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New boro amino amide organocatalysts for asymmetric cross aldol reaction of ketones with carbonyl compounds†

 Zubeda Begum,^a Chigusa Seki,^a Yuko Okuyama,^b Eunsang Kwon,^{*c} Koji Uwai,^a Michio Tokiwa,^d Suguru Tokiwa,^d Mitsuhiro Takeshita^d and Hiroto Nakano  

Distinct types of new boron fused primary amino amide organocatalysts were designed and synthesized from commercially available amino acids. Their catalytic activities were investigated in asymmetric crossed aldol reaction of ketones with aromatic aldehydes to afford the corresponding chiral *anti*-aldol adducts with good chemical yields, moderate diastereoselectivity and good to excellent enantioselectivities (up to 94% yields, up to 90 : 10 dr, up to 94% ee).

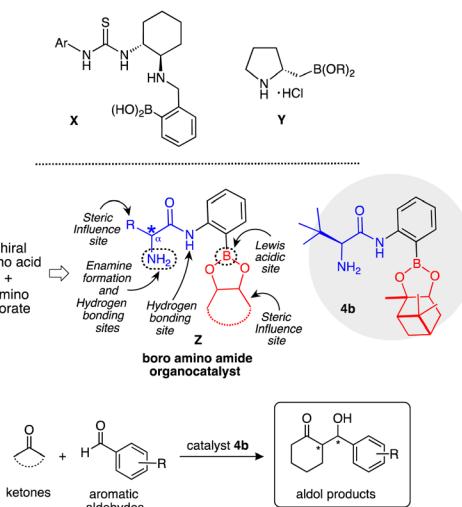
1. Introduction

The rapidly growing interest in the area of asymmetric organocatalysis is not only due to the versatile character of small organic molecules which function as efficient and selective catalysts but is also attributed to their important role in the construction of complex and enantiopure molecular skeletons.¹ Several contributions to the study of asymmetric aldol reactions were reported earlier² and with the development of the proline catalysed direct intermolecular asymmetric aldol reaction by List, Lerner and Barbas III,³ the synthesis and application of organocatalysts based on enamine-iminium ion activation and hydrogen bonding activation has received further considerable attention.⁴ Most organocatalysts currently used are functionally synergic systems which have two or more distinct functionalities within the same molecule. Among the various polyfunctional organocatalysts available, one functional group works as enamine-iminium formation or Brønsted basic sites and the other works as a Lewis acidic site.⁵ Our group is also exploring new polyfunctional organocatalysts based on primary amino alcohols and amino amides, which are easily derived from commercially available amino acids, in numerous asymmetric reactions.⁶ However, only a few examples have been reported on the polyfunctional organocatalysts with boron functional

groups as Lewis acidic sites, such as thiourea-boronic acid **X** by Takemoto⁷ and proline boronate **Y** by Whiting,⁸ so far.

Based on the above background, we designed a boron derived amino amide organocatalyst **Z**, obtained by facile synthetic transformation. Catalyst **Z** contains an amino group acting as an enamine formation site, amino amide group for hydrogen bonding site, boron atom acting as a Lewis acidic site, and also pinene and the β -position substituent act as steric influence sites in a single molecule (Scheme 1). The cross aldol reaction of ketones with aldehydes was chosen to explore the activity of **Z** as an organocatalyst. The aldol reaction⁹ is one of the most versatile and popular method for the formation of C–C bonds¹⁰ in modern organic synthesis.

Herein, we describe new boro amino amide **Z** as an organocatalyst, which showed an efficient catalytic activity in



^aDivision of Sustainable and Environmental Engineering, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto-cho, Muroran 050-8585, Japan. E-mail: catanaka@mmm.muroran-it.ac.jp

^bTohoku Medical and Pharmaceutical University, 4-4-1 Komatsushima, Aoba-Ku, Sendai 981-8558, Japan

^cResearch and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-Ku, Sendai 980-8578, Japan

^dTokiwakai Group, 62 Numajiri Tsuduri-Chou Uchiga, Iwaki 973-8053, Japan

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Scheme 1 Asymmetric cross aldol reaction of ketones with carbonyl compounds.



crossed aldol reaction of ketones with aromatic aldehydes to afford aldol products. Especially, catalyst **4b** showed satisfactory catalytic activity in this reaction to afford the corresponding aldol products (up to 94%, up to *anti* : *syn* 90 : 10, up to 94% ee) in eco-friendly sea-H₂O-tap H₂O solvent condition.

2. Results and discussion

2.1. Catalyst design and synthesis

Initially, we synthesized catalysts **4a-f** having primary amino group by the coupling of protected amino acids **1a-f** with amines **2a** and **2b** having boron substituents, respectively, followed by the deprotections of protected boro amino amides **3a** and **3b-f**, respectively, in good yields (Scheme 2). Moreover, secondary amino catalyst **4g** having proline ring was synthesized by condensation of **1g** with **2b**, followed by the deprotection of **3g**. Catalyst **4h** having secondary amino group was derived from **4b** by methylation with MeI and K₂CO₃.

2.2. Catalytic efficiency

To find out the best catalyst, our preliminary investigations were focused on screening of the synthesized catalysts **4a-h** in the crossed aldol reaction of cyclohexanone **5a** as an aldol donor with *p*-nitro benzaldehyde **6a** as an aldol acceptor (Table 1). First, the catalytic activity of boro amino amide **4a** with primary amino group and pinacolyl boron substituent was examined under THF at room temperature, but the formation of the corresponding aldol product **7a** or **8** was not observed (entry 1). Next, this reaction using benzoic acid as a co-catalyst was examined (entries 2-9). The reaction was carried out with 10 mol% of **4a** and 20 mol% of benzoic acid in THF at room temperature. Initially, the functionality of catalyst **4a** was examined (entry 2). However, this catalyst **4a** did not work enough and the corresponding aldol product **7** was obtained in low chemical yield as racemate. Next, catalysts **4b-f** with primary amino group, several substituents at α -position and bulky pinenyl boron group on amide amino group were investigated (entries 2-7). As a result, all the catalysts showed catalytic activity. Especially, the use of catalyst **4b** with *tert*-butyl group afforded *anti*-aldol product **7a** as a main product with

Table 1 Asymmetric aldol reaction of **5a** and **6a** with organocatalysts **4a-h**

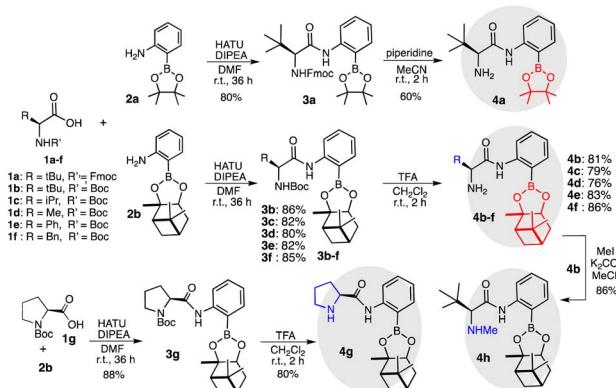
Entry	Cat.	Co-cat.	Yield ^a (%)	dr ^b <i>anti</i> : <i>syn</i>	ee ^c (%)
1	4a	—	nr	—	—
2	4a	Benzoic acid	15	58 : 42	racemic
3	4b	Benzoic acid	24	60 : 40	66
4	4c	Benzoic acid	12	54 : 46	33
5	4d	Benzoic acid	22	55 : 45	40
6	4e	Benzoic acid	20	58 : 42	27
7	4f	Benzoic acid	13	33 : 67	20
8	4g	Benzoic acid	28	60 : 40	56
9	4h	Benzoic acid	nr	—	—

^a Isolated yields (a mixture of diastereomer). ^b The dr values were determined by ¹H NMR. ^c The ee values were determined by HPLC analysis (Daicel Chiralpak AD-H column).

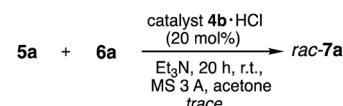
moderate diastereo and enantioselectivity (*anti* : *syn* 60 : 40, 66% ee), although chemical yield was low (24%) (entry 3). We also screened the activity of secondary amino catalyst **4g** having pyrrolidine ring that is valid for forming enamine with ketone **5a** (entry 8). However, the sufficient improvement of both chemical yield and stereoselectivities (28%, *anti* : *syn* 60 : 40, 56% ee) in the reaction using **4g** was not observed in comparison with the result of catalyst **4b** having primary amino group. Based on the above results, the functionality of catalyst **4h** which is obtained by a change of primary amino group on **4a** to secondary amino group was also examined under similar reaction condition (entry 9). However, contrary to expectation, catalyst **4h** did not work in this reaction. In addition, the aldol reaction was also carried out in the similar conditions as reported by Whiting *et al.*, using the HCl salt of our best catalyst **4b**, but **4b** HCl salt catalyst only showed less catalytic activity and the aldol product **7a** was observed as racemate (Scheme 3). From all of the above results, it was observed that catalyst **4b** with primary amino group and both *tert*-butyl group at α -position and bulky pinenyl boron group on amide amino group as a steric influence sites performed better comparatively with other catalysts **4a,c-h**. The absolute configuration and *anti/syn* diastereoselectivity of **7a** and **8** were identified based on comparison with literature data.¹¹

2.3. Improving catalytic efficiency

To improve the catalytic efficiency, the reaction conditions such as solvent, co-catalysts, and reaction times were examined by



Scheme 2 Preparations of catalysts **4a-h**.



Scheme 3 Aldol reaction under Whiting *et al.* condition.



using superior catalyst **4b** (Table 2). First, solvent effect was examined with THF, i-PrOH, MeOH and H₂O as polar protic solvent, DMF as a polar aprotic solvent, dioxane as ethereal solvent (entries 1–6), neat condition (entry 7) and CH₂Cl₂ as halogenated solvent (entry 8) in the presence of catalyst **4b** (10 mol%) and benzoic acid as a co-catalyst (20 mol%) at room temperature for 96 h. As a result, only tap H₂O had a quite influence on the enantioselectivity of the reaction to afford *anti*-aldol product **7a** with moderate chemical yield and diastereoselectivity (50%, *anti* : *syn* / 64 : 36, 85% ee) (entry 4). It was observed that based on the previous reports¹² of aldol reaction in water, which suggest that water molecule facilitates the ease of the condensation process and enhances the reactivity of the reaction, with no less influence on the transition state, especially in the asymmetric aldol reaction. Next, a series of co-catalysts were examined using superior tap H₂O as solvent (entries 9–12). With all the co-catalysts, the results were found to be inferior to benzoic acid in terms of chemical yield and stereoselectivity suggesting benzoic acid as superior co-catalyst. Next, the reaction was carried out in different types of H₂O (Table 3). Initially, sea H₂O was used in this reaction and the product **7a** was obtained with moderate enantioselectivity (60% ee), but chemical yield was increased to 86% with moderate diastereoselectivity (*anti* : *syn* / 68 : 32) (entry 1). Using distilled H₂O, chemical yield was low (48%), but the enantioselectivity was relatively good (77% ee) with moderate diastereoselectivity (*anti* : *syn* / 67 : 33) (entry 2). The use of brine afforded **7a** with moderate chemical yield and stereoselectivities (50%, *anti* : *syn* / 62 : 38, 67% ee) (entry 3). From those results, it was indicated that sea H₂O is effective to increase the chemical yield of the aldol product **7a**. This might be due to the high density, higher electrical conductivity, slight basic nature of sea water in combination with mineral contents were assumed to accelerate the reaction yields of the aldol reaction, although the reason is

not clear. We then changed the time duration of the reaction using sea water for 72 h and 120 h. As a result, 72 h of reaction time was better for obtaining **7a** in good chemical yield, moderate diastereoselectivity and enantioselectivity (80%, *anti* : *syn* / 68 : 32, 75% ee) (entry 4). On further increase of reaction time to 120 h resulted in the aldol product in low enantioselectivity (90%, *anti* : *syn* / 66 : 34, 11% ee) (entry 5).

Good yield was observed with sea water and relatively good enantioselectivity was observed with tap water. Therefore, we attempted the aldol reaction in a mixture of sea H₂O and tap H₂O (1 : 1) while varying the co-catalysts and catalyst mol ratio. Initially, the reaction using mixed sea H₂O-tap H₂O with 10 mol% of catalyst **4b** and 20 mol% of benzoic acid as a co-catalyst was investigated (82%, *anti* : *syn* / 68 : 32, 94% ee) (entry 6). To our surprise, the aldol product **7a** was obtained in good enantioselectivity (94% ee), good chemical yield and moderate diastereoselectivity (82%, *anti* : *syn* / 68 : 32). Further, on changing the catalyst and co-catalyst mol ratios (entries 7–10) with the solvent system as sea H₂O-tap H₂O, the obtained results were found to be inferior to the result of entry 6. Based on the above results, the catalyst **4b** (10 mol%) and benzoic acid (20 mol%) as a co-catalyst in the mixed solvent of sea H₂O-tap H₂O at 72 h was confirmed as the optimum condition.

2.4. Substrate scope

After the optimisation of reaction conditions, we examined the generality of the superior catalyst **4b** in the aldol reactions of various ketones **5a–h** with aldehydes **6b–k** (Scheme 4). The reactions were carried out in the presence of catalyst **4b** (10 mol%) and benzoic acid as a co-catalyst (20 mol%) under the best reaction condition (sea H₂O-tap H₂O, 72 h, 25 °C).

Initially, substituent influences on the aromatic ring of aldehydes **6b–j** were examined. The reactions of **5a** with nitro aromatic aldehydes [**6b** (*m*-NO₂), **6c** (*o*-NO₂)] gave the

Table 2 Optimisation of reaction conditions using catalyst **4b**

Entry	Solvent	Co-cat.	Yield ^a (%)	dr ^b <i>anti</i> : <i>syn</i>	ee ^c (%)
1	THF	Benzoic acid	24	60 : 40	66
2	i-PrOH	Benzoic acid	20	63 : 37	53
3	MeOH	Benzoic acid	25	52 : 48	67
4	Tap H ₂ O	Benzoic acid	50	64 : 36	85
5	DMF	Benzoic acid	10	55 : 45	51
6	1,4-Dioxane	Benzoic acid	trace	—	—
7	Neat	Benzoic acid	51	54 : 46	59
8	CH ₂ Cl ₂	Benzoic acid	20	61 : 39	60
9	Tap H ₂ O	4-NO ₂ Benzoic acid	45	58 : 42	40
10	Tap H ₂ O	TFA	50	66 : 33	60
11	Tap H ₂ O	Acetic acid	41	60 : 40	72
12	Tap H ₂ O	2-F-Benzoic acid	40	63 : 37	54

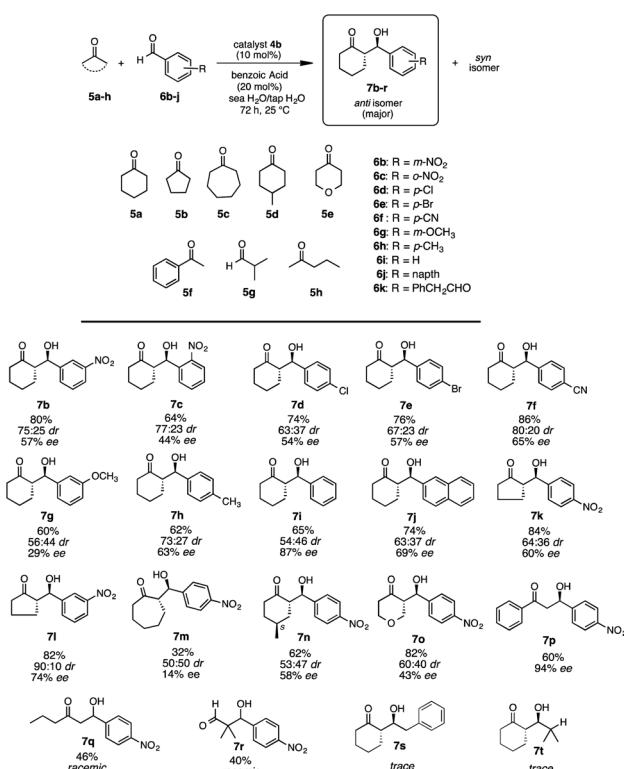
^a Isolated yields (a mixture of diastereomer). ^b The dr ratios were determined by ¹H NMR. ^c The ee values were determined by HPLC analysis (Daicel Chiralpak AD-H column).



Table 3 Optimisation of reaction condition using H_2O solvent using 4b

Entry	Solvent	Time (h)	Cat. (mol%)	Co-cat. (mol%)	Yield ^a (%)	dr ^b anti : syn		ee ^c (%)
						catalyst 4b (10 mol%)	benzoic acid (20 mol%)	
1	Sea H_2O^d	96	10	20	86	68 : 32		60
2	Distilled H_2O	96	10	20	48	67 : 33		77
3	Brine H_2O	96	10	20	50	62 : 38		67
4	Sea H_2O	72	10	20	80	68 : 32		75
5	Sea H_2O	120	10	20	90	66 : 34		11
6	Sea H_2O /tap H_2O	72	10	20	82	68 : 32		94
7	Sea H_2O /tap H_2O	72	20	20	94	43 : 57		64
8	Sea H_2O /tap H_2O	72	20	10	90	68 : 32		72
9	Sea H_2O /tap H_2O	72	10	10	44	67 : 33		71
10	Sea H_2O /tap H_2O	72	5	10	30	69 : 31		83

^a Isolated yields (a mixture of diastereomer). ^b The dr ratios were determined by ^1H NMR. ^c The ee values were determined by HPLC analysis (Daicel Chiralpak AD-H column). ^d Sea H_2O source: Itanki beach, Pacific sea, Higashi Muroran, Hokkaido, Japan. Tap H_2O : obtained from the laboratory tap H_2O .



Scheme 4 The aldol reactions of 5a-h with different aromatic aldehydes 6b-k.

corresponding aldol products **7b,c** respectively, with moderate to good chemical yield and diastereoselectivities, but with moderate enantioselectivities (**7b**: 80%, *anti* : *syn* : 75 : 25 dr, *anti* : 57% ee, *syn* : 58% ee; **7c**: 64%, *anti* : *syn* : 77 : 23 dr, *anti* : 44% ee, *syn* : 25% ee). Whereas the reaction of **5a** with halogenated aromatic aldehydes [**6d** (*p*-Cl), **6e** (*p*-Br)] gave the corresponding aldol products **7d,e** respectively, with good chemical yields,

diastereoselectivities and moderate enantioselectivities (**7d**: 74%, *anti* : *syn* : 63 : 37 dr, *anti* : 54% ee, *syn* : 10% ee; **7e**: 76%, *anti* : *syn* : 67 : 23 dr, *anti* : 57% ee, *syn* : 16% ee). Furthermore, the reactions of **5a** with aldehyde **6f** (*p*-CN), having electron withdrawing group afforded the aldol product **7f** in good chemical yield and moderate to good diastereoselectivities and moderate enantioselectivity (**7f**: 86%, *anti* : *syn* : 80 : 20 dr, *anti* : 65% ee, *syn* : 60% ee). The influence of electron donating group on aldehydes were also examined by the reactions of **5a** with **6g** (*m*-methoxy) and with **6h** (*p*-methyl) to afford the corresponding *anti*-aldol products **7g** and **7h** in moderate chemical yields, moderate to good diastereoselectivities and low to moderate enantioselectivities (**7g**: 60%, *anti* : *syn* : 56 : 44 dr, *anti* : 29% ee, *syn* : 34% ee; **7h**: 62%, *anti* : *syn* : 73 : 27, *anti* : 63% ee, *syn* : 12% ee), respectively. When benzaldehyde **6i** and bulkier naphthaldehyde **6j** were used, the chemical yields, diastereoselectivities and enantioselectivities were moderate to good (**7i**: 55%, *anti* : *syn* : 54 : 46 dr, *anti* : 87% ee, *syn* : 12% ee; **7j**: 74%, *anti* : *syn* : 63 : 37 dr, *anti* : 69% ee, *syn* : 40% ee). Furthermore, the reactions of 5 membered cyclopentanone **5b** with **6a,b** and 7 membered cycloheptanone **5c** with **6a**, respectively, was carried out in the presence of catalyst **4b** (10 mol%) and benzoic acid as a co-catalyst (20 mol%) under the best reaction conditions. The product **7k** derived from the reaction of **5b** with **6a** was obtained in good chemical yield, moderate diastereoselectivity and enantioselectivity (84%, *anti* : *syn* : 64 : 36 dr, *anti* : 60% ee, *syn* : 57% ee). The product **7l** derived from the reaction of **5b** with **6b** in good chemical yields and stereoselectivities (82%, *anti* : *syn* : 90 : 10 dr, *anti* : 74% ee, *syn* : 63% ee). Whereas, the reaction of 7 membered **5c** with **6a** did not proceed well giving the aldol product **7m** in low chemical yield and diastereoselectivity with poor enantioselectivity (32%, *anti* : *syn* : 50 : 50 dr, *anti* : 14% ee, *syn* : 4% ee). Moreover, the use of substituted cyclohexanone **5d** also afforded the product **7n** with moderate chemical yield and stereoselectivities (62%, *anti* : *syn* : 53 : 47 dr, *anti* : 58% ee, *syn* : 57% ee). The product **7o** derived from the reaction of **5c** with **6b** in good chemical yields and stereoselectivities (82%, *anti* : *syn* : 60 : 40 dr, *anti* : 43% ee). The product **7p** derived from the reaction of **5c** with **6a** in good chemical yield and stereoselectivities (60%, *anti* : *syn* : 94 : 56 dr, *anti* : 54% ee). The product **7q** derived from the reaction of **5c** with **6b** in good chemical yields and stereoselectivities (46%, *anti* : *syn* : 90 : 10 dr, *anti* : 74% ee, *syn* : 63% ee). Whereas, the reaction of 7 membered **5c** with **6a** did not proceed well giving the aldol product **7r** in low chemical yield and diastereoselectivity with poor enantioselectivity (40%, *anti* : *syn* : 50 : 50 dr, *anti* : 14% ee, *syn* : 4% ee). Moreover, the use of substituted cyclohexanone **5d** also afforded the product **7s** with moderate chemical yield and stereoselectivities (trace, *anti* : *syn* : 53 : 47 dr, *anti* : 58% ee, *syn* : 57% ee). The product **7t** derived from the reaction of **5c** with **6b** in good chemical yields and stereoselectivities (trace, *anti* : *syn* : 53 : 47 dr, *anti* : 58% ee, *syn* : 57% ee).

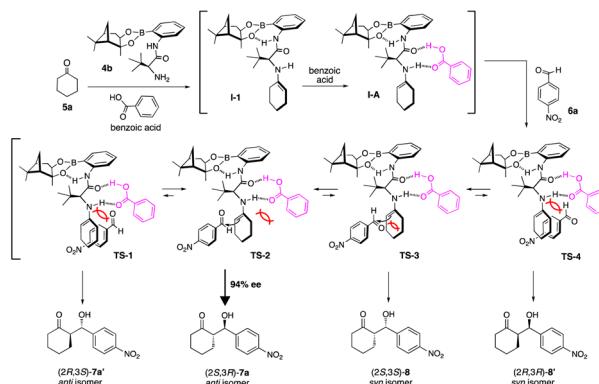


49% ee). In addition, the reaction using pyranone **5e** as heterocyclic ketone was also examined and the aldol product **7o** was afforded in good chemical yield and diastereoselectivity with moderate enantioselectivity (82%, *anti* : *syn* / 60 : 40 dr, *anti* : 43% ee, *syn* : 42% ee). The reaction of acetophenone **5f** with **6a** afforded the aldol product **7p** in good enantioselectivity but moderate yields (60%, 94% ee). The reaction of acyclic ketones **5g,h** with **6a**, respectively, gave the aldol products **7q,r** as racemate with low chemical yields. The aldol reaction of cyclohexanone with aliphatic aldehydes like **6k** and **5g** as acceptors, was also tried but the desired product was not observed.

2.5. Reaction mechanism

Considering both the good enantioselectivity (94% ee) of the chiral aldol product [*2S,3R*]-**7a** that was obtained in the reaction of **5a** with **6a** and the results of its calculation studies (Fig. 1–3), an enantioselective reaction course is proposed as follows (Scheme 5).

For the estimation of enantioselective reaction course, initially the conformational analysis using the scan of total energies for the enamine intermediate **I** was carried out and the result indicated the conformation of enamine intermediate **I-1**, with an intramolecular hydrogen bonding between hydrogen



Scheme 5 Plausible reaction course of the reaction.

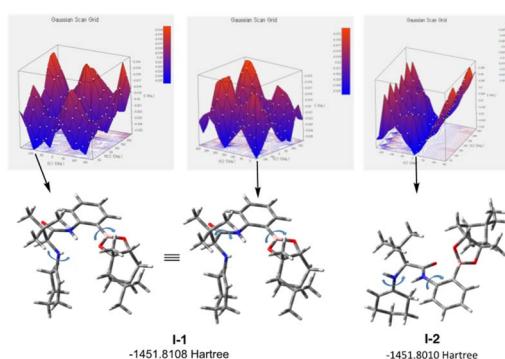


Fig. 1 Scan of total energies (up) and DFT optimized structures (down, at the B3LYP/6-31G(d) level of theory) of the enamine intermediate **I** generated by varying the torsion angles (the dihedral scans showed with u-shaped arrows: **I-1**).

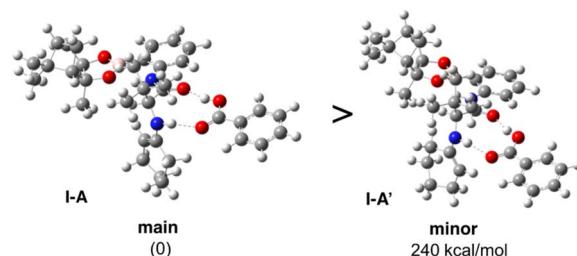


Fig. 2 The scan of total energies for **I-A** and **I-A'**.

atom of amide amino group and oxygen atom adjacent to boron atom, suggesting **I-1** is better than **I-2**, as **I-2** does not have similar intramolecular hydrogen bonding (Fig. 1). Furthermore, when benzoic acid as a co-catalyst is coordinated to more stable **I-1** by hydrogen bonding, it is suggested that **I-A**, in which **I-1** and benzoic acid are hydrogen bonded at two points to each other, is more stable than **I-A'** (Fig. 2). In addition, it is also indicated that in **I-1**, the olefin of the enamine was anterior, but in **I-A**, its olefin has a posterior conformation (Fig. 3). Moreover, to examine the regioselectivity of the reaction between **I-1** and **6a**, the calculation of the energies (Fig. 1 and 3) and coefficients of their frontier orbitals (Fig. 4) were conducted. The energy levels of the orbitals calculation clearly showed the interaction between the LUMO of **6a** and the HOMO of **I-1**, and their orbital phase clearly demonstrated a matching in favor of overlapping to afford the observed configuration of major aldol product **7a** (Fig. 4).

Based on the above calculation results, the reaction might pass through enamine intermediate **I-1** and complex **I-A** (**I-1**-

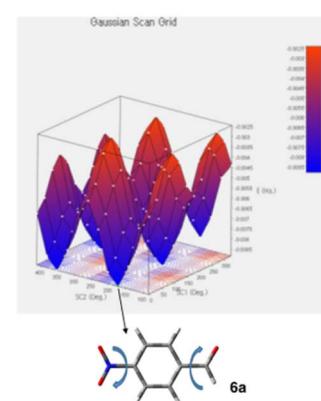


Fig. 3 Scan of total energies (up) and DFT optimized structures (down, at the B3LYP/6-31G(d) level of theory) of **6a** generated by varying the torsion angles (the dihedral scans showed with u-shaped arrows).

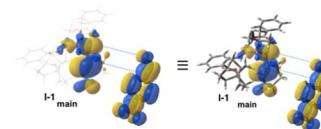


Fig. 4 The frontier orbital between **I-1** and **6a**.



benzoic acid) and subsequently, it was indicated that the reaction of **I-A** with **6a** might progress through proposed four different transition states **Ts-1-4** as shown in Scheme 5. However, among the proposed **Ts-1-4**, the reaction might proceed through **Ts-2**, based on the scan of total energy of **I-A** (Fig. 2) and the frontier orbital analysis (Fig. 3), having smaller steric interaction both between **I-A** and aldehyde **6a** than those of **Ts-1, 3, 4**.

In contrary to the expectations, the calculation results suggest that, the boron atom on the catalyst does not coordinate the substrate **6a** as a Lewis acid moiety. However, the boron atom has three covalent bonds in the plane, and its configuration may contribute to the formation of preferable transition states in affording aldol product **7a** with a high stereoselectivity. Furthermore, it is also suggested that boron atom might coordinate with water solvent, forming an efficient conformation of the transition state, affording high enantioselectivity, although it is not clear why the solvent system is effective.

3. Conclusion

We have developed a new boron fused primary amino amides and their functionality as organocatalysts were examined in the asymmetric cross aldol reactions of various ketones **5a-h** with different aromatic aldehydes **6a-k** to afford the desired chiral aldol products **7a-r**. The developed catalysts showed catalytic activity in this reaction. Particularly, catalyst **4b** showed good catalytic activity to afford the various chiral aldol products in satisfactory chemical yields and stereoselectivities (up to 94%, *anti* : *syn* / 68 : 32 dr, up to 94% ee) and interestingly, the effective solvent of the reaction was the mixture of sea H_2O and tap H_2O .

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. 1H 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 μ m). 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 Chiraldak AD-H, AS-H, OD-H columns. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. MS were taken on a JEOL-JMS-700V spectrometers.

4.2. General procedure for catalytic asymmetric aldol reaction of various ketones **5** with aromatic aldehydes **6**

Catalyst **4b** (10 mol%) and co-catalyst (20 mol%) were added to a solution of ketones (0.4 mmol) and the respective aldehydes

(0.1 mmol) under the sea H_2O -tap H_2O (1 : 1) as solvent reaction condition. The reaction is allowed to stir at room temperature for appropriate time until the reaction completion. After the reaction completion, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (*n*-hexane/CH₃CO₂Et) to give the corresponding aldol products. The compounds are the known compounds and the structures were identified by spectral data which were in good agreement with those reported. The enantiomeric excess (ee) was determined using high pressure liquid chromatography (HPLC) principle by Daicel Chiraldak AD-H, AS-H, OD-H columns.^{11a-q}

Conflicts of interest

There are no conflicts to declare.

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