Asymmetric Michael addition using sugar derived organocatalysts

P.B. Lalthanpuii$^{1,2}$, C. Lalhriatpuia$^1$, K. Vanlaldinpuia$^1*$

$^1$Department of Chemistry, $^2$Department of Zoology, Pachhunga University College, Aizawl 796001, Mizoram

Sugars are low-molecular-weight carbohydrates which consist of polyhydroxyl and carbonyl (aldehyde or ketone) functional groups. Different types of compounds derived from sugars have been used extensively as powerful and effective catalysts for asymmetric synthesis. They are readily available at a reasonable price, easily prepared, no metal contamination and are inert towards moisture and air. They are highly functionalized and have well defined stereogenic centres. Most of them are employed as chiral ligands in metal based asymmetric catalysis and are used for various asymmetric transformations. Different compounds derived from sugars have also been used recently as organocatalysts for asymmetric synthesis. The present article provides some of the organocatalysts used for asymmetric synthesis.

Key words: Asymmetric Michael addition, organocatalysts, sugar.

Introduction

The word ‘sugar’ is often signified as a synonym for carbohydrates in general, but in everyday usage it means the table sugar, sucrose.$^1$ The carbohydrates (saccharides) are a group of organic compounds which consists of polyhydroxyl and carbonyl (aldehyde or ketone) functional groups with the capability of forming an intramolecular hemiacetal or hemiketal.$^2,3$ They are divided into three groups namely: monosaccharides, oligosaccharides, and polysaccharides. The nomenclature suffix “ose” is used to denote carbohydrates. The name carbohydrate originates from “carbon hydrate” (hydrate of carbon), as they were originally believed to consist solely of carbon and water and thus were commonly designated by the generalised formula $C_n(H_2O)_3$.$^4$

Nowadays, the definition of carbohydrates has been much expanded to include substances derived from reduction or oxidation of monosaccharides and also those containing other elements (nitrogen, sulphur and halogens).$^5$

Generally, among the carbohydrates mentioned above, monosaccharides and oligosaccharides (usually disaccharides and trisaccharides) having lower molecular weight are commonly referred to as sugars.$^6$

Monosaccharides (Fig. 1) are divided into two main groups depending on which carbonyl functionalities they contain: “aldoses” for those containing aldehyde and “ketoses” for those having ketone functional group.$^4$ They can further be classified according to the number of carbon atoms in the monomeric chain into triose (n = 3), tetrose (n = 4), pentose (n = 5), hexose (n = 6),...
heptose (n = 7), etc. and the types of functional groups that are present.

(+)-D-glucose, also known as grape sugar, is the most abundant monosaccharide found in nature followed by (+)-D-mannose and (+)-D-galactose. On the other hand, (+)-D-fructose is the sweetest of all naturally occurring carbohydrates and regarded as 1.73 times sweeter than sucrose. It is also the most abundant ketose.

Carbohydrates are the most abundant biomolecule and play an important role in a number of biological reactions. They are the main source of energy in most cells. For example, polysaccharides such as starch and glycogen serve as the storage of energy. Cellulose and chitin are important structural components in plants and arthropods respectively. The 5-carbon monosaccharide ribose is an important component of co-enzymes (e.g. ATP, FAD, and NAD) and the backbone of the genetic molecule known as RNA. Likewise, the related deoxyribose is a component of DNA. Carbohydrates and their derivatives include many important biomolecules that play key roles in the cell-cell recognition, immune system, embryogenesis, hormonal activities, fertilization, preventing pathogenesis, blood clotting, neuronal development, viral and bacterial infections, proliferation of cells and tumour cell metastasis.

In recent years, different types of compounds derived from sugars have emerged as powerful and effective catalysts for asymmetric synthesis. They are readily available at a reasonable price, are highly functionalized, and have several well
defined stereogenic centres. Most of them are employed as chiral ligands (Fig. 2) in metal based asymmetric catalysis and are used for various asymmetric transformations.6,15

Recently, different compounds derived from sugars are also used as organocatalyst for asymmetric synthesis. In continuation with our efforts to explored different types of organocatalysts used for asymmetric Michael addition,16 here we will highlight a short historical review on the synthesis and applications of sugar derived chiral organocatalysts for the said reaction.

Michael addition using sugar derived organocatalysts

Though asymmetric Michael addition using organocatalysts has been well documented, there are only few reports of sugar derived organocatalysts used for enantioselective Michael addition. In 2007, Liu et al.17 reported a highly enantioselective Michael addition of aromatic ketones to nitro olefins promoted by bifunctional thiourea catalyst (2) readily prepared from commercially available β-D-glucopyranose (1) via acetylation, bromination, substitution reac-
tion and subsequent addition of chiral 1, 2-
cyclohexylidiamines (Scheme 1). The other two
thiouraea catalyst 2c and 2d were synthesised
from maltose and lactose, respectively. With
catalyst 2b, Michael addition adducts was ob-
tained in good yields (up to 99%) and high enan-
tioselectivity (up to 98%) (Scheme 2). The origin
of enantioselectivity seems to arise from the
attack of the enamine to the si-face of the nitro-
olefins as the re-face attack was block by cy clo-
hexyl group of the catalyst (Fig. 4).
In 2008, Gao et al.18 employed bifunctional
thiouraea organocatalysts 3a, 3b and 3c (Fig. 5)
synthesised from α-D-glucopyranose, galactose
and lactose, respectively for asymmetric Michael
addition of acetyl acetone to nitro olefins. Using
β-nitrostyrene as a test substrate, thiouraea 3a
gave the best result in terms of enantioselectiv-
ity. The reaction was done at -40 °C using ex-
actly 10 mol% catalyst and β-nitrostyrene con-
centration of 0.4 M in toluene to get the best
possible result. Under the optimized condition,
the versatility of the reaction was investigated
using various nitro olefins. The reactions gave
up to >99% yield and up to 96% enantioselectiv-
ity (Scheme 3).
In the same year Li et al.19 also reported enan-
tioselective Michael addition of malonates to
nitroolefins catalyzed by chiral bifunctional ter-
tiary amine-thiouraes based on saccharides (Fig.
6). Using 4a and 4b as catalysts in the presence
of toluene as a solvent and at -20 °C, the reaction
gave up to 99% yield and 99% ee (Scheme 4).
Pu et al.20 developed a series of new organo-
catalysts (7) from both α-amino acids and carbo-
hydrates (Figure 7) which were consequently
used for asymmetric Michael addition of acetyl-
acetone to nitroolefins. The catalysts were read-
ily prepared by coupling amines (5) derived from
α-amino acids and isothiocyanate (6) derived
from D-glucopyranose (Scheme 5). They also
described the "matched" and "mismatch" effect of
two different chiral units in a chiral organo-
catalysts, in which both the enantiomers of the
product was obtained in almost the same enan-
tioselectivity with "matched" and "mismatched"
organocatalysts simply by changing the solvent
system from THF to toluene. With 7a (derived
from L-valine and D-glucopyranose), addition of
acetylacetone to β-nitrostyrene gave 88% yield
and 85% enantiomeric excess having (S)-
configuration when THF was used as a solvent.
On the other hand, the use of 7a’ (derived
from D-valine and D-glucopyranose) in THF gave
the opposite enantiomer with lower enantiose-
lectivity (76% ee) which suggest that L-
configuration of valine matched the D-glucopyranose,
whereas D- configuration of valine mismatched
the D-glucopyranose. But, by changing the sol-
vent from THF to toluene, 7a’ gave the product
with the opposite absolute configuration in al-
most the same enantiomeric excess (86%).
Doubly stereo controlled catalytic conjugate
addition of acetylacetone to nitroolefins was
also achieved with thiouraea catalyst 7e and 7e’
in the same solvent (i.e. toluene). Addition of
acetylacetone to a variety of nitroolefins in the
presence of 7e and 7e’ gave the desire products
with (S) or (R) configuration (Scheme 6 & 7) in
high yields (up to 90%) and good enantioselectiv-
ity (up to 91%).
Lu et al.21 also reported a newly designed pyr-
rolidine thiourea for asymmetric Michael addi-
tion of cyclohexanone to nitro olefins. (S)- or (R)-
tert-butyl 2-(amino-methyl)pyrrolidine-1-
carboxylate (8) coupled with glucosyl isothiocya-
inate (6) to give the catalysts (Scheme 8). With
9a, the reactions gave γ-nitroketones with good
yields (up to >99%) and excellent diastere- (up
to >99/1 di) and enantioselectivity (up to 97% ee)
(Scheme 9). They proposed a transition state in
which nucleophilic attack of the enamine to the
nitroolefin from re-face resulted in the forma-
tion of the desired product (Figure 8).
Another new class of carbohydrate-based bifunc-
tional organocatalysts for nucleophilic
Michael addition to nitroolefins and imines was
reported by Puglisi et al.22 They prepared the
catalysts from readily available D-glucosamine
to prepare 11a-d, which were subsequently con-
verted to the desired thiourea catalysts as
shown in the Scheme 9 and 10. With 12b, addition
of acetylacetone to nitroolefins gave up to
93% yield and up to 83% enantioselectivity
(Scheme 12). Asymmetric addition of diethyl
malonate to N-lox imine of benzaldehyde was
Scheme 1 | Synthesis of primary amine-thiourea catalyst.

**Scheme 2** | Enantioselective Michael addition using thiourea catalyst 2.

Fig. 3 | Sugar derived organocatalyst used for asymmetric Michael addition.

Fig. 4 | Transition state model.
**Fig. 5** | Bifunctional thiourea catalysts from sugars.

**Scheme 3** | Asymmetric Michael addition of acetylacetone to nitroolefins using 3.

![Chemical Structure of 3a, 3b, and 3c](image)

\[ R\text{NO}_2 + \text{Acetylacetone} \xrightarrow{3\text{ 10 mol\%}} \text{R}\text{NO}_2\text{Acetylacetone} \]

Yield = Upto 99 %
ee = Upto 96 %

**Fig. 6** | Saccharides based bifunctional tertiary amine-thioureas catalysts.

**Scheme 4** | Enantioselective Michael addition of malonates to nitro olefins.

![Chemical Structure of 4a, 4b](image)

\[ \text{MeO}_2\text{C} + R\text{NO}_2 \xrightarrow{4\text{a or 4b 10 mol\%}} \text{MeO}_2\text{C}R\text{NO}_2\]

Yield = Upto 99%
ee = Upto 99%
Scheme 5 | Synthesis of thiourea catalyst 7.

Fig. 7 | Different thiourea catalyst derived from amino acids and carbohydrates.
Scheme 6 | Asymmetric addition of acetylacetone to nitroolefins giving (S) configuration.

\[
\text{Acac} + R\text{NO}_2 \xrightarrow{7 \text{a-e} (10 \text{ mol} \%) \text{THF, rt}} R\text{NO}_2
\]

Yield = Upto 88 %

ee = Upto 90 %

Scheme 7 | Asymmetric addition of acetylacetone to nitroolefins giving (R) configuration.

\[
\text{Acac} + R\text{NO}_2 \xrightarrow{7 \text{a-e}' (10 \text{ mol} \%) \text{Toluene, rt}} R\text{NO}_2
\]

Yield = Upto 88 %

ee = Upto 90 %

Scheme 8 | Synthesis of pyrrolidine thiourea catalyst.

\[
\text{8} + \text{6} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt then CF}_3\text{CO}_2\text{H}} \text{9a : (S)-Pyrrolidine thiourea}
\]

\[
\text{9b : (R)-Pyrrolidine thiourea}
\]

Scheme 9 | Asymmetric addition of cyclohexanone to nitro olefins.

\[
\text{Cyclohexanone} + R\text{NO}_2 \xrightarrow{9\text{a} (20 \text{ mol} \%) \text{Et}_3\text{N} (20 \text{ mol} \%) \text{PrCOOH(10 mol\%), -15 °C}} R\text{NO}_2
\]

Yield = Upto 99 %

dr = Upto 99/1 (syn/anti)

ee = Upto 97 %

Fig. 8 | Proposed transition model.
Scheme 10 | Synthesis of glucosaminylurea-based organocatalyst. i) PPh$_3$, ArNCS, THF; ii) Pd(PPh$_3$)$_4$, Bu$_3$SnH, AcOH, CH$_2$Cl$_2$, then HCHO, NaCNBH$_3$, THF; iii) NaOMe, MeOH, (qu).

Scheme 11 | Synthesis of glucosaminylurea-based organocatalyst 12f. i) Pd(PPh$_3$)$_4$, Bu$_3$SnH, AcOH, CH$_2$Cl$_2$, then HCHO, NaCNBH$_3$, THF (57%); ii) H$_2$, Pd/C, ArNCS, THF (46%).

Scheme 12 | Asymmetric Michael addition of acetylacetone to nitroolefins with 12b.
Fig. 9 | Sugar based prolinamides from L-proline and D-glucosamine.

Scheme 13 | Asymmmetric Michael addition of diethyl malonate to N-Boc imine.

13a

13b

13c

Scheme 14 | Asymmetric addition of cyclohexanone to nitroolefins with 13c.
Scheme 15 | Synthesis of the catalysts; (a) NaN₃, DMF, 70°C, 6 h, 94%; (b) NaOMe, MeOH, rt, 1h, 80%; (c) (i) Tf₂O, pyridine, CH₂Cl₂, 0°C, 2 h, (ii) amine, DMF, 45°C, 10 h, 50-70%; (d) (i) propanedithiol, MeOH, rt, 48 h (18a and 18b), or PPh₃, H₂O, THF, 80°C, (18c and 18d), (ii) isothiocyanate, MeOH, rt, 4 h, 30-50%.

Scheme 16 | Synthesis of organocatalysts; (a) piperidine, DMF, 70°C, 50 h, 90%; (b) NaOMe, MeOH, reflux, 2 h, 85%; (c) Tf₂O, pyridine, DCM, 0°C, 2 h, (ii) NaN₃, DMF, 45°C, 72 h, 40%; (d) (i) propanedithiol, MeOH, rt, 48 h, (ii) phenyl isothiocyanate, MeOH, rt, 8 h, 69%.
Scheme 17 | Synthesis of catalysts 26: (a) piperidine or morpholine, LiClO₄, MeCN, 90°C, 24 h, 80-90%; (b) (i) PPh₃, DIAD, THF, 0°C, (ii) DPPA, THF, rt, 24 h, 60-80%; (c) (i) PPh₃, THF, H₂O, 80°C, (ii) isothiocyanate, MeOH, rt, 8 h, 60-80%.

Scheme 18 | Michael addition of acetylacetone to β-nitrostyrene using 18, 22 and 26.

Scheme 19 | Sugar amide-pyrrolidine catalyst for the asymmetric Michael addition.
Scheme 20 | Asymmetric Michael addition of ketones to nitroolefins using catalyst 31.

Scheme 21 | Synthesis of thiourea derived 3-C-aminomethyl-hexafuranose (35).

Scheme 22 | Organocatalyst 35 catalyzed Michael addition of nitromethane to trans-chalcone.

also investigated using 12b, 12c, 12d and 12f. In terms of enantioselectivity, 12b gave the best result (81% ee) but the yield was low (25% only) (Scheme 14).

Agarwal and Peddinti also describe a sugar-based prolinamides organocatalysts for asymmetric Michael addition in solvent-free condition. The catalysts (13a-13c, Fig. 9) were prepared from commercially available L-proline and D-glucosamine. The reaction condition was found to be optimum at -20°C in the absence of solvent with 20 mol% catalysts and another 20 mol% organic acid additive (benzoic acid). The Michael adducts were obtained in excellent yields (up to 98%), high diastereoselectivity (up to 99/1) and moderate enantioselectivity (up to 84/16 for syn) (Scheme 14). The catalytic system was found to provide (1R,2S)-syn adducts as a major antipodes.

In 2014, Agoston and Fugedi designed and prepared a group of new-bifunctional-thiourea-amine catalysts starting from D-glucose. The
Conclusion

Different types of compounds derived from sugars are used recently as organocatalyst for asymmetric synthesis. These are due to their commercial availability, low cost and inertness towards moisture and air. The catalysts described in this paper mainly showed high yield and enantioselectivity leading to huge demand and widespread utility. The highest yield and enantioselectivity (both 99%) were seen in Michael addition of malonates to nitroolefins catalyzed by chiral bifunctional tertiary amine-thiourea based on saccharides in the presence of toluene as a solvent and at -20°C. However, the lowest yield and enantioselectivity, 30% and 48% respectively were seen in the synthesis of thiourea derived 3-C-aminomethylhexafuranose which was employed for the asymmetric addition of nitromethane to trans-chalcone. As organic catalysts are easily available, cheap, easily prepared and are useful in complex steric reactions, they may be used as an alternative to the present transition metals catalysis.

Acknowledgement

The author KVL gratefully acknowledges UGC, Government of India, for Major Research Project, Grant No: UGC F.No.- 43-210/2014(SR), for financial support.

References


