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# NEW SUGAR BASED γ-AMINO SILYL ETHER ORGANOCATALYSTS FOR ASYMMETRIC MICHAEL ADDITION OF β-KETO ESTERS WITH NITROOLEFINS

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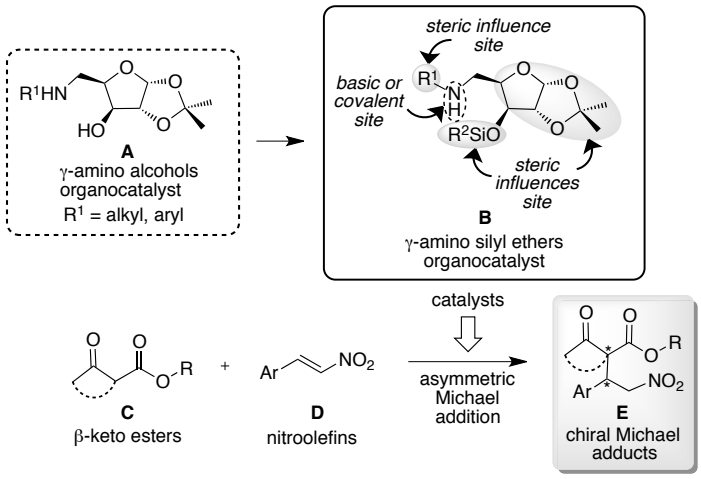
**Abstract** - New sugar based γ-amino silyl ether organocatalysts were synthesized and their catalytic ability was examined in asymmetric Michael addition of β-keto esters with nitroolefins affording chiral Michael adducts with quaternary carbon stereocenter in good to excellent chemical yields, diastereoselectivities and moderate enantioselectivities (up to 97%, up to *dr.* 85:15, up to 56% *ee*).

## INTRODUCTION

Remarkable intensive attempts have been devoted in establishing optically active organocatalysts that are used in the asymmetric synthesis, for the induction of chirality[1] and tremendous progress has been accomplished towards the evolution of numerous covalent and non-covalent organocatalysts for a wide range of reactions to date.[2] Our research group also, has been continuously developing efficient organocatalysts based on the simple amino alcohols and amino amides towards the asymmetric reactions.[3] Most recently, we have demonstrated the effectiveness of sugar based γ-amino alcohol organocatalysts **A**[4]

* Dedicated to Prof. Somsak Ruchirawat on the occasion of his 80th birthday

in the asymmetric Michael addition of β-keto esters **C** with nitroolefins **D** affording chiral Michael adducts **E** with quaternary carbon stereocenter.[5] However, this catalyst **A** could not afford the adduct **E** (up to 84% ee)[4] with high to excellent levels of enantioselectivity. In order to improve the catalytic efficiency of the sugar based γ-amino organocatalyst to this reaction, we have designed a distinct sugar



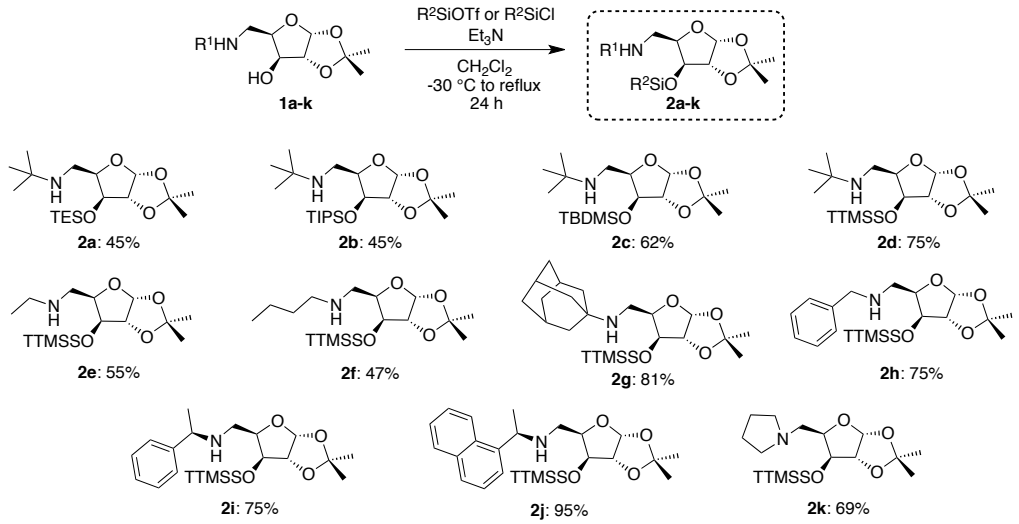

**Scheme 1.** Concept of sugar based γ-amino silyl ether organocatalysts **B**

based γ-amino silyl ether **B**, which can be easily derived from the reaction of γ-amino alcohol precursor **A** with different silyl protecting reagents. Newly designed and prepared organocatalyst **B** has variable potential characteristics to function as an organocatalyst such as, secondary amino group acting as a basic or covalent site, both bulky silyl ether group and substituents on nitrogen atom acting as steric influences site, and 1,2-isopropylidene-xylofuranose structure serving as a rigid backbone in the single molecule (Scheme 1). Additionally, catalyst **B** has multiple features, including long-term moisture and air storage stability, and ease of preparation. Herein, we describe the efficiency of new xylofuranose based γ-amino silyl ethers **B** as an organocatalyst in the asymmetric Michael addition of β-keto esters **C** with various nitroolefins **D** to afford the corresponding chiral Michael adduct **E**.

## RESULTS AND DISCUSSION

Sugar based γ-amino silyl ether organocatalysts **2a-k** were easily prepared from the reaction of corresponding γ-amino alcohols **1a-k** with various silyl protecting reagents such as, triethylsilyl chloride (TESCl), triisopropylsilyl triflate (TIPSOTf), *tert*-butyldimethylsilyl chloride (TBDMSCl) and tris(trimethylsilyl)silyl chloride (TTMSSCl), in the presence of $Et_3N$ in moderate to good yields (45-95%), respectively (Scheme 2).[4]

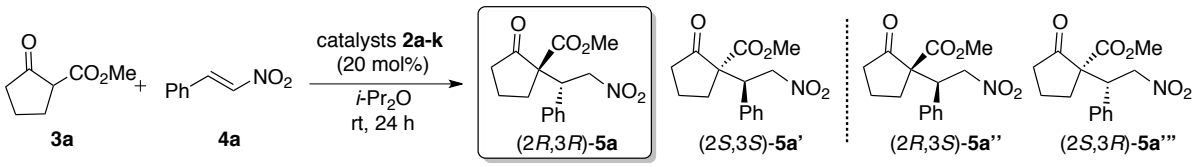
The catalytic activity of the obtained γ-amino silyl ethers **2a-k** were examined in the asymmetric Michael addition of methyl 2-oxocyclopentanecarboxylate **3a** with *trans*-β-nitrostyrene **4a** (Table 1). The reaction




**Scheme 2.** Preparation of sugar based γ-amino silyl ether organocatalysts **2a-k**

was performed at room temperature for 24 h using catalysts **2a-k** (20 mol%) in *i*-$Pr_2O$. Initially, the reactions using *N*-*tert*-butylated γ-amino silyl ethers **2a-d** with TES, TIPS, TBDMS and TTMSS groups on oxygen atom were examined, respectively (entries 1-4). The catalyst **2a** with TES group, showed catalytic activity in this reaction to afford (2*R*,3*R*)-**5a** in moderate chemical yield, diastereoselectivity and low enantioselectivity (entry 1). The reactions using catalysts **2b** and **2c** with bulkier TIPS and TBDMS groups, respectively, afforded **5a** in good chemical yield, diastereoselectivity but enantioselectivity was slightly increased to 42 and 44% ee (entries 2,3). From these results, it was indicated that the enantioselectivity of adduct **5a** might increase depending on the size of silyl group. Based on this observation, catalyst **2d** with the bulkiest super silyl (TTMSS) group was applied in this reaction. Consequently, catalyst **2d** showed good catalytic activity and the adduct **5a** was obtained in good chemical yield, diastereoselectivity and slightly enhanced enantioselectivity (56% ee) (entry 4). Next, the catalytic activity of γ-amino silyl ethers **2e-k** with several substituents on nitrogen atom and TTMSS group on the oxygen atom were examined in this reaction (entries 5-11). The use of *N*-ethylated catalyst **2e** afforded **5a** with moderate chemical yield, diastereoselectivity, but enantioselectivity was significantly decreased (25% ee) (entry 5). *N*-*n*-Butylated catalyst **2f** gave **5a** with good chemical yield, diastereoselectivity, whereas enantioselectivity was increased to 41% ee (entry 6). Bulkier *N*-adamantylated catalyst **2g** also afforded, almost similar results to catalyst **2f** (entry 7). Furthermore, *N*-benzylated, *N*-phenylethylated and *N*-naphthylethylated catalysts **2h-j** performed with good catalytic activities and afforded **5a** with good chemical yields and diastereoselectivities, respectively (entries 8-10). However, satisfactory enantioselectivities were not observed in either catalyst **2h-j** (39-42% ee). The use of catalyst **2k** with pyrrolidinyl group also promoted the reaction to afford **5a** in moderate chemical yield, diastereoselectivity (85%, *dr*. 84:26), but with low enantioselectivity (23% ee) (entry 11). From these results, *N*-*tert*-butylated catalyst **2d** with TTMSS group was found to be the best catalyst among the

**Table 1.** Screening of catalysts **2a-k** in asymmetric Michael addition




| entry | catalyst **2** | yield (%)[a] | *dr*[b] (**5a, a'/5a'', a'''**) | *ee* (%)[c] **5a** | *ee* (%)[c] **5a''** |
|---|---|---|---|---|---|
| 1 | **a** | 65 | 74:26 | 37 | 14 |
| 2 | **b** | 76 | 75:25 | 42 | 48 |
| 3 | **c** | 81 | 79:21 | 44 | 29 |
| 4 | **d** | 85 | 73:27 | 56 | 23 |
| 5 | **e** | 65 | 71:29 | 25 | 4 |
| 6 | **f** | 76 | 85:15 | 41 | 18 |
| 7 | **g** | 65 | 73:27 | 26 | 46 |
| 8 | **h** | 69 | 70:30 | 42 | 26 |
| 9 | **i** | 81 | 76:24 | 40 | 9 |
| 10 | **j** | 76 | 80:20 | 39 | rac |
| 11 | **k** | 85 | 84:26 | 23 | 53 |

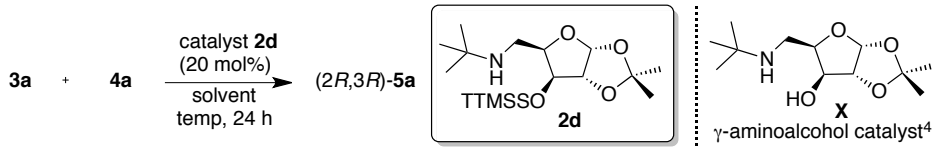
[a]Yield was calculated after purification. [b]The *dr* was determined by $^1$H NMR. [c]The *ee* was determined by HPLC analysis using a CHIRALCEL OD-H.

applied catalysts **2a-k** to the asymmetric Michael addition of **3a** and **4a** to afford chiral Michael adduct **5a** (85%, *dr*. 73:27%, 56% ee) (entry 4). Stereochemistry of chiral adduct **5a** was determined by comparing with the literature data.[6]

In order to optimize the reaction conditions using the superior catalyst **2d**, we next examined the effect of solvent, the molar ratio of catalyst, and the reaction temperature (Table 2). At first, the solvent effect to this reaction was examined using catalyst **2d** (20 mol%) at room temperature. With the polar protic ($H_2O$, MeOH, 2-PrOH) and polar aprotic (DMSO, MeCN, DMF) solvents, the reaction proceeded smoothly and the corresponding chiral **5a** was obtained with good to excellent chemical yields and moderate to good diastereoselectivities (82-97%, *dr*. 65:35-82:18), but enantioselectivities were lowered (5-35% ee) (entries 1-6). Furthermore, the reactions in ethereal (THF, $Et_2O$) and halogenated ($CH_2Cl_2$, $CHCl_3$) solvents also afforded **5a** with good chemical yields and good to moderate diastereoselectivities, and also slight increase in the enantioselectivities (30-39% ee) was observed (entries 7-10). When the reaction was carried out in aromatic (toluene, benzene, xylene) and nonpolar (hexane) solvents, the adduct **5a** was obtained in good chemical yields, moderate to good diastereoselectivities and with low to moderate enantioselectivities (39-48% ee) (entries 11-14). From these results, it was observed that *i*-$Pr_2O$ was a suitable solvent to promote the Michael addition of **3a** with **4a** using catalyst **2d** (entry 4, Table 1).

Next, the molar ratios (10, 5, 1 mol%) of catalyst **2d** was examined in *i*-$Pr_2O$ at room temperature, respectively (entries 15-17). When 10 mol%, 5 mol% of **2d** was used, enantioselectivity of **5a** decreased in comparison to the 20 mol% of **2d** (entries 15,16). Moreover, the use of 1 mol% of **2d** brought about the

**Table 2.** Optimization of the reaction condition using catalyst **2d**



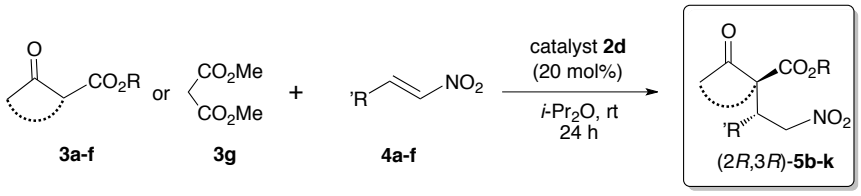

| entry | solvent | mol (%) | temp | yield (%)[a] | *dr*[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $H_2O$ | 20 | rt | 97 | 82:18 | 16 |
| 2 | MeOH | 20 | rt | 92 | 75:25 | 25 |
| 3 | *i*-PrOH | 20 | rt | 95 | 78:22 | 8 |
| 4 | DMSO | 20 | rt | 94 | 65:35 | 5 |
| 5 | MeCN | 20 | rt | 82 | 77:23 | 9 |
| 6 | DMF | 20 | rt | 94 | 66:34 | 35 |
| 7 | THF | 20 | rt | 94 | 64:36 | 30 |
| 8 | $Et_2O$ | 20 | rt | 94 | 65:35 | 32 |
| 9 | $CH_2Cl_2$ | 20 | rt | 90 | 75:25 | 39 |
| 10 | $CHCl_3$ | 20 | rt | 91 | 77:23 | 35 |
| 11 | toluene | 20 | rt | 85 | 69:31 | 48 |
| 12 | benzene | 20 | rt | 77 | 72:28 | 48 |
| 13 | xylene | 20 | rt | 80 | 74:26 | 46 |
| 14 | hexane | 20 | rt | 91 | 76:24 | 39 |
| 15 | *i*-$Pr_2O$ | 10 | rt | 83 | 70:30 | 48 |
| 16 | *i*-$Pr_2O$ | 5 | rt | 70 | 68:32 | 28 |
| 17 | *i*-$Pr_2O$ | 1 | rt | 59 | 66:34 | 12 |
| 18 | *i*-$Pr_2O$ | 20 | 0 | 67 | 73:27 | 37 (**5a"**) |
| 19 | *i*-$Pr_2O$ | 20 | -30 | 10 | 72:28 | 54 (**5a"**) |
| 20 | *i*-$Pr_2O$ | 20 | 40 | 55 | 70:30 | 43 |

[a]Isolated yield. [b]The *dr* was determined by $^1$H NMR. [c]The *ee* was determined by HPLC analysis using CHIRALCEL OD-H.

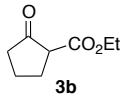
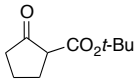
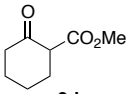
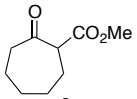
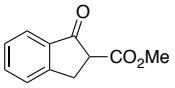
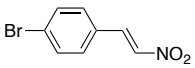
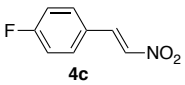
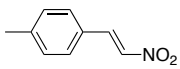
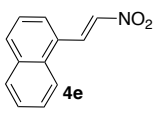
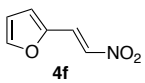
decrease of both chemical yield and enantioselectivity (entry 17). Finally, the reaction temperature was also examined using catalyst **2d** (20 mol%) in *i*-$Pr_2O$ at different reaction temperatures (0, -30, 40 °C), respectively (entries 18-20). At the temperatures, 0 and -30 °C, chemical yields and enantioselectivities were decreased, although diastereoselectivities were slightly increased. Interestingly, the diastereomer Michael adduct **5a"** of **5a** was obtained at these reaction temperatures (entries 18,19). On the other hand, the reaction at 40 °C afforded **5a**, and its chemical yield and enantioselectivity were lowered than the result at room temperature (entry 20). This reaction might have proceeded by kinetic control at below 0 °C and by thermodynamic control at or above room temperature, although the reason is not clear. From the above optimization reaction conditions result, the use of catalyst **2d** (20 mol%) in *i*-$Pr_2O$ at room temperature was observed as a suitable condition for the asymmetric Michael addition reaction of **3a** and **4a** (entry 4, Table 1), although high satisfactory optical yield was not observed. Unfortunately, superior γ-silyl ether catalyst **2d** was not relatively effective in comparison with the result of our previously reported γ-amino alcohol catalyst **X**[4] (cat. **2d**: 85%, 73:27, 56% ee, **X**: 65%, 87:13, 84% ee) in this reaction of **3a** with **4a**.

Under the optimized conditions, a wide range of various β-keto esters **3a-g** and nitroolefins **4a-f** were investigated using superior catalyst **2d** (Table 3). At first, the reactions of cyclic β-keto esters **3b-f** with **4a** were examined (entries 1-5), respectively. The reaction with five membered ethyl 2-oxocyclopentane-carboxylate **3b** afforded the corresponding chiral Michael adduct **5b** in good chemical yield,

**Table 3.** Asymmetric Michael addition of various β-keto esters **3a-g** with nitroolefins **4a-f** using catalyst **2d**




**3a-f** **3g** **4a-f** (2*R*,3*R*)-**5b-k**

| entry | 3a-g | 4a-f | 5b-k | yield (%)[a] | *dr*[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| 1 |  **3b** | **4a** | **5b** | 73 | 75:25 | 46 |
| 2 |  **3c** | **4a** | **5c** | 31 | 72:28 | *rac* |
| 3 |  **3d** | **4a** | **5d** | 69 | 61:39 | 39 |
| 4 |  **3e** | **4a** | **5e** | 71 | 63:37 | 27 |
| 5 |  **3f** | **4a** | **5f** | 55 | 60:40 | 49 |
| 6 | **3a** |  **4b** | **5g** | 85 | 82:18 | 45 |
| 7 | **3a** |  **4c** | **5h** | 81 | 66:34 | 34 |
| 8 | **3a** |  **4d** | **5i** | 78 | 65:35 | 21 |
| 9 | **3a** |  **4e** | **5j** | 47 | 59:41 | 20 |
| 10 | **3a** |  **4f** | **5k** | 58 | 60:40 | 51 |
| 11 | **3g** | **4a** | *trace* | — | — | — |

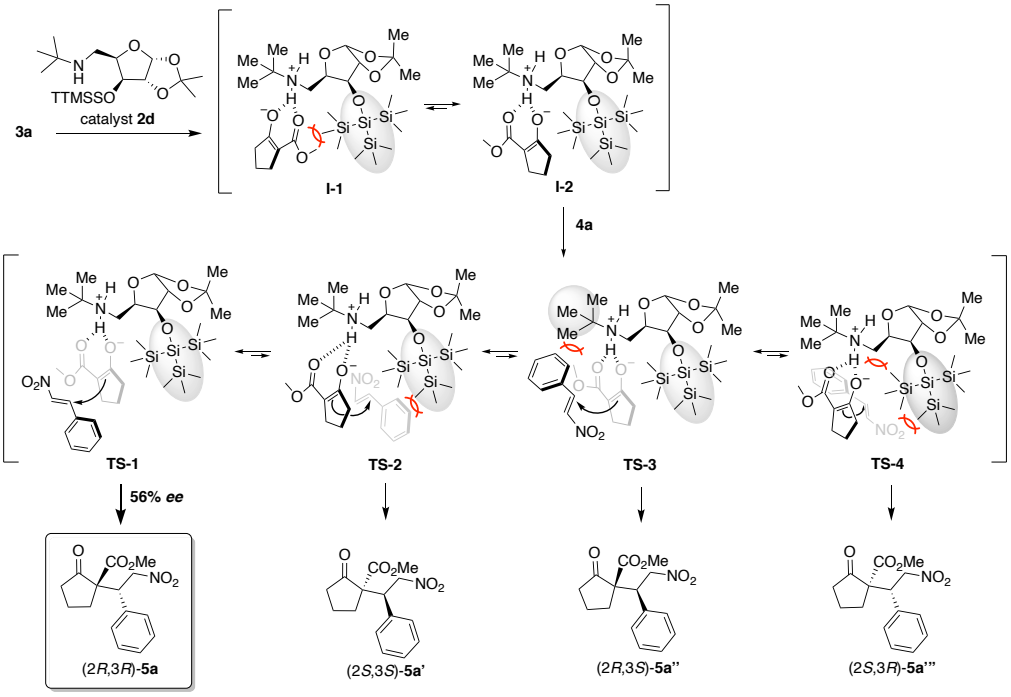
[a]Isolated yield. [b]The *dr* was determined by $^1$H NMR. [c]The *ee* was determined by HPLC analysis using CHIRALCEL OD-H or AS H columns.

diastereoselectivity and with moderate enantioselectivity (73%, *dr*. 75:25, 46% ee) (entry 1).[7] Furthermore, the reaction with bulkier *tert*-butyl 2-oxocyclopentanecarboxylate **3c** brought about the decease of chemical yield and the corresponding Michael adduct **5c**[10] was racemate (31%, *dr.* 72:28, *racemate*) (entry 2). The use of six membered methyl 2-oxocyclohexanecarboxylate **3d** also afforded the corresponding chiral **5d** in moderate chemical yield, diastereoselectivity, and low enantioselectivity (69%, *dr*. 61:39, 39% ee) (entry 3).[7]

On the other hand, the reaction with 7-membered 2-oxocycloheptanecarboxylate **3e** brought about the large decrease of enantioselectivity, although chiral **5e** was obtained in good chemical yield and moderate diastereoselectivity (71%, *dr*. 63:37, 27% ee) (entry 4).[7] Furthermore, the use of aromatic ring fused indanone based β-keto ester **3f** gave the corresponding **5f** with moderate chemical yield, diastereoselectivity and enantioselectivity (55%, *dr*. 60:40, 49% ee) (entry 5).[7] Next, the reactions of β-keto ester **3a** with various nitroolefins **4b-f** using catalyst **2d** were tried under same reaction condition (entries 6-10). The reaction with bromine substituted nitroolefin **4b** afforded the adduct **5g** in good chemical yield, diastereoselectivity and with moderate enantioselectivity (85%, *dr*. 82:18, 45% ee) (entry 6).[8] Furthermore, the use of fluorine substituted nitroolefin **4c** afforded **5h** in good chemical yield, diastereoselectivity and low enantioselectivity (81%, *dr*. 66:34, 34% ee) (entry 7).[7] When the reaction using methyl substituted nitroolefin **4d** was carried out, the corresponding **5i** was furnished in good chemical yield and moderate diastereoselectivity, but enantioselectivity was low (78%, *dr*. 65:35, 21% ee) (entry 8).[7] Nitroolefin **4e** with bulky naphthyl group afforded **5j** in moderate chemical yield, diastereoselectivity and with low enantioselectivity (47%, *dr*. 59:41, 20% ee) (entry 9).[9] Moreover, the reaction using heterocyclic furanyl nitroolefin **4f** afforded adduct **5k** in moderate chemical yield and stereoselectivities (58%, *dr*. 60:40, 51% ee) (entry 10).[7] To expand the generality and scope of the keto ester, the reaction of dimethyl malonate **3g** with **4a** was also examined in the same reaction condition, but only *trace* of the corresponding Michael adduct was observed (entry 11).

Based on the best enantiopurity (56% ee) of the obtained chiral Michael adduct (2*R*,3*R*)-**5a**, we proposed plausible enantioselective reaction course as shown in Scheme 3. At first, catalyst **2d** acts as a base to β-keto ester **3a** and the generated enolate species is fixed with ammonium hydrogen atom on catalyst species by hydrogen bonding interactions to generate intermediates **I-1** or **I-2**. In intermediate **I-1** and **I-2**, **I-2** might be more stable than **I-1** that shows less steric interaction between TTMSS group on catalysts species and methoxy substituent on enolate species **3a**. Subsequently, the enantioselective reaction might proceed through **TS-1** that has comparatively less steric interactions in three cases such as, between nitroolefin **4a** and TTMSS group (**TS-2**), between the substituent of the ammonium catalyst species and nitroolefin **4a** (**TS-3**), and between **4a** and xylofuranose backbone as well as TTMSS substituent (**TS-4**). Newly prepared γ-amino silyl ether catalyst **2d** was not found to be effective in comparison to our

previously reported γ-amino alcohol catalyst **A**,[4] in this reaction using **3a** and **4a** under same reaction condition (cat. **2d**: 73:27, 56% ee, **A**: 87:13, 84% ee), although, chemical yield was better than that of **A** (cat. **2d**: 85%, **A**: 65%). The reason why better stereoselectivities were not achieved by catalyst **2d** might be assumed that the ammonium group fixing the enolate species at γ-position on catalyst species is flexible, and the direction of the attack of enolate to electrophile **4a** might not be controlled by the bulky TTMSS group to show enough stereoselectivities. Therefore, enantioselectivity might have decreased, however, the chemical yield was better.




**Scheme 3.** Plausible reaction course

In conclusion, sugar based γ-amino silyl ether organocatalysts **2** were developed and their catalytic activity were examined in the asymmetric Michael addition of β-keto esters **3a-g** with nitroolefins **4a-f**. All catalysts showed catalytic activity in the reaction and afforded the corresponding chiral Michael adducts **5a-k** in moderate to excellent chemical yields, diastereoselectivities and low to moderate enantioselectivities (up to 97%, up to *dr.* 85:15, up to 56% *ee*). Especially, *N-tert*-butylated catalyst with TTMSS group **2d** showed better catalytic activity than that of others. However, the catalytic activity of catalysts **2** could not attain the satisfactory level to this reaction. Further studies on modification of sugar based γ-amino silyl ether organocatalysts and their application in this reaction are now in progress.

## EXPERIMENTAL

Reagents and analytical grade solvents were obtained from commercial suppliers and used without further purification. All reactions were carried out under a positive atmosphere of argon, glass wares were

flame-dried and cooled in desiccator. The reactions were monitored by thin layer chromatography (TLC). TLC was performed on Merck pre-coated silica gel 60 F-254 plates. Spots were visualized by exposure to UV light, by immersion into a solution of *p*-anisaldehyde followed by heating at ca. 200 °C. Column chromatography was performed on Kanto Chemical silica gel 60 N (Spherical, neutral, 40-50 μm). The melting points were determined using a micro-melting point apparatus. IR spectra were recorded on JASCO FT/IR-4100 and the major absorbance bands were all reported in wavenumbers ($cm^{-1}$). MS were taken on a JEOL-JMS-700V spectrometers. NMR spectra were recorded on a JEOL JNM-ECA500 spectrometer, operating at 500 MHz for $^{1}H$ NMR, 100 MHz for $^{13}C$ NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (δ = 0 ppm) for $^{1}H$ NMR. For $^{13}C$ NMR, chemical shifts were reported downfield from TMS (δ = 0 ppm) or in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. Coupling constants (*J*) are reported as hertz (Hz). Splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. The enantiomeric excess (*ee*) was determined by HPLC analysis. HPLC was measured at column, CHIRALPAK AS H, CHIRALCEL OD-H (4.6 mm Å~ 25 cm) and 2-propanol/hexane system was employed as a mobile phase.

**General procedure for Michael addition of β-keto esters 3a-g with *trans*-β-nitroolefins 4a-f**

To a stirred solution of *trans*-β-nitroolefins **4a-f** (0.34 mmol) and organocatalysts **2a-k** (0.06 mmol, 20 mol%) in *i*-$Pr_2O$ (0.5 mL) were added β-keto esters **3a-f** or dimethyl malonate **3g** (0.67 mmol) at room temperature. After the reaction completion was monitored by TLC, the mixture was extracted with $CH_2Cl_2$ and the organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under a reduced pressure. The residue was purified by flash column chromatography on $SiO_2$ (*n*-hexane/EtOAc = 9:1) to afford the corresponding chiral Michael adducts **5a-k**. The ee were determined by HPLC using DAICEL CHIRALCEL OD-H or CHIRALPAK AS H columns.

**General procedure for the preparations of catalysts 2a-k**

To a stirred solution of compounds **1a-k** (0.20 g, 0.82 mmol) and $Et_3N$ (2.05 mmol) in $CH_2Cl_2$ (15 mL) was added corresponding silyl protecting reagents (1.2 mmol) at 0 $^{o}C$ for 30 min. After that, reaction mixture was allowed to stir at room temperature for 24 h. Upon completion of reaction that was monitored by TLC, solvents were evaporated under reduced pressure and organic layer was extracted using $CH_2Cl_2$ as three portions (3 × 10 mL) from aqueous layer. The obtained combined organic layers were dried on $Na_2SO_4$, concentrated and purified by flash chromatography using on $SiO_2$ ($CH_2Cl_2$/MeOH = 9:1) afforded the compounds **2a-k**.

**1,2-*O*-Isopropylidene-3-*O*-triethylsilyl-5-*N*-(*t*-butylamine)-α-D-xylofuranose 2a:**

Yellowish solid; $[\alpha]_D^{29}$ +2 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2968, 1635, 1456, 1252, 1118, 1067 $cm^{-1}$; $^1H$ NMR (500 MHz, $CHCl_3$) δ 5.91 (d, *J* = 3.4 Hz, 1H), 4.56-4.59 (m, 1H), 4.39 (d, 1H), 4.14 (d, *J* = 2.9 Hz, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 3.11 (dd, *J* = 4.0 Hz, 2H), 1.6 (s, 3H), 1.45 (s, 9H), 1.30 (s, 3H), 0.91 (s, 9H), 0.66 (s, 6H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 111.6, 104.8, 85.8, 81.4, 76.2, 50.3, 42.0, 28.9, 26.8, 26.4, 25.7, 18.1, -4.6, -5.1; MS (EI) *m/z*: 359 $[M]^+$, HRMS [EI] calculated for $C_{18}H_{37}NO_4Si$ $[M]^+$: 359.2492. Found $[M]^+$: 359.2504.

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

Colorless syrup; $[\alpha]_D^{29}$ +14 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2942, 1635, 1457, 1215, 1140, 1121 $cm^{-1}$; $^1H$ NMR (500 MHz, $CHCl_3$) δ 5.91 (d, *J* = 3.4 Hz, 1H), 4.43 (q, *J* = 3.2 Hz, 2H), 4.35 (dd, *J* = 8.9, 3.2 Hz, 1H), 2.99 (dd, *J* = 11.7, 8.9 Hz, 1H), 2.90 (dd, *J* = 11.7, 3.2 Hz, 1H), 1.50 (s, 3H), 1.30 (s, 3H), 1.20 (s, 9H), 1.08 (d, *J* = 8.0 Hz, 21H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 112.1, 104.9, 86.2, 80.5, 77.1, 42.4, 28.3, 27.1, 26.7, 18.2, 12.6; MS (EI) *m/z*: 401 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{21}H_{43}NO_4Si$ $[M]^+$: 401.2961. Found $[M]^+$: 401.2963.

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

Colorless syrup; $[\alpha]_D^{29}$ +20 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2956, 1636, 1253, 1137, 1117 $cm^{-1}$; $^1H$ NMR (500 MHz, $CHCl_3$) δ 5.91 (d, *J* = 3.4 Hz, 1H), 4.35 (d, *J* = 4.0 Hz, 1H), 4.25-4.22 (m, 1H), 4.14 (d, *J* = 2.9 Hz, 1H), 2.88 (dd, *J* = 11.5, 8.0 Hz, 1H), 2.68 (dd, *J* = 11.5, 4.0 Hz, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.10 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 111.6, 104.8, 85.8, 81.4, 76.2, 50.3, 42.0, 28.9, 26.8, 26.4, 25.7, 18.1, -4.6, -5.1; MS (EI) *m/z*: 359 $[M]^+$, HRMS [EI] calculated for $C_{18}H_{37}NO_4Si$ $[M]^+$: 359.2492. Found $[M]^+$: 359.2497.

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

Colorless syrup; $[\alpha]_D^{29}$ +15 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2953, 1652, 1361, 1244, 1215, 1113, 1074 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 3.4 Hz, 1H), 4.31 (d, *J* = 4.0 Hz, 1H), 4.22 (td, *J* = 6.0, 2.9 Hz, 1H), 3.86 (d, *J* = 2.9 Hz, 1H), 2.86 (dd, *J* = 11.5, 8.6 Hz, 1H), 2.64 (dd, *J* = 11.5, 2.9 Hz, 1H), 1.47 (s, 3H), 1.29 (s, 3H), 1.11 (s, 9H), 0.22 (s, 27H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 111.6, 104.8, 85.4, 81.8, 80.3, 50.4, 42.4, 28.9, 26.9, 26.3, 0.4; MS (EI) *m/z*: 491 $[M]^+$, HRMS [EI] calculated for $C_{21}H_{49}NO_4Si_4$ $[M]^+$: 491.2739. Found $[M+H]^+$: 492.2811.

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

Yellow syrup; $[\alpha]_D^{29}$ +4 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2949, 1455, 1213, 1164, 1075 $cm^{-1}$; $^1H$ NMR (500

MHz, $CDCl_3$) δ 5.77 (d, *J* = 4.0 Hz, 1H), 4.24 (d, *J* = 4.0 Hz, 1H), 4.20 (td, *J* = 5.7, 3.1 Hz, 1H), 3.78 (d, *J* = 2.9 Hz, 1H), 2.80 (dd, *J* = 12.6, 8.6 Hz, 1H), 2.68 (dd, *J* = 12.3, 3.7 Hz, 1H), 2.61 (q, *J* = 7.1 Hz, 2H), 1.40 (s, 3H), 1.22 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.15 (s, 27H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 112.0, 105.2, 85.7, 81.1, 80.6, 49.4, 45.0, 27.3, 26.7, 15.7, 0.9; MS (EI) *m/z*: 463 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{19}H_{45}NO_4Si_4$ $[M]^+$: 463.2426. Found $[M+H]^+$: 464.2497.

**1,2-*O*-Isopropylidene-3-*O*-tris(trimethylsilyl)silyl-5-*N*-(*n*-butylamine)-α-D-xylofuranose 2f:**
Pale yellow syrup; $[\alpha]_D^{29}$ +8 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2949, 1558, 1361, 1456, 1214, 1123 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 4.0 Hz, 1H), 4.31 (d, *J* = 3.4 Hz, 1H), 4.26 (td, *J* = 5.7, 3.1 Hz, 1H), 3.84 (d, *J* = 2.9 Hz, 1H), 2.86 (dd, *J* = 12.3, 8.3 Hz, 1H), 2.73 (dd, *J* = 12.3, 3.7 Hz, 1H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.48-1.44 (m, 5H), 1.38-1.32 (m, 2H), 1.29 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.22 (s, 27H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 112.1, 105.3, 85.8, 81.3, 80.7, 50.7, 49.8, 32.9, 27.4, 26.8, 21.1, 14.7, 1.0; MS (EI) *m/z*: 491 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{21}H_{49}NO_4Si_4$ $[M]^+$: 491.2739. Found $[M+H]^+$: 492.2820.

**1,2-*O*-Isopropylidene-3-*O*-tris(trimethylsilyl)silyl-5-*N*-(adamantyl)-α-D-xylofuranose 2g:**
Yellow solid; $[\alpha]_D^{29}$ +8 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2947, 1636, 1242, 1164, 1075 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 3.4 Hz, 1H), 4.30 (d, *J* = 4.0 Hz, 1H), 4.20 (td, *J* = 6.0, 2.9 Hz, 1H), 3.85 (d, *J* = 2.9 Hz, 1H), 2.91 (dd, *J* = 11.5, 8.6 Hz, 1H), 2.65 (dd, *J* = 11.7, 3.2 Hz, 1H), 2.06 (s, 3H), 1.67 (d, *J* = 9.7 Hz, 6H), 1.59 (d, *J* = 11.5 Hz, 6H), 1.47 (s, 3H), 1.29 (s, 3H), 0.22 (s, 27H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 112.1, 105.3, 86.1, 85.9, 82.4, 80.8, 51.1, 43.1, 40.8, 37.3, 30.2, 27.4, 26.8, 1.0; MS (EI) *m/z*: 570 $[M+H]^+$, HRMS *m/z*: [EI] calculated for $C_{27}H_{55}NO_4Si_4$ $[M]^+$: 569.3208. Found $[M+H]^+$: 570.3285.

**1,2-*O*-Isopropylidene-3-*O*-tris(trimethylsilyl)silyl-5-*N*-(benzylamine)-α-D-xylofuranose 2h:**
Colorless syrup; $[\alpha]_D^{29}$ +12 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2947, 1698, 1652, 1455, 1215, 1072 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H), 7.27 (q, *J* = 3.4 Hz, 3H), 5.94 (d, *J* = 3.8 Hz, 1H), 4.50 (d, *J* = 4.0 Hz, 1H), 4.29 (d, *J* = 2.9 Hz, 1H), 4.23-4.21 (m, 1H), 3.79 (d, *J* = 6.3 Hz, 2H), 3.40 (dd, *J* = 12.9, 3.7 Hz, 1H), 3.01 (dd, *J* = 12.9, 1.4 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H), 0.18 (s, 27H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 137.8, 128.3, 127.9, 127.2, 111.1, 104.7, 85.5, 77.7, 76.5, 53.3, 47.3, 26.5, 25.8, -0.9; MS (EI) *m/z*: 525 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{24}H_{47}NO_4Si_4$: $[M]^+$: 525.2582. Found $[M+H]^+$: 526.2668.

**1,2-*O*-Isopropylidene-3-*O*-tris(trimethylsilyl)silyl-5-*N*-(*R*-phenylethylamine)-α-D-xylofuranose 2i:**
Pale yellow syrup; $[\alpha]_D^{29}$ +11 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2948, 1452, 1244, 1213, 1139, 1074 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.26 (m, 4H), 7.22-7.19 (m, 1H), 5.85 (d, *J* = 4.0 Hz, 1H), 4.26 (d, *J*

= 4.0 Hz, 1H), 4.19 (td, *J* = 5.9, 3.1 Hz, 1H), 3.77 (q, *J* = 6.5 Hz, 1H), 3.72 (d, *J* = 2.9 Hz, 1H), 2.71 (dd, *J* = 12.6, 9.2 Hz, 1H), 2.47 (dd, *J* = 12.3, 2.6 Hz, 1H), 1.48 (s, 2H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.28 (s, 3H), 0.12 (s, 27H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 145.9, 129.0, 127.5, 112.1, 105.4, 86.0, 81.9, 80.9, 59.8, 48.3, 27.4, 26.8, 25.2, 0.9; MS (EI) *m/z*: 540 $[M+H]^+$, HRMS *m/z*: [EI] calculated for $C_{25}H_{49}NO_4Si_4$ $[M]^+$: 539.2739. Found $[M+H]^+$: 540.2809.

**1,2-*O*-Isopropylidene-3-*O*-tris(trimethylsilyl)silyl-5-*N*-(*R*-naphthylamine)-α-D-xylofuranose 2j:**
Red syrup; $[\alpha]_D^{29}$ +5 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2947, 1652, 1456, 1242, 1215, 1074 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 6.3 Hz, 1H), 7.55-7.47 (m, 3H), 6.01 (d, *J* = 3.4 Hz, 1H), 4.62 (q, *J* = 6.7 Hz, 1H), 4.51 (d, *J* = 3.4 Hz, 1H), 4.22 (d, *J* = 2.3 Hz, 1H), 4.16-4.15 (m, 1H), 3.29 (dd, *J* = 12.9, 3.7 Hz, 1H), 2.91 (dd, *J* = 13.2, 1.1 Hz, 1H), 1.53 (d, *J* = 6.3 Hz, 2H), 1.45 (s, 3H), 1.32 (s, 3H), 0.19 (s, 27H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 139.6, 134.6, 129.7, 128.3, 126.7, 126.4, 126.1, 123.5, 123.2, 112.1, 105.6, 86.5, 78.6, 47.3, 46.5, 27.4, 26.8, 24.2, 0.0; MS (EI) *m/z*: 590 $[M+H]^+$, HRMS *m/z*: [EI] calculated for $C_{29}H_{51}NO_4Si_4$ $[M]^+$: 589.2895. Found $[M+H]^+$: 590.2980.

**1,2-*O*-Isopropylidene-3-*O*-tris(trimethylsilyl)silyl-5-*N*-(pyrrolidine)-α-D-xylofuranose 2k:**
Yellow syrup; $[\alpha]_D^{29}$ +6 (*c* 1.0, $CH_2Cl_2$); IR (neat) 2939, 1636, 1455, 1218, 1066 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.85 (d, *J* = 3.4 Hz, 1H), 4.29 (d, *J* = 3.4 Hz, 1H), 4.27 (td, *J* = 5.6, 2.9 Hz, 1H), 3.83 (d, *J* = 2.9 Hz, 1H), 2.74 (dd, *J* = 12.9, 8.3 Hz, 1H), 2.62 (dd, *J* = 12.9, 3.2 Hz, 1H), 2.56 (s, 4H), 1.78 (t, *J* = 4.6 Hz, 3H), 1.48 (d, *J* = 4.6 Hz, 3H), 1.29 (s, 3H), 0.22 (s, 27H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 111.9, 105.5, 85.4, 81.0, 80.4, 55.7, 55.2, 27.5, 26.8, 24.0, 1.0; MS (EI) *m/z*: 489 $[M]^+$, HRMS *m/z*: [EI] calculated for $C_{21}H_{47}NO_4Si_4$ $[M]^+$: 489.2582. Found $[M+H]^+$: 490.2659.

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