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Thiourea fused γ-amino alcohol organocatalysts for asymmetric Mannich reaction of β-keto active methylene compounds with imines†

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Catalytic functionality of new optically active thiourea fused γ-amino alcohols was examined in the asymmetric Mannich reaction of β-keto active methylene compounds with imines to afford chiral Mannich products, β-amino keto compounds, with continuous chiral centers, that are versatile synthetic intermediates for deriving various biologically active compounds. In particular, the thiourea fused γ-amino alcohols showed satisfactory catalytic activity in this reaction and afforded chiral Mannich products in excellent chemical yield (up to 88%) and stereoselectivities (up to *syn* : *anti*/93 : 7 dr, up to 99% ee).

1. Introduction

The development of new optically active organocatalysts and their application in asymmetric synthesis has attracted considerable interest in the scientific community over the past 20 years.[1] Excellent covalent and non-covalent organocatalysts have been developed and applied over a wide range of reactions.[2] In recent years, we have also developed various β-amino alcohols **X**, which were utilized effectively as organocatalyst in different enantioselective reactions.[3] Most recently, we have also reported the effectiveness of di-amino alcohol organocatalyst **Y** in aldol reactions.[4] Based on these backgrounds, we have designed a new thiourea fused γ-amino alcohol organocatalyst **Z** (Scheme 1) that contains thiourea and hydroxy groups acting as hydrogen bonding sites, and a *tert*-amino group acting as a basic and steric influence site. Furthermore, diaryl groups may work as steric influence site for controlling the stereoselective reaction course. A large number of bifunctional tertiary amine-thioureas have emerged as efficient organocatalysts and were explored in a variety of asymmetric transformations.[5] The

key to the great success of these thiourea-based catalysts is the functionality of the thiourea moiety as a hydrogen bond donor, which is a general structural unit in the design of bifunctional catalysts. As a reaction for exploring the catalytic ability of catalysts **X**, **Y** and designed **Z**, we have selected the Mannich reaction of β-keto active methylene compounds with imines, which is a versatile reaction for affording chiral Mannich products **W**, β-amino keto carbonyl compounds containing continuous chiral quaternary carbon center, which are useful intermediates for synthesis of various biologically active compounds and pharmaceuticals.[6] Although thioureas fused

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Scheme 1 Plan of catalyst design.

amine organocatalysts such as bifunctional catalysts **V** (ref. 6a), **W** (ref. 6f) and others are commonly used in this reaction, to the best of our knowledge, there have been no references using amino alcohol **X**, di amino alcohol **Y** and thiourea fused γ-amino alcohol **Z** organocatalysts deriving from various low-cost amino acids (Scheme 1). In particular, the newly designed trifunctional catalyst **Z** has a good tertiary basic site, two strong hydrogen bonding sites (thiourea and hydroxy groups), and steric control sites (diphenyl groups at α-position, tertiary amino group at γ-position and aryl group on thiourea group) in its molecule, as well as molecular flexibility according to substrate structure. Therefore, it is expected to activate substrates strongly and to be able to coordinate two substrates to one catalyst, effectively controlling the enantioselective reaction direction and giving Mannich products **W** with good chemical yields and stereoselectivities.

We herein describe the functionality of amino alcohol **X**, di-amino alcohol **Y**, and newly designed thiourea fused γ-amino alcohols **Z** in the asymmetric Mannich reaction of β-keto active methylene compounds with imines. In this study, catalyst **Z** showed superior activity and the desired Mannich products **W** were obtained in satisfactory chemical yields and stereoselectivities (up to 88%, up to syn : anti/93 : 7 dr, up to 99% ee).
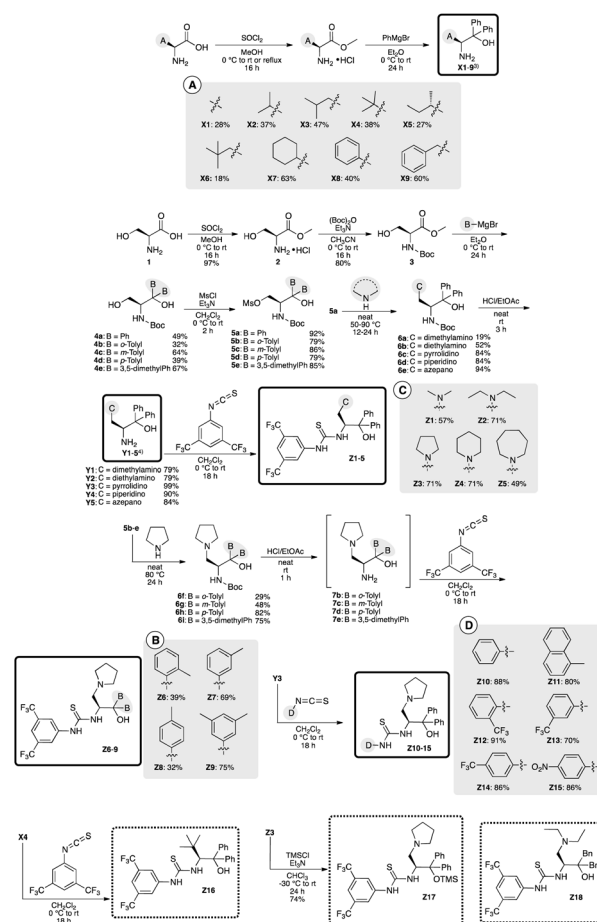
2. Results and discussion

2.1. Synthesis of organocatalysts

Amino alcohols **X1–9** (ref. 3e) and **Y1–5** (ref. 4) were prepared according to our previous reported methods[3e,4] (Scheme 2). Thiourea fused γ-amino alcohols **Z1–9** were derived from L-serine **1** based on the synthetic route of di-amino alcohols **Y** (Scheme 2). The deprotections of **6a–e** afforded the corresponding di-amino alcohols **Y1–5** in good yields, followed by the reactions of the obtained **Y1–5** with 3,5-di(trifluoromethyl) phenyl isocyanate afforded the desired corresponding catalyst **Z1–5** having different tert-amino groups at β-position, respectively. Thiourea fused catalysts **Z6–9** with different di-aryl groups at α-position were also prepared by the reactions of **5b–e** with pyrrolidine, the deprotections of the obtained **6f–i**, followed by the reaction of **7b–e** with isothiocyanate, respectively. Furthermore, catalysts **Z10–15** having different thiourea groups were also prepared by the reactions of **Y3** with isothiocyanates at good yields. Also, catalyst **Z16** (ref. 7) with no amino group at γ-position was prepared by the reaction of **X4** with isothiocyanates for the confirmation of the functionality of amino group as a base. In addition, amino silyl ether **Z17** that masked the hydroxyl group was also prepared by the reaction of **Z3** with TMSCl (Scheme 2) for the confirmation of the functionality of hydroxy group as a hydrogen bonding site. Furthermore, **Z18** (ref. 8) were prepared according to previous reported method.[8]
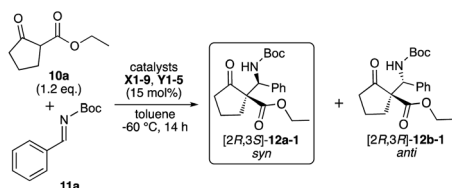
2.2. Catalytic efficiency in Mannich reaction

We examined the catalytic activity of the prepared organocatalysts **X1–9**, **Y1–5**, and **Z1–19** in the asymmetric Mannich reactions of β-keto ester **10a** with imine **11a**. First, the catalytic

Scheme 2 Preparation of organocatalysts.

activity of β-amino alcohols **X1–9** and di-amino alcohols **Y1–5** were examined, respectively (Table 1). The reaction of **10a** with **11a** (ref. 9) was carried out in the presence of 15 mol% of catalysts in toluene at −60 °C for 14 h. Although every catalyst showed catalytic activities and afforded the Mannich product **12** (**12a-1**, **12b-1**) in moderate to good chemical yields, good to excellent diastereoselectivities, enough enantioselectivity were not obtained in this reaction condition (entries 1–9). In the uses of every **X1–9**, only β-amino alcohol catalyst **X4** with tert-butyl group at β-position afforded **12a-1** as a major product in moderate enantioselectivity (62% ee) with good chemical yield and diastereoselectivity (entry 4). On the other hand, all diamino alcohol catalysts **Y1–5** did not show satisfactory catalytic activity similarly to **X** (entries 10–14). Secondly, newly synthesized thiourea fused γ-amino alcohols **Z1–19** were examined in the same reaction condition of the case of catalysts **X** and **Y** (**10a**: 1.2 eq., solvent: toluene, catalyst: 15 mol%, reaction temperature: −60 °C) (Table 2). First, catalytic activity of catalysts **Z1–5** with acyclic or cyclic amino substituents at γ-position and diphenyl groups at α-position were examined (entries 1–5). Every catalyst showed good catalytic activities and afforded the chiral Mannich product **12′-1** (ref. 6a) as a major product. Especially, catalyst **Z3** with pyrrolidine ring at γ-position afforded totally good results for chemical yield, diastereoselectivity and enantioselectivity (74%, **12a′-1/12b-1**: 83/17 dr,
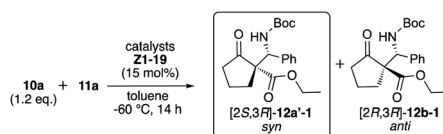
Table 1 Mannich reaction of β-keto ester **10a** with imino ester **11a** using catalysts **X1–9**, **Y1–5**

Entry	Catalyst	Yield[a] (%)	dr[b] syn/anti	ee[c] syn/anti
1	**X1**	57	88/12	4/−2
2	**X2**	57	91/9	−19/−5
3	**X3**	66	89/11	−8/14
4	**X4**	74	98/2	62/15
5	**X5**	68	92/8	−28/−8
6	**X6**	74	91/9	8/1
7	**X7**	75	83/17	−18/−6
8	**X8**	53	91/9	rac/−3
9	**X9**	51	94/6	−1/−2
10	**Y1**	78	85/15	32/−3
11	**Y2**	64	81/19	36/−26
12	**Y3**	82	83/17	51/−5
13	**Y4**	55	89/11	3/−2
14	**Y5**	64	83/17	rac/−2

[a] Isolated yield. [b] Diastereoselectivity was determined by HPLC of the reaction mixture. [c] The ee of isomer was determined by HPLC using CHIRALCEL AD-H column (n-hexane : 2-propanol = 98 : 2).

Table 2 Mannich reaction of β-keto ester **10a** with imino ester **11a** using catalysts **Z1–19**

Entry	Catalyst	Yield[a] (%)	dr[b] syn/anti	ee[c] syn/anti
1	**Z1**	79	84/16	82/94
2	**Z2**	84	86/14	92/91
3	**Z3**	83	83/17	97/99
4	**Z4**	82	84/16	90/93
5	**Z5**	72	86/14	93/91
6	**Z6**	70	77/23	82/80
7	**Z7**	63	85/15	95/97
8	**Z8**	84	85/15	91/92
9	**Z9**	68	87/13	93/95
10	**Z10**	77	80/20	41/23
11	**Z11**	72	82/18	18/15
12	**Z12**	61	72/28	34/7
13	**Z13**	88	85/15	86/94
14	**Z14**	68	87/13	66/50
15	**Z15**	81	88/12	84/91
16	**Z16**	49	73/27	10/−5
17	**Z17**	72	71/29	50/62
18	**Z18**	63	93/7	89/98

[a] Isolated yield. [b] Diastereoselectivity was determined by HPLC of the reaction mixture. [c] The ee of isomer was determined by HPLC using CHIRALCEL AD-H column (n-hexane : 2-propanol = 98 : 2).

97% ee) (entry 3). Next, catalysts **Z6–9** with pyrrolidine ring at β-position and several substituted diphenyl groups at β-position were applied in this reaction (entries 6–9). Catalysts **Z6–9** also showed good catalytic activity to afford **12b** as a major product similarly to **Z1–5**. Furthermore, the catalytic activity of catalysts **Z10–15** with pyrrolidine ring, diphenyl groups and several thiourea groups at β-position also screened (entries 10–15) and these catalysts also showed good catalytic activity, but enantioselectivity widely varied by the substitution of thiourea group having aryl group on nitrogen atom. From the result, it was appeared that catalyst **Z3** with pyrrolidine ring at β-position and diphenyl groups at α-position and thiourea group having ditrifluoromethyl phenyl group on nitrogen atom works as best catalyst in this reaction (entry 3). In order to predict the functionalities of tert-amino group at γ-position acting as basic site and hydroxy group at α-position acting as hydrogen bonding site of catalysts, the reactions using catalysts **Z16** with no amino group and **Z17** that protected hydroxy group by TMS group were attempt (entries 16 and 17). The use of **Z16** was significantly decreased chemical yield and stereoselectivity (entry 16). From this fact, it is indicated that tert-amino group acts as basic site for proceeding the reaction. On the other hand, **Z17** showed satisfactory catalytic activity for proceeding the reaction, but diastereoselectivity and enantioselectivity were decreased (entry 17). It may be indicated that hydroxy group at α-position may participate to the control of stereoselectivity as hydrogen bonding site in the reaction. The known catalyst **Z18** also showed good catalytic activity similar to **Z3**, but caused a significant decrease in chemical yield (entry 18).
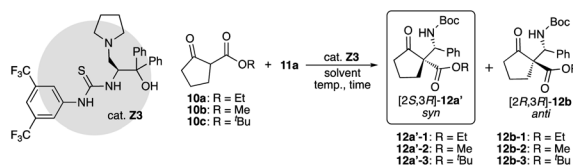
With these results in hand, we tried to optimize the reaction conditions using superior catalyst **Z3** improving the chemical yield and stereoselectivities (Table 3). An extensive screening of the reaction were further carried out by varying different parameters such as solvent, catalyst and substrate loading, and reaction temperature. First, the reaction of three kinds of β-keto esters **10a–c** (ref. 10) with imine **11a** were examined in toluene using 15 mol% of superior catalyst **Z3** under −60 °C at 14 h (entries 1–3). As a result, the use of β-keto ester **10a** with ethoxy carbonyl group afforded **12a′-1** in the best results for chemical yield and stereoselectivities (83%, syn : anti/83 : 17 dr, 97% ee) (entry 1). The differences of chemical yields and stereoselectivities might be due to the steric interaction between catalyst and of the interaction between catalyst and substrates with the different alkyl groups on carboxyl group of **10a–c** in the corresponding transition states, respectively. Next, the reaction temperature (25, −25 and −78 °C) were also examined in the presence of 15 mol% of catalyst **Z3** in toluene for 14 h (entries 4–6). Although the reactions under these temperatures (entries 4–6) afforded **12a′-1** in good chemical yield and stereoselectivities, −60 °C gave better overall results with respect to chemical yield and stereoselectivities (entry 1). Although it is not clear, the thermal energy imparted by the temperature change might have changed the state of the catalyst–substrate interaction in the transition state. Moreover, the ratio of substrate used among **10a** and **11a** (entries 7 and 8) was also examined and both equivalents are effective to afford the product **12a′-1** in

Table 3 Optimization of the reaction conditions using catalyst **Z3**

Entry	**10**	Temp (°C)	**10** (eq.)	Cat. (mol%)	Solvent	Time (h)	Yield[a] (%)	dr[b] syn/anti	ee[c] syn/anti
1	a	−60	1.2	15	Toluene	14	83	83/17	97/99
2	b	−60	1.2	15	Toluene	14	62	85/15	93/89
3	c	−60	1.2	15	Toluene	14	72	93/7	41/−23
4	a	25	1.2	15	Toluene	14	74	80/20	86/90
5	a	−25	1.2	15	Toluene	14	79	82/18	91/93
6	a	−78	1.2	15	Toluene	14	82	83/17	94/98
7	a	−60	0.5	15	Toluene	14	69	84/16	95/98
8	a	−60	2	15	Toluene	14	81	85/15	96/99
9	a	−60	1.2	20	Toluene	14	81	84/16	98/92
10	a	−60	1.2	10	Toluene	14	79	84/16	96/97
11	a	−60	1.2	5	Toluene	14	81	82/18	8783
12	a	−60	1.2	2.5	Toluene	14	72	78/22	81/74
13	a	−60	1.2	1	Toluene	14	70	72/28	75/43
14	a	−60	1.2	15	Et$_2$O	14	61	85/15	91/94
15	a	−60	1.2	15	Hexane	14	71	77 : 23	86/93
16	a	−60	1.2	15	CH$_2$Cl$_2$	14	85	84/16	83/94
17	a	−60	1.2	15	CHCl$_3$	14	78	82/18	76/84
18	a	−60	1.2	15	EtOH	14	63	89/11	49/51
19	a	−60	1.2	15	DMF	14	63	81/19	11/rac
20	a	−60	1.2	15	Toluene	1	73	83/17	91/89
21	a	−60	1.2	15	Toluene	3	81	84/16	89/94
22	a	−60	1.2	15	Toluene	7	83	85/15	95/98

[a] Isolated yield. [b] Diastereoselectivity was determined by HPLC of the reaction mixture. [c] The ee of isomer was determined by HPLC using CHIRALCEL AD-H column (*n*-hexane : 2-propanol = 98 : 2).

satisfactory chemical yield and stereoselectivities. However, the use of 1.2 equivalent of **10a** was totally effective (entry 1). We examined the effect of catalyst loading by varying from 20, 10, 5 mol%, 2.5 and 1 mol% under superior reaction condition (entries 9–13). Good result (81%, *syn* : *anti*/84 : 16 dr, 98% ee) was obtained in the presence of 20 mol% of catalyst **Z3** (entry 9). The use of 10 mol% of **Z3** also afforded good chemical yield and stereoselectivities similar to the use of 20 mol% of **Z3** (entry 10). When the reaction was carried out in the presence of 5 mol% of **Z3**, chemical yield and diastereoselectivity were maintained, but enantioselectivity was slightly decreased to 87% ee (entries 11). Furthermore, the uses of both 2.5 mol% and 1 mol% of **Z3** brought about the small decrease of chemical yields and stereoselectivities (2.5 mol% : 72%, *syn* : *anti*/78 : 22 dr, 81% ee, 1 mol% : 72%, *syn* : *anti*/72 : 28 dr, 75% ee) (entries 12 and 13). These results indicate that overall the use of 15 mol% of **Z3** was favourable (entry 1). Solvent screening was performed with ethereal (entry 14), non-polar aliphatic (entry 15), chlorinated (entries 16 and 17), protic and aprotic polar (entries 18 and 19) solvents. Catalyst **Z3** showed catalytic activity in all solvents to afford the Mannich product **12a′-1**. However, the uses of protic polar EtOH and aprotic polar DMF brought about the decrease in enantioselectivity (entries 18 and 19). From these results,

toluene was observed to be superior solvent to this reaction using catalyst **Z3**. The reactions at both 1 h and 3 h brought about decrease in chemical yields, although stereoselectivity were kept to good values (entries 20 and 21). On the other hand, the catalytic activity of catalyst **Z3** did not change, when this reaction was carried out at 7 h (entry 22). From these screening, catalyst **Z3** showed best catalytic activity when the reaction was carried out using β-keto ester **10a** and imine **11a** under the reaction condition (**10a**: 1.2 eq., solvent: toluene, catalyst: 15 mol%, reaction temperature: −60 °C) as shown at entry 1.

2.3. Substrate scope

After optimization of the reaction conditions, we examined the generality of superior catalyst **Z3** in the reactions of β-keto active methylene compounds **10a,d–h** with imines **11a,b**, respectively (Table 4). The reaction of cyclohexyl **10d** with **11a** afforded Mannich product **13** (ref. 6*i*) in moderate chemical yield (37%) and good diastereoselectivity (*syn* : *anti*/93 : 7 dr), although enantioselectivity was low (22% ee (*syn*)). Similarly, this reaction using heterocyclic β-keto ester **10e** with **11a** also afforded the corresponding Mannich product **14** in moderate chemical yield (42%) and good stereoselectivities (*syn* : *anti*/85 : 15 dr, 71% ee (*syn*)). It might be for the steric influence of ring size of

cyclohexyl group (entry 1) in β-keto ester **10d** and for the electronic influence of oxygen atom in hydrofuran ring of β-keto ketone **10e** (entry 2). They might have caused a change of the interaction between catalyst and substrates in the transition state and affected the chemical yield and stereoselectivity, although it is not clear. In addition, the reaction using β-keto nitrile **10f**[11] with **11a** also smoothly proceed and afforded **15** in satisfactory chemical yield and stereoselectivities (79%, *syn* : *anti*/80 : 20 dr, 85% ee (*syn*)). Furthermore, the use of dicyclic **10g** (ref. 12) with **11a** also afforded **16** in satisfactory chemical yield and enantioselectivity (87%, 99% ee), although diastereoselectivity was low (*syn* : *anti*/55 : 45 dr). The uses of acyclic **10h** (ref. 6i) and **11a** also afforded **17** (ref. 6i) in satisfactory chemical yield and enantioselectivity, although diastereoselectivity was low (74%, *syn* : *anti*/57 : 43 dr, 91% ee (*syn*)). Moreover, reaction of **10a** with thiophene based imine **11b** (ref. 13) also afforded **18** in moderate chemical yield and good stereoselectivities (61%, *syn* : *anti*/91 : 9 dr, 94% ee (*syn*)) from these results, it was indicated that catalyst **Z3** is effective for a variety of substrates.
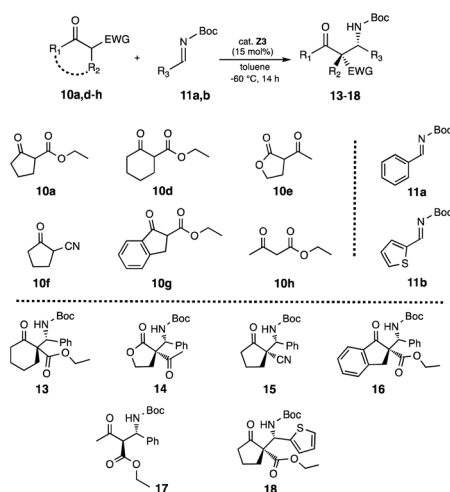
2.4. Reaction mechanism

The use of catalyst **Z3** afforded Mannich product **12a'-1** with best chemical yield and stereoselectivities in the reaction of **10a**

Table 4 Substrate scope using catalyst **Z3**

Entry	10	11	Product	Yield[a] (%)	dr[b] (syn/anti)	ee[c] (%) syn/anti
1	10d	11a	13	37	93/7	22/45[d]
2	10e	11a	14	42	85/15	71/99[d]
3	10f	11a	15	79	80/20	85/64[d]
4	10g	11a	16	87	55/45	99/97[d]
5	10h	11a	17	74	57/43	91/99[d]
6	10a	11b	18	61	91/9	94/91[d]

[a] Isolated yield. [b] Diastereoselectivity was determined by HPLC of the reaction mixture. [c] The ee of isomer was determined by HPLC using CHIRALCEL AD-H, CHIRALCEL OD-H, CHIRALPAC IC column, (*n*-hexane : 2-propanol = 96 : 4, 95 : 5, 80 : 20, 70 : 30, *n*-hexane : EtOH = 90 : 10). [d] Absolute configurations of **13** (*anti*)–**18** (*anti*) are not determined.

and **11a** (Tables 2 and 3). Based on both the good enantioselectivity (97% ee) of the obtained chiral Mannich product [2*S*,3*R*]-**12a'-1** and the results of its calculation studies (Fig. 1 and 2), an enantioselective reaction course is proposed as follows (Scheme 3). Thus, the stable conformations of both β-keto ester **10a** and imine **11a** were indicated by the scan of total energy and the DFT optimization calculations of structures (Fig. 1).

Furthermore, the conformation of catalyst **Z3** was also estimated by X-ray analysis (Scheme 3), the scan of total energy and the DFT optimization calculations (Fig. 2). Moreover, the regioselectivity of the interaction between **10a** and **11a** was estimated by the calculations of the energies and coefficients of their frontier orbitals (Fig. 2). The energy levels of the orbitals calculation clearly showed the interaction between the LUMO of **10a** and the HOMO of **11a**, and their orbital phase clearly demonstrated a matching in favor of overlapping to afford the observed configuration of major Mannich product **12a'-1** (Fig. 2). In addition, the direction of coordination of **Z3** and imine **11a** was indicated by the electrostatic potential calculation (Fig. 2). Based on these results, firstly, catalyst **Z3** acts as a base to **10a** and generate an enolate species of **10a** and then the species is fixed with ammonium site of catalyst by two points of hydrogen bonding interactions to form intermediates **I-1** or **I-2**. In **I-1** or **I-2**, **I-1** has less steric interaction of between catalyst and enolate species than that of intermediate **I-2** that has high steric interaction of between di-trifluorophenyl group on catalyst species and enolate (Scheme 3). Then, after adding imino ester **11a** might be proceed through any proposed **Ts-1-4** in which the amino hydrogen atom on thiourea part fixes by the intramolecular hydrogen bonding interaction with hydroxy group at α-position on the ammonium catalyst species. In the proposed **Ts-1-4**, the reaction might be proceeded through **Ts-1** that has smaller steric interactions between substrates **10a**, **11a** and the ammonium catalyst species than those of **Ts-2-4** that have a larger steric interaction between substrates **10a**, **11a** and the ammonium catalyst species. In this reaction, thiourea fused catalyst **Z3** showed a great difference of the catalytic activities compared to amino alcohol catalyst **X4**, namely, the reaction using catalyst **Z3** afforded the chiral Mannich product [2*S*,3*R*]-**12a'-1** in excellent enantioselectivity (97% ee, entry 1, Table 2
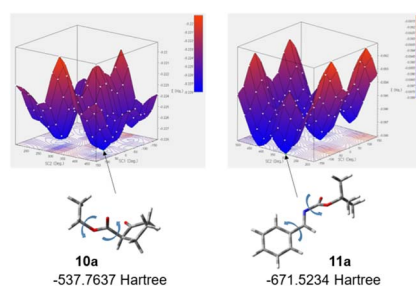

Fig. 1 Scan of total energies (up) and DFT optimized structures (down, at the B3LYP/6-31G(d) level of theory) of compounds **10a** and **11a** generated by varying the torsion angles (the dihedral scans showed with u-shaped arrows).
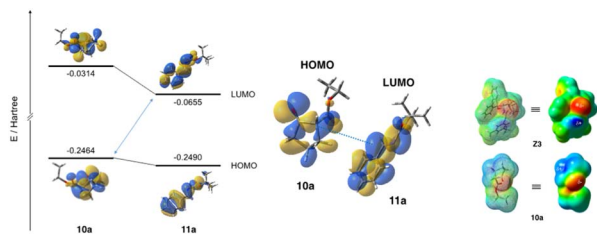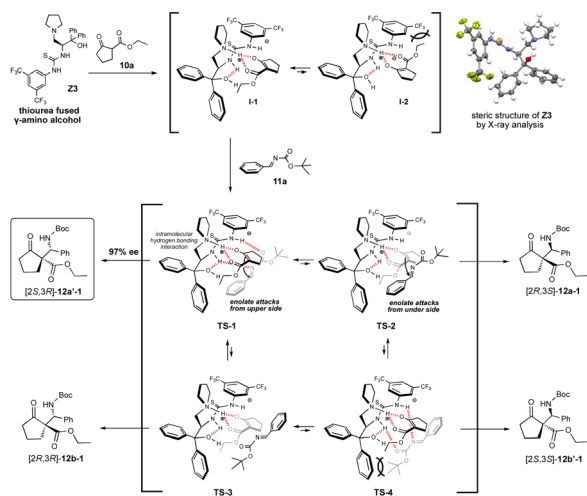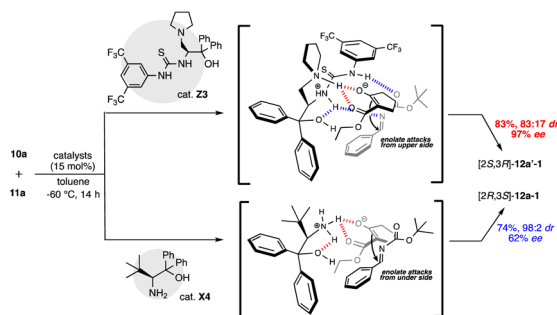
Fig. 2 Frontier orbital calculation and electrostatic potential calculation.

Scheme 3 Plausible reaction course.

and entry 1, Table 3) and the use of catalyst **X4** afforded enantiomeric [2S,3R]-**12a-1** (62% ee, entry 9, Table 1). It might be reasons of that **Z3** could highly immobilize both substrates **10a** and **11a** and for the steric influences of substituents on catalyst **Z3** (Scheme 4). Catalyst **Z3** can immobilize two substrates and may be able to control the direction of attack of **16a** to a high degree of steric control through the influence of substituent to afford **12a'-1**. On the other hand, catalyst **X4** can immobilize only substrate **10a** and may not be sufficiently influenced by substituents to provide an enough degree of steric control over the direction of attack of **11a** to afford **12b-1**.

Scheme 4 Differences of enantioselectivities by catalysts **Z3** and **X4**.

3. Conclusions

A new thiourea fused γ-amino alcohol organocatalysts **Z** were explored based on a new catalyst design concept and their catalytic activity were examined in asymmetric Mannich reaction of various β-keto active methylene compounds with imines. In the catalyst **Z**, **Z3** showed best catalytic performance and afforded the corresponding chiral Mannich products with good to excellent chemical yields, diastereoselectivities and enantioselectivities (up to 88%, up to *syn* : *anti*/93 : 7, up to 99% ee). Furthermore, the plausible stereoselective reaction course of Mannich reaction was predicted with the support of Frontier orbital and DFT calculations. The γ-amino alcohol organocatalysts **Z** designs modifications, further substrate scope of catalyst **Z** and the detailed mechanistic studies are in progress.

4. Experimental

4.1. General information

All reagents and dry solvents were purchased from commercial vendors and used directly without further purification. All reactions were placed in dried sample vials inserted with magnetic beads. ^{1}H and ^{13}C NMR spectroscopic data were recorded using a JEOL JNM-ECA500 instrument with tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates and the analytes were identified under UV light. Flash column chromatography was performed using silica gel pore size 60 N (40–100 μm). Infrared (IR) spectra were measured with a JASCO FT/IR-4100 spectrophotometer. HPLC data were collected using the TOSOH instrument equipped with (UV-8020, DP-8020, and SD-8022) detectors using Daicel CHIRALPAK AD-H OD-H column, CHIRALPAK IC column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. MS were taken on a JEOL-JMS-700 V spectrometers. The data for the X-ray crystallographic structure of **Z3** is available free of charge from the Cambridge Crystallographic Data Centre under accession number CCDC 2179025.

4.2. General procedure for the catalytic asymmetric Mannich reaction of β-keto carbonyl compounds 10a,d–h with NBoc imines 11a,b

To a solution of the corresponding catalyst (15 mol%) in solvent (1.0 mL) were added NBoc imine (0.10 mmol) and β-keto active methylene compounds (0.12 mmol) at −60 °C under an argon atmosphere and the solution was stirred at same temperature. After 14 h, the solvent was removed under reduced pressure and the residue was purified by preparative thin-layer chromatography. (*n*-hexane : EtOAc/25 : 1 to 8 : 1 to 6 : 1) to give the chiral Mannich products **12–18**. Compounds **12–18** are the known compounds and the structures were identified by spectral datas which were in good agreement with those reported. The enantiomeric ratio and diastereomeric ratio of the products were determined by using chiral HPLC analysis.[6i]

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395; (b) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726; (c) C. Bolm and J. A. Gladysz, *Chem. Rev.*, 2003, **103**, 2761; (d) Z. Tang, F. Jiang, L. T. Yu, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang and Y. D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262; (e) Y. Chi and S. H. Gellman, *Org. Lett.*, 2005, **7**, 4253; (f) A. Lattanzi, *Org. Lett.*, 2005, **7**, 2579; (g) D. Enders, C. Grondal and R. M. Matthias, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (h) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (i) S. Bertelsen and K. A. Jorgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (j) S. Kobayashi, Y. Mori, J. S. Fossey and M. M. Salte, *Chem. Rev.*, 2011, **111**, 2626; (k) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703; (l) P. Kasaplar, C. R. Escrich and M. A. Pericas, *Org. Lett.*, 2013, **15**, 3498; (m) D. L. SIlverio, S. Torker, T. Pilyugina, E. M. Vieria, M. L. Snapper, F. Haeffener and A. H. Hoyeda, *Nature*, 2013, **494**, 7436; (n) S. Saravanan, N. H. Khan, R. I. Kureshy, S. H. Abdi and H. C. Bajaj, *ACS Catal.*, 2013, **3**, 2873; (o) D. F. Chen, Z. Y. Han, X. L. Zhou and L. Z. Gong, *Acc. Chem. Res.*, 2014, **47**, 2365; (p) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (q) X. Fang and C. J. Wang, *Chem. Commun.*, 2015, **51**, 1185; (r) L. Xu, J. Huang, Y. Liu, Y. Wang, B. Xu, K. Ding, Y. Ding, Q. Xu, L. Yu and Y. Fan, *RSC Adv.*, 2015, **5**, 42178; (s) T. Sekikawa, T. Kitaguchi, H. Kitaura, T. Minami and Y. Hatanaka, *Org. Lett.*, 2016, **18**, 646; (t) U. Varal, M. Durmaz and A. Sirit, *Org. Chem. Front.*, 2016, **3**, 730; (u) H. Zhang, M. Han, T. Chen, L. Xu and L. Yu, *RSC Adv.*, 2017, **7**, 48214; (v) Y. Zheng, A. Wu, Y. Ke, H. Cao and L. Yu, *Chin. Chem. Lett.*, 2019, **30**, 937; (w) S. H. Xiang and B. Tan, *Nat. Commun.*, 2020, **11**, 3786.

2 (a) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (b) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580; (c) S. L. Zhang, H. X. Xie, J. Zhu, H. Li, X. S. Zhang, J. Li and W. Wang, *Nat. Commun.*, 2011, **211**(2), 211–217; (d) Y. Q. Zou, F. M. Hormann and T. Bach, *Chem. Soc. Rev.*, 2018, **47**, 278; (e) X. Fang and C. J. Wang, *Chem. Commun.*, 2015, **51**, 1185; (f) X. Yu and W. Wang, *Chem.–Asian J.*, 2008, **3**, 516; (g) H. Y. Bae, S. Some, J. Soh, Y. S. Lee and C. E. Song, *Chem. Commun.*, 2011, **47**, 9621.

3 (a) J. Kumagai, Y. Kohari, C. Seki, K. Uwai and Y. Okuyama, *Heterocycles*, 2014, **90**, 1124; (b) Y. Kohari, Y. Okuyama, E. Kwon, T. Furuyama, N. Kobayashi, T. Otuki, J. Kumagai, C. Seki, K. Uwai, G. Dai, T. Iwasa and H. Nakano, *J. Org. Chem.*, 2014, **79**, 9500; (c) H. Nakano, I. A. Owolabi, M. Chennapuram, Y. Okuyama, E. Kwon, C. Seki, M. Tokiwa and M. Takeshita, *Heterocycles*, 2018, **97**, 647; (d) D. Ganesan, M. Chennapuram, Z. Begum, C. Seki, K. Uwai, Y. Okuyama, E. Kwon, M. Tokiwa, M. Takeshita and H. Nakano, *Heterocycles*, 2019, **98**, 1536; (e) P. Parasuraman, Z. Begum, M. Chennapuram, C. Seki, K. Uwai, Y. Okuyama, E. Kwon, M. Tokiwa, M. Takeshita and H. Nakano, *RSC Adv.*, 2020, **10**, 17486; (f) Z. Begum, H. Sannabe, C. Seki, K. Uwai, Y. Okuyama, E. Kwon, M. Tokiwa, M. Takeshita and H. Nakano, *RSC Adv.*, 2021, **11**, 203; (g) D. Ganesan, P. Parasuraman, Z. Begum, R. Thiyagarajan, C. Seki, K. Uwai, Y. Okuyama, E. Kwon, M. Tokiwa, M. Takeshita and H. Nakano, *Heterocycles*, 2022, **105**, 369; (h) Z. Begum, C. Seki, K. Uwai, Y. Okuyama, E. Kwon, M. Tokiwa, M. Takeshita and H. Nakano, *RSC Adv.*, 2023, **13**, 888.

4 U. V. Subba Reddy, M. Chennapuram, K. Seki, C. Seki, B. Anusha, E. Kwon, Y. Okuyama, K. Uwai, M. Tokiwa, M. Takeshita and H. Nakano, *Eur. J. Org. Chem.*, 2017, **26**, 3874.

5 (a) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (b) E. A. Peterson and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2009, **48**, 6328; (c) W.-Y. Siau and J. Wang, *Catal. Sci. Technol.*, 2011, **1**, 1298; (d) O. V. Serdyuk, C. M. Heckel and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2013, **11**, 7051; (e) Y. Wang, H. Lu and P.-F. Xu, *Acc. Chem. Res.*, 2015, **48**, 1832.

6 (a) X. Jiang, D. Fu, G. Zhang, Y. Cao, L. Liu, J. Song and R. Wang, *Chem. Commun.*, 2010, **46**, 4294–4296; (b) Y. P. Lou, C. W. Zheng, R. M. Pan, Q. W. Jin, G. Zhao and Z. Li, *Org. Lett.*, 2015, **17**, 688; (c) Y. Yamada, H. Miyabe, Y. Yasui and Y. Takemoto, *Synthesis*, 2007, **16**, 2571; (d) A. J. Neuvonen and P. M. Pihko, *Org. Lett.*, 2014, **16**, 5152; (e) M. Hatano and K. Ishihatra, *Synthesis*, 2010, **22**, 3785; (f) A. L. Tillman, J. Ye and D. J. Dixon, *Chem. Commun.*, 2006, **11**, 1191; (g) Y. K. Kang and D. Y. Kim, *J. Org. Chem.*, 2009, **74**, 5734; (h) M. Hatano, K. Moriyama, T. Maki and K. Ishihara, *Angew. Chem., Int. Ed.*, 2010, **49**, 3823; (i) M. Hatano, T. Horibe and K. Ishihara, *J. Am. Chem. Soc.*, 2010, **132**, 56–57; (j) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1525; (k) O. Marianacci, G. Michelettin, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani and A. Ricci, *Chem.–Eur. J.*, 2007, **13**, 8338; (l) S. Lou, P. Dai and S. E. Schaus, *J. Org. Chem.*, 2007, **72**, 9998; (m) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 2896; (n) A. Ting, S. Lou and S. E. Schaus, *Org. Lett.*, 2006, **10**, 2003–2006; (o) N. H. Nguyen, A. B. Hughes and B. E. Sleebs, *Curr. Org. Chem.*, 2014, **18**, 260; (p) J. Vesely and R. Rios, *Chem. Soc. Rev.*, 2014, **43**, 611.

7 K. Moria, T. Yamauchia, J. Maddalunob, K. Nakanoa, Y. Ichikawaa and H. Kotsuki, *Synlett*, 2011, **14**, 2080.

8 T. Tatsumi, T. Misaki and T. Sugimura, *Chem.–Eur. J.*, 2015, **21**, 18971.

9 R. Pedrosa, J. M. Andrés, D. P. Ávila, M. Ceballosa and R. Pindadoa, *Green Chem.*, 2015, **17**, 2217.

10 X. Gu, Y. Zhang, Z. Xu and C. Che, *Chem. Commun.*, 2014, **50**, 7870.

11 (*a*) F. F. Fleming, V. A. Vu, B. C. Shook, M. Rahman and O. W. Steward, *J. Org. Chem.*, 2007, **72**, 1431; (*b*) Z. Jia, E. Gálvez, R. M. Sebastián, R. Pleixats, Á. Álvarez-Larena, E. Martin, A. Vallribera and A. Shafir, *Angew. Chem., Int. Ed.*, 2014, **53**, 1.

12 Y. Duan, L. Cui, L. Zuo and C. Zhang, *Chem.–Eur. J.*, 2015, **21**, 13052.

13 A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964.