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Synthesis of D-Fructose-Based Bifunctional Primary Amine-Thiourea Organocatalysts and Their Applications in Asymmetric Reactions

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Abstract: The preparation of a new class of six bifunctional thiourea organocatalysts having a D-fructose scaffold and a primary amino group was demonstrated. In the present study, the novel organocatalysts exhibited excellent enantio- and moderate diastereoselectivities in the asymmetric Michael addition of aliphatic ketones and 1,3-diketone to substituted nitroolefins at room temperature. In addition, the direct asymmetric aldol reaction between cyclic aliphatic ketone and aromatic aldehydes was also studied in the presence of the saccharide-thiourea organocatalysts giving excellent yield with moderate enantioselectivity.

Keywords: carbohydrates; bifunctional thiourea; organocatalyst; enantioselective; Michael addition; aldol reaction

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1. Introduction

The development of cost-effective and highly efficient synthetic techniques for the formation of carbon–carbon bonds remains an active field of research in organic chemistry [1,2]. Among the variants of these reactions, asymmetric Michael addition and Aldol reactions represent one of the most powerful and attractive transformations, mainly due to their widespread applications in the synthesis of several important biological and pharmaceutical compounds [3–5]. Significant efforts have been made in recent years to produce metal-free organocatalysts that are capable of promoting these asymmetric processes with exceptionally high yields and stereoselectivity [6–8]. In this context, the applications of chiral bifunctional amine-thioureas have emerged as a promising prospect and they have been successfully employed for a number of asymmetric transformations [9–14]. Their high efficacy in stereoselective synthesis is mainly attributed to their unique capability of multiple hydrogen-bonding donors as well as the readily accessible chiral diamines [15]. Some prominent examples include Jacobsen's thioureas [16–22] and Takemoto's amino thioureas [23–28], which were employed as catalysts in various asymmetric syntheses. Recently, with the aim of enhancing reactivity, widening substrate scope and improving the stereoselectivity of the organocatalytic reactions, the development of a bifunctional amine-thiourea-bearing saccharide moiety has also drawn the attention of various research groups [29,30].

Despite the variety of Michael acceptors employed in asymmetric Michael reactions, nitroalkenes have garnered particular interest due to their high reactivity and suitability as reaction partners for various aldehydes and ketones [31–33]. In addition, the generated functionalized nitroalkane adducts have a wide range of synthetic applications and can be converted into diverse functionalities, earning them the title of "synthetic chameleon" [34,35]. With a rise in the number of studies conducted in this field, several highly tuned and effective organocatalysts have been designed and developed. And, the potential of carbohydrate-based amine thioureas as a catalyst for the enantioselective Michael addition of ketones [36–39] and 1,3-dicarbonyl compound [40–44] to electron-poor nitroalkenes has also been extensively evaluated. In most of the cases, the resultant products obtained are in moderate to excellent yields and enantioselectivities.

Aside from the outstanding progress made with saccharide-based tertiary amine thiourea [36,45–49], laboratory efforts were also directed towards the creation of chiral thiourea, which contains a primary amino group and a carbohydrate scaffold. These chiral organic molecules, which were initially developed by Ma and co-workers in 2007 [36], were demonstrated to successfully facilitate reaction between ketone and nitroalkenes with high yields and excellent stereochemical results. In light of these important precedents, as well as our ongoing interest in asymmetric synthesis [50,51], we explored the asymmetric Michael addition reaction of aliphatic ketones and acetylacetone to substituted β-nitrostyrene using a new class of D-fructose-derived bifunctional primary amine-thiourea catalysts.

D-Fructose, a compound characterized by its abundant availability, cost-effectiveness, and well-defined stereogenic centers, has been explored for a number of asymmetric organic transformations. However, there has been no previous report on the utilization of D-Fructose as a saccharide scaffold in the synthesis of carbohydrate-based thiourea organocatalysts. Furthermore, there are only limited reports of the application of saccharide-based thioureas for the direct asymmetric Aldol reaction between ketones and aldehydes [52]. And the utilization of thiourea compounds containing carbohydrate scaffolds as organocatalysts continues to pose a significant challenge for the said transformation. So, the effectiveness of the newly synthesized compounds was further extrapolated for the asymmetric aldol reaction between cyclohexanone and aromatic aldehydes.

2. Materials and Methods

2.1. General

All reagents and solvents were commercial grade and purified prior to use when necessary. Optical rotations were measured with an Autopol IV, Rudolph Research Analytical Polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA) in chloroform, and described as follows: $[\alpha]_D^{25}$ (c in mg per 10 mL, solvent). FT-IR spectra were recorded on an Agilent Cary 630 FT-IR spectrometer (Agilent, Santa Clara, CA, USA), with absorptions in cm^{-1}. NMR spectra were recorded on a Bruker Avance II spectrophotometers. Chemical shifts for ^1H NMR and ^{13}C NMR spectra are reported (in parts per million) with reference to internal tetramethylsilane (Me_4Si = 0.0 ppm) using $CDCl_3$ and DMSO-d_6 as solvents. ESI-MS was carried out on an Agilent 6520 Q-TOF Mass spectrometer (Agilent, Santa Clara, CA, USA) with an Agilent 1200 HPLC system (Agilent, Santa Clara, CA, USA). HRMS was recorded on XEVO G2-XS QTOF instrument (Waters, Milford, MA, USA) using CH_3CN as a solvent. The elemental analyses of the catalyst were carried out on a Perkin–Elmer-2400 CHN/S analyzer (Perkin Elmer, Waltham, MA, USA). Using a Chiralpak OD-H or AD-H column (Diacel Corporation, Konan, Tokyo, Japan) with n-hexane and iso-propanol as the eluent, the enantioselectivity of the adducts was examined using a Waters 1525 binary pump (Waters, Milford, MA, USA) and a Waters UV detector 2489 (Waters, Milford, MA, USA).

2.2. Synthesis of Saccharide-Based Isothiocyanates **3** *and* **4**

To a stirred solution of sugar amines (1.5 g, 5.8 mmol), **1** or **2**, in absolute ethanol (5 mL) were added CS_2 (3.50 mL, 58 mmol) and NEt_3 (0.806 mL, 5.8 mmol) [53] The reaction mixture was stirred for 2 h at room temperature and then cooled on an ice bath. Next,

Boc_2O (6.38 mmol) and 3 mol% of DMAP were added to the reaction mixture and allowed to reach room temperature. After stirring for another three hours, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (5:95, ethyl acetate: hexane) to afford the desired product. (see Supplementary Materials Figures S1, S2, S9 and S10 for the ^{1}H NMR, ^{13}C NMR, and mass spectra data of compounds **3** and **4**).

1,2:4,5-Di-*O*-isopropylidene-3-(isothiocyanato)-3-deoxy-α-D-fructopyranose (**3**): yield: 82% as white solid; mp: 64–66 °C. $[\alpha]_D^{25}$ −198.00° (c 0.001, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46–4.44 (m, 1H), 4.27–4.19 (m, 2H), 4.04–3.94 (m, 2H), 3.84–3.77 (m, 2H), 1.46 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.54, 111.54, 110.77, 104.35, 73.31, 72.50, 72.42, 62.76, 58.79, 27.02, 26.52, 26.04, 25.35 ppm. IR (KBr): 2937, 2344, 2067, 1698, 1460, 1378, 1198, 1077, 854, 742 cm^{-1}. ESI-MS (*m/z*): 324.0 (M^+ + Na). HRMS: calculated for [$C_{13}H_{19}NO_5S$+H]: 302.1062, found 302.1064. Elemental Analysis for $C_{13}H_{19}NO_5S$: calculated C 51.67, H 6.66, N 5.25, O 26.04, S 10.38; found C 51.88, H 6.75, N 5.11, O 26.08, S 10.18.

1,2:4,5-Di-*O*-isopropylidene-3-(isothiocyanato)-3-deoxy-β-D-fructopyranose (**4**): yield: 77% as white solid; mp: 68–70 °C. $[\alpha]_D^{25}$ −248.83° (c 0.002, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35–4.33 (m, 1H), 4.20–4.02 (m, 5H), 3.59 (d, 1H, *J* = 4 Hz), 1.52 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.04, 113.08, 109.57, 103.08, 75.95, 72.35, 72.32, 60.06, 60.01, 27.96, 26.08, 25.94, 25.75 ppm. IR (KBr): 2927, 2106, 1684, 1364, 1208, 1087, 863 cm^{-1}. ESI-MS (*m/z*): 324.0 (M^+ + Na). HRMS: calculated for [$C_{13}H_{19}NO_5S$+H]: 302.1062, found 302.1063. Elemental Analysis for $C_{13}H_{19}NO_5S$: calculated C 51.81, H 6.36, N 4.65, O 26.54, S 10.64; found C 51.72, H 6.29, N 4.91, O, 26.52, S 10.56.

2.3. Synthesis of Saccharide-Derived Amine Thiourea **5a**–**d** *and* **6a**–**b**

To a stirred solution of sugar isothiocyanate **3** or **4** (0.3 g, 1 mmol) in anhydrous dichloromethane (2 mL) were added the corresponding chiral diamines (1 mmol). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using dichloromethane: methanol (100:5) as an eluent to obtain the desired product (see Supplementary Materials Figures S3–S8 and S11–S16 for the ^{1}H NMR, ^{13}C NMR, and mass spectra data of compounds **5** and **6**).

1,2:4,5-Di-*O*-isopropylidene-3-[(1S,2S)-2-aminocyclohexyl-1-thioureido]-3-deoxy-α-D-fructopyranose (**5a**): yield: 68% as pale-yellow solid; mp: 58–60 °C. $[\alpha]_D^{25}$ −117.00° (c 0.002, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.27 (s, 1H), 4.88 (d, 1H, *J* = 4 Hz), 4.46–3.76 (m, 8H), 2.04 (s, 1H), 1.84 (s, 1H), 1.63–1.25 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.81, 110.26, 110.11, 105.56, 74.50, 73.90, 72.30, 62.76, 60.26, 60.24, 54.50, 31.79, 31.77, 27.17, 26.82, 26.20, 26.16, 24.92, 24.74 ppm. IR (KBr): 3282.52, 3067.99, 2925.76, 2869.35, 2344.94, 1533.49, 1360.49, 1212.71, 1045.06, 855.95, 728.83. ESI-MS (*m/z*): 416.3 (M^+ + H). HRMS: calculated for [$C_{19}H_{33}N_3O_5S$+H]: 416.2219, found 416.2222. Elemental Analysis for $C_{19}H_{33}N_3O_5S$: calculated C 54.92, H 8.00, N 10.11, O 19.25, S 7.72; found C 54.88, H 7.85, N 10.22, O 19.39, S 7.65.

1,2:4,5-Di-*O*-isopropylidene-3-[(1R,2R)-2-aminocyclohexyl-1-thioureido]-3-deoxy-α-D-fructopyranose (**5b**): yield: 72% as pale-yellow solid; mp: 63–65 °C. $[\alpha]_D^{25}$ −65.00° (c 0.001, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 4.94 (s, 1H), 4.58–4.56 (m, 1H), 4.32–3.85 (m, 8H), 1.77 (s, 2H), 1.48–1.17 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.93, 110.46, 109.60, 104.77, 72.93, 72.71, 62.24, 62.17, 61.07, 55.86, 55.45, 34.21, 32.27, 31.59, 26.63, 25.66, 24.90, 24.78, 24.66 ppm. IR (KBr): 3278.32, 2926.35, 2342.06, 1540.11, 1455.98, 1361.81, 1233.65, 1054.62, 851.62. ESI-MS (*m/z*): 416.3 (M^+ + H). HRMS: calculated for [$C_{19}H_{33}N_3O_5S$+H]: 416.2219, found 416.2221. Elemental Analysis for $C_{19}H_{33}N_3O_5S$: calculated C 55.12, H 8.09, N 10.20, O 18.95, S 7.63; found C 54.99, H 8.27, N 10.35, O 19.01, S 7.37.

1,2:4,5-Di-*O*-isopropylidene-3-[(1R,2R)-2-amino-1,2-diphenylethyl-1-thioureido]-3-deoxy-α-D-fructopyranose (**5c**): yield: 68% as white solid; mp: 61–64 °C. $[\alpha]_D^{25}$ −80.50°

(c 0.001, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.26 (m, 10H), 6.04 (d, 1H, *J* = 8 Hz), 5.16 (s, 1H), 4.44–3.78 (m, 9H), 1.69 (s, 2H), 1.44 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.65, 141.83, 129.17, 129.09, 129.04, 128.81, 128.07, 128.06, 127.97, 126.83, 126.64, 104.55, 104.47, 102.48, 73.03, 71.87, 64.26, 61.89, 60.33, 55.28, 55.26, 26.65, 26.12, 25.96, 25.02 ppm. IR (KBr): 3308.63, 3055.27, 2955.48, 2919.75, 2342.90, 2085.47, 1670.42, 1521.56, 1369.01, 1220.54, 1063.22, 857.54, 765.60, 683.20. ESI-MS (*m/z*): 514.3 (M^+ + H). HRMS: calculated for [$C_{27}H_{35}N_3O_5S$+H]: 514.2376, found 514.2386. Elemental Analysis for $C_{27}H_{35}N_3O_5S$: calculated C 62.72, H 7.02, N 7.88, O 16.04, S 6.34; found C 62.56, H 7.16, N 7.64, O 16.28, S 6.36.

1,2:4,5-Di-*O*-isopropylidene-3-[(1S,2S)-2-amino-1,2-diphenylethyl-1-thioureido]-3-deoxy-α-D-fructopyranose (**5d**): yield: 74% as white solid; mp: 88–91 °C. $[\alpha]_D^{25}$ −61.67° (c 0.001, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 10H), 6.58 (s, 1H), 4.80 (s, 1H), 4.47–3.72 (m, 9H), 1.65 (s, 2H), 1.43 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.26, 141.79, 139.24, 136.97, 136.87, 129.26, 128.78, 128.51, 128.36, 128.03, 126.91, 126.81, 111.64, 109.48, 104.50, 73.04, 71.95, 71.88, 64.65, 61.63, 61.49, 55.58, 26.47, 26.40, 25.74, 25.23 ppm. IR (KBr): 3299.65, 3050.39, 2989.10, 2923.72, 2342.79, 2080.59, 1674.68, 1530.30, 1372.98, 1215.66, 1058.34, 1009.98, 852.66, 760.72, 691.52. ESI-MS (*m/z*): 514.3 (M^+ + H). HRMS: calculated for [$C_{27}H_{35}N_3O_5S$+H]: 514.2376, found 514.2384. Elemental Analysis for $C_{27}H_{35}N_3O_5S$: calculated C 65.44, H 6.34, N 7.68, O 14.24, S 6.30; found C 65.34, H 6.49, N 7.89, O 14.07, S 6.21.

1,2:4,5-Di-*O*-isopropylidene-3-[(1R,2R)-2-amino-1,2-diphenylethyl-1-thioureido]-3-deoxy-β-D-fructopyranose (**6a**): yield: 61% as white solid; mp: 130–134 °C. $[\alpha]_D^{25}$ −197.33° (c 0.001, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, 1H, *J* = 8 Hz), 7.96 (d, 1H,), 7.43–7.18 (m, 10), 5.44 (s, 1H), 4.62–3.56 (m, 10H), 1.44 (s, 3H), 1.40 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.11, 140.64, 126.45, 125.80, 125.39, 125.14, 109.19, 106.69, 103.95, 72.80, 72.69, 70.79, 69.52, 62.06, 58.08, 53.13, 26.38, 25.14, 25.06, 24.72 ppm. IR (KBr): 3267.08, 3070.26, 2959.88, 2341.63, 1529.65, 1376.04, 1207.78, 1068.85, 880.52, 687.55. ESI-MS (*m/z*): 514.3 (M^+ + H). HRMS: calculated for [$C_{27}H_{35}N_3O_5S$+H]: 514.2376, found 514.2387. Elemental Analysis for $C_{27}H_{35}N_3O_5S$: calculated C 62.94, H 6.91, N 8.51, O 15.23, S 6.40; found C 62.78, H 6.86, N 8.33, O 15.47, S 6.55.

1,2:4,5-Di-*O*-isopropylidene-3-[(1S,2S)-2-amino-1,2-diphenylethyl-1-thioureido]-3-deoxy-β-D-fructopyranose (**6b**): yield: 59% as white solid; mp: 102–105 °C. $[\alpha]_D^{25}$ −155.67° (c 0.002, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, 1H, *J* = 8 Hz), 7.96 (d, 1H, *J* = 12 Hz), 7.43–7.20 (m, 10H), 5.18 (s, 1H), 4.63–3.57 (m, 10H), 1.44 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 184.93, 143.74, 142.52, 128.34, 127.71, 127.29, 127.07, 127.02, 111.09, 108.59, 105.86, 74.71, 72.70, 71.44, 63.93, 59.99, 59.87, 55.04, 28.29, 26.97, 26.90, 26.67 ppm. IR (KBr): 3281.74, 3059.45, 2979.95, 2930.55, 2351.66, 2093.87, 1538.91, 1376.04, 1227.08, 1078.88, 989.53, 880.52, 767.06, 692.19. ESI-MS (*m/z*): 514.3 (M^+ + H). HRMS: calculated for [$C_{27}H_{35}N_3O_5S$+H]: 514.2376, found 514.2389. Elemental Analysis for $C_{27}H_{35}N_3O_5S$: calculated C 63.14, H 6.87, N 8.18, O 15.57, S 6.24; found C 63.04, H 6.66, N 8.09, O 15.77, S 6.44.

2.4. Typical Procedure for Asymmetric Michael Addition Reaction

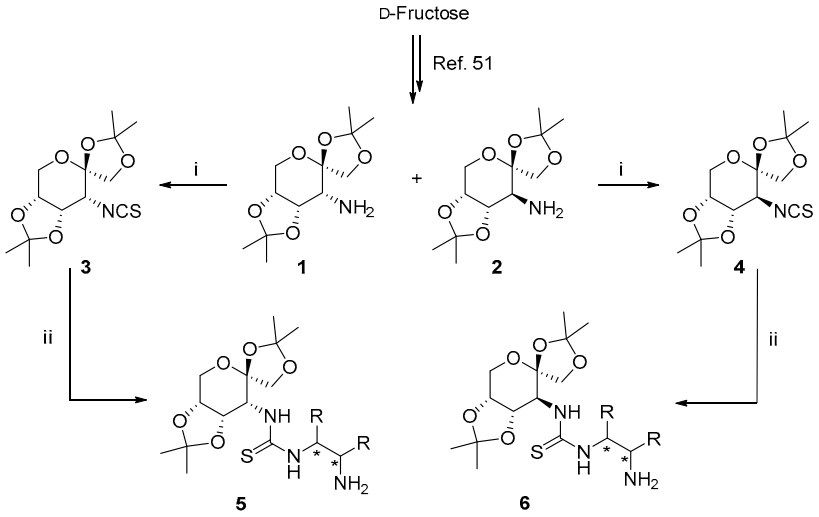
To a stirred solution of β-nitrostyrene (0.2 mmol) and ketone (3 equiv.) in dry dichloromethane (0.25 mL), 15 mol% saccharide-based amine-thiourea organocatalyst and benzoic acid were added. The reaction mixture was then stirred at room temperature for an appropriate reaction time, followed by concentration under vacuum. The reaction mixture was then subjected to purification by column chromatography using silica gel (60–120 mesh) with a hexane:EtOAc mixture as an eluent to obtain the desired product. The enantiomeric excess values of the product were determined by HPLC analysis on a chiral column using a mixture of n-hexane and iso-propanol as the mobile phase (see Supplementary Materials Figures S17–S46 for the ^{1}H NMR, ^{13}C NMR, and HPLC data for Michael adducts).

2.5. Typical Procedure for the Asymmetric Aldol Reaction

A solution of 20 mol% of the saccharide-based amine-thiourea organocatalyst 6a, 20 mol% of benzoic acid, aldehydes (0.2 mmol) and ketone (4 equiv.) in water (0.5 mL) was stirred at 0 °C. The reaction mixture was then concentrated under vacuum, followed by purification with column chromatography using silica gel with hexane:EtOAc mixture. The enantiomeric excess values of the products were identified by HPLC analysis on a chiral column using a mixture of n-hexane and iso-propanol as the mobile phase (see Supplementary Materials Figures S47–S56 for the ^{1}H NMR, ^{13}C NMR, and HPLC data for Aldol products).

3. Results and Discussions

As described in Scheme 1, sugar amines **1** (1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-*α*-D-fructopyranose) or **2** (1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-*β*-D-fructopyranose) prepared from D-fructose [50,51], were converted to the corresponding isothiocyanates (**3** and **4**) according to the reported procedure [53]. Subsequently, the newly prepared isothiocyanates were coupled with commercially available chiral 1,2-diamines to afford the desired bifunctional thiourea organocatalysts **5** and **6** (Figure 1) in good yields.



Scheme 1. Preparation of the saccharide-derived amine thiourea organocatalysts, (i) CS_2, NEt_3, Boc_2O, EtOH, DMAP; (ii) 1,2-diamine, CH_2Cl_2, rt. * an optically active carbon center [51].

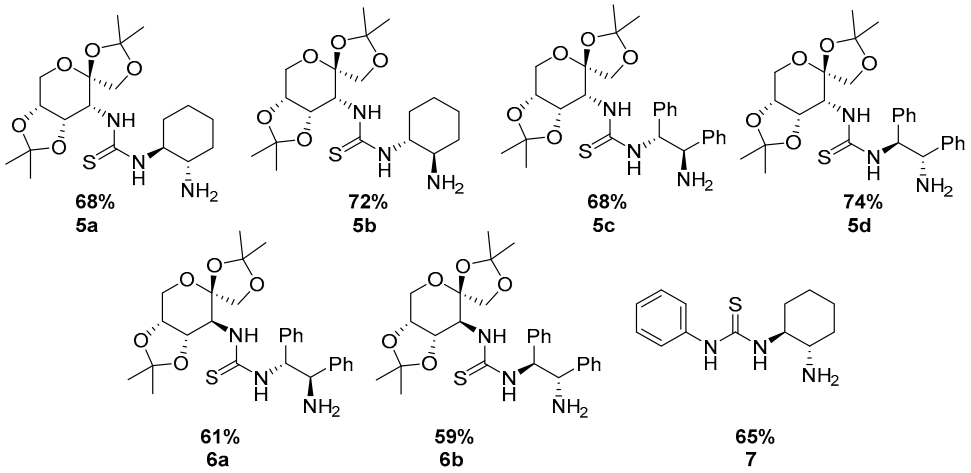
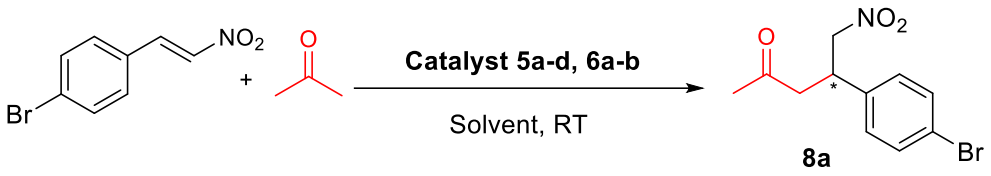


Figure 1. D-fructose-based bifunctional amine-thioureas.

Our investigations started with the reaction of acetone with *trans*-4-bromo-β-nitrostyrene at room temperature using 10 mol% of amine-thiourea catalysts (**5** and **6**) in the presence of DCM as solvent. After completion of the reactions as shown by TLC, the products were separated using column chromatography. The enantiomeric excess (ee) of the final products was estimated using a chiral column and compared with the chromatograms of racemic mixtures, which were prepared by using DL-proline as a catalyst. Table 1 summarizes the results of these preliminary studies. The desired product was generated with a reasonable yield and enantioselectivity when a saccharide-derived amine catalyst with an *S*,*S*-configured 1,2-diaminocyclohexane moiety **5a** was utilized (Table 1, entry 1). In order to improve the yield as well as stereoselectivity, several additives were subsequently examined, and they were found to play a crucial role in the outcome of the reactions (Table 1, entries 2–6). The potential function of the acidic co-catalyst appears to lie in its ability to facilitate the generation of an enamine intermediate, which arises from the interaction between the primary amine catalyst and ketones. Remarkably, the best result was obtained when the catalyst was employed in conjunction with benzoic acid, affording the Michael adduct **8a** with an 89% yield and 96% ee. Other chiral primary-amine-thioureas (**5b**–**d** and **6a**–**b**) were also explored for the reaction (Table 1, entries 7–11), and it was observed that all of the examined thioureas could promote the addition reaction, with yield and selectivity ranging from moderate to good. However, the thiourea catalyst **5a** was found to be the most promising catalyst for the asymmetric process. Further, a primary amine-thiourea **7**, which do not contain a saccharide scaffold was also evaluated for this asymmetric reaction. The catalyst afforded the desired product in 78% yield and 88% enantioselectivity (entry 12), which demonstrate that the carbohydrate moiety is essential for maintaining high level of enantioselectivity.

After identifying the principal catalyst and additive for the asymmetric transformation, we next examined the influence of their concentrations in the reaction medium. The reaction could only be completed after 72 h when the catalyst loading was reduced to 5 mol%, resulting in a 73% yield and 95% ee (Table 1, entry 13). However, when the catalyst loading was raised to 15 mol%, the reaction time was shortened to 52 h, and the yield (92%) and enantioselectivity (97% ee) of the product also improved significantly (Table 1, entry 14). Increasing the catalyst concentration to 20% resulted in a further reduction in reaction time but a slightly lower ee value (Table 1, entry 15); therefore, it was decided that 15 mol% was the optimal amount for the catalyst concentration. The observed initial rise in product formation as well as the increase in enantiomeric excess %, noticed after increasing the catalyst loading, can be attributed to the simultaneous increase in the number of actives within the reaction medium. On the other hand, the utilization of a lesser amount of catalyst causes the catalyst stereocontrol to erode, leading to a reduction in the ee of the resultant adducts [41,46]. Another variable that influenced the final result of the reaction was the amount of benzoic acid employed; decreasing the amount had a detrimental effect on the reaction, whereas raising the concentration improved the yield and ee of the products (Table 1, entries 16–18). Furthermore, a brief investigation of the solvents revealed that the reaction is substantially solvent-dependent, with DCM being the most reactive (Table 1, entries 19–22). Moreover, reducing the reaction temperature prolonged the reaction time while having no influence on the product's yield or selectivity (Table 1, entry 23). Thus, the optimal reaction conditions for this reaction were determined to be 0.2 mmol of nitrostyrene, 15 mol% of **5a**, 15 mol% of benzoic acid, and three equivalents of ketones in 0.25 mL of dichloromethane at room temperature.

Table 1. Optimization of reaction condition for the asymmetric Michael addition of acetone to *trans*-4-bromo-β-nitrostyrene [a].



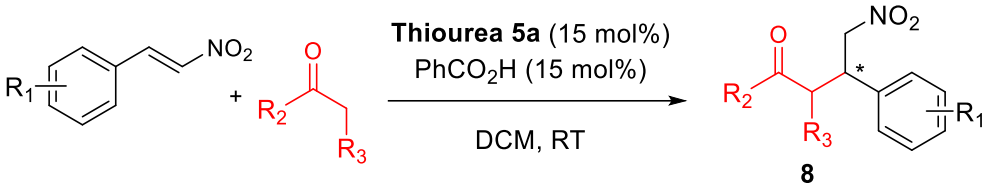
Entry	Solvent	Catalyst (mol%)	Additives (mol%)	Time (h)	Yield (%) [b]	ee (%) [c]
1	CH_2Cl_2	**5a** (10)	-	96	48	57
2	CH_2Cl_2	**5a** (10)	AcOH (10)	56	76	92
3	CH_2Cl_2	**5a** (10)	$PhCO_2H$ (10)	54	89	96
4	CH_2Cl_2	**5a** (10)	CF_3CO_2H (10)	77	54	76
5	CH_2Cl_2	**5a** (10)	4-$NO_2C_6H_4CO_2H$ (10)	48	87	32
6	CH_2Cl_2	**5a** (10)	4-$BrC_6H_4CO_2H$ (10)	52	83	43
7	CH_2Cl_2	**5b** (10)	$PhCO_2H$ (10)	52	82	90
8	CH_2Cl_2	**5c** (10)	$PhCO_2H$ (10)	66	77	93
9	CH_2Cl_2	**5d** (10)	$PhCO_2H$ (10)	96	81	86
10	CH_2Cl_2	**6a** (10)	$PhCO_2H$ (10)	49	88	89
11	CH_2Cl_2	**6b** (10)	$PhCO_2H$ (10)	72	81	92
12	CH_2Cl_2	**7** (10)	$PhCO_2H$ (10)	24	78	88
13	CH_2Cl_2	**5a** (5)	$PhCO_2H$ (10)	72	73	95
14	CH_2Cl_2	**5a** (15)	$PhCO_2H$ (10)	52	92	97
15	CH_2Cl_2	**5a** (20)	$PhCO_2H$ (10)	44	93	96
16	CH_2Cl_2	**5a** (15)	$PhCO_2H$ (5)	58	92	93
17	CH_2Cl_2	**5a** (15)	$PhCO_2H$ (15)	48	95	>99
18	CH_2Cl_2	**5a** (15)	$PhCO_2H$ (20)	44	96	98
19	Toluene	**5a** (15)	$PhCO_2H$ (15)	72	60	88
20	THF	**5a** (15)	$PhCO_2H$ (15)	96	43	93
21	CH_3CN	**5a** (15)	$PhCO_2H$ (15)	120	51	66
22	Neat	**5a** (15)	$PhCO_2H$ (15)	48	78	82
23 [d]	CH_2Cl_2	**5a** (15)	$PhCO_2H$ (15)	120	66	98

[a] Unless otherwise stated, the reactions were conducted with 0.2 mmol trans-4-bromo-β-nitrostyrene, three equivalents of acetone and 0.25 mL solvents. [b] Isolated yield of the product. [c] The enantiomeric excess values were determined by HPLC. [d] The reaction was performed at 0 °C.

After determining the optimal reaction conditions, the scope of the reaction was investigated using a range of nitrostyrenes and ketones. (Table 2). It was observed that all the addition processes between acetone and β-nitrostyrene derivatives (Table 2, entries 1–6) proceeded smoothly, furnishing high yields (81–95%) with excellent enantiomeric excess values (up to >99%). The findings also demonstrated that the reactions worked extremely well with both the electron-withdrawing and electron-donating substituted nitroolefins. However, when acetylacetone was employed as a substrate (Table 2, entries 7 and 8), thiourea **5a** afforded the corresponding products **8g** and **8h** in good yield, albeit with poor stereoselectivity. Interestingly, even after prolonging the reaction period to 6 days, the conjugate addition of cyclohexanone to β-nitrostyrene failed entirely (Table 2, entry 9). The above findings are similar to those reported previously by Ma [39], Tvrdoňová [44] and

Wu [37], that the thiourea derivatives having 1,2-diaminecyclohexane scaffolds perform well with acetone but abysmally with acetylacetone and cyclic ketones.

Table 2. Asymmetric Michael addition of ketones to nitroolefins [a].



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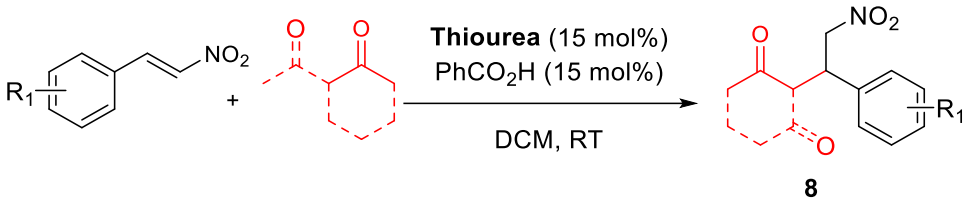
Entry	R_1	R_2	R_3	Time (h)	Yield (%) [b]	ee (%) [c,d]
1	4-Bromo	Me	H	48	95 **(8a)**	>99 (*S*)
2	4-Chloro	Me	H	48	90 **(8b)**	91 (*S*)
3	4-Methyl	Me	H	68	81 **(8c)**	85 (*S*)
4	2-Chloro	Me	H	48	95 **(8d)**	83 (*S*)
5	2-Methoxy	Me	H	94	92 **(8e)**	81 (*S*)
6	H	Me	H	36	93 **(8f)**	95 (*S*)
7	4-Chloro	Me	COMe	100	88 **(8g)**	32 (*S*)
8	4-Methyl	Me	COMe	120	91 **(8h)**	22 (*S*)
9	H	$R_2 = R_3 = (CH_2)_4$	-	168	Nr [e]	Nd [f]

[a] The reaction was conducted with nitroolefins (0.2 mmol), ketone (3 equiv.), catalyst **5a** (0.03 mmol), and benzoic acid (0.03 mmol) in 0.25 mL DCM at room temperature. [b] Isolated yield. [c] The ee values were determined by HPLC. [d] The configuration was assigned according to the reference [37]. [e] No reaction. [f] Not determined.

Therefore, additional investigation on thiourea organocatalysts **5b–d** and **6a–b** was conducted under the optimum conditions in order to identify the best catalyst for the asymmetric addition of ketones (other than acetone) to nitrostyrene, and the results are presented in Table 3, entries 1–5. The experimental results showed that by substituting the cyclohexane-1,2-diamine moiety with 1,2-diphenylethane-1,2-diamine scaffolds, the enantioselectivity of the products could be considerably enhanced (Table 3, entry 1 vs. entry 2–5). Amongst the tested catalysts, amine-thiourea **6a** bearing the *R,R*-configured 1,2-diphenylethylenediamine scaffold delivered the best result (Table 3, entry 4) in terms of enantioselectivity (84% ee), and it was selected as the optimal catalyst. With the catalyst 6a at hand, the enantioselective addition of ketones to derivatives of nitroalkenes was conducted and the corresponding Michael adducts **8h–l** were obtained in high yields (73–85%) with good enantioselectivities (between 71 and 81%) (Table 3, entries 5–9). Additionally, the reactions of substituted and electron-neutral nitroolefins with cyclohexanone could be completed, giving moderate yields (up to 55%) and stereoselectivities (up to 83% ee and 68:32% *dr*) (Table 3, entries 11–13).

The enantioselectivity of the adducts generated by the present saccharide-derived amine thioureas was compared to that described in the previous literature (Figure 2). So far, there is only one report available that discusses the application of an organocatalyst containing a primary-amine thiourea and saccharide scaffold for the asymmetric Michael addition reaction of acetone to nitroolefins. In this report, different saccharide moieties such as D-glucose, D-galactose, and D-mannose were employed. After a fine examination, the desired product could be obtained with a good yield (up to 94%) and enantioselectivity levels of 84% or higher. Accordingly, when the reported data are compared to our experimental findings, it can be concluded that the primary-amine thiourea organocatalyst, which incorporates a saccharide scaffold of D-glucose, D-galactose, D-mannose, or D-fructose, were all able to achieve comparable stereochemical results.

Table 3. Asymmetric Michael addition of ketones to various β-nitroolefins [a].



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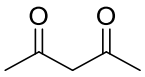
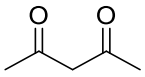
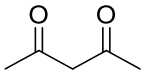
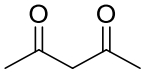
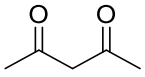
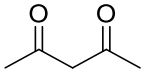
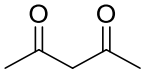
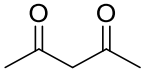
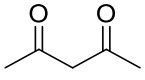
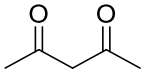
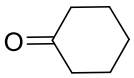
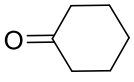
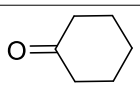
Entry	Catalyst (mol%)	R_1	Ketone	Time (h)	Yield (%) [b]	*dr* (%) [c] *syn*/*anti*	ee (%) [d,e]
1	**5b** (15)	4-Cl		92	82 (**8g**)	-	12 (*R*)
2	**5c** (15)	4-Cl		96	81 (**8g**)	-	79 (S)
3	**5d** (15)	4-Cl		76	66 (**8g**)	-	43 (S)
4	**6a** (15)	4-Cl		72	80 (**8g**)	-	84 (*S*)
5	**6b** (15)	4-Cl		88	84 (**8g**)	-	72 (*R*)
6	**6a** (15)	4-Me		72	73 (**8h**)	-	81 (*S*)
7	**6a** (15)	4-Br		81	78 (**8i**)	-	81 (*S*)
8	**6a** (15)	2-Cl		96	85 (**8j**)	-	76 (*S*)
9	**6a** (15)	2-MeO		120	77 (**8k**)	-	71 (*S*)
10	**6a** (15)	H		96	81 (**8l**)	-	74 (*S*)
11	**6a** (15)	4-Me		168	46 (**8m**)	68/32	78 [f] (*R*,*S*)
12	**6a** (15)	4-Br		168	55 (**8n**)	68/32	20 [f] (*S*,*R*)
13	**6a** (15)	H		180	42 (**8o**)	67/33	79 [f] (*S*,*R*)

[a] The addition reaction was performed with nitroolefins (0.2 mmol), ketone (3 equiv.), thiourea catalyst (0.03 mmol), and benzoic acid (0.03 mmol) in 0.25 mL DCM at room temperature. [b] Isolated yield. [c] The dr values were obtained from ^{1}H NMR data. [d] The ee values were determined by HPLC. [e] The configuration was assigned according to the references [41,54–58]. [f] Enantioselectivity of the syn-diastereomer.

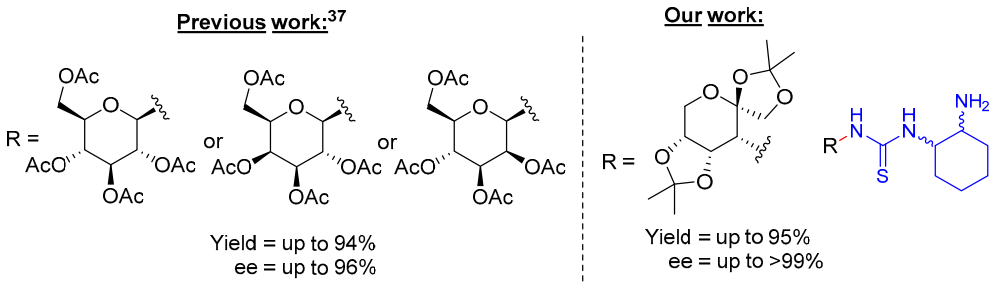


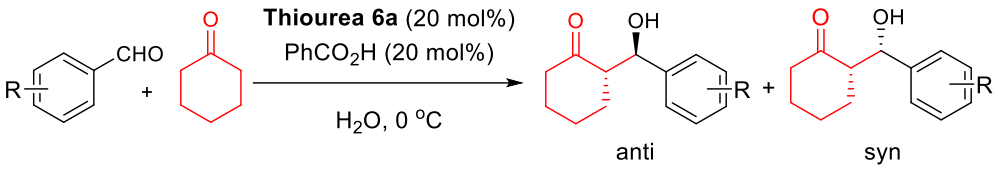
Figure 2. Comparison of the catalytic activity of primary-amine thiourea organocatalysts containing different saccharide scaffold on the asymmetric Michael addition of acetone to nitroolefins [37].

The saccharide-derived organocatalysts **5a**–**d** and **6a**–**b** were also examined for the asymmetric aldol addition of cyclohexanone to 4-nitro-benzaldehyde, and the results are summarized in Table 4. According to the experimental results (Table 4, entries 2–7), the bifunctional thioureas were able to promote the conjugate reaction when water was used as a reaction medium and benzoic acid (20 mol%) was added as an acidic co-catalyst. The amine-thiourea catalyst **6a** has been shown to be the most effective for the transformation, producing the required product in moderate yield but with poor adduct stereocontrol. Additional testing of various additives and solvents failed to improve the catalyst's stereoselectivity (entries 8–12). However, the enantioselectivity was slightly increased when the reaction temperature was lowered to 0 °C (entry 13). Even after establishing the optimized reaction condition, the corresponding aldol adducts **9a**–**e** could only be obtained in modest yields with enantioselectivity up to 73% and *dr* up to 33:67 (*syn:anti*) (Table 5, entries 1–5).

Table 4. Optimization of reaction condition for asymmetric Aldol reaction using catalysts **5** and **6**.

Entry	Catalyst (mol%)	Temp	Additives (mol%)	Solvent	Time (h)	Yield (%)	dr (%) *Syn:anti*	er (%) *Syn:anti*
1	**5a** (20)	RT	-	Neat	12 h	85	50:50	Racemic
2	**5a** (20)	RT	$PhCO_2H$ (20)	H_2O	24 h	63	48:52	15:21
3	**5b** (20)	RT	$PhCO_2H$ (20)	H_2O	36 h	65	56:44	8:16
4	**5c** (20)	RT	$PhCO_2H$ (20)	H_2O	38 h	55	51:49	14:24
5	**5d** (20)	RT	$PhCO_2H$ (20)	H_2O	38 h	34	58:42	6:25
6	**6a** (20)	RT	$PhCO_2H$ (20)	H_2O	58 h	54	43:57	13:39
7	**6b** (20)	RT	$PhCO_2H$ (20)	H_2O	48 h	44	48:52	12:35
8	**6a** (20)	RT	CH_3CO_2H (20)	H_2O	72 h	65	52:48	9:28
9	**6a** (20)	RT	DNP (20)	H_2O	48 h	72	47:53	11:3
10	**6a** (20)	RT	TFA (20)	H_2O	56 h	66	43:57	19:12
11	**6a** (20)	RT	$PhCO_2H$ (20)	DMSO	96 h	48	44:56	Racemic
12	**6a** (20)	RT	$PhCO_2H$ (20)	DCM	126 h	trace	-	-
13	**6a** (20)	0 °C	$PhCO_2H$ (20)	H_2O	144 h	62	47:53	30:47
14	**6a** (20)	0 °C	$PhCO_2H$ (20)	Neat	110 h	72	45:55	9:38

Table 5. Asymmetric Aldol reaction of cyclohexanone with aldehydes [a].



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Entry	Aldehydes	Reaction Time (h)	Yield (%) [b]	*dr* (%) [c] *Syn*:*anti*	ee (%) [d,e]
1	4-Nitro	144	58 (**9a**)	47:53	30 (*R*,*R*)
2	3-Nitro	120	52 (**9b**)	46:54	15 (*R*,*R*)
3	2-Nitro	168	46 (**9c**)	55:45	40 (*R*,*R*)
4	3-Chloro	128	54 (**9d**)	54:46	23 (*R*,*R*)
5	4-Bromo	120	50 (**9e**)	33:67	69 (*R*,*R*)

[a] The reaction was performed with aldehydes (0.2 mmol), cyclohexanone (4 equiv.), thiourea (0.04 mmol), and benzoic acid (0.04 mmol) in 0.5 mL of water at 0 °C. [b] Isolated yield. [c] The diastereoselectivity was obtained from ^{1}H NMR data. [d] The enantioselectivity values of the adducts were determined by HPLC. [e] The configuration of the syn-adduct was assigned according to references [59–61].

4. Conclusions

In summary, we have successfully reported the synthesis of a new class of D-fructose-derived primary amine-thiourea organocatalysts. It is demonstrated that the chiral organic molecules are highly enantioselective for the asymmetric Michael addition of aliphatic ketones and 1,3-diketone to a series of substituted nitroalkenes. The functionalized γ-nitro ketones could be obtained in good yield (up to 95%) with excellent enantioselectivities (>99%) and diastereomeric ratios up to 67:33 (*syn*:*anti*). Further investigation of the efficacy of the novel bifunctional organocatalysts in the asymmetric aldol reaction yielded the corresponding aldol products with low-to-moderate enantio- and diastereoselectivities.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry5040156/s1, ^{1}H and ^{13}C NMR data of the synthesized novel sugar-derived compounds, Michael and aldol products. Figures S1–S8: ^{1}H and ^{13}C NMR spectra of the catalysts. Figures S9–S16: HRMS data of the catalysts. Figure S17–S31: ^{1}H and ^{13}C NMR spectra of Michael adducts. Figures S32–S46: HPLC data of enantioenriched and racemic data of compound **7a**–**o**. Figures S47–S51: ^{1}H and ^{13}C NMR spectra of Aldol adducts. Figures S52–S56: HPLC data of enantioenriched and racemic data of compound **8a**–**e**.

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