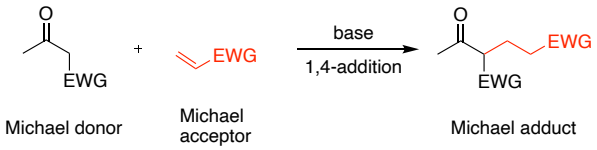
xylose chiral starting material via few steps (Scheme 25). Additionally, catalytic activity of xylofuranose based γ-amino alcohol **A** as an organocatalysts leftovers undisclosed in the field of asymmetric synthesis till the date. Asymmetric Michael addition has widely recommended for chiral C-C bond formation tool in the field of organic synthesis. Particularly, asymmetric Michael reaction of β-keto esters **B** and nitroolefins **C** to deliver the chiral Michael adduct **D** is preferred mostly to construct the product with contagious chiral centers.[34] The chiral Michael adduct **D** affords from that reaction possess quaternary chiral center which is existing as highly challenging task to construct in the field of natural and bio-active molecule synthesis. Hence, author decided to study their catalytic activity in asymmetric Michael addition of β-keto esters **B** and nitroolefins **C** to deliver the chiral Michael adduct **D**.



Scheme 25. Concept of sugar-based γ-amino alcohol organocatalyst.

2.2 Michael Addition

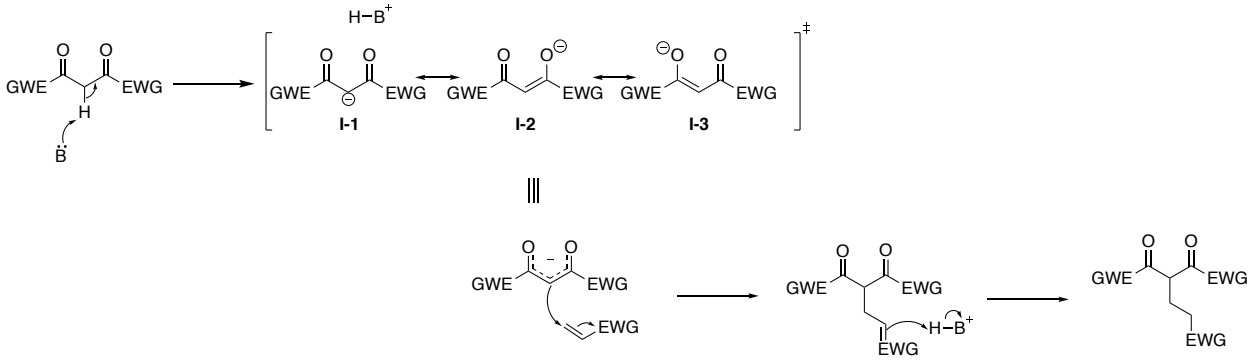
Michael addition is fundamental organic reaction and established by American organic scientist called Arthur Michael by the year of 1887, which has been widely employing for the construction C-C bond.[35] The term for Michael addition is 1,4-conjugate addition or nucleophilic addition of resonance stabilized carbanion (Michael donor) produced by proton abstraction using base to electron deficient α,β-unsaturated compound (Michael acceptor). General reaction for Michael addition usually takes place between Michael donor and Michael acceptor in the presence of base was depicted below. (Scheme 26).



Scheme 26. General reaction of Michael addition

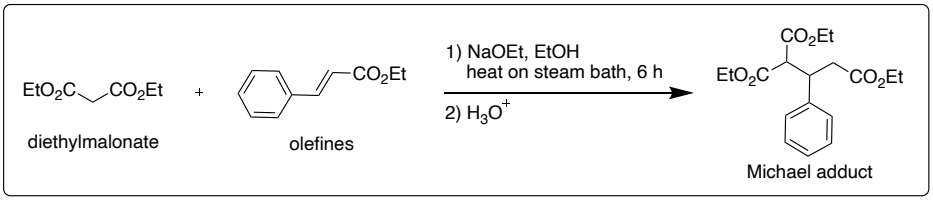
2.3 Mechanism

In initiation step of reaction, base abstracts the acidic proton from donor substrate and generates anion which stabilizes themself by involving conjugation with adjacent double bonds to form three stable intermediates. Followed, conjugate addition of electron from carbanion to electron deficient Michael acceptor creates new C-C bond between the substrates. Finally, protonation from base leads to the 1,4-conjugated Michael adduct product with new C-C bond formation. (Scheme 27)



Scheme 27. Mechanism for Michael addition reaction.

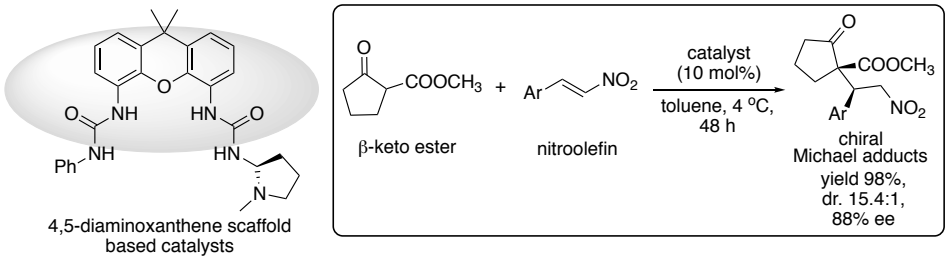
The first report in Michael addition by Arthur and research group of diethylmalonate esters with aromatic olefines in the presence of base afforded Michael adducts in heating condition on steam bath for 6 hours (Scheme 28).[36]



Scheme 28. Michael addition of diethylmalonate and olefines.

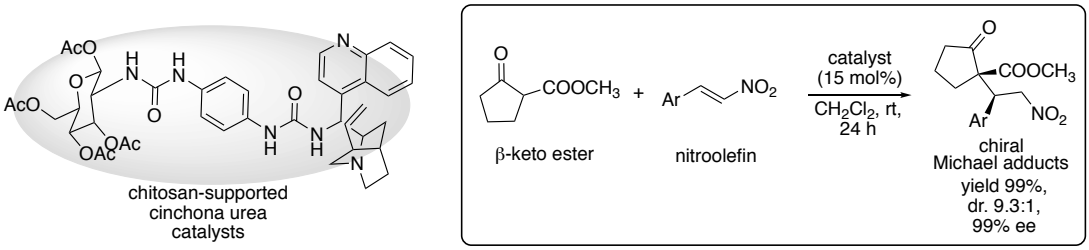
Consequently, enormous progress on the development of various stabilized carbanions have been studied by different research groups. In the field of asymmetric synthesis, this reaction has been recommended as one of the atom economical and effortless chiral C-C bond formation tools. Due to this reason, several chiral organocatalysts were continuously explored in this reaction and

studied their catalytic efficiency to afford chiral Michael adducts. Frequently, studies were on focused intensively to develop effective chiral catalyst and explored in asymmetric Michael addition of methyl-2-oxocyclopentanone with nitrostyrene to obtain chiral Michael adduct. Construction of chiral quaternary carbon center remains highly challenging task, which can achieve by this reaction with less efforts. Considering this necessity, several research crews have developed effective chiral organocatalysts and studied in this reaction to afford chiral Michael adducts, since a decade. There are few examples of chiral organocatalysts were studied in asymmetric Michael addition reaction. Few years back, Hamada and group workers reported 4,5-diaminoxanthane scaffold-based urea catalyzed asymmetric Michael addition of β-keto ester and nitroolefin reaction afforded chiral Michael adducts in excellent chemical yield (98%), diastereoselectivity (15.4:1%) and good enantioselectivity (88%) (Scheme 29).[37]



Scheme 29. Asymmetric Michael addition using 4,5-diaminoxanthene scaffold-based urea catalysts

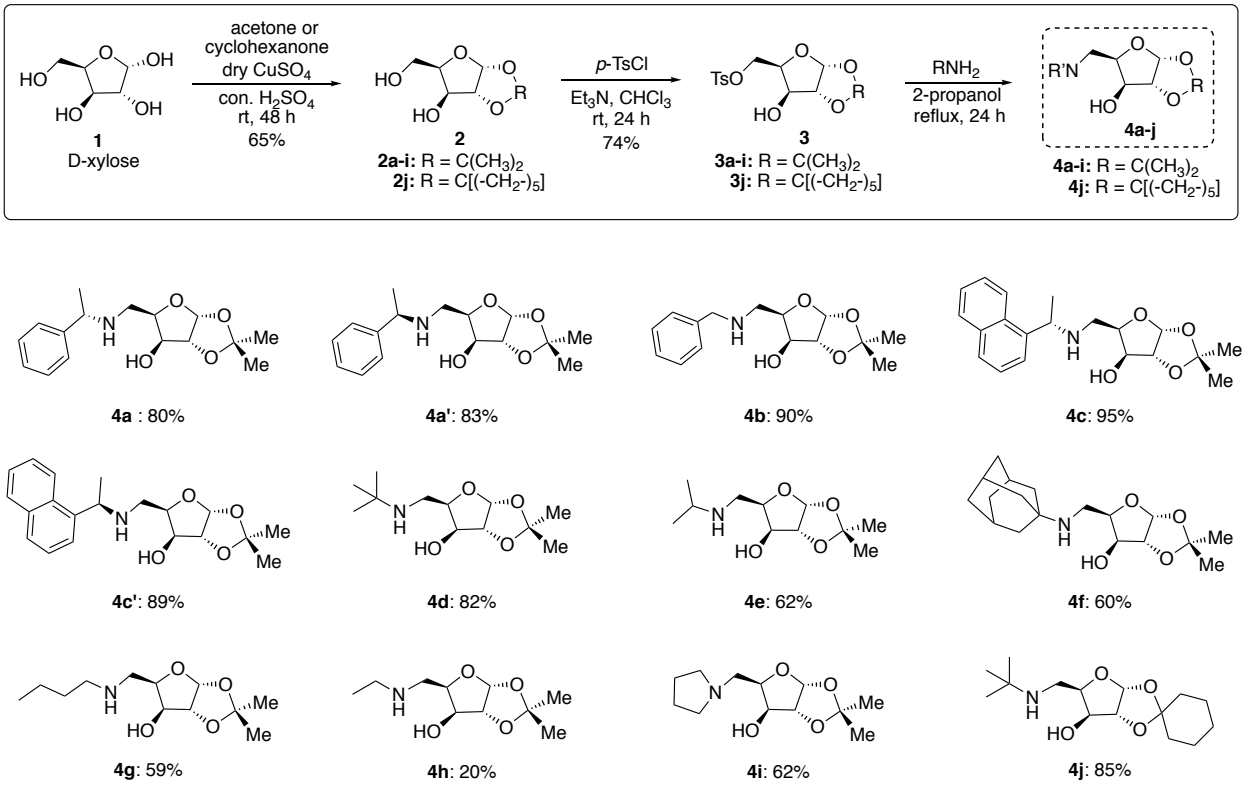
Recently, Itsuno and group workers reported Chitosan-supported chinchona urea catalyzed asymmetric Michael addition of β-keto ester and nitroolefin afforded chiral Michael adducts in excellent chemical yield (99%), diastereoselectivity (19.3:1%) and enantioselectivity (99%) (Scheme 30).[38]



Scheme 30. Asymmetric Michael addition using Chitosan-supported cinchona urea catalysts

2.4 Result and discussion

Based on this background, Author have decided to initiate to synthesis the compounds of sugar-based γ-amino alcohol **4a-j** with 1,2-*O*-isopropylidene-D-xylofuranose as a rigid backbone and covalent and non-covalent active sites from D-xylose **1** via simple few steps according to previous report (Scheme 31).[39]



Scheme 31. Preparation of catalysts **4a-j**

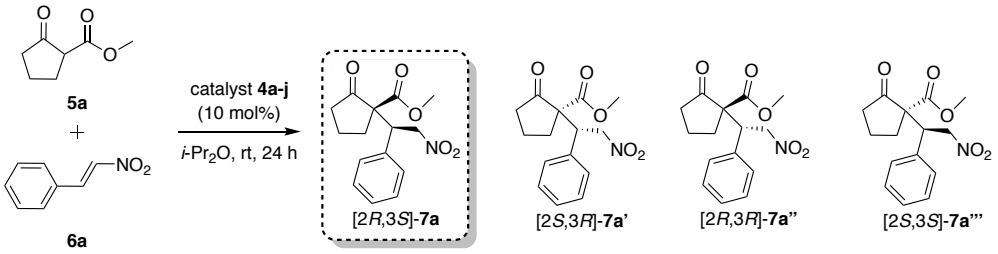
1,2-*O*-Isopropylidene-α-D-xylofuranoses **2a,b** of protected compounds were prepared by the reactions of D-xylose **1** with acetone or cyclohexanone in the presence of catalytic amount of con.H_2SO_4. Followed by the selective mono-tosylation of hydroxyl group on **2a,b** afforded the tosylate compound **3a,b** in 74% of yield. Furthermore, the substitution reactions of the obtained **3a,b** with several amines afforded the desired γ-amino alcohols **4a-j**. In those catalysts **4a-j**, several alkyl and aryl substituents on nitrogen atom of primary and secondary amine catalysts were employed to study their significance in asymmetric reaction. First, various aromatic substituents were nominated on nitrogen atom of catalysts **4a-c'** to study their steric and electronic repulsion

effect on chirality induction. Two stereo isomers, catalysts **4a** and **4a'** contains phenyl group attached with hydrocarbon atom on nitrogen atom was prepared for the screening. After that, simple aromatic of benzyl substituted catalyst **4b** was introduced. Later, bulky polycyclic aromatic compound of naphthyl ethyl group attached on nitrogen atom in catalysts with two isomers **4c** and **4c'** were developed. Consequently, to ascertain the effect of alky substituents on amine atom in catalysts structure **4d-j**, several substituents were introduced like, bulky acyclic, linear acyclic, cyclic and cage compounds. Acyclic bulky compounds, *t*-butyl **4d** and *i*-propyl **4e** substituents on nitrogen atom containing catalysts were preferred which substituents might allow free rotation along the axis to realize better results. Followed by, compound having cage type cyclic adamantane group on nitrogen atom **4f** was developed. Linear alkyl chain, *n*-butyl group assisted amino alcohol catalyst **4g** was introduced to study their influence. In some cases, simple substituents can provide better outcome so that ethyl group was introduced in catalyst **4h**. Compound **4j** having 5-membered cyclic aliphatic substituent on nitrogen atom was developed. Eventually, catalysts **4j** having t-butyl group on nitrogen atom but 1,2-diol protection was modified to 1,2-hexylidene instead 1,2-isopropylidene to study the backbones effect.

2.5 Screening of catalysts 4a-j

In order to study, the catalytic activities of obtained γ-amino alcohols **4a-j** as an organocatalyst were explored in the Michael addition of methyl-2-oxocyclopentanone **5a** with nitro styrene **6a** (Table 1). The reactions were carried out in the presence of 10 mol% of catalysts **4a-j** in *i*-Pr_2O at room temperature, respectively. As a result, all catalysts **4a-j** showed catalytic activities to afford the desired chiral Michael adduct [2*R*,3*S*]-**7a**, as a main product. First, catalysts **4a** having *R*-phenylethyl substituent was explored which promoted chiral Michael adduct **7a** in excellent yield, good diasteroselectivity, but low enantioselectivity was realized (98%, *dr*. 81:19, 12% ee) (Table 1, entry 1). Another enantiomer of that same catalysts **4a'** delivers adduct in moderate chemical yield, good diastereoselectivity, enantioselectivity was improved (53%, *dr*. 77:29, 52% ee) (entry 2). Later, simple aromatic benzyl group assisted catalysts showed moderate performance and affords adduct **7a** in moderate results (entry 3).

Table 1. Michael addition of **5a** with **6a** using **4a-j**



entry	catalyst **4**	yield (%)[a]	*dr*[b]	ee %[c]
1	**a**	98	81:19	12
2	**a'**	53	77:23	52
3	**b**	65	59:41	27
4	**c**	71	71:29	52
5	**c'**	57	88:12	28
6	**d**	73	89:11	64
7	**e**	61	63:37	23
8	**f**	74	75:25	13
9	**g**	76	82:18	33
10	**h**	79	83:17	25
11	**i**	53	77:23	39
12	**j**	70	85:15	58

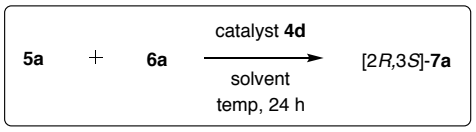
[a]Isolated yield. [b]Determined by H^1 NMR of crude reaction mixture. [c]The *ee* was determined by HPLC using CHIRALCEL OD-H column.

In the next case, the *R*- and *S*-naphthyl ethyl substituted catalysts **4c** and **4c'** were furnishes corresponding chiral adducts **7a** in moderate enantioselectivities (52-28% ee) (entries 4 & 5). Followed, bulky aliphatic *t*-butyl group substituted catalysts **4d** promotes chiral Michael adduct **7a** in good chemical yield, diastereoselectivity and moderate enantioselectivity (73%, *dr*. 89:11 64%) (entry 6). In less bulky case, catalysts **4e** contains *i*-propyl substituent showed moderate activity and affords adducts in moderate results (yield 61%, *dr*. 63:37, 23% ee) (entry 7). The cage type compound, adamantane group attached on nitrogen atom of catalyst **4f** delivers adduct in good chemical yield, diastereoselectivity, but enantioselectivity was significantly low (13% ee) (entry 8). Catalysts **4g** with linear alkyl chain of *n*-butyl group on nitrogen atom, afforded chiral adduct **7a** in good chemical yield, diastereoselectivity, enantioselectivity was moderate (76%, *dr*. 82:18, 33% ee) (entry 9). In the case of simple alkyl, ethyl substituted catalyst **4h** showed moderate catalytic activity (79%, *dr.* 83:17, 25% ee) (entry 10). After that, cyclic tertiary amine contain catalysts **4i** was studied and chiral adduct **7a** obtained in moderate results (53%, *dr*. 77:23, 39% ee) (entry 11). Eventually, catalysts **4d** showed better catalysts activity that other catalysts, 1,2-O-isohexylidene back bone was introduced in catalyst structure **4j** and explored in reaction. The catalysts **4j** also did not afforded chiral adduct **7a** better than catalyst **4d** (entry 12). Based on these data, catalysts **4d** contains *t*-butyl group on nitrogen atom showed better catalytic activity in asymmetric Michael reaction of β-keto ester **5a** and nitroolefin **6a** to afford chiral Michael adduct **7a**-[2*R*,3*S*] (73%, *dr.* 89:11, 64% ee) (entry 6). The determination of absolute stereochemistry of **7a** was conformed on comparison with previous report.[40]

2.6 Optimization of reaction condition

In order to optimize the reaction conditions using superior catalyst **4d**, the effect of solvent, the molar ratio of catalyst, and the reaction temperature were examined (Table 2). First, the effects of solvents were examined in the presence of 10 mol% of superior catalyst **4d** at room temperature for 24 h (entries 1-12). In that screening, various solvents have been employed for screening such as, ethereal, aromatic, aliphatic, chlorinated, aprotic and polar solvents. In ethereal solvent, reactions were conducted in *i*-Pr_2O and Et_2O, respectively, corresponding chiral adducts **7a** were obtained in good to moderate chemical yields, good diastereoselectivities, and moderate enantioselectivities (up to 73-50%, *dr*. 89:11-84:16, up to 64% ee) (entries 1 and 2).

Table 2. Screening of the reaction conditions using superior catalyst **4d**



entry	solvent	mol (%)	temp (°C)	Yield (%)[a]	dr[b] **(7a,a'/7a",a''')**	ee (%)[c] **7a**
1	*i*-Pr_2O	10	rt	73	89:11	64
2	Et_2O	10	rt	50	84:16	24
3	toluene	10	rt	50	89:11	43
4	benzene	10	rt	71	88:12	21
5	hexane	10	rt	63	86:14	28
6	$CHCl_3$	10	rt	53	90:10	10
7	CH_2Cl_2	10	rt	92	80:20	46
8	THF	10	rt	53	90:10	54
9	CH_3CN	10	rt	61	85:15	64
10	acetone	10	rt	85	83:17	35
11	DMF	10	rt	90	73:27	18
12	MeOH	10	rt	43	78:22	13
13	*i*-Pr_2O	1	rt	43	87:13	34
14	*i*-Pr_2O	5	rt	55	88:12	53
15	*i*-Pr_2O	20	rt	65	87:13	84
16	*i*-Pr_2O	20	0	66	90:10	60
17	*i*-Pr_2O	20	-10	65	90:10	32
18	*i*-Pr_2O	20	-20	64	92:08	23
19	*i*-Pr_2O	20	40	71	87:13	75

[a]Isolated yield. [b]Determined by H^1 NMR of crude reaction mixture. [c]The ee was determined by HPLC using CHIRALCEL OD-H column.

Followed by, aromatic solvents of toluene and benzene were employed, corresponding chiral adducts were obtained in moderate to good yields, good diasteroselectivities, enantioselectivity was maintained as moderate (up to 50-71%, up to *dr*. 89:11-88:12, up to 43-21%) (entries 3 & 4). In the case of non-polar, reaction was carried out using hexane as a solvent that afforded chiral adducts **7a** in moderate chemical yield, good diastereoselectivity, and enantioselectivity was moderate (63%, *dr*. 86:14, 28% ee) (entry 5). At next, chlorinated solvents were employed such as, $CHCl_3$ and CH_2Cl_2 which delivers corresponding chiral adducts **7a** in moderate to good yields, good diastereoselectivities, low to moderate enantioselectivities (up to 53-92%, up to *dr*. 90:10-80:20, up to 10-46%) (entries 6 & 7). Polar protic and polar aprotic solvents were also examined that also did not affords better results in chemical yields and stereoselectivities (up to 43-90%, up to *dr.* 70:30-90:10, 13-64% ee) (entries 8-12). Chemical yields and stereoselectivities were mostly depended on the nature of solvents and the utilization of *i*-Pr_2O as a solvent afforded the Michael adduct **7a** in good chemical yield, diastereoselectivity and moderate enantioselectivity (73%, *dr*. 89:11, 64% ee) (entry 6, Table 1 and entry 1, Table 2) than other solvents (entry 2-12, Table 2). Next, we examined the molar ratios of catalyst **4d** in superior *i*-Pr_2O solvent at room temperature (entries 13-15).

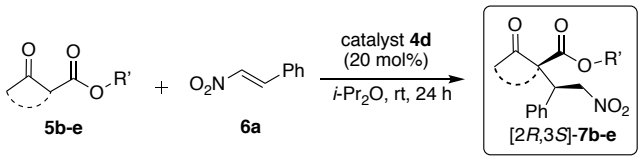
From this optimization, best enantioselectivity (84% ee) was obtained when the reaction was carried out in the presence of 20 mol% of catalyst **4d** to afford **7a** with moderate chemical yield and good diastereoselectivity, and good enantioselectivity (65%, *dr.* 87:13, 84% ee) (entry 15).

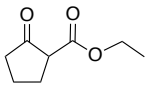
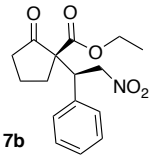
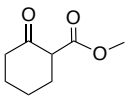
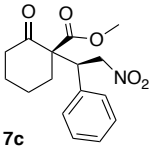
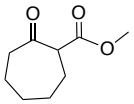
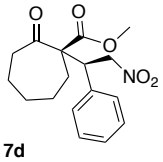
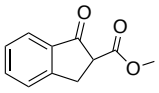
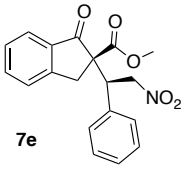
Furthermore, reaction temperature was also screened at 0 °C, -10 °C, -20 °C and 40 °C, respectively (entries 16-19). Chemical yield and diastereoselectivity were remains unchanged when reactions were carried out in different temperatures 0 °C, -10 °C and -20 °C (entries 16-18). However, satisfactory enantioselectivity were not observed in those temperatures. On the other hand, chemical yield improved to 75% at 40 °C, but enantioselectivity was reduced to 75% ee (entry 19). Considering of these results, it was assumed that the use of 20 mol% of catalyst **4d**, *i*-Pr_2O as a solvent, and the reaction at room temperature is the superior reaction condition to deliver the chiral Michael adduct **7a** with comparatively good satisfactory chemical yield and stereoselectivities (65%, *dr*. 87:13, 84% ee) (entry 15).

2.7 Substrate scope of asymmetric Michael addition using catalyst 4d

To extend the catalytic activity, the ability of superior catalyst **4d** was prolonged to the Michael addition using various β-keto esters **5b-e** and nitroolefin **6a** (Table 3). At first, reaction between Ethyl 2-cyclopentane carboxylate **5b** with nitrostyrene **6a** using catalysts **4d** which afforded Michael adduct **7b** in good chemical yield (73%), diastereoselectivity (75:25) and moderate enantioselectivity (42%) (entry 1).

Table 3. Substrate scope for Michael addition of **5b-e** with **6a** using catalyst **4d**



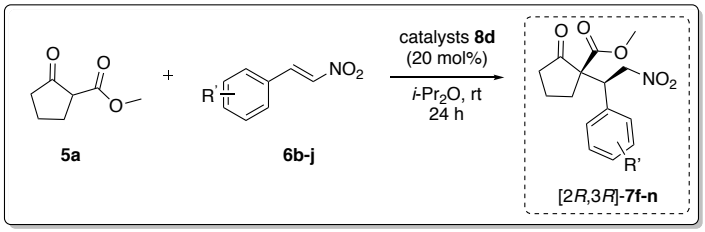
entry	5b-e	products 7b-e	yield (%)[a]	dr[b]	ee (%)[c]
1	 b	 7b	73	75:25	42
2	 c	 7c	45	92:8	38
3	 d	 7d	70	78:22	7
4	 e	 7e	80	90:10	8

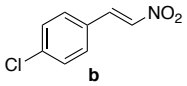
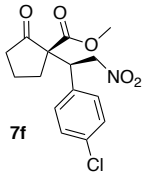
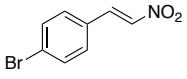
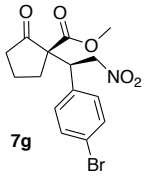
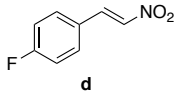
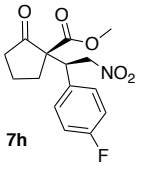
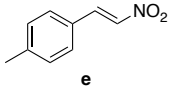
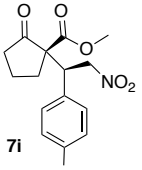
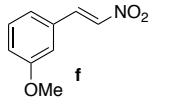
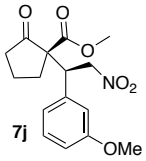
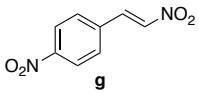
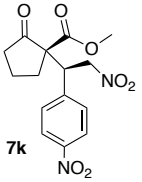
[a]Isolated yield. [b]Determined by ^{1}H NMR of crude reaction mixture. [c]ee was calculated by HPLC using CHIRALCEL OD-H column.

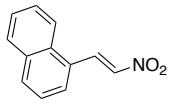
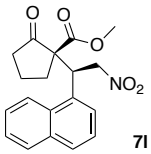
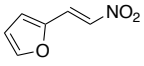
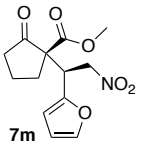
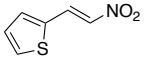
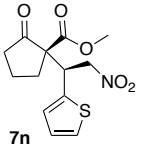
Followed by, reaction of 6-membered carbocyclic β-keto ester **5c** with **6a** were afforded Michael adduct **7c** in moderate chemical yield, excellent diastereoselectivity though, enantioselectivity was slightly decreased (45%, *dr*. 92:8, 38% ee) due to the ring size expansion (entry 2). Later, 7-membered carbocyclic β-keto ester **5d** with **6a** afforded chiral adduct **7c** in good chemical yield, diastereoselectivity, but drastic compression on enantioselectivity was observed (7% ee) (entry 3). Eventually, reaction of aromatic indanone β-keto ester **5e** and **6a** using catalysts **4d** was conducted that affords adduct **7e** with excellent chemical yield, diastereoselectivity and enantioselectivity maintained as low (80%, *dr*. 90:10, 8% ee) (entry 4). As a result, catalyst **4d** showed moderate to comparatively good catalytic activities to afford the corresponding Michael adducts **7b-e** for chemical yields and diastereoselectivities (up to 69-80%, up to *dr*. 75:25-90:10). However, those enantioselectivities were low to moderate (up to 7-42% ee) in all of cases, the reason might be steric issue of the ring size expansion.

Followed by, asymmetric Michael addition of β-keto ester **5a** and various nitrostyrenes **5b-j** was examined using catalyst **4d** in *i*-Pr_2O solvent at room temperature for 24 h (entries 1-9, Table 4). Initially, derivatives of halogenated nitroolefin at para position with **5a** in presence of catalyst **4d** was demonstrated and corresponding Michael adducts **7f-h** were obtained in moderate to good chemical yields, good diastereoselectivities (up to 29-89%, up to *dr*. 86:14-90:10, up to 29-35% ee), though enantioselectivity maintained as moderate in all the cases (entries 1-3). Reaction of **5a** and 4-methyl substituted nitroolefin **6e** delivers **7i** in good chemical yield and diastereoselectivity, but significantly low enantioselectivity realized (12% ee) (entry 4). Afterwards, electron withdrawing methoxy and nitro substituted nitroolefins **6f, g** furnishes corresponding chiral adducts in moderate to good compound yields (65-72%), good diastereoselectivities (80:20-87:13), although enantioselectivities did not improved (15% ee) (entries 5 and 6). In aromatic polycyclic, moderate enantioselectivity (63% ee) were conformed when reaction was carried out with **5a** and nitroolefin **6** assisted bulky naphthyl group, but chemical yield and excellent diastereoselectivity was obtained (78%, *dr*. 95:5, 63% ee) (entry 7). At last, heterocyclic aromatic compound based nitroolefins furanyl **6i,** and thiophenyl **6j** were examined with **5a** using catalyst **4d** (entries 8 and 9).

Table 4. Substrate scope for Michael addition of **5a** and **6b-j** using catalyst **4d**



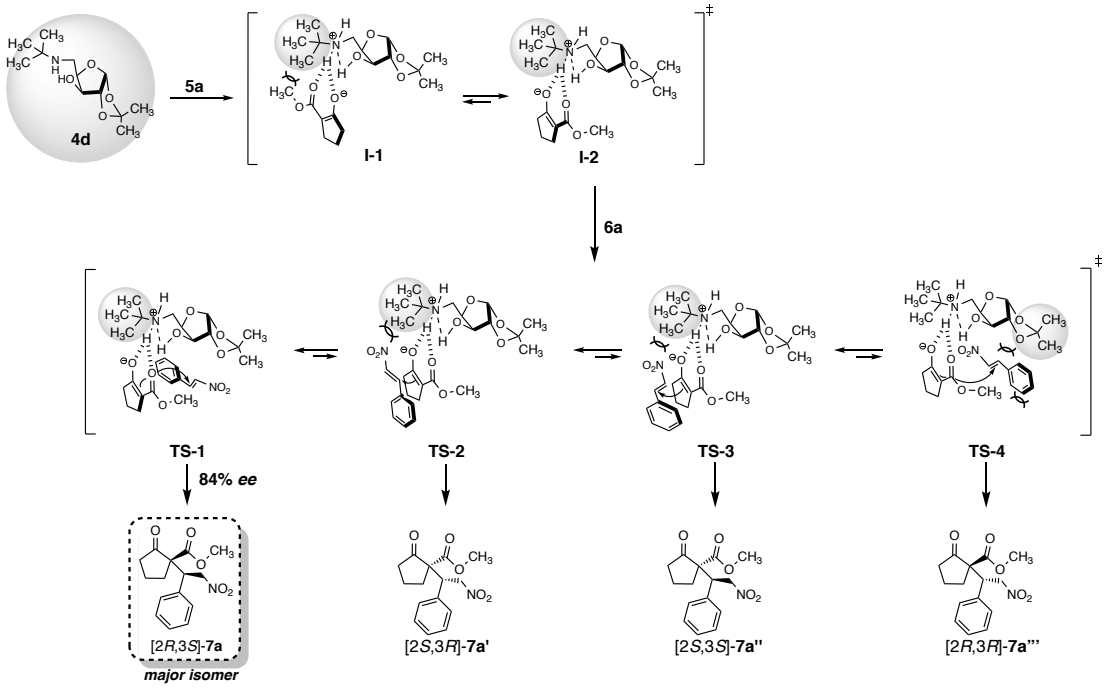
entry	6b-j	products 7f-n	yield (%)[a]	dr[b]	ee (%)[c]
1	 **b**	 **7f**	75	90:10	34
2	 **c**	 **7g**	29	89:11	29
3	 **d**	 **7h**	84	86:14	35
4	 **e**	 **7i**	80	87:13	12
5	 **f**	 **7j**	65	87:13	15
6	 **g**	 **7k**	72	80:10	15

7	 **h**	 **7l**	78	95:5	63
8	 **i**	 **7m**	70	89:11	55
9	 **j**	 **7n**	97	89:11	55

[a]Isolated yield. [b]Determined by 1H NMR of crude reaction mixture. [c]ee was calculated by HPLC using CHIRALCEL OD-H column.

The heterocyclic corresponding Michael adducts **7m-n** was furnishes with good chemical yields, diastereoselectivities, and moderate enantioselectivities (up to 70-97%, up to *dr.* 89:11-95:5, 55% ee) (entries 8-9). The determination of absolute stereochemistries of **7f-n** were conformed on comparison with previous reports.[40]

2.8 Plausible reaction course

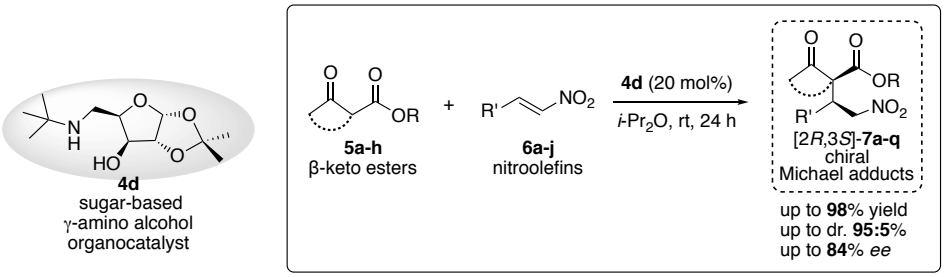


Scheme 32. Plausible reaction course

The plausible enantioselective reaction course was proposed for the observed enantiopurity of chiral Michael adduct [2*R*,3*S*]-**7a** (84% ee) Scheme X. At first, catalyst before acts as a base to β-keto ester **5a**, involves in intramolecular hydrogen bonding between hydroxy hydrogen atom and amine atom which construct 6-membered stable intermediate. The generated enolate of β-keto ester fixed with ammonium hydrogen atom on catalyst species by hydrogen bonding interactions that generate stable intermediate **I-2**. As compared with intermediate **I-1**, that has less steric interaction between *t*-butyl substituent on ammonium of catalyst and enolate. Subsequently, the enantioselective reaction might proceed through **Ts-1** that has comparatively less steric interactions in both cases such as, the substrate **6a** and *t*-butyl group on amino substituent of the ammonium catalyst species, also between **6a** and xylofuranose backbone of the catalyst species. As compared with other transition states, less steric influence and more stability could be realized in **Ts-1**.

2.9 Summary

In summary, xylofuranose based γ-amino alcohol **4** as an organocatalysts was utilized for the first time in asymmetric Michael addition of β-keto esters **5a-h** with nitroolefins **6a-j** and the corresponding several Michael adducts **7a-q** bearing quaternary chiral carbon center were obtained (up to 98%, up to *dr.* 95:5, up to 84% *ee*). Although, catalyst **4** did not show remarkable catalytic activity in this reaction, the development of still more effective xylofuranose based amino alcohol and its derivates as an organocatalysts to this reaction and others, this study might be supportive.



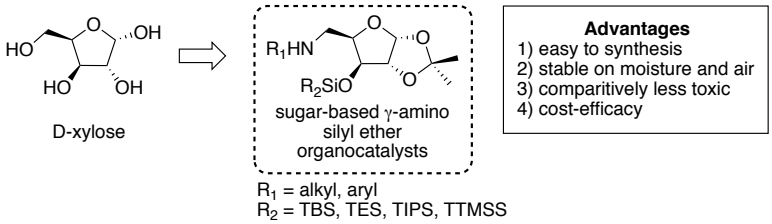
Chapter 3

Sugar based γ-amino silyl ether organocatalysts for asymmetric Michael addition of β-keto ester and nitroolefin

3. Sugar based γ-amino silyl ether organocatalysts for asymmetric Michael addition of β-keto ester and nitroolefin

3.1 Author strategy

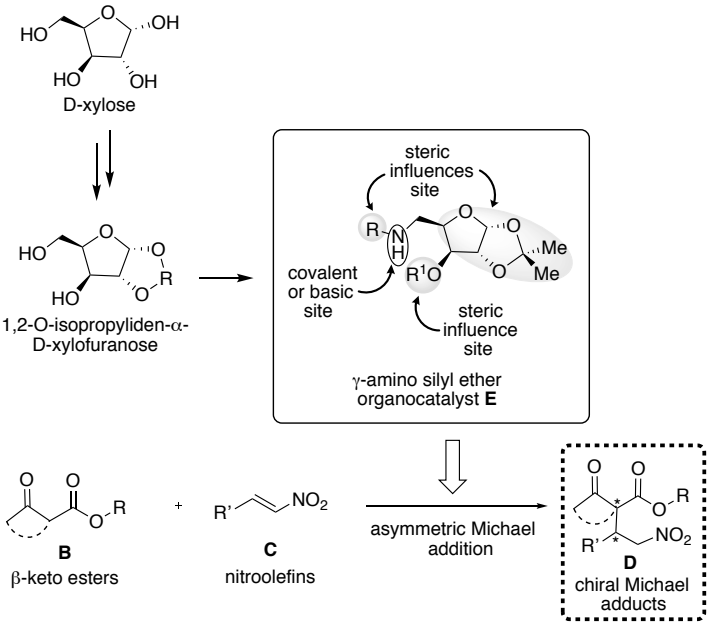
In the field of organocatalysis, silyl ether associated chiral compounds serving significant performance on catalytic activity and rigid steric influence of silyl ether group indicates majorly on stereoselectivity of product.[28-31] Additionally, silyl ether groups can be introduced into compounds via simple effort as compared with other transformations. Hence, enormous silyl ether assisted catalysts were employing continuously towards asymmetric reactions. Sugar based γ-amino alcohol catalysts can also protect using silyl protecting reagents which was previously demonstrated in asymmetric reaction. Further, sugar-based γ-amino silyl ether contains several advantages such as, easy to synthesis, stability towards moisture and air, atom economy, comparatively less toxic and cheap starting material (Scheme 33). However, reports were on xylofuranose derived γ-amino silyl ether not found till now.



Scheme 33. Development of γ-amino silyl ether organocatalyst

Therefore, Author aim to develop new xylofuranose based γ-amino silyl ether organocatalysts **E** by protecting hydroxy group of γ-amino alcohol **A** which could syntheses from simple commercially available D-xylose (Scheme 34). To enrich the chirality induction of product, it has multiple essential functionalities including, amino group could act as covalent or basic sites, both, 1,2-O-isoprpylidene and substituent on nitrogen atom might perform as steric influences site and rigid silyl ethers also could act as steric influence site. Additionally, catalytic activity of xylofuranose based γ-amino silyl ether **E** as an organocatalysts remains unrevealed in the field of asymmetric synthesis. Asymmetric Michael addition has widely recommended for chiral C-C bond formation tool in the field of organic synthesis. Particularly, asymmetric Michael reaction of β-

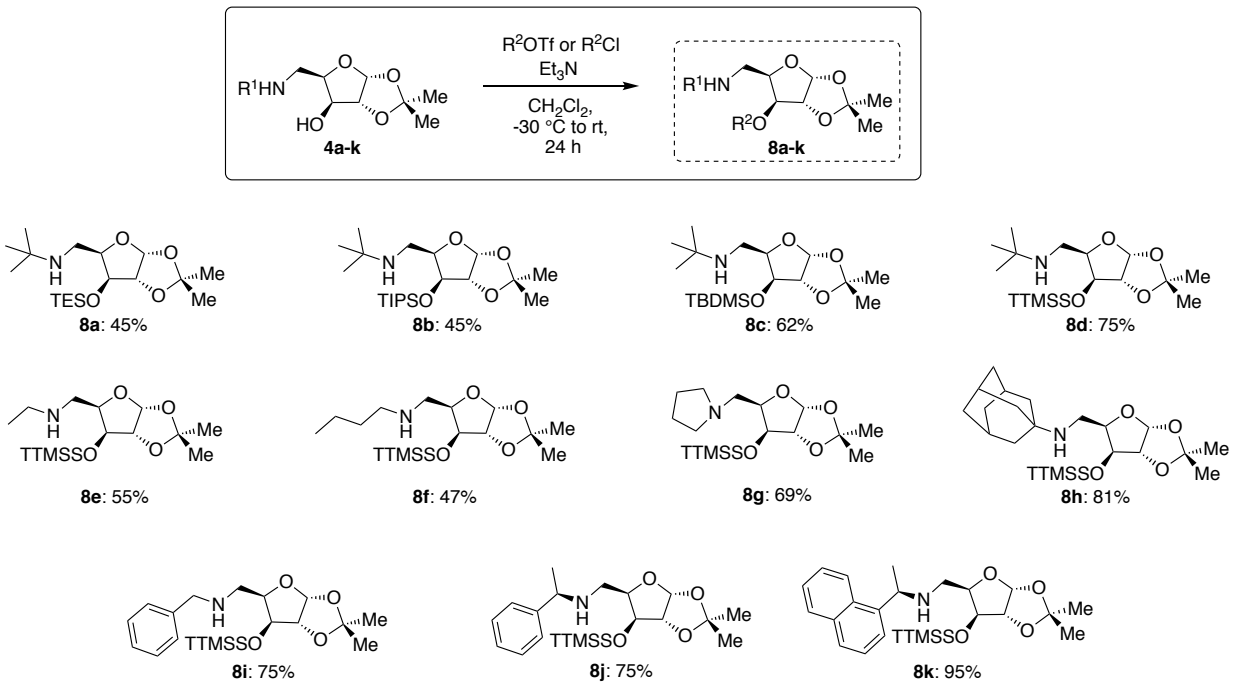
keto esters **B** and nitroolefins **C** to deliver the chiral Michael adduct **D** is preferred mostly to construct contagious chiral centers. The chiral Michael adduct **D** affords from that reaction possess quaternary chiral center which is existing as highly challenging task to construct in the field of natural and bio-active molecule synthesis. Hence, author has decided to study their catalytic activity in asymmetric Michael addition of β-keto esters **B** and nitroolefins **C** to deliver the chiral Michael adduct **D**.



Scheme 34. Concept of sugar-based γ-amino silyl ether organocatalysts **E**

3.2 Result and discussion

Author decided to synthesis xylofuranose-based γ-amino silyl ether **8a-k** using compound **4a-k** by simple silyl protecting reagents as described in scheme X. Compound **8a-k** was obtained by protection reaction hydroxy group of corresponding γ-amino alcohol **4a-k** in presence of Et_3N base, CH_2Cl_2 as solvent for 24 h. Several silyl protecting reagents were employed for the synthesis of compounds **8a-k** such as, triethylsilyl (TES), triisopropylsily (TIPS), *tert*-butyldimethylsilyl (TBDMS) and tris(trimethylsilyl) (TTMSS) (Scheme X).



Scheme 35. Preparation of catalysts **8a-k**

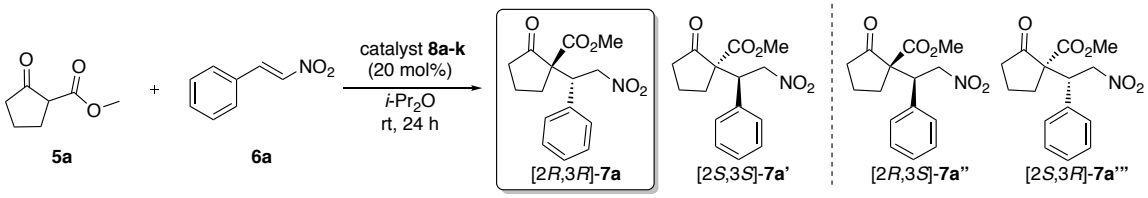
Initially, author decided to protect hydroxy group on γ-amino alcohol catalyst that possess *tert*-butyl group on nitrogen atom which has delivered better catalytic performance on previous study. Catalysts **8a-d** was prepared using various small (TES) to bulkier group (TTMSS) silyl protecting reagents. In that preparation, TES protected γ-amino silyl ether **8a** was introduced to initiate the catalyst study in reaction. Silyl group containing *i*-propyl used for the protection to obtain the catalysts **8b** and explored in reaction. Followed by, modest bulkier silyl protection of TBDMS group was attached to attain desired catalyst **8c** (62%). Followed by, huge rigid bulky substituent of super silyl (TTMSS) group attached silyl ether catalyst **8d** was obtained (75%). In catalysts

structure, positioning super silyl ether group unmodified, various substituents on nitrogen atom have introduced including, acyclic, cyclic, cage and aromatic groups. To examine the substituents effect, small ethyl group on nitrogen atom contains γ-amino alcohol was protected using super silly reagent and desired catalysts **8e** obtained with (55%) of chemical yield. Catalyst **8f** having linear *n*-butyl group on nitrogen atom along with super silyl ether group was obtained in (47%) yield. For cyclic substituent. Catalysts possess 5-membered tertiary amino group of pyrrolidine based organocatalysts **8g** with super silly ether group was prepared. Interestingly, catalyst **8h** bearing cage type adamantane substitution on nitrogen atom was obtained with (81%) of yield. Eventually, to study aromatic groups effect, benzyl, phenyl ethyl, naphthyl ethyl contains γ-amino alcohol was protected using super silyl reagent and corresponding catalysts were obtained **8i-k** (75%-95% yield).

3.3 Catalysts 8a-k screening in asymmetric Michael addition

Those obtained new γ-amino silyl ether organocatalysts **8a-k** were explored in asymmetric Michael addition of 2-methyl cyclopentane carboxylate **5a** with nitroolefin **6a** in the presence of *i*-Pr_2O solvent at room temperature for 24 h. All catalysts were showed catalytic activity on that reaction and afforded corresponding chiral Michael adduct **7a** with [2*R*,3*R*] stereochemistry as a main product (entries 1-11, Table X). Initially, catalysts **8a-d** having *tert*-butyl group on nitrogen atom was protected with various silyl protecting groups, explored in Michael addition of **5a** with **6a** which afforded corresponding chiral Michael adducts **7a** in moderate to good chemical yields, good diastereoselectivities, moderate enantioselectivities (65-85%, *dr*. 73:27-79:21, 37-56% ee). Moreover, catalysts **8d** having TTMSS group on hydroxy atom showed better catalytic activity as compared with other three **8a-c** (85%, *dr*. 73:27, 56% ee) (entry 3). From this data, it clarifies that enantioselectivity of product **7a** increases as the size of silyl protection increase in catalysts structure.

Table 5. Asymmetric Michael addition of **5a** with **6a** using **8a-j**



entry	catalyst **8**	yield (%)[a]	*dr*[b] (**7a, a'/7a'', a'''**)	*ee* (%)[c] **7a**
1	**a**	65	74:26	37
2	**b**	76	75:25	42
3	**c**	81	79:21	44
4	**d**	85	73:27	56
5	**e**	65	71:29	25
6	**f**	76	85:15	41
7	**g**	65	73:27	26
8	**h**	69	70:30	42
9	**i**	81	76:24	40
10	**j**	76	80:20	39
11	**k**	85	84:26	23

[a]yield was calculated after purification. [b]*dr* was determined by ^{1}H NMR using crude reaction mixture. [c]The *ee* was determined by HPLC analysis using a CHIRALCEL OD-H

After that, substituents on nitrogen atom of catalysts were modified by fixing super silyl ether group remains unchanged and their activities also examined in that reaction (entries 5-11). Catalysts with small ethyl **8e** and linear *n*-butyl **8f** substituents on nitrogen atom were afforded corresponding chiral adducts **7a** in moderate to good yield, diastereoselectivities, moderate enantioselectivities (65-76%, *dr*. 71:29-85:25, 25-41% ee) (entries 5-6). Further, cyclic alkyl pyrrolidine and cyclic cage adamantane substituents on nitrogen atom contains catalysts **8g** and **8h**, afforded corresponding adduct **7a** in moderate chemical yields, good diastereoselectivities, and moderate enantioselectivities (65-69%, *dr*. 70:30-73:27, 26-42% ee) (entries 7-8). Eventually, catalysts **8i-k** contains aromatic substituents like benzyl, phenyl ethyl and naphthyl were also examined which delivered corresponding chiral Michael adducts in good chemical yield, good diastereoselectivities, and low to moderate enantioselectivity (76-85%, *dr*. 76:24-84:26, 23-40% ee) (entries 9-10).

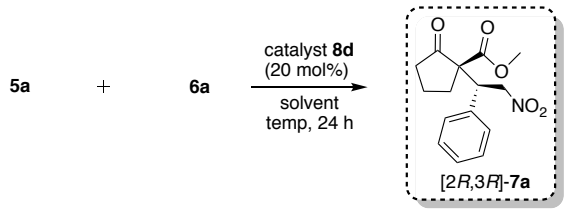
As a result, catalysts **8d** possess *tert*-butyl group on nitrogen atom and super silyl ether protection was best catalysts among other catalysts for asymmetric Michael reaction to afford chiral Michael adducts **7a** (85%, *dr*. 73:27%, 56% ee) (entry 4).

3.4 Optimization of reaction condition

After that catalysts screening, analysis of suitable reaction conditions requires for the further enhancement in activity of superior catalyst **8d** in asymmetric Michael addition of **5a** and **6a**. As a part of optimization, several screenings were conducted to analyze suitable reaction condition of catalysts **8d** such as, screening of solvents, catalysts loading ratios and temperature (Table 6). In solvent screening, asymmetric Michael addition was conducted using catalyst **8d** in the presence of numerous solvents including, polar, aprotic polar, aromatic and non-polar solvents. In polar protic solvents, reactions were conducted using catalysts **8d** (20 mol%) in the presence of H_2O, MeOH, 2-PrOH and DMSO solvents at room temperature which produces corresponding chiral adducts **7a** in excellent chemical yields, moderate to good diastereoselectivity, but enantioselectivity was low to moderate (92-97%, *dr*. 65:35-82:18, 5-8% ee). Followed, reaction in the presence of CH_3CN and DMF solvents afforded corresponding Michael adducts in good to excellent chemical yield, moderate to good diastereoselectivities and low to moderate enantioselectivities (82-94%, *dr*. 66:34-74:26, 9-35% ee). Reaction in ethereal solvents such as, THF and Et_2O promotes chiral adducts **7a** in excellent chemical yields, moderate diastereoselectivities and moderate enantioselectivities (entries 8 & 9). In the case of chlorinated solvents, catalysts afforded adducts in excellent chemical yields, good diastereoselectivities and moderate enantioselectivities (entries 10 & 11). When reaction was carried out in the presence of aromatic solvents like, toluene, benzene and xylene, corresponding adducts were obtained with unaffected results (entries 12-14). At last, hexane was employed to that reaction which delivers adduct with excellent chemical yield, good diastereoselectivity, and moderate enantioselectivity (91%, *dr*. 76:24, 39% ee). From all these data, it was confirmed that *i*-Pr_2O as suitable solvent for this catalysts **8d** to promote Michael addition of **5a** with **6a** (Table 1, entry 4). For screening of catalysts mole ratio, reactions were carried out in presence of *i*-Pr_2O solvent using best catalysts **8d** with various catalysts mole ratios including, 10 mol%, 5 mol%, 1 mol% (entries 16-18). As a result, enantioselectivity of product **7d** was significantly reduced, while reaction carry out using catalyst reduces than 20 mol% loading. Finally, temperature screening was examined using catalysts **8d** with 20 mol% loading, in the presence of *i*-Pr_2O solvent at different temperatures such as, 0 ^oC, -30 ^oC and 40 ^oC (entries 19-21). In temperature study, results were clearly indicating that changes in reaction temperature affects the product results other than room temperature. From this table results, optimization results were confirmed as catalyst **8d** (20 mol%) in the presence of best

i-Pr_2O solvent, at room temperature is suitable conditions for asymmetric Michael addition reaction of **5a** and **6a** (Table 6, entry 4).

Table 6. Screening of reaction conditions using catalyst **8d**



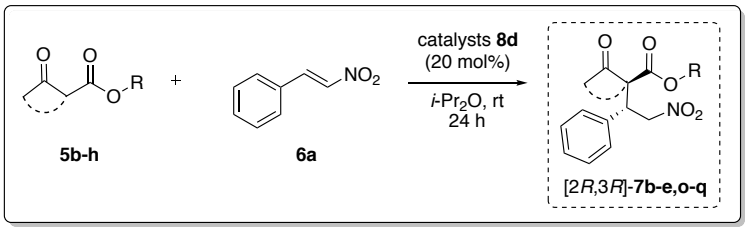
entry	solvent	mol (%)	temp (ºC)	yield (%)[a]	dr[b]	*ee* (%)[c]
1	H_2O	20	rt	97	82:18	16
2	MeOH	20	rt	92	75:25	25
3	*i*-PrOH	20	rt	95	78:22	8
4	DMSO	20	rt	94	65:35	5
5	CH_3CN	20	rt	82	77:23	9
6	DMF	20	rt	94	66:34	35
7	acetone	20	rt	80	74:26	9
8	THF	20	rt	94	64:36	30
9	Et_2O	20	rt	94	65:35	32
10	CH_2Cl_2	20	rt	90	75:25	39
11	$CHCl_3$	20	rt	91	77:23	35
12	toluene	20	rt	85	69:31	48
13	benzene	20	rt	77	72:28	48
14	xylene	20	rt	80	74:26	46
15	hexane	20	rt	91	76:24	39
16	*i*-Pr_2O	10	rt	83	70:30	48
17	*i*-Pr_2O	5	rt	70	68:32	28
18	*i*-Pr_2O	1	rt	59	66:34	12
19	*i*-Pr_2O	20	0	67	73:27	48
20	*i*-Pr_2O	20	-30	10	72:28	30
21	*i*-Pr_2O	20	40	55	70:30	35

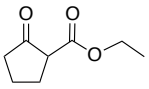
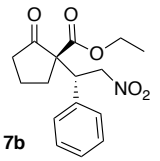
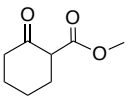
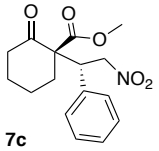
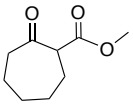
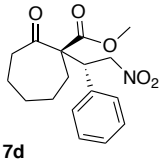
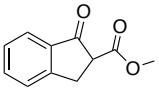
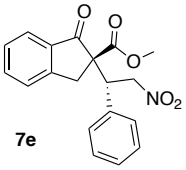
[a]yield was calculated after purification. [b]*dr* was determined by ^1H NMR of crude reaction mixture. [c]The *ee* was determined by HPLC analysis using chiral stationary phase

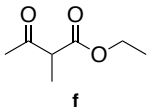
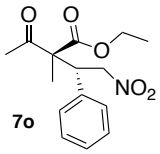
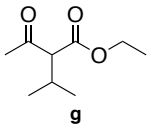
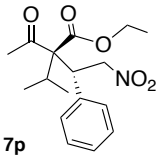
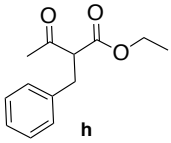
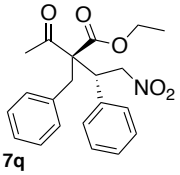
3.5 Asymmetric Michael addition of various β-keto esters 5b-h and nitroolefins 6c-e,h using catalysts 8d

Further extension of catalysts application, substrate scope of asymmetric Michael addition of various β-keto esters **5b-h** and nitroolefins **6a** was examined using superior catalyst **8d** in *i*-Pr_2O at room temperature (entries 1-7, Table 7). Most of the corresponding adducts **7b-e,o-q** were furnishes in moderate to good yields, diastereoselectivities and low to moderate enantioselectivities (55-73%, 40:20-75:25, 8-46%). In first case, reaction of Ethyl 2-cyclopentane carboxylic ester **5b** and **6a** afforded chiral adduct **7b** in good chemical yield, diastereoselectivity and moderate enantioselectivity (73%, *dr*. 75:25, 46% ee) (entry 1).

Table 7. Michael reaction of various β-keto esters **5b-h** and nitroolefin **6a** using catalyst **8d**



entry	5b-h	products 7k-q	yield (%)[a]	dr[b]	ee (%)[c]
1	 **b**	 **7b**	73	75:25	46
2	 **c**	 **7c**	69	61:39	30
3	 **d**	 **7d**	71	63:37	12
4	 **e**	 **7e**	55	40:20	8

5	 f	 7o	trace	trace	trace
6	 g	 7p	trace	trace	trace
7	 h	 7q	trace	trace	trace

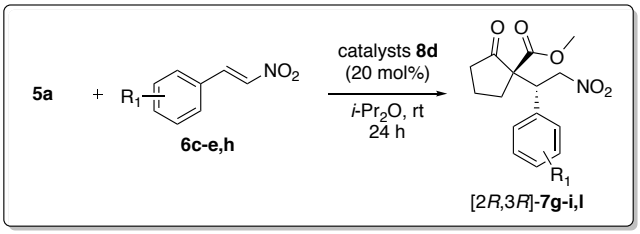
[a]Isolated yield. [b]Determined by 1H NMR of crude reaction mixture. [c]ee was calculated by HPLC using CHIRALCEL OD-H column.

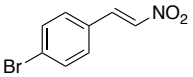
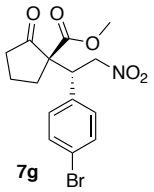
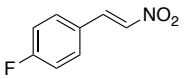
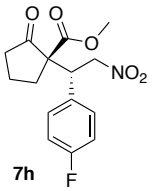
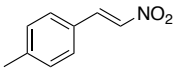
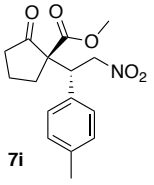
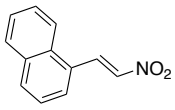
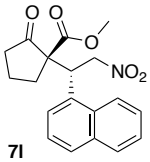
At next, Michael addition of methyl 2-oxocyclohexane carboxylate **5c** and **6a** was obtained corresponding chiral adduct **7c** in moderate chemical yield, diastereoselectivity, but enantioselectivity was slightly decreased (69%, *dr*. 61:39, 30% ee) (entry 2). Followed by 7-membered cyclic β-keto ester **5d** and **6a** using catalyst **8d** was furnishes adduct **7d** in good chemical yield, moderated diastereoselectivity, though enantioselectivity was drastically decreased (71%, *dr*. 63:27, 12% ee) (entry 3). In the case of aromatic ester, reaction of indanone based β-keto ester **5e** afforded chiral adduct **7e** in moderate chemical yield, diastereoselectivity and low enantioselectivity (55%, *dr*. 40:20, 8% ee) (entry 4). Followed by, various acyclic ethyl esters **5f-h** and **6a** were performed using catalysts **8d**. Unfortunately, small trace quantity of product formation only observed (entries 5-7).

After that, reaction of β-keto ester **5a** and various nitroolefins **6c-e,h** using catalyst **8d** to afford corresponding chiral adducts **7g-i,l** in good to moderate chemical yields, diastereoselectivities, and moderate enantioselectivities (up to 85-47%, up to *dr*. 59:41-82:18, up to 36-44% ee) (entries 1-4). At first, nitroolefin **5c** contains bromine substituent at para position and **5a** reaction afforded chiral adducts **7g** in good chemical yield, diastereoselectivity and moderate diastereoselectivity (85%, *dr*. 82:18, 36% ee) (entry 1, Table 8). Fluorine attached nitroolefin **6d** afforded chiral adduct

7h in good chemical yield, diastereoselectivity and moderate enantioselectivity (81%, *dr*. 76:24, 44% ee) (entry 2).

Table 8. Michael reaction of various nitroolefins **6c-e,h** using catalyst **8d**



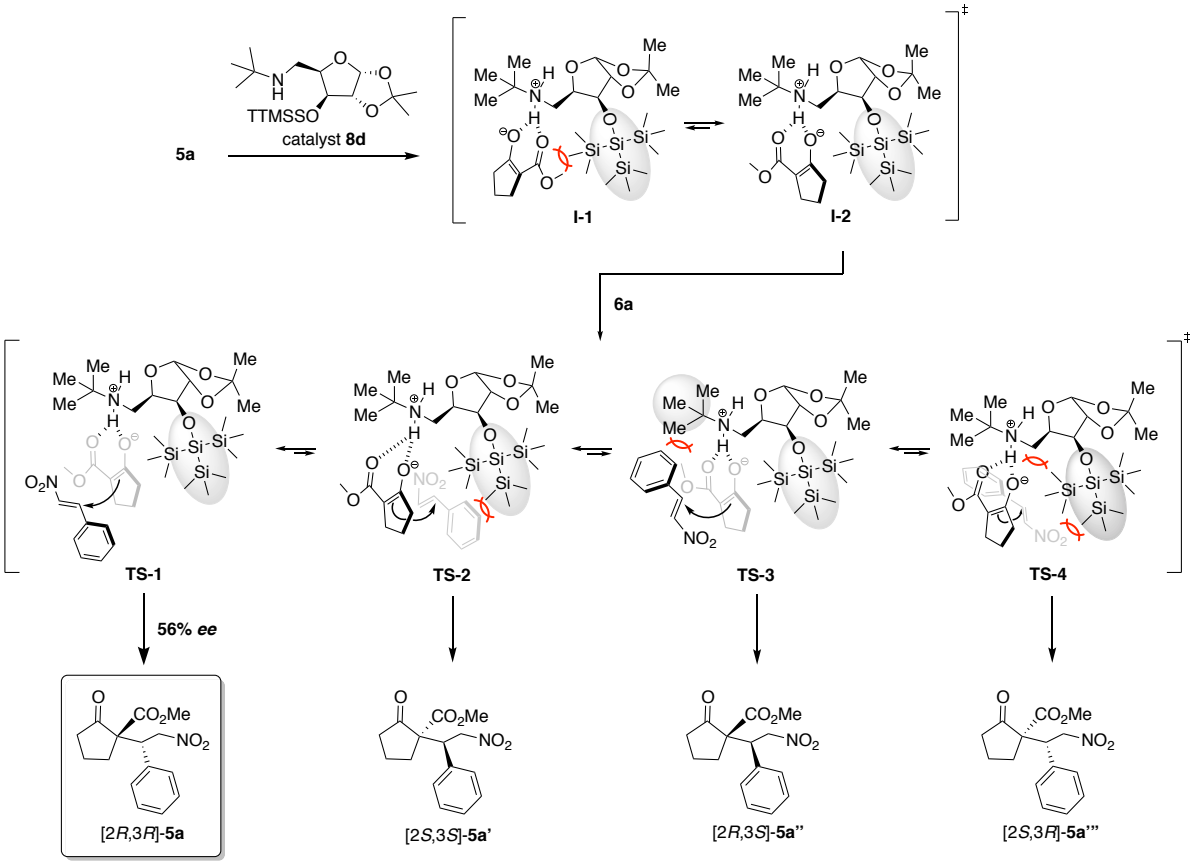
entry	5b-h	products 7c-e,h	yield (%)[a]	dr[b]	ee (%)[c]
1	 **c**	 **7g**	85	82:18	36
2	 **d**	 **7h**	81	76:24	44
3	 **e**	 **7i**	55	65:35	40
4	 **h**	 **7l**	47	59:41	41

[a]Isolated yield. [b]Determined by 1H NMR of crude reaction mixture. [c]ee was calculated by HPLC using CHIRALCEL OD-H column.

After that, methyl substituted nitroolefin **5e** delivers chiral adduct **7i** in moderate chemical yield, diastereoselectivity and enantioselectivity (55%, *dr*. 65:35, 40% ee) (entry 3). Followed by, reaction of **5a** with naphthyl nitroolefin **6h** corresponding adduct **7l** was afforded in moderate chemical yield, diastereoselectivity and enantioselectivity (47%, *dr*. 59:41, 41% ee) (entry 4).

3.6 Plausible reaction course

As realized enantiopurity of chiral Michael adduct [2*R*,3*S*]-**7a** (54% ee), author was proposed plausible enantioselective reaction course shown in Scheme 35. At first, catalysts **8d** acts as a base to β-keto ester **5a** and generated enolate of β-keto ester via hydrogen bonding interactions fixed with ammonium hydrogen atom on catalyst species to generate stable intermediate **I-2**. As compared with intermediate **I-1**, that shows less steric interaction between silyl protecting group of catalyst and methoxy substituent of **5a**. Subsequently, the enantioselective reaction might proceed through **Ts-1** that has comparatively less steric interactions in three cases such as, the substrate **6a** and *t*-butyl group on amino substituent of the ammonium catalyst species, also between **6a** and xylofuranose backbone of the catalyst species, then between **6a** and xylofuranose

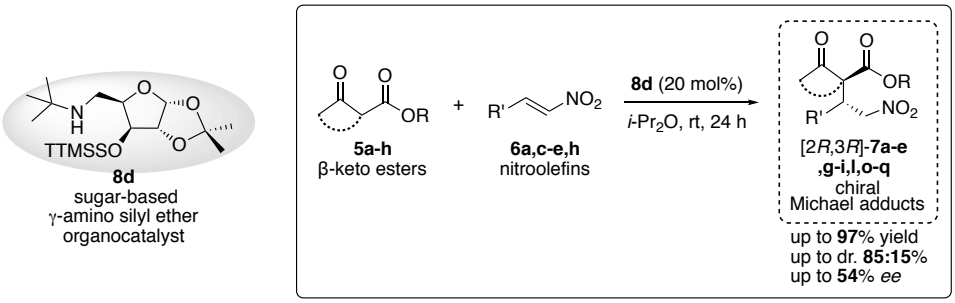


Scheme 35. Plausible reaction course

backbone as well as silyl ether protection. As compared with other transition states, less steric influence and more stability could be realized via **Ts-1**.

3.7 Summary

In summary, xylofuranose based γ-amino silyl ether **8a-k** was developed and utilized as an organocatalysts for the first time in asymmetric Michael addition of β-keto esters **5a-h** with nitroolefins **6c-e,h**. catalysts **8a-k** furnishes the corresponding several Michael adducts **7a-e,g-i,l,o-q** bearing quaternary chiral carbon center were obtained (up to 97%, up to *dr.* 85:15, up to 54% *ee*). Although, the catalytic activity of catalysts **8** in this reaction was not satisfactory. This study might be supportive for the further development on xylofuranose based amino ether and its derivates as an organocatalysts to this reaction and others.



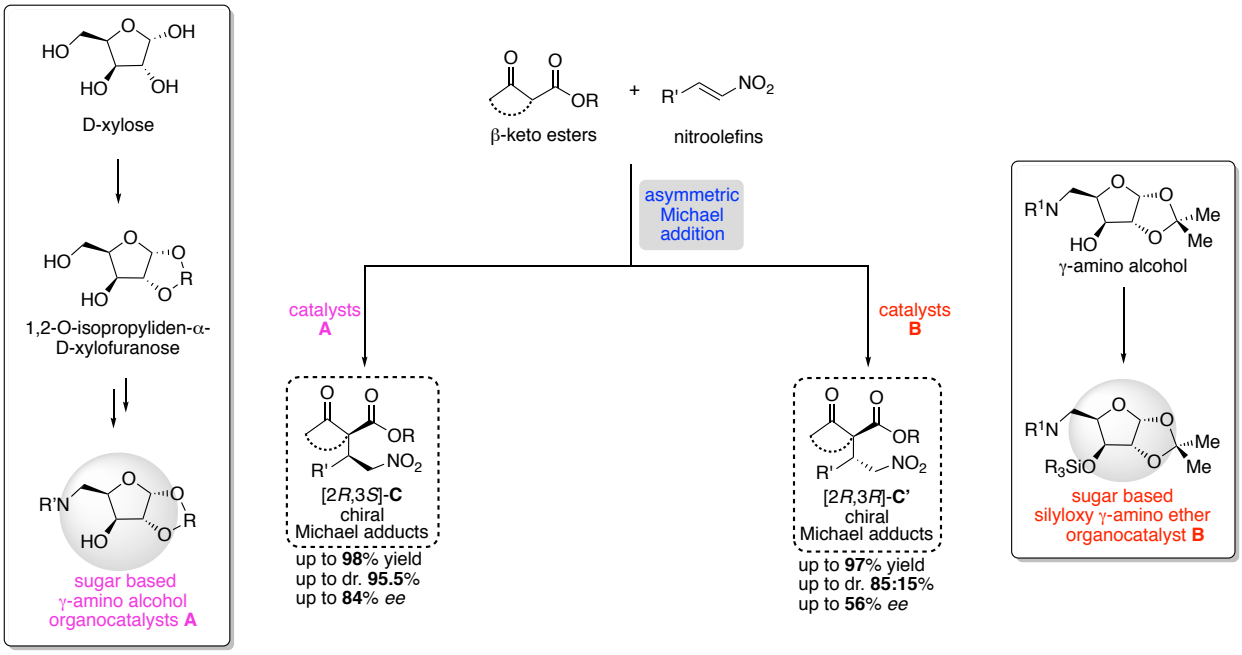
4. Conclusion

Numerous biological active molecules, including pharmaceuticals, are contains often optically active chiral compounds. To biological systems of human beings mostly only one isomer existing active and plays major role in treatment of diseases. Therefore, synthesis of optically active molecules is often demanded as well as more challenging task in the field of synthetic organic chemistry. The asymmetric synthesis enables easy access to synthesis optically active chiral molecule in imbalanced ratio. Though, various catalytic version of asymmetric reactions where been demonstrated, organocatalysis field grabs predominant attentions over scientific community other than asymmetric metal catalysis and enzyme catalysis. Organocatalysts employed in asymmetric reactions 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 two different sugar-based γ-amino organocatalysts to asymmetric Michael addition. In first case, sugar-based γ-amino alcohol catalyst possesses multiple vital functionalities including, amino group could act as covalent or basic sites, hydroxy group as non-covalent site, and 1,2-O-isoprpylidene 5-membered ring back bone and substituent on nitrogen atom both might perform as steric influences site. On the other hand, sugar-based γ-amino silyl ether catalyst has multiple essential functionalities including, amino group could act as covalent or basic sites, both, 1,2-O-isoprpylidene and substituent on nitrogen atom might perform as steric influences site and rigid silyl ether could also act as steric influence site. The prepared sugar-based γ-amino alcohol organocatalysts (chapter 2) and sugar-based γ-amino silyl ether organocatalysts (chapter 3) were successfully applied for asymmetric Michael addition

In chapter 2, author discussed about the detailed application of sugar-based γ-amino alcohol organocatalysts. The sugar-based γ-amino alcohol organocatalysts **4a-j** were prepared from D-xylose and examined in asymmetric Michael addition of β-keto esters **5a-e** with nitromethane **6a-j**. Among the prepared γ-amino alcohol organocatalysts, the catalysts **4d** has showed the best catalytic activity to afford the chiral Michael adduct **7a-n** in excellent chemical yields and diastereoselectivities and good enantioselectivities (up to 98%, up to *dr*. 95:5%, up to 84% ee). The obtained chiral Michael adducts **7a-n** possess quaternary chiral center which is present in many biologically active compounds sand difficult to construct.

In chapter 3, author discussed about the development and detailed application of sugar-based γ-amino silyl ether organocatalysts **8a-k** to asymmetric Michael addition. The new sugar-based γ-amino silyl ether organocatalysts **8a-k** showed catalytic activity and adducts were afforded in excellent chemical yield, diastereoselectivities and moderate enantioselectivities (up to 98%, up to *dr.* 95:5, up to 54% *ee*).

In conclusion, author developed new two different sugar-based γ-amino organocatalysts such as, γ-amino alcohol and γ-amino silyl ether from D-xylose as a synthetic precursor. The prepared sugar-based γ-amino organocatalysts were successfully applied in asymmetric Michael addition which afforded the biological active chiral synthetic intermediates in excellent chemical yields and enantioselectivities. It is expected that these results might be able to contribute greatly in the development of new synthetic drugs in the field of synthetic organic chemistry.



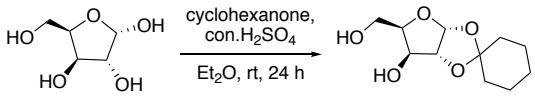
5. Experimental section

General Methods

Reagents and analytical grade solvents were obtained from commercial suppliers and used without further purification. All reactions were carried out under a positive atmosphere of argon, glass wares were flame-dried and cooled in desiccator. The reactions were monitored by thin layer chromatography (TLC). TLC was performed on Merck pre-coated silica gel 60 F-254 plates. Spots were visualized by exposure to UV light, by immersion into a solution of *p*-anisaldehyde followed by heating at ca. 200 °C. Column chromatography was performed on Kanto Chemical silica gel 60 N (Spherical, neutral, 40-50 μm).The melting points were determined using a micro-melting point apparatus. IR spectra were recorded on JASCO FT/IR-4100 and the major absorbance bands are all reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were measured on EI and FAB using sector instruments [Hitachi RMG-GMG and JEOL JNK- DX303]. NMR spectra were recorded on a JEOL JNM-ECA500 spectrometer, operating at 500 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (δ = 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported downfield from TMS (δ = 0 ppm) or in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. Coupling constants (*J*) are reported as hertz (Hz). Splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. The enantiomeric excess (*ee*) was determined by HPLC analysis. HPLC was measured at column, CHIRALPAK IC, CHIRALCEL OD-H (4.6 mm Å~ 25 cm) and 2-propanol/hexane system was employed as a mobile phase.

Chapter 2: Sugar based γ-amino alcohol organocatalysts for asymmetric Michael addition of β-keto ester and nitroolefin

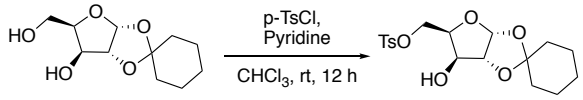
General procedure for synthesis of compound 2b



1 **2b**

A mixture of D-xylose **1** (5 g, 0.33 mmol) and cyclohexanone (8.6 ml, 0.83 mmol) in dry acetone (30 ml) stirred at room temperature under argon environment for 24 h. After the reaction completion monitored by TLC, solvent was removed under reduced pressure. Obtained reaction mixture was neutralized with $NaHCO_3$ and extracted using Et_2O. The combined organic layers were successively washed with H_2O and brine. After the general drying procedure, the solvent was concentrated under reduced pressure followed by recrystallisation using hexane and EtOH:H_2O-8:2 afforded residue of *1,2:3,5-di-O-cyclohexylidene-α-D-xylofuranose* in 85% (0.411 g) of yield. The obtained residue was diluted with 50% of AcOH and heated at 100 °C for 25-30 mins. After the reaction completion, reaction mixture was basified with solid $NaHCO_3$ at 0 °C, adjusted to pH-7 and stirred for 10-15min by bringing the temperature gradually from 0 °C to room temperature. The organic layer was extracted in three portions (3 × 50 mL) using $CHCl_3$ and the combined organic layers were dried using Na_2SO_4 and concentrated under reduced pressure. The obtained crude residue was subjected to recrystallization using benzene and hexane resulting the compounds **2b** as a white solid at 90% (0.498 g) yield.

1,2-cyclohexylidene-5-O-(*p*-tolylsulfonyl)-α-D-xylofuranose 3b

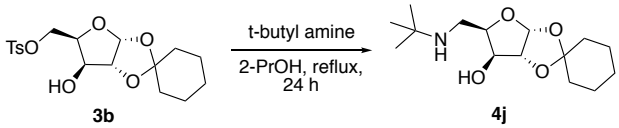


2b **3b**

To a solution of $CHCl_3$ (20 ml) in 50 mL RB were added compound **2b** (2 g, 0.086 mmol) and *p*-TsCl (1.58 g, 0.0825 mmol) at 0 °C. After stirring for 10min, pyridine (2.8 ml, 0.34 mmol) was added slowly and reaction was further stirred for 30 mins at 0 °C, gradually reaction was bought to room temperature and allowed continuous stirring for 12 h. After 12h, 0.2 ml of H_2O was added and allowed to stir for 30 min. Finally, the reaction was quenched with ice cooled water and neutralized with conc.H_2SO_4 and adjusted to pH 7. The organic layer was extracted in three

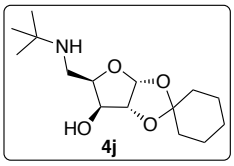
portions using $CHCl_3$ (3 × 20 mL). The obtained combined organic layers were dried on Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography afforded compound **3b** with 80% yield.

1,2-cyclohexylidene-5-O-(t-butylamine)-α-D-xylofuranose 4j



A solution of 2-propanol (15 mL) was taken in in RB flask, to this was added compound **3b** (200 mg, 0.005 mmol) and *t*-butylamine (0.17 ml, 0.024 mmol) and subjected to heating under reflux condition for 24 h. Upon completion of reaction, solvents were evaporated under reduced pressure. Neutralized with solid $NaHCO_3$ and organic layer was extracted using ether as three portions (3 × 10 mL). The obtained combined organic layers were dried on Na_2SO_4, concentrated and recrystallized using hexane promote compound **4j**.

1,2-Cyclohexylidene-5-O-(t-butylamine)-α-D-xylofuranose 4j: Yellow solid; m.p. 76.7 °C. IR



(neat): = 2936, 1391, 1298, 1109 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.90-5.86 (1H), 4.40-4.36 (1H), 4.23-4.13 (1H), 3.30-3.24 (1H), 2.92-2.86 (1H), 1.68-1.27 (8H), 1.19-1.08 (1H), 1.08-0.92 (7H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 110.34 (s, 1C), 104.06 (s, 2C), 85.10 (s, 2C), 77.30 (s, 2C), 76.17 (t, J = 31.2 Hz, 5C), 49.20 (s, 1C), 40.38 (s, 2C), 27.41 (s, 5C), 25.85 (s, 2C), 25.16 (s, 2C). HRMS (MStation) m/z: $[M+H]^+$ calculated for $C_{15}H_{27}NO_4$: 285.19; found: 285.1945.

Compounds **4a-i** were prepared based on previous reports and obtained compounds were all matched with previously reported data.[39]

General procedure for the Michael addition of β-keto esters 5a-e to *trans*-β-nitroolefins 6a-j

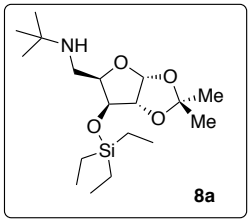
To a stirred solution of *trans*-β-nitroolefins **6a-j** (0.34 mmol) and organocatalysts **4a-j** (0.03 mmol, 20 mol%) in *i*-Pr_2O (0.5 mL) were added β-keto esters **5a-e** (0.67 mmol) at room temperature. After the reaction completion was monitored by TLC, the mixture was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under a reduced pressure. The residue was purified by flash column chromatography on SiO_2 (*n*-hexane/EtOAc = 9:1) to afford the corresponding chiral Michael adducts **7a-n**. The ee were determined by HPLC using DAICEL CHIRALCEL OD-H or CHIRALPAK IC columns.

Chapter 3: Sugar based γ-amino silyl ether organocatalysts for asymmetric Michael addition of β-keto ester and nitroolefin

General procedure for the preparations of γ-amino silyl ether organocatalysts 8a-k

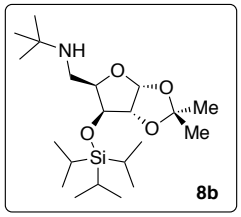
To a stirred solution of compounds **4a-k** (0.20 g, 0.82 mmol) and Et_3N (2.05 mmol) in CH_2Cl_2 (15 mL) was added corresponding silyl protecting reagents (1.2 mmol) at 0 ºC for 30 mins. After that, reaction mixture was allowed to stir at room temperature for 24 h. Upon completion of reaction that was monitored by TLC, solvents were evaporated under reduced pressure and organic layer was extracted using CH_2Cl_2 as three portions (3 × 10 mL) from aqueous layer. The obtained combined organic layers were dried on Na_2SO_4, concentrated and purified by flash chromatography using on SiO_2 (CH_2Cl_2/MeOH = 9:1) afforded the compounds **8a-k**.

1,2-O-isopropylidene-3-O-triethylsilyl-5-*N*-(*t*-butylamine)-α-D-xylofuranose 8a: yellow solid.



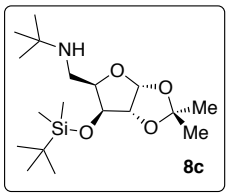
Yellowish solid $[\alpha]_D^{29}$ = 2 (c = 1.0, CH_2Cl_2). IR (neat) 2968, 1635, 1456, 1252, 1118, 1067 cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ = 5.91 (d, J = 3.4 Hz, 1H), 4.35 (d, J = 4.0 Hz, 1H), 4.25-4.22 (m, 1H), 4.14 (d, J = 2.9 Hz, 1H), 2.88 (dd, J = 11.5, 8.0 Hz, 1H), 2.68 (dd, J = 11.5, 4.0 Hz, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.10 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), ^{13}C NMR (126 MHz, $CDCl_3$) δ = 111.6, 104.8, 85.8, 81.4, 76.2, 50.3, 42.0, 28.9, 26.8, 26.4, 25.7, 18.1, -4.6, -5.1. MS (EI) *m/z* : 359 $[M]^+$, HRMS [EI] calculated for $C_{18}H_{37}NO_4Si$ $[M]^+$: 359.58. found: 359.25.

1,2-O-isopropylidene-3-O-triisopropylsilyl-5-*N*-(*t*-butylamine)-α-D-xylofuranose 8b:



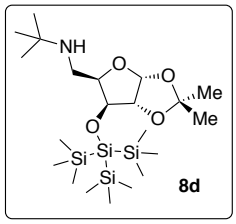
colorless syrup. $[\alpha]_D^{29}$ = 14 (c = 1.0, CH_2Cl_2). IR (neat) 2942, 1635, 1457, 1215, 1140, 1121cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ = 5.91 (d, J = 3.4 Hz, 1H), 4.43 (q, J = 3.2 Hz, 1H), 4.35 (dd, J = 8.9, 3.2 Hz, 2H), 2.99 (dd, J = 11.7, 8.9 Hz, 1H), 2.90 (dd, J = 11.7, 3.2 Hz, 1H), 1.50 (s, 3H), 1.30 (s, 3H), 1.20 (s, 12H), 1.08 (d, J = 8.0 Hz, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 112.1, 104.9, 86.2, 80.5, 77.1, 42.4, 28.3, 27.1, 26.7, 18.2, 12.6. MS (EI) *m/z* : 401 $[M]^+$, HRMS m/z: [EI] calculated for $C_{21}H_{43}NO_4Si$ $[M]^+$: 401.66. found: 401.29.

1,2-O-isopropylidene-3-O-*t*-butyldimethylsilyl-5-*N*-(*t*-butylamine)-α-D-xylofuranose 8c:



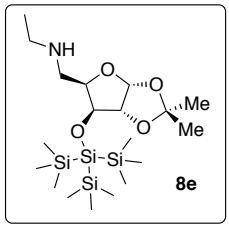
colorless syrup. $[\alpha]_D^{29} = 20$ (c = 1.0, CH_2Cl_2). IR (neat) 2956, 1636, 1253, 1137, 1117 cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ = 5.91 (d, J = 3.4 Hz, 1H), 4.35 (d, J = 4.0 Hz, 1H), 4.25-4.22 (m, 1H), 4.14 (d, J = 2.9 Hz, 1H), 2.88 (dd, J = 11.5, 8.0 Hz, 1H), 2.68 (dd, J = 11.5, 4.0 Hz, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.10 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), ^{13}C NMR (126 MHz, $CDCl_3$) δ = 111.6, 104.8, 85.8, 81.4, 76.2, 50.3, 42.0, 28.9, 26.8, 26.4, 25.7, 18.1, -4.6, -5.1. MS (EI) *m/z* : 359 $[M]^+$, HRMS [EI] calculated for $C_{18}H_{37}NO_4Si$ $[M]^+$: 359.58. found: 359.24.

1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(*t*-butylamine)-α-D-xylofuranose 8d:



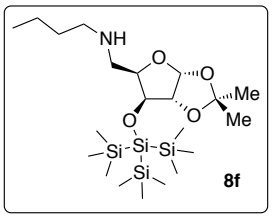
Colorless syrup. $[\alpha]_D^{29} = 15$ (c = 1.0, CH_2Cl_2). IR (neat) 2953, 1652, 1361, 1244, 1215, 1113, 1074 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.84 (d, J = 3.4 Hz, 1H), 4.31 (d, J = 4.0 Hz, 1H), 4.22 (td, J = 6.0, 2.9 Hz, 1H), 3.86 (d, J = 2.9 Hz, 1H), 2.86 (dd, J = 11.5, 8.6 Hz, 1H), 2.64 (dd, J = 11.5, 2.9 Hz, 1H), 1.47 (s, 3H), 1.29 (s, 3H), 1.11 (s, 9H), 0.22 (s, 27H), ^{13}C NMR (126 MHz, $CDCl_3$) δ = 111.6, 104.8, 85.4, 81.8, 80.3, 50.4, 42.4, 28.9, 26.9, 26.3, 0.4. MS (EI) *m/z* : 491 $[M]^+$, HRMS [EI] calculated for $C_{21}H_{49}NO_4Si_4$ $[M]^+$: 491.97. found: 492.28.

1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(ethylamine)-α-D-xylofuranose 8e:



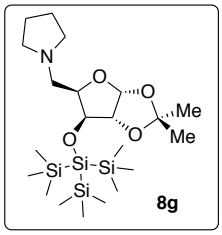
Yellow syrup. $[\alpha]_D^{29} = 4$ (c = 1.0, CH_2Cl_2). IR (neat) 2942, 1635, 1457, 1215, 1140, 1121cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.77 (d, J = 4.0 Hz, 1H), 4.24 (d, J = 4.0 Hz, 1H), 4.20 (td, J = 5.7, 3.1 Hz, 1H), 3.78 (d, J = 2.9 Hz, 1H), 2.80 (dd, J = 12.6, 8.6 Hz, 1H), 2.68 (dd, J = 12.3, 3.7 Hz, 1H), 2.61 (q, J = 7.1 Hz, 2H), 1.40 (s, 3H), 1.22 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H), 0.15 (s, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 112.0, 105.2, 85.7, 81.1, 80.6, 49.4, 45.0, 27.3, 26.7, 15.7, 0.9; MS (EI) *m/z* : 463 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{19}H_{45}NO_4Si_4$ $[M]^+$: 463.91. found: 464.24.

1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(*n*-butylamine)-α-D-xylofuranose 8f:



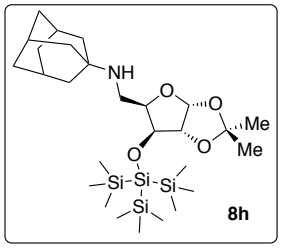
Pale yellow syrup. $[\alpha]_D^{29} = 13$ (c = 1.0, CH_2Cl_2). IR (neat) 2949, 1558, 1361, 1456, 1214, 1123 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, J = 4.0 Hz, 1H), 4.31 (d, J = 3.4 Hz, 1H), 4.26 (td, J = 5.7, 3.1 Hz, 1H), 3.84 (d, J = 2.9 Hz, 1H), 2.86 (dd, J = 12.3, 8.3 Hz, 1H), 2.73 (dd, J = 12.3, 3.7 Hz, 1H), 2.62 (t, J = 7.2 Hz, 2H), 1.48-1.44 (m, 5H), 1.38-1.32 (m, 2H), 1.29 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.22 (s, 27H), ^{13}C NMR (126 MHz, $CDCl_3$) δ = 112.1, 105.3, 85.8, 81.3, 80.7, 50.7, 49.8, 32.9, 27.4, 26.8, 21.1, 14.7, 1.0. MS (EI) *m/z* : 491 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{21}H_{49}NO_4Si_4$ $[M]^+$: 491.97. found: 492.28.

1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(pyrrolidine)-α-D-xylofuranose 8g:



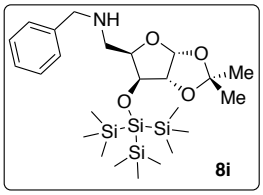
Yellow syrup. $[\alpha]_D^{29} = 12$ (c = 1.0, CH_2Cl_2). IR (neat) 2939, 1636, 1455, 1218, 1066 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.85 (d, J = 3.4 Hz, 1H), 4.29 (d, J = 3.4 Hz, 1H), 4.27 (td, J = 5.6, 2.9 Hz, 1H), 3.83 (d, J = 2.9 Hz, 1H), 2.74 (dd, J = 12.9, 8.3 Hz, 1H), 2.62 (dd, J = 12.9, 3.2 Hz, 1H), 2.56 (s, 4H), 1.78 (t, J = 4.6 Hz, 3H), 1.48 (d, J = 4.6 Hz, 3H), 1.29 (s, 3H), 0.22 (s, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 111.9, 105.5, 85.4, 81.0, 80.4, 55.7, 55.2, 27.5, 26.8, 24.0, 1.0. MS (EI) *m/z* : 489 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{21}H_{47}NO_4Si_4$ $[M]^+$: 489.95. found: 490.26.

1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(adamantyl)-α-D-xylofuranose 8h:



Yellow solid. $[\alpha]_D^{29} = 8$ (c = 1.0, CH_2Cl_2). IR (neat) 2947, 1636, 1242, 1164, 1075 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.84 (d, J = 3.4 Hz, 1H), 4.30 (d, J = 4.0 Hz, 1H), 4.20 (td, J = 6.0, 2.9 Hz, 1H), 3.85 (d, J = 2.9 Hz, 1H), 2.91 (dd, J = 11.5, 8.6 Hz, 1H), 2.65 (dd, J = 11.7, 3.2 Hz, 1H), 2.06 (s, 3H), 1.67 (d, J = 9.7 Hz, 6H), 1.59 (d, J = 11.5 Hz, 6H), 1.47 (s, 3H), 1.29 (s, 3H), 0.22 (s, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 112.1, 105.3, 86.1, 85.9, 82.4, 80.8, 51.1, 43.1, 40.8, 37.3, 30.2, 27.4, 26.8, 1.0. MS (EI) *m/z*: 525 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{15}H_{27}NO_4$: 525.98. found: 526.26.

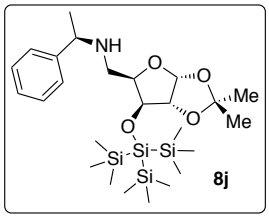
1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(benzylamine)-α-D-xylofuranose 8i:



8i

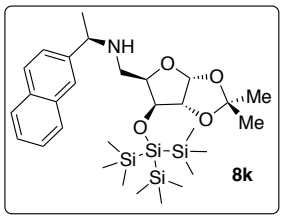
Colorless syrup. $[\alpha]_D^{29} = 21$ (c = 1.0, CH_2Cl_2). IR (neat) 2947, 1698, 1652, 1455, 1215, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35-7.32 (m, 2H), 7.27 (q, J = 3.4 Hz, 3H), 5.94 (d, J = 3.8 Hz, 1H), 4.50 (d, J = 4.0 Hz, 1H), 4.29 (d, J = 2.9 Hz, 1H), 4.23-4.21 (m, 1H), 3.79 (d, J = 6.3 Hz, 2H), 3.40 (dd, J = 12.9, 3.7 Hz, 1H), 3.01 (dd, J = 12.9, 1.4 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H), 0.18 (s, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 137.8, 128.3, 127.9, 127.2, 111.1, 104.7, 85.5, 77.7, 76.5, 53.3, 47.3, 26.5, 25.8, -0.9. MS (EI) *m/z*: 540 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{25}H_{49}NO_4Si_4$ $[M]^+$: 540.01. found: 540.28.

1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(*R*-phenylethylamine)-α-D-xylofuranose 8j: Pale yellow syrup. $[\alpha]_D^{29} = 8$ (c = 1.0, CH_2Cl_2). IR (neat) 2947, 1636, 1242, 1164, 1075 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.33-7.26 (m, 4H), 7.22-7.19 (m, 1H), 5.85 (d, J = 4.0 Hz, 1H), 4.26 (d, J = 4.0 Hz, 1H), 4.19 (td, J = 5.9, 3.1 Hz, 1H), 3.77 (q, J = 6.5 Hz, 1H), 3.72 (d, J = 2.9 Hz, 1H), 2.71 (dd, J = 12.6, 9.2 Hz, 1H), 2.47 (dd, J = 12.3, 2.6 Hz, 1H), 1.48 (s, 2H), 1.36 (d, J = 6.3 Hz, 3H), 1.28 (s, 3H), 0.12 (s, 27H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.9, 129.0, 127.5, 112.1, 105.4, 86.0, 81.9, 80.9, 59.8, 48.3, 27.4, 26.8, 25.2, 0.9. MS (EI) *m/z*: 590 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{29}H_{51}NO_4Si_4$ $[M]^+$: 590.07. found: 590.29.



8j

1,2-O-isopropylidene-3-O-tris(trimethylsilyl)silyl-5-*N*-(*R*-naphthylamine)-α-D-xylofuranose 8k: Red syrup. $[\alpha]_D^{29} = 5$ (c = 1.0, CH_2Cl_2). IR (neat) 2947, 1652, 1456, 1242, 1215, 1074 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 8.11 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 6.3 Hz, 1H), 7.55-7.47 (m, 3H), 6.01 (d, J = 3.4 Hz, 1H), 4.62 (q, J = 6.7 Hz, 1H), 4.51 (d, J = 3.4 Hz, 1H), 4.22 (d, J = 2.3 Hz, 1H), 4.16-4.15 (m, 1H), 3.29 (dd, J = 12.9, 3.7 Hz, 1H), 2.91 (dd, J = 13.2, 1.1 Hz, 1H), 1.53 (d, J = 6.3 Hz, 2H), 1.45 (s, 3H), 1.32 (s, 3H), 0.19 (s, 27H). MS (EI) *m/z* : 570 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{27}H_{55}NO_4Si_4$ $[M]^+$: 570.08. found: 570.32.



8k

General procedure for the Michael addition of β-keto esters 5a-e to *trans*-β-nitroolefins 6a-j

To a stirred solution of *trans*-β-nitroolefins **6a,c-e,h** (0.34 mmol) and organocatalysts **8a-k** (0.03 mmol, 20 mol%) in *i*-Pr_2O (0.5 ml) were added β-keto esters **5a-h** (0.67 mmol) at room temperature. After the reaction completion was monitored by TLC, the mixture was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under a reduced pressure. the residue was purified by flash column chromatography on SiO_2 (*n*-hexane/EtOAc = 9:1) to afford the corresponding chiral Michael adducts **7a,c-e,h,k-q**. the enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OD-h column.

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