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REGULAR ARTICLE

Monofunctional primary amine: A new class of organocatalyst for asymmetric Aldol reaction

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Abstract. A new class of organocatalysts involving a primary amine as the only functional group is developed for catalytic asymmetric aldol reaction of cyclohexanone/cyclopentanone with various aryl aldehydes in the presence of benzoic acid as an additive at −10°C. In an unexpected observation, the primary amine catalyzed reactions gave excellent yield and good to excellent stereoselectivity, while secondary amines were found to have little or no reactivity under similar reaction conditions.

Keywords. D-Fructose; primary amine; monofunctional organocatalyst; asymmetric aldol.

1. Introduction

Recently, chiral primary amines[1] have shown tremendous synthetic potential in asymmetric functionalization of sterically hindered carbonyl compounds, which cannot be functionalized using either secondary amines or metal-based catalyst. As a result, organocatalysis using bifunctional/multifunctional primary amines derived from amino acids,[2] chincona,[3] and carbohydrates[4] have emerged. Interestingly, most of the asymmetric organocatalysts involving amine are bifunctional or multifunctional in nature. In contrast, only a few L-proline derived pyrrolidine based monofunctional amine organocatalysts are reported for asymmetric organocatalysis.[5] Unlike the bifunctional amines where the functional groups are involved in activation of both the donor and acceptor by forming highly organized transition state that controls overall stereochemical outcome of the product, controlling stereochemical outcome employing only one functional group remains a huge challenge. More so in case of the primary amine where it reacts with carbonyl compound to form a less nucleophilic and unstable iminium ion[6] that have unfavorable imine-enamine equilibrium.[7] To the best of our knowledge, monofunctional primary amine catalyzed asymmetric aminocatalysis has never been reported (Figure 1).

Since its discovery back in 1872[8] by Charles-Aldolphe Wurtz, aldol reaction has evolved as one of the most important and powerful carbon-carbon bond forming reactions in modern organic chemistry.[9] Moreover, the β-hydroxy carbonyl moiety that formed as a result of aldol reaction, is found in many biologically active compounds[10] such as carbohydrates, antibodies, alkaloids, and terpenes.

Although numerous methods involving metal enolates[11] were developed to control the stereochemical outcome of the aldol reaction, the use of L-proline as a catalyst by List *et al.*,[12] opened up an interesting new field of oragnocatalysis. Since then, various organocatalysts bearing secondary amine,[13] amides,[14] chiral bifunctional-thioureas,[15] and diamines[16] have been applied for the said synthesis. Very recently, Ricci and co-workers[4a] used chitosan aerogel as a heterogeneous organocatalyst for asymmetric direct aldol reaction in water. Zhang *et al.*,[4b] also reported D-glucosamine derived amino alcohols catalyzed enantioselective aldol reaction of isatins with ketones in dichloromethane. Along the similar line, Peddinti *et al.*,[4c] reported the use of glucosamine derived amino alcohol to achieve organocatalytic aldol reaction. Here, we report a highly selective asymmetric aldol reaction between aryl aldehydes and cyclohexanone/cyclopentanone catalyzed by D-fructose derived monofunctional primary amine **1a** (Scheme 1).

2. Experimental

2.1 *General remarks*

Chemicals and reagents were purchased from commercial sources and used without further purification. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz)

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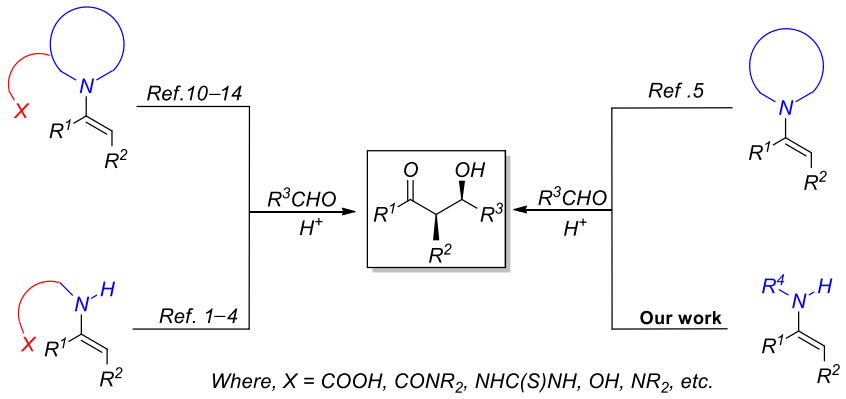
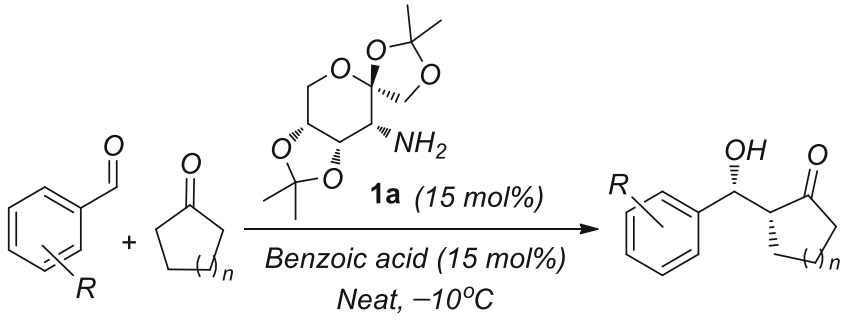


Figure 1. Schematic presentation of aminocatalysis.



Scheme 1. Asymmetric aldol reaction catalyzed by fructose-derived amines.

spectra were obtained on a Bruker AC-400 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the complexes were performed on a Perkin–Elmer-2400 CHN/S analyzer. Reactions were monitored by thin layer chromatography (TLC). The melting points of the compounds were recorded by open capillary method and were uncorrected. HPLC analysis was carried out on a Waters M515 equipped with Chiracel OD-H, Chiralcel AD-H, and Chiral OJ columns using *n*-hexane and 2-propanol as mobile phase at room temperature.

2.2 *Synthesis of 1,2:4,5-Di-O-isopropylidene-β-D-fructo-pyranose (**3**)*

To a suspension of D-fructose (36 g, 200 mmol) and 2, 2-dimethoxy propane (400 mmol) in dry acetone (200 mL) was added 5 mol% of phosphotungstic acid and was stirred at room temperature under nitrogen atmosphere for 4 h. After completion of the reaction, the solvent was removed under reduced pressure. Water was added to the residue and extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum to get the crude product, which was recrystallized by dissolving in boiling ether (5 mL/g), cooling, and adding hexane (5 mL/g) to give 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (37 g, 71%). IR (KBr): 3547, 2983, 2839, 1478, 1325, 1210, 1130, 1070, 825 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 4.17–4.05 (5H, m), 3.93 (1H, d, J = 8.8 Hz), 3.61 (1H, t, J = 7.6, 7.6 Hz), 2.11 (1H, d, J = 8.0 Hz), 1.49 (3H, s), 1.46 (3H, s), 1.39 (3H, s), 1.32 (3H, s); ^{13}CNMR (100 MHz, $CDCl_3$): δ 112.0, 109.6, 104.7, 28.13, 26.62, 26.46, 26.14 ppm. ESI-MS (m/z): 283.2 (M^++Na); Elemental analysis for $C_{12}H_{20}O_6$: Calculated (%) C 55.37, H 7.74; Found (%) C 55.62, H 7.89.

2.3 *Synthesis*

2.3a *1,2:4,5-Di-O-isopropylidene-3-amino-3-deoxy-α-D-fructopyranose (**1a**) and 1,2:4,5-Di-O-isopropylidene-3-amino-3-deoxy-β-D-fructopyranose (**2a**)*: To a solution of $NiCl_2.6H_2O$ (9.50 g, 40 mmol) in MeOH (200 mL) was added $NaBH_4$ (1.5 g, 40 mmol) portion wise at 0°C. The reaction mixture was stirred at 0°C for 30 min and then sugar oxime (**3**, 10.96 g, 40 mmol) dissolved in MeOH was added portion-wise along with $NaBH_4$ (9 equiv.) for over a period of 8 h. After completion of the reaction, the reaction mixture was run through a celite and washed with ethyl acetate. The organic portion collected was concentrated under reduced pressure to get the crude product which was purified by column chromatography using 50% ethyl acetate in hexane as an eluent to achieve 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-β-D-fructopyranose (**2a**, 2.18 g, 21%), followed by 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-α-D-fructo-pyranose (**1a**, 6.42 g, 62%).

2.3b *1,2:4,5-Di-O-isopropylidene-3-amino-3-deoxy-α-D-fructopyranose (**1a**)*: Colourless oil, IR (KBr): 3410, 3328, 2928, 2839, 1652, 1475, 1425, 1327, 1211, 1110, 1070, 845 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 4.42 (dd, 1H, J = 3.2, 3.6 Hz), 4.21 (d, 2H, J = 9.6 Hz), 3.92–3.76 (m, 4H), 3.03 (d, 1H, J = 2.8 Hz), 1.46 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 109.34, 109.10, 106.27, 73.73, 73.03, 71.88, 61.93, 52.19, 26.60, 26.12, 25.49, 24.59 ppm. ESI-MS (m/z): 260 (M^+); Elemental analysis for $C_{12}H_{21}NO_5$: Calculated (%) C 55.58, H 8.16, N 5.40; Found (%) C 55.81, H 8.29, N 5.31.

2.3c *1,2:4,5-Di-O-isopropylidene-3-amino-3-deoxy-β-D-fruc-topyranose (**2a**)*: White solid, IR (KBr): 3410, 3328, 2928, 2839, 1652, 1475, 1425, 1327, 1211, 1110, 1070, 845 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 4.25 (d, 1H, J = 8.4 Hz), 4.14–4.03 (m, 3H), 3.95 (d, 1H, J = 8.4 Hz), 3.88 (dd, 2H, J = 1.6, 1.6 Hz), 2.78 (d, 1H, J = 8.4 Hz), 1.51 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 111.70, 109.02, 105.82, 79.39, 73.02, 72.30, 60.27, 53.87, 28.39, 26.35, 26.29, 26.14 ppm. ESI-MS (m/z): 260 (M^+); Elemental analysis for $C_{12}H_{21}NO_5$: Calculated (%) C 55.58, H 8.16, N 5.40; Found (%) C 55.73, H 8.26, N 5.31.

2.4 *Synthesis of 1,2:4,5-di-O-isopropylidene-3-(N-benzyl) amino-3-deoxy-α-D-fructopyranose (**1c**)*

A mixture of 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-α-D-fructo-pyranose (1.3 g, 5 mmol) and benzaldehyde (530 mg, 5 mmol) was ground with a glass rod for about 10 min by which time, a slightly yellow solid (**8**) was formed. Dry dichloromethane (20 mL) was then added to dissolve the compound (**8**) followed by the addition of sodium cyanoborohydride (378 mg, 6 mmol). Upon stirring at room temperature for 6 h, the reaction mixture was passed through celite and washed with ethyl acetate. The combined organic layers were washed with water, dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product so obtained was purified by column chromatography on silica gel using 30% ethyl acetate in hexane as an eluent to obtain 1,2:4,5:di-*O*-isopropylidene-3-(*N*-benzyl)amino-3-deoxy-α-D-fructopyranose as a pale yellow solid (1.48 g, 88%). IR (KBr): 3328, 3025, 2983, 2873, 1621, 1540, 1443, 1324, 1297, 1210, 1108, 847 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 4.47 (dd, 1H, J = 2.4, 2.4 Hz), 4.42 (d, 1H, J = 9.2 Hz), 4.20 (d, 1H, J = 8.0 Hz), 4.03–3.90 (m, 3H), 3.78-3.68 (m, 3H), 3.00 (d, 1H, J = 2.4 Hz), 1.49 (s, 3H), 1.47 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 138.98, 128.31, 128.22, 127.98, 127.79, 127.56, 110.12, 109.87, 106.71, 75.28, 73.02, 72.89, 65.16, 58.56, 53.34, 26.54, 26.42, 26.27, 26.14 ppm. ESI-MS (m/z): 373.1 (M^++Na); Elemental analysis for $C_{19}H_{27}NO_5$: Calculated (%) C 65.31, H 7.79, N 4.01; Found (%) C 65.79, H 7.63, N 4.23.

2.5 *Synthesis of 1,2:4,5-di-O-isopropylidene-3-(N-benzyl) amino-3-deoxy-β-D-fructopyranose (**2c**)*

Compound **2c** was synthesized from 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-α-D-fructopyranose (1.3 g, 5 mmol) by the procedure similar to that of **1c**. Pale yellow solid (1.47 g, 87%); IR (KBr): 3328, 3025, 2983, 2873, 1621, 1540, 1443, 1324, 1297, 1210, 1108, 847 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.30–7.15 (m, 5H), 4.39 (dd, 1H, J = 2.4, 2.4 Hz), 3.40 (d, 1H, J = 9.2 Hz), 4.11 (d, 1H, J = 7.6 Hz), 3.94–3.82 (m, 3H), 3.69-3.59 (m, 3H), 2.92 (d, 1H, J = 2.0 Hz), 1.41 (s, 3H), 1.38 (s, 3H), 1.38 (s, 3H), 1.23 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 139.85, 128.51, 128.44, 128.12, 127.14, 126.95, 109.37, 109.03, 106.20, 73.47, 72.31, 72.06, 62.33, 56.77, 52.08, 26.68, 26.28, 25.73, 24.74 ppm. ESI-MS (m/z): 373.1 (M^++Na); Elemental analysis for $C_{19}H_{27}NO_5$: Calculated (%) C 65.31, H 7.79, N 4.01; Found (%) C 65.81, H 7.61, N 4.37.

2.6 *Synthesis of N-Cbz-1,2:4,5-di-O-isopropylidene-3-amino-3-deoxy-α − D-fructopyranose (**6**)*[3]

To a mixture of phosphotungstic acid hydrate (0.05 mmol) and benzylchloroformate (1.1 mmol) was added a solution of the amine **1a** (0.260 g, 1.0 mmol) in dichloromethane (4 mL). After stirring for 10 min, the reaction mixture was filtered through ordinary filter paper and the filtrate was concentrated by distillation under reduced pressure. The resulting crude product was then purified by flash chromatography using 40% ethyl acetate in hexane as eluent to get the pure product (**6**). White solid, 0.362 g, 92% yield. IR ($CHCl_3$): 3327, 3101, 2928, 2875, 1710, 1600, 1537, 1456, 1372, 1230, 1088, 967 cm^{-1}; ^{1}HNMR (400MHz, $CDCl_3$): δ 7.22–7.12 (m, 5H); 5.02–4.94 (m, 1H); 4.98 (s, 2H); 4.33 (dd, J = 5.6, 4.8 Hz, 1H); 4.07 (dd, J = 2.4, 2.0 Hz, 1H); 3.97–3.79 (m, 4H); 1.32 (s, 3H); 1.29 (s, 3H); 1.20 (s, 3H); 1.17 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 156.14, 136.20, 128.50, 128.30, 128.20, 111.50, 109.20, 104.45, 73.31, 71.72, 71.70, 67.09, 61.34, 51.85, 26.29, 26.09, 25.73, 24.98 ppm. ESI-MS (m/z): 416.3 (M^++Na); Elemental analysis for $C_{20}H_{27}NO_7$: Calculated (%) C 61.06, H 6.92, N 3.56; Found (%) C 61.33, H 7.21, N 3.87.

2.7 *Synthesis of 1,2:4,5-Di-O-isopropylidene-3-(N-methyl) amino-3-deoxy-α-D-fructopyranose (**1b**)*

To a solution of *N*-Cbz-1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-α-D-fructopyranose (0.787 g, 2 mmol) in dry DMF (5 mL) was added NaH (0.053 g, 2.2 mmol) at 0°C and stirred for 10 min. Freshly distilled MeI (0.296 g, 2.1 mmol) was then added and the reaction was allowed to run for 2 h. After completion of the reaction, ice-cooled water (20 mL) was added and the compound was extracted with ethyl acetate (20 mL × 3). The combined organic layer was

washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the crude product, which was purified using column chromatography to obtain the product (**7**) as an oily liquid in 92% yield. IR (KBr): 3018, 2991, 2980, 2892, 1712, 1600, 1550, 1455, 1382, 1240, 1087, 968 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.38–7.29 (m, 5H), 5.16 (d, 2H, J = 12.0 Hz), 4.48 (dd, 1H, J = 1.6, 1.2 Hz), 4.33–4.29 (m, 1H), 4.20 (d, 1H, J = 9.2 Hz), 3.99–3.87 (m, 3H), 3.72 (d, 1H, J = 13.6 Hz), 3.15 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 157.54, 136.57, 128.83, 128.45, 128.21, 128.08, 110.10, 109.24, 105.45, 75.23, 73.90, 71.63, 67.64, 63.20, 54.91, 29.70, 26.34, 26.01, 25.86, 25.19 ppm; ESI-MS (m/z): 296.3 (M^++Na); Elemental analysis for $C_{13}H_{23}NO_5$: Calculated (%) C 57.13, H 8.48, N 5.12; Found (%) C 56.81, H 8.43, N 5.23.

To a solution of **7** (0.407 g, 1 mmol) in ethyl acetate (5 mL) was added Pd/C (15 mg/mmol) and the reaction mixture was stirred at room temperature under hydrogen atmosphere (1 atm) for 24 h. The solution was filtered and the residue was washed thoroughly with ethyl acetate. The combined filtrate was concentrated to get the crude product which was purified by column chromatography using 30% ethyl acetate in hexane as an eluent. The pure product, 1,2:4,5-Di-*O*-isopropylidene-3-(*N*-methyl)amino-3-deoxy-β-D-fructopyranose (**1b**) was obtained as a colourless oily liquid with 87% yield (0.237 g). IR (KBr): 3344, 2989, 2893, 1640, 1541, 1487, 1345, 1321, 1248, 1180, 1087, 874 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 4.55 (dd, 1H, J = 1.2, 0.8 Hz), 4.36 (d, 1H, J = 8.8 Hz), 4.15 (m, 1H), 3.83 (d, 1H, J = 8.8 Hz), 3.69 (dd, 2H, J = 1.6, 1.6 Hz), 3.55 (d, 1H, J = 13.2 Hz), 2.61 (s, 1H), 2.42 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.25 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 109.60, 108.97, 106.94, 74.65, 72.29, 70.82, 63.70, 62.62, 44.96, 26.59, 26.42, 26.36, 25.15 ppm. ESI-MS (m/z): 296.3 (M^++Na); Elemental analysis for $C_{13}H_{23}NO_5$: Calculated (%) C 57.13, H 8.48, N 5.12; Found (%) C 56.83, H 8.36, N 5.22.

2.8 *Synthesis of N-Cbz-1,2:4,5-di-O-isopropylidene-3-amino-3-deoxy-β-D-fructopyranose (**8**)*

The compound **8** was synthesized from the amine **2a** following similar procedure adopted for the synthesis of the compound **6**. White solid, 0.358 g, 91% yield. IR ($CHCl_3$): 3328, 3100, 2928, 2876, 1712, 1601, 1537, 1456, 1372, 1230, 1088, 967 cm^{-1}; ^{1}HNMR (400MHz, $CDCl_3$): δ 7.28–7.19 (m, 5H); 5.08 (d, J = 3.2 Hz, 1H); 5.05 and 5.03 (both singlet, 2H, $C_6H_5C\underline{H}_2-$); 4.77 (m, 1H); 4.08−3.76 (m, 5H); 1.53 (s, 3H); 1.40 (s, 3H); 1.31 (s, 3H); 1.30 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 156.51, 136.16, 128.58, 128.53, 128.44, 128.30, 128.19, 128.05, 111.79, 109.58, 105.10, 75.94, 72.88, 72.37, 72.11, 67.16, 60.13, 52.87, 28.04, 26.44, 26.37, 26.04 ppm. ESI-MS (m/z): 416.3 (M^++Na); Elemental analysis for $C_{20}H_{27}NO_7$: Calculated (%) C 61.06, H 6.92, N 3.56; Found (%) C 61.39, H 7.25, N 3.84.

2.9 *Synthesis of 1,2:4,5-di-O-isopropylidene-3-(N-methyl) amino-3-deoxy-β-D-fructopyranose (**2b**)*

The compound (**2b**) was synthesized from *N*-Cbz-1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-β-D-fructopyranose (**8**) *via* the compound (**9**) following similar procedure adopted for the synthesis of the compound (**1b**).

Compound (**9**): Colourless gum in 95% yield. IR (KBr): 3025, 2989, 2982, 2876, 1715, 1602, 1537, 1455, 1382, 1235, 1088, 968 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 5H), 5.15 (d, 2H, J = 2.0 Hz), 4.53 (d, 1H, J = 10.0 Hz), 4.48–4.44 (m, 1H), 4.30–4.22 (m, 2H), 4.11–3.87 (m, 3H), 3.02 (d, 3H, J = 2.8 Hz), 1.56 (s, 3H), 1.46 (s 3H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 156.84, 136.08, 128.54, 128.46, 128.32, 127.95, 127.62, 112.09, 109.63, 105.46, 73.28, 72.22, 71.11, 67.51, 69.82, 56.14, 30.21, 28.02, 26.53, 26.37, 26.26 ppm; ESI-MS (m/z): 429.3 (M^++Na); Elemental analysis for $C_{21}H_{29}NO_7$: Calculated C (%) 61.90, H 7.17, N 3.44, O 27.49; Found (%) C 62.01, H 7.21, N 3.58, O 27.76.

Compound (**2b**): White solid in 90% yield (0.245 g). IR (KBr): 3340, 2989, 2893, 1642, 1541, 1487, 1348, 1321, 1248, 1180, 1087, 874 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 4.61–4.57 (m, 1H), 4.36 (d, 1H, J = 8.0 Hz), 4.19 (m, 1H), 4.08–3.99 (m, 3H), 3.90 (d, 1H, J = 8.0 Hz), 2.72 (d, 1H, J = 9.2 Hz), 2.52 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 111.82, 108.88, 107.04, 73.68, 72.56, 72.04, 63.46, 59.79, 43.62, 28.54, 26.58, 26.49, 26.12 ppm. ESI-MS (m/z): 296.3 (M^++Na); Elemental analysis for $C_{13}H_{23}NO_5$: Calculated (%) C 57.13, H 8.48, N 5.12; Found (%) C 56.79, H 8.35, N 5.24.

2.10 *Typical procedure for aldol reaction*

D-Fructose derived amine **4** (39 mg, 0.15 mmol), benzoic acid (18 mg, 0.15 mmol) and cyclohexanone (392 mg, 4 mmol) were stirred at −10°C for 30 min. Then, the *p*-nitrobenzaldehyde (151 mg, 1 mmol) was added and the mixture was stirred for the specified time as shown in Table 3. After completion of the reaction, the mixture was stirred vigorously with aqueous 2.0 N HCl solution (10 mL) and extracted with ethyl acetate (10 mL × 3). The organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated to get the crude product which was subjected to HPLC analysis. The product was purified through flash column chromatography on silica gel (hexane/ethyl acetate) to obtain the pure aldol product, **5a** in 92% (229 mg, 0.92 mmol) yield.

2.10a *2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone (**5a**)*[17]: Yield 92%; *Syn/anti*: 3/1; IR (KBr): 3435, 3330, 3025, 2889, 2789, 1720, 1602, 1547, 1440, 1320, 1284, 1220, 1180 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 1.2 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.42 (t, J = 8.8, 8.0 Hz, 2H), 5.44 (d, J = 2.0 Hz, 1H for *syn*), 4.83 (d, J = 8.4 Hz, 1H for *anti*), 2.53−1.29 (m, 9H); ^{13}CNMR

(100 MHz, $CDCl_3$): δ 214.77 (*anti*), 214.05 (*syn*), 149.14, 148.53, 127.87, 126.60, 123.55, 73.97 (*anti*), 70.08 (*syn*), 57.16 (*anti*), 56.77 (*syn*), 42.66, 30.73, 27.63, 25.88, 24.74 ppm; ESI-MS (m/z): 272.9 (M^++Na); Elemental analysis for $C_{13}H_{15}NO_4$: Calculated (%) C 62.64, H 6.07, N 5.62; Found (%) C 62.71, H 6.12, N 5.68. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 95/5, 0.5 mL/min, 254 nm, 20°C): *syn* product t_R (minor) 56.31 min, t_R (major) 64.62 min, *ee*: 86%, *anti* product t_R (minor) 71.71 min t_R (major) 103.06 min, *ee*: 62%.

2.10b *2-[Hydroxy-(3-nitro-phenyl)-methyl]-cyclohexanone, (**5b**)*[17]: Yield 94%; *Syn/anti*: 1.6/1; IR (KBr): 3440, 3331, 3020, 2889, 2878, 1725, 1605, 1550, 1432, 1328, 1220, 1120 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.17–7.49 (m, 4H), 5.48 (d, J = 2.0 Hz, 1H for *syn*), 4.88 (d, J = 8.4 Hz, 1H for *anti*), 2.66–1.17 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 214.79 (*anti*), 214.03 (*syn*), 148.17, 143.91, 143.25, 133.94, 129.08, 121.06, 120.82, 73.88 (*anti*), 69.75 (*syn*), 57.07 (*anti*), 56.6 (*syn*), 42.43, 27.72, 25.86, 24.68 ppm; ESI-MS (m/z): 272.6 (M^++Na); Elemental analysis for $C_{13}H_{15}NO_4$: Calculated (%) C 62.64, H 6.07, N 5.62; Found (%) C 62.69, H 6.17, N 5.68. HPLC analysis Chiralcel OD-H (Hexane/i-PrOH = 95/5, 0.5 mL/min, 254 nm, 20°C): *syn* product t_R (minor) 26.30 min, t_R (major) 28.20 min, *ee*: 53%, *anti* product t_R (minor) 31.13 min t_R (major) 45.12 min, *ee*: 46%.

2.10c *2-[Hydroxy-(4-bromo-phenyl)-methyl]-cyclohexanone (**5c**)*[17]: Yield 96%; *Syn/anti*: 2.6/1; IR (KBr): 3445, 3320, 3018, 2889, 2877, 1725, 1602, 1540, 1423, 1322, 1240, 1184, 1120 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 5.27 (d, J = 2.4 Hz, 1H for *syn*), 4.68 (d, J = 8.4 Hz, 1H), 2.48–1.18 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 215.16 (*anti*), 214.43 (*syn*), 140.51, 140.29, 131.19, 131.06, 127.72, 127.54, 121.01, 120.64, 74.03 (*anti*), 70.07 (*syn*), 57.25 (*anti*), 56.93 (*syn*), 42.98, 42.21, 27.82, 27.10, 25.87, 24.76, 24.72 ppm; ESI-MS (m/z): 307.1 (M^++Na); Elemental analysis for $C_{13}H_{15}BrO_2$: Calculated (%) C 55.14, H 5.34; Found (%) C 55.27, H 5.43. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 95/5, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (minor) 24.40 min, t_R (major) 25.86 min, *ee*: 77%, *anti* product t_R (minor) 35.79 min t_R (major) 51.10 min, *ee*: 30%.

2.10d *2-[Hydroxy-(3-bromo-phenyl)-methyl]-cyclohexanone, (**5d**)*[18]: Yield 91%; *Syn/anti*: 1.8/1; IR (KBr): 3440, 3331, 3018, 2889, 2878, 1721, 1600, 1543, 1421, 1323, 1280, 1220, 1185, 1123 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.49–7.40 (m, 2H), 7.24–7.17 (m, 2H), 5.32 (d, J = 2.0 Hz, 1H for *syn*), 4.75 (d, J = 8.4 Hz, 1H for *anti*), 2.60–1.22 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 215.28 (*anti*), 214.73 (*syn*), 143.85, 143.32, 131.84, 130.01, 129.88, 128.77, 125.75, 122.56, 122.45, 74.29 (*anti*), 70.64 (*syn*), 57.21, 42.62, 30.74, 27.76, 25.88, 24.67, 24.56 ppm; ESI-MS (m/z): 307.3 (M^++Na); Elemental analysis for $C_{13}H_{15}BrO_2$: Calculated (%) C 55.14, H 5.34; Found (%) C 55.22, H 5.39. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 95/5, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 15.20 min, t_R (minor) 16.24 min, *ee*: 33%, *anti* product t_R (minor) 18.58 min t_R (major) 25.51 min, *ee*: 44%.

2.10e *2-[Hydroxy-(4-chloro-phenyl)-methyl]-cyclohexanone (**5e**)*[19]: Yield 90%; *Syn/anti*: 2.7/1; IR (KBr): 3440, 3353, 3025, 2885, 2789, 1727, 1610, 1541, 1452, 1324, 1284, 1220, 1186, 1121 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.36–7.17 (m, 4H), 5.34 (d, J = 2.4 Hz, 1H for *syn*), 4.76 (d, J = 8.0 Hz, 1H for *anti*); 2.64−1.14 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 215.23 (*anti*), 214.37 (*syn*), 139.95, 139.71, 133.49, 132.86, 129.98, 129.78, 128.41, 128.20, 74.07 (*anti*), 70.04 (*syn*), 57.32 (*anti*), 57.05 (*syn*), 42.69, 42.53, 30.18, 27.86, 27.78, 25.81, 24.87, 24.73 ppm; ESI-MS (m/z): 261.7 (M^++Na); Elemental analysis for $C_{13}H_{15}ClO_2$: Calculated (%) C 65.41, H 6.33; Found (%) C 65.23, H 5.99. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 90/10, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 12.80 min, t_R (minor) 15.32 min, *ee*: 81%, *anti* product t_R (major) 20.07 min t_R (minor) 22.85 min, *ee*: 40%.

2.10f *2-[Hydroxy-(2-chloro-phenyl)-methyl]-cyclohexanone (**5f**)*[17]: Yield 87%; *Syn/anti*: 19/1; IR (KBr): 3441, 3325, 3018, 2889, 2877, 1721, 1602, 1541, 1423, 1320, 1248, 1185, 1120 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.53–7.23 (m, 4H), 5.70 (d, J = 2.0 Hz, 1H for *syn*), 5.34 (d, J = 8.4 Hz, 1H for *anti*), 2.83–1.32 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 215.17 (*anti*), 214.58 (*syn*), 139.00, 138.91, 132.65, 131.17, 130.49, 130.45, 129.03, 128.73, 127.01, 126.74, 70.38 (*anti*), 67.57 (*syn*), 57.84 (*anti*), 53.53 (*syn*), 42.61, 42.55, 30.31, 27.89, 27.74, 25.86, 24.89, 24.71 ppm; ESI-MS (m/z): 261.8 (M^++Na); Elemental analysis for $C_{13}H_{15}ClO_2$: Calculated (%) C 65.41, H 6.33; Found (%) C 65.32, H 6.11. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 94/6, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (minor) 8.64 min, t_R (major) 12.32 min, *ee*: 99%, *anti* product t_R (major) 19.50 min t_R (minor) 24.43 min, *ee*: 44%.

2.10g *2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone (**5g**)*[17]: Yield 89%; *Syn/anti*: 1/2.1; IR (KBr): 3430, 3334, 3018, 2898, 2789, 1732, 1541, 1432, 1328, 1284, 1187, 1121 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.93–7.37 (m, 4H), 5.92 (d, J = 2.4 Hz, 1H for *syn*), 5.39 (d, J = 8.0 Hz, 1H for *anti*), 2.78–1.35 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 214.56 (*anti*), 213.77 (*syn*), 149.54, 148.65, 137.98, 134.03, 129.94, 127.67, 124.56, 69.83 (*anti*), 66.36 (*syn*), 57.21 (*anti*), 54.78 (*syn*), 42.38, 42.37, 27.32, 26.42, 24.67 ppm; ESI-MS (m/z): 272.6 (M^++Na); Elemental analysis for $C_{13}H_{15}NO_4$: Calculated (%) C 62.64, H 6.07, N 5.62; Found (%) C 62.76, H 6.17, N 5.76. HPLC analysis Chiralcel OD-H (Hexane/i-PrOH = 94/6, 0.5 mL/min, 254 nm, 20°C): *syn* product t_R (major) 19.54 min, t_R (minor) 22.77 min, *ee*: 65%, *anti* product t_R (major) 26.97 min t_R (minor) 35.31 min, *ee*: 95%.

2.10h *2-[Hydroxy-(2-hydroxyphenyl)-methyl]-cyclohexanone (**5h**)*: Yield 87%; *Syn/anti*: 2/1; IR (KBr): 3441, 3332, 3025, 2879, 1712, 1600, 1545, 1432, 1421, 1384, 1220, 1184 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.54−6.83 (m, 4H), 5.36 (d, J = 2.4 Hz, 1H for *syn*), 4.86 (d, J = 9.2 Hz, 1H for *anti*), 2.18–0.81 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 229.12, 161.16, 160.01, 132.96, 1321.71, 130.08, 128.42, 118.79, 118.47, 117.34, 109.94, 109.89, 109.44, 109.37, 67.85, 63.02, 61.97, 51.93, 26.51, 26.32, 26.20, 26.07, 25.77, 25.44 ppm; ESI-MS (m/z): 243.4 (M^++Na); Elemental analysis for $C_{13}H_{16}O_3$: Calculated (%) C 70.89, H 7.32, O 21.79; Found (%) C 70.91, H 7.42, O 21.86. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 90/10, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 12.53 min, t_R (minor) 19.83, *ee*: 92%; *anti* product t_R (minor) 23.57 min, t_R (major) 26.47 min, *ee*: 2%.

2.10i *2-(Hydroxy-phenyl-methyl)-cyclohexanone (**5i**)*[17]: Yield 89%; *Syn/anti*: 2.7/1; IR (KBr): 3440, 3330, 3018, 2879, 1710, 1600, 1540, 1430, 1384, 1220, 1184 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.29–7.19 (m, 4H), 5.31 (d, J = 2.4 Hz, 1H for *syn*), 4.71 (d, J = 8.8 Hz, 1H for *anti*), 3.90 (s, 1H), 2.55–1.18 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 215.55 (*anti*), 214.84 (*syn*), 140.95, 139.72, 127.89, 126.79, 126.23, 126.13, 74.74 (*anti*), 70.67 (*syn*), 57.41 (*anti*), 57.14 (*syn*), 42.62, 30.88, 27.85, 27.67, 25.88, 24.71, 24.63 ppm; ESI-MS (m/z): 227.4 (M^++Na); Elemental analysis for $C_{13}H_{16}O_2$: Calculated (%) C 76.44, H 7.90; Found (%) C 76.39, H 7.82. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 90/10, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 15.12 min, t_R (minor) 16.29, *ee*: 56%; *anti* product t_R (minor) 18.82 min, t_R (major) 30.07 min, *ee*: 34%.

2.10j *2-[Hydroxy-(pyridin-2-yl)-methyl]-cyclohexanone (**5j**)*: Yield 88%; *Syn/anti*: 6/1; IR (KBr): 3450, 3343, 3100, 2898, 2789, 1724, 1600, 1537, 1474, 1398, 1321, 1286, 1224, 1189, 1121 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.21–8.08 (m, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.55–7.50 (m, 2H), 7.26 (s, 1H), 5.48 (d, J = 2.0 Hz, 1H for *syn*), 4.89 (d, J = 8.4 Hz, 1H for *anti*), 3.19 (s, 1H), 2.65–1.52 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 214.76 (*anti*), 214.21 (*syn*), 143.74, 143.21, 133.19, 131.94, 129.31, 129.15, 122.89, 122.10, 122.02, 120.86, 74.06 (*anti*), 69.90 (*syn*), 57.13, 56.75, 42.67, 42.62, 30.74, 27.88, 27.62, 25.89, 24.75, 24.66 ppm; ESI-MS (m/z): 229.0 (M^++Na); Elemental analysis for $C_{12}H_{15}NO_2$: Calculated (%) C 70.22, H 7.37, N 6.82; Found (%) C 70.38, H 7.58, N 7.03. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 47/3, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 24.51 min, t_R (minor) 27.90 min, *ee*: 32%, *anti* product t_R (minor) 32.47 min t_R (major) 37.84 min, *ee*: 98%.

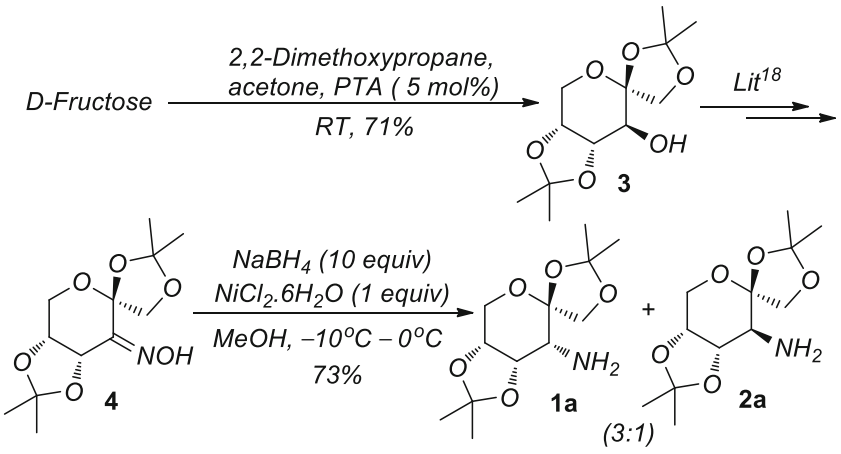
2.10k *2-[(2-Chlorophenyl)(hydroxy)methyl]cyclopentanone, (**5k**)*: Yield 92%; *Syn/anti*: 4.9/1; IR (KBr): 3330, 3025, 2887, 2784, 1742, 1600, 1472, 1380, 1322, 1286, 1224, 1182, 827 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.53–7.10 (m, 4H), 5.60 (d, J = 2.4 Hz, 1H for *syn*), 5.22 (d, J = 9.2 Hz, 1H for *anti*), 2.61−1.18 (m, 7H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 222.99, 220.24, 140.14, 139.09, 133.53, 132.41, 130.99, 130.12, 130.11, 129.99, 129.94, 129.32, 129.25, 129.93, 128.43, 128.36, 128.34, 128.31, 127.46, 127.37, 126.85, 126.55, 75.86, 70.34, 67.88, 55.52, 53.54, 39.05, 38.67, 37.91, 29.64, 29.26, 26.41, 22.48, 20.53, 20.34 ppm; ESI-MS (m/z): 247.6 (M^++Na); Elemental analysis for $C_{12}H_{13}ClO_2$: Calculated (%) C 64.15, H 5.83, Cl 15.78, O 14.24; Found (%) C 63.89, H 5.91, Cl 15.65, O 14.41. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 47/3, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 20.45 min, t_R (minor) 27.53 min, *ee*: 82%, *anti* product t_R (major) 36.82 min t_R (minor) 43.17 min, *ee*: 78%.

2.10l *2-[Hydroxy(2-nitrophenyl)methyl]cyclopentanone (**5l**)*[20]: Yield 91%; *Syn/anti*: 1.5/1; IR (KBr): 3441, 3342, 3098, 2893, 2787, 1735, 1601, 1526, 1473, 1346, 1280, 1189, 907 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.84–7.24 (m, 4H), 5.92 (d, J = 2.0 Hz, 1H for *syn*), 5.44 (d, J = 8.4 Hz, 1H for *anti*), 2.84−1.46 (m, 7H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 221.59, 219.33, 148.34, 147.73, 137.03, 136.11, 132.59, 132.31, 128.81, 128.73, 128.23, 128.04, 123.85, 123.76, 69.08, 65.13, 56.01, 51.69, 39.16, 38.29, 26.92, 26.83, 21.05, 20.25 ppm; ESI-MS (m/z): 258.3 (M^++Na); Elemental analysis for $C_{12}H_{13}NO_4$: Calculated (%) C 61.27, H 5.57, N 5.95, O 27.21; Found (%) C 61.19, H 5.54, N 5.87, O 27.14. HPLC analysis Chiralcel OD-H (Hexane/i-PrOH = 47/3, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 22.21 min, t_R (minor) 28.57 min, *ee*: 20%, *anti* product t_R (major) 33.80 min t_R (minor) 43.08 min, *ee*: 94%.

2.10m *2-[Hydroxy(p-tolyl)methyl]cyclopentanone (**5m**)*[21]: Yield 88%; *Syn/anti*: 1.3/1; IR (KBr): 3340, 3100, 2989, 2898, 2789, 1745, 1601, 1535, 1482, 1397, 1324, 1280, 1222, 1189, 1120 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.43–7.13 (m, 4H), 5.13 (d, J = 2.0 Hz, 1H for *syn*), 4.62 (d, J = 9.2 Hz, 1H for *syn*), 3.00 (s, 1H), 2.88 (m, 1H), 2.48–1.17 (m, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 222.55, 221.74, 133.65, 133.12, 132.72, 132.54, 130.82, 130.60, 130.23, 130.16, 129.88, 129.72, 129.54, 129.47, 129.20, 129.04, 128.45, 75.04, 71.53, 56.12, 55.30, 39.27, 38.77, 27.00, 26.55, 21.51, 20.17, 14.13 ppm; ESI-MS (m/z): 227.8 (M^++ Na); Elemental analysis for $C_{13}H_{16}O_2$: Calculated (%) C 76.44, H 7.90, O 15.67; Found (%) C 76.79, H 8.11, O 15.94. HPLC analysis Chiralcel OD-H (Hexane/ i-PrOH = 47/3, 0.5 mL/min, 220 nm, 20°C): *syn* product t_R (major) 10.54 min, t_R (minor) 13.63 min, *ee*: 80%, *anti* product t_R (major) 15.46 min t_R (minor) 25.31 min, *ee*: 78%.

3. Results and Discussion

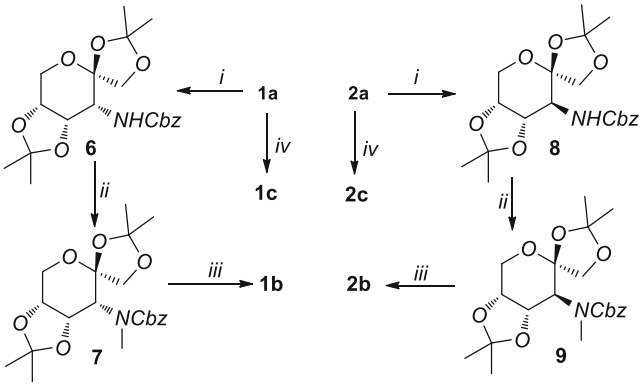
To start with, we synthesized the catalyst **1a** following the Scheme 2. The acetonation of D-fructose



Scheme 2. Synthesis of the catalyst **1a** and **2a**.

was accomplished by stirring D-fructose in 2,2-dimethoxypropane (DMP)/acetone in the presence of a catalytic amount of phosophotungstic acid (PTA).[22] The product, so obtained, was converted to oxime *via* Shi's ketone following literature protocol.[23] The conversion of the oxime to amine by literature procedure[18] hardly gave any yield (reported yield 11%). Therefore, we developed a new protocol to synthesize the amine by treatment of the oxime **4** with a mixture of $NaBH_4$ (10 equiv), $NiCl_2.6H_2O$ (1 equiv) in methanol at −10 to 0°C to achieve the corresponding amines in 73% yield. The yield of the amine derivative **1a** was three times higher than that of its enantiomer **2a**.

In our bid to evaluate the catalytic activity of **1a**, we chose the aldol reaction between p-nitrobenzaldehyde and cyclohexanone as our pilot reaction. To begin with, a mixture of the amine catalyst **1a** (15 mol%), benzoic acid (15 mol%) and cyclohexanone (1 mmol) in water (1 mL) was stirred at room temperature for 30 min. To this reaction mixture, p-nitrobenzaldehyde (1 mmol) was added and the reaction was allowed to stir at room temperature for 30 h. Ironically, the reaction resulted in very poor yield (17%) and diastereoselectivity (*syn*:*anti* = 59:41). Assuming that the reactants might not have mixed properly in water, we screened a series of solvents, *viz.* ethanol, acetonitrile, methylene chloride, DMF, DMSO, and THF to observe that the reaction was insignificant in terms of yield and selectivity in most of these solvents (See Table S1 in the Supplementary Information). Interestingly, when the reaction was carried out as neat with excess amount of cyclohexanone (4 mmol), the reaction was complete within 12 h to generate the desired product in 92% yield. HPLC analysis of the crude product indicated much improved selectivity; diastereoselectivity (syn/anti) ratio of 2.6:1 and enantiomeric excess of 21% and 15% for *syn*- and *anti*-product, respectively. Studies on the role of different acid additives



Scheme 3. Synthesis of D-fructose derived monofunctional secondary amines.

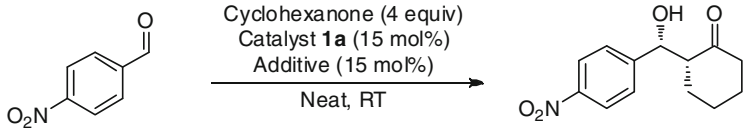
to increase the yield and selectivity of the pilot reaction confirmed that benzoic acid as the best choice (Table 1).

To improve upon the selectivity, the reaction was carried out by lowering the temperature while keeping the other parameters unchanged (entries 1–5, Table 2). The diastereomeric ratio of the *syn*- and *anti*-products and their enantioselectivities were found optimum at −10°C (entry 4). Keeping in mind that the catalyst loading has a big role to play in organocatalytic reactions,[18] catalytic efficiency at optimum temperature in different catalyst loading (entries 6–8) were studied to find 15 mol% of **1a** (entry 4) as the optimum loading.

Given the fact that many secondary amines have been proven as organocatalysts for various asymmetric transformations, we synthesized some secondary amines such as **1b**, **2b**, **1c**, and **2c** (Figure 2) starting from their corresponding primary amines.

For the synthesis of monomethylated amines **1b** and **2b**, the primary amines **1a** and **2a** were first protected with benzylchloroformate in the presence of a catalytic amount of phosphotungstic acid (1 mol%).[24] The Cbz derivatives, so obtained, were methylated with MeI and

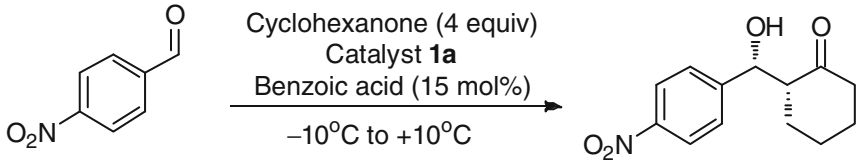
Table 1. Effect of additives.



Entry	additives	t/h	% yield[a]	*syn*/*anti*[b]	%ee[b]
1	None	72	67	1.2/1	19
2	PhCOOH	12	92	2.6/1	21
3	TFA	36	70	1.1/1	8
4	CH_3COOH	36	65	1/1	3
5	CSA	36	20	nd	–
6	*p*-TsOH	36	20	nd	–

[a]Isolated yields.
[b]Stereoselectivity was determined by HPLC analysis of the crude mixture using Chiralcel OD-H columns.

Table 2. Effect of temperature and catalyst loading.



Entry	**1a** (mol%)	T/°C	t/h	% yield[a]	*syn*/*anti*	%ee[b]
1	15	10	30	91	1.6 : 1	45
2	15	0	36	89	2.6 : 1	70
3	15	−5	36	89	2.4 : 1	72
4	15	−10	36	92	3.0 : 1	86
5	15	−20	48	71	2.8 : 1	84
6	10	−10	60	77	3.0 : 1	86
7	5	−10	72	54	2.8 : 1	85
8	20	−10	36	94	2.6 : 1	84

[a]Isolated yields.
[b]Stereoselectivity was determined by HPLC analysis of the crude mixture using Chiralcel OD-H columns.

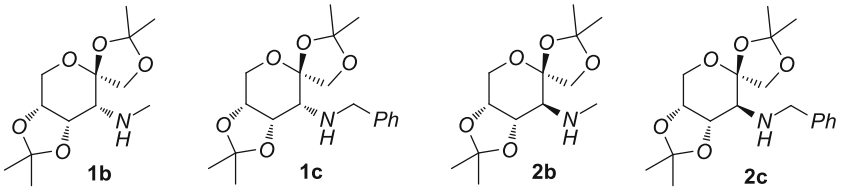
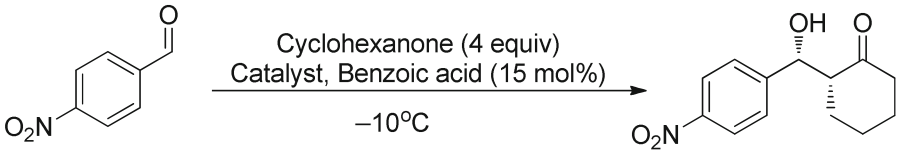


Figure 2. Fructose derived monofunctional secondary amines.

NaH in DMF and the resulting compounds (**7** and **9**, Scheme 3) were deprotected by hydrogenation on 10% Pd/C to achieve the desired products, **1b** and **2b**. The synthesis of benzylamines, **1c** and **2c** were accomplished by reducing a ground mixture of benzaldehyde and the primary amine in dichloromethane with sodium cyanoborohydride at room temperature.

To study the catalytic efficiency of newly synthesized monofunctional amines for asymmetric aldol reaction, the same pilot reaction was carried out under optimized reaction conditions by varying the amine catalysts. Catalyst **2a** gave excellent yield (91%) and good enantioselectivity for *syn* (67%) and *anti* (71%) products, but almost no diastereoselectivity was observed (Table 3). The same reaction in the presence of *N*-methyl amine derivatives **1b** and **2b** gave the aldol products in less than 10% yield. The pilot reaction did not proceed at all in the presence of catalysts **1c** and

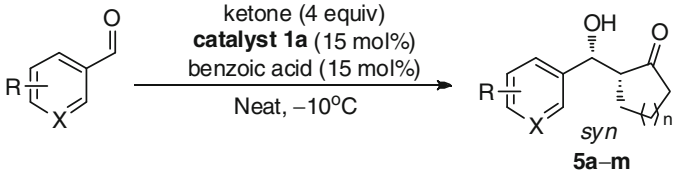
Table 3. Screening of various amine catalysts for Aldol reaction.



Entry	Catalysts	T/h	% yield[a]	*syn*: *anti*	% ee (*syn*)	% ee (*anti*)
1	**1a**	36	92	3.2 : 1	86	62
2	**1b**	120	<10	–	–	–
3	**1c**	120	–	–	–	–
4	**2a**	36	91	1 : 1.2	67	71
5	**2b**	120	<10	–	–	–
6	**2c**	120	–	–	–	–

[a]Isolated yields.
[b]Stereoselectivity was determined by HPLC analysis of the crude mixture using Chiralcel OD-H columns.

Table 4. Asymmetric aldol reaction catalyzed by organocatalyst **1a**.[a]



Entry	R	X	n	5	t/h	% yield[b]	*syn*/*anti*[c]	% ee[c,d]
1	*p*-NO_2	CH	2	**a**	36	92	3 : 1	86
2	*m*-NO_2	CH	2	**b**	36	94	1.6 : 1	53
3	*p*-Br	CH	2	**c**	36	96	2.6 : 1	77
4	*m*-Br	CH	2	**d**	36	91	1.8 : 1	33
5	*p*-Cl	CH	2	**e**	24	90	2.7 : 1	81
6	*o*-Cl	CH	2	**f**	36	87	19 : 1	99
7	*o*-NO_2	CH	2	**g**	36	89	1: 2.2	95[e]
8	*o*-OH	CH	2	**h**	24	85	2 : 1	92
9	H	CH	2	**i**	32	89	2.7 : 1	56
10	H	N	2	**j**	36	88	6 : 1	32
11	*o*-Cl	CH	1	**k**	24	92	4.9 : 1	82
12	*o*-NO_2	CH	1	**l**	24	91	1.5 : 1	20
13	*p*-Me	CH	1	**m**	24	88	1.3 : 1	88

[a]Reaction conditions: aldehyde (1 mmol), catalyst (15 mol%), benzoic acid (15 mol%) and ketone (4 mmol).
[b]Isolated yields.
[c]Determined by HPLC analysis of the crude products using Chiralcel OD-H and AD-H columns.
[d]%ee of the major diastereomer.

2c. Such results might be attributed to the fact that steric hindrance caused by introduction of the bulky substituents such as methyl and benzyl groups on the primary amine which might have blocked the initial formation of enamine with cyclohexanone.

After optimizing the reaction conditions such as solvent, temperature, acid additive, and catalyst loading, the substrate scope of our method was explored for asymmetric aldol reaction of cyclohexanone with a variety of aromatic aldehydes in the presence of benzoic acid (Table 4, entries 1–10). The reaction gave excellent yields in all the cases with moderate to excellent enantioselectivity for both *syn*- and *anti*- products. Especially, the aldehydes having ortho-substituents (entries 6–7, Table 4) gave very good enantioselectivities (up to 99%), while those with meta-substituents

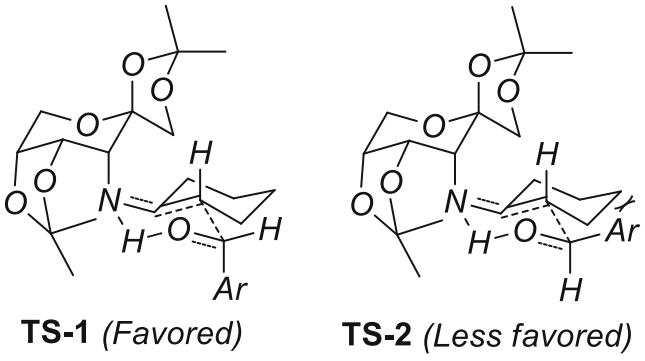


Figure 3. Plausible mechanism of *syn*-selectivity.

(entries 2, 4) gave poorer enantioselectivity. Interestingly, diastereoselectivity of *o*-nitrobenzaldehyde derived aldol product (5 g) was found to be opposite to all other aldehydes where *syn*- diastereomer was formed as the major product. Given the fact that cyclopentanone forms enamine faster than that of cyclohexanone,[25] we screened aminocatalysis of cyclopentanone with aryl aldehydes to synthesize corresponding β-hydroxy ketones. In all the three cases, reaction time was found to be reduced substantially to give comparable diastereoselectivity with similar starting aldehydes.

The plausible mechanism to account for the stereoselectivity might be the formation of the transition states **TS-1** and **TS-2** wherein the catalyst **1a** could catalyze the aldol reaction as shown in Figure 3. The aldehyde might be activated by hydrogen-bonding with NH group of cyclohexenylamine via formation of the six-membered transition states. In **TS-2**, the plane of aryl group might experience substantial steric hindrance due to cyclohexane ring making the transition state less favorable than **TS-1**. Therefore, the approach of the enamine carbon from re-face of aldehyde in **TS-1** led to *syn*-selective aldol product.

4. Conclusions

In conclusion, we have established monofunctional primary amine, 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-α-D-fructopyranose (**1a**) as an efficient aminocatalyst for stereoselective synthesis of β-hydroxy ketones by aldol reaction. Under optimal conditions, very high diastereoselectivities (up to 95%) and enantioselectivities (up to 99%) were achieved. It may be noted that this is the first report on any stereoselective organocatalysis employing monofunctional primary amine, albeit monofunctional secondary amine catalysis exist in literature. Interestingly, the fructose derived secondary amines (**1b**, **1c**, **2b**, and **2c**) were found to be ineffective.

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Supporting Information (SI)

^{1}H and ^{13}C NMR spectra of new compounds and HPLC data are available free of charge at www.ias.ac.in/chemsci.

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